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Dapagliflozin Reduces Albuminuria Over 2 Years in Diabetic Patients with Renal Impairment
Bergur V. Stefansson, 1 Paola Fioretto, 3 Eva K.A. Johnsson, 2 Valerie A. Cain, 3 David Sjostrom. 2

Background: Pooled clinical data has shown reductions in albuminuria during dapagliflozin (DAPA) treatment. This analysis explored the long term effect of DAPA on albuminuria and renal safety. 

Methods: This is a post hoc analysis of patients with CKD3 and albuminuria (³30 mg/g) from study NCT00663260. Percent change in urinary albumin/creatinine ratio (UACR) was evaluated up to 104 weeks. At baseline 57 placebo (PBO), 53 DAPA 5 mg and 56 DAPA 10 mg patients were identified. 

Results: The baseline (BL) median (range) values for UACR, mg/g, were: PBO: 180 (30 to 9262), DAPA 5 mg: 397 (31 to 4970) and DAPA 10 mg: 179 (32 to 4792). The corresponding mean (SD) values for eGFR, mL/min/1.73 m² were: 45.1 (9.37), 43.9 (8.36) and 44.1 (11.1), respectively. A reduction in UACR was already evident at Week 1. At 104 weeks the mean (95% CI) PBO-corrected reduction in UACR was --44% (--71.9, 0.0) and --57% (--77.7, --20) for DAPA 5 and 10 mg, respectively. After adjusting for changes in blood pressure, HbA1c and eGFR, the reductions were largely maintained. During the 104 week period 7% of PBO patients regressed to normoalbuminuria, the corresponding numbers for DAPA 5 and 10 mg were 19 and 18%, respectively. 

After a transient decrease in eGFR in DAPA-treated patients, the DAPA 5 and 10 mg groups showed PBO-corrected 104 week changes of 2.1 (--1.3, 5.5) and --0.7 (--4.0, 2.6) mL/min/1.73 m². 

Conclusions: Dapagliflozin reduces UACR for up to 2 years in subjects with CKD3, without increases in serious renal AEs. The UACR reduction remained present after adjustments for changes in blood pressure, HbA1c and eGFR, indicating a direct effect independent of changes in these variables. 

Funding: Pharmaceutical Company Support - AstraZeneca

TH-OR002
Structural Predictors of Loss of Renal Function in Type 2 Diabetes
Guadeta D. Fufaa, 1 E. Jennifer Beisswenger, 2 Kevin V. Lemley, 1 William Knowler, 1 Frank C. Brosius, 3 Berne Yee, 1 Michael Mauer, 1 Robert G. Nelson, 1 NIDDK, 1 Univ of Southern California, 1 Univ of Michigan, 3 Southwest Kidney Inst; 1 Univ of Minnesota

Background: Diabetes is the leading cause of kidney failure in the US, but the early structural determinants of renal function loss are poorly understood. We examined the association between morphometrically-determined renal structural variables and renal function loss in 111 Pima Indians with type 2 diabetes who volunteered for a research kidney biopsy and for annual measurement of glomerular filtration rate (GFR, iothalamate). 

Methods: Renal function loss was defined as ≥40% loss of GFR from baseline. Associations with renal function loss were evaluated by Cox proportional-hazards regression. Hazard ratios (HR) were reported per 1 SD increment for each morphometric variable. 

Results: Of the 111 participants (82% women, baseline mean age 46 years, diabetes duration 16 years, HbA1c 9.4%, GFR 147 ml/min, and median albumin/creatinine ratio [ACR] 41 mg/g), 51 (46%) developed renal function loss during a median follow-up of 6.6 years (95% CI 6.0-7.0). Higher megalin fractional volume (HR=2.33, 95% CI 1.63-3.33), and lower megalin cell length (HR=0.67, 95% CI 0.47-0.94) were each associated with loss of renal function after adjustment for baseline age, sex, duration of diabetes, HbA1c and GFR. Although power was reduced when 14 participants with baseline GFR <90 ml/min were excluded from the analysis, baseline structure still predicted renal function loss. 


Funding: NIDDK Support

TH-OR003
Mitic catastrophe in Diabetic Nephropathy
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Background: Podocyte apoptosis is involved in the progression of diabetic nephropathy. Apoptosis is thought to be a major mechanism for loss of podocytes. However, apoptotic podocytes (Podo) are not seen in renal biopsy specimens with diabetes. Instead mitotic catastrophe (MC) is a newly recognized form of podocyte death characterized by Podo multination, aberrant mitotic spindles and micronuclei. Because injured podocytes may die and released in the urine, in this study we sought to quantitate MC in urine samples from diabetic patients. 

Methods: Urine samples from patients with diabetes type 2 (n=41), microalbuminuria (8, macroalbuminuria 33) were used. All samples were evaluated for the presence of urinary Podo by immunofluorescence (IF) using anti-podocalyxin (PCX) antibody and the only PCX positive Podo (PCX-podo) were selected for further immunohistochemical study. 

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

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1A

TH-OR004
Advanced Glycation End Products Predict Loss of Renal Function and Correlate with Diabetic Nephropathy Lesions in Type 2 Diabetes
Pierre Jean Saunder, 1 Kevin M. Wheelock, 2 William Knowler, 1 Robert G. Nelson, 1 Paul James Beisswenger, 2 Scott K. Howell. 2 NIDDK; 2PreventAGE Healthcare

Background: We examined the associations of serum advanced glycation end-products (AGEs) with loss of renal function and with the structural lesions of diabetic nephropathy in a post hoc analysis of a clinical trial of renoprotection with losartan in Pima Indians with type 2 diabetes (ClinicalTrials.gov number, NCT00340678). 

Methods: Free AGEs were measured at baseline in 168 subjects by LC triple quadrupole mass spectrometry. Glomerular filtration rate (GFR, iothalamate) was measured annually, and kidney biopsies were performed in 109 of the subjects 6 years later. Loss of renal function was defined as ≥40% loss of GFR from baseline. Multivariable associations between AGEs and loss of renal function were examined by Cox proportional-hazards regression, and between AGEs and morphometric variables by linear regression, after adjustment for age, sex, diabetes duration, HbA1c, treatment, albumin/creatinine ratio (ACR), and GFR. Hazard ratios (HR) were reported per doubling for each AGE. Linear regression results were reported as the difference in the structural measurement in SD units of doubling of AGE. 

Results: Of the 168 subjects (73% women, mean age 41±11 years, diabetes duration 11±6 years, HbA1c 9.2±2.3%, median GFR=165 ml/min/1Q=135-190), and median ACR=51 mg/g (IQR=14-76), 104 (62%) lost ≥40% of their renal function during a median follow-up of 8.0 years (IQR=4.9-13.1). After multivariable adjustment, higher concentrations of carboxyethyllysine (CEL) and methylhydroxymydalgamines (MG1M) were associated with loss of renal function (HR for CEL=1.7, 95% CI 1.1-2.5; HR for MG1M=1.3, 95% CI 1.1-1.7). MG1M (p=0.23, P=0.018) and CEL (P=0.36, P=0.033) were also positively associated with mesangial fractional volume, and MG1M (p=0.27, P=0.009) and 3D hydroigmolizylaminoglycine (3DHB) (p=0.27, P=0.047) were inversely associated with total filtration surface per glomerulus. 

Conclusions: Higher baseline dicarbonyl-derived AGEs are associated with loss of renal function and its structural correlated, including increased mesangial fractional volume and the corresponding loss of total filtration surface per glomerulus. 

Funding: NIDDK Support

TH-OR005
Serum Amyloid A and Increased Risk of End-Stage Renal Disease and Death in Diabetic Kidney Disease
Brad Dieter, 1 Sterling Mcpherson, 2 Maryam Afkarian, 3 Jan H. De Boer, 2, 3 Rajnish Mehrota, 2 Rick L. Mckee, 2 Katherine R. Tuttle, 1, 3 Providence Health Care, Spokane, WA; 3Washington Univ, Spokane, WA; 1Univ of Washington, Seattle, WA.

Background: Serum amyloid A (SAA) activates inflammation and apoptosis in kidney cells. SAA is also increased in the blood, urine, and kidneys of mice and people with DKD. The objective of this study was to determine if SAA adds to risk prediction models for death and end-stage renal disease (ESRD) in DKD. 

Methods: Serum SAA was measured in a longitudinal cohort with type 2 diabetes and prevalent DKD, defined by urine protein-to-creatinine ratio >0.5 g/g (n=135). Cox-proportional hazard models tested whether SAA was associated with a composite primary outcome of death and ESRD, adjusting for age, sex, race, hemoglobin A1c, diabetes duration, body mass index, renin-angiotensin system inhibitor use, systolic and diastolic blood pressure, albuminuria and estimated glomerular filtration rate (eGFR). Improvement in risk prediction was assessed by receiver-operating curves (ROC), goodness-of-fit, and Akaike Information Criterion (AIC). 

Results: Participants were 73% Mexican-American (99/135) with mean (SD) age of 57 (7.4) years, 55% male (75/135), mean eGFR 56 (22) ml/min/1.73m², and median (IQR) urine albumin-to-creatinine of 1 9 (7.3-9.3) g/day. The incident rate for the primary outcome was 44 % (60/135). Risk of the composite primary outcome was higher in the 3rd tertile of SAA (≥1.0 g/ml) compared to the 1st tertile (0<0.55 g/ml): adjusted HR=3.7, 95% CI 1.7-8.3, p<0.001. The risk of death was markedly increased in the 3rd versus 1st tertile of SAA: adjusted HR 8.2, 95% CI 2.7-24.2, p<0.001. The C-statistic, generated from ROC analysis, showed improved prediction of the model for the primary outcome (0.71 and 0.74, without versus with SAA). Goodness-of-fit and AIC also improved with inclusion of SAA.
Conclusions: In DKD, higher serum SAA concentration is associated with increased risk of death and ESRD. SAA improves risk prediction when added to traditional risk factors. SAA is a candidate biomarker that may advance DKD risk assessment and is a potential therapeutic target.

Funding: Private Foundation Support

TH-OR006

Biomarkers of Early Decline in Renal Function: A Translational Study in Type 2 Diabetes Jennifer W. Xu,1 Carla Cavallini,1 Sona Hakus,2,3 Michael S. Simonson,2,3 Nephrology and Hypertension, Univ Hospitals Case Medical Center and CWRU School of Medicine, Cleveland, OH; 2Dept of Medical Science and Cardiovrenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan.

Background: Kidney disease in type 2 diabetes (DKD) is the leading cause of end-stage renal disease. Early detection and treatment of DKD can prevent or slow progression to end-stage disease, but identifying early decline in renal function can be problematic because albuminuria is insensitive. In a Phase I preclinical exploratory study we measured the performance of candidate biomarkers from mouse models of early renal function decline.

Methods: Patients with type 2 diabetes (median baseline eGFR = 80.3 ± 29.5 ml/min/1.73m²) were recruited into training (n=56) and independent, non-overlapping test (n=37) groups. Biomarkers were measured in spot urine collections by ELISA, and performance was assessed as area under the receiver operating characteristic curve (AUC) with 95% confidence intervals of DKD.

Results: For classifying participants with baseline early renal function decline (eGFR 90 – 60 vs normal function (i.e., >90), the highest performing biomarkers were: transforming growth factor b (TGFb, AUC = 0.887 ± 0.070), interleukin-6 (IL-6, 0.815 ± 0.065), and endothelin-1 (ET-1, 0.720 ± 0.082; all P < 0.01 compared to ACR, 0.465 ± 0.093). Interleukin-10 (IL-10), angiotensinogen (0.465) and angiotensin(ogen) (0.465 ± 0.090). Performance was validated in the independent test group.

AUCs were unchanged after multivariate adjustment for age, sex, race, duration of diabetes, HbA1c, hypertension, cardiovascular disease, body mass index, and use of angiotensin converting enzyme inhibitors or receptor blockers. In participants with eGFR 90 – 60 at baseline, TGFb, IL-6 and ET-1 predicted a composite renal outcome at 5 years (eGFR < 60 OR ESRD) better than ACR (0.769 ± 0.105, 0.690 ± 0.128, and 0.793 ± 0.091, all P < 0.05 versus ACR, 0.520 ± 0.119).

Conclusions: Urine levels of TGFb, IL-6 or ET-1 may identify patients with early renal function decline and aid development of novel therapeutics.

Funding: Other NIH Support - R01DK096549

TH-OR007

Primary Prevention of Albuminuria Using Renin-Angiotensin-System Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis Frederik I. Persson,1 Bianca Hemmingsen,2 Morten Lindhardt,1 Peter Rossing,1,3,4 Hans-Henrik Parving,3,5 Steno Diabetes Center, Gentofte, Denmark; 2Copenhagen Trial Unit, Copenhagen Univ Hospital, Copenhagen, Denmark; 3HEALTH, Univ of Aarhus, Aarhus, Denmark; 4Novo Nordisk Foundation Center for Basic and Metabolic Research, Univ of Copenhagen, Copenhagen, Denmark; 5Dept of Medical Endocrinology, Rigshospitalet, Copenhagen Univ Hospital, Copenhagen, Denmark.

Background: Early prevention of diabetic nephropathy by way of blocking the renin angiotensin system (RAS) in patients with normoalbuminuria seems rational, but trials have so far shown conflicting results. The present meta-analysis was undertaken to investigate if such treatment can prevent development of microalbuminuria and also to assess whether available trials can provide sufficient information for such conclusions.

Methods: We searched MEDLINE, EMBASE and the Cochrane Library for double-masked randomised controlled trials, with a population of patients with type 2 diabetes and normoalbuminuria, comparing angiotensin enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) to placebo. At least one year of follow-up was considered reasonable for the development of micro- or macroalbuminuria, and studies had to have at least 50 participants in each arm. Random and fixed effect models were performed as well as trial sequential analysis.

Results: Six trials were identified and included in the analysis (n=16921). Overall risk of bias was low. In a fixed model analysis ACE or ARB treatment was superior to placebo in relation to development of microalbuminuria, relative risk 0.84 (95% CI 0.79, 0.89) P<0.001, I² 23%, risk difference -0.04 (-0.05, -0.03), p< 0.001. Similar results were seen with the random model approach. Trial sequential analysis revealed a Z-value of 6.53 and an information size of 4163 patients (O’Brien twosided 5% boundaries).

Conclusions: Sufficient trial data are available for the meta-analysis to conclude that in patients with type 2 diabetes and normoalbuminuria, ACEInhibitors or ARBs reduces the risk for development of microalbuminuria.

Funding: NIDDK Support, Veterans Administration Support

TH-OR008

The Impact of Pre-ESRD Glycemic Status on Early Post-ESRD Mortality Among U.S. Veterans: A Transition of Care in CKD Study Connie Rhee,1 Elani Streja,1 Melissa Soochoo,1 Jennie Jing,1 Danh V. Nguyen,2 Steven M. Brunelli,3 Gregory Brent,2 Csaba P. Kovessy,2 Kamyar Kalantar-Zadeh.1 1UC Irvine; 2DaVita Clinical Research; 3UCLA; 4UTHSC.

Background: In the general population randomized controlled trials show no benefit and possible harm with intensive glycemic targets in diabetics. Non-dialysis dependent ESRD (CKD) and ESRD patients experience both hypo- and hyperglycemia through multifactorial pathways, and studies of glycemic status and mortality in dialysis patients have shown mixed findings. Little is known about the net effect of kidney dysfunction on glucose homeostasis in NDD-CKD patients transitioning to dialysis, and how pre-ESRD glycemic status impacts early post-ESRD mortality.

Methods: We first examined the longitudinal trajectory of glycemic status defined by HbA1c during the 5-year pre-ESRD prelude period among veterans with NDD-CKD transitioning to dialysis from 10/2007-9/2011. In a subcohort of patients with at least one HbA1c measure during the 6 month prelude period, we then examined HbA1c levels averaged over 6 months as a continuous predictor of all-cause mortality using restricted cubic spline analysis. Associations with mortality in the first 3 months of ESRD were estimated using Cox models adjusted for age, sex, race, ethnicity, ESRD cause, and geographic region.

Results: Among 24,129 veterans transitioning to dialysis, there was a decline in mean HbA1c over the 5 year prelude period. Among 13,720 patients with at least one HbA1c in the 6 month prelude period, higher HbA1c was monotonically associated with a higher risk of post-ESRD death.

Conclusions: In veterans transitioning to dialysis there is a steady decline in HbA1c as they approach ESRD. Higher HbA1c levels in the pre-ESRD period are associated with higher early post-ESRD mortality. Further studies are needed to determine if glycemic lowering strategies in the pre-ESRD period improves post-ESRD outcomes.

Funding: NIH Support, Veterans Administration Support

TH-OR009

Glycemic Markers and 2-Year Diabetic Hemodialysis Outcomes from the Glycemic Indices in Dialysis Evaluation Study Mark E. Williams,1 Neal Mittman,2 Lin Ma,3 Julia I. Brennan,1 Chiu M. Jani,1 Curtis D. Johnson,4 Franklin W. Maddux,1 Eduardo K. Laczon,5 1Joslin Diabetes Center; Boston, MA; 2Kidney Care of Brooklyn and Queens, Brooklyn, NY; 3Fresenius Medical Care North America, Waltham, MA; 4Spectra Laboratories, Rockleigh, NJ; 5Physician, Lexington, MA.

Background: Initial results from the GIDE (Glycemic Indices in Dialysis Evaluation) Study have added to concerns about sole reliance on hemoglobin A1c (HbA1c) in patients with diabetes on hemodialysis (HD). We reported correlations of HgbA1c with nontraditional glycemic markers [albumin-adjusted and unadjusted fructosamine (AlbF; F) and glycated albumin (GA) or percent GA (%GA)]. One-year results indicated a potential association only with high AlbF and outcomes. We report here two-year outcomes.

Conclusions: In veterans transitioning to dialysis there is a steady decline in HbA1c as they approach ESRD. Higher HbA1c levels in the pre-ESRD period are associated with higher early post-ESRD mortality. Further studies are needed to determine if glycemic lowering strategies in the pre-ESRD period improves post-ESRD outcomes.

Funding: NIDDK Support, Veterans Administration Support

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2A
Methods: 1,424 active HD patients with DM from 26 FMCNA facilities with glycemic marks from Jan-March 2013 were followed until April 2015. Poor glycemic control was based on: HgbA1c >7% (sensitivity analysis >8%), AlbF ≥ 974 µmol/L, F ≥ 285 µmol/L, %GA>15.7%, and GA>300 µmol/L. Standard and Time-dependent (TD) Cox models with adjustment for age, sex, race, ethnicity, vintage, BMI, HD catheter, and baseline comorbid illnesses were utilized to determine associations between each dichotomized glycemic index and hospitalization/death outcomes.

Results: Poor glycemic control was found in 28% according to HgbA1c<7% (13% for HgbA1c<8%), but 35% by AlbF, 87% by F, 81% by %GA, and 68% by GA. Elevated AlbF was significantly associated with 2-year hospitalization (Standard Cox: Hazard Ratio (HR)=1.66, 95% CI (1.28,2.15), p<0.0001; TD Cox: HR=1.83, 95% CI (1.37,2.44), p<0.0001) and mortality [Standard Cox: HR=1.53, 95% CI (1.21,1.93), p<0.0004; TD Cox: HR=1.65, 95% CI (1.28,2.13), p<0.0001]. For all other glycemic indices, there were no such associations, at the proposed thresholds for glycemic control.

Conclusions: A strong association between poor glycemic control, determined by elevated AlbF, and worse 2-year hospitalization and mortality risks has emerged from the GIDE study data. Future analyses will include longer follow-up, use of continuous values for glycemic indices, and cardiovascular mortality outcomes.

TH-OR010
Renal Biopsy for Diabetic Nephropathy Is Useful for the Prediction of Cardiovascular Events – 10-Year Follow Up
Katsuhiko Akai, Miho Akai, Miharu Tagawa, Yoshishiko Saito. First Dept of Internal Medicine, Nara Medical Univ, Kashihara, Japan.

Background: Diabetic nephropathy has a higher risk of cardiovascular (CV) events and end-stage renal disease (ESRD). However, the association between renal histopathology, especially vascular lesion, and CV risk in diabetic nephropathy remains to be elucidated. We investigated the relationship between the glomerular or vascular lesions of renal specimens and CV events or ESRD in the patients with biopsy-proven diabetic nephropathy.

Methods: Three hundred ninety patients with biopsy-proven diabetic nephropathy with type 2 diabetes were enrolled in this retrospective study. According to the Renal Pathological Society (RPS) classification, the glomerular lesions were divided into three groups as IIa, IIb, and III – IV and vascular lesions were classified into 2 groups according to the absence or presence of vascular involvement.

Results: The background features were as follows: mean age of 57.7 ± 11.3 years old, the average observation period of 9.3 ± 8.0 years. During the observation period 164 patients had outcome of CV events and 71 patients reached ESRD. In Kaplan-Meier survival analysis, significant difference among different glomerular lesion class and vascular class were observed in terms of CV events and ESRD, respectively.

Conclusions: Vascular lesion of renal tissue had predictive value for the development of CV events.

TH-OR011
Racial Differences in Hospitalization Rates Among U.S. Veterans with and without Chronic Kidney Disease Jennifer L. Bragg-Gresham,1 Hal Morgenstern,2 Neil R. Powe,2 Deidra C. Crews,3 Rakhi Grams,4 Julichie Ishigami,5 Morgan Grams,5 Rakhi Naik,5 Josef Coresh,1 Kunihiro Matsushita,4 and without Chronic Kidney Disease

Methods: This cohort study included 2.6 million black and white veterans who attended 1 or more clinic visit, had a serum creatinine value during the baseline period (10/1/09-9/30/10), and had no indication of ESRD on 9/30/11. Cox regression was used to estimate the combined effects of race and CKD status on first hospitalization during the next 2 years, adjusting for age, gender, comorbidities, and prior hospitalization during the baseline period. CKD was defined by clinical diagnosis or eGFR <60 ml/min 1.73m². Results: Black patients were younger with a higher prevalence of diabetes, but lower prevalence other comorbidities, including hypertension. Although the overall prevalence of CKD at baseline was higher in whites (21.0% vs. 15.8%), the prevalence of a clinical diagnosis was higher in blacks (11.8% vs. 9.4%). The rate of first hospitalization was greater for blacks in both with and without CKD (HR=1.30, 95% CI: 1.29-1.31 & HR=1.16, 95% CI: 1.15-1.17, respectively). The 2-year risk of hospitalization was greatest (27.9%) in black patients with CKD, compared with the other groups (figure; p for interaction <0.001).

Conclusions: In an integrated health-care system with presumably less disparity in access to care between racial groups, the 2-year risk of hospitalization was greater for blacks than for whites, especially among patients with CKD. Further research is warranted to better understand these differences.

Funding: Other U.S. Government Support

TH-OR012
Optimal Endpoint Definition for Transition in Albuminuria Stage in Clinical Trials Tobias Felix Kröpelin,1 Dick de Zeeuw,4 Rudolf W. Bilous,2 Giuseppe Remuzzi,1 Hans-Henrik Parving,5 Hiddo Jan Lambers Heerspink,1 Clinical Pharmacy and Pharmacology, UMCG, Groningen,4 Newcastle Univ, United Kingdom,4 IRCCS Mario Negri Inst for Pharmacological Research, Ospedale Papa Giovanni XXIII, Bergamo, Italy,4 Medical Endocrinology, Univ of Copenhagen, Denmark.

Background: Albuminuria transition (normo- to micro- to macroalbuminuria) is used as an endpoint in clinical trials that assess renoprotective drug efficacy. Current definitions vary between trials in: number of urine collections, requirement of a confirmation visit, if yes at what time, and the requirement of an additional percentage albuminuria change when transitions occur. We tested whether more frequent study visits with albuminuria measurement would improve the impact of these limitations.

Methods: We used 3 clinical trials that tested the effect of RAS intervention on albuminuria class transition in diabetic patients (BENEDICT, DIRECT, IRMA 2). We assessed the drug effect per trial using varying transition definitions: 1) class transition based on a single urine sample confirmed by a next visit (within 2 - 8 weeks, next planned visit), 3) class transition and 10 - 40% increase in albuminuria. Results: Neither increasing the number of urine collections at a visit, nor the inclusion of a confirmation visit, nor the time to the confirmation visit, nor the addition of a percentage albuminuria change altered the average drug effect or standard error.

Conclusions: Our results suggest that the optimal transition endpoint for a clinical trial measuring a drug effect can use a single urine collection per study visit. It needs to be tested whether more frequent study visits with albuminuria measurement would improve the precision of the drug effect, as suggested in our previous work on quantitative albuminuria change (Kroppelin 2014).

TH-OR013

Background: Patients on dialysis have increased risk for gastrointestinal (GI) bleeding. However, GI bleeding risk across the full spectrum of CKD has not been comprehensively investigated.

Methods: We studied 11,143 participants in the ARIC Study, a bi-ethnic community-based cohort. Baseline CKD measures (eGFR and ACR) were assessed at visit 4 (1996-
1998), and follow-up was continued through 2011. The primary outcome was hospitalization with relevant ICD codes of upper- or lower-GI bleeding. Logistic regression models were used to estimate incident rate and hazard ratios of GI bleeding, respectively.

Results: A total of 693 hospitalizations related to GI bleeding was observed during a median follow-up of 13.9 years (incident rate 4.9 per 1,000 person-years). After adjusting for potential confounders, both lower eGFR and higher ACR were independently associated with increased risk of GI bleeding (Table). Compared to eGFR <90 ml/min/1.73m², the association was particularly strong in eGFR <30 ml/min/1.73m² (HR 8.37 [5.04-13.88] in Model 2), but eGFR between 30-60 also reached significance (HR 1.55 [1.16-2.06]). Compared to ACR <10 mg/g, both microalbuminuria (10-29 mg/g) and macroalbuminuria (>300 mg/g) were associated with 2-2.5 greater hazard of GI bleeding (HR 2.14 [1.69-2.72] and 2.40 [1.59-3.62], respectively, in Model 2). Of note, high-normal albuminuria (10-29 mg/g) was also significantly associated with GI bleeding (HR 1.36 [1.09-1.70]). These results were generally consistent even after adjusting for each of kidney measures (Model 3) or accounting for cardiovascular events and incident dialysis during follow-up.

Conclusions: Both low eGFR (<60 but especially <30 ml/min/1.73m²) and high ACR (particularly >30 but also >10 mg/g), were associated with incidence of GI bleeding, warranting clinical attention for GI bleeding risk among persons with even mild to moderate CKD.

Table: Hazard ratios of GI bleeding events according to eGFR and ACR categories

<table>
<thead>
<tr>
<th>Model</th>
<th>eGFR category (mL/min/1.73m²)</th>
<th>Events N</th>
<th>Reference Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>90+</td>
<td>reference</td>
<td>2264703</td>
<td>reference</td>
</tr>
<tr>
<td>Model 2</td>
<td>60-69</td>
<td>1.23 (1.03-1.46)</td>
<td>1.19 (1.00-1.42)</td>
<td>1.19 (0.99-1.41)</td>
</tr>
<tr>
<td>Model 3</td>
<td>30-39</td>
<td>1.70 (1.52-1.90)</td>
<td>1.55 (1.19-2.00)</td>
<td>1.42 (1.06-1.91)</td>
</tr>
</tbody>
</table>

Conclusions: Patients with stage 3–5 CKD have a differential association between obesity classes I–III and mortality compared with the general population, indicating an obesity paradox in the CKD population.

Funding: NIDDK Support

TH-OR015
Risk Factors for Cognitive Impairment in Chronic Kidney Disease – The Brain in Kidney Disease Study
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Background: Cognitive impairment (CI) in patients with chronic kidney disease (CKD) poses a substantial public health burden. The extent that factors beyond estimated glomerular filtration rate (eGFR) contribute to the increased risk of CI in CKD has not been adequately measured.

Methods: We used cross-sectional data from the baseline exam (2011-2015) of the BRain IN Kidney disease study. Level of CI was determined using an algorithm based on neuropsychological tests that incorporates the DMS-JV dementia criteria. We assessed the relation between baseline characteristics and moderate to severe CI (yes/no) using logistic regression, controlling for potential confounding variables: age, gender, race, education, diabetes, hypertension, smoking status, cholesterol, BMI, and eGFR.

Results: The CKD cohort includes 422 community-dwelling participants (mean age=70, mean eGFR=34) with eGFR <60 mL/min/1.73 m² but not on dialysis. Of these, 149 had CI at baseline. Prior stroke, phosphorus ≥4.5 mg/dL and African American race were associated with a higher risk of CI. EGR, markers of inflammation (TNFα and IL-6) and microalbuminuria (UACR), cholesterol and hemoglobin were not associated with CI.

Conclusions: We identified elevated phosphorus, prior stroke and African American race as potential risk factors for CI in community-dwelling CKD patients. Phosphorus is a potentially modifiable risk factor. Longitudinal analyses are needed to confirm these findings and identify potential preventive interventions against CI.

Adjusted odds ratios for CI

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unit change</th>
<th>Odds ratio (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>-10 ml/min/1.73 m²</td>
<td>1.19 (0.99-1.44)</td>
</tr>
<tr>
<td>Price stroke</td>
<td>Yes vs no</td>
<td>1.89 (1.09-3.27)</td>
</tr>
<tr>
<td>UACR</td>
<td>100 mg/g</td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>TNFα</td>
<td>3 pg/mL</td>
<td>1.02 (0.87-1.20)</td>
</tr>
<tr>
<td>IL-6</td>
<td>6 pg/mL</td>
<td>1.17 (0.94-1.44)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>≥4.5 mg/dL vs &lt;4.5</td>
<td>2.42 (1.15-5.10)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>≥45 mg/dL</td>
<td>1.26 (0.99-1.61)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10.5 g/dL vs ≥10.5</td>
<td>1.36 (0.64-3.82)</td>
</tr>
<tr>
<td>African American</td>
<td>Yes vs no</td>
<td>4.86 (2.44-9.64)</td>
</tr>
</tbody>
</table>

Funding: Other NIH Support - National Institute on Aging, Pharmaceutical Company Support - Satellite Healthcare Research Foundation
Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease and Mortality in Diabetic Patients with Comorbid Depression

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Background: Depressed patients with diabetes have worse diabetes self-care and worse clinical outcomes. Here we aimed to determine the association of depression and the risk of incident CKD, cardio-vascular (CV) outcomes and all-cause mortality in a population of US veterans with diabetes mellitus (DM).

Methods: From a nationally representative prospective cohort of over 3 million US veterans, we assessed the association between glomerular filtration rate (eGFR), 10-year all-cause mortality, and 10-year CV mortality using the Kaplan-Meier method, and Cox proportional hazard models.

Results: Mean age was 64.11 years, 97% were male and 18% African-American. Depression was present in 340,806 patients at enrollment. Depressed patients were younger (61 ± 11 years) vs. non-depressed (65 ± 15 years). Depression was associated with 33% higher risk of incident CHD (HR: 1.35; 1.32-1.39), 24% higher risk of incident CHD mortality (HR: 1.24; 1.22-1.27) and 25% higher risk of all cause mortality (HR: 1.25; 1.24-1.26) during the follow-up.

Conclusions: Comorbid depression is associated with increased risk of developing CKD and CHD in diabetic patients. The presence of depression is associated with worse CV outcomes. Prospective studies are needed to determine if treating depression in patients with diabetes would prevent CKD and CV disease.

Funding: Veterans Administration Support

Cardiorespiratory Fitness and Neurocognitive Function in Older Adults with Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) is associated with an increased risk for neurocognitive impairment in older adults, while greater cardiorespiratory fitness (CRF) is associated with better neurocognitive function among healthy older adults. This relationship has not been adequately explored in patients with CKD. This study examines whether CRF, as measured by VO2peak, is associated with neurocognitive function in older adults with CKD stage 3a-4.

Methods: Baseline data from a multi-center randomized controlled trial of exercise training was used. The Mini-Mental State Exam (MMSE), Digit Symbol Substitution Test (DSST), Montreal Cognitive Assessment (MoCA), Trail Making Test Part A (TMT-Part A), and Trail Making Test Part B (TMT-Part B) were utilized to quantify neurocognitive function. The association between VO2peak and neurocognitive function was assessed using multiple linear regression, adjusted for age, sex, and education level.

Results: Among 71 participants, with mean age 68.4 ± 7.74 years and mean eGFR=33.2 ± 10.6 ml/min/1.73m², higher VO2peak was associated with better performance on the MMSE (β=0.08, p=0.04), and DSST (β=0.75, p=0.03). While not statistically significant, directionality was similar for other cognitive tests, including the MoCA (β=0.12, p=0.20), TMT-Part A (β=0.47, p=0.30) and TMT-Part B (β=1.39, p=0.38).

Conclusions: Better cardiorespiratory fitness, as assessed by VO2peak, is associated with better performance on several neurocognitive tests in older adults with advanced CKD. Further research is needed to better understand the underlying mechanisms of this relationship and whether improved fitness can modify cognitive performance.

Funding: NIDDK Support

Low Birth Weight and Risk of Progression to End Stage Renal Disease in IgA Nephropathy

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Background: Low Birth Weight (LBW) is a surrogate for fetal undernutrition and is associated with impaired nephron development in utero. Low birth weight is associated with fewer and larger glomeruli and increased risk of hypertension and renal disease in later life. In this study, we investigate whether low birth weight (LBW) and low birth weight for gestational age (LBWGA) predict progression to ESRD in IgAN patients.

Methods: The Medical Birth Registry has recorded medical data for all births in Norway since 1967 and the Norwegian Renal Registry has recorded all patients With ESRD since 1980. From the Norwegian Kidney Biopsy Registry we retrieved all patients who had been diagnosed with IgAN from 1988-2013. These registries were linked and we analysed risk of progression to ESRD associated with LBW (defined as less than the 10th percentile of gender-specific birth weight) and/or LBW-GA (defined as less than the 10th percentile of birth weight for gestational age) by regression statistics.

Results: We included 471 patients, of whom 74 (15.7%) developed ESRD. As compared to patients without LBW, patients with LBW had a hazard ratio (HR) of 2.0 (95% confidence interval 1.0-3.7) for the total cohort, HR 2.2 (1.1-4.4) for males and HR 1.3 (0.30-5.8) for females. Corresponding HRs for LBW-GA were 2.2 (1.1-4.2), 2.7 (1.4-5.5) and 0.8 (0.1-5.9). After adjustments for GFR at time of diagnosis, the association was lost. Further analyses showed that as compared to patients who were neither LBW nor LBW-GA, patients who were LBW-GA but not LBW had a HR of 1.3 (0.39-4.0), patients who were LBW but not LBW-GA had a HR of 1.4 (0.51-3.9) and patients who were both LBW and LBW-GA had a HR of 3.2 (1.5-6.8).

Conclusions: Among IgAN patients, having had low birth weight or low birth weight for gestational age predicted progression to ESRD. The association was only significant in male patients.

Funding: NIDDK Support

The Relevance of Systolic Blood Pressure to Renal Progression: Observations from the Study of Heart and Renal Protection (SHARP)


Background: Meta-analysis of intensive versus standard blood pressure (BP) lowering trials has demonstrated that lower BP reduces the risk of end-stage renal disease (ESRD), but there is uncertainty about optimal BP targets in chronic kidney disease (CKD), particularly in the setting without albuminuria.

Methods: Systolic blood pressure (SBP), creatinine and renal outcomes were assessed using data from 2000 to 2013 data, the lifetime risk of ESRD from birth using 2013 data was 3.08% for non-Hispanic (NH) whites, 8.06% for NH blacks, 3.80% for NH Native Americans, 5.05% for NH Asians/Pacific Islanders, and 6.23% for Hispanics. Among females, the lifetime risks were 2.03% for NH whites, 6.80% for NH blacks, 3.63% for NH Native Americans, 3.78% for NH Asian/Pacific Islanders, and 4.34% for Hispanics. The 10-year risk was highest at age 70 at 1.52% for males and 1.03% for females. Comparing risk estimates based on 2013 data to 2000 data, the lifetime risk of ESRD from birth increased from 3.95% to 3.96% in males and decreased from 2.96% to 2.85% in females, but these changes were not uniform across racial/ethnic groups.

Conclusions: The risk of ESRD in the U.S. varies substantially among racial/ethnic groups for both sexes. Lifetime risks increased a little during the previous decade in males, but decreased slightly in females. The statistical approach used in this study could be applied routinely to USRDS data to estimate the probability of individuals being diagnosed with ESRD. To be most useful in clinical practice, this application will require additional data elements (e.g., comorbidities, CKD stage).

Funding: NIDDK Support

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Background: Meta-analysis of intensive versus standard blood pressure (BP) lowering trials has demonstrated that lower BP reduces the risk of end-stage renal disease (ESRD), but there is uncertainty about optimal BP targets in chronic kidney disease (CKD), particularly in the setting without albuminuria.

Methods: Systolic blood pressure (SBP), creatinine and renal outcomes were assessed 6 monthly for 5 years among 6245 SHARP participants not on dialysis at baseline of whom 2137 (33%) developed ESRD. Regression models adjusted for confounders assessed the relevance of usual SBP to ESRD and to annual rate of change in CKD-EPI eGFR. High BP may cause or be caused by albuminuric CKD, so analyses were performed with and without adjustment for albuminuria.
Results: Each 20 mmHg higher usual SBP was associated with an average increase of 71% in the risk of ESRD (adjusted hazard ratio [HR] 1.71, 95% CI 1.50-1.95). The risk of ESRD was substantially attenuated, but remained statistically significant, after adjustment for albuminuria (HR 1.18, 1.02-1.35). Among those with at least 3 creatinine measurements, each 20 mmHg higher usual SBP was associated with a 1.3 (95% CI 1.0-1.6) mL/min/1.73m²/year greater mean decline in eGFR, which reduced to 0.7 (0.4-1.0) after adjustment for albuminuria. Mean rate of reduction in eGFR was similar irrespective of baseline albuminuria (macroalbuminuria 0.7 [0.1-1.3]; microalbuminuria 0.6 [0.2-1.0]; normoalbuminuria 0.6 [0.1-1.1]).

Conclusions: In CKD, the true relevance of SBP to renal progression is difficult to quantify precisely as the relative risks are substantially attenuated by adjustment for albuminuria (which may not be appropriate if this is on the causal pathway). Nevertheless, after such adjustment, higher SBP is significantly associated with renal progression irrespective of the presence or absence of albuminuria.

Funding: Pharmaceutical Company Support - Merck/Schering-Plough Pharmaceuticals (North Wales, PA, USA), Government Support - Non-U.S.

TH-OR021

The Significance of Urinary Podocalyxin Level and Urinary Podocyte Number in Lupus Nephritis: A Longitudinal Study

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Background: Podocalyxin is shed from injured podocytes. We have previously reported that urinary podocalyxin levels (U-PCX) and urinary podocytes numbers (U-POD) were highly elevated in active lupus nephritis (LN) before treatment (Arthritis Rheum, 2013, 65:10 S377). In the current study, we examined the changes of U-PCX and U-POD levels after treatment and the impact of baseline U-PCX and U-POD on the response to treatment.

Methods: Patients with active LN (n=37), whose urinary protein levels (U-Prot) >1.0 g/gCr and who required initiation or intensification of treatment, were examined. Early proteinuric remission was defined as U-Prot <0.3 g/gCr at 3 months, which was observed in 15 patients.

Results: Although the significant improvement of U-Prot was observed at 1 month after treatment, U-Prot and U-POD decreased more gradually (Fig). A weakly positive correlation was found between U-PCX and U-POD (R=0.363, P=0.027), but not between U-Prot and U-PCX or U-POD. Multivariate logistic regression analysis showed that U-Prot >3 g/gCr, U-PCX >600 mg/gCr and U-POD 1 cell/mgCr at baseline were risk factors for not achieving early proteinuric remission (sensitivity 80%, specificity 86%, PPV 80%, NPV 86%).

Conclusions: urinary podocalyxin levels (U-PCX) and urinary podocytes numbers (U-POD) were highly elevated in active lupus nephritis (LN) before treatment. Response to therapy and outcome were compared to those with proliferative (III or IV, n=38) and mixed-class LN (III+V, IV+V, n=112).

Results: Fifty one patients with MLN were distributed by induction drug in 3 groups: MMF (mean 2.6±0.4 g/day), IV cyclophosphamide (5.4g/m²BSA accumulative dose), azathioprine (mean 2.1±0.6 mg/kg/d). Median follow-up was 44 months (IQR 15-94). At presentation, patients in IVC group had a trend to worse urinary protein to creatinine ratio (uPCR) and a longer time from symptoms to start of treatment. Complete remission rates at 6, 12 and 24 months were 24.6, 44.5 and 57.5%, respectively, for MMF, 25.0, 55.9 and 71.4% for IV group and 27.3, 40.5 and 47.9% for AZA. MMF induction was superior to IVC on Kaplan-Meier analysis (HR 5.42, 95% CI 1.38-21.2, p=0.006). There were no differences between groups in adverse effects and thrombotic events. Only two MLN patients developed ESRD on follow-up. When compared with an historical cohort, patients with proliferative (HR 8.8, 95% CI 3.8-20.1, p=0.001) and mixed histological classes (HR 4.3, 95% CI 1.8-9.9, p=0.001) were more likely to develop ESRD.

Conclusions: Mycophenolate mofetil, AZA, and IV cyclophosphamide are effective for induction treatment of MLN. At our center, there is a trend to treat severe nephrotic patients with IV cyclophosphamide and less severe cases with MMF or AZA. MLN has a similar rate of response to treatment and better long-term outcome than proliferative and mixed classes.
Impact of Tabalumab on the Kidney in Lupus: Results from Two Phase 3 Clinical Trials

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Background: Tabalumab (TAB) is a monoclonal antibody that neutralizes membrane and soluble B-cell activating factor. Two 52-week, randomized, double-blinded, placebo (PBO)-controlled Phase 3 trials evaluated the safety and efficacy of TAB for non-renal disease in lupus.

Methods: Patients with moderate-severe active lupus, but without severe active lupus nephritis (e.g., urine protein/creatinine ratio [uPCR] >200 mg/mmol or estimated creatinine clearance <30 mL/min) were randomized 1:1 to TAB (120 mg subcutaneously [SC] every 4 weeks [Q4W] or 120 mg SC every 2 weeks [Q2W]) or PBO for 52 weeks. Serum creatinine (SCr), glomerular filtration rate (GFR), uPCR, and renal adverse events were determined monthly. Data were analyzed for the intent-to-treat (ITT) population and for ITT patients with a baseline uPCR >20 mg/mmol (ITT+uPCR) using an ANCOVA model.

Results: The trials enrolled 2262 patients. Baseline demographics, lupus disease activity, use of lupus drugs, SCr, GFR, and uPCR were similar among treatment arms. In the ITT and ITT+uPCR populations, there were no differences between treatment arms in baseline-to-endpoint change in SCr, GFR, or uPCR. Renal adverse events were not different among treatment arms.

Table 1. The respective biomarker with a mean expression is given in active and inactive disease. CRP, C3a, C5a, IL-18 in plasma as well as MCP-1 and C5a in urine yielded significance (all p<0.05).

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Active Mean ± SD</th>
<th>Remission Mean ± SD</th>
<th>p-value vs PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP mg/l</td>
<td>18.7 ± 6.4</td>
<td>6.4 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sFlt1 ng/ml</td>
<td>0.8 ± 0.8</td>
<td>0.8 ± 0.8</td>
<td>0.737</td>
</tr>
<tr>
<td>C3a ng/ml</td>
<td>253 ± 135</td>
<td>135 ± 66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C5a ng/ml</td>
<td>10.2 ± 6.2</td>
<td>6.2 ± 3.0</td>
<td>0.006</td>
</tr>
<tr>
<td>IL-17A pg/ml</td>
<td>0.8 ± 0.3</td>
<td>0.3 ± 0.1</td>
<td>0.115</td>
</tr>
<tr>
<td>IL-18 pg/ml</td>
<td>8.5 ± 5.2</td>
<td>5.2 ± 3.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Hyaluronan ng/ml</td>
<td>43.3 ± 46.3</td>
<td>46.3 ± 45.6</td>
<td>0.894</td>
</tr>
<tr>
<td>MCP-1 urine ng/ml</td>
<td>2.4 ± 0.4</td>
<td>0.4 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C5a urine ng/ml</td>
<td>0.4 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.010</td>
</tr>
<tr>
<td>sC5bC9 urine ng/ml</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.639</td>
</tr>
<tr>
<td>C3a urine ng/ml</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.384</td>
</tr>
</tbody>
</table>

Conclusions: Compared to PBO, TAB did not significantly affect SCr, GFR, or uPCR over 52 weeks in ITT or ITT+uPCR patients. There were no significant renal safety signals.

Funding: Pharmaceutical Company Support - Eli Lilly and Company

Evaluation and Validation of a Biomarker Panel in ANCA-Associated Renal Vasculitis

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Background: Emerging studies in ANCA-associated vasculitis identified markers of disease activity. The aim of the study was to evaluate and validate encouraging markers identified by literature search and the creation of respective panels.

Methods: 161 marker molecules were identified by a systematic literature review. ELISA assays were performed to validate a panel of biomarkers in an independent cross-sectional cohort of patients with renal involvement. Active vasculitis as assessed by BVAS v3 was defined as BVAS v3 >1 and inactive disease as BVAS v3 = 0. Statistical analysis was performed with SPSS 21 © and the Salford Predictive Modeler 7.0E © was used to generate a biomarker panel.

Results: Our review indicated increased expression of monocyte chemotactic protein (MCP)-1, sC5bC9, C3a and C5a in urine, whereas GM-CSF, sFlt1, CRP, IL-17A, C5a, hyaluronan, C3a and IL-18 bp were identified to be diversely regulated in active and inactive disease in blood samples. Our cross-sectional analysis revealed increased expression of CRP, C5a, C3a, IL-18 bp in blood and C5a and MCP-1 in urine samples during active AAV (all p<0.05).

Conclusions: We could find a significant increase in CRP, C3a, C5a, IL-18 in blood and MCP-1 and C5a in urine samples. Moreover, we propose a biomarker panel comprising CRP and urinary MCP-1 in patients with ANCA-associated renal vasculitis.

Further investigations to confirm our results are desired, including the reliability to predict renal relapses.
TH-OR026

Pharmacogenetics of Rituximab in ANCA Associated Vasculitis
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Background: Rituximab (RTX) is effective for induction and maintenance of remission in ANCA associated vasculitis (AAV), however optimal dosing approach is still unclear, relapse is common after discontinuation and predictors of response do not exist. This study assesses potential genetic determinants of response to RTX in AAV.

Methods: We included AAV-patients treated with RTX from European centers (primary cohort) and UK (replication cohort). Genotyping of 18 single nucleotide polymorphisms (SNPs) is identified according to a biological rationale was performed using TaqMan and Sequenom platforms. End points were treatment failure rate (TF) 6 months after RTX and time to TF or relapse (TTR). Bonferroni correction was applied.

Results: 213 patients were enrolled in the primary and 109 in the replication cohorts. A SNP in the TNFSF13B gene region (BAFF) was associated to TTR in the primary (HR12.4, p=7x10-04) and replication cohorts (HR5.4, p=0.0024). Meta-analyses showed an association with both end-points.

<table>
<thead>
<tr>
<th>Carriers of the risk genotype</th>
<th>OR-HR</th>
<th>p</th>
<th>OR-HR</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>TF at 6 months</td>
<td>0.8</td>
<td>0.07</td>
<td>9.8</td>
<td>0.009</td>
</tr>
<tr>
<td>TTR</td>
<td>12.4</td>
<td>7x10^4</td>
<td>5.4</td>
<td>0.002</td>
</tr>
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</table>

Conclusions: These results demonstrate that combining MEST with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than our current best methods, and should allow modification of treatment based on risk assessment using data readily available at the time of biopsy.

TH-OR027

The MEST Score in IgA Nephropathy: Implications for Clinical Management
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Background: The MEST score from the Oxford classification of IgA nephropathy (IgAN) is independently associated with renal outcome. Current risk stratification in IgAN requires clinical data over 2 years of follow-up. Using modern prediction tools, we examined whether combining MEST with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than our current best methods that use 2 years of follow-up data.

Methods: We used a cohort of 901 adults with IgAN from the Oxford derivation, North American validation and VALIGA studies to analyze the risk of a 50% decrease in eGFR or ESRD using Cox regression models. Median follow-up was 3.4 years. We considered the three groups after receiving combined, steroid or conservative therapy during a mean follow-up of 6.2 ± 3.4 years.

Results: The ratio of urinary remission at final observation was significantly higher in the groups given combined, than steroid or conservative therapy (mild proteinuria: 63% vs. 46% and 42%; moderate proteinuria, 52% vs. 44% and 23%; severe proteinuria, 43% vs. 33% and 16%, respectively). In contrast, the ratio of a 50% increase in serum creatinine decreased more groups given combined, than steroid or conservative therapy (mild proteinuria, 3.7% vs. 10.8% and 14.6%; moderate proteinuria, 7.6% vs. 6.5% and 19.8%; severe proteinuria, 16.7% vs. 25.0% and 36.8%, respectively). Cox proportional hazards models revealed that the combined therapy significantly prevented a 50% increase in serum creatinine compared with conventional therapy in the groups with moderate and severe proteinuria (hazards ratio, 3.4 and 1.09, respectively).

Conclusions: Tonsillectomy combined with steroid pulse therapy induces urinary remission and prevents the decline in renal function in patients with moderate and severe proteinuria.

TH-OR029

Pregnancy and IgA Nephropathy: Renal, Maternal and Fetal Outcomes
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Background: Impact of pregnancy on long term renal prognosis of IgA nephropathy (IgAN) remains controversial. Also, there are few information about maternal and fetal outcomes of pregnancy in IgAN women.

Methods: This study included women with biopsy proven IgAN from 1979 to 2013 and all mothers with delivery record from 1999 to 2014 in Seoul National University Hospital.

Conclusions: These results demonstrate that combining MEST with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than our current best methods, and should allow modification of treatment based on risk assessment using data readily available at the time of biopsy.

TH-OR028

Effects of Tonsillectomy Combined with Steroid Pulse Therapy upon IgA Nephropathy Depending on Proteinuria Status at Diagnosis
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Background: Little is known about the effects of tonsillectomy combined with steroid pulse therapy on IgA nephropathy (IgAN) with a hard end-point and long-term observation. We therefore examine the effects of the combined therapy on renal outcomes of IgAN in a large, nationwide cohort study in Japan.

Methods: We divided 669 of 1,174 patients who were diagnosed with IgAN between 2002 and 2004 into three groups based on their having mild (0.50 - 0.99 g/day; n = 258), moderate (1.00 - 1.99 g/day, n = 225), or severe (≥ 2.00 g/day; n = 186) proteinuria at diagnosis. Ratios of decline in renal function and urinary remission were compared among the three groups after receiving combined, steroid or conservative therapy during a mean follow-up of 6.2 ± 3.4 years.

Results: The ratio of urinary remission at final observation was significantly higher in the groups given combined, than steroid or conservative therapy (mild proteinuria: 63% vs. 46% and 42%; moderate proteinuria, 52% vs. 44% and 23%; severe proteinuria, 43% vs. 33% and 16%, respectively). In contrast, the ratio of a 50% increase in serum creatinine decreased more groups given combined, than steroid or conservative therapy (mild proteinuria, 3.7% vs. 10.8% and 14.6%; moderate proteinuria, 7.6% vs. 6.5% and 19.8%; severe proteinuria, 16.7% vs. 25.0% and 36.8%, respectively). Cox proportional hazards models revealed that the combined therapy significantly prevented a 50% increase in serum creatinine compared with conventional therapy in the groups with moderate and severe proteinuria (hazards ratio, 3.4 and 1.09, respectively).

Conclusions: Tonsillectomy combined with steroid pulse therapy induces urinary remission and prevents the decline in renal function in patients with moderate and severe proteinuria.
A survey was done by medical chart review and telephone poll. Primary outcome for kidney was end-stage renal disease (ESRD) progression or doubling of serum creatinine. Secondary outcomes were pre eclampsia, gestational hypertension, and proteinuria. Fetal outcomes were preterm birth, fetal death and fetal growth restriction (FGR). Matched analysis was done by 2:1 propensity score matching (PSM).

Results: A total of 803 IgAN women were enrolled including 88 patients with 166 pregnancy experiences. In addition, 15,028 women with 17,432 pregnancies were enrolled as control. After PSM, no significant difference of baseline parameters was found between matched groups. For renal outcome, pregnancy affect neither ESRD progression nor creatinine doubling in overall IgAN women. However, renal progression was accelerated by pregnancy (HR, 2.90; 95% CI, 1.171–7.179, P = 0.023) in IgAN women with moderate kidney dysfunction (eGFR <60). In maternal outcome, pregnancy of IgAN showed more proteinuria, gestational hypertension, and pre eclampsia than normal pregnancies. Moreover, risks of fetal death and FGR were elevated. We found that this adverse pregnancy outcomes of IgAN patients occurred inversely to their pregestational kidney function. Unexpectedly, this trend started even from preserved pregestational renal function (eGFR <75%), not from advanced renal dysfunction.

Conclusions: We demonstrated pregnancy accelerated renal progression in IgAN women with impaired kidney function. Moreover, we found that IgAN women suffered from a substantial burden of pregnancy even in those with relatively preserved pregestational renal function.

TH-OR030

Semaphorin 3F (SEMA3F) Expression Is Reduced in Pregnancy Complicated by Pre-eclampsia (PE) Giovanni Staallone, Adelaide Di Lorenzo, Giuseppe S. Netti, Barbara Infante, Francesca Bruno, Pantaleo Greco, Maria Matteo, Stefania Carlucci, Federica Trezza, Giuseppe Grandalano. Medical and Surgical Sciences, Univ of Foggia, Foggia, Italy.

Background: PE, characterized by the new onset of hypertension and proteinuria after 20 weeks of gestation, affects 2-10% of pregnancies worldwide. It is characterized by an ineffective remodeling of maternal vessels perfusing the placenta. SEMA3F is a well-known anti-angiogenic mediator. We aimed to investigate whether SEMA3F placenta expression and serum levels are modulated in PE.

Methods: To this purpose, we performed an observational single center, cohort study in our unit from March 2013 to July 2014. We enrolled 132 consecutive pregnant women (PE n=13), undergoing an elective cesarean section (cross-sectional study) and 150 consecutive pregnant women undergoing amniocentesis for routine clinical indications at 16-18 week of gestation (perspective study). SEMA3F concentration was evaluated in maternal peripheral blood, venous umbilical blood and amniotic fluid at the time of delivery in the first group. In addition, in this group we examined placental SEMA3F protein expression. We then investigated amniotic fluid SEMA3F level at 16-18 weeks of gestation in the second group of pregnant women.

Results: SEMA3F placenta expression was significantly reduced in PE (Control 3.2±3 vs PE 1.3±6AU, P<0.01). In addition, SEMA3F level at the time of delivery was significantly lower in serum (2.0±4 vs 2.9±6 ng/mL, P=0.04), amniotic fluid (133.6±41.9 vs 202.4±102.2 ng/mL, P<0.01) and cord blood (358.27 vs 92±20 ng/mL, P<0.02) of PE patients compared with normal pregnant women. SEMA3F level in maternal serum was significantly associated with placental weight (R²=802; P<0.001) and newborn weight (R²=532; P<0.01) at birth. In the prospective cohort study 14 women developed PE. In this setting, SEMA3F level in the amniotic fluid was lower in women developing PE compared to those who had normal pregnancy (12.9±8.9 vs 30.1±8.9 mg/mL, P<0.01).

Conclusions: Our findings demonstrate, for the first time, that SEMA3F amniotic fluid levels might represent a biomarker of PE.

Funding: Government Support - Non-U.S.

TH-OR031

Efficacy in Diabetic Nephropathy in a Phase 2 Clinical Trial of Chemokine Receptor 2 Inhibitor CCX140-B Richard J. Glassock,1 Elena Henkel,2 Heidrun Mohling,3 Christoph Hasslacher,1 Ioanna Gioumi-Berthold,1 Vladimir Tesar,1 Antonia Potarca,1 Pirou Bekker,1 Thomas J. Schall,1 David Geffen School of Med,2 Technical Univ,3 Free Univ,1 Univ Heidelberg,1 Univ of Cologne,4 Charles Univ,5 ChemoCentrx.

Background: The orally administered inhibitor of C-C chemokine receptor 2 (CC2R) CCX140-B blocks the deleterious effects of monocyte chemoattractant protein-1, including macrophage infiltration, podocyte injury and dysfunction. The aim was to test CCX140-B in diabetic nephropathy (DN).

Methods: This is a randomized, one-year clinical trial. Primary efficacy measure: change in urinary albumin/creatinine ratio (UACR) over 52 weeks. Eligible patients were on stable ACE inhibitor or ARB, and anti-diabetic treatment for ≥8 weeks prior to entry, with UACR ≥1000-3000 mg/g creatinine, Hba1c ≤6.10%, and eGFR ≥25 mL/min/1.73 m². Patients were stratified based on baseline UACR and eGFR, and then randomized to receive placebo, 5 mg, or 10 mg CCX140-B once daily (QD) plus standard of care (SOC) for 52 weeks.

Results: 332 pts were enrolled. Baseline characteristics (mean±SD): 63±8 yrs, 77% males, BMI 33±5 kg/m², duration of diabetes 16±6 yrs, UACR (geo mean) 461 (range 77-292) mg/g creatinine (1.73 m²), mean eGFR 12±6 mL/min/1.73 m². The primary endpoint was met: 5 mg CCX140-B QD plus SOC showed a statistically significant (p<0.01) reduction in UACR compared to SOC alone. The maximum effect (24% reduction) was at 12 weeks, with sustained reduction in UACR over the full year. 10 mg CCX140-B QD did not provide further improvement in UACR vs. placebo. Furthermore, CCX140-B QD showed an improvement in fasting plasma glucose (-1.1±2 mmol/L). In a covariate analysis, CCX140-B was effective across patient groups. In a pre-specified subgroup with high baseline UACR (>800 mg/g creatinine), CCX140-B resulted in a placebo-corrected 28% improvement in albuminuria over 52 weeks, and a slower rate of decline in eGFR. CCX140-B did not affect systemic BP or body weight, and appeared to be well tolerated with a low overall dropout rate (10%).

Conclusions: CCX140-B improved albuminuria over 52 weeks in a broad patient population. Patients with high baseline UACR may benefit most from CCX140-B treatment, relevant for design of a renal endpoint study.

Funding: Pharmaceutical Company Support - ChemoCentrx, Inc.

TH-OR032

A First in Human Study of Implantation of Neo-Kidney Augment, an Autologous Selected Renal Cell Population, in Type-2 Diabetic CKD Stage 3-4 Patients Peter Stenvinkel,1 Torbjörn Lundgren,1 Jonas Wadstrom,2 Pontus Blomberg,3 Torkel Brismar,4 Randall K. Detwiler,2 5 Karolinska Univ Hospital, Sweden; 6 Univ of North Carolina.

Background: Animal models of CKD show that a selected population of bioactive renal cells (Selected Renal Cells; SRC) can be delivered to the kidney through intra-renal parenchymal injection resulting in a decrease in disease progression. We have used a laparoscopic technique to perform the first-in-human study with Neo-Kidney Augment (NKA).

Methods: 7 male type-2 diabetic (108±11kg) patients (63±6yrs) with CKD were selected. After evaluation of renal function and radiology they underwent renal biopsy. Two cores were shipped to the manufacturing plant for cell isolation, culture and product preparation. NKA was shipped back to the clinical centre (44-87d after biopsy) and injected into the left kidney.

Results: Implantation of 8 mL NKA was uneventful. 1 postop complication was observed (ileocolic volvulus). Infectious complications were observed in 3 patients during the follow-up period. Antihypertensive medication has been reduced in 3/7 during the first 6 months. Creatinine has remained stable at 6 and 12 months after autologous renal cell implantation in 6/7 patients. In one patient a rise in serum creatinine has, at least partly, been due to prostatic hypertrophy. 2 patients have only been followed for 6 months. Kidney volume was stable at 3, 6, and 12 m (ns).

Conclusions: NKA was safely implanted in 7 diabetic CKD patients. Complications after the implantation were found to be related to the surgical procedure. Longer follow-up and a larger number of patients is needed to reveal if this novel technique can arrest progression of CKD and delay the start of renal replacement therapy. Perioperative findings indicate that image-guided percutaneous techniques (“reversed biopsy”) could facilitate the procedure in this patient group.

TH-OR033

Selective Inhibition of CCR2/5 Chemokine Receptors Reduces Macroalbuminuria in Subjects with Type 2 Diabetes and Overt Nephropathy. Jeremy D. Gale,1 Steven A. Gilbert,1 Samuel S. Blumenthal,2 Sabhoo E. Perera,3 Svetlana I. Konovalova,4 Douglas Girgenti,5 William H. Scheele,1 Robert Webster,2 Christelle Huguat Perros.1 1Pfizer Inc, Cambridge, MA; 2Zablocki VAMC, Milwaukee, WI; 3Renal Associates PA, San Antonio, TX; 4BCDiabetes, Vancouver, Canada.

Background: Recruitment, infiltration and activation of inflammatory cells appears important in diabetic nephropathy (DN). Inhibition of MCP-1/CCR2 receptor pathways may have renoprotective effects in DN and clinical data support a potential protective role of CCR5 receptors. Our hypothesis was that combined blockade of CCR2 and CCR5 receptors could decrease proteinuria in subjects with nephropathy.

Methods: The effect on albuminuria of the novel and specific dual CCR2/5 receptor antagonist, PF-04634817, was assessed in a multinational, randomized, double-blind, placebo-controlled, parallel group trial of subjects with Type 2 diabetes and overt nephropathy already receiving ACEi and/or ARB. Subjects with eGFR 20-75 mL/min/1.73 m² and urinary albumin creatinine ratio (UACR) >300mg/g (33.9 mg/mmol) at baseline were assigned to receive PF-04634817 200mg (150mg if baseline eGFR <30 mL/min/1.73 m²) once daily for 12 weeks. Longer follow-up and a larger number of patients is needed to reveal if this novel technique can arrest progression of CKD and delay the start of renal replacement therapy. Perioperative findings indicate that image-guided percutaneous techniques (“reversed biopsy”) could facilitate the procedure in this patient group.

Results: 226 subjects (mean UACR of 180.78 ± 160.53 mg/mmol Cr and mean eGFR of 41.46 ± 12.64 mL/min/1.73 m² at baseline) were randomised. A modest placebo-adjusted
reduction in UACR of 8% (95% CI 1.9- to 23%) was observed in response to treatment with PF-04631841 using the pre-defined primary assessment of efficacy (Bayesian analysis with informative prior). Ad hoc analysis, of those with eGFR >60 mL/min/1.73m² at baseline, showed a placebo-adjusted reduction of UACR approaching 19%. However, interpretation of subgroups are difficult due to the 3:1 randomization and the presence of data outliers. Adverse events (AEs) were mostly mild, the most common related-treatment AEs being nausea, acne and diarrhea.

Conclusions: The efficacy of PF-04631841 to reduce UACR in this study appears modest, although may be greater in a subset of subjects with more advanced disease. This pooled combined with good safety supports further investigation of its potential as a novel therapeutic strategy to improve renal outcome in DN. Funding: Pharmaceutical Company Support - Pfizer

TH-OR034
Baricitinib in Diabetic Kidney Disease: Biomarker Analysis from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Frank C. Brotzis,a Katherine R. Tuttle,a Sharon G. Adler,a Matthias Kretzler,b Ravindra L. Mehta,c James A. Tumlin,c Kevin L. Duffinc,Joseph Y. Haasc,Jaijun Liu,a Maria E. Silk,b William Macias,a Jonathan M. Janesc, Marian Mayesc, Nathan A. Willams, aUniv Med Sch, Ann Arbor; bUniv WA Sch Med, Spokane; cLA BioMed, Torrance; dUniv CA, San Diego; eUniv TN Coll Med, Chattanooga; fElly Lilly & Co, IN.

Background: New therapies for diabetic kidney disease (DKD) are needed as standard care (SC) fails to prevent progressive DKD. Baricitinib (baci) is an oral Janus Kinase (JAK1/2) inhibitor. The study met its primary endpoint of significantly reducing albuminuria/creatinine ratio (UACR) at 6 months (m) in diabetics with albuminuria despite SC.

Methods: To examine effects of bari treatment (tx) on key secondary endpoints: 24h urine protein, 30% UACR decrease; inflammatory biomarkers: urinary interferon gamma-induced protein-10 (IP10), monocyte chemotactic protein-1 (MCP1), and plasma soluble tumor necrosis factor receptor (sTNFR) 1&2. Type 2 diabetes at high-risk for progressive DKD on SC were randomized to bari 0.75 mg BD (n=25), 1.5 mg BD (n=26), 4mg BD (n=25), or placebo (PBO;n=27) for 6 m.

Results: Reductions in 24h proteinuria compared with PBO were observed at 6m of bari tx (LSM ratio vs PBO for 0.75 mg BD, 1.5 mg BD, 4 mg BD, 0.59, 0.58, 0.60, resp; p<.05). Benefits were maintained during a 1-2 m washout period. The proportion with ≥30% UACR decline was increased by bari tx. IP10, MCP1, and plasma soluble tumor necrosis factor receptor (sTNFR) 1&2 decreased by 0.35±0.35 in a numerically dose-dependent manner. Estimated glomerular filtration rate by cystatin C was unchanged. At 6m, only 4mg bari had decreased hemoglobin vs PBO (-1.01±0.35 g/dL). No other safety concerns were observed.

Conclusions: Analysis of proteinuria and inflammatory biomarkers supports efficacy of bari in high-risk DKD. Data suggest an anti-inflammatory tx response encouraging further study of baricitinib in DKD. Tuttle et al, ADA Jun 2015, Post. 114-LB.

Funding: Pharmaceutical Company Support - Eli Lilly and Company

TH-OR035
Patiromer Lowers Serum K+ and Prevents Recurrent Hyperkalemia in CKD Patients ≥65 Years of Age on RAAS Inhibitors Matthew R. Weirc, David A. Bushinsky,a Martha Mayo,a Dahlia Garza,a Yuri Stasiv,a Daniel J. Wilson,a Susan Arthur,a Lance Berman,a George L. Bakris,a 1Univ of Rochester; 2Univ of Chicago.

Background: Older pts are at risk for hyperkalemia (HK) due to combo/meds and K-altering medications. The active moiety of patiromer is a nonabsorbed K+-binder. We present a prespecified subgroup analysis in pts ≥65 y with CKD or HK on RAASi from a 2-p pat, single-blind, phase 3 patiromer trial (OPAL-HK).

Methods: Pts (n=243) with baseline (BL) serum K+(s-K+) >5.5 to ≤6.5 mEq/L received patiromer (4.2 or 8.4 g BID) in a 4-wk treatment phase (part A); then pts with BL s-K+ >5.5 to ≤6.5 mEq/L were randomized to continue patiromer or switch to placebo (PBO) in an 8-wk withdrawal phase (part B). Primary endpoints were Ds-K+ from BL at 4 wk in part A and between-group difference in Ds-K+ from part B BL to part B wk 4.

Results: 131 (54%) pts were ≥65 y at BL. Consistent with overall results, primary endpoints were significant for pts ≥65 y (Table). Overall and in pts ≥65 y, 76% and 73%, respectively, had s-K+ 3.8 to <3.1 mEq/L (2e endpoint) at part A wk 4. More PBO pts (p=0.001) developed recurrent HK in part B. In all pts, mild-moderate constipation was the most common AE in part A (11%).

Conclusions: Patiromer significantly reduced s-K+ in pts ≥65 y and, vs. PBO, maintained control of s-K+.

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

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>Mean±SE BL</th>
<th>Mean±SE-K+/SE (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Overall (n=237)</td>
<td>5.38±0.03</td>
<td>-1.01±0.03 (-1.07, -0.95) p&lt;0.001</td>
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<tr>
<td>≥65 yr (n=126)</td>
<td>5.56±0.04</td>
<td>-1.01±0.05 (-1.10, -0.92) p&lt;0.001</td>
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Excludes 6 (overall) and 5 (≥65 yr) pts with no s-K+ value at wkly visit after Day 3. ‘Or earlier timepoint if pt first had s-K+ <3.8 mEq/L or ≥5.5 mEq/L. ‘Between-group difference in mean ranks of change.

Funding: Pharmaceutical Company Support - Relypsa, Inc

TH-OR036
The Microalbuminuria Intervention Study: Effects of Different Losartan Combination Antihypertensive Therapy in Patients with CKD, MIDLAND-CKD Yoshinari Yasuda,a Takeyuki Hiramatsua, Seiichi Matsucc, Shoichi Maruyama,b aCKD Initiatives/Nephrol/CAMCR, Nagoya Univ, Nagoya, Aichi, Japan; bNephrol, Konanosei Hosp, Konan, Aichi, Japan.

Background: GUARD study reported that ACEI with a diuretic resulted in a greater reduction in albuminuria compared to ACEI and calcium channel blocker (CCB), however GFR significantly declined in ACEI and diuretic group and superiority between diuretics and CCB in combination with ACEI remains controversial. In addition the effect of combination antihypertensive therapy with ARB has not been fully evaluated. Thus the effect to reduce albuminuria was studied between amlosipine and HCTZ in combination with losartan, ARB.

Methods: Study design was randomized control trial. Eligible subjects were hypertensive CKD patients (age 20-79) treated with ACEI or ARB more than 2 months, BP 140±90 mmHg and above, and suspected albuminuria. Suspected albuminuria was defined as albuminuria creatinine ratio (ACR) greater than 30 mg/gCr in an single spot urinalysis, or ≥3.8 mg/dl in urine dipstick test more than 2 times within 1 year. Exclusion criteria were renal insufficiency, prescription of CCB/diuretics, cardiovascular events within 6 months, abnormal liver function, and uncontrolled diabetes/hyperuricemia within 3 months. Written informed consent were obtained from all patients. This study was approved by the ethical committee and registered to UMIN (ID:000004062). Patients were randomly assigned to group A (losartan and amlosipine) or B (combining agent of losartan and HCTZ12.5mg) for 6 months.

Results: 48 and 46 patients were assigned to group A and B. There was no significant difference in patient characteristics between 2 groups at baseline, and BP were well controlled in both groups, ACR were decreased in both groups at 3 and 6 months without statistical significance. Among patients with ACR 30mg/gCr and above, ACR was significantly decreased in group B compared to A at 3 and 6 months (17.5 ± 7.4 vs -56.3 ± 37.5 %, p<0.01 and -278 ± 63.4 vs -63.8 ± 34.0 %, p<0.01). DeGFR were not significantly different in 2 groups.

Conclusions: Combining agent of losartan and HCTZ was superior to losartan and amlosipine treatment in hypertensive CKD patients with albuminuria.

Funding: Private Foundation Support
TH-OR037
Blood Pressure and Outcome in Diabetic Kidney Disease: Results from the VA Nephron-D Study
David J. Leehey,1 Jane Hongyun Zhang,2 Nicholas Emanuele,1 Adam Whaley-Connell,1 Paul M. Palevsky,3 Robert F. Reilly,2 Peter Guarino,2 Linda F. Fried,4 Edward Hines, Jr., Veterans Affairs (VA) Hospital, Hines, IL; 1 Cooperative Studies Program Coordinating Center; 2 VA Connecticut Healthcare System, West Haven, CT; 3 Harry S. Truman Memorial VA Hospital, Columbia, MO; 4 VA Pittsburgh Healthcare System, Pittsburgh, PA; 5 VA North Texas Healthcare System, Dallas, TX; 6 VA Nephron-D Study Group.

Background: Proteinuric diabetic kidney disease (DKD) frequently progresses to end-stage renal disease (ESRD). Control of blood pressure (BP) delays progression, but the optimal BP to improve outcomes remains unclear. The objective of this analysis was to evaluate the relationship between BP and renal outcomes in proteinic DKD.

Methods: BP data from all 1448 randomised participants in the Nephron-D study included in a post-hoc analysis. The effects of mean on-treatment BP on the primary endpoint (decline in the estimated GFR [eGFR], ESRD, or death), renal endpoint (decline in eGFR or ESRD), rate of eGFR decline, and mortality were measured.

Results: In univariate analyses, both mean systolic BP (SBP) and mean diastolic BP (DBP) were strongly associated (p<0.001) with the primary endpoint. After multivariable adjustment, the hazard of developing the primary endpoint increased as mean SBP rose from <120 to >150 mmHg (p=0.018); a significant increase in hazard ratio was seen when mean SBP was >140 mmHg. There was also a significant effect of mean DBP on the hazard of developing the primary endpoint (p=0.005), with an increase in hazard ratio when mean DBP was >80 mmHg. Associations between BP and both renal endpoint and rate of eGFR decline were similar to those with the primary endpoint. No effect of BP on mortality was observed, possibly because of the limited number of mortality events.

Conclusions: In patients with proteinic DKD, mean SBP >140 mmHg and mean DBP >80 mmHg were associated with worse renal outcomes.

Funding: Veterans Administration Support

TH-OR038
Hemoglobin (HGB) Response in a Phase 2b Study of AKB-6548 for the Treatment of Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-DD)
Bruce S. Spinowitz,1 Pablo E. Pergola,2 Volker H. Haase,3 Tasha M. Farmer,4 Charlotte S. Hartman,5 Bradley J. Maroni,6 New York Blood Center, New York, NY; 2 Renal Association and University of Texas Health Science Center, San Antonio, TX; 3 Vanderbilt Univ, Nashville, TN; 4 Akebia Therapeutics, Inc., Cambridge, MA.

Background: AKB-6548 is a novel, once-daily, oral hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) that preferentially stabilizes HIF-2a. Studies have shown AKB-6548 produces physiologic increases in erythropoietin, enhances iron mobilization and utilization, and produces a dose dependent increase in HGB.

Methods: A randomized, double-blind, placebo-controlled study assessed HGB response of AKB-6548 over 20 weeks in CKD subjects with anemia. 210 subjects were enrolled into one of 3 groups: 1) ESA naïve with HGB 10.5 g/dL, 2) previously treated with ESA with HGB 10.5 g/dL, or 3) actively treated with ESA with HGB ≥9.5 and ≤12.0 g/dL, and randomized (2:1) to once daily AKB-6548 or placebo. Primary endpoint was percent of subjects with mean HGB of >11.0 g/dL or increase in HGB by ≥1.2 g/dL from baseline.

Results: Overall, 54.9% of AKB-6548 vs. 10.3% of placebo subjects met the primary endpoint (p<0.001) and mean change in HGB at end of treatment was 0.84 g/dL in the AKB-6548 group as compared to 0.02 g/dL in the placebo group (p<0.0005 for Week 2, p<0.0001 at all time points Week 4 and beyond). HGB responses in the naïve and Previously Treated groups were similar to each other and the overall group. In subjects converting from active ESA, AKB-6548 maintained a stable HGB throughout the study. HGB response with AKB-6548 was associated with an increase in reticulocytes and TIBC, and a decrease in serum hepcidin and ferritin across all three treatment groups. AKB-6548 was generally well tolerated and overall adverse events were balanced between treatment groups (74.6% vs. 73.6%).

Conclusions: AKB-6548, a novel HIF-PHI being developed for the treatment of anemia of CKD, raised and maintained HGB, while increasing iron mobilization and utilization, providing a more physiologic approach to the treatment of renal anemia. This study forms the basis for future Phase 3 studies.

Funding: Pharmaceutical Company Support - Akebia Therapeutics, Inc.

TH-OR039
Anemia Correction with Roxadustat Improves Health Related Quality of Life (HRQOL) in Chronic Kidney Disease (CKD) Patients

Background: The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat is a novel drug developed for treatment of CKD anemia. This analysis of two phase 2 trials was undertaken to assess the effect of roxadustat on HRQOL in non-dialysis (NDD) and dialysis dependent (DD) CKD.

Methods: HRQOL was assessed by SF-36 and FACT-An questionnaires in efficacy-evaluable populations in 2 open-label studies, CKD-NDD (041) and ESA-naïve incident CKD-DD (053). HRQOL was assessed at baseline (BL), 8 and 16 weeks [end of treatment (EOT)] in 041 and at BL, 8, and 12 weeks (EOT) in 053 [mean SE change form BL (A)]. Missing data were imputed by last observation carried forward.

Results: Data from 141 subjects with CKD-NDD and 55 subjects with CKD-DD were available. In both populations, SF-36 physical component summary and FACT-An scores improved compared to BL (p<0.005 & 0.001, CKD-NDD; p<0.01 & 0.02, CKD-DD). SF-36 vitality norm-based domain scores (NBDs) and FACT-An anemia score increased by an average of >4 points. Benefits were seen particularly among those with lower BL scores. In Study 053, subjects with BL SF-36 Physical Functioning NBDs <50 increased by 6.7 (p<0.0001). Subjects with BL FACT-An Anemia score <55 increased 10.3 (p<0.0001), and those with BL FACT-An Total Score increased 15.6 (p=0.0005).

Conclusions: Roxadustat consistently improved mean HRQOL sub- and summary scores. Improvements were greatest in subjects with low BL scores. Roxadustat is currently being evaluated in phase 3 trials in which HRQOL is further explored.

Funding: Pharmaceutical Company Support - FibroGen

TH-OR040
Hepcidin Response to Intravenous (IV) or Oral Iron in the Randomized FIND-CKD Trial of Patients with Non-Dialysis Dependent CKD (ND-CKD)
Carlo A. Giaglia1, Andreas H. Bock,2 Fernando Carrera,3 Kai-Uwe Eckardt,4 David B. Van Wyck,5 Sukhvinder Singh Bansal,6 Bernard Roubert,6 Maureen Cronin,7 Simon D. Roger,8 Iain C. Macdougall,9 Uni. of Groningen, Groningen, Netherlands; 2 Kantonsstipital, Aarau, Switzerland; 3 Eurodial, Leiria, Portugal; 4 Uni. of Erlangen-Nuremberg, Erlangen, Germany; 5 Davita Healthcare Partners, Denver, CO; 6 King’s College Hospital, London, United Kingdom; 7 Vifor Pharma Ltd, Glattbrugg, Switzerland; 8 Renal Research, Gosford, NSW, Australia.

Background: Hepcidin is the key regulator of iron homeostasis but its temporal response to iron therapy, and response to IV vs oral iron therapy, are unexplored.

Methods: In the 56-week, open-label, multicenter, prospective, randomized FIND-CKD study, 626 anemic patients with ND-CKD and iron deficiency not receiving ESA therapy were randomized (1:1:2) to IV ferric carboxymaltose (FCM), targeting higher (400-600µg/L) or lower (100-200µg/L) ferritin, or oral iron. In a subset of patients enrolled in the UK, serum hepcidin was measured centrally by a validated liquid chromatography tandem mass spectrometry assay.

Results: 61 patients provided baseline and 1 post-baseline hepcidin values. Mean (SD) baseline hepcidin level was 4.9(1.6) ng/mL. Mean hepcidin level was 7.0(2.7) ng/mL in the high ferritin FCM, low ferritin FCM and oral iron groups. The mean (SD) endpoint value (i.e. the last post-baseline value) was 26.0(9.1), 15.7(7.7) and 16.3(11.0) ng/mL, respectively. The increase in hepcidin from baseline was smaller with low ferritin FCM and oral iron vs high ferritin FCM up to week 52 (all p<0.05). Correlations were significant between the post-baseline increases in hepcidin and ferritin (r=0.70, p<0.0001), TSAT (r=0.42, p<.0001) and previously FCM up to week 52 (all p<0.05). correlations were significant between the post-baseline increases in hepcidin and ferritin (r=0.70, p<0.0001), TSAT (r=0.42, p<.0001) and previously FCM up to week 52 (all p<0.05).

Conclusions: These prospective, 1-year data from a randomized trial show that hepcidin levels rose in response to either IV or oral iron therapy, but that the speed and extent of the rise was greater with IV iron targeting a higher ferritin level. Oral iron and IV targeting a lower ferritin level resulted in similar hepcidin levels.

Funding: Pharmaceutical Company Support - Vifor Pharma, Glattbrugg, Switzerland
Isolation of Live Nephron Progenitors Cells Expressing Six2+ and Cited1+ from Human Embryonic Kidneys and Amniotic Fluid Laura Perin,1 Stefano Da Sacco,1 Astigk Petroyan,2 Matthew Edward Thornton,2 Brendan Grubbs,2 Roger E. De Filippo,1 Urology, Children's Hospital Los Angeles, Los Angeles, CA; 1Univ of Southern California, Los Angeles, CA.

Background: In the developing kidney, formation of new nephrons relies on a small population of self renewing progenitors co-expressing Six2 and Cited1. Unfortunately, despite their essential role in the renal formation, direct isolation and expansion of human nephrogenic progenitor cells has not been successfully achieved and our knowledge is mostly based on rodent models. We have identified a small niche of Six2+Cited1+ cells within human amniotic fluid (hAF) and in this project we report for the first time the isolation and expansion of this population from both hAF and human embryonic kidneys (hEKA).

Methods: Six2+ Cited1+ live cells from hAF and hEKA were sorted using SmartFlare RNA probes. RNAseq on positive and negative selections was performed immediately after sorting to evaluate their genetic profile without the confounding effects of cell culture. Integration into developing renal structures was assessed. Potential for a glomerular fate was tested by differentiation toward podocyte lineage.

Results: Six2+Cited1+ cells were successfully isolated from hEKA (0.17%) and hAF (0.2%). RNAseq confirmed expression of genes such as Six2, Cited1, Osr1, suggesting a nephrogenic signature. Clones and subclones were derived and expanded for many passages in specific nephrogenic media maintaining Six2 and Cited1 expression. These populations were able to integrate in developing renal structures when co-cultured with dissociated/ re-aggregated hEKA. Differentiation into podocyte-like cells was evaluated by expression of specific markers including WT1 and nephrin, deposition of collagen IV alpha3-4-5 and functional response to angiotensin II.

Conclusions: Our preliminary results suggest the possibility of deriving and expanding for the first time, Six2+Cited1+ cells from hAF as well as from an exogenous source of cells like hAF without genetic manipulation. This system might represent an accessible and novel source of nephron progenitors that can guide studies of renal cell specification, thus increasing our knowledge on human renal development.

Funding: Private Foundation Support

Patient-Derived Induced Pluripotent Stem Cell (iPSC) Modeling of Genetic Renal Disease (GRD) Andrew John Malletti,1,2 Barbara Maier,1,2 Pei Xuan Ei,1 Minoru Takasato,1,2,1,4 Jane Sun,1,2 Ernst J. Wolvetang,2 Stephen I. Downes,1,2 1Kidney Research Centre, Inst for Molecular Bioscience, The Univ of Queensland, Brisbane, Australia; 2Murdoch Children's Research Inst, Melbourne, Australia; 3Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane and Women's Hospital, Australia; 4School of Medicine, UQ, Australia; 5Australian Inst of Bioengineering and Nanotechnology, UQ, Australia; 6Dept of Nephrology, Children's Hospital at Westmead, Australia.

Background: The reprogramming of somatic cells into iPSCs provides potential to model human diseases in vitro, as has been demonstrated in the cardiac and neuronal fields. Nephrology has not yet benefited from these advancements primarily due to lack of a robust kidney differentiation protocol.

Methods: We aimed to generate and characterize iPSCs from patients with different GRDs. Families with clinically diagnosed GRD were recruited from a Renal Genetics Clinic. Concurrent research-based massively parallel sequencing (MPS) and iPSC generation. One affected and unaffected member of each family was recruited. To establish transgene-free iPSC lines, fibroblasts were isolated from skin biopsy and reprogrammed using non-integrating Sendai virus (21 day protocol).

Results: 7 families (14 participants) were recruited with a variety of GRD diagnoses. Fibroblast culture was successful in 6 families. Established iPSC line have typical hESC-like morphology and express pluripotency makers after 4 (TRA1-60) and 15 passages (NANOS). Moreover, iPSC lines have cleared the Sendai virus vectors, as confirmed by RT PCR after only 7 passages. G-band analysis of 2 lines from each isolation confirmed that each of the derived lines had maintained the normal karyotype after reprogramming. Paired patient and control iPSC are being redifferentiated towards kidney employing an established protocol. Renal organoids will be analyzed using IF, FACS and transcriptional profiling.

Conclusions: iPS cells derived from patients with different GRDs provide an in vitro tool to investigate the renal disease pathogenesis. We hope to uncover the biological consequences of novel genetic variants causing GRD as identified via MPS, thereby beginning to explain patient phenotypes and disease pathogenesis.

Funding: Private Foundation Support

Multi-Segmented Nephron Organoids Derived from Human Pluripotent Stem Cells Model Kidney Development and Injury Ryujii Morizane, Albert Q. Lam, Benjamin S. Freedman, Seiji Kishi, M. Todd Valerius, Joseph V. Bonventre. Medicine, Brigham and Women's Hospital, Boston, MA.

Background: Kidney differentiation from human pluripotent stem cells (hPSCs) is limited by the inability to generate complete nephrons, which has inhibited efforts to model kidney development and disease. One important problem is the low efficiency of SIX2+ nephron progenitor cell (NPC) generation by published protocols. We hypothesized that more precise recapitulation of the stages of in vivo metanephric development with hPSCs might lead to the generation of more pure populations of NPCs with the capacity to form nephrons.

Methods: We developed a chemically defined protocol to direct the differentiation of hPSCs into NPCs that form multi-segmented nephron structures in 2D and 3D organoids, modelled on stages of in vivo development. We have been able to guide intermediates of early renal progenitors (primitive mesoderm (IM), SIX2+ metanephric mesenchyme (NPCs), renal vesicles (RVs)), and nephrons. NPC-derived nephron organoids were tested for the ability to model kidney development and injury.

Results: Efficient differentiation of hPSCs into late PS followed by WT1+HOXD11+ posterior IM enabled the induction of SIX2+2SALL1+WT1+PAHX+ NPCs with ~90% efficiency within 9 days. Treatment with Wnt and FGF signals induced differentiation into PAHX+LHX1+ RVs, which spontaneously differentiated into multi-segmented nephron
structures containing podocytes (Nephri/PODXL1-WT1), foot process formation shown by EM), proximal tubules (LTL+CDH6-AQP1+), loops of Henle (CDH1+TJP1+), and distal tubules (CDH1+BRN1+) in an organized, contiguous arrangement in both 2D and 3D culture. Inhibition of Notch signaling during organoid formation resulted in specific defects in proximal tubules, indicating that nephron organoid model kidney development. Moreover, treatment with the nephotxin, gentamicin or cisplatin, induced KiM-1 expression in LTL+ tubules in a dose dependent manner.

Conclusions: We developed a novel method to differentiate hPSCs into NPCs with -90% efficiency within 9 days of differentiation. NPCs formed organized, contiguous, multi-segmented nephron structures in 2D and 3D organoids, which could be used to model kidney development and injury. Funding: NIDDK Support, Government Support - Non-U.S.

TH-OR046
A Developmentally Plastic Adult Mouse Kidney Cell Line Spontaneously Generates Multiple Adult Kidney Structures
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Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD) in the US. Although the precise causes are not well understood, DN is characterized by fibrosis within the glomeruli and tubular interstitium. Dialysis and kidney transplantation are currently the only successful therapies for ESRD. The renal transplantation approach suffers from donor shortages and complications of immune rejection. New therapies for renal replacement are needed. At this time the derivation of kidney lineage cells from either mouse or human induced pluripotent stem cells leads to limited nephron-like structures. To date, no one has been able to regenerate or model functional nephrons from normal or diseased kidneys.

Methods: In this study, we explored the utility of the absence of the epigenetic regulator ARID3A as an adult mouse kidney cell line (KPP5) for generating nephron structures in both in vivo and in vitro model systems.

Results: We discovered that KPP55 acquires renal progenitor surface markers as an alternative cell source and further develop into multilayered nephron-like structures within a few days in 3-D matrigel. Moreover, when these cells are engrafted into immunocompromised medaka adult kidney they formed mouse nephron structures. We are unable to detect the existence of other cell lines that exhibit this unique multipotent property.

Conclusions: These data implicate KPP5 cells provide a unique advantage for exploring kidney development. Moreover, we predict our findings will be relevant for future therapeutic manipulations in kidney disease. Funding: Private Foundation Support

TH-OR047
Decellularized Renal Extracellular Matrix ScaffoldS Serve as 3D Biological Templates for Regeneration of Nephron Structures by Human Kidney Cells
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Background: An alternative to current renal replacement therapy options aims to utilize renal tissues developed ex vivo using patient-derived cells for implantation to augment or replace failing kidneys. Our objective was to characterize the phenotypic effects of culturing particular populations of human nephron-derived cells within 3D decellularized renal extracellular matrix scaffolds (ECMs) as a step toward regenerating functional nephrons.

Methods: Rat kidneys were perfused integrade with detersgents to completely remove the autologous cells. The resultant renal ECMs were injected arterially with select populations of immortalized or primary human renal epithelial or progenitor cells (RPC) and cultured using specialized perfusion bioreactors. We compared proliferation, metabolism, gene expression, and morphological adaptation in cells derived from different nephron components.

Results: Intraluminal cells infused into ECMs dispersed in periglomerular tubules. Distal tubule-derived RCCTE cells formed patent, polarized E-cadherin- tubular structures, and steadily proliferated over 1 week of perfusion culture. Proximal tubule-derived RPTE cells similarly distributed in the tubular space, with some cells found in glomeruli and Bowman’s capsules. Both epithelial lines showed downregulation of EMT markers S100A4 and vimentin after culture within renal ECMs. After 7 days, kidney-specific-cadherin was upregulated in RPTE cells. Injury markers KIM-1 and CD24 were downregulated in RCTE cells alone. Cadaver-derived CD133+ RPC formed tubular structures within renal ECMs, and gradually decreased proteolytic KIM-1 shedding over 7 days.

Conclusions: We conclude that renal ECMs have inductive properties that may eventually be used in concert with exogenous biological or chemical stimuli to promote differentiation of stem or progenitor cells into mature, functional nephron-specific epithelial cells.

Funding: Private Foundation Support

TH-OR048
Systems Biology of Polycystic Kidney Disease Suggests It Is a Metabolic Disease

Background: The major gene mutated in autosomal dominant polycystic kidney disease was identified over 20 years ago yet its function remains poorly understood. We have used a systems-based approach to examine the effects of acquired loss of Pkd1 in an orthologous model of human ADPKD as the kidney development and injury.

Methods: A total of 135 Pkd1(−/−);Tg(Cre/Esr1) mice animals in which Pkd1 knockout was induced by tamoxifen at P40 were harvested between P100 and P210 and kidney/body weight curves were fitted for males and females separately. Gene expression in 50 kidneys was analyzed with Illumina arrays, followed by differential gene expression analysis with Ingenuity Pathway analysis. Predictions were tested using: 1) metabolite and complex lipids profiling in 14 male kidneys; 2) diet manipulations in 33 Pkd1(−/−);Tg(Cre/Esr1) mice induced at P7 and harvested at P21 and in 52 Pkd1(+/−);Tg(Cd16+cre) mice harvested at P14.

Results: We found in the P40-induction model that females were significantly protected from cystic kidney disease but had more severe cystic liver disease. Furthermore, the transcriptional profiles of normal male and female kidneys differed almost as much as those of normal and cystic kidneys and the differentially expressed gene modules were enriched for genes involved in lipid metabolism. Gene ontology of the differentially expressed genes common to both sexes showed enrichment for metabolic pathways. Metabolic and lipid profiling confirmed differences in cystic kidneys. We also found that the P7- and P40-induced mice share common transcriptional signatures, suggesting similar mechanisms of cyst initiation and growth. Finally, we showed that a modest change in the lipid composition of diet could significantly affect the progression of disease.

Conclusions: Gene expression and network analysis accompanied by global metabolites and complex lipid profiling suggested that metabolic status could be a major regulator of disease susceptibility. By manipulating the lipid content of mouse diets we have to elaborate this hypothesis and suggest that metabolic pathways are a major component of polycystic kidney disease, possibly underlying some of the sex effects.

Funding: NIDDK Support

TH-OR049
Smyd2 Synergistically Activates STAT3 and NF-κB and Represses p53 to Promote Cyst Growth
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Background: Protein methylation has emerged as a post-translational modification that exerts key roles in defining protein functions, at the level of signaling mediators and at the level of epigenetic regulation of transcription, in polycystic kidney disease (PKD). Smyd2, as a SET-domain-containing histone (lysine) methyltransferase, methylates both histone and non-histone proteins, including PKD associated p53, Rb and HSP90. However, the roles and underlying mechanisms of Smyd2 in regulating cyst development remain unknown.

Methods: To understand the role of Smyd2 in cyst growth in vivo, we generated Pkd1 and Smyd2 double conditional knockout mice (Pkd1(−/−);Smyd2(−/−);Ksp-Cre), and we treated Pkd1(−/−) mutant mice with the Smyd2 specific inhibitor, AZ505. To identify novel Smyd2 target genes involved in cystogenesis, we performed ChIP-seq analysis.

Results: We found that knockdown of Smyd2 or inhibition of Smyd2 with AZ505 delayed the growth as seen by decreased cystic index, kidney weight (BW) ratios, blood urea nitrogen (BUN) levels, cyst lining epithelial cell proliferation, and increased cyst lining epithelial cell apoptosis in Pkd1(−/−) mutant mice (all p < 0.01). We further found that Pkd1(−/−) Smyd2 double knockout mice lived longer, to a mean age of 25 days (Pkd1(−/−)Pkd1(−/−);Ksp-Cre) mouse knocked out at a mean age of 17 days (p = 0.001). We found that STAT3 and the p65 subunit of NF-κB are novel non-histone substrates of Smyd2, which methylates and activates them leading to increased cystic epithelial cell proliferation and survival. Smyd2 also regulates cystic epithelial cell apoptosis by repressing p53 activity and function. Further, we identified novel Smyd2 target genes, including the primary cilia associated Ahi1 (Abelson helper integration site 1) gene and HYDIN gene, by ChIP-seq analysis, which may connect Smyd2 signaling to the ciliopathy hypothesis in PKD.

Conclusions: Smyd2 promotes renal cyst growth in ADPKD through STAT3 and NF-κB signaling as well as p53 and ciliopathy associated signaling. Targeting Smyd2 in cystic renal epithelial cells may be a viable new therapy for ADPKD.

Funding: NIDDK Support

TH-OR050
Novel Insights Into Polycystin-1 Function from the Xenopus Pronephric Kidney
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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is caused by mutations in Polycystin-1 (PKD1) or Polycystin-2 (PKD2). PKD1 is a large transmembrane, mechanoreceptor-like protein that forms multiprotein complexes at focal adhesions, cell–cell junctions and cilia. It is thought to transmit a signal to PKD2, which in turn releases calcium. Studies in mice and other model organisms have led to the prevailing hypothesis that Polycystin-1 and Polycystin-2 regulate a range of cellular pathways, which together ensure that renal epithelial tubules establish and maintain a correct diameter. While there has been significant progress over the years, the molecular mechanism of PKD1 action is still obscure.

Methods: To address the function of PKD1 we used the Xenopus pronephros as a model for PKD. We knocked down Pkd1 expression using antisense morpholino oligomers and characterized the kidney by morphology, histology, immunofluorescence and in vivo...
A Forward Genetic Screen Identifies a Calcium-Regulated Mitochondrial Metabolite Carrier as a Downstream Target of Polycystin-2

**Background:** Polycystin-2 (aka TRPP2) is a cation channel that localizes to primary cilia and regulates developmental programs ranging from tubular morphogenesis to establishment of left-right (LR) asymmetry. Loss of TRPP2 results in polycystic kidney disease and randomized LR asymmetry. TRPP2-mediated calcium signals are thought to regulate morphogenesis. But the molecular events translating these calcium signals into morphogenic outcomes remain unknown.

**Methods:** To identify evolutionarily conserved core constituents of the TRPP2 signaling pathway, we conducted an unbiased forward genetic screen in *D. melanogaster* mutants that phenocopy the TRPP2 loss of function phenotype. To test the conservation of newly identified genes in vertebrates, the function of candidate genes was investigated in zebrafish. The molecular function of genes was studied in mIMCD3 cells using TALEN-mediated gene deletion in combination with metabolomics.

**Results:** We identified a calcium-dependent mitochondrial metabolite carrier (MC) as a downstream target of TRPP2 in a large-scale mutagenesis screen for mutants that phenocopy loss of TRPP2 in *D. melanogaster*. Calcium regulation of this MC appears to be critical, since loss of MC in flies was rescued by WT MC, but not by MC with EF-hand mutations, which abolish calcium binding. In zebrafish, TRPP2 is essential for the establishment of LR asymmetry. We show that MC is also required for the determination of LR asymmetry in zebrafish. Rescue experiments in flies and zebrafish suggest that MC acts downstream of TRPP2, which is consistent with the calcium-dependence of this carrier. To investigate the molecular function of MC and TRPP2, we deleted the genes in mIMCD3 cells. Metabolomic analyses showed that TRPP2- and MC-deficient cells display impaired mitochondrial metabolism and concordant changes of several metabolites which may contribute to morphogenetic signaling processes.

**Conclusions:** We show that a calcium-dependent mitochondrial metabolite carrier acts in a conserved pathway linking TRPP2-mediated ciliary calcium signals to mitochondrial metabolism in vivo.

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

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Modeling Polycystic Kidney Disease Cystogenesis with Genome-Modified Human Pluripotent Stem Cells

**Background:** Human pluripotent stem cells (hPSCs) can self-renew extensively and differentiate into diverse tissues, including tubules expressing kidney markers. To date, however, no study has demonstrated a phenotype in these tubules relevant to kidney disease. Using the CRISPR/Cas9 genome editing system, we tested the ability of hPSCs derived from PKD1- or PKD2-deficient kidney cells to model features of polycystic kidney disease (PKD) cystogenesis.

**Methods:** Cas9 nuclease and guide RNAs targeting PKD1 or PKD2 were transfected into hPSCs. Chromatogram analysis and immunoblotting indicated biallelic, frame-shift mutations at target sites and the absence of the corresponding full-length proteins. hPSCs were treated with specific growth factors to direct stepwise differentiation into kidney progenitor cells (SIX2/PAX2^+^) and subsequently proximal tubules (WTP1-LRP2^+^). PKD hPSCs and derived tubules were inspected for cystogenesis phenotypes, compared to unmodified control cultures of otherwise dermal genetic background.

**Results:** PKD hPSCs exhibited self-renewal and pluripotency characteristics comparable to isogenic controls, and differentiated into tubular organoids with similar efficiencies. Interestingly, in PKD hPSC cultures, we observed formation of large, transversely arranged, kidney-like structures. Cross-sections of these tubules revealed cystic epithelia retracted strongly with LTL and surrounded hollow interior compartments devoid of cells. Time-lapse imaging revealed that cysts arose from a small minority of differentiating tubular structures. Importantly, isogenic control hPSCs, plated and differentiated in an identical manner to the PKD hPSCs, did not form cysts.

**Conclusions:** Our findings suggest that PKD-specific cyst formation from tubules can be reproducibly modeled in a minimal system in vitro. Cysts arise from both PKD1^+^ or PKD2^+^ hPSCs, but not from parental hPSCs of otherwise identical genetic background.

**Funding:** NIDDK Support, Private Foundation Support

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Inactivation of Ift88 Gene Rescues the Phenotype in a Genetic Model of Autosomal Dominant Polycystic Kidney Disease

**Background:** Mutations in PKD1 and PKD2 genes are responsible for autosomal dominant polycystic kidney disease, the most common life threatening genetic disease in humans. The gene products polycystin-1 (PC1) and -2 (PC2) are localized to the primary cilium and function as a receptor channel complex on the primary cilium, with potential for ‘clinical trials in a dish’ to evaluate candidate therapeutics.

**Funding:** NIDDK Support, Private Foundation Support

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Other Signaling Pathways Rapidly Compensate for Loss of mTORC1 in Driving Cystic Kidney Disease

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is the leading monogenetic cause of end-stage renal disease. In both mice and humans, cystic kidney disease is consistently linked to an activation of the mTORC1 pathway. Yet, the utility of mTORC1 inhibitors to treat patients with ADPKD remains controversial despite promising preclinical data.

**Methods:** To conclusively define the cell-intrinsic role of mTORC1 for cyst development, the essential mTORC1 scaffolding protein Raptor was selectively inactivated in renal tubular cells lacking cilia due to deletion of Kif3A.

**Results:** In comparison to a rapid onset of cyst formation and renal failure in mice with defective ciliogenesis alone, both renal function and overall survival were strikingly improved in mice additionally lacking Raptor. However, eventually these mice succumbed to cystic kidney disease despite mTORC1 inactivation. In-depth transcriptome analysis showed a rapid activation of other growth-promoting pathways, overriding the effects of mTORC1 deletion.

**Conclusions:** Our findings indicate that cystic kidney disease can adopt bypass mechanisms frequently observed in drug-resistant cancers. Thus future clinical trials will need to consider combinatorial or sequential therapies to improve efficacy in patients with cystic kidney disease.

**Funding:** Government Support - Non-U.S.
Results: DLG1+/−; CASK−/− mice exhibit cysts as early as 90 days with severe but variable pathology by 9 months. Analysis of DLG1+/−; CASK−/− tubules segments indicates proximal tubule origin of cysts and dysregulation of matrix proteins, but with preservation of apico-basal polarity. Ciliary length was up to 2-fold longer in the majority of DLG1+/−; CASK−/− tubules, but was only longer in dilated DLG1+/−; CASK−/− tubules. Curiously, wild-type (WT)-Amp induced dilations in wild-type embryonic renal tubules, DLG1+/− or CASK−/− embryonic kidneys did not exhibit tubular dilations.

Conclusions: Our data indicate that DLG1 and CASK co-regulate renal development as well as homeostasis of renal epithelium independently of apico-basal polarity. IHC analysis of tubular molecular features confirmed cilia and trichrome staining. In unusual elongation of cilia. A cAMP-stimulated model of cystogenesis revealed a failure in PKA-dependent tubular dilations in DLG1+/− or CASK−/− embryonic kidneys. Coupled with cilia elongation and PKA effects on cilary function, these results indicate a previously unrecognized regulation of PKA by MAGUK family members in the kidney.

Funding: NIDDK Support

TH-OR056

Serum Lupins, Pre-Existing Vascular Disease, and Arteriovenous Fistula Maturation Failure Jin-kyung Kim1, Sun Ryong Choi, Mi Jin Park, Sung-gyun Kim2. 1Internal Medicine, Hallym Univ Sacred Heart Hospital, Kidney Research Inst, Anyang, Republic of Korea; 2Internal Medicine, Shemyook Medical Center, Seoul, Republic of Korea; 3Clinical immunology, Hallym Univ Sacred Heart Hospital, Anyang, Republic of Korea.

Background: Pre-existing vascular diseases is one of the important causes of maturation failure of arteriovenous fistula (AVF). Recently, a growing proportion of incident dialysis patients are obese, and leptin is regarded as a pivotal mediator between obesity and cardiovascular diseases. We investigated the association between serum leptin and pre-existing vascular disease and AVF maturation failure in patients with end-stage renal disease (ESRD).

Methods: Vein samples from 62 patients were collected at the time of AVF creation near the same AVF anastomosis. Histological (hematoxylin and eosin, and trichrome staining), immunohistochemical and morphometric (smooth muscle actinin [SMA], vimentin and desmin) studies were performed. AVF maturation failure was defined as an AVF not to use successfully for hemodialysis by the third month after its creation despite medical or surgical interventions.

Results: Mean age was 63.3±13.7 years and the prevalence of obesity (BMI ≥25 kg/m²) was 49.1%. Mean serum leptin levels were 2.10±1.41 pg/mL (log transformed), and patients in the highest leptin tertile had significantly increased BMI, higher triglyceride, interleukin-6, and hs-CRP levels (P<0.01). AVF maturation failure occurred in 21 (35.6%) patients, and the failure rate progressively increased from the lowest to the highest leptin tertile (P<0.001). On histological examinations, increased leptin tertiles were closely associated with interstitial hyperplasia (13.3±4.5 vs. 18.2±5.2 vs. 30.3±14.3 mm in each tertile, P=0.02). As well as medial fibrosis, the number of cells in the media was increased in each tertile. Insulin resistance was significant positive for negative for being associated with changes in leptin and C-reactive protein levels. Interestingly, a number of vascular sections in lowest leptin tertile also had desmin-positive contractile smooth muscle cells.

Conclusions: Obesity related fistula maturation failure may be mediated by higher serum leptin level - associated preexisting vascular diseases in ESRD patients.

Funding: NIDDK Support, Private Foundation Support

TH-OR057

Characterization of Cystic Kidneys in Mice Deficient in the Polarity Proteins DLG1 and CASK Steven Daniel Funk, Jinzhi Wang, Moe Mahjoub, Jeffrey H. Miner. Renal Div, Washington Univ School of Medicine, St. Louis, MO.

Background: Polycystic kidney disease involves dysregulation of tubular proliferation and cellular polarity leading to cystogenesis. Deletion of various apico-basal and planar cell polarity (PCP) proteins in mice, including members of the membrane-associated guanylate kinase (MAGUK) family, is sufficient for cystogenesis. DLG1-deficient mice exhibit cystogenesis but only occasional unilateral renal agenesis or hypoplasia. Co-deletion or hypomorphic expression of DLG1 and CASK in nephron progenitors (via Six2Cre) induces hypoplasia and cystogenesis, respectively. This work aimed to characterize the cyst phenotype in DLG1−/−; CASK−/− mice.

Methods: DLG1−/−; CASK−/− mice were analyzed histologically by immunohistochemistry, western blotting, and qRT-PCR at various ages. Additionally, for mechanistic insight we employed a model of cystogenesis in which cell-permeant cAMP (8-Br-cAMP) drives tubular dilation in cultured embryonic kidneys through luminal fluid flux.

Results: Deletion of CASK, a member of the MAGUK family, in embryonic kidneys leads to cilia length defects in patient's fibroblasts and in fibroblasts. We provide evidence that the p.P269L mutation led to cilia length defects in patient's fibroblasts and Δk47 knockdown IMCD3 cells, associated with disorganization of the Invs compartment. Moreover, it affects the interaction of ANKS3 with NPHP1 and led to defects in tight-junction and lumen formation in 3D culture, reminiscent of NPHP1 knockdown. We next generated an ANKS3 zebrafish mutant (TALEN) that exhibits laterality defects. In contrast to DLG1−/−; CASK−/−, our analysis suggests that SDCCAG8 function at the basal body is impaired DNA damage response signaling as an underlying disease mechanism in the kidney.

Conclusions: Our morphometric analysis showed that the greatest change in amount of arterial and venous hypoplasia was observed from the contralateral control (29±3% vs 110±15%; p=0.006) (figure 1), but endothelial-dependent response to SNP was similar to the contralateral control (9±12% vs 11±15% vs 12% vs 11±15%; p=0.047, suggesting smooth muscle dysfunction.

Funding: NIDDK Support, Private Foundation Support

TH-OR058


Background: Vascular endothelial function plays a critical role in arteriovenous fistula (AVF) remodeling and neointimal hyperplasia development. The goal of our study was to characterize the natural course of endothelial dysfunction following AVF creation.

Methods: AVFs were created using an end to side anastomosis between the femoral vein and artery in 12-16 week old Sprague-Dawley rats. Contralateral vessels served as controls. Rats were sacrificed at 1, 7, 14, and 21 days after AVF creation and vein and artery segments were collected for immunohistochemical and morphometric analysis. Segments from the arterial anastomosis were isolated at these time points and mounted on wire myographs to assess endothelial-dependent and -independent function by concentration-response curves to acetylcholine (Ach) and sodium nitroprusside (SNP), respectively.

Results: Maximal relaxation to Ach was significantly decreased at 7 days compared to the contralateral control (29.12±11.05 vs 20.06±0.01) (figure 1), but endothelial-dependent function was fully restored by 21 days (94±2% vs 93±2%; p=0.598).

Funding: NIDDK Support, Private Foundation Support

TH-OR059

Endothelial-independent response to SNP was similar to the contralateral control artery at 1, 7, and 14 days time points, suggesting an adequate smooth muscle cell response necessary for vasodilation. However, at 21 days vascular relaxation to SNP was impaired compared to control (84±6% vs 99±2%; p=0.047), suggesting smooth muscle dysfunction. Our morphometric analysis showed that the greatest change in amount of arterial and venous inner hyperplasia occurs in the 1st 7 days following AVF creation.

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

Underline represents presenting author.
Conclusions: Creation of AVF results in a time-dependent endothelial dysfunction within 7 days after surgery. Therapies targeted at restoring endothelial function via increasing nitric oxide production shortly after AVF creation may help improve AVF remodeling and inhibit neointimal hyperplasia. Late changes in endothelial-independent vascular function following AVF creation needs further evaluation.

Funding: NIDDK Support, Private Foundation Support

TH-OR060

Improper Vein Morphology Associated to Vascular Access Outcome? 

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Background: Vascular access (VA) stenosis is histologically characterized as neointimal hyperplasia (NH). Smooth muscle cells initially proliferate in media, and migrate to the intima where endothelial cell proliferation and angiogenesis occur. Venous NH has been primarily associated with hemodynamic stress, surgical injury, grafts and cannulation. According to recent data, uremia is likely to exacerbate endothelial dysfunction and predispose to NH before VA creation. Primary end point was to evaluate preoperative vein morphology and how it would affect VA outcome. Secondary end points were to find if other demographic and clinical factors could also have any impact.

Methods: Transversal observational study performed in 26 patients with end-stage renal disease. Venous specimens obtained during VA creation were evaluated for intimal inflammatory infiltrate/angiogenesis, media abnormalities and intima/global wall thickness.

Postoperative clinical function and demographic parameters recorded.

Results: The majority of patients were male (64.6%); age 71.4±15.1y; 57.7% diabetic; 50% had central venous catheter at surgery time; maturation occurred in 53.8%. Intimal angiogenesis and media abnormality were both seen in 66.7% of patients in which VA didn’t mature, but only in 14.3% and 21.4% of the ones that matured, respectively. Chi-square analysis showed that both previous findings were significantly associated with VA failure (p 0.006 and p 0.020). Intimal and global wall thicknesses were 0.0607±0.0715 and 0.700±0.2228mm in matured VA; 0.2600±0.2442 and 1.0318±0.3227mm in non-matured VA, respectively (p 0.006 and p 0.005). Gender, age, diabetic status and catheter presence didn’t affect VA function.

Conclusions: Preexisting venous thickness, intimal angiogenesis and media abnormalities predispose to postoperative VA nonmaturation. It is possible that uremia and other pre-dialysis factors may contribute to preexisting venous abnormalities which, independently of the future hemodynamic stress, predispose patients to more aggressive NH after VA creation, contributing to inferior outcomes.

TH-OR061

The Effect of Far Infrared Therapy on the Maturation of Newly Created Arteriovenous Fistula and the Parameters of Inflammation, Endothelial Function and Oxidative Stress in Patients with Advanced Chronic Kidney Disease

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Background: We had demonstrated that far infrared (FIR) therapy could improve the access flow and unassisted patency of arteriovenous fistula (AVF) in prevalent HD patients; however, the effect of FIR on the endothelial function as well as the markers of inflammation and oxidative stress of the newly created AVF is unknown.

Methods: We enrolled patients with advanced chronic kidney disease (CKD) by the definition of eGFR <20 ml/min/1.73m2. Patients were randomly and equally allocated to FIR group (receiving FIR therapy for 40 minutes thrice weekly for 3 months) and control group (without FIR therapy). This study is aimed to evaluate (1) the effect of newly-created AV access on the markers of inflammation (hsCRP), endothelial function [asymmetric dimethyl arginine (ADMA) and L-arginine], and oxidative stress [serum malondialdehyde (MDA), serum advanced oxidation protein products (AOPPs), blood glutathione (GSH), erythrocyte glutathione peroxidase (GPx), and erythrocyte superoxide dismutase (SOD) activities], (2) the effect of FIR on access flow and the levels of the above-mentioned inflammatory, endothelial and oxidative stress markers in patients with advanced CKD in the first 3 months after the creation of AVF.

Results: Totally, 122 advanced CKD patients finished this study with 60 in FIR group and 62 in control group. In comparison with control patients, the patients in FIR group had lower mean values of incremental change of the plasma concentrations of hs-CRP [ -0.68±0.93 vs. 0.39±0.46 mg/L, P=0.04] and ADMA (+0.10±0.05 vs. 0.02±0.05, P=0.02) but a higher incremental change of blood glutathione (2.45±0.46 vs. 0.93±0.93 mg/L, P=0.04) and ADMA (-0.10±0.05 vs. 0.02±0.02, P=0.03) and access flow of AVF from 1st to 3rd month.

Conclusions: In patients with advanced stages of CKD, AVF malfunction is associated with a higher level of plasma hs-CRP, ADMA and a lower level of blood glutathione at baseline, which could be improved by FIR therapy. Henceforth, FIR therapy improves blood flow and the maturation of AVF possibly through the mechanism of correcting inflammation, endothelial dysfunction and oxidative stress.

Funding: Government Support - Non-U.S.

TH-OR062

Use of Arteriovenous Fistula/Graft Access for Continuous Renal Replacement Therapy: A Single Center Experience

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Background: Use of arteriovenous fistula or graft (AVF/AVG) access is widely considered to be contraindicated for continuous renal replacement therapy (CRRT), yet insertion of hemodialysis (HD) catheters can carry high risk of complications in critically ill stage renal disease (ESRD) patients. Here we report our single-center experience with using AVF/AVG access for CRRT.

Methods: Retrospective review of 43 consecutive hospitalized ESRD patients on maintenance HD who received CRRT in 2012. After exclusions (16 catheter-dependent at admission, 4 with AVF/AVG thrombosis before CRRT start), our cohort consisted of 23 patients. Data collection included patient and treatment characteristics, and access outcomes.

Results: Mean±SD age was 57±15 yrs, 48% were male, and median HD duration was 54 months (range 8-300); 14 (61%) patients had AVF and 9 (39%) had AVG. Most (83%) patients required vasopressor support at CRRT start. Mental status at CRRT initiation showed 35% to be oriented and following commands, 9% awake but confused, and 56% sedated. Median duration of AVF/AVG use for CRRT was 4 days (2-34). Complications related to use of the AVF/AVG for CRRT (with subsequent requirement of HD catheter placement) developed in 3 patients (13%); hematoma in 2 patients with AVF and thrombosis of AVG in 1 patient. All 3 patients with complications had documented pre-existing access problems; 1 had known subclavian vein stenosis and 2 required access intervention within the previous 1 year. Of these three patients, 1 was awake and confused while the other 2 were sedated. Among them, 1 required blood product transfusion for line insertion and 1 developed a catheter-associated bloodstream infection. Of the cohort, 16 (70%) patients survived to hospital discharge; among the survivors, AVF/AVG access was functional at the time of discharge in 15 (94%) patients.

Conclusions: Our experience suggests that use of AVF/AVG for CRRT is feasible with a relatively low complication rate and low risk of access failure. This approach may aid in avoiding the potential complications associated with HD catheter insertion in ESRD patients with a functioning vascular access.

TH-OR063

Improvements in Time to Fistula Use in Incident Hemodialysis Patients in the Rapid Response Pilot Program

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Background: It is known that use of a catheter hemodialysis (HD) access is associated with increased morbidity and mortality, as compared to arteriovenous fistulas (AVFs) and grafts (AVGs). FMCNA has initiated the Rapid Response (RR) pilot program in an attempt to improve time to use of AVF accesses in incident HD (iHD) patients who initiated dialysis with a catheter. The aim of this study was to determine if the RR program is associated with improvements in AVF access use in iHD patients.

Methods: In September 2014, 59 clinics initiated the RR pilot program. Clinics were selected by high census (>95 patients) and high catheter rates (>30%). The program consisted of sequential, educational modules designed to build awareness of catheter exposure, engage staff in standardized and simplified vascular access monitoring, and address lack of AVF maturation as a root cause of high catheter rates. All patients initiating dialysis with a catheter access were followed. Non-RR clinics in the same geographical location were randomly identified for controls. To determine the change in time to AVF use, the mean time to AVF use over 12 months at the end of each month from June 2014 to March 2015 was calculated.

Results: 5,248 and 4,159 iHD patients starting dialysis with a catheter at RR and non-RR clinics were included in this analysis. The mean time to AVF use was reduced in RR clinics after initiation of the program in September of 2014, as compared to control clinics (p<0.05).

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

16A
Conclusions: This study demonstrates improvements associated with time to AVF use in incident patients initiating HD with a catheter at clinics participating in the RR program. Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-OR064

Impact of Poverty and Health Care Insurance on Arteriovenous Fistula Use Among Incident Hemodialysis Patients

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Background: The use of AVF has been shown to have superior outcomes compared to use of HD initiated with a catheter, the only exception being patients with VA healthcare benefits. Efforts to improve incident AVF use may require focusing on pre-ESRD care to be successful. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of the Air Force, or the United States Government.]

Methods: In this retrospective cohort study using the United States Renal Data System dataset, we identified 669,206 patients initiated on maintenance HD from January 1, 2007 through December 31, 2012. We assessed the Medicare-Medicaid dual eligibility status as an indicator of individual-level poverty and ZIP code-level median household income (MHI) data obtained from the 2010 United States Census. We conducted logistic regression of AVF use at start of dialysis as the outcome variable, as reported on the Medical Evidence Form 2728.

Results: The proportions of dual-eligible and non-dual eligible patients who initiated HD with an AVF were 12.53% and 16.17%, respectively (p<0.001). Dual-eligibility was associated with significantly lower likelihood of AVF use upon initiation of HD (adjusted odds ratio [aOR] 0.91; 95% confidence interval [CI] 0.90-0.93). Patients in the lowest area MHI quintile (aOR 0.90, 95% CI 0.90-0.90) compared to those in higher quintile levels. However, dual eligibility and area-level MHI were not significant in patients with Veterans Affairs (VA) coverage.

Conclusions: Individual and area level measures of poverty were independently associated with lower likelihood of AVF use at the start of HD, the only exception being patients with VA healthcare benefits. Efforts to improve incident AVF use may require focusing on pre-ESRD care to be successful. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of the Air Force, or the United States Government.]

Funding: Other U.S. Government Support

TH-OR065

A Subset of CD64+ F4/80int CD11b+ CD11cint Macrophages Protects against Chronic Ischemic Kidney Injury

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Background: Macrophages (Mfs) have been implicated in both progression and resolution of renal injury. We tested the hypothesis that a specific Mfs subtype regulates fibrosis in chronic murine ischemic renal artery stenosis (RAS).

Methods: After 28 days of unilateral RAS in mice, stenotic kidneys were harvested and 3 Mfs populations (Figure 1), black circles) quantified using polychromatic flow cytometry by expression of the CD11b, CD11c, F4/80, MHCII, CD64, MerTK, Ly6c & CD206. Mouse macrophages were ablated using i.p. injections of liposomal clodronate (2/week for 28 days), and macrophage populations were flow-sorted to study gene expression andfibrosis in chronic murine ischemic renal artery stenosis.

Results: DKO mice showed many inflammatory cells in the renal interstitium with decline in renal function. The histology in WT and SKO kidneys appeared normal. In contrast, kidneys were removed and analyzed at P70.

Conclusions: Other U.S. Government Support

Figure 1 Clodronate significantly reduces Clodronate

(object population). Top panel: Representative H&E staining showing atrophy. Middle: Flow cytometry identifying different subsets of mononuclear phagocytes. Bottom right: Trichrome staining.

Funding: Private Foundation Support

TH-OR066

Spliced XBP1p Rescues Renal Interstitial Inflammation due to Loss of Sec63 in Collecting Ducts

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Background: Sec63 is one of two genes which cause human autosomal dominant polycystic liver disease, and is located in the membrane of the endoplasmic reticulum (ER). A number of disease states alter ER function and result in ER stress, thus initiating the unfolded protein response (UPR). UPR is mediated by three major stress sensors, IRE1α, PERK and ATF6. In particular, IRE1α is the most conserved of the three branches and phosphorylation of IRE1α results in spliced XBP1 (XBP1s), a transcription factor that activates transcription of chaperones and proteins involved in ER-associated degradation. We have shown that loss of Sec63 and Xbp1 in collecting ducts causes phosphorylation of IRE1α and progressive renal interstitial inflammatory changes leading to CKD (ASN, 2014 TH-OR162). It is known that phosphorylated IRE1α activates NFκβ, JNK, and NALP3 inflammasomes. In the current work we investigated the interaction of the SEC63 and IRE1-XBP1 pathways and their role in CKD.

Methods: Animal models used in this study: WT (wild type), SKO (Sec63fl/fl;Pkhd1-cre), DKO (Sec63fl/fl;Xbp1+/+;Pkd1-cre) and TNO (Sec63fl/fl;Xbp1+/+;Ire1a+/+;Pkd1-cre), as well as DKO-Nalp3- and DKO expressing a cre activated ROSA-XBP1s allele. The kidneys were removed and analyzed at P70.

Results: Analysis of NFκβ and JNK phosphorylation states were no different between WT, SKO and DKO. The histology in WT and SKO kidneys appeared normal. In contrast, DKO mice showed many inflammatory cells in the renal interstitium with decline in renal function. By removing Ire1a and Nalp3, respectively, on the DKO background did not rescue the inflammation nor ameliorate decline in renal function. In addition, double knockout of Sec63 and Ire1a in the collecting duct also resulted in renal interstitial inflammation similar to what was observed in the DKO kidneys. Re-expression of a human XBP1 transgene that produces spliced XBP1 on the DKO background rescued the inflammatory phenotype.

Conclusions: Spliced XBP1 rescues renal interstitial inflammation due to loss of Sec63 in collecting ducts.

TH-OR067

Specific Deletion of Rictor in Macrophages Ameliorates Macrophage Activation and Obstructive Nephropathy in Mice

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Background: Rictor/mTORC2 signaling is activated in both tubular and interstitial cells in mouse kidneys with obstructive nephropathy. Our published studies reported that Rictor/mTORC2 signaling mediates TGFβ1-induced fibroblast activation and kidney fibrosis. Regarding the critical role for macrophages infiltration in kidney fibrosis, deciphering the role and mechanisms for mTORC2 signaling in macrophage activation and its contribution to kidney fibrosis are very necessary.

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

Funding: other U.S. Government Support

Oral Abstract/Thursday
Methods: In this study, a mouse model with tamoxifen-induced macrophage-specific deletion of Rictor and primary cultural macrophages from bone marrow were employed.

Results: Here, we found that Rictor/mTORC2 signaling was activated in the kidney interstitial F4/80+ macrophages in mice with uUO nephropathy. A mouse model with tamoxifen-induced macrophage-specific deletion of Rictor was generated. Compared with the control, the kidney weight was significantly increased at 2 weeks post-uUO surgery. In the primary cultured macrophages, compared with wild type cells, cell proliferation stimulated by M-CSF treatment was similar, whereas cell migration was markedly inhibited in Rictor-deleted macrophages. Additionally, the mRNA abundance for arginase 1, fork1, and YM1 were largely induced in wild type macrophages treated with IL-4, which were much less in Rictor-deleted macrophages.

Conclusions: Together, these results suggest that Rictor/mTORC2 signaling plays an important role for promoting macrophage activation and contributes to the development of kidney fibrosis.

Funding: Government Support - Non-U.S.

TH-OR068
Non-HLA Antibodies Targeting Angiotensin II Type 1 Receptor and Endothelin-1 Type A Receptor Induce mTOR Signaling and Endothelial Injury in Human Microvascular Endothelium

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Background: Functional non-HLA antibodies (Abs) targeting G-protein-coupled receptors Angiotensin II Type 1 (AT1) and Endothelin-1 Type A receptor (ETAR) are implicated in pathogenesis of renal transplant vasculopathy. Both antibodies activate canonical G-protein related ERK1/2. The molecular link between receptor stimulation and development of vascular obliterative lesion has not been fully established. We hypothesized the involvement of PI3K/Akt downstream signaling target mTOR and assessed functional consequences of AT1R- and ETAR-activation by non-HLA Abs.

Methods: Human microvascular endothelial cells were stimulated with AT1R-Abs and ETAR-Ab containing IgG from patients with oligoarteritis vasculopathy. Phospho-specific antibodies against ERK and mTOR downstream targets were used to assess activation of mTORC1 and mTORC2. Scratch assay was employed to study effect of non-HLA-antibodies on wound healing. Involved AT1R ETAR activation in non-HLA antibody down-streaming was addressed by use of specific inhibitors for AT1R (Valsartan) and ETAR (Sitaxentan).

Results: Signaling activity of both, mTORC1 and mTORC2, was increased after short and long term treatment with patient IgG compared to cells treated with IgG from healthy controls. This effect could be inhibited by preincubating the cells with specific inhibitors of AT1R and ETAR. Both, activation of mTORC1 and mTORC2 were PI3K-dependent and independent from ERK-activation. mTOR inhibitor rapamycin completely abolished non-HLA Abs induced activation of mTORC1 and in addition mTORC2 after long term treatment. Impaired wound healing by non-HLA Abs could be restored by either use of specific AT1R or ETAR inhibitors.

Conclusions: We provide evidence that functional targeting AT1R and ETAR antibodies induce mTORC1 and mTORC2 signalling which is independent of canonical ERK 1/2 activation in human microvascular endothelium. Our data on impaired AT1R and ETAR-dependent wound healing induced by non-HLA Abs may provide a translational rationale for therapeutic AT1R and mTOR inhibitors in patients with non-HLA Abs.

Funding: Government Support - Non-U.S.

TH-OR069
Memory Effector T Cells and OX40 Signaling Could Contribute to Chronic T-Cell Mediated Rejection

Claudia Cupo, Fabio Sallustio, Giuseppe De Palma, Mirko Ippoliti, Loreto Gesualdo, Marco Quaglia, Paolo Riggott, Francesco Paolo Schena, Jan C.A.R.S.O. Consortium, Bari, Italy; 1  M. Trpevski, 1C.A.R.S.O. Consortium, Bari, Italy; 2Univ of Bari, Bari, Italy; 3Univ of Eastern Piedmont, Novara, Italy; 4Univ of Eastern Piedmont, Novara, Italy; 5Univ of Padua, Padua, Italy.

Background: Chronic T-cell mediated rejection (TCMR) is characterized by the reduction of vessel lumen with marked intimal thickening, fibrous hyperplasia and a large component of leukocyte infiltrate. Aim of our work was the study of gene expression profile in renal tissue, including the cellular infiltrate, in chronic TCMR.

Methods: We performed transcriptomics study using RNA extracted from archival formalin-fixed and paraffin-embedded (FFPE) renal biopsies obtained from 21 patients with chronic TCMR and 10 with acute TCMR. Controls were renal tissue samples from 52 cadaveric donors (CD). Genome-wide expression profiles were generated by Illumina platform. Real-Time PCR and immunofluorescence were used for validation of the identified transcripts.

Results: Using a FC?2 and a FDR 0.05, we identified 164 genes differentially expressed in renal tissue of patients with chronic and 165 genes differentially expressed in acute TCMR, compared to CDUs. Partial Least Square showed a clear difference in the gene expression of the three groups of biopsies. The study of gene pathways showed up-regulation of OX40 signaling, that is involved in the differentiation of CD8+ memory effector T cell, and up-regulation of KLRG1, BLIMP1 and CD25 that characterized short-lived memory effector T cells. Interestingly, we found that OX40 signaling was specific for chronic TCMR. Next, the validation study by qRT-PCR, KLRG1, BLIMP1 and CD25 in 52 clinical samples demonstrated that these genes were expressed by CD8+ T cells in chronic but not in acute TCMR.

Conclusions: Our data suggest, for the first time, the involvement of memory committed CD8+ effector T cells specifically in chronic TCMR. The generation of memory effector T cells is mediated by OX40 pathway, that may be considered a potential target for specific treatment of chronic TCMR of kidney graft.

Funding: Government Support - Non-U.S.

TH-OR070
Dendritic Cell-Targeted CD40 DNA Vaccination Suppresses Th17 and Ameliorates Renal Injury in Experimental Autoimmune Glomerulonephritis

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Background: The CD40-CD154 co-stimulatory pathway is critical for T cell activation in autoimmune disease. Our group previously found that blocking this pathway using CD40 DNA vaccine enhanced by targeting dendritic cell receptor DEC205 prevent development of Heymann nephritis. In this study, we used DEC-CD40 DNA vaccine to treat the disease and explored its effect on Th17-mediated pathogenesis of experimental autoimmune glomerulonephritis (EAG).

Methods: The rat EAG model was established by NC1 protein injection, and DEC-CD40 vaccination was administered at week3 and week6 after NC1 injection. Renal function and histology were assessed at week12. Th subsets, key transcription factors and relevant cytokines in kidneys, spleens and lymph nodes were examined.

Results: Administration of DEC-CD40 DNA vaccine at week3 and week6 after NC1 injection reduced renal structural and functional injury in EAG. DEC-CD40 vaccination reduced the number of Th17 cells and inhibited Th17 immune responses in kidney, spleen and lymph nodes, but did not alter the number of Th1, Th2 and Treg cells. Early and late treatment showed similar effects on kidney injury and Th17 immune responses, indicating DEC-CD40 vaccination has both preventative and therapeutic roles in EAG. Serum from rats with DEC-CD40 suppressed Th17 in vitro, but not Th1 differentiation. B cell activation and M1 macrophage polarization were inhibited when co-cultured with Th17 cells induced with DEC-CD40-EAG serum but not EAG serum.

Conclusions: DNA vaccine encoding CD40 and targeting dendritic cells ameliorates renal injury in both early and late stages of experimental autoimmune glomerulonephritis. Its preventative and therapeutic effect was associated with suppression of Th17 differentiation and Th17-dependent B cell activation as well as M1 macrophage polarization.

Funding: Government Support - Non-U.S.

TH-OR071
Pharmacologic Targeting of Sirtuin-1 (Sirt1) Enhances Treg Function, Markedly Prolongs Renal Allograft Survival and Protects against Renal Allograft Dysfunction


Background: Published data show that the pharmacologic regulation of Foxp3+ T-regulatory (Treg) function provides safer, more consistent, potent and less expensive outcomes than Treg-based cell therapy. However, Treg treatments have only been studied or more times post-transplant (Txs). In the case of sirtuins biology, conditional deletion of the sirtuin 1 gene within Foxp3 + Treg cells augments Foxp3 acetylation and Treg suppressive function, and enhances heterotopic cardiac allograft survival.However, such data remain of uncertain translational significance until tested in life-supporting models using pharmacologic approaches in normal recipients. We now report such data.

Methods: To this end, C57BL/6 mice were engrafted with BALB/c kidneys (i.e. full MHC-mismatch) and underwent native nephrectomy, and blood chemistries, renal function and hematocrit were monitored weekly thereafter.

Results: Allograft recipients were divided into two groups, and treated with either a Sirt1 inhibitor, EX-527 (1 mg/kg for 14 days), or vehicle control. We found that allograft survival at 100 days post-Tx was 87.5% in the EX-527 group, but only 28.6% in control mice (P=0.037, Mantel-Cox test). Moreover, at 100 days post-Tx, the EX-527 treated group had lower BUN (71 ± 0.02 mg/dL, P<0.001) than survivors in the control group. Histologic examination revealed lower proteinuria, interstitial fibrosis and tubular atrophy in the EX-527 treated vs. control groups, respectively.

Conclusions: Pharmacologic inhibition of Sirt1 is effective at prolonging allograft survival and function. These data provide clear evidence that pharmacologic regulation of Treg function is of demonstrable value in stringent allograft models, and provide a compelling rationale for testing of Sirt1 inhibitors in pre-clinical models.

Funding: Other NIH Support - NIAID

TH-OR072
Immunologic Mechanisms of Rejection and Kidney Injury

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

18A

Oral Abstract/Thursday
A Novel IL-2 and IL-33 Hybrid Cytokine for Lupus Glomerulonephritis (GN) Therapy

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Background: Autoimmune Lupus GN is caused by T-cell and immune complex (IC) mediated inflammation resulting in renal failure. Low interleukin (IL)-2 levels and T-regulatory cell (Treg) deficiency is implicated in lupus GN. Based on our findings that IL-2, which is critical for Tregs, also regulates the expression of ST2 (receptor for IL-33) and TH2 promoting cytokine), and (b) a major subset of Tregs express ST2, we hypothesized that both IL-2 and IL-33 will be beneficial for treating lupus GN by simultaneously targeting Tregs and TH2. Further, linking IL-2 and IL-33 in a single molecule will target Tregs and TH2 efficiently.

Methods: We made a recombinant hybrid cytokine (IL23) bearing activities of IL-2 and IL-33 and tested its efficacy to treat GN using lupus prone NZM228 female mice, in which disease was accelerated by injection of IFNα-expressing adenovirus (Ad-IFNα). NZM228 female mice were infected with saline or 60nmol/day of IL23 or IL23/IL33 alone or in combination for 5 days before Ad-IFNα injection.

Results: IL23 and the IL-2 and IL-33 combination protected 80% and 60% respectively from severe proteinuria and mortality, whereas 80% of mice treated with saline or IL-2 or IL-33 alone succumbed to severe proteinuria. IL23 treatment induced robust and sustained increase in Tregs. Renal histology of mice that succumbed to proteinuria showed glomerular hypertrophy, mesangial expansion and leukocytic infiltration, which were absent in IL23 treated mice. While complement deposition was similar, IL23 treated mice showed increased kidney size and skewing towards IgG2a compared to saline treated group. IgG2a deposits in the control mice. Further, treatment with IL23 (60nmol/day for 5 days) of mice with established proteinuria (100-300mg/dl for 2 consecutive weeks) induced persistent remission in 9 out of 11 mice, which survived beyond 10 months of age, while 70% of the NZM228 female mice die of severe proteinuria. IL23 treated mice had higher circulating IgG2b without any symptoms of allergic diseases.

Conclusions: IL23 hybrid cytokine can prevent and reverse lupus GN by enhancing Tregs and bears therapeutic potential.

Funding: Private Foundation Support.

Regulation of the Apical Cotransporter NKCC2 by a Novel Kinase: TNIK

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Background: The apical cotransporter NKCC2 mediates NaCl absorption by the thick ascending limb (TAL), maintaining blood pressure. Abnormally enhanced NKCC2 activity contributes to salt-sensitivity hypertension. Phosphorylation of NKCC2 at threonines 96 and 101 (NKCC2-Th96,101) is a unique feature of TAL cell. NKCC2 expression in TAL is regulated at multiple levels. In the kidney medulla, TALs are the only nephron segment that expresses a predominant number of naive, CD69+ CD44+ T regulatory cells (Tregs). Tregs promote TAL NaCl absorption. In activated Tregs, the transcription factor TNIK phosphorylates NKCC2 at Thr-96,101 and mediates total and surface NKCC2 expression in TALs.

Methods: We measured NKCC2-TNIK interaction by co-immunoprecipitation in rat TALs. TNIK and NKCC2 are co-localized in TALs.

Results: We observed NKCC2 phosphorylation in isolated perfused TALs. NKCC2 and TNIK co-immunoprecipitate in TAL lysates and NKCC2 directly phosphorylates NKCC2 at Thr-96,101 and total NKCC2 expression in TALs was increased by 32% (p<0.05) and phospho/NKCC2 was increased by 23% (p<0.05).

Conclusions: Targeting TNIK in TALs may enhance NKCC2 expression in TALs, therefore promoting TAL NaCl absorption and decreasing blood pressure.

Funding: Private Foundation Support.
Inhibition of Mitochondrial Complex-1 Prevents the Downregulation of NKCC2 and ENaC in Obstructive Nephropathy 

Methods: C57BL/6 mice were subjected to the sham surgery or unilateral ureteral obstruction (UUO) for 7 days. Then kidney tissues were harvested for the analyses.

Results: Following UUO, sodium transporters including NHE3, α-Na-K-ATPase, NCC, NKCC2, p-NKCC2, ENaCα, and ENaCγ were remarkably reduced by 60-90% contrasted to unaltered expression of ENaCβ, as determined by qRT-PCR, Western blotting, and immunohistochemistry. This global downregulation of sodium transporters was accompanied by striking reduction of mitochondrial DNA copy number (mtDNA), mitochondrial transcription factor (mtTFAm), and mitochondria-encoded NADH dehydrogenase 1 (mtNdi1) indicating a mitochondrial abnormality. Strikingly, specific inhibition of mitochondrial complex-I by rotenone (500ppm in diet) completely abolished the downregulation of NKCC2, p-NKCC2, and ENaCα without affecting other sodium transporters. To study the potential mechanisms mediating the rotenone effects on sodium transporters, we examined a number of known sodium modulators, including PGE2, ET1, Ang II, natriuretic peptides (ANP, BNP, and CNP), and nitric oxide synthases (iNOS, nNOS, and eNOS) and found that all of them were strikingly elevated by 3 to 80 folds except for nNOS in obstructed kidneys. However, after rotenone administration, only BNP with a 80-fold increase and iNOS with a 4-fold increase but not others were significantly reduced by 62% and 96%, respectively.

Conclusions: These findings demonstrated a substantial role of mitochondrial dysfunction in mediating the downregulation of NKCC2 and ENaCα in obstructive nephropathy, possibly via iNOS-derived nitric oxide and BNP.
Methods: To examine the effects of disrupting both SPAK and OSR1, we manipulated distal convoluted tubules (DCT) and thick ascending limbs (TAL) in adult mice in which decreased NCC was induced by constitutive expression of APOL1. We performed in vitro and in vivo experiments to elucidate the physiological role of NHA2 in the kidney.

Results: Numerous founders for both G0 (n=29) and G2 (n=8) were obtained and progeny transmated the transgenics consistent with Mendelian expectations. Founders and offspring expressed variable levels of APOL1 in podocytes, but even in the highest expressing G0 and G2 mice, markers for necrosis, apoptosis, or autophagic cell death were not identified in podocytes. Aged (~300 days) G0 and G2 mice did not develop spontaneous kidney pathology, proteinuria, or azotemia. An unexpected phenotype in young mice was developed in G0 and G2 founders and their offspring was sporadic seizures and sudden death during pregnancy. Pregnant mice from both G0 and G2 models exhibited hallmarks of preeclampsia including hypertension, proteinuria, glomerular endothelial damage, and elevated sFlt-1 levels. APOL1 was expressed in placental tissues, confirming prior reports of preeclampsia expression of Nephrin and APOL1.

Conclusions: Constitutive expression of the APOL1 G0 and G2 protein in vivo was not cytotoxic to podocytes regardless of expression level, mimicking the observations in humans that APOL1 risk genotypes are insufficient to cause kidney disease in the absence of an additional stressor. The preeclampsia phenotype was not variant-dependent and may represent placental injury related to ectopic transgene expression, however, a role for APOL1 in placental function may warrant further investigation.

Funding: NIDDK Support

TH-OR085

The Sodium/Proton Exchanger NHA2 Is a Novel Regulator of Sodium, Calcium and Blood Pressure Homeostasis in the Distal Convoluted Tubule of the Kidney

Background: Patients with HIV-associated-nephropathy (HIVAN) present with proteinuria but often lack edema, suggesting renal Na wasting. We have shown that the Kir4.1 potassium channel, which resides in the basolateral membrane of the distal nephron. KCNJ10 encodes the Kir4.1 potassium channel, which is characterized by epilepsy, ataxia, sensorineural deafness and a salt-wasting tubulopathy resembling Gitelman syndrome. KCNJ10 encodes the Kir4.1 potassium channel, which is characterized by epilepsy, ataxia, sensorineural deafness and a salt-wasting tubulopathy resembling Gitelman syndrome. KCNJ10 KO mice exhibited normal renal sodium handling in vivo. We found that the Kir4.1 potassium channel, which resides in the basolateral membrane of the distal nephron.

Methods: We performed in vitro and in vivo experiments to elucidate the physiological role of NHA2 in the kidney.

Results: We found NHA2 expression restricted to distal convoluted tubules in both murine and human kidney. By confocal imaging, NHA2 had an apical to subapical tubular localization. Blood pressure, measured by invasive telemetry, was significantly lower in NHA2 KO mice compared to WT mice on low, normal and high sodium diets. In addition, NHA2 KO mice exhibited normal renal sodium handling in vivo. We found that the Kir4.1 potassium channel, which resides in the basolateral membrane of the distal nephron.

Conclusions: Together, our data reveal the sodium/proton exchanger NHA2 as a sodium regulator of calcium, sodium and blood pressure homeostasis in the distal convoluted tubule of the kidney.

Funding: Government Support - Non-U.S.

TH-OR084

Inducible Kidney-Specific KCNJ10 Knockout Mice Show a Salt Losing Phenotype

Background: Missense mutations of KCNJ10 cause EAST/SeSAME syndrome, which is characterized by epilepsy, ataxia, sensorineural deafness and a salt-wasting tubulopathy resembling Gitelman syndrome. KCNJ10 encodes the Kir4.1 potassium channel, which resides in the basolateral membrane of the distal nephron. KCNJ10 KO mice have a severe phenotype and die during the first two weeks of life, limiting the useful of this model. Results obtained in young mice show reduced basolateral K conductance, sodium chloride transporter (NCC) and SPAK/Stc2-related proneuraminic kinase (rak) abundances. Here, we determine the renal phenotype of kidney-specific KCNJ10-/- adult mice.

Methods: We used Doxycycline-inducible kidney-specific KCNJ10 KO mice were generated using the TetOn/CreLoxP system under the control of Pax8 promoter. Doxycycline was administered for two weeks in the drinking water (0.2 mg/ml in 5% sucrose) of 2 month old mice. KCNJ10 KO mice were assayed in a Na deficient diet and renal tissue in KCNJ10-/- mice after two weeks of the doxycycline treatment.

Results: Kir4.1 was absent in the KS-KCNJ10-/- mice, which displayed hypokalemia, hypochloremia with metabolic alkalosis, hypercalciuria, proteinuria, and renal loss of sodium and potassium (P<0.05). At protein level, we observed that disruption of KCNJ10 decreased the expression of NCC and pNCC (Na+/K+-Cl cotransporter) without affecting the levels of WNK4 (with no lysine kinase 4) and SPANK.

Conclusions: In conclusion, disruption of KCNJ10 in adult mice induces a severe renal phenotype highlighted by hypokalemic metabolic alkalosis and renal loss of sodium with hypercalciuria. In contrast to constitutive KCNJ10-/- mice in which decreased NCC and SPANK abundance may be explained by a reduction in DCT mass, the disruption of KCNJ10 in adult mice causes a sodium wasting phenotype accompanied by decreased Na+/K+-pump and NCC abundances, suggesting a more widespread tubulopathy involving both DCT and TAL in our model.

Funding: NIDDK Support

TH-OR083

HIV Vpr Antagonizes Mineralocorticoid Receptor Activity, Explaining Salt Wasting

Background: Patients with HIV-associated-nephropathy (HIVAN) present with proteinuria but often lack edema, suggesting renal Na wasting. We have shown that the HIV accessory protein Vpr binds transcriptional regulators including the glucocorticoid-receptor (GR) and mineralocorticoid receptor (MR) activity.

Methods: We have developed transgenic mice that express Vpr in proximal tubules (PEPCCK-creTA-X-TetOff/Vpr). Wild type and transgenic mice were fed a high protein diet for 2 weeks to induce transgene expression. After 6 days on a Na deficient diet, urine and kidneys were obtained. A human distal cortical tubular (DCT) cell line was exposed to Vpr, we found that the peak signal of TSC promoter was disappeared after treatment with Vpr.

Conclusions: Vpr binds MR and inhibits MR transcriptional activity, providing a molecular mechanism for renal salt wasting in HIVAN.

Funding: NIDDK Support

TH-OR082

The Sodium/Proton Exchanger NHA2 Is a Novel Regulator of Sodium, Calcium and Blood Pressure Homeostasis in the Distal Convoluted Tubule

Background: Patients with HIV-associated-nephropathy (HIVAN) present with proteinuria but often lack edema, suggesting renal Na wasting. We have shown that the Kir4.1 potassium channel, which resides in the basolateral membrane of the distal nephron. KCNJ10 encodes the Kir4.1 potassium channel, which is characterized by epilepsy, ataxia, sensorineural deafness and a salt-wasting tubulopathy resembling Gitelman syndrome. KCNJ10 encodes the Kir4.1 potassium channel, which resides in the basolateral membrane of the distal nephron.

Methods: We determined the renal phenotype of kidney-specific KCNJ10-/- adult mice.

Results: Kir4.1 was absent in the KS-KCNJ10-/- mice, which displayed hypokalemia, hypochloremia with metabolic alkalosis, hypercalciuria, proteinuria, and renal loss of sodium and potassium (P<0.05). At protein level, we observed that disruption of KCNJ10 decreased the expression of NCC and pNCC (Na+/K+-Cl cotransporter) without affecting the levels of WNK4 (with no lysine kinase 4) and SPANK.

Conclusions: In conclusion, disruption of KCNJ10 in adult mice induces a severe renal phenotype highlighted by hypokalemic metabolic alkalosis and renal loss of sodium with hypercalciuria. In contrast to constitutive KCNJ10-/- mice in which decreased NCC and SPANK abundance may be explained by a reduction in DCT mass, the disruption of KCNJ10 in adult mice causes a sodium wasting phenotype accompanied by decreased Na+/K+-pump and NCC abundances, suggesting a more widespread tubulopathy involving both DCT and TAL in our model.

Funding: NIDDK Support

TH-OR081

Inducible Kidney-Specific KCNJ10 Knockout Mice Show a Salt Losing Phenotype, Explaining Salt Wasting
Podocytes and Beyond: New Targets and Mechanisms of Injury

TH-OR086
Kidney Disease Associated Variants of Apolipoprotein L1 Changes Conformational Dynamics of the C-Terminal Domain

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Background: APOL1 risk variants associate with non-diabetic kidney diseases in African Americans; however, the mechanisms of variant APOL1-mediated kidney injury remain unknown. We have shown a SNARE protein VAMP9 interacts with the C-terminus of APOL1; APOL1 variants change the C-terminal amino acid sequence and attenuate this interaction. Given this, we hypothesize that the structures of variant APOL1s are altered and disrupt protein interactions.

Methods: We modeled the 3D structure of the APOL1 C-terminus (residues 305-398) with the threading program ITASSER. We expressed the C-terminus of APOL1 with and without variants, (G0: reference, G1: S342G & I384M, and G2: del388-389NY) and used circular dichroism (CD) spectroscopy to experimentally verify the predicted secondary structure. Molecular Dynamics (MD) simulations assessed conformational behavior over time of G0, G1 and G2. PyMOL software modeled the APOL1:VAMP9 interaction.

Results: The computationally modeled structures of G0, G1, and G2 (residues 305-398) initially overlapped as three α-helices folded into a bundle, linked by short loops, and CD spectroscopy confirmed the predicted alpha helical content. APOL1-G0 adopted an “open” conformation in MD simulations (over 40 ns) while the G1 and G2 variants both remained in a “closed” conformation, assessed as Cu deviation from starting structure. Fluctuations of the Cα over the last 10 ns and principal component analysis of protein motion also demonstrated increased mobility of the G0 C-terminus compared to G1 and G2. De novo formation of intramolecular H-bonds mediated the structural stability of G1 and G2. The APOL1-G0:VAMP9 interaction is most stable with a 3:1 stoichiometry and does not involve the G1 and G2 residues.

Conclusions: APOL1-G0 adopts an “open” conformation but G1 and G2 both generate a “closed” C-terminal conformation, which limits protein interactions and explanations attenuation of the APOL1:VAMP9 interaction. Kidney disease induced by G1 and G2 may result from protein conformational changes that limit interactions with SNARE proteins.

TH-OR087
SS-31, a Peptide Targeting Mitochondria, Restores Podocytes in Diabetic Nephropathy (DN) in BTBR ob/ob Mice

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Background: SS-31 is a novel peptide that selectively binds to cardiolipin in the mitochondrial inner membrane, where it promotes Dickkopf-3 expression and activates non-canonical pathway. In this study, we examined the effect of SS-31 on podocyte damage in diabetic nephropathy.

Methods: 18 week male diabetic BTBR ob/ob and wild type (WT) mice were randomly assigned to 5 groups: ob/ob with infusion of SS-31 via osmotic pump for 6 weeks, ob/ob with saline infusion, untreated ob/ob, WT, and WT with SS-31 infusion. Podocyte density, mesangial matrix (% tuft area occupied by collagen IV matrix), and glomerular macrophages were quantified by morphometry and immunohistochemistry.

Results: Podocyte density, diminished in ob/ob mice, was significantly restored in ob/ob with SS-31 infusion (147.2 ± 33 podocytes/10µm²) compared with saline treated ob/ob mice (107.6 ± 4.78) or untreated mice (100.5 ± 6.14) (p=0.0026 & 0.0002).

Conclusions: Podocyte density was restored and mesangial matrix decreased in SS-31 treated diabetic ob/ob mice compared to untreated controls. SS-31, currently in human clinical trials for other diseases, may be useful in treatment of DN and potentially other glomerular diseases in which podocytes are lost.

Funding: NIDDK Support

TH-OR088
Genetic and Pharmaceutical Targeting of GSK3β in Podocytes Reinforces the Nrf2 Antioxidant Response and Ameliorates Podocytopathy and Proteinuria

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Background: Evidence suggests that the GSK3β-directed Nrf2 nuclear exclusion and degradation is pivotal for switching off the self-protective antioxidant response following injury. This study aimed to examine the role of the GSK3β regulated Nrf2 antioxidant response in podocyte pathobiology.

Methods: The regulatory effect of GSK3β on Nrf2 response was examined in cultured podocytes and in a murine model of adriamycin nephropathy by genetic targeting of GSK3β or by using SB216763, a selective small molecule inhibitor of GSK3.

Results: In cultured podocytes, adriamycin injury caused cell death, concomitant with GSK3 hyperactivation and minimal Nrf2 activation. Inhibition of GSK3 by SB216763 exerted a prosurvival effect, which was dependent on the enhanced Nrf2 antioxidant response, marked by increased expression and nuclear accumulation of Nrf2 and elevated production of the Nrf2-target hemoxysgenase-1. Epoxic expression of the kinase-dead mutant of GSK3β, the isofrom of GSK3β predominantly expressed in glomerular podocytes, reinforced the Nrf2 antioxidant response upon adriamycin injury and prevented cellular death. Conversely, GSK3β overactivity induced by a constitutively active mutant resulted in a blunted Nrf2 response and exacerbated podocyte death following adriamycin injury, which could be abolised by SB216763. In adriamycin injured mice, genetic targeting of GSK3β by the doxycycline inducible podocyte specific knock out or pharmacological targeting by SB216763 attenuated albuminuria and ameliorated podocytopathic lesions, including glomerulosclerosis, loss of podocyte markers, de novo expression of podocyte injury marker desmin and ultrastructural changes of podocytes, like foot process effacement. This beneficial outcome was likely attributable to the enhanced Nrf2 response in podocytes, because trionelmine, a selective antagonist of Nrf2, largely abrogated the podocyte reducing and podoprotective effect.

Conclusions: The GSK3β regulated Nrf2 antioxidant response might represent a novel therapeutic target to protect podocytes and treat proteinuric glomerulopathies.

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

TH-OR089
Ablation of Podocyte-Derived Wnts Aggravates Proteinuria and Kidney Injury

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Background: Activation of canonical Wnt signaling has been implicated in podocyte injury and proteinuria. However, as Wnts are secreted extracellular signal proteins, whether podocyte-derived Wnts are obligatory for developing proteinuria remains elusive. Wntless (Wl), a cargo receptor protein, is required for the secretion of Wnt proteins.

Methods: We generated conditional knockout mice in which Wl was specifically ablated in podocytes by using the Cre-LoxP system. The mice were subjected to adriamycin administration, and urine and kidney were analyzed at 7 days and 21 days, respectively. We utilized another proteinuric kidney disease model by chronic infusion of angiotensin II for 4 weeks.

Results: Mice with podocyte-specific ablation of Wl(podo-Wl-/-) developed normally. No albuminuria or overt pathologic lesions was observed up to 6 months of age, suggesting that Wl is dispensable for podocyte maturation, survival, and function under normal physiologic conditions. However, after adriamycin treatment for 7 days, podo-Wl-/- mice developed more severe podocyte injury and albuminuria than their control littermates. Surprisingly, ablation of Wl resulted in even more profound upregulation of β-catenin, accompanied by reduction and aberrant distribution of nephrin, Wilms tumor 1 (WT1), synaptopodin, and podocalyxin. In chronic injury induced by adriamycin or Ang II infusion, increased albuminuria, aggravated tuft lesions, and podocyte apoptosis were evident in Podo-Wl-/- mice. Mechanistically, specific ablation of Wl in podocyte caused significant down-regulation of Dickkopf-3 expression. Meanwhile, NFAT1, a key downstream mediator in non-canonical Wnt signaling, was largely inhibited in Podo-Wl-/- mice after ADR injection.

Conclusions: These results indicate that podocyte-derived Wnts may play an important role in protecting podocytes from injury by repressing canonical Wnt/β-catenin signaling via promoting Dickkopf-3 expression and activating non-canonical pathway.

Funding: NIDDK Support
Blockade of Wnt/β-Catenin Signaling Exhibits Superior Therapeutic Efficacy Than Ras Inhibition in Ckd

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Background: CKD has become a public health problem worldwide. Treatment options for CKD are limited and ineffective, undergoing enormous unmet medical need. The mainstay of clinical therapy for kidney disease is inhibition of the renin-angiotensin-aldosterone system (RAAS)-IIa receptor (ATII) blocker (ARB). However, current therapy with RAS inhibition is insufficient, partially because of compensatory upregulation of renin expression. Thus it is paramount to develop new RAAS inhibitors with better outcomes.

Methods: Using two mouse models of CKD induced by adriamycin (ADR) or unilateral ischemic/reperfusion injury (UIRI), we directly compared the therapeutic efficacy of small-molecule Wnt/β-catenin inhibitor ICG-001 with trandolapril (AR-L), alone or the combination of trandolapril and losartan (ARB). The effect of renin on fibroblast activation was also assessed in vitro.

Results: Compared to ACEI, or ACEI plus ARB, ICG-001 displayed superior therapeutic efficacy in both models. ICG-001 almost completely abolished proteinuria, ameliorated glomerular injury and fibrotic lesions and reduced serum creatinine in ADR nephropathy, whereas trandolapril, or trandolapril plus losartan only displayed 50% efficacy as ICG-001. Similar results were obtained in UIRI model. We found that ICG-001 almost completely abolished renal expression of all RAS components including angiotensinogen, renin, ACE and ATII in both models. However, trandolapril or trandolapril plus losartan actually induced angiotensinogen and renin expression in the kidneys. In vivo, incubation of kidney interstitial fibroblasts (NRK-49F) with renin protein induced fibronectin expression, and this effect was dependent on ERK-1/2 activation. Losartan did not block renin-induced fibroblast activation, suggesting that renin elicited its effect by an angiotensin-II independent mechanism.

Conclusions: Our studies demonstrate that blockade of Wnt/β-catenin, the master upstream regulator of all RAS genes, has superior therapeutic efficacy for the treatment of CKD than RAS inhibition. Funding: Government Support - N-U.S.

Distinct Populations of FOXD1-Derived Renal Interstitial Cells Regulate Erythropoietin Production

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Background: In adults, the kidney is the main physiologic production site of erythropoietin (EPO), a hypoxia-inducible factor (HIF)-2-regulated hormone that is essential for normal erythropoiesis. However, renal EPO producing cells (REPCs) are derived and are heterogeneous with regard to HIF-2-dependent oxygen sensing and their distinct subpopulations, a) a PHD2-sensitive cell population and b) a subpopulation, in both mutants, demonstrating that REPCs are exclusively derived from FOXD1-expressing cells following hypoxia exposure or PHD3 mutants). However, EPO (sEPO) levels in control mice, the renal EPO response was completely abrogated in Foxd1-Epo-/- mice developed anemia. While pharmacologic PHD inhibition and hypoxia exposure (10% O2) for 2 days increased renal Epo mRNA and serum EPO (Lipo) levels in control mice, the renal EPO response was completely abrogated in both mutants, demonstrating that REPCs are exclusively derived from FOXD1-expressing stroma. To investigate the role of individual PHDs, we inactivated PHD1, PHD2 and/or PHD3 in FOXD1-lineage cells and used multi-color fluorescent in situ hybridization for a detailed characterization of the REPc pool. Deletion of PHD2 alone (Foxd1-Phd2-), but not of PHD1 or PHD3, was sufficient to induce Epo in a subpopulation of GFP+ interstitial cells (0.8 ± 0.5% in control vs. 39.0 ± 5.5% in Foxd1-Phd2- mutants). However, EPO synthesis was induced in additional GFP+ Phd2- cells following hypoxia exposure or PHD3 deletion (3.0 ± 4.1% and 64.1 ± 8.4% respectively).

Conclusions: Our genetic studies demonstrate that REPCs consist of at least two distinct subpopulations, a) a PHD2-sensitive cell population and b) a subpopulation, in which in addition to PHD2 inactivation, hypoxia and/or PHD3 inactivation are required for EPO production. In conclusion, our data suggest that REPCs are entirely FOXD1-stroma derived and are heterogeneous with regard to HIF-2-dependent oxygen sensing and their ability to synthesize EPO.

Funding: NIDDK Support, Veterans Administration Support

microRNA-21 in Human Glomerular Aging

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Background: Loss of podocytes is sufficient to cause progressive glomerulosclerosis (the podocyte depletion hypothesis). We have recently shown that podocyte loss and glomerulosclerosis hyperphenotypes are common features of normal human aging (Hodgin, Bitzer, et al. Kidney Int 2015) indicating that miR-21 plays a role in the pathogenesis of glomerular injury. We now explore the role of miR-21 in aging of human and mouse glomeruli.

Methods: Kidney tissue samples were collected from 41 patients who underwent unilateral nephrectomy at the University of Michigan. DNA was extracted from formalin fixed paraffin embedded sections by standard chemical and immunohistochemical stains. Gene expression profiles (Affymetrix human ST 2.1) and small RNA expression (Luminna tru-seq) were generated from RNA isolated from micro-dissected glomeruli and corresponding tubulointerstitium of the same individuals. Associations between gene expression and quantitative phenotypes were then determined. In addition miR-21 deficient mice and wild type littermates (C57BL/6J and DBA/2J; n≥6 for each genotype) were aged in excess of two years and assessed for the same morphometric parameters.

Results: In human kidneys podocyte density declined with age and was significantly associated with increases in mesangial index (p=<0.003), podocyte cytoplasmic size (p=<0.001) and focal global glomerulosclerosis (FGGS) (p=0.009). FGGS was significantly associated with interstitial fibrosis (p=0.006). miR-21 expression was inversely correlated with podocyte density (p=0.041) and inversely correlated with mesangial index (p=0.02) and podocyte size (p=0.01). miR-21 expression increases with age in murine kidneys and miR-21-null mice exhibited decreased podocyte density (p=<0.001) and increased mesangial index (p=0.001) compared to wildtype littermates.

Conclusions: Both humans and mice experience an age-associated loss of loss of podocytes, and a concomitant increase in podocyte size and mesangial index. In mice miR-21 ameliorates phenotypes of glomerular aging. Candidate transcripts targeted by miR-21 that may mediate the observed phenotypes are being explored.

Funding: NIDDK Support, Other NIH Support - NUA

Murine Double Minute-2 Inhibition Ameliorates Established Crescentic Glomerulonephritis

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Background: Rapidly progressive glomerulonephritis (RPGN) is characterized by glomerular necroinflammation and crescent formation. The E3-ubiquitin ligase murine double minute (MDM-2) is a non-redundant element of NF-kB signalling and the negative regulator of p53-mediated cell cycle arrest. We hypothesized that the MDM2 would drive crescentic GN via NF-kB-dependent glomerular inflammation and via p53-dependent parietal epithelial cell (PEC) hyperproliferation.

Methods: We used injection of 75 μl of sheep anti- rat anti-GBM serum in C57BL/6 wild type and p53-deficient mice to induce crescentic GN and injection of MDM2 inhibitor nustin-3a or vehicle every alternate day starting on day -1 for pre-emptive or day +1 for therapeutic intervention. Evaluation was performed 7 days after antisera injection. For in vitro studies murine glomerular endothelial cells and PECs were transfected with MDM2 or p53 siRNA and analysed with qPCR or proliferation assay.

Results: The pre-emptive MDM2 blockade with nustin-3a ameliorated all aspects of crescentic GN such as vascular necrosis, podocyte loss, glomerular crescent formation, albuminuria, as well as inflammation, preventing cytokine induction, and recruitment of glomerular leukocytes and macrophages. MDM2 inhibition with nustin-3a had identical protective effects in p53 knockout mice, with the exception of crescent formation. In vivo experiments confirmed the MDM2 requirement for induction of NF-kB-dependent cytokines in murine glomerular endothelial cells as well as the p53-dependency of MDM2-mediated PEC proliferation. To evaluate MDM2 blockade as a therapeutic intervention in RPGN, we treated mice with established crescentic GN. Delayed initiation of nustin-3a treatment was equally protective as the pre-emptive treatment in abrogating crescentic GN.

Conclusions: The pathogenic effects of MDM2 are mostly p53-independent, associated with NF-kB activation and increased intraglomerular inflammation, but the p53-dependent function of MDM2 regulates the PEC proliferation and crescent formation. We therefore propose MDM2 blockade as a potential novel therapy in RPGN.

The Bone Marrow Initiates and Propagates suPAR-Mediated Kidney Disease

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Background: Proteinuria is a hallmark of glomerular kidney dysfunction, seen in both, native and post-transplant focal segmental glomerulosclerosis (FGS). Systemic soluble urokinase plasminogen activator receptor (suPAR) is implicated in FGS, yet the origin of suPAR in FGS remains unclear.

Methods: Humanization techniques, adoptive transfer, cell depletion, ELISA, flow cytometry, histology, and electron microscopy were performed.

Results: Here we report that bone marrow (BM) myeloid progenitor cells (MPCs) are responsible for the production of suPAR, resulting in kidney damage and proteinuria. Using a chimeric mouse model, we found that engraftment of CD434 peripheral blood mononuclear cells (PBMCs), but not CD344 PBMCs, from patients with recurrent FGS into immunocompromised mice resulted in an expansion of Gr-1+ murine BM myeloid cells, leading to proteinuria and FGS-like glomerulopathy. Furthermore, adoptive transfer experiments demonstrated that Gr-1+ BM myeloid cells are capable of causing suPAR-mediated proteinuria and therefore transmitting disease in healthy mice. We immunophenotypically characterized suPAR/Sca-1-Gr-1+ cells as “diseased” BM myeloid progenitor cells (MPCs), which are responsible for the production of suPAR competent to invest in kidney damage and podocyte loss.

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

Underline represents presenting author.

23A
C-Reactive Protein and Myeloid Derived Suppressor Cells in Acute Kidney Injury

**Background:** Myeloid derived suppressor cells (MDSCs) are best known for their anti-proliferative effects on immune cells. Their contribution in renal cell carcinoma and chronic kidney disease has been investigated and their association with kidney transplant survival documented, but their role in acute kidney injury (AKI) has not been studied. Renal ischemia reperfusion injury (IRI) is a frequent cause of AKI; the former triggering a systemic inflammatory response that leads to increased blood levels of C-reactive protein (CRP), a biomarker of worsened outcomes. Recently, using a CRP transgenic mouse model, we observed that CRP infusion into the injured kidney, CRP lowering therapy might be an effective treatment option for AKI.

**Methods:** We compared myeloid cell populations in the kidneys of wild type (WT), human CRP transgenic (CRPtg), and deficient (CRP−/−) mice subjected to bilateral renal IRI. **Results:** In CRP−/− mice, we observed a dramatic reduction in g-MDSC infiltration into the injured kidneys. Using in vitro T-cell proliferation assays we confirmed that these g-MDSCs were suppressive and in vivo in CRPtg, depletion of g-MDSCs prior to renal IRI using anti-Gr-1 antibody (Ly6G+/Ly6c−) reduced serum/urine biomarkers of AKI. Importantly, CRPtg treated with an antisense oligonucleotide that specifically lowered human CRP levels, showed both dramatic improvement in renal biomarkers of AKI and dramatic reduction in renal IRI. **Conclusions:** To our knowledge these are the first data showing that g-MDSCs contribute to the renal response to IRI and that (i) CRP amplifies this contribution. By reducing g-MDSC infiltration into the injured kidney, CRP lowering therapy might be an effective treatment option for AKI.

**Funding:** NIDDK Support, Other NIH Support - NIGMS

**TH-OR096**

C-Reactive Protein Promotes AKI by Impairing TEC Regulation via the CD32-mSmad3-P27 Pathway

**Background:** We have previously shown that C-reactive protein (CRP) plays a pathogenic role in acute kidney injury (AKI) by inhibiting tubular epithelial cell (TEC) regeneration. The present study tested a hypothesis that CRP may promote AKI via Smad3-p27 dependent inhibition of tubular epithelial cell (TEC) regeneration in vivo and in vitro.

**Methods:** The hypothesis was examined in a mouse model of AKI induced in human CRP transgenic (Smad3) knockout (CRP-Tg/Smad3−/−KO), CRP-Tg/Smad3−/−, CRP-Tg/Smad3−/−WT mice by clamping bilateral renal arteries for 40 minutes and in cultured HK-2 TECs.

**Results:** After 24 hours of AKI, CRP-Tg/Smad3−/−WT showed a significant increase in serum levels of creatinine and severe tubular necrosis, which was further enhanced in CRP-Tg/Smad3−/−WT mice but blunted in CRP-Tg/Smad3−/−KO. Further studies revealed that enhanced AKI in CRP-Tg/Smad3−/−WT mice was associated with a marked activation of TGF-β/Smad3, upregulation of p27, and inactivation of CDK2 kinase, thereby reducing cyclin E expression and impairing TEC proliferation as determined by BrdU incorporation and PCNA. In contrast, deletion of Smad3 in CRP-Tg mice prevented the development of AKI as demonstrated by normal serum levels of creatinine and suppressing the Smad3-p27 pathway, thereby promoting CDK2/cyclin E-dependent TEC proliferation. In vitro studies confirmed these findings that CRP acted through its receptor CD32b to activate Smad3 signaling via both TGF-β-dependent and ERK1/2 MAPK crosstalk pathways. Furthermore, we also found that activated Smad3 then bound directly to p27 to suppress CDK2/cyclin E-dependent TEC proliferation, which was inhibited by a Smad3 inhibitor (SIS3).

**Conclusions:** CRP promotes AKI by impairing the TEC regeneration via the CD32-mSmad3-p27 mediated inhibition of CDK2/cyclin E mechanism.

**Funding:** Other NIH Support - R01 HL103708, R01 DK101005, 1R01 DK101005, 1R56 DK101005

**TH-OR097**

Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO

**Background:** Ischemic acute kidney injury (AKI) is a devastating clinical problem without effective therapy. We recently showed that peptidylarginine deiminase-4 (PAD4) that converts peptidylarginine to peptidylcitrulline plays a critical role in ischemic AKI by promoting renal tubular inflammation. We hypothesized that PAD4 induces renal inflammation and exacerbates AKI by citrullinating IKKγ (also known as NEMO Essential MODulator or NEMO) and promoting renal tubular pro-inflammatory NFκB signaling. Furthermore, we tested whether targeted NEMO inhibition attenuates renal inflammation and protects against ischemic AKI.

**Methods:** We first tested whether recombinant human PAD4 (1-10 mg/ml) directly citrullinates human recombinant NEMO or NEMO in human proximal tubule (HK-2) cells. We also tested whether NEMO neutralization with NEMO binding peptide (NBP, 10 μM) attenuates PAD4-mediated nuclear NFκB translocation and induction of pro-inflammatory mRNAs in HK-2 cells. Finally, after Columbia IACUC approval, we tested whether NEMO neutralization (5 mg/kg) in mice attenuates PAD4-mediated exacerbation of 20 min ischemic AKI and renal inflammation.

**Results:** PAD4 directly citrullinated NEMO in a cell free system as well as in HK-2 cells. In addition, PAD4 directly caused nuclear NFκB-p65 subunit translocation which was attenuated by NEMO neutralization. Furthermore, NEMO neutralization significantly attenuated PAD4-mediated induction of pro-inflammatory genes (MCP-1 by 59±11%, MIP-2 by 43±10%, TNF-α by 59±12% and IL-6 by 83±3%) in HK-2 cells (P<0.05, N=5-6). Next, NEMO neutralization significantly attenuated PAD4-mediated exacerbation of ischemic AKI (PAD4+veh Cr(mg/dL)=2.4±0.4 vs. PAD4+NBP Cr=1.2±0.1, N=6, P<0.01) and renal inflammation (assessed with pro-inflammatory gene expression, neutrophil infiltration) in mice.

**Conclusions:** Our studies show that PAD4 exacerbates ischemic AKI and inflammation by promoting renal tubular NFKB activity via NEMO citrullination. Furthermore, we show that NEMO inhibition attenuates kidney injury and reduces the inflammatory response after renal IR injury. Selective NEMO neutralization may serve as a potential therapy for this devastating clinical problem.

**Funding:** NIDDK Support, Other NIH Support - NIGMS
Proximal Tubule Necroptosis Is Mediated by Mixed Lineage Kinase Domain Like (MLKL) In Vivo and Ex Vivo

Mingjun Shi, Brianna Flores

Results: RIP3K-dependent necroptosis is of critical relevance for many diseases including hypoxic organ damage in AKI (Linkermann and Green, NEJM 2014). However, the putative downstream mediators, such as mixed lineage kinase domain like (MLKL) have not been investigated in detail, but may trigger local tissue inflammation in a process referred to as necroinflammation (Linkermann et al, NRI 2014). Ferroptosis, an iron dependent cell death, is thought not to be affected by MLKL.

Methods: We employed video-monitoring of microperfused freshly isolated renal tubules, intravital microscopy, biochemistry, and diverse in vivo models of AKI and SIRS in wild type, MLKL-deficient- and RIP3K-deficient mice in the presence of newly developed necrostatins and ferrostatins.

Results: MLKL-deficient mice exhibit stronger protection against all investigated models of AKI in direct comparison to RIP3K-deficient mice. In SIRS models, RIPK3 and MLKL-k0 mice are protected compared to wild type littermates, but there is no statistically significant difference between these two. In intravital microscopy, MLKL-k0, unlike RIPK3-k0, do not exhibit wider peripheral capillaries compared to wild type, but the perfusion is increased due to increased flow. In isolated renal tubules, erastin-induced synchronized renal tubular necrosis was significantly attenuated in MLKL-k0 mice.

Conclusions: We identify MLKL as a master regulator of AKI and SIRS. In contrast to RIPK3, which exclusively functions in necroptosis, MLKL might affect ferroptosis.

CRP Exacerbates Ischemia-Reperfusion Injury in the Kidney by Down-Regulating Autophagy

C Run, Mingqian Shi, Brianna Flores, Nancy Gillings, orphan W. Moe, Ming Chang Hua

Conclusions: Starting as late as 24 hour after AKI, activation of the HGF/cMet pathway with BB3 mitigates renal injury and improves renal function. These data together with the expanded window for therapeutic intervention support the use of BB3 in Angion’s Phase 2 GUARD study in AKI patients and Phase 3 GIFT study in kidney Tx recipients presenting with delayed graft function. Funded by DK-062592, -066654, -079399.

TH-OR101

CRP Exacerbates Ischemia-Reperfusion Injury in the Kidney by Down-Regulating Autophagy

The effect of CRP on autophagy in AKI induced by renal ischemia-reperfusion injury (IRI), we studied transgenic CRP overexpressing mice (CRP;LC-3-GFP) with a autophagy reporter mouse (CRP;LC-3-GFP). In vivo: Mice were studied 2 days after IRI. Ex vivo: Renal tubules were isolated from LC-3-GFP mice at baseline for primary culture. In vitro: OK cells transfected with LC-3-GFP were used. The ex vivo and in vitro studies complement the in vivo study to define the direct effect of CRP on the kidney.

Results: Compared with LC-3-GFP mice, CRP;LC-3-GFP mice had higher serum creatinine (P<0.05), more tubular necrosis, and higher NGAL expression in the kidney after IRI. CRP addition exacerbated H2O2-induced LDH release from both primary cultured renal tubules and OK cells treated with CRP + H2O2 compared to H2O2 alone. Immunohistochemistry showed much fewer LC-3-GFP puncta in kidneys of CRP;LC3-GFP compared to LC-3-GFP mice after IRI. Similarly, CRP addition reduced LC-3-GFP puncta induced by H2O2 in primary cultured renal tubules and in OK cells transfected with LC-3-GFP plasmid. Autophagy inducers (rapamycin and LC3) rescued the impaired autophagy and blunted the LDH release from OK cells treated with CRP + H2O2 (P<0.05).

Conclusions: CRP renders the kidney more susceptible to ischemic-oxidative injury by down-regulation of autophagy flux. Autophagy inducer repairs down-regulated autophagy triggered by CRP and protects the kidney against ischemia reperfusion injury.

TH-OR101

The Therapeutic Effects of BB3, a Small Molecule Hepatocyte Growth Factor Mimetic, in Kidney Reperfusion Injury

Prakash Narayan, Bin Duan, Xingxi Peng, Kai Jiang, Latha Paka, Michael A. Yamin, Itzhak D. Goldberg

Background: Activation of the hepatocyte growth factor (HGF)/cMet pathway is therapeutic in ischemia-reperfusion (IR)-related acute kidney injury (AKI). However poor half-life makes clinical use of recombinant protein therapy in settings such as AKI or kidney transplantation (Tx) challenging. We investigated the effects of a unique and novel small molecule with HGF-like activities, BB3, in models of AKI and Tx. BB3 selectively phosphorylates cMet and triggers the HGF/cMet pathway in multiple in vitro assays.

Methods: IR: Adult male rats had 60 min normothermic renal artery occlusion. At reperfusion, the contralateral kidney was excised. BB3 (2 mg/kg) was administered QD starting at 24 hour into reperfusion. Tx: Kidneys from adult male Lewis rats were cold-preserved (~4°C) for 4 hr and transplanted into syngeneic recipients whose native kidneys were excised. BB3 (2.0 mg/kg, QD) was administered until sacrifice on Day 14.

Results: IR: Treatment with BB3, starting 24 hr after reperfusion, increased tubular cMet expression in vivo 3.5-fold (p<0.01). BB3 decreased tubular expression of kidney injury marker-1 (KIM-1), decreased tubular apoptosis, enhanced preservation of tubular integrity, improved urine output and reduced serum creatinine (figure1) Tx: BB3 improved recipient survival (60% vs 30% for control) and mitigated renal dysfunction (e.g., Day 7 Scr: 0.84 mg/dl vs 2.72 mg/dl for control; p<0.05).

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

Underline represents presenting author.
Signal Inhibitory Regulatory Protein-α Regulates Pathologic Reactive Oxygen Species Generation in Acute Kidney Injury

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Background: Ischemia reperfusion injury (IRI) is a major cause of acute kidney injury mediated by oxidative stress. We recently reported that signal regulatory inhibitory protein-α (SIRPα) is up-regulated in renal tubular epithelial cells (TEC), that the protein thrombomodulin-1 (TSP1) is increased following renal IRI, and SIRPα binds to TSP1. However, it is unclear how TSP1-SIRPα signaling contributes to IRI pathophysiology.

Methods: Wild-type (WT) mice, and SIRPα mutant (SIRPa-mice) lacking cytoplasmic recruitment domains, underwent bilateral IRI followed by assessment of renal function and biomolecular analysis after 24 h reperfusion. Murine WT and SIRPa-mice were studied in vitro. Mice were also irradiated and rescued with WT or SIRPa- bone marrow.

Results: IRI resulted in elevated serum creatinine in WT mice which was mitigated in SIRPa-mice (2.3±0.5 versus 9.8±4.0 mg/dl, P<0.001). Changes in renal function reflected improvements in renal histology, including tubular necrosis and inflammatory infiltrate. TSP1 was expressed to a similar degree in all mice post-IRI. Measurement of reactive oxygen species (ROS) in kidney demonstrated a 3-fold increase in superoxide in WT mice post-IRI (P<0.001) but no increase in SIRPa-mice when compared to sham. Expression of 3-nitrosotyrosine protein modification was reduced in SIRPa-mice compared to WT mice, although total renal expression of NADPH oxidase 1 and 2 were unchanged. In vitro, WT TEC displayed upregulation of ROS in response to TSP1 (P<0.01), which was not reflected in SIRPa-mice cells. SIRPα is expressed by all renal cells, and chimeric mice were generated to explore differences in cell compartment contribution to IRI. SIRPa-mice, regardless of hematopoietic reconstitution, were fully protected against renal dysfunction, tubular damage and ROS generation following IRI.

Conclusions: These data provide evidence for a role in SIRPα promoting renal IRI through generation of pathologic ROS, and blockade of SIRPα may provide a therapeutic target to modify IR-mediated damage.

Funding: NIDDK Support

“Urine Sediment” the Ignored Treasure Chest in the Search for Biomarkers in Acute Kidney Injury

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Background: In the last decade novel urine biomarkers have been identified in urine supernatant. Urine sediment is extensively used in clinical practice for microscopy but has not been used for AKI biomarker discovery. We examined whether urinary sediment from can be used to identify biomarkers and determine the proportion of sediment proteins that originate from brush border (BB), and mitochondria (MX).

Methods: Urine samples from patients admitted to the medical ICU at the Medical University of South Carolina were collected from 8 patients (4 without AKI and 4 with AKIN stage 3 AKI at the time of collection). The urine was centrifuged to separate sediment from supernatant. We performed liquid chromatography, tandem mass spectrometry (LC MS/MS) on each sediment and supernatant sample. We estimated the relative abundance of brush border, and mitochondrial proteins using Exponentially Modified Protein Abundance Index (emPAI). Database of BB, and MX proteins were used to identify BB and MX proteins from our experiment. The molar fraction of each protein in the sample relative to the total moles of all proteins in the sample was calculated for each protein. We used this to calculate the percent of moles of protein for BB, and MX proteins in the sediment.

Results: We identified 479 proteins in sediment (396 from the AKI 3 and 430 in No AKI). We identified 556 proteins from the no AKI samples, 239 proteins were present only in the sediment and 126 were identified only in the supernatant. In AKI 3 samples we identified 570 proteins, 169 proteins were unique to the sediment and 174 to the supernatant. The molar abundance percentage of BB proteins in the AKI 3 sediment and no AKI 3 sediment was 3.7 and 27.6% and MX proteins was 2.7 and 14.6% respectively.

Conclusions: We have developed an LC MS/MS technique for proteomic analysis of urine sediment. Urine sediment from no AKI and AKI 3 have proteins that are not found in supernatant. These proteins are potential biomarkers. As a percent of the molar amount of protein BB and MX is markedly less in AKI sediment. This finding has implication for the pathophysiology of shedding of renal tubular material in AKI.

FGF23 Drives Progression of Chronic Kidney Disease in Mice

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Background: Circulating fibroblast growth factor 23 (FGF23) is associated with disease progression in human chronic kidney disease (CKD).

Methods: Here, we elucidate the role of Fgf23 and its co-receptor Klotho in pathogenesis of CKD in mice by a dual approach, using genetic loss-of-function together with pharmacological inhibition models. CKD was induced by 5/6 nephrectomy in 3-month old mice, vitamin D receptor (Vdr) mutant mice, Fgf23-/-, and Klotho-/-VDR-/- compound mutant mice. All mice were kept on a rescue diet to prevent secondary hyperparathyroidism in VDR mutant mice. Sham-operated (SHAM) mice served as controls. In SHAM and CKD WT, VDR, and Klotho/VDR mice were treated with low dose anti-FGF23 antibody (anti-FGF23Ab, 50 g/mouse, 2 times/ week) over 8 weeks.

Results: Genetic ablation of Fgf23 in Fgf23+/VDR compound mutant or treatment of Wt, VDR, and Klotho/+ mice with anti-FGFB3Ab to tesp 1 (P<0.01), which was increased by the highest circulating Fgf23 concentrations among all CKD groups, reduced mortality and slowed disease progression in these mice to levels found in Fgf23+/VDR mutants, demonstrating that Fgf23 also has Klotho independent effects at high circulating levels. Fgf23-/-, but not Fgf23+/VDR or Fgf23+/VDR mice, showed increased hyperphosphatemia and volume overload in CKD mice by down-regulating renal sodium-transporting molecules, and increasing urinary excretion of sodium and calcium.

Conclusions: Collectively, our data suggest that elevated Fgf23 contributes to the pathogenesis of CKD in a vitamin D hormone- and partially Klotho-independent manner. Hence, our study may provide a mechanistic explanation for the association between circulating FGF23 and disease progression in CKD patients.

The Increased Bone Fibroblast Growth Factor 23 Expression Is Mediated by the Fibroblast Growth Factor Receptor in Experimental Uremia

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Background: Serum FGF23 is markedly elevated in CKD and has been associated with poor long-term outcomes. FGF23 expression is increased by activation of the FGF receptor (FGFR1) in rats with normal renal function and in vitro in UR106 osteoblast-like cells. We now demonstrate a role for FGFR in the regulation of FGF23 in a mouse model of acute kidney injury (AKI) due to high dose folic acid (FA), in rats with adenine high phosphorus induced CKD and in UR106 osteoblast-like cells.

Methods: Mice were injected with 250 mg/kg folic acid ip to induce AKI and sacrificed at 3 and 6 h. The FGFR inhibitor PD173074 was given to the mice 1 h before FA. Rats were fed an adenine high phosphorus diet for 14 d and PD173074 given for the last 2 d of the diet. Serum biochemistry, FGF23 and PTH levels were analyzed and calvaria FGF23 mRNA levels were measured by qRT-PCR. FGFR inhibitor PD173074 were added to UR106 cells for 24 h and FGF23 mRNA levels measured.

Results: FA increased serum BUN and phosphate levels as expected from 3 h. Calvaria FGF23 mRNA and serum FGF23 levels were increased 2-3 fold at 6 h. PTH levels increased 6-fold from 3 h after FA. The FGFR inhibitor PD173074 prevented the FA induced increase in both FGF23 mRNA and serum levels but had no effect on serum PTH levels. A more prolonged uremia due to an adenine high phosphorus diet for 14 d resulted in high levels of serum PTH (30-fold increase) and FGF23 (3.5-fold increase). PD173074 decreased
serum FGF23 and mRNA levels with no effect on PTH in the adenoine high phosphorus induced uremic rats. Addition of FGF2 to UMR106 cells increased FGF23 expression that was also prevented by PD173074.

Conclusions: A derangement in FGF-23 regulation starts early in the course of AKI, is in part independent of the increase in serum PTH and involves activation of FGFR. This is the first study demonstrating the contribution of FGFR blockade to the high levels of FGF23 in both acute and chronic experimental uremia. FGFR in the osteocyte may be activated by locally produced canonical FGFs such as FGF2.

TH-OR108
Acute and Chronic Inflammation Raises the Blood Levels of FGF23 in Normal Mice Shweta Bansal,1,2 William E. Friedrichs,1 Chakradhar Velagapudi,1 Sherry L. Werner,1 Paolo Fanti,1,2 Medicine/Renal, Univ of Texas Health Science Center at San Antonio, San Antonio, TX; 2Renal Section, South Texas Veterans Healthcare System, San Antonio, TX.

Background: High levels of FGF23 are not fully explained by abnormal mineral metabolism in CKD. We and others found association of FGF23 with inflammation in CKD patients, but knowledge about the role of inflammation in FGF23 regulation is limited. Methods: Inflammation was induced in B6 mice as follows (n=5 each Gr): Gr1-acute inflammation: single ip injection of 3.3 μg/kg of LPS (E.Coli 0111:B4) or vehicle control (Vb); Gr2-chronic pulsatile inflammation: daily ip injections of 3.3 μg/kg of LPS x 2 weeks; Gr3-chronic persistent inflammation: SQ injection of pellets releasing 2 mg/kg/day of LPS vs LPS + Vb daily injection x 2 weeks; and Gr4-acute on chronic inflammation: SQ LPS pellets x 2 weeks and single IP LPS injection before sacrifice. Plasma FGF23 (c-term) and TNFα levels and spleen weight measured at sacrifice. Results: In Gr1, FGF23 levels were 0.5±0.1 ng/ml 5 hours after LPS injection vs. 0.2±0.04 ng/ml in Vb (p=0.001). In Gr2, FGF23 was 0.2±0.02 ng/ml after 2-week daily LPS injections vs. 0.14±0.04 in Vb (p=0.05). In Gr3, FGF23 was 0.8±0.6 after 2-weeks LPS pellet vs. 0.14±0.04 ng/ml in Vb (p=0.04). In Gr4, FGF23 was the highest i.e., 1.3±0.7 after 2-week LPS pellets and single LPS injection, vs. 0.14±0.04 in Vb (p=0.006). TNFα levels were significantly higher in Gr3 and Gr4 vs. Vb (respectively 11±0.9, 14±0.8, and 8.0±0.8 pg/ml). Spleen weights were significantly higher in Gr3 and Gr4 as further indication of presence of inflammation. Summary: Both acute and chronic exposure to LPS caused inflammation and stimulated the synthesis of FGF23. The effects of acute and chronic LPS exposure seemed to be synergistic. Conclusions: Inflammation raises the FGF23 levels in B6 mice. The inflammation experienced by the Gr4 mice mimics events in CKD, where low-grade chronic inflammation is often aggravated by sporadic acute inflammation, e.g., caused by infections or translocation of inflammatory agents across the gut barrier. More studies are needed to delineate the role of inflammation in the regulation of FGF23 in the context of CKD.

Funding: NIDDK Support

TH-OR109
FGF23 Directly Targets Hepatocytes to Promote Inflammation in CKD Saurav Singh,1 Alexander Grabner,1 Karla J. Schramm,1 Christopher Yanucil,1 Alexis J. Sloan,1 Ansel P. Amaral,1,2 Myles S. Wolf,1 Christian Faul.1 Medicine, Univ of Miami Miller School of Medicine, Miami, FL; 2Medicine, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Background: Chronic inflammation is a hallmark of chronic kidney disease (CKD), and biomarkers of inflammation are strong predictors of poor clinical outcome. The molecular mechanisms underlying the interrelationship between deterioration of renal function and the inflammatory state are unknown. CKD patients develop marked elevations in circulating levels of the phosphorus-regulating hormone, fibroblast growth factor (FGF) 23. Our recent data indicate that FGF23 directly induces cardiac injury by activating FGF receptor (FGFR) 4 in cardiac myocytes, independent of α-klotho. Since hepatocytes express high levels of FGF23, we postulate that FGF23 can directly target the liver. Methods: Using HepG2 cells, a hepatocellular carcinoma cell line, and primary mouse hepatocytes, we analyzed signal transduction and expression of inflammatory cytokines, including C-Reactive protein (CRP) and interleukin-6 (IL-6) upon FGF23 treatment. FGF23 was injected intravenously into wild-type mice for 5 days, and FGF4R knockout mice were fed a 2% phosphorus diet for 12 weeks. 5/6 nephrectomized rats were administered an FGF4R-specific blocking antibody. Results: FGF23 induces expression of inflammatory cytokines in hepatocytes by activating calcineurin/NFAT signaling in an FGF4-dependent and α-klotho-independent manner. Elevation of serum FGF23 in wild-type mice via injections of recombinant FGF23 or administration of a high phosphorus diet increases CRP levels in liver and blood. High phosphorus diet does not elevate CRP expression in FGF4R knockout mice. Pharmacologically FGF4R blockade reduces the expression of CRP in rats with CKD. Conclusions: We provide a causative link between FGF23 elevations and the induction of an inflammatory response in the liver, and suggest a novel mechanism to explain the development of chronic inflammation in patients with CKD. Pharmacologic FGF4R blockade might have anti-inflammatory effects in CKD.

TH-OR110
Differential Effects of Calcitriol on FGF23/Klotho System and LVH in Experimental Uremia Maren Leifheit-Nestler,1 Laura Hermann,1 Dagmar-Christiane Fischer,1 Dieter Haffer,1 1Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; 2Dept of Pediatrics, Univ Hospital Rostock, Rostock, Germany.

Background: Vitamin D (vitD) deficiency and excess of circulating FGF23 are significant contributors to cardiovascular (CV) mortality in CKD patients. In vivo, vitD metabolites downregulate the calcemic response of FGF23 and Klotho components. In vitro, FGF23 treatment decreases FGF receptors (FGFRs), and blockages of the FGF23 signaling pathway, pathological cardiac remodeling, and LVH. Cardiomyocyte cross-sectional area was quantified by immunofluorescence microscopy. Renal Klotho expression was investigated by quantitative real-time PCR. Results: Cardiac Fgf23 levels, Fgfr1 and Fgfr4 mRNA, and LVH were increased significantly in 5/6Nx rats compared with controls. The calcineurin-NFAT signaling pathway was activated in uremia demonstrated by enhanced calcineurin accompanied by a strong reduction of phosphorylated NFAT protein. Pro-hypertrophic genes were increased in myocardial tissue of 5/6Nx rats. In general, vitD treatment of 5/6Nx rats resulted in reduced cardiomyocyte cross-sectional area. Although, cardiac Fgf23 levels, and Fgfr1 and Fgfr4 mRNA were further stimulated by vitD, vitD treated 5/6Nx rats showed reduced activation of NFAT ameliorating cardiac remodeling processes and LVH. Interestingly, renal Klotho expression was markedly reduced in uremic animals, and almost normalized after vitD treatment. Conclusions: Cardiac Fgf23 levels are enhanced in experimental uremia, and associated with LVH. VitD enhances NFAT phosphorylation and thereby blocks pathological remodeling processes induced by FGF23. In addition, vitD restores renal Klotho expression, and consequently enhances soluble Klotho, which may further be cardioprotective via binding to and neutralizing FGF23 in the heart.

TH-OR111
FGF4 Activation Is Sufficient to Induce LVH in Mice Alexander Grabner,1 Karla J. Schramm,1 Saurav Singh,1 Christopher Yanucil,1 Alexis J. Sloan,1 Ansel P. Amaral,1,2 Christian Faul.1 1Medicine, Univ of Miami Miller School of Medicine, Miami, FL; 2Medicine, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Background: Previously, we demonstrated that fibroblast growth factor (FGF) 23 is a causal factor in the pathogenesis of left ventricular hypertrophy (LVH). FGF23 directly targets cardiac myocytes via FGF receptors (FGFR) and activates calcineurin/NFAT signaling. Mammals express four FGR isoforms (FGFR1-4). Using two loss-of-function approaches (delivery of a blocking antibody in a rat model of chronic kidney disease (CKD) and gene deletion in mice), we could show that FGF4 is required for the development of LVH in rodents with high FGF23. To confirm this finding in a gain-of-function approach, we studied a genetic knock-in mouse model carrying a FGF4 mutation (G385R) that causes constitutive and ligand-independent activation of FGF4R.

Methods: We studied 6 months old homozygous Fgfr4-G385R knock-in mice and wild-type littermates. LVH was assessed echocardiography, H&E staining of cardiac cross sections, and cross sectional area of individual myocytes. We analyzed cardiac fibrosis by Picrosirius Red staining and qPCR. Activation of calcineurin/NFAT signaling in cardiac tissue was studied by qPCR and Western blot analysis, and serum levels of cleaved FGF23 were determined by ELISA.

Results: Compared to wild type littermates, Fgfr4-G385R mice develop LVH as evident by significantly increased LV wall thickness, cross sectional myocyte area and ejection fraction. Fgfr4-G385R hearts are not fibrotic, and show a significant elevation of NFAT mRNA gene expression. Although serum FGF23 levels were increased in Fgfr4-G385R mice, the elevation did not correlate with the cardiac phenotype.

Conclusions: Activation of FGF4R per se is sufficient to induce LVH in mice independently of serum FGF23 levels. We postulate that FGF4R is part of a novel pro-hypertrophic signaling pathway in the heart that could be activated in patients with cardiomyopathies. FGF4R blockade might not only serve as a novel pharmacological intervention for LVH in CKD patients with elevated FGF23, but also in patients with primary cardiac disease and increased FGF4R activity in the heart.

Funding: NIDDK Support, Private Foundation Support.

TH-OR112
Downregulation of Thrombomodulin Expression in Endothelial Cells by Fibroblast Growth Factor-23 and Klotho Kenji Tanaka,1 Yoko Oyama,2 Teruhide Tsuchida,1 Yasuhiko Kato,1 Kenji Tanaka,3 Shotaro Kitsuhara, Narita, Japan; 2Dept of Laboratory and Vascular Medicine, Kagoshima Univ Graduate School of Medical and Dental Sciences, Kagoshima, Japan; 3Dept of Pharmacology, Faculty of Dentistry, Mahidol Univ, Bangkok, Thailand.

Background: Chronic kidney disease (CKD) is regarded as a state of excessive fibroblast growth factor-23 (FGF-23) and a Klotho (KL) deficiency. Moreover, the increased mortality risk in CKD patients associated with cardiovascular disease and endothelial dysfunction. Increasing evidence demonstrates that thrombomodulin (TM)
plays an important role in endothelial barrier. The mechanism responsible for the linkage of FGF-23 with underlying endothelial damage in these patients is unclear. Here we report a downregulation of membrane TM in human umbilical vein endothelial cells (HUVEC) after FGF-23/ KL stimulation.

Methods: HUVECs were cultured in endothelial basal medium with supplement. SDS-PAGE analysis was performed to confirm the dose dependent effect of FGF-23 on TM expression in HUVECs, and to confirm the effect of KL. Next, membrane TM expression was performed by flow cytometry to confirm the effect of FGF-23 in HUVEC cell surface. Finally, immunofluorescence (IF) staining for TM expression on HUVECs was performed. Cells were visualized by double staining for TM expression and nucleus.

Results: SDS-PAGE and flow cytometry analysis shows that TM expression was markedly decreased when HUVECs were stimulated with 10 ng/ml FGF-23/ KL whereas this effect was less pronounced upon 1 ng/ml FGF-23/ KL treatment and that KL stimulation for 12 and 16 hours induced TM production significantly as compared to the controls and FGF-23 and FGF-23/ Klotho -treated cells. IF staining shows that TM is expressed on the cell surface in control cells while this number was dramatically increased after KL stimulation and that TM expression was reduced after FGF-23 and FGF-23/ KL stimulation.

Conclusions: TM is constitutively expressed in HUVEC and is suppressed by FGF-23 and FGF-23/ KL dose-dependently. Our results imply that TM response by FGF-23/ KL is a possible mechanism that leads to vascular complications in CKD patients.

Funding: Private Foundation Support

TH-OR114
Tenapanor, an NHE3 Inhibitor, Reduces Serum Phosphate in Patients with CKD Stage 5D and Hyperphosphatemia

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Background: Tenapanor (AZD1722), a first-in-class small molecule with minimal systemic availability, is an inhibitor of the Na+/H+ exchanger NHE3. Healthy volunteer studies show that tenapanor treatment increases stool sodium and phosphate and concomitantly reduces urinary sodium and phosphate. This double-blind, dose-finding study (NCT020181534) examined the effect of tenapanor on serum phosphate in patients with CKD stage 5D (hemodialysis).

Methods: After a 1–3-week washout of phosphate binders, 162 patients with baseline serum phosphate 6.0–<10.0 mg/dL and ≥1.5 mg/dL increase from pre-washout levels were randomized to placebo or one of six tenapanor groups (1, 3, 10 or 30 mg bid, or 3 or 30 mg qd) for 4 weeks. Blood samples were collected weekly. The primary endpoint was change in serum phosphate from baseline. Dose–response analysis was a secondary endpoint.

Results: Tenapanor treatment resulted in dose-dependent reductions in serum phosphate (Table), with a significant difference between the treatment groups (p=0.012, ANCOVA). Gastrointestinal AEs were more common with tenapanor than with placebo, with higher doses associated with higher rates of diarrhea.

Conclusions: Tenapanor provided clinically and statistically significant reductions in serum phosphate. Higher doses of tenapanor were associated with higher rates of diarrhea, as expected based on its additional pharmacodynamic effect on stool sodium. Once or twice-daily administration of tenapanor may offer a new treatment mechanism to reduce serum phosphate in patients with CKD.

Funding: Pharmaceutical Company Support - AstraZeneca

TH-OR115
Racial Differences in Association of Serum Calcium with Mortality and Incident Cardio- and Cerebrovascular Events

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Background: In CKD patients, both high and low serum calcium (CA) is associated with higher mortality. Calcium metabolism is different in African American (AA) vs. white individuals. It is unclear if CA is associated with mortality and vascular events in patients with normal kidney function and if such association differs by race.

Methods: We examined racial differences in associations between corrected CA and mortality or incident coronary disease (CHD) and stroke in a national cohort of 1,967,685 US veterans with eGFR >60ml/min/1.73m². We used multivariable Cox proportional hazards models with interaction terms for CA and race, adjusted for age, BMI, social-economics, eGFR, BP, comorbidities, and medications.

Results: The mean age (SD) was 60.6(13.5), and the mean eGFR (SD) was 83.3 (15.4) ml/min/1.73m². 15.5% of patients were AA, with a mean baseline CA of 9.5±0.4 mg/dl. Over a median follow-up of 8.2-years, there were 47,790 (15.7%) deaths, 8,129 (2.7%) strokes, and 6,617 (2.0%) CHD events in AA, compared to 299,137 (21.1%), 30,300 (2.1%) and 34,304 (2.4%) events in whites. A U-shaped association between CA and mortality was present in both races, but AA patients experienced lower risk relative to white patients with CA>8.8mg/dl (Figure, p<0.01 for interaction). No associations were found between CA and CHD/stroke in either race.

Conclusions: Tenapanor provided clinically and statistically significant reductions in serum phosphate. Higher doses of tenapanor were associated with higher rates of diarrhea, as expected based on its additional pharmacodynamic effect on stool sodium. Once or twice-daily administration of tenapanor may offer a new treatment mechanism to reduce serum phosphate in patients with CKD.

Funding: Pharmaceutical Company Support - AstraZeneca
Conclusions: Both higher and lower CA are associated with higher mortality in patients with normal kidney function. AA patients appear to experience relatively lower risk of death compared to white patients when CCA=8.8 mg/dl, but this could not be attributed to differences in incident occlusive vascular events.

Funding: NIDDK Support, Veterans Administration Support

TH-OR116

Relevance of LDL Cholesterol and C-Reactive Protein to Cardiovascular Risk Among Patients with Chronic Kidney Disease – Results from the Study of Heart and Renal Protection

Ben Storey, On behalf of the SHARP Collaboration Group, Univ of Oxford.

Background: Previous observational studies have found J-shaped relationships between LDL-C and cardiovascular risk among patients with CKD and suggested this association may be modified by inflammation: that it is positive in the absence of inflammation but negative in its presence. Conversely, other studies suggest that statins may be most effective in people with inflammation.

Methods: SHARP was a randomised controlled trial of LDL-C lowering with ezetimibe/simvastatin (E/S) in 9270 patients with CKD. Hazard ratios (HR) for all atherosclerotic vascular events (A VE) over 4.9 years were estimated with Cox regression. The effect of E/S on major atherosclerotic events (MAE) was estimated in the presence and absence of inflammation; defined as CRP >10 mg/L (the study median) or in a sensitivity analysis as CRP >3 mg/L (90% & 10% centiles in 3 NHANES respectively).

Results: Among all patients, usual LDL-C was positively, and approximately log-linearly, associated with risk of AVE (HR per 1 mmol/L [39 mg/dL] higher LDL-C: 1.38 [95% CI 1.22-1.56]). Compared to patients with low CRP, patients with high CRP were at higher risk, but the relationship between LDL-C and AVE risk was similar in both groups (HR per 1 mmol/L 1.29 [1.07-1.54] and 1.43 [1.21-1.69] respectively, p for interaction=0.58). E/S was similarly effective at reducing MAE in patients with low and high CRP. (Rate Ratio 0.84 and 0.83 respectively, p for heterogeneity=0.96). Sensitivity analyses gave similar results.

Figure: Effect of allocation to E/S on major atherosclerotic events, by level of CRP

Conclusions: LDL-C was positively associated with risk of AVE irrespective of baseline inflammation. Furthermore, lowering LDL-C with E/S was similarly effective in the presence or absence of inflammation. While CRP is associated with vascular risk, it does not modify the association between LDL-C and risk nor the efficacy of lowering LDL-C.

Funding: Pharmaceutical Company Support - Study of Heart and Renal Protection (SHARP) was initiated, conducted and interpreted independently of the principal study funder (Merk & Co. and by Schering Plough Corporation, who merged in 2009)

TH-OR117

Utilization of Statin Medications in Non-Dialysis Dependent Chronic Kidney Disease (CKD) Patients

Holly J. Kramer, Talar Markossian, Nicholas Burger, Benjamin Ling, Julia Koval, David J. Leechy, Kevin Stouppe, Loyola Univ Chicago; ‘Hines VA Medical Center.

Background: KDIGO and KDOQI guidelines recommend statin medications for adults age ≥ 50 years with non-dialysis dependent chronic kidney disease (CKD) due to demonstrated benefits of statins in reducing the risk for cardiovascular events and mortality for these patients. Results from few empirical studies suggest that statins are underused for CKD patients.

Methods: Retrospective analysis of U.S. Department of Veterans Affairs Healthcare System (VA) national databases to determine statin use in patients with non-dialysis dependent CKD. Patients with non-dialysis dependent CKD stages 3-5 with no history of kidney transplantation were included in the analysis. Statin use was ascertained from pharmacy dispensing records in 2012 and 2013.

Results: Approximately sixty percent of patients with non-dialysis dependent CKD were prescribed statins. Among patients prescribed statins in 2012, 11.0% lacked statin prescriptions during 2013. Statin use varied by age (33.9% ≤50, 53.0% 50-59, 64.6% 60-74, 58.0% ≥ 75 years). Table 1 shows the frequency of statin use by CKD stage and by presence of comorbidities.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CKD Stage undetected (&lt;147, 508)</th>
<th>CKD Stage 3A (&lt;147, 528)</th>
<th>CKD Stage 3B (&lt;194, 470)</th>
<th>CKD Stage 4 (&lt;51, 299)</th>
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<tr>
<td>% Using statin</td>
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Conclusions: Despite KDIGO and KDOQI guidelines recommending statins for adults with non-dialysis dependent CKD, statin use is suboptimal in adults with CKD receiving care in the VA healthcare system. Interventions are needed to increase knowledge regarding the clinical importance of statin use in adults with non-dialysis dependent CKD.

Funding: Veterans Administration Support

TH-OR118

Associations of Conventional Echocardiographic Measures with Incident Heart Failure and Mortality: The Chronic Renal Insufficiency Cohort Study

Ruth E. Dubin, Amanda Hyre Ayerden, Wei Yang, Alan S. Go, Martin Keane, Rajat Deo, Nisha Bansal, Raymond R. Townsend, Michael Shlipak, Univ of California, San Francisco/SP YAMC; Univ of Pennsylvania School of Medicine; Kaiser Permanente, California; Temple Univ School of Medicine; Univ of Washington.

Background: Heart failure (HF) is the most common cardiac complication for patients with chronic kidney disease (CKD). Left ventricular hypertrophy (LVH) develops early in CKD, but studies have not adequately evaluated the association of left ventricular mass index (LVMI) with HF incidence among men and women with CKD.

Methods: We evaluated two-dimensional echocardiograms from 2964 participants of the Chronic Renal Insufficiency (CRIC) Study without cardiovascular disease (CVD). LVMI was calculated using the linear method, indexed to height and analyzed using gender-specific quartiles. The primary outcomes of incident HF and all-cause mortality were adjudicated, HF analyses were censored for death.

Results: Among 2964 participants, 45% were women, 54% were non-white race, mean(SD) age was 59±11 years, mean(SD) eGFR was 44±17 ml/min/1.73m² at baseline. Over a median[IQR] follow up of 6.6 [5.7-7.6] years, 262 participants developed incident HF, and 470 participants died. In both men and women, LVMI was a strong, independent predictor of incident HF and mortality, even after adjustment for BNP and troponin T.

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Conclusions: Despite KDIGO and KDOQI guidelines recommending statins for adults with non-dialysis dependent CKD, statin use is suboptimal in adults with CKD receiving care in the VA healthcare system. Interventions are needed to increase knowledge regarding the clinical importance of statin use in adults with non-dialysis dependent CKD.

Funding: Veterans Administration Support

* Model adjusted for: age, race, site, comorbidities, medications, proteinuria, eGFR, hemoglobin, PTH, FGF-23, BNP, Troponin T

There was no significant interaction for gender in this association, but the LVMI-HF association was stronger in persons without diabetes: per SD LVMI, HR([95%CI]) 1.3 [1.1-1.6] with diabetes and 2.2 [1.6-2.8] without diabetes (p for interaction=0.01).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Among persons with CKD and without history of CVD, LVMi is a strong predictor of incident HF and death, even after adjustment for major cardiovascular biomarkers.

Funding: NIDDK Support

TH-OR119
Prevalence and Prognostic Significance of Apparent Treatment Resistant Hypertension in Chronic Kidney Disease: A Report from the CRIC Study

George Thomas,1 Dawei Xie,2 Hisiang-Yu Chen,3 Amanda Hyre Anderson,2 Lawrence J. Appel,4 Carolyn S. Breckin,1 Paul E. Drawz,5 John M. Flack,6 Edgar R. Miller,7 Susan P. Steigerwald,1 Raymond R. Townsend,2 Matthew R. Weir,2 Jackson T. Wright,1 Mahboob Rahman.1 1Cleveland Clinic, Cleveland, OH; 2CRIC Investigators.

Background: While hypertension is common in patients with chronic kidney disease (CKD), the association between apparent treatment resistant hypertension (ATRH) and clinical outcomes is not well studied in this population.

Methods: We analyzed data on 3367 hypertensive participants in the Chronic Renal Insufficiency Cohort (CRIC) to determine prevalence, associations, and clinical outcomes of ATRH in non-diabetic CRIC patients. ATRH was defined as blood pressure (BP) > 140 mm Hg on ≥3 antihypertensives, or use of ≥4 antihypertensives with BP at goal baseline.

Results: The prevalence of ATRH was 40.4%. Older age, male gender, black race, diabetes, and higher BMI were independently associated with significantly higher odds of having ATRH. Compared to participants without ATRH, after adjustment for common covariates, participants with ATRH had a higher risk of clinical events (composite of myocardial infarction (MI), stroke, peripheral arterial disease (PAD), congestive heart failure (CHF), and all-cause mortality) (HR [95% CI]): 1.38 [1.22, 1.56]; renal events (ESRD or 50% decline in GFR) (1.28 [1.11, 1.46]); CHF (1.77 [1.44, 2.16]); and all-cause mortality (1.24 [1.06, 1.45]). The subset of participants with ATRH and BP goal on ≥4 medications also had significantly higher risk of composite of MI, stroke, PAD, CHF, and all-cause mortality (HR [95% CI]) (1.30 [1.2, 1.51]) and CHF (1.68 [1.32, 2.12]) compared to those without ATRH. The association between ATRH and CHF and renal outcomes differed depending on baseline GFR interaction (p<0.05). ATRH was associated with a significantly higher risk for CHF and renal events only among those with GFR ≥90 mL/min/1.73 m².

Conclusions: Our findings show that ATRH is common, and associated with high risk of adverse outcomes in a cohort of patients with CKD.

Funding: NIDDK Support, Other NIH Support - Perelman School of Medicine at the University of Pennsylvania Clinical and Translational Science Award NINHCACTUS UL1TR000003, Johns Hopkins University Ul1 TR-000424, University of Maryland GCRC M01 RR-16500, Clinical and Translational Science Collaborative of Cleveland, Ul1TR00439 from the National Center for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and NIH roadmap for Medical Research, Michigan Institute for Clinical and Health Research (MICHIR) Ul1TR00433, University of Illinois at Chicago CTSA UL1RR028979, Tulane University Translational Research in Hypertension and Renal Biology P30MO10337, Kaiser Permanente NCI-NH S URF UCRTS U11ULTR-024131

TH-OR120
Aryl Hydrocarbon Receptor Is Activated during Chronic Kidney Disease and Is Associated with Mortality

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Background: Aryl hydrocarbon receptor (AhR) is a transcription factor activated by numerous pollutants, like dioxin. Its activation is associated with cardiovascular risk. In CKD, AhR is activated in vivo in patients with CKD. Serum AhR and its targets were measured in 2466 CRIC subjects. Cox proportional hazards models were used to examine the association between biomarker concentrations indexed to urinary creatinine and death.

Methods: We show for the first time that endogenous Klotho is expressed in human heart. To may associated with high risk factors of CKD and cardiovascular disease, the major risk factor for patients with CKD. Emerging evidence suggests that fibroblast growth factor 23 (FGF23) is associated with both kidney function and cardiovascular events in ESRD patients. Klotho and fibroblast growth factor receptor (FGFR) serve as co-receptors for FGF23. We previously showed that endogenous Klotho is expressed in human heart, and that Klotho is a state of Klotho deficiency, but whether human heart expresses Klotho and whether Klotho levels is correlated with kidney function or cardiac fibrosis in CKD patients is unknown.

Methods: Human atrial appendage specimens were collected during cardiac surgery from individuals with and without CKD. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation. Klotho was defined as a reduction in Klotho (≤29% and ≤30% in the lowest (Q1) Klotho/Cr value <66.1 pg/mL q; Q1 Klotho/Cr ≥2.6 ng/mL q) in the highest quintile of Klotho/Cr levels (Q5 Klotho/Cr >12.2 pg/mL q; Q5 Klotho/Cr ≥11.7 pg/mL q). Klotho/Cr was associated with death in the continuous analysis only [HR per log SD increase of Klotho/Cr=1.38 (1.22,1.56)]; renal events (ESRD or death [HR per log SD increase of Klotho/Cr=1.28 (1.11,1.46)]; CHF (1.77 [1.44,2.16]); and all-cause mortality (1.24 [1.06,1.45]). The subset of patients with ATRH and BP goal on ≥4 medications also had significantly higher risk of composite of MI, stroke, PAD, CHF, and all-cause mortality (HR [95% CI]) (1.30 [1.2, 1.51]) and CHF (1.68 [1.32, 2.12]) compared to those without ATRH. The association between ATRH and CHF and renal outcomes differed depending on baseline GFR interaction (p<0.05). ATRH was associated with a significantly higher risk for CHF and renal events only among those with GFR ≥90 mL/min/1.73 m².

Conclusions: Our findings show that ATRH is common, and associated with high risk of adverse outcomes in a cohort of patients with CKD.

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

min/1.73m

independent of eGFR and UPCR. Furthermore, cTNFRs could be relevant predictors for

years. 261 participants (24.2%) had DM. The mean serum creatinine was 1.9 ±

on review of hospital records and yearly electrocardiograms.

who had baseline FGF23 measurements. For longitudinal time-to-incident AF analyses,

longitudinal analyses of 3879 participants in the Chronic Renal Insufficiency Cohort Study

AF.

failure, and eGFR. When FGF23 was expressed in quartiles or in models that censored

proportional hazards models, elevated baseline FGF23 was a risk factor for incident AF

and in quartiles was associated with greater prevalence of AF (Table 1). Over a median

RU/ml). In multivariable logistic regression models, higher FGF23 expressed continuously

after adjustment for clinical covariates, such as UPCR, eGFR, and cTNFRs level, than those without CVD. In

duration of 4 years, 51 patients experienced CVD event. Participants with CVD were older

and had lower eGFR level, higher SBP, higher cTNFRs level than those without CVD. In

cox proportional hazard analyses, cTNFR1 (HR 1.907, 95% CI 1.025-3.550, p value=0.0042) and cTNFR2 (HR 2.271, 95% CI 1.269-4.065, p value=0.006) predicted risk for CVD even

for CVD patients.

Background: Levels of fibroblast growth factor 23 (FGF23) are elevated in chronic kidney disease (CKD) and are strongly associated with cardiovascular disease and mortality. Atrial fibrillation (AF) is a common complication in CKD that is associated with poor outcomes, but whether FGF23 is an independent risk factor for AF in CKD is unknown.

Methods: We tested the associations of FGF23 with AF in cross-sectional and longitudinal analyses of 3879 participants in the Chronic Renal Insufficiency Cohort Study who had baseline FGF23 measurements. For longitudinal time-to-incident AF analyses, we excluded the 660 individuals with AF at baseline. Incident AF was adjudicated based on review of hospital records and yearly electrocardiograms.

Results: Mean estimated glomerular filtration rate (eGFR) was 44.3 ± 15.0 ml/

min/1.73m² and median eGFR value was 43 RU/ml (interquartile range 96, 239 RU/ml). In multivariable logistic regression models, higher FGF23 expressed continuously and in quartiles was associated with greater prevalence of AF (Table 1). Over a median follow up of 7 years, 248 incident AF events occurred. In multivariable-adjusted Cox proportional hazards models, elevated baseline FGF23 was a risk factor for incident AF (Table 2). These associations remained significant across strata of sex, race, prior heart failure, and eGFR. When FGF23 was expressed in quartiles or in models that censored individuals at end-stage renal disease onset (loss of 55 incident AF events), FGF23 was no longer associated with incident AF.

FR-OR001

Effects of Cyclosporine on Renal Handling of Divalent Cations in Claudin 16-Deficient Mice

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1Anatomy, Charité-Universitätsmedizin, Berlin, Germany; 2Physiology, Charité-Universitätsmedizin, Berlin, Germany; 3Pediatric Nephrology, Charité-Universitätsmedizin, Berlin, Germany; 4Vegetative Physiology, Charité-Universitätsmedizin, Berlin, Germany.

Background: Calcineurin inhibitors tacrolimus and cyclosporine are instrumental for immunosuppression after organ transplantation but cause substantial renal side effects including hypomagnesemia and hypercalcuria. The tight junction protein Claudin 16 (Cldn16) mediates paracellular reabsorption of divalent cations along the cortical thick ascending limb and has been implicated in the adverse effects of cyclosporine. We have compared effects of cyclosporine in wild type (WT) and Cldn16-deficient (Cldn16/-) mice.

Methods: Mice received cyclosporine (25 mg/kg) for 7 days and their kidney performance was analysed in metabolic cages. Expression of distal transport proteins has been studied by quantitative PCR and immunoblotting.

Results: Physiological analysis revealed baseline hypomagnesemia and hypercalcuria in Cldn16/-/- mice. Administration of cyclosporine induced marked hypomagnesemia in WT mice but did not significantly alter plasma magnesium levels in Cldn16/-/- mice. In contrast, cyclosporine-induced increase in urinary calcium was significantly greater in Cldn16/-/- mice compared to WT controls along with more pronounced decrease of plasma calcium levels in Cldn16/-/- mice. Cyclosporine stimulated distal sodium transporters leading to sodium retention in both genotypes.

Conclusions: In sum, our data corroborate the pivotal role of Cldn16 in the renal magnesium and calcium handling and suggest that Cldn16 may be involved in the cyclosporine-induced renal magnesium loss and hypomagnesemia, since genetic deletion of Cldn16 prevented these effects. In contrast, the strong manifestation of cyclosporine-induced hypercalcuria in Cldn16/-/- mice suggests that cyclosporine may affect transcellular calcium reabsorption pathways rather than the Cldn16-mediated paracellular transport.

FR-OR002

Ogr1 and Acid-Induced Hypercalcuria

Pedro Henrique Imenez Silva,1 Kessara Chan,1 Marie-Gabrielle Ludvig,1 Jürg Andreas Gasser,2 Timothy R. Arnett,3 Olivier Bonny,1 Klaus Seuwen,1 Carsten A. Wagner,1

1Northwestern Univ of Chicago, Chicago, Illinois, USA; 2Novartis Insts for Biomedical Research, Basel, Switzerland; 3Dept of Cell and Developmental Biology, Univ College London, London, United Kingdom; 4Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland.

Background: The ovarian cancer G protein-coupled Receptor 1 OGR1 (GPR68) is an extracellular proton activated GPCR that stimulates inositol triphosphate (IP3) production and increases intracellular Ca2+ levels. However, the physiological roles of OGR1 are not well established. In this work we aimed to identify the roles of OGR1 in acid-base and mineral balance.

Methods: Wild type (OGR1+/+) and an OGR1 mice-deficient model (OGR1 -/-) were subjected to metabolic acidosis (260 mM NH4Cl) or non-acidotic control condition for 12 h. The wild type and basic physiological parameters were collected from blood and urine and analysed. Several organs were isolated such as kidneys, intestine, brain, heart, etc. in order to extract RNA and perform RT-PCR/real time PCR. Kidneys were also used for protein extraction/ western blotting.

Results: OGR1 mRNA was found in many organs including kidney where mRNA was detected in all nephron segments. No acid-base modifications were observed in OGR1-/- mice, except for a higher plasma pH in the 1 day metabolic acidosis group (7.20 ± 0.04 vs 7.12 ± 0.03, p=0.05). As was expected, metabolic acidosis caused an increase in calcium and magnesium excretion in OGR1+/+ mice, but this was not observed in OGR1-/- mice. The mRNA levels of proteins involved in Ca2+ and Mg2+ reabsorption like Calbindin D28k, TRPV5/6, TRPM6 and Claudins 16 and 19 were not altered in OGR1-/- mice. The protein expression of TRPV5, the main apical distal convoluted tubule route for calcium, was 2.4 - fold increased (p=0.01) in OGR1-/- under metabolic acidosis which may explain the diminished Ca2+ excretion in these mice.

Conclusions: OGR1 is involved in the hypomagnesemia and hypercalcuria developed during metabolic acidosis, by a mechanism involving the Ca2+ channel, TRPV5. Funding: Government Support - Non-U.S.

FR-OR003

Conditional Nfat5 Knockout Causes Impaired Urinary Concentrating Ability with Renal Diabetes Insipidus and Hypernatremia without Renal Medullary Injury

Christoph Kueper,1 Franz Xavier Beck,2 Zoran Popovic,2 Hennayun-Josef Groene,2 Bernhard K. Kriemler,3 Wolfgang Neuhofer1

1Cellular Physiology, Univ of Munich, Munich, Germany; 2Molecular Pathology, German Cancer Research Inst, Heidelberg, Germany; 3Div of Nephrology, Univ Hospital Mannheim, Mannheim, Germany.

Background: This study addressed the effects of inducible deletion of Nfat5 in adult mice on the expression of components of urinary concentration, i.e. AQP-2, CIC-K1, bartin, and UT-A1. In parallel, Nfat5-depended osmoprotective genes AR, HSP70, and others were determined along with renal functional, morphological, and systemic parameters.

Methods: Mice with tamoxifen-inducible deletion of Nfat5 were established. At the age of 3-4 weeks, conditional Nfat5 KO mice or control animals were fed with a diet

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

Underline represents presenting author.

31A
FR-OR004

Effect of Concurrent P2Y2 Receptor Deletion and P2Y12 Receptor Blockade on Lithium-Induced Nephrogenic Diabetes Insipidus in Mice

Yue Zhang, Kristina M. Heiney, Bellamkinadora K. Kishore. Internal Medicine, Univ of Utah & VA Med Ctr, Salt Lake City, UT.

Background: Chronic lithium (Li) administration for bipolar disorder causes nephrogenic diabetes insipidus (NDI), characterized by polyuria, natriuresis and kaliuresis, resulting in a debilitating condition. Previously we reported that mice lacking ATP/UTP-activated P2Y2 receptor are significantly, but not completely resistant to Li-induced polyuria. Recently in a mouse model we observed that pharmacological blockade of ADP-activated P2Y12 receptor offers near complete amelioration of Li-induced polyuria. However, there were differences between these two approaches in terms of natriuresis, kaliuresis and blood Li levels. Hence, we tested the concurrent effect of both in mice.

Methods: Groups (n = 5 to 7) of age-matched adult wild type B6D2 (WT) and syngeneic P2Y2-R knockout (KO) mice were fed Li-added diet (40 mmol/Li/kg food) ad libitum, with or without administration of clopidogrel bisulfate (CLPD, 80 mg/kg bw/day) in drinking water for 14 days and euthanized. Twenty-four hour urine samples were collected prior to and toward the end of the experimental period. Blood samples were collected for electrolytes and blood Li.

Results: Compared to Li-fed WT mice: (i) Li-fed KO mice had ~50% less polyuria associated with significant amelioration of Li-induced natriuresis and kaliuresis; and (ii) Li-fed WT mice treated with CLPD had near complete amelioration of polyuria, but had no effect on Li-induced natriuresis and kaliuresis. Interestingly, Li-fed KO mice concurrently treated with CLPD showed significant amelioration of natriuresis and kaliuresis, in addition to almost complete suppression of polyuria. P2Y2-R deletion had no effect on blood Li levels, whereas P2Y12-R blockade caused modest, but significant increase in blood Li levels. However, the concurrent approach neutralized the effect of P2Y2-R blockade on blood Li levels.

Conclusions: Our results demonstrate that concurrent blockade of P2Y2 and P2Y12 receptors has the potential for better outcomes in amelioration of Li-induced NDI without causing a rise in blood Li levels. By proper optimization of CLPD dose, it should be possible to achieve better control of all parameters of NDI.

Funding: Veterans Administration Support

FR-OR005

The V-ATPase B1 Subunit B1 Polymorphism p.E161K Is Associated with Impaired Urinary Acidification in Recurrent Stone Formers

Daniel G. Fuster,1,2 Nasser Dhayat,1,3 Giuseppe Albano,1,3 Andreas Pasch,1,3 Bruno Vogt,1,3 Orson W. Moe,3 1Nephrology, Hypertension and Clinical Pharmacology, Univ Hospital of Bern, Bern, Switzerland; 2Div of Nephrology, UT Southwestern Medical Center, Dallas, TX; 3Dept of Clinical Research, Univ of Bern, Bern, Switzerland.

Background: Mutations in the V-ATPase B1 subunit gene ATP6V1B1 cause autosomal recessive distal renal tubular acidosis. We previously identified a single nucleotide polymorphism (SNP) in the human V-ATPase B1 subunit (c.481G>A; p.E161K) that displayed greatly diminished pump function in vitro.

Methods: To investigate the impact of this p.E161K SNP on urinary acidification in vivo, we conducted a genotype-phenotype analysis of recurrent stone formers in the Dallas and Bern kidney stone registries.

Results: 32 of 555 (5.77%) of the patients examined were heterozygous for the p.E161K SNP, the remaining 523 patients (94.23%) carried two wild-type alleles. Adjusted for sex, age, BMI and dietary acid and alkali intake, p.E161K SNP carriers had a tendency for higher urinary pH under a random diet (6.31 versus 6.09; p = 0.089). Under an instructed low calcium and sodium diet, urinary pH was higher in p.E161K SNP carriers (6.55 versus 6.005; p = 0.005). Kidney stones of p.E161K carriers were significantly more likely to contain calcium phosphate than stones of wild-type patients. In acute ammonium chloride loading, p.E161K carriers displayed a higher trough urinary pH (5.34 vs 4.89; p = 0.01) than wild-type patients. 14.58% of wild-type patients and 52.38% of p.E161K carriers were unable to acidify their urine below 5.3 and thus had incomplete distal renal tubular acidosis.

Conclusions: In summary, our data indicate that recurrent stone formers with the p.E161K SNP, a single nucleotide polymorphism (SNP) exhibiting a urinary acidification deficit with an increased prevalence of calcium phosphate containing kidney stones. The burden of E161K heterozygosity may be a forme fruste of distal RTA.

Funding: Government Support - Non-U.S.

FR-OR006

Proximal Tubule-Specific Glutamine Synthetase Deletion Alters Basal and Acidosis-Stimulated Renal Ammonia Excretion

Hyun-Wook Lee.1 Gunars Osis,1 Mary E. Handlogten,1 Jill W. Verlander,1 I. David Weiner.2 1Renal Div, Univ of Florida, Gainesville, FL; 2Nephrology and Hypertension, NF/SCVHIS, Gainesville, FL.

Background: Glutamine synthetase (GS) mediates the recycling of NH3, and glutamate back to glutamine. In the kidney, the majority of GS is expressed in the proximal tubule where it may decrease net ammoniagenesis and limit ammonia available for net acid excretion. This study’s purpose was to determine the role of proximal tubule (PT) GS in normal acid-base homeostasis and in the renal response to metabolic acidosis.

Methods: We generated mice with proximal tubule-specific glutamine synthetase deletion (PT-GS-KO) by using Cre-loxP techniques. PT-GS-KO mice had loxp sites flanking exons 1 and 7 (GSαβ) and expressed Cre-recombinase under control of the phosphoenolpyruvate carboxykinase (PEPCK) promoter (PEPCK-Cre). Control (C) mice were GSαβ−/− but PEPCK-Cre normal.

Results: Immunoblot analysis showed PT-GS-KO decreased GS protein expression by 47 ± 4% in the cortex and 89 ± 1% in the outer stripe of the outer medulla; immunohistochemistry showed efficient and specific PT GS deletion with occasional residual GS-positive cells. Under basal conditions, proximal tubule GS deletion increased urinary ammonia excretion: 102 ± 10 vs 75 ± 8 mmol/day in PT-GS-KO and C mice, respectively, consistent with our hypothesis that GS deletion increases net ammoniagenesis and thereby increases ammonia excretion. However, ammonia excretion after acid loading for 7 days increased similarly in PT-GS-KO and C mice during the first 4 days of acid loading but on days 5-7 was significantly less, by ~33%, in PT-GS-KO as compared to C mice. In acid-loaded mice, adaptive responses to PT-GS-KO included increased expression of cortical phosphate-dependent glutaminase (PDG), PEPCK, and the glutaminase transporter, SN1, compared to C.

Conclusions: We conclude: 1) proximal tubule GS expression contributes to both basal and acidosis-stimulated renal ammonia excretion; and, 2) elimination of the contribution of proximal tubule GS downregulation to enhance ammoniagenesis during acid-loading is partially compensated for by adaptive increases in PDG, PEPCK and SN1 expression.

Funding: NIDDK Support, Veterans Administration Support

FR-OR007

The B1 H+-ATPase (AtP6v1b1) Subunit Is Required for Non-Type A Intercalated Cell Function and Defense against Alkalosis

Soline Bourgeois, Jana Kovackova, Carsten A. Wagner. Inst of Physiology, Univ of Zurich, Zurich, Switzerland.

Background: The final urine pH is fine-tuned by type A and non-type A intercalated cells (IC) along the connecting tubule (CNT) and collecting duct (CCD) involving the action of vascular H+-ATPases. Mutations in the B1 subunit of H+-ATPase (ATP6V1B1) in man cause distal renal tubular acidosis due to its importance in acid secretion by type A-ICs. Non-type A-IC also express the vascular H+-ATPases containing the B1 subunit isoform at their luminal and basolateral plasma membrane together with the luminal Cl−/HCO3− exchanger pendrin. The main function of non-type A-ICs is the excretion of bicarbonate during metabolic alkalosis. However, the function of the B1 isoform in non-type A-ICs has remained elusive.

Methods: We studied the metabolic behaviour of B1 deficient mice during an alkali load induced by a 4-day desoxycorticosterone (DOCA, 2 mg/mouse s.c) and 0.28M NaHCO3 treatment in the drinking water.

Results: Induction of metabolic alkalosis resulted in a more pronounced alkalosis in B1 deficient mice associated with increased blood bicarbonate, hypokalemia, and hypochloremia. Furthermore, while, pendrin localization was preserved, total pendrin expression was reduced and pendrin activity was altered in B1 deficient mice whereas the relative abundance of pendrin expressing cells was increased. In parallel, H+-ATPase activity in non-type A-IC from B1 deficient mice was also decreased. Finally, the E and A subunits of H+-ATPase did not associate with the basolateral domain of B1 deficient non-type A-ICs leading to the non-association of V, domain while basolateral expression of A4 subunit, part of the V0 domain, was not disrupted.

Conclusions: Thus, the B1 subunit is required for the formation of a complete and functional basolateral H+-ATPase complexes and is critical for normal non-type A-IC function cells during alkalosis.

Funding: Government Support - Non-U.S.
Comparing the Effect of Combination of Acetazolamide and Hydrochlorothiazide Followed by Furosemide versus Combination of Hydrochlorothiazide and Furosemide Followed by Furosemide in Treating Refractory Edema Associated with Nephrotic Syndrome: A Randomized, Double-Blind Trial

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Background: The CI/HCO3 exchange pendrin and Na+/cotransporter (NCC) play important role in distal tubule salt reabsorption. A recent animal study has shown simultaneous inhibition of pendrin and NCC by acetazolamide and hydrochlorothiazide, respectively results in significant diuresis. The aim of this study was to evaluate the efficacy of combination of acetazolamide and hydrochlorothiazide followed by furosemide in treatment of refractory edema associated with nephrotic syndrome.

Methods: In this randomized, double-blind trial we enrolled 20 patients with nephrotic syndrome who had refractory edema despite receiving maximum furosemide dose. All patients had GFR<60 mL/min. 1.73 m2. After a 2-week washout period when patients received no diuretics, they were randomly assigned to 2 equal groups. Group 1 received 250-mg oral acetazolamide and 50-mg oral hydrochlorothiazide daily for 1 week. Group 2 received 40 mg oral furosemide and 50-mg oral hydrochlorothiazide daily for 1 week. Then patients in both groups received 40-mg oral furosemide daily for 2 weeks. The primary outcome was the amount of change in weight from baseline to the end of the treatment phase.

Results: Although weight reduction occurred in both groups, it was significantly higher in group 1 as compared to group 2 at the end of first week (-1.4 ±0.02 kg vs. -0.65 ±0.41 kg; p=0.001) and of third week of treatment phase (-3.6 ±0.94 kg vs. -1.15 ±0.47 kg; p=0.001). Increase in 24-hour urine volume was also significantly higher in group 1 at the end of treatment phase. Serum Na and K levels were in reference range in all the patients during the treatment phase.

Conclusions: Combination of acetazolamide and hydrochlorothiazide followed by furosemide may be a novel and safe diuretic therapy in refractory edema associated with nephrotic syndrome.

Tissue Na+ in Chronic Kidney Disease and Effect of Renal Transplantation on Na+ Stores

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Background: Diminished kidney function as occurs in Chronic Kidney Disease (CKD) causes salt sensitive hypertension. By using Na-Magnetic Resonance Imaging (Na-MRI) technology we recently could detect Na+ storage in humans, which was associated with hypertension. Whether impaired Na+ excretion in CKD results in tissue Na+ accumulation and if kidney transplantation affects tissue Na+ stores is not known.

Methods: We recruited 32 patients with CKD Stage 4 and 5 prior to preemptive living donor transplantation or dialysis treatment and 30 age- and gender-matched control subjects. Na-MRI at 3Tesla was used to quantify muscle and skin Na+. We determined plasma [Epo] levels and Epo glycosylation patterns in 19 moderate non-dialyzed CKD patients (stage III-IV) and compared these to values obtained in healthy volunteers, rEPO and umbilical cord plasma (derived from Epo treated newborns).

Results: Despite higher Epo levels (15.75 (11.3 - 24.2) IU/L), CKD patients were moderately anemic ([Hb]=113 ± 11 g/dL). Half of the patients presented higher Epo levels than expected from the calculated values corrected for anemia. Glycosylation was increased in CKD patients (49 ± 12 %; measured as percent migrated isoform, PMI,open bars) when compared to healthy controls (8.4 (7.56 - 8.98) IU/L, p<0.01). CKD patients were moderately anemic ([Hb]=113 ± 11 g/dL). Half of the patients presented higher Epo levels than expected from the calculated values corrected for anemia. Glycosylation was increased in CKD patients (34 ± 12 %; measured as percent migrated isoform, PMI,open bars) when compared to healthy controls (8.6 ± 1 %; p<0.01, black bars) and rEPO samples (1.4:1.4<0.01, hatched bars), whereas the pattern did not differ from umbilical cord plasma (55 ± 10 %, p>0.05, lined filled bars) which is known to contain mainly liver derived Epo.

Conclusions: Our findings suggest pendrin inhibition as a novel approach to amplify the diuretic action of loop diuretics. Such combination therapy might enhance diuresis and salt excretion for treatment of hypertension and edema, including diuretic-resistant edema.

Funding: NIDDK Support

Increased Synthesis of Liver Erythropoietin in Patients with Chronic Kidney Disease

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Background: Anemia of chronic kidney disease (CKD) is thought to be related to impaired renal erythropoietin (Epo) production. Epo may be synthesized by the kidney but also by the liver in humans. Epo glycosylation pattern is dependent on its synthesizing cell, thereby indicating its origin. Here we tested the hypothesis that synthesis of Epo from non-kidney cells increases to compensate for insufficient renal Epo production in patients with moderate CKD.

Methods: We determined plasma [Epo] levels and Epo glycosylation patterns in 19 moderate non-dialyzed CKD patients (stage III-IV) and compared these to values obtained in healthy volunteers, rEPO and umbilical cord plasma (derived from Epo treated newborns).

Results: Despite higher Epo levels (15.75 (11.3 - 24.2) IU/L) compared to healthy controls (8.4 (7.56 - 8.98) IU/L, p<0.01), CKD patients were moderately anemic ([Hb]=113 ± 11 g/dL). Half of the patients presented higher Epo levels than expected from the calculated values corrected for anemia. Glycosylation was increased in CKD patients (34 ± 12 %; measured as percent migrated isoform, PMI,open bars) when compared to healthy controls (8.6 ± 1 %; p<0.01, black bars) and rEPO samples (1.4:1.4<0.01, hatched bars), whereas the pattern did not differ from umbilical cord plasma (55 ± 10 %, p>0.05, lined filled bars) which is known to contain mainly liver derived Epo.

Conclusions: These results suggest that moderate CKD patients exhibit preserved Epo levels despite declining renal function 2) this may be achieved by increasing liver Epo synthesis 3) and Epo originating from liver seems less erythropoietic.

Funding: Government Support - Non-U.S.

Small-Molecule Inhibitors of Pendrin (Slc26a4a) Augment the Diuretic Action of Furosemide


Background: Pendrin (Slc26a4a) is a chloride/bicarbonate exchanger expressed in type-B and non-A, non-B intercalated cells of connecting tubule and cortical collecting duct, where it mediates Cl absorption and modulates ENaC function by changing luminal HCO3 concentration. Under normal conditions, pendrin has a minimal role in renal salt metabolism; pendrin knock-out mice and patients with Pendred Syndrome (caused by loss-of-function Slc26a4a mutations) do not manifest salt wasting. Previous studies demonstrated that double knock-out of pendrin with other renal salt transporters causes increased urine output, volume depletion and salt wasting. It has been hypothesized that pendrin may attenuate diuretic-induced salt loss.

Methods: A cell-based high-throughput screen was established to identify pendrin inhibitors involving fluorescence plate reader measurement of chloride influx in epithelial cells stably coexpressing human pendrin and a chloride-sensing fluorescent protein. Screening of ~30,000 drug-like small molecules produced three chemical classes of pendrin inhibitors with IC50 down to 1 μM. The pendrin inhibitors were administered to mice intraperitoneally (10 mg/kg) either alone or with low (5 mg/kg), intermediate (10 mg/kg) or high (20 mg/kg) dose furosemide. Urine was collected in metabolic cages for 3 hours after injection, and blood was collected afterwards.

Results: In furosemide-treated mice pendrin inhibitors of two chemically different classes produced an approximate 40% increase in urine output and osmolar clearance, without changing urine osmolality. The compounds had no effect in mice when administered alone. LC/MS analysis showed predicted therapeutic inhibitor concentrations in blood and urine.

Conclusions: Our findings suggest pendrin inhibition as a novel approach to amplify the diuretic action of loop diuretics. Such combination therapy might enhance diuresis and salt excretion for treatment of hypertension and edema, including diuretic-resistant edema.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-OR012

 Associations Among Erythroferrone and Biomarkers of Erythropoiesis and Iron Metabolism, and Treatment of Long-Term Erythropoiesis-Stimulating Agents in Patients on Hemodialysis  
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 Background: The present study aimed to identify associations between erythroferrone (ERF), a regulator of hepcidin 25, and biomarkers of erythropoiesis and iron metabolism. We also investigated the effects of the erythropoiesis-stimulating agents (ESA), continuous erythropoietin receptor activator (CERA) and darbepoetin-α (DA), on ERF production in patients on hemodialysis (HD).

 Methods: Blood samples were obtained from 59 patients before HD sessions on day 0 (baseline) for baseline cross-sectional analysis. Twenty patients who were injected with either CERA (N = 10) or DA (N = 10) at the end of the dialysis week (day 0), who were not iron-deficient (ferritin < 100 ng/mL and transferrin saturation < 20%) and had hemoglobin levels > 9 g/dL were selected from among the 59 patients. Blood was sampled serially before HD sessions on days 3, 5, 7 from patients on DA and on the same days and day 14 from those on CERA to assess impact of ESA on iron metabolism including ERF.

 Results: Levels of ERF correlated inversely with those of hepcidin 25 and ferritin, and positively with soluble transferrin receptor. The hepcidin 25:ERF ratio and hepcidin 25 levels positively correlated with ferritin levels. Levels of ERF significantly increased from day 3 of treatment with DA and CERA and decreased by days 7 and 14, respectively. Levels of hepcidin 25 were decreased by ESA in accordance as those of ERF increased.

 Conclusions: Erythroferrone might be associated with iron metabolism in patients on HD. Both DA and CERA increased levels of ERF that regulated hepcidin 25 and led to iron mobilization from body stores during erythropoiesis.

 FR-OR013

 Dynamics of ESA Resistance Index in Incident Hemodialfiltration and High-Flux Hemodialysis Patients  
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 Background: Hemodiafiltration (HDF), combining diffusion and convection, provides an efficient blood detoxification over a wide molecular weight range that may include erythropoietin inhibiting agents. Study aim: to compare ESA resistance index (ERI) in incident HDF and high-flux hemodialysis (HD) patients. ERI is the weekly weight-adjusted ESA dose (U/kg/week) divided by hemoglobin level (g/dL).

 Methods: 20,694 incident patients (7,674 HDF; 13,020 HD,) from 436 NephroCare clinics in 20 countries with ≥6 mths follow-up were studied between January 1, 2007 and December 31, 2013. Baseline (BL) was 6 mths after dialysis initiation; follow-up was 3.1±0.69 yrs. Exclusion criteria: BL presence of metastatic tumors, malnourishment (BMI <18.5 kg/m^2), treatment via catheter, age <18 years, less/more than thrice weekly dialysis, and missing ESA dose after BL. After propensity score matching to reduce bias by indication, a total of 6,568 patients (3,284 in each arm) remained.

 Results: At BL, HDF patients had a non-significant higher ERI than HD patients (7.43±2.2 vs 7.12±2.2 U/kg/g/dL) (p=0.06). ERI decreased by 0.087 U/kg/g/dL per mth in HDF patients and significantly less in HD patients (0.050 U/kg/g/dL per mth). The difference between both groups increased by 0.036 U/kg/g/dL per mth. At 8.4 mths of follow-up, ERI was lower in HDF patients compared to HD patients. The delta ERI for each time interval versus BL also reveals ERI change dynamics (Figure).

 Conclusions: ERI progressively decreased during the first 24 months on dialysis, but more sharply and to a great extent in the HDF group compared to the HD group. The dynamics of ERI change over the first year on dialysis may explain why previous studies encountered difficulties in recognizing ERI trends when various dialysis vintages are grouped together.

 FR-OR014

 Serum Ferritin Variations and Mortality in Incident Hemodialysis Patients  
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 Background: Previous studies on maintenance hemodialysis (MHD) patients have shown that higher serum ferritin may be associated with inflammation and higher mortality. Additional studies have shown that serum ferritin increase sharply in the first year of MHD and gradually increase over time. However, associations between changes in serum ferritin levels over the first 6 months of dialysis and mortality are unknown. We hypothesized that a rapid rise in serum ferritin is associated with higher risk of mortality.

 Methods: In a cohort of 93,996 incident MHD patients receiving treatment from a large dialysis organization during 2007-2011, we examined mortality associations of change in serum ferritin from baseline patient quarter (first 91 days from dialysis start) to subsequent quarters using Cox proportional hazard models. Models were adjusted for demographics, comorbidities, markers of the malnutrition and inflammation complex (MICS) and intravenous iron dose. Serum ferritin change was divided into five strata: (<-400, -400 to <-100, -100 to <100, 100 to <400, and ≥400 ng/ml over 3 months). Associations were examined across strata of baseline serum ferritin (<200, 200 to <500, 500 to <800 and ≥800 ng/ml).

 Results: Patients were 63±15 years old, 44% female, 32% African-American, and 60% diabetic. In patients with baseline serum ferritin ≥200 ng/ml, a rise in serum ferritin ≥400 ng/ml/quarter was associated with higher all-cause mortality during the 5-year follow-up compared with no change in serum ferritin (<100 to <100 ng/ml).
Conclusions: Rapid rise in serum ferritin levels >400 ng/ml/quarter during the first 6 months after MII initiation is associated with higher 3-year mortality in patients with elevated baseline serum ferritin. Studies evaluating the conditions influencing these serum ferritin changes and their associations with mortality are needed. 

Funding: NIDDK Support

FR-OR015
Decreasers ESA Dosage Can Be a Factor of the Increase in Ferritin Under the Administration of Ferric Citrate with Improving ESA Resistance Index

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Background: Ferric citrate (an iron based phosphate binder) controlled serum phosphorus with lower concentrations and reduced the doses for ESA and intravenous iron in HD patients. Also, serum ferritin concentrations had a tendency to increase (Phase 3 trial).

Methods: To explore potential factors associated with an increase in ferritin values, data from the 52-week phase3 clinical study in Japanese HD patients were analyzed by a mixed model for repeated measurement (MMRM) including variables that were selected based on the results of correlation, simple linear regression, and multiple regression analyses. In addition, ESA resistance index (ERI) was analyzed to determine factors which contribute to it based on the result from the MMRM.

Results: The factor of the increase in ferritin was associated with not only the dosage of ferric citrate but also the degree of decrease in ESA dosage (Q1< dosage was decreased in the course of study. Q1< to Q3> dosage was not changed. Q3< dosage was increased.).

In subjects whose ESA dosage was decreased in the course of the study, the ERI went lower by the administration of ferric citrate in spite of that initial dosage of ESA and ERI were higher than other subjects group.

Conclusions: Decreasing ESA dosage might increase serum ferritin level under the administration of ferric citrate with improving ERI.

Funding: Pharmaceutical Company Support - TORII PHARMACEUTICAL CO.

FR-OR016
Triferic Maintains Hemoglobin and Iron Balance Long Term: Open-Label Phase III Extension Studies


Background: The objective of the Phase 3 extension studies was to confirm the safety of Triferic administered via dialysate for up to 18 months of treatment and to assess hemoglobin and iron status.

Methods: Patients who completed the Phase 3 randomized controlled treatment studies (RCT) could continue in the open-label (OL) extension studies for up to 18 months of combined participation. In the OL extensions, patients received ESA according to their site protocol and IV iron could be administered for presumed development of iron deficiency. Results: Approximately 70% of patients completed the pivotal RCT and enrolled in the OL extension, providing a total of 412 patient-years of exposure to Triferic. Triferic administered long term (up to 18 months) reliably delivered iron with every treatment. Triferic administered via dialysate maintained Hgb while not increasing iron stores or increasing ESA doses. The safety profile was similar to that observed in the pivotal Phase 3 RCT studies. No anaphylaxis was observed in over 45,000 individual doses administered in this program.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

FR-OR017
Longer Sustained Reduction of Serum Hepcidin Level (Hep) During the Treatment of Anemia with Epoetin Beta Pegol (CERA) as Compared to Epoetin Beta (rEPO) in Predialysis Stage-5 CKD Patients

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Background: Efficient iron utilization is required in ESA-induced erythropoiesis in CKD patients, Hep being a key factor to modulate iron turn-over in this situation. In the present study, changes in Hep and the related iron markers were examined before and after CERA administration in comparison with rEPO in predialysis-naive stage 5 CKD patients.

Methods: Twenty-three patients were subjected to the study; age 70±13 [SD] y/o, m/ f=15:8, DM=10/13, rEPO 14±5 ml/min/1.73m2, HB 9.7±1.1 g/dL. They were assigned randomly to 2 groups, being treated with either rEPO (n=13) or CERA (n=10). Their baseline data were as follows; HB 9.8±1.0 (rEPO) vs. 9.6±1.3 (CERA) g/dL, serum iron (SFe) 75±25 vs. 77±17 mg/dL, TSAT 28±8 vs. 31±9 %, ferritin 129±117 vs. 173±91 ng/ml, albumin 3.7±0.5 vs. 3.6±0.6 g/dL, IL-6 3.2±2.8 vs. 3.8±2.3 pg/ml, hs CRP 1038±2539 vs. 1730±4191 ng/ml, and Hep 34±19 vs. 52±29 ng/ml, respectively. Hep was given in the morning, SFe and Hep were measured before and on the 2nd, 4th, 7th, 14th and 28th day. On the first day, circadian variation of SFe and Hep was evaluated. Hematological parameters, TSAT and ferritin were measured before and on the 28th day.

Results: Hep level was highest at 3 pm on the first day. HB rose significantly in both group in association with steep decrease in Hep in rEPO, being 34±19 to 7±18.5, and was returned to the baseline in 14 days. In CERA, Hep reduction was also observed but the trend was mild from 52±29 to 27±17 mg/dL on the 14th days. The decrease in Hep correlated significantly with the increase in reticuloocyte production index, a marker of erythropoietic output, in all patients (r=0.66, n=0.01). These changes were associated with the significant decrease in SFe.

Conclusions: CERA has a sustained suppressive effect on Hep, which might contribute to its longer erythropoietic activity via enhancing iron utilization.

FR-OR018
Clinical Pharmacology, Efficacy, and Safety of the Anti-hepcidin Spiegelmer Lexpetapend Pegol: A Pilot Trial

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Background: Elevated hepcidin is frequent in hemodialysis patients and contributes to ESA-resistant anemia. Inhibiting hepcidin may therefore reduce resistance to ESA therapy and improve anemia. The anti-hepcidin LRNA-Aptamer (Spiegelmer®) lexaptepid pegol binds and inactivates hepcidin and in development for treatment of anemia.

Methods: We studied the pharmacological effects on iron metabolism, on anemia, and the safety of lexaptepid in 109 healthy subjects and patients with myeloma/luphoma or on hemodialysis. A trial in dialysis patients with functional iron deficiency is ongoing.

Results: Lexpetapend increased iron concentrations and prevented the serum iron decrease after endotoxin challenge in healthy subjects. In patients with myeloma /lymphoma and functional iron deficiency, 2 doses/week of lexaptepid over 1 month increased hemoglobin by 1 g/dL in patients with low reticuloocyte Hb and high soluble transferrin receptor. In ESA-hyporesponsive dialysis patients, cross-over comparison with placebo showed increases in serum iron concentrations following lexaptepid administration, consistent with its anti-hepcidin action.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Neutrophil Gelatinase-associated Lipocalin (NGAL) Is Associated with Iron Status in Anemic Patients with Chronic Kidney Disease

Background: Neutrophil gelatinase-associated lipocalin (NGAL) is known as a biomarker of acute kidney injury and predictor of the progression of CKD. In addition, recent studies have shown that NGAL is associated with iron metabolism by binding siderophores, small molecules containing iron. We investigated whether serum NGAL levels are associated with iron status in CKD patients with anemia.

Methods: This study included 257 CKD patients [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m²] who had anemia at the time of study enrollment. Serum NGAL levels were measured by the eGFR and transferrin saturation (TSAT). TSAT (β = 0.370, P < 0.001) was independently associated with serum NGAL (TSAT), eGFR, albumin, uric acid, lipid profile, calcium, phosphate, and C-reactive protein (CRP) were assessed.

Results: The CKD patients with TSAT ≤ 30% had lower serum NGAL values than those with TSAT > 30% (274.9 ± 228.3 vs. 394.7 ± 232.2 ng/ml). In univariate analysis, serum NGAL correlated with eGFR (r = -0.367, P < 0.001), TSAT (r = -0.296, P < 0.001), and ferritin (r = 0.295, P < 0.001). In multivariate regression analysis, TSAT (β = -0.370, P < 0.001) was independently associated with serum NGAL in addition to CRP (β = -0.268, P < 0.001) and eGFR (β = -0.365, P < 0.001). However, ferritin lost its association with serum NGAL (β = 0.093, P = 0.132).

Conclusions: This study suggests serum NGAL is associated with iron status in anemic patients with CKD. Further studies are needed to demonstrate the role of NGAL in the assessment of iron deficiency and in the management of iron therapy for CKD patients.

FR-OR019

Safety and Hemoglobin Effect of Sotatercept, Administered Intravenously and Subcutaneously, for Maintenance of Hemoglobin in Hemodialysis Subjects: Interim Analysis of a Phase 2 Study

Methods: In part 1 of a 2-part phase 2 study, ESA-responsive ESKD/HD subjects with Hb between 10 and 12 g/dL were randomized to randomized open-label study to evaluate the safety and effectiveness of sotatercept (NCT03501612).Subjects were randomized to placebo or one of five sotatercept treatment groups: 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg. CKD-3 decreased renal tubular klotho levels and produced marked (10 fold) elevations in FGF23 levels. Inhibiting activin by an ActRIIA ligand trap surprisingly reduced osteoblast number and surfaces, decreased osteoclast numbers and eroded surfaces, increased bone formation rates (BFR) but a significant decrease in BFR/osteoblast. CKD-3 decreased renal tubular klotho levels and produced marked (10 fold) elevations in FGF23 levels. Inhibiting activin by an ActRIIA ligand trap surprisingly reduced osteoblast number and surfaces, decreased BFR but increased osteoclast numbers and eroded surfaces. MicroCT imaging showed that RAP-011 increased cortical bone thickness and cortical bone area compared to CKD-3. RAP-011 treatment did not affect hyperphosphatemia, PTH levels or FGF23 levels. Inhibiting activin signaling increased renal tubular klotho levels.

Conclusions: Activin is a critical factor in the pathogenesis of the CKD-MBD causing a loss of osteoblast function. A small molecule that targets activin signaling may be an effective treatment for CKD-MBD.

FR-OR020

Increase in Trabecular Bone Volume by Inhibition of GSK-3β in Uremic Mice

Methods: The present in vivo study was performed to determine whether inhibition of GSK-3β could increase bone volume in adenine-induced CKD mice. Wild type mice were divided into three groups. One group was fed a control diet (CNT) and the other two groups were fed a diet containing 0.2% adenine with or without lithium chloride (LiCl), a GSK-3 inhibitor; CKD and CKD-LiCl group. GSK-3β heterozygous knockout mice were also fed a diet containing 0.2% adenine (CKD-GSK-3β-/-). Bone and blood samples were collected after 6 weeks and trabecular (Tb) and cortical (Ct) bone were analyzed by micro-computed tomography.

Results: CKD mice developed azotemia, hyperphosphatemia, and secondary hyperparathyroidism, followed by a decrease in Ct bone thickness and no change in Tb bone volume after 6 weeks. Treatment with LiCl increased Tb bone volume, accompanied by polyuria and polydipsia. Tb bone volume increased in CKD-GSK-3β-/- mice compared with CNT and CKD mice. There were no significant differences in kidney function, hyperphosphatemia, hyperparathyroidism, and Ct bone thickness among three CKD groups.

Conclusions: GSK-3 inhibition increased Tb bone volume in adenine-induced uremic mice.
Sclerostin Knock-Out Protects from Uremia-Induced Cortical Bone Loss in a Murine Model of Chronic Renal Failure: Marie Celka,1 Diego Michael Parada Rodriguez,1 Stefanie Pichler,1 RodrigoMarculescu,1Inka Kramer,1 Michaela Kneissl,1Thomas Gross,2 Andreas G. Reisinger,3 DieterPahrt,4 Marie-Claudie Faugere,4Martin Haas,3 Hartmut Malliche.1 1Div of Nephrology & Dialysis, Dept of Medicine III, Medical Univ Vienna, Vienna, Austria; 2Musculoskeletal Imaging Research Group, The Univ of Queensland, Brisbane, Australia; 3Dept of Nephrology, Bone and Mineral Metabolism, Dept of Medicine, Medical Univ Vienna, Vienna, Austria; 4Div of Nephrology, Bone and Mineral Metabolism, Dept of Internal Medicine, Univ of Kentucky, Lexington, KY; 5Dept of Laboratory Medicine, Medical Univ Vienna, Vienna, Austria.

Background: Renal osteodystrophy (ROD) affects the majority of patients with advanced chronic kidney disease (CKD) and is characterized by progressive bone loss. This study investigates the effect of sclerostin-knockout mice in a murine model of CKD.

Methods: Severe CKD was surgically induced in sclerostin-knock-out (mice (SOST-KO-CKD) and wild-type (WT-CKD). Mice with normal kidney function serve as controls (SOST-KO-CTRL, WT-CTRL). After 3 months of CKD, blood was drawn and vertebral and tibia were collected for histomorphometric and µCT analyses.

Results: Cortical thickness (Ci.Th) of the tibia was significantly higher in Sost-k0-CKD mice compared to wt-CKD mice (p<0.001). WT-CKD mice had lower Ci.Th compared to WT-CTRL (p<0.05), whereas no significant differences in Ci.Th were found between SOST-KO-CKD and SOST-KO-CTRL groups. Compared to WT-CKD mice, SOST-KO-CKD mice had higher trabecular number (p<0.001) and trabecular thickness (p<0.001) and lower trabecular separation (p<0.001). Minimal steroid dose, but not PTH level was identified as a significant correlate.

Conclusions: Sclerostin knock-out leads to increased bone mass and improved microarchitectures but does not alter osteoid mineralization in a murine model of CKD. Inhibition of sclerostin may be a promising approach to prevent bone loss in CKD.

Funding: Clinical Revenue Support

FR-OR203

Vascular Calcification Is Mediated by ERK-Dependent Upregulation of Pitinfraca1/NADPH/MR Activity: Victor Manuel Barrientos,1 Néstor Aburzúa,1 Diego Varela,1 Rodrigo Alzamora, Luis F. Michéa.1 1ICBM, Univ de Chile, Chile; 2Milennium Inst on Immunology and Immunotherapy, Chile.

Background: Vascular calcification (VC) is a major mortality risk factor in patients with chronic kidney disease. During VC, vascular smooth muscle cells (VSMC) of the tunica media transdifferentiate into osteoblast-like cells. High extracellular phosphate (HP) promotes VC through the induction of the sodium-dependent phosphate cotransporter (Pit1) activity, increased NADPH oxidase activity (Nox1) and the expression of osteochondrogenic factors (OCF). Recent studies indicate that antagonists of the mineralocorticoid receptor (MR) ameliorate VC. The present study uses Pit1 knock-out (KO) mice and demonstrates whether HP facilitates VC and whether Pit1 modulates MR and Nox activity in VC.

Methods: Pit1 KO mice (Pit1-/-) on the C57BL6 background were induced with either WT or Pit1 KO bone marrow chimeras. Pit1 KO chimeras were divided as Pit1 KO/WT-CKD or Pit1 KO/Pit1 KO-CKD. VC was studied histologically, using traditional hematoxylin and eosin (H&E) staining and immunohistochemistry.

Results: Pit1 KO mice showed a significant reduction in VC, compared to WT controls. Pit1 KO mice showed a significant decrease in VC compared to WT-CKD. VC was significantly reduced in Pit1 KO/WT-CKD compared to WT-CKD. Nox activity was significantly reduced in Pit1 KO/WT-CKD compared to WT-CKD.

Conclusions: Pit1 knock-out ameliorates VC and reduces Nox activity. These findings support the potential therapeutic role of Pit1 KO in VC.

Funding: Pharmaceutical Company Support - Shire Australia, Private Foundation Support, Clinical Revenue Support

Results: Calcium in VSMC incubated with serum drawn after MCO dialysis was reduced compared to Highflux serum. Serum from patients, who started on a Highflux membrane showed a 35% reduction (p<0.0001) of alizarin red staining after 4 weeks and a 49% (p<0.0001) reduction after 12 weeks of MCO dialysis. Alkaline phosphatase showed a 23% reduction after 4 weeks and a 32% reduction after 12 weeks MCO. Accordingly, serum from patients, who started on MCO showed an increase of calcification after switch to highflux dialysis.

FR-OR028
Calciphylaxis Is Characterized by Vitamin K Deficiency and Impaired Matrix Gla Protein Carboxylation  †Dawar U. Nigwekar, †Rajeev Malhotra, †Julia Beth Wenger, †Sarah Booth, †Ravi I. Thadhani. †Massachusetts General Hospital; †Tufts Univ.

Background: Calciphylaxis, a dermal arteriolar calcification disorder linked with high mortality, has unclear pathogenesis. We investigated vitamin K metabolism and its effects on vitamin K dependent carboxylation of calcification inhibitor, Matrix Gla Protein (MGP), in calciphylaxis patients.

Methods: We prospectively recruited 20 ESRD patients with biopsy-confirmed calciphylaxis and obtained plasma samples and clinical information at the time of calciphylaxis diagnosis. Plasma samples and clinical information were also obtained from 20 controls (ESRD patients without calciphylaxis) matched to cases by age, sex, race, and warfarin status. Plasma levels of Proteins Induced by Vitamin K Absence (PIVKA-II) a sensitive measure of vitamin K deficiency, carboxylated MGP (c-MGP), and uncarboxylated MGP (uc-MGP) were measured using ELISA assays. MGP carboxylation status was derived from the c-MGP/uc-MGP ratio. Prevalence of vitamin K deficiency (defined by PIVKA-II levels >2 ng/mL) was compared between cases and controls using Chi-square analysis. MGP ratios were compared between cases and controls using a Mann Whitney U test and multivariable linear regression.

Results: Prevalence of vitamin K deficiency was higher in cases compared to controls (90% vs. 50%, P=0.006) including in patients not on warfarin/vitamin K antagonist therapy (83% vs. 35%, P=0.014). Median MGP ratio was lower in cases compared to controls (1.29 vs. 2.42, p=0.001) including in patients not on warfarin (1.64 vs. 2.98, p<0.001).

Conclusions: High prevalence of vitamin K deficiency and its potential impact on MGP carboxylation in calciphylaxis call for a therapeutic trial of vitamin K supplementation in calciphylaxis.

Funding: Private Foundation Support

FR-OR029
Dialysis with Medium Cut-Off (MCO) Filters Reduces In Vitro Calcification of Human VSMC: Lessons from a Randomized Clinical Trial  †Daniel Zeckler, †Markus Storr, †Matthias Girndt, †Roman Friedler, †Kevin Willy, †Ralf Schnidler. †Dept of Nephrology and Internal Intensive Care Medicine, Charité Univ Medicine, Berlin; †Dept of Internal Medicine II, Martin-Luther-Univ, Halle; †Research & Development, Gambro Dialysatoren GmbH, Hechingen.

Background: Vascular calcification is increased in CKD patients, partly caused by insufficient removal of inflammatory proteins with conventional dialysis filters. We assessed whether dialysis with MCO filters, which allow elimination of middle-sized inflammatory proteins with only limited permeability for albumin, influences vascular calcification in vitro.

Methods: 50 patients were dialysed in a randomized controlled clinical “first-in-man” trial with a MCO and a Highflux filter for four weeks in a randomized order. To test for longterm effects the patients were continued on their filter for eight more weeks. After each phase serum samples were drawn. In human VSMC calcification was induced and serum samples were added. After 7-12 days in vitro calcification was assessed via Alizarin red and Alkaline phosphatase assays and normalized to WST-8.

Results: In multivariable analyses adjusted for clinical characteristics, vitamin K deficiency was associated with a 48% reduced MGP ratio (P=0.004).

Conclusions: High prevalence of vitamin K deficiency and its potential impact on MGP carboxylation in calciphylaxis call for a therapeutic trial of vitamin K supplementation in calciphylaxis.

Funding: Private Foundation Support

FR-OR030
First Experience with a Novel Inhibitor of Vascular Calcification (SNF472) in Healthy Volunteers and ESRD Patients on Hemodialysis  †Joan Perello, †Carolina Salcedo, †Pieter H. Joubert, †Ana-Zeraldia Canals, †Miquel D. Ferrer. Sanifit, Palma, Spain.

Background: SNF472, an intravenous (i.v.) formulation of myo-inositol hexaphosphate, is being developed for treating calciphylaxis and for preventing vascular calcification progression in patients with end-stage renal disease on hemodialysis. It selectively inhibits the final common pathway in the etiology of vascular calcification, the formation and growth of hydroxyapatite (HAP) crystals. Non-clinical investigations showed adequate evidence of efficacy and safety to warrant a first study in humans.

Methods: A double-blind, randomized, phase 1 clinical trial was performed in two cohorts of 8 male healthy volunteers (HV) and one cohort of 8 hemodialysis (HD) patients. Single ascending doses of 0.5, 5, 9 and 12.5 mg/kg of SNF472 were administered through 4-hour i.v. infusion to HV into a forearm vein. HD patients received a single i.v. dose of 9 mg/kg through the dialysis tubing before the filter during the 4 hours of dialysis. Safety parameters, including extensive ECG monitoring, were recorded. Blood samples were obtained up to 24h for safety and pharmacokinetics. A PD (pharmacodynamics) assay was used to assess the potential of ex vivo formation of HAP crystals.

Results: SNF472 was well tolerated and no systemic adverse events were observed. Several HV reported irritation at the infusion site. This effect was concentration-dependent (not dose-dependent). In HD patients SNF 472 was diluted >500-fold in the dialysis system before reaching the patient and no local irritation occurred. No effects were seen in safety parameters, including ECG. Ionized calcium was slightly below the lower limit of normal in HV at 12.5 mg/kg. The 5, 9 and 12.5 mg/kg doses produced measurable plasma concentrations above the anticipated EC50 (5µM) and showed a 70-80% reduction in the ex vivo HAP crystal formation PD assay. HD patients had similar SNF472 plasma concentrations (suggesting low SNF472 clearance through the dialysis membrane) and PD effects to HV. Plasma ionized calcium levels were stable.

Conclusions: The data available suggests a favourable benefit/risk ratio of SNF472 and supports further studies in the target population. Supported by RETOS COLABORACION RTC-2014-2460-1.


FR-OR031
Use of Peritoneal Dialysis (PD) Before and After the Bundled Prospective Payment System (PPS)  †Richard Hirth, †Tammie A. Nahra, †Adam S. Wilk, †Marc Turekne, †Jonathan H. Segal, †John Wheeler, †Kathryn Sleeman, †Wei Zhang. †UM-KECC, Univ of Michigan, Ann Arbor, MI; †Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: PD rates steadily eroded prior to the PPS. Because the PPS bundles injectable drugs, which are used less in PD relative to hemodialysis (HD) while paying the same rate for PD and HD, the PPS increases the incentive to provide PD. PD rates began to rise in anticipation of the PPS and continued to rise after its implementation. This study extends these early observations to include 4 years under the PPS and examines whether the PD supply shortages of 2014 impacted the growth of PD.

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

Underline represents presenting author.

38A
FR-OR032
The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS): Preliminary Findings from the First Year
Jeffrey Perl,1 Junhui Zhao,2 Brian Bieber,2 Yun Li,3 Simon J. Davies,4 David W. Johnson,5 James A. Sloand,3 Hideki Kawanishi,4 Bruce M. Robinson,2 Francesca Torrenti,2,5 St. Michael’s Hospital, Univ of Toronto, Toronto, ON, Canada; 4 Arbor Research Collaborative for Health, Ann Arbor, MI; 5 Univ of Michigan, Ann Arbor, MI; 1 Univ Hospital of North Midlands, Stoke-on-Trent, United Kingdom; 3 Princess Alexandra Hospital, Brisbane, Queensland, Australia; 2 Baxter Healthcare Corporation, Deerfield, IL; 6 Tsuchiya General Hospital, Hiroshima, Japan; 1 Vanderbilt Univ, Nashville, TN.

Background: The PDOPPS is a prospective cohort study underway in the United States (US), Australia, Canada, Japan, and the United Kingdom, in collaboration with the International Society for Peritoneal Dialysis. PDOPPS aims to understand the impact of clinical practices on patient outcomes, including patient and technique survival. Here, we present results from the first year of data collection.

Methods: 170 randomly selected facilities and 6000 patients will participate in the initial study. A stratified random selection of facilities has yielded national samples of facilities and patients, with 20-45 patients per site. Clinical, demographic, biochemical, and treatment data are collected at 4-month intervals. Follow up is 3-years or until death, kidney transplantation, or 120-days after a change in permanent dialysis modality. Early descriptive data are presented for the three countries.

Results: To date, 99 facilities and 2211 patients have been recruited. Selected patient and treatment characteristics vary widely across countries (Table 1).

Table 1: Selected patient and treatment characteristics in the three initial PDOPPS countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Canada</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.2</td>
</tr>
<tr>
<td>Female</td>
<td>40%</td>
</tr>
<tr>
<td>Time on PD, years</td>
<td>1.9</td>
</tr>
<tr>
<td>Glomerulonephritis*</td>
<td>29%</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>14%</td>
</tr>
<tr>
<td>PD treatment</td>
<td></td>
</tr>
<tr>
<td># of PD patients per facility</td>
<td>39</td>
</tr>
<tr>
<td># of overnight exchanges</td>
<td>73%</td>
</tr>
<tr>
<td>&gt; 1 daytime exchange</td>
<td>4.6</td>
</tr>
<tr>
<td>CAPD</td>
<td>27%</td>
</tr>
<tr>
<td>Residual kidney function, peritoneal membrane function, and dialysis adequacy</td>
<td></td>
</tr>
<tr>
<td>Urine volume, L/24hr</td>
<td>0.71</td>
</tr>
<tr>
<td>D/P creatinine</td>
<td>0.67</td>
</tr>
<tr>
<td>Total Kt/V</td>
<td>2.32</td>
</tr>
</tbody>
</table>

As of May 2015; results are shown as mean ± SD

Background: Hyponatremia is common in hemodialysis patients and has been linked with higher mortality risk. In peritoneal dialysis (PD) patients, few studies have examined the association of hyponatremia with mortality which have shown mixed findings. We sought to examine predictors of hyponatremia in a national PD cohort, and hypothesized that lower serum sodium (Na) is associated with higher death risk.

Methods: We examined a 5-year (1/2007-5/2011) cohort of 4687 incident PD patients from a large US dialysis organization with one or more serum Na measures within the 1st 91-days of dialysis. We examined predictors of baseline hyponatremia (Na<140mEq/L) using Cox models with adjusted logistic regression models. We then examined the association of Na with all-cause mortality. Baseline and time-dependent Na as a proxy of long- and short-term exposure—mortality associations, respectively, were estimated using Cox models with 3 adjustment levels: Unadjusted, case-mix, and case-mix+laboratory adjusted. We then examined the association of Na with all-cause mortality. Baseline and time-dependent Na as a proxy of long- and short-term exposure—mortality associations, respectively, were estimated using Cox models with 3 adjustment levels: Unadjusted, case-mix, and case-mix+laboratory adjusted.

Results: Having diabetes; lower residual kidney function, albumin, PTH; and higher glucose, calcium, and ferritin were associated with higher risk of hyponatremia. Baseline Na levels <140mEq/L were associated with higher mortality across all 3 models (ref: Na 140–142mEq/L). In time-dependent analyses, Na levels <140mEq/L were also associated with incrementally higher death risk in case-mix models. After further adjustment for laboratory covariates, Na—mortality associations persisted for levels <134mEq/L.

FR-OR033
Risk Factors and Sequelae of Hyponatremia in a National Peritoneal Dialysis Cohort Vanessa A. Ravel,1 Rajnish Mehrotra,2 John J. Sim,2 Kevin T. Harley,3 Alpesh Amin,4 Juan Carlos Ayus,4 Steven M. Brunelli,2 Elani Streja,1 Csaba P. Kovacs,1 Kamiyar Kalantar-Zadeh,1 Connie Rhee,1 UC Irvine; 2 UWashington; 3 Kaiser Perm SC; 4 Renal Consultants Houston; 5 DaVita Clin Research; 6 UTHSC.

Background: Hyponatremia is common in hemodialysis patients and has been linked with higher mortality risk. In peritoneal dialysis (PD) patients, few studies have examined the association of hyponatremia with mortality which have shown mixed findings. We sought to examine predictors of hyponatremia in a national PD cohort, and hypothesized that lower serum sodium (Na) is associated with higher death risk.

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FR-OR032
The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS): Preliminary Findings from the First Year
Jeffrey Perl,1 Junhui Zhao,2 Brian Bieber,2 Yun Li,3 Simon J. Davies,4 David W. Johnson,5 James A. Sloand,3 Hideki Kawanishi,4 Bruce M. Robinson,2 Francesca Torrenti,2,5 St. Michael’s Hospital, Univ of Toronto, Toronto, ON, Canada; 4 Arbor Research Collaborative for Health, Ann Arbor, MI; 5 Univ of Michigan, Ann Arbor, MI; 1 Univ Hospital of North Midlands, Stoke-on-Trent, United Kingdom; 3 Princess Alexandra Hospital, Brisbane, Queensland, Australia; 2 Baxter Healthcare Corporation, Deerfield, IL; 6 Tsuchiya General Hospital, Hiroshima, Japan; 1 Vanderbilt Univ, Nashville, TN.

Background: The PDOPPS is a prospective cohort study underway in the United States (US), Australia, Canada, Japan, and the United Kingdom, in collaboration with the International Society for Peritoneal Dialysis. PDOPPS aims to understand the impact of clinical practices on patient outcomes, including patient and technique survival. Here, we present results from the first year of data collection.

Methods: 170 randomly selected facilities and 6000 patients will participate in the initial study. A stratified random selection of facilities has yielded national samples of facilities and patients, with 20-45 patients per site. Clinical, demographic, biochemical, and treatment data are collected at 4-month intervals. Follow up is 3-years or until death, kidney transplantation, or 120-days after a change in permanent dialysis modality. Early descriptive data are presented for the three countries.

Results: To date, 99 facilities and 2211 patients have been recruited. Selected patient and treatment characteristics vary widely across countries (Table 1).
Conclusions: In PD patients, lower serum Na levels are associated with higher mortality. Further studies are needed to determine if correction of hyponatremia improves outcomes in this population.

Funding: NIDDK Support, Private Foundation Support

FR-OR034
Center-Specific Factors Associated with Peritonitis Risk - A Multi-Center Registry Analysis

Annie-Claire Nadeau-Fredette,1,2 David W. Johnson,1,2 Carmel M. Hawley,1,2 Elaine M. Pascoe,1 Yeoung Jee Cho,1 Philip A. Clayton,2 Sunil V. Badve,1 Kamal Sud,1 Monique Renee Borlace,1,2 Neil Boulville,2 Stephen P. McDonald.2 1Princess Alexandra Hospital, Australia; 2Australia and New Zealand Dialysis and Transplant Registry; Maisononneuve-Rosemont Hospital, Canada.

Background: Previous studies have reported significant variation in peritonitis rates across dialysis centers. Limited evidence is available to explain this variability. This study aimed to assess the center-level predictors of peritonitis and their relationship with peritonitis rate variation.

Methods: This registry study included all incident peritoneal dialysis (PD) patients treated in Australia between October 2003 and December 2013. The primary outcome was peritonitis rate, evaluated in a mixed effects negative binomial regression model including patient and center-level characteristics. Peritonitis-free survival was assessed as a secondary outcome in a Cox proportional hazards model.

Results: Overall, 8711 incident PD patients from 51 dialysis centers were included. Center-level predictors of lower peritonitis rates included small center size (HR 0.78, 95% CI 0.69-0.90), high proportion of PD (HR 0.87, 95% CI 0.77-0.99), low performance of peritoneal equilibration test at dialysis start (HR 0.78, 95% CI 0.66-0.93), and low proportion of hospitalisation for peritonitis (HR 0.88, 95% CI 0.75-0.96). In contrast, low proportion of automated PD exposure (HR 1.24, 95% CI 1.10-1.39), large icodextrin exposure (1.26, 95% CI 1.10-1.44) and low (HR 1.25, 95% CI 1.10-1.44) or high (HR 1.14, 95% CI 1.01-1.30) use of antifungal prophylaxis at the time of peritonitis were associated with a higher peritonitis rate. Similar results were obtained for peritonitis-free survival. Accounting for center-level characteristics appreciably decreased peritonitis variability among dialysis centers (p<0.02).

Conclusions: This study identified specific center-level characteristics associated with variation in peritonitis risk. Whether or not these factors are causally related to peritonitis risk or surrogate markers of other characteristics is uncertain and should be validated in further studies.

FR-OR035
Successful Reduction in Peritonitis Rates in U.S. Pediatric Dialysis Units: Results of the SCOPE Collaborative

Alicia Neu,1 Troy Richardson,2 John P. Lawlor,2 Jayne Stuart,2 Nancy McAfee,1 Jason Newland,4 Bradley Warady.4 1JHMI; 2CHA; 3Seattle Children’s; 4Children’s Mercy.

Background: The Children’s Hospital Association’s Standardizing Care to Improve Outcomes in Pediatric ERSD (SCOPE) Collaborative seeks to minimize peritonitis in children on chronic peritoneal dialysis (PD) by increasing compliance with standardized PD catheter care practices.

Methods: Peritonitis rates and compliance with care bundles focused on PD catheter insertion, pt/caregiver training and follow-up care were collected monthly. Center-specific monthly peritonitis rates were calculated as (#infections/#pts). Changes in peritonitis rates and compliance were modeled using Generalized Linear Mixed Model techniques assuming a negative binomial distribution with a natural log link function and a binomial distribution with a logit link function, respectively. Models included random effects to accommodate PD center-specific variability.

Results: Data from 24 SCOPE sites that provided peritonitis rates for the 12 mos prior to Collaborative launch were included in the analysis. In the first 36 mos, 751 catheter insertions in 644 pts, 644 training sessions and 7,977 follow up encounters were captured. Compliance with the follow up bundle increased from 11% to 88% (p<0.001) over the 36 mos, but neither insertion (22% to 36%, p=0.064) nor training compliance (75% to 71%, p=0.105) increased significantly. The peritonitis rate decreased significantly (p=0.026) from an average monthly rate of 0.052 (95% CI 0.036, 0.076) pre-launch to 0.035 (95% CI 0.026, 0.047) at 36 mos, figure 1.

Conclusions: Using quality improvement methodology pediatric dialysis units participating in SCOPE significantly increased implementation of standardized follow up care practices and significantly reduced peritonitis rates. Efforts to increase compliance with insertion and training bundles and further reduce infection rates are ongoing.

FR-OR036
Diuretic Prescription and Outcomes Among Peritoneal Dialysis Patients in the BRAZPD Study

Jennifer L. Brage-Gresham,1 Ludimila Guedin de Campos,2 Thyago Proença de Moraes,2 Ana Elizabeth Figueiredo,1 Pasqual Barretti,2 Rajiv Saran,1 Roberto Pecoitos-Filho.1 1KECC, Univ of Michigan, Ann Arbor, MI; 2Pontifícia Unv Católica do Paraná, Curitiba, Brazil; 3Pontifícia Unv Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil; 4Univ Estadual do Estado de São Paulo - UNESP, Botucatu, Brazil.

Background: Diuretics are prescribed to individuals with reduced renal function (RRF), but can continue to play a role in dialysis patients, to manage extracellular fluid volume and hypertension. We assess the prescription (Rx) of diuretics and their association with survival in a representative sample of PD patients.

Methods: We examined diuretic Rx among 9,905 patients from the BRAZPD study, a prospective cohort study launched in Dec 2004. Cox regression was used to estimate associations between baseline diuretic use and mortality, adjusting for age, sex, hypertension, diabetes, Davies score, pre-dialysis care, prior HD, and prior kidney Tx; interaction used to assess Rx by 90-day incident status.

Results: At baseline, 33.9% of patients had diuretic Rx. Patients with Rx were older, had higher BMI, more comorbidities, but longer pre-dialysis care (p<0.0001). A higher proportion of patients with Rx had incident to PD, male, diabetic, hypertensive, taking other anti-hypertensive medications and had received pre-dialysis care; while a smaller proportion of patients with Rx were incident to PD, male, diabetic, hypertensive, taking other anti-hypertensive medications and had received pre-dialysis care; while a smaller proportion of patients with Rx had received a prior Tx or HD (p<0.01). Accounting for these differences, patients with Rx had a lower risk of mortality (HR=0.87, p=0.005). The association was seen among both incident and non-incident patients.

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

40A
Conclusions: Despite being older and sicker, patients with diuretic Rx had lower mortality. While more striking in incident patients, association was also seen in non-incident patients. If diuretic Rx is a marker of RRF or independently associated with better outcomes remains to be elucidated.

FR-OR037
In-Hospital Mortality Outcome of Cirrhotic Patients with End Stage Renal Disease on Hemodialysis versus Peritoneal Dialysis
Mark Abi Nader,1 Fernando Rodrigo Aguilar,1 Michael S. Lipkowitz,2 Parasuram Krishnamoorthy,2 Ping Li,1 Serban A. Dragoi,1 Alex Montero,1 Wen Shen,1 Chianigai Nilubol,1 Judith Gordon.1 1Nephrology and Hypertension, Georgetown Univ Hospital, Washington, DC; 2Internal Medicine, Mount Sinai School of Medicine.

Background: Renal disease is a common complication in cirrhotic patients related to electrolyte and acid-base alterations, inadequate response to diuretic drugs, and hemodynamic instability, often leading to end stage renal disease (ESRD) with need for dialysis. It is little known about the preferred dialysis modality in these patients. We aimed to compare the mortality outcomes between cirrhotic patients on either Hemodialysis (HD) or peritoneal dialysis (PD).

Methods: Nationwide Inpatient Sample database between 2005 and 2012 was queried. Patients with ESRD (ICD9 S58.0) and liver cirrhosis (ICD9 571.2; 571.5; 571.6; 572.3; 572.4) were included in the study. Patients having hepatocellular carcinoma were excluded (ICD9 155.0). Both groups were matched, undergoing propensity matching score, for chronic conditions including anemia, diabetes mellitus, hypertension, hepatic encephalopathy, esophageal variceal bleeding, gastrointestinal bleeding (GBB), pancreatitis, hepatitis C as well as sex, race, Charlson Comorbidity Index and age. Logistic regression was used for multivariable analysis.

Results: 28,622 cirrhotic patients with incident ESRD were identified. 1.7% of them were on PD. After propensity score matching and multivariable regression analysis, cirrhotic on HD had higher mortality compared to PD patients [4.79% vs 2.70% P = 0.024]. Age>65 and female gender were significant predictors of mortality in both HD and PD groups. Anemia was associated with less mortality rate.

Conclusions: Cirrhotic patients admitted to the hospital for dialysis have higher mortality when started on HD compared to PD.

FR-OR038
AQP1 in Peritoneal Dialysate as Predictive Biomarker of Integrity of the Peritoneal Barrier and Ultrafiltration Efficiency
Simone Corcino,1 Maria Celeste Nicoletti,2 Roberto Corcillo,2 Roberto Russo,2 Giuseppe Grandaliano,1 Maria Svelto,1 Giuseppe Proctino,3 Loretta Gesualdo.1 1Dept of Emergency and Organ Transplantation, Univ of Foggia, Foggia, Italy; 2Dept of Biosciences, Biootechnologies and Biopharmaceutics, Univ of Bari, Bari, Italy; 3Dept of Emergency and Organ Transplantation, Univ of Bari, Bari, Italy.

Background: The water channel Aquaporin 1 (AQP1) plays a pivotal role in the mechanism of free water ultrafiltration during peritoneal dialysis (PD). Whether or not is AQP1 exclusively expressed in peritoneal capillaries or also in the mesothelial cells (MC) is still debated. It has been hypothesized that decreased expression or function of AQP1 may be responsible for some cases of ultrafiltration failure (UFF). Plasma membrane proteins are released in biological fluids through the exosome pathway to an extent proportional to their abundance at the plasma membrane.

Methods: In this work we investigated the localization of AQP1 in human peritoneum and its presence in exosomes isolated from PD effluent.

Results: Proteomic analysis of peritoneal-derived exosomes showed a significant expression of AQP1. Interestingly, the same samples were devoid of the endothelial marker CD31 but were positive for the mesothelial marker mesothelin, thus suggesting a mesothelial, rather than endothelial origin for these vesicles.

Conclusions: Despite being older and sicker, patients with diuretic Rx had lower mortality. While more striking in incident patients, association was also seen in non-incident patients. If diuretic Rx is a marker of RRF or independently associated with better outcomes remains to be elucidated.

FR-OR039
Vascular Endothelial Cell Damage Is an Important Factor in the Development of Encapsulating Peritoneal Sclerosis
Mitsuhiro Tawada,1 Yasuhiko lto,1 Chieko Hamada,2 Kazuho Honda,3 Masashi Mizuno,1 Yasuhiro Suzuki,1 Fumiko Sakata,1 Shoichi Maruyama,1 Seiichi Matsuo,1 1Nephrology, Nagoya Univ, Nagoya, Japan; 2Nephrology, Juntendo Univ, Tokyo, Japan; 3Pathology, Tokyo Women’s Medical Univ, Tokyo, Japan; 4Biochemistry, Nagoya Univ, Nagoya, Japan.

Background: Encapsulating peritoneal sclerosis (EPS) is a rare, but serious and life-threatening complication of peritoneal dialysis (PD), however, the precise pathogenesis remains unclear and predictors have not yet been established. This present study aimed to determine predictors of EPS in peritoneal membrane tissues obtained at catheter removal.

Methods: Eighty-three biopsy samples (10 EPS, 73 non-EPS) were assessed by pathological and immunopathological techniques to identify predictors of EPS. Tissue samples obtained at the time of catheter removal for reasons of peritonitis and a peritonitis episode within the past one month were not included. Furthermore, based on these analyses, the effects of PD solution on human umbilical vein endothelial cells (HUVEC) were studied.

Results: Univariate analysis of the pathological findings associated a thickened peritoneal membrane (P = 0.045), new membrane formation scores (P = 0.006), decreased ratio of lumen diameter to vessel diameter (L/V ratio, P = 0.024), CD31-negative vessels (P = 0.021) and fibrin deposition (P < 0.001) with the development of EPS. Stepwise Firth’s multivariate logistic regression analysis identified glucose exposure scores (odds ratio 2.03, P = 0.011) among clinical factors, the L/V ratio (AUC, 0.899; OR, 0.50; P = 0.002) and fibrin deposition (OR, 8.50; P = 0.023) among the pathological factors as independent predictors of EPS. Multivariate logistic regression analysis of the 10 patients with EPS and 20 controls matched for PD treatment period, diabetes and PD solution (acidic or neutral pH) identified decreased L/V ratio as an independent predictor. In cultured HUVEC, acidic condition and high glucose concentration of PD solution induced necrosis and apoptosis, respectively.

Conclusions: Vascular endothelial cells that become damaged mainly by bioincompatible PD solution might induce vascular leakage leading to EPS, and could serve as a predictor of EPS.

Funding: Government Support - Non-U.S.
the causative microorganisms of PD-related peritonitis earlier than the conventional standard method. The average time saved was 64 hours for all pathogens, 52 hours for Gram-positive bacteria, 65 hours for Gram-negative bacteria, 37 hours for Staphylococcus species, 68 hours for Streptococcus species, and 67 hours for E. coli and Klebsiella species. MALDI-TOF MS method group had a shorter length of hospital stay than the conventional standard group (5.2 ± 4.8 days vs 8.2 ± 4.5 days, P = 0.001).

**Conclusions:** We demonstrate the clinical effects of pathogen identification using MALDI-TOF MS in PD-related peritonitis. Integration of MALDI-TOF MS with blood culture system can promote early pathogen identification and timely pathogen-directed antibiotic therapy, and may confer outcome benefit. We propose that it is time to speed up the pathogen identification in PD-related peritonitis.

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

**FR-OR041**

**Higher Systolic Blood Pressure Variability Is Associated with Increased Mortality, Coronary Heart Disease, Stroke, and End Stage Renal Disease**

Margit Mikkelsen,1 Miklos Zsolt Molnar,2 Jun Ling Lu,3 Lenar T. Yessayan,3 Elvira Gosmanova,4 Kamyar Kalantar-Zadeh,4 Csaba P. Kovacs,5,12 1VA Medical Center, Memphis, TN; 2Univ of California, Irvine, CA. *1Henry Ford Hospital, Detroit, MI; 3Univ of California, Irvine, CA.

**Background:** Blood pressure does not remain constant, but instead fluctuates dynamically. The implications of this variability in blood pressure are not yet fully understood.

**Methods:** From among 3,285,684 US veterans with normal eGFR during 2005-2006, we identified 2,869,157 patients who had more than 7 outpatient blood pressure measurements. Systolic blood pressure variability (SBPV) was measured using the standard deviation (SD) of all SBP values (normally distributed) in one individual. Associations of SD quartiles (<10.28, 10.28-12.68, 12.69-15.60, ≥15.61 mmHg) with all-cause mortality, coronary heart disease (CHD), stroke, and end stage renal disease (ESRD) was examined using Cox models adjusted for age, gender, race, and baseline eGFR, comorbidities, BMI, SBP, DBP, and antihypertensive medication use.

**Results:** Higher SBPV was associated with significantly higher risk of all-cause mortality, CHD, stroke, and ESRD. In fully adjusted models SD quartiles 2 through 4 (compared to the first quartile) were associated with mortality hazard ratios of 1.10, 1.32, and 1.79; CHD hazard ratios (95%CI) of 2.12, 3.60, and 6.01; stroke hazard ratios of 2.05, 3.64, and 6.72; and ESRD hazard ratios of 0.88, 1.32, and 4.48.

**Conclusions:** Higher SBPV is associated with increased risk for mortality, CHD, and stroke independent of confounders. The highest SD quartile was associated with increased risk for ESRD. The effect of interventions that lower SBPV on mortality will need to be examined in clinical trials.

**Funding:** NIDDK Support, Veterans Administration Support

**FR-OR042**

**Left Ventricular Mass in Early Autosomal Dominant Polycystic Kidney Disease**

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**Background:** Autosomal dominant PKD (ADPKD) associates with hypertension and left ventricular hypertrophy (LVH). HALT PKD study A was designed to assess the effect of intensive BP control and dual renin angiotensin blockade on progression of total kidney volume (TKV) and left ventricular mass (LVM). A randomized controlled trial (RCT) was performed comparing two regimens: 1) intensive BP control and dual renin-angiotensin-aldosterone blockade (IBP+DRA) and 2) standard BP control (SBC) including antihypertensives, as tolerated. The average duration of follow-up was 33 months (range 12-60 months).

**Methods:** 543 subjects with eGFR ≥60 ml/min aged 15-50 were randomized to lisinopril (L) and placebo (P) vs L and telmisartan (T) with two levels of BP control: standard (SBC) (120-130/70-80 mmHg) vs low (LBP) (95-110/65-75 mmHg). Cardiac magnetic resonance measurement of LVM was done at baseline, 24, 48, and 60 months. LVM adjusted for body surface area was expressed as LVM index (LVMI, g/m²).

**Results:** The prevalence of LVH at baseline was <1%. LBP reduced LVMI compared to SBC (p=0.0001) but there was no effect of dual blockade (p=NS). There was no impact of baseline parameters (eGFR, age, systolic BP, TKV, serum K, urine Na or K, albuminuria, urine aldosterone, sex) on the BP effect on LVMI. Higher baseline TKV and systolic BP had significant associations with more rapid LVMI decline (p=0.0001); a trend of lower baseline eGFR also associated with LVMI decline (p=0.07); females had significantly reduced LVMI decline vs males (p=0.0001) irrespective of BP group.

**Conclusions:** LVMI decreased significantly after intensive vs standard BP control. Larger TKV, higher systolic BP, male sex, and possibly decreased eGFR were associated with a greater reduction in LVMI, irrespective of the level of BP control. Patient factors associated with a worse kidney outcome predicted improvement in LVMI after a long period of carefully controlled BP. BP reduction in ADPKD shows cardiac benefit and should be a focus of treatment.

**Funding:** NIDDK Support, Private Foundation Support

**FR-OR043**

**Asymmetric and Symmetric Dimethylarginine and Sympathetic Nerve Traffic After Renal Denervation in Patients with Resistant Hypertension: A Longitudinal Study**

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**Background:** The plasma concentration of the endogenous inhibitor of nitric oxide synthase asymmetric dimethyl arginine (ADMA) associates with sympathetic activity in patients (pts) with chronic kidney disease but the driver of this association is unknown.

**Methods:** In this longitudinal study (followup: 2 weeks-6 months) we performed repeated measurements over time of muscle sympathetic nerve activity (MSNA), plasma levels of ADMA and symmetric dimethyl arginine (SDMA) and blood pressure (BP) and heart rate (HR) in 14 pts with drug-resistant hypertension who underwent bilateral renal denervation. Stability of ADMA, SDMA, BPs and MSNA over time (6 months) was assessed in 2 historical control groups of patients maintained on stable anti-hypertensive treatment.

**Results:** Time integrated changes in MSNA following renal denervation ranged from -40.6% to +10% (average -15.1%) and these changes were strongly associated with the corresponding changes in plasma ADMA (r=0.62, P=0.02) and SDMA (r=0.72, P=0.004). Changes in MSNA went along with simultaneous changes in standardized systolic (r=0.65, P=0.01) and diastolic BP (r=0.67, P=0.02). In the historical control groups, no change in ADMA, SDMA, BPs and MSNA levels was recorded during a 6-months follow up.

**Conclusions:** In pts with resistant hypertension changes in sympathetic activity after renal denervation associate with simultaneous changes in plasma levels of ADMA and SDMA. These observations are compatible with the hypothesis that the sympathetic nervous system exerts an important role in modulating circulating levels of ADMA and SDMA in this condition.

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

**FR-OR044**

**Intensive Blood Pressure Lowering and Kidney Function Decline Among Persons with prior Lacunar Stroke: The SP3 Randomized Trial**

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**Background:** The effect of intensive blood pressure (BP) lowering on kidney function among persons with vascular disease and preserved glomerular filtration rate (eGFR) is not known.

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

Underline represents presenting author.

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Methods: SP53 was a multi-center trial to test effectiveness of two BP targets on secondary prevention of stroke. In a post-hoc analysis of 2611 participants randomized to lower SBP (<130 mmHg) vs. higher (130-149 mmHg) with yearly creatinine measurements, we evaluated differences in eGFR decline and rapid decline (>30 ml/min/1.73m²) using linear mixed models and logistic regression, respectively.

Results: Mean age was 63±11; 949(36%) were diabetic, mean eGFR was 80±19 and 410(16%) had eGFR <60 ml/min/1.73m² at randomization. At 9 months, achieved SBP was 137±15 mmHg in higher vs. 127±14 mmHg in the lower BP group, and differences persisted throughout follow-up (mean 3.2 years). Relative to higher BP arm, use of ACE/ARB, diuretic and calcium channel blocker were all increased by 20% among persons in the lower BP arm. Compared with higher, lower BP target had faster eGFR decline. Differences were most pronounced during the first year, whereas rates of eGFR decline did not differ between assigned BP groups after year 1.

A total of 313(24%) persons in the lower BP group had rapid kidney function decline, compared with 247(19%) in higher (OR 1.43[1.11 to 1.8]). Differences were apparent in the first year (OR 1.4, 1.1-1.8), but were not statistically significant after year 1 (OR 1.0, 0.73-1.4).

Conclusions: In persons with prior lacunar stroke and relatively preserved kidney function, intensive BP lowering was associated with faster renal function decline. Differences were primarily observed during the first year of anti-hypertensive treatment with no evidence of renal protection during follow up.

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

FR-OR046
Effect of Uric Acid Lowering on Ambulatory Blood Pressure: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial
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Background: Higher levels of uric acid are associated with higher blood pressure (BP) an increased risk of hypertension in many cohort studies, suggesting that uric acid may be a target for prevention of hypertension. However, the effect of lowering serum uric acid on BP is unclear.

Methods: We performed a randomized, double-blind, placebo-controlled trial of normotensive individuals with body mass index (BMI) ≥25 and uric acid level ≥ 5.0 mg/dL, who were randomized to receive either allopurinol 300/600mg, probenecid 500/1000mg or placebo daily for 8 weeks. Mean 24 hour systolic BP(24hSBP) was measured using 24 hour ambulatory blood pressure monitoring at baseline and 8 weeks.

Results: By the end of the trial, 22, 24 and 26 participants assigned to receive probenecid, allopurinol and placebo, respectively, had adequate 24 hour BP measurements at baseline and 8 weeks. Uric acid levels changed over 8 weeks from means of 5.9, 5.6 and 5.6 mg/dL to 3.5, 2.9 and 5.8 mg/dL in the probenecid, allopurinol and placebo groups, respectively. 24hSBP was not reduced after 8 weeks of uric acid lowering: from 127±10 mmHg to 124±8 mmHg (p-value=0.25) in the probenecid group; 125±9 to 124±10 mmHg (p-value=0.71) in the allopurinol group; and 121±9 to 122±10 mmHg (p-value=0.61) in the placebo group. Similarly, treatment had no effect on 24 hour diastolic BP.

Conclusions: In contrast to observational studies, this randomized, double-blind, placebo-controlled trial found that uric acid lowering does not improve mean 24 hour BP in normotensive individuals with high uric acid levels, suggesting that uric acid may not be a modifiable target for prevention of hypertension.

Funding: NIDDK Support

FR-OR047
Central Role for Altered Arginine Methylation in Salt-Sensitive Hypertension in CKD: A Metabolomic Profiling Study
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Background: As the nitrogen donor in nitric oxide (NO) synthesis by NO synthase (NOS), arginine and its metabolic products are integrally linked to blood pressure (BP) regulation, however their role in chronic kidney disease (CKD), salt sensitivity and BP response has not been systematically studied. We explored if arginine metabolites alter with sodium restriction and predict favorable blood pressure in response to dietary sodium restriction (DSR).

Methods: Samples from 34 subjects enrolled in the LoSalt trial, a randomized crossover trial of CKD 3-4 patients who underwent DSR (<2g/day) were utilized. Targeted metabolomic analysis of arginine metabolism in pre and post DSR plasma and urine was performed by isotope dilution liquid chromatography mass spectrometry including N⁴,N⁴-dimethylarginine (ADMA), N⁶,N⁶-dimethylarginine (SDMA), N⁶-monomethyl-L-arginine (NMMA), arginine and citrulline. Salt sensitivity was determined by isotope dilution liquid chromatography mass spectrometry including N⁴,N⁴-dimethylarginine (ADMA), N⁶,N⁶-dimethylarginine (SDMA), N⁶-monomethyl-L-arginine (NMMA), arginine and citrulline. Salt sensitivity was determined by salutary changes to volume status and BP as measured by bioelectrical impedance spectroscopy (whole-body, segmental and calf) and 24-hour ambulatory blood pressure monitoring (ABPM). Pearson correlation assessed the associations between the metabolites and clinical parameters.

Results: After 4 weeks of DSR, mean urinary sodium decreased by 73±7 11mmol/24hr and 24-hour systolic BP reduced by 10.8 ± 13.8 mmHg. Higher urinary ADMA/creatinine ratio correlated with lower total body water at baseline (r=-0.57; p<0.01). Changes in urine ADMA/creatinine ratio (r=-0.46) and urine NOS inhibition index (NMMA/ADMA+NMDA+SDMA, r=-0.46) negatively correlated with changes in mean arterial ABPM (p<0.05). Urine Total Arginine Methylation Index (TAMI, (ADMA+SDMA+NMMA/arginine, r=-0.47, p<0.05) negatively correlated with change in extracellular volume.

Conclusions: Our results strongly implicate altered arginine methylation and NOS inhibition with BP response following DSR. Further research should examine whether urinary markers of altered arginine methylation (ADMA, NI and TAMI) can consistently serve as markers of salt sensitivity in both CKD and non-CKD subjects following DSR.

Funding: Private Foundation Support
FR-OR048

Mutations in TBX18 Cause Dominant Urinary Tract Malformations via Transcriptional Dysregulation of Ureter Development

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the leading cause of CKD in children. Identification of monogenic causes of CAKUT permits the first insights into disease mechanisms.

Methods: We performed whole exome sequencing in a large kindred followed by high-throughput sequencing in individuals with CAKUT. Furthermore, we performed a transcriptional reporter assay, protein-protein and protein-DNA interaction studies, as well as in vivo studies in Xenopus laevis.

Results: We identified a heterozygous truncating mutation (p.G337Vfs*19) of the T-box transcription factor 18 gene (TBX18) in all 7 affected members of a large kindred. We also detected 2 mutations (p.H524Y and p.K163E) in 3 of 1,295 unrelated families with CAKUT. TBX18 is essential for development of the ureteric mesenchyme and ureteric smooth muscle cells. We found that all 3 TBX18 mutant proteins still dimerize with the wild-type protein, but had prolonged half-life, and exhibited reduced transcriptional repression. The mutation p.K163E altered a residue critical for TBX18-DNA binding in a cellular context. In vivo overexpression in Xenopus laevis revealed decreased biological activity on pronephric kidney development for p.G337Vfs*19 and p.K163E.

Conclusions: We discovered dominant negative TBX18 mutations as a novel cause of human CAKUT that act via lack of repression of TBX18 transcriptional activity. Our studies implicate ureter smooth muscle cell development in the pathogenesis of human CAKUT.

FR-OR049

ACTN4 Mutations Lead to Increased Contractility of Human Podocytes in Response to Injurious Stimuli and Matrix Stiffening

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Background: Alpha-actinin-4 gene (ACTN4) mutations cause a rare form of familial focal segmental glomerulosclerosis (FSGS) in humans. Individuals with kidney disease-causing ACTN4 mutations tend to have mild to moderate proteinuria, with many developing a progressive decline in kidney function, and eventual end stage kidney disease. All of the disease-causing ACTN4 mutations identified to date are located within the actin-binding domain (ABD) of the encoded protein, increasing its binding affinity to F-actin and leading to abnormal cellular aggregates. The mechanism by which the mutations give rise to FSGS is not well understood.

Methods: We used traction force microscopy to quantify contractile force exerted by immortalized human podocytes on their underlying substrate. Immunofluorescence staining was used to examine the localization of ACTN4 and actin in podocytes transfected with mutant ACTN4 or wildtype ACTN4. We also examined podocytes transfected with mutant ACTN4 in response to the injurious stimulus TGF-beta compared to podocytes transfected with WT ACTN4. We also found that podocytes seeded on a stiff substrate (26 kilopascal) and transfected with mutant ACTN4 are more contractile than podocytes transfected with WT ACTN4. This difference in contractile force between WT and mutant was blunted when podocytes are seeded on a softer substrate (1 kilopascal). Additionally, mutant ACTN4 transfected podocytes show much more prominent actin stress fibers, which are largely absent from WT ACTN4 transfected podocyte.

Conclusions: We demonstrated that mutations in the ACTN4 ABD resulted in increased podocyte contractility in response to injurious circulating stimuli and increased matrix stiffness. These observations raise the hypothesis that reducing the contractility of podocytes by pharmaceutical agents in vivo might mitigate podocyte disease due to ACTN4 mutation. Funding: NIDDK Support

FR-OR050

Assessing Two Novel Steroid-Resistant Nephrotic Syndrome Candidate Genes Using the Drosophila Model

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Background: Steroid-resistant nephrotic syndrome (SRNS) is a genetically heterogeneous disease. Using exome sequencing we previously identified two homozygous, potentially damaging, missense variants in ADD3 and KAT2B in the affected members of a consanguineous family presenting syndromic SRNS. The first gene encodes adducin, an important regulator of the actin cytoskeleton, and the second the lysine acetyltransferase KAT2B responsible for histone acetylation.

Methods: To address the importance of ADD3 and KAT2B on podocyte function and the impact of the mutations we used the Drosophila model KD and rescue experiments with the WT and mutated genes were performed using the GAL4-UAS system in Drosophila nephrocytes, the fly counterparts of podocytes. Defects at a molecular and ultrastructural level were assessed using immunostaining and electron microscopy and functional assays were used to assess the filtration/endocytic functions of nephrocytes.

Results: In 3rd instar nephrocytes, adducin KD, but not KAT2B KD, disrupted the actin cytoskeleton, delocalized the slit diaphragm protein Kirre and led to decreased filtration/endocytosis. At the ultrastructural level ADD3 KD led to decreased number of slit diaphragms and foot process effacement. At the adult stage, both adducin and KAT2B KD induced a reduction of nephrocytes. While KAT2B rescue experiments are still pending, the WT but not the mutated form of ADD3 rescued the ADD3 KD phenotypes, namely the actin cytoskeleton defects and Kirre mislocalization.

Conclusions: These findings suggest that ADD3 plays a major role on podocyte morphology and function and that ADD3 mutations maybe causative to some forms of SRNS. However the impact of the KAT2B mutation in the patient phenotype cannot be excluded. Funding: Government Support - Non-U.S.

FR-OR051

A Novel Mutation in CLCN5 Gene Associated with Steroid Resistant Nephrotic Syndrome

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Background: It is increasingly recognized that focal segmental (FSGS) and focal global glomerulosclerosis (FGGS) may be seen as a dominant feature in some patients with Dent disease and lead to an erroneous diagnosis of primary FSGS.

Methods: We identified two brothers, 37 and 32 years old, who presented with low grade proteinuria and renal failure. Kidney biopsies of both revealed FSGS and no nephrocalcinosis. Four additional male family members had kidney disease without an established diagnosis.

Results: Pedigree analysis suggested an X-linked mode of inheritance. Extensive evaluation of the medical history from affected individuals revealed no rickets, nephrocalcinosis or nephrolithiasis. We performed whole exome sequencing on 7 family members and identified a variant of the intracellular chloride channel 5 (CLCN5) which had neither previously been described. The mutation resulted in a substitution of leucine for phenylalanine at position 521 (L521F). We constructed expression vectors (pCMV6-AC-GFP) that encode for wild-type and mutant L521F CLCN5, respectively, and transfected HK2 cells. Transfection of HK2 cells with wild-type CLCN5 revealed protein localization to both the cell surface and throughout the cytoplasm. Cells transfected with the mutant construct displayed only intracellular perinuclear localization. CLCN5 encodes the chloride hydrogen exchanger and is important for endocytosis in the proximal tubule. Recent evidence suggested that CLCN5 also resides in the podocytes and may play an important role in proper function of the slit diaphragm. Thus, CLCN5 mutations may affect podocyte integrity and lead to FSGS or FGGS. We have identified a novel variant of CLCN5 associated with histologic FSGS. Whether glomerular or tubular expression of the variant is responsible for the kidney disease is not yet clear.

Conclusions: We identified a new mutation in the CLCN5 gene in adult patients who presented with a histologic diagnosis of FSGS but without clinical manifestations of Dent disease. In cell culture, the mutation results in aberrant localization that may underlie pathogenic significance.

Funding: Private Foundation Support
FR-OR052

Defects of the Nuclear Pore Proteins NUP93, NUP205, or Exportin-5 Link Nephrotic Syndrome to Disrupted SMAD Signaling  Daniela A. Braun,1 Carolin Sadowski,1 Stefan Kohl,1 Svjetlana Lovric,1 Susanne Astrindri,1 Shazia Ashraf,2 Werner Lukas Pabst,1 Wei Zhien Tan,1 Jennifer A. Lawson,1 Merlin Airik,1 Richard P. Lifton,1 Heon Yung Gee,1 Wolffram Antonini,2 Friedhelm Hildebrandt,2,4 Nephrology, Boston Children’s Hospital, Boston, MA; 2Friedrich Miescher Laboratory, Max Planck Society, Tübingen, Germany; 3Dep. of Genetics, Yale Univ School of Medicine, New Haven, CT; 4Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Steroid resistant nephrotic syndrome (SRNS) is a frequent cause of end-stage renal disease in the first decades of life. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis. However, additional genes and disease mechanisms remain unknown.

Methods: We combined homology mapping with whole exome sequencing (WES) in 100 individuals with SRNS. To identify additional mutations, we screened our cohort of ~800 individuals with SRNS by microfluidic multiplex PCR (Fluidigm Access Array™) and next generation sequencing. We examined nuclear translocation of SMAD4, utilized a luciferase reporter construct under the control of a SMAD responsive element, and performed co-immunoprecipitation to test the pathogenicity of the identified human disease alleles.

Results: By WES and multiplex PCR, we identified mutations in the genes NUP93, NUP205, and XPO3 (encoding for nucleoporin 93, 205 and exportin-5) in 8 unrelated families with SRNS. All individuals had early onset SRNS with rapid disease progression. We show that all three proteins localize to WT1 positive podocyte precursor cells in developing rat kidney. Human mutations in NUP93 disrupt the assembly and integrity of the nuclear pore complex (NPC). A human mutation in NUP205 abrogates the interaction with NUP93 within the NPC. We demonstrate that NUP93 and exportin-5 interact with the transcription factor SMAD4, and that human mutations of NUP93 abrogate this interaction. Furthermore, human mutations of NUP93 interfere with SMAD dependent transcription downregulation of BMP7.

Conclusions: We identify mutations of NUP93, NUP205, or XPO3 as novel monogenic causes of steroid-resistant nephrotic syndrome in humans, and implicate disrupted SMAD signaling in its pathogenesis.

Funding: Other NIH Support - DK076683

FR-OR053

A Heterozygous Rare Variant in IL-1R Contributes to Autosomal Dominant FSGS in an African American Kindred  Gionton Hall,1,2 Jose A. Gomez,1 Peter J. Lavin,1 Eugene C. Kovalik,2 Peter J. Conlon,2 Rashheed A. Gbadegesin,1,2,4 1Internal Medicine, Duke Univ; 2Pediatrics, Duke Univ; 3Nephrology, Duke Univ; 4Duke Molecular Physiology Inst, Duke Univ; 5Trinity College, Ireland; 6Beaumont Hospital, Ireland.

Background: FSGS is a disorder characterized by podocyte injury, focal glomerulosclerosis, and rapid progression to ESKD. Although FSGS disproportionately affects African Americans (AA), there is no report of a causal FSGS gene identified in an AA index kindred. Here we report the discovery of a rare heterozygous missense variant in the interleukin-1 receptor (IL-1R) as contributory to autosomal dominant (AD) FSGS in an AA kindred from the US.

Methods: We identified an AA kindred with six affected individuals spread over three generations. We performed whole-exome sequencing on three affected members of the family. We confirmed all pathogenic variants by direct sequencing and performed segregation analysis on the family. Complementary molecular genetic analyses were performed in conditionally immortalized human podocytes to evaluate the effects of the segregating variant on JAK/STAT signaling and cell proliferation.

Results: We identified a segregating heterozygous rare variant (K47R) within the ligand binding domain of IL-1R in the kindred. The variant was absent from 8,600 Caucasian chromosomes and has a minor allele frequency of 0.003 in the AA population in EVS. The change is conserved in evolution and is considered damaging by SIFT. The rare variant in IL-1R enhanced basal STAT3 activation and induced hyperproliferation.

Conclusions: We report the identification of a heterozygous rare variant in IL-1R as a contributor to AD FSGS in an AA kindred. IL-1R is expressed in the kidney and podocytes and overexpression of IL-1R significantly enhanced basal STAT3 activation and podocyte proliferation in vitro.

Funding: NIDDK Support

FR-OR054

Genetic Investigation and Phenotypic Characterization of Uromodulin Associated Kidney Disease  Christine Gass,1,2 Monica Arenas Hernandez,2 Anthony Marinaki,2 Gopalakrishnan Venkat-Raman,2 1Wessex Kidney Centre, Portsmouth Hospitals Trust, Portsmouth, United Kingdom; 2‘Genetic and Genomic Medicine, Univ of Southampton, Southampton, United Kingdom; 3Purine Research Laboratory, St. Thomas’ Hospital, London, United Kingdom.

Background: Uromodulin associated kidney disease (UAKD) is a difficult to diagnose, rare autosomal dominant genetic disorder caused by mutations in the UMOD gene. We aimed to determine the frequency and distribution of pathogenic UMOD mutations in a familial kidney disease cohort and to investigate any distinguishing clinical features.

Methods: CKD patients with a family history (FHx) of renal disease were ascertained from a large tertiary renal center through a questionnaire study and database search. Patients with a FHx suggesting an unknown genetic diagnosis or UAKD were recruited. DNA was extracted from blood or saliva and sequenced for UMOD exons 3-5. Phenotypic characteristics were compared between patients with and without UMOD mutations, with significance testing in SPSS.

Results: Of 3,760 patients in CKD stages 3-5, 131 patients with a compatible FHx were identified and recruited. Of these, 30 patients (23%) from 17 families had 11 distinct pathogenic UMOD mutations. In 12 patients (9%) from 7 families this was previously unsuspected. UAKD patients had significantly lower protein creatinine ratios (median 28, versus median 222, Mann-Whitney-U p=0.001), less hematuria (22 p=0.0003), more electrolyte abnormalities (c2 p=0.02) and less severe anaemia (c2 p=0.049) pre renal replacement therapy (RRT). There were no statistically significant differences in uric acid, gout, allpurinol use, hypertension, renal cysts, renal size, and age at presentation or RRT.

Conclusions: UAKD is common amongst familial nephropathy patients, and is poorly predicted by clinical features. Hyperuricaemia or gout, both typical of early UAKD, did not distinguish from prevalent familial nephropathies, but less proteinuria and haematuria did. More electrolyte abnormalities in UAKD could be due to an alteration in tubular water permeability; the reason for less anaemia is unclear. Having demonstrated a high prevalence of UAKD, we advise UMOD testing guided by family history regardless of typical phenotype.

Funding: Private Foundation Support

FR-OR055

Chaperone Therapy in Stem Cells Derived from Fibroblasts with Missense Mutations in X-Linked Alport Syndrome  Dongmiao Wang,1 Sharon D. Ricardor,2 Judith A. Savige,1 Medicine, The Univ of Melbourne (Melbourne Health), Melbourne, VIC, Australia; 2Anatomy and Developmental Cell Biology, Monash Univ, Clayton, VIC, Australia.

Background: Forty % of mutations in X-linked Alport syndrome are caused by missense changes, often where Gly is substituted with another amino acid. Chaperone treatment has been useful in other diseases due to missense mutations. The aim of this study was to produce iPFS from fibroblasts from a male with X-linked Alport syndrome and determine the effects of the chemical chaperone, 4 phenyl butyric acid.

Methods: Stem cells were made by the Ricardor lab from skin fibroblasts of a male with X-linked Alport syndrome due to p.G624D. He had developed renal failure at the age of 54, and had hearing loss, but no lenticulocentral retinopathy. Stem cells were induced to become podocytes, and examined for collagen IV a1-ab expression, and for markers of ER stress (ATF6, HSPA5, DDIT3), autophagy (ATG5, BECN1, ATG7) and apoptosis (CAP3, BAD, BCL2) using qRT-PCR (Applied Biosystems 7500). Levels of collagen IV a5 chain were quantitated in an in-house inhibition ELISA. These measurements were repeated after incubation with the chemical chaperone, 10 mM 4-phenyl butyric acid.

Results: The iPFS expressed collagens IV a3 and a4 mRNA consistent with a podocyte phenotype. Levels of collagen IV a5 mRNA and protein were not different from those in normal male fibroblasts. However levels of both intra and extracellular collagen IV a5 were reduced suggesting degradation. The Alport iPFS had increased transcripts for HSPA5, and apoptosis (CAP3 and BCL2) compared with normal. Incubation with 4 phenyl butyric acid, resulted in a reduction in all markers of autophagy and of CAP3.

Conclusions: iPS derived from Alport fibroblasts represent a model system in which to examine novel treatments. Chemical chaperone therapy has beneficial effects on cells derived from individuals with Alport syndrome due to missense mutations.

Funding: Private Foundation Support

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

Underline represents presenting author.

45A
Massively Parallel Sequencing (MPS) in Diagnostically Refractory Genetic Renal Disease (GRD) Andrew John Mallett,1,2,4 Chirag Patel,1,3,4 Joanna Crawford,1 Bruce Bennett,1 Melissa H. Little,1,5,7 Helen G. Healy,1,2,6 Stephen I. Alexander,1 Valentine Hyland,3 Cas Simons,4 * Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane and Women’s Hospital, Australia; 2School of Medicine, The Univ of Queensland, Australia; 3Genetic Health Queensland, RBWH, Australia; 4Inst for Molecular Biosciences, UQ, Australia; 5Dep of Molecular Genetics and Nephropathy, Children’s Hospital at Westmead, NSW, Australia; 6Molecular Genetics Laboratory, Pathology Queensland, Australia; 7Murdock Children’s Research Inst, Melbourne, VIC, Australia.

Background: GRD accounts for 10% of adults and 50% of children with end stage kidney disease. An unknown proportion of cases remain refractory to current genetic tests. Although MPS is applicable in a research setting. We aimed to utilize MPS with pedigree analysis in unresolved cases of GRD.

Methods: Families with clinically diagnosed GRD were recruited in whom clinical genetic testing was either negative or not available. Whole exome sequencing was undertaken and analyzed with custom in house bioinformatics assessment tools accounting for all inheritance patterns. Identified variants of interest were confirmed using Sanger sequencing in clinical laboratories.

Results: 14 families (62 participants) were recruited with a variety of GRD diagnoses and modes of inheritance. A molecular genetic diagnosis has been resolved in 5 families. These included mutations in MDM4 (compound heterozygous), IFT44L (compound heterozygous), HNF1A (heterozygous), COL4A5 (hemizygous) and INR4/Phe (mtDNA) genes. All have been confirmed in a clinical diagnostic laboratory and reported back to the participants with further genetic counseling. Research continues in the remaining 9 families, including application of whole genome sequencing. No reportable incidental genetic findings were identified.

Conclusions: MPS confirmed and clarified a clinical genetic diagnosis in 5/14 families with previously and diagnostically refractory GRD. These results were integrated into clinical practice and demonstrated the potential of MPS in the delivery of clinical care. Further studies are required to resolve the remaining families.

Funding: Private Foundation Support

FR-OR056

Development and Validation of Targeted Genomic Enrichment and Massively Parallel Sequencing as a Diagnostic Test for Genetic Renal Diseases Christie P. Thomas,1,2 M. Adela Mansilla,1 Ramakrishna Sompallae,1 Sara Mason,1 Anne E. Kwitek,1 Colleen Ann Campbell,1 Richard J. Smith,1 * Internal Medicine, Univ of Iowa, Iowa City, IA; 1Inst of Human Genetics, Univ of Iowa, Iowa City, IA; 4Veternars Affairs Medical Center, Iowa City, IA.

Background: Many renal diseases have a genetic basis, although definite genetic confirmation of precise etiology is rarely sought, in spite of the value of genetic screening in patients with ESRD both to confirm a diagnosis and to guide the evaluation of living related kidney donors, who may be at increased risk of ESRD.

Methods: To enable comprehensive screening for genetic diseases, we developed a panel that combines targeted genomic enrichment with massively parallel sequencing to simultaneously interrogate 120 genes implicated in 75 renal diseases. To validate this panel, a panel that combines targeted genomic enrichment with massively parallel sequencing to undertake and analyzed with custom in house bioinformatics assessment tools accounting for all inheritance patterns. Identified variants of interest were confirmed using Sanger sequencing in clinical laboratories. Patients with further genetic counseling. Research continues in the remaining 9 families, including application of whole genome sequencing. No reportable incidental genetic findings were identified.

Conclusions: MPS confirmed and clarified a clinical genetic diagnosis in 5/14 families with previously and diagnostically refractory GRD. These results were integrated into clinical practice and demonstrated the potential of MPS in the delivery of clinical care. Further studies are required to resolve the remaining families.

Funding: Private Foundation Support

FR-OR057

Mechanisms of Anti-CD20 B Cell Treatment of Experimental Autoimmune MPO-ANCA Glomerulonephritis Poh-Yi Gan,1 Joshua D. Ooi,2 A Richard Kitching,1,2 * Dept of Medicine, Monash Univ, Clayton, Victoria, Australia; 2Dept of Nephrology, Monash Health, Clayton, Victoria, Australia.

Background: Depletion of B cells with anti-CD20 monoclonal antibody (mAb), rituximab, is an effective therapeutic for human MPO-ANCA GN. Its capacity to attenuate established disease suggests that CD20+ B cells are important in maintaining ANCA production, their role in maintaining established nephritogenic anti-MPO anti-CD4 T cell driven autoimmune is unknown. This study assesses this role and its importance in this disease model.

Conclusions: We report a novel observation that TACI, not BAFF-R, is the predominant B cell receptor promoting BAFF-mediated murine lupus nephritis. These findings suggest that TACI may be an important therapeutic target in SLE, particularly in patients with high BAFF levels.

Funding: Other NIH Support - K08 Career Development Award (NIAID), Private Foundation Support

FR-OR058

The B Cell Survival Cytokine BAFF Promotes Murine Lupus Nephritis via Activation of TACI, Not BAFF Receptor Shaun W. Jackson,1,2,4 Holly Jacobs,1,2 Nicole Scharping,1,2,4 Tanvi Arkatkar,1,3 David Rawlings,1,2,3 Seattle Children’s Research Inst, Seattle, WA; 2Dept of Pediatrics, Univ of Washington, Seattle, WA.

Background: Transgenic (Tg) over-expression of the B cell survival cytokine BAFF (also known as BLYS) promotes immune-complex glomerulonephritis in mice. Consistent with this, lupus nephritis patients have increased serum BAFF levels and the BAFF-targeted monoclonal Belimumab is an approved SLE therapy. BAFF binds two B cell receptors, BAFF-R and TACI. Since BAFF-R is required for mature B cell survival, this receptor is important to explain BAFF-Tg autoimmunity. However, potential important roles for TACI have not been addressed.

Methods: To test the impact of TACI on BAFF-driven autoimmune, we crossed BAFF-Tg and TACI−/− mice. Autoantibodies and urine albumin were measured by ELISA, and B cell phenotyping was performed by FACS.

Results: Despite marked splenic B cell hyperplasia, deletion of TACI abrogated serum anti-nuclear autoantibodies (ANA) in BAFF-Tg mice. In addition, lack of TACI prevented autoantibodies targeting RNA- and DNA-associated self-antigens, including anti-DNA, anti-Sm, anti-U1RNP, and anti-SSA/Ro. Consistently, anti-MPO IgM, IgG1, IgG2b, IgG2c, IgG3. Aged BAFF-Tg mice develop prominent immune-complex glomerulonephritis, characterized by mesangial expansion, glomerular basement membrane thickening and capillary occlusion. Consistent with the lack of serum autoantibodies, TACI−/−BAFF-Tg were completely protected from murine lupus nephritis, as evidenced by lack of albuminuria and restoration of renal histology.

Conclusions: We report the novel observation that TACI, not BAFF-R, is the predominant B cell receptor promoting BAFF-mediated murine lupus nephritis. These findings suggest that TACI may be an important therapeutic target in SLE, particularly in patients with high BAFF levels.

Funding: Other NIH Support - K08 Career Development Award (NIAID), Private Foundation Support

FR-OR059

B Cell-Intrinsic Interferon Gamma (IFNγ) Signals Promote B Cell Activation and the Development of Lupus Nephritis Shuan W. Jackson,1,2,4 Nicole Scharping,1,2,4 Holly Jacobs,1,2,4 Tanvi Arkatkar,1,3,4, David Rawlings,1,2,3 Seattle Children’s Research Inst, Seattle, WA; 2Dept of Pediatrics, Univ of Washington, Seattle, WA.

Background: The TH1 cytokine interferon gamma (IFNγ) has been implicated in lupus pathogenesis via direct activation of autoreactive T cells. Whether IFN-γ also exerts cell-intrinsic impacts on autoantigen-producing B cells has not been studied. We developed a chimeric lupus model in which Wiskott-Aldrich syndrome protein (WAS)-deficient B cells promote spontaneous humoral autoimmunity (Jackson, et al, J Immunol 2014). An important advantage of the WAS chimeras model is that dysregulated immune responses are limited to the B cell compartment, allowing genetic manipulation in a B cell-intrinsic fashion. In the current study, we contrast the impact of global, T cell- and B cell-intrinsic deletion of the IFNγ receptor (IFNγR) on development of lupus nephritis.

Results: We established lupus-prone WAS chimeras in which IFN-γR was deleted on all immune cells (global IFN-γR-null) or specifically on B or T cells. Chimeras were analyzed for autoantibodies, immune activation and immune-complex glomerulonephritis (IC GN) by ELISA, flow cytometry and immunohistochemistry.

Results: Global IFNγR deletion prevented autoantibody (Ab) production and systemic inflammation in WAS chimeras. Strikingly, cell-intrinsic deletion of IFNγR on either T cells or B cells recapitulated the phenotype of global IFNγR deficiency. Mechanistically, deletion of IFNγR on B cells prevented the formation of spontaneous germinal centers (GCs), required for class-switched Ab formation. Consistent with lack of serum autoantibodies, IgC GN was abrogated in B cell IFNγR-null chimeras. Interestingly, B cell-intrinsic deletion of the TH1 transcription factor T-bet prevented pathogenic IgG2c subclass Ab, but did not impact spontaneous GCs or systemic inflammation.

Conclusions: We report a novel T-bet-independent mechanism whereby IFNγ promotes lupus nephritis via direct actions on B cells. This study is the first to directly address the impact of B cell IFN-γ activation in murine lupus, of relevance to both the understanding of disease pathogenesis and to efforts to target IFN-γ therapeutically in lupus.

Funding: Other NIH Support - K08 Career Development Award (NIAID), Private Foundation Support

FR-OR060

Oral Abstract/Friday Immunologic Basis of Glomerular Injury
Methods: Experimental anti-MPO autoimmunity was induced by immunizing C57BL/6 (Wt) mice with MPO in Freund’s adjuvant and GN triggered using a subtherapeutic dose of anti-Globulin globulin. Mouse anti-C20 mAb (or control mouse anti-IgG2a mAb) was administered to mice with established anti-MPO autoimmunity (day 14) and continued through the development of GN (terminated on day 32).

Results: Anti-C20 mAb induced profound and continued B cell depletion and protected mice from the development of renal injury, compared to controls (segmental glomerular necrosis: 16/16 vs 4/4±0%, albuminuria: 221.0±81.6 vs 895.8±330.3 mg/24hrs and glomerular CD4 T cell influx: 0.4±0.07 vs 0.9±0.1, P<0.05). Systemic IgG autoantibodies were also reduced; serum anti-MPO IgG (ANCA) titers (0.21±0.02 vs 0.34±0.07 OD450nm, P<0.05) and dermal MPO induced DTH swelling (0.07±0.02 vs 0.2±0.03 Dnm, P<0.01). Anti-C20 mAb treatment decreased MPO specific recall proliferation in draining lymph node cells (104.5±12.7 vs 217.7±55.3 counts per minute, P<0.05). In vitro production of IFN-γ and IL-17A producing cells (ELISPOT: 22.6±11.5 vs 27.7±13.2 cells, P<0.01 and 6.3±0 vs 40.18±0 cells, P<0.05, respectively). Furthermore anti-C20 mAb increased the proportion of proliferating Foxp3+ T regulatory cells (2.9±0.1 vs 1.7±0.1, P<0.001). 15% of proliferating Foxp3+ T cells in both groups produced IL-10.

Conclusions: In addition to its known capacity to reduce humoral autoimmunity, this study shows that anti-C20 mAb induced B cell depletion significantly reduces anti-MPO CD4 T cell effectors and enhances T regulatory cells.

Funding: Government Support - Non-U.S.

FR-OR061 Novel Anti-Peroxidasin Antibodies Are Part of the Autoimmune Milieu in Preclinical and Clinical Goodpasture’s Disease Abraham Scott McColl,1, 2 Gautham B. Bhave,1 Vadim Pechenko,1 Agnes B. Fogo,1 Dustin J. Little,1 Thomas P. Baker,1 Storherr K. Olson,1 Billy G. Hudson,1 Nephrology, Hypertension, Vanderbilt Univ Medical Center, Nashville, TN; 2Nephrology, Walter Reed Army Medical Center, Bethesda, MD; 3Pathology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Goodpasture’s disease (GP) is an autoimmune disorder characterized by autoantibodies directed against the NC1 domain of the α3(IV) chains of collagen IV in the glomerular and alveolar basement membranes. Epidemiologically, anti-MPO positivity often occurs with GP diagnosis. The normally cross-linked collagen IV scaffold forms through the action of the heme peroxidase, peroxidasin, via its HOBr production to from a sulfinitine (S=N) crosslink in the NC1 domain, however loss of the S=N crosslink changes recognition of the NC1 domain by GP antibodies.

Methods: A Vanderbilt GP patient cohort and a retrospective case-control Department of Defense Serum Repository (DoDSR) cohort were tested for recognition of peroxidasin, MPO, α3 and α5(IV) NC1 domains by ELISA with 3:1 age, sex, and race, and age of serum matched controls from the DoDSR. Competition binding ELISA was performed to determine antigen specificity and immunofluorescence was performed on GP biopsies for peroxidasin levels. Peroxidasin HOBr production in vitro was fluorometrically tested in the presence of purified antibodies.

Results: Anti-peroxidasin autoantibodies are present in GP patient sera 33%/8/24%) at diagnosis, and in 66%/4/6 of pre-diagnosis GP patients. Unexpectedly, the anti-peroxidasin specific antibodies cross-react with coated, but not native MPO, accounting for a subset of the currently defined dual-positive patients. We also found significantly elevated focal peroxidasin staining in crescentic glomeruli of GP patients. Importantly, patient IgG containing anti-peroxidasin antibodies significantly inhibited of peroxidasin’s HOBr production rate.

Conclusions: Peroxidasin is a novel autoantigen in a subset of GP patients validated in two independent cohorts. Anti-peroxidasin antibodies potentially contribute to disease pathogenesis in GP with possible implications to be explored in other anti-MPO associated diseases.

Funding: NIDDK Support, Other U.S. Government Support

FR-OR062 Autoantibodies against Thrombospondin Type-1 Domain-Containing 7A Induce Membranous Nephropathy in Mice Nicola M. Tomás,1 Elion Hoxha,1 Lars Fester,1 Udo Martin Helmchen,1 Gerth H. Jens,2 Friederike Bachmann,2 Klemens Budde,2 Friedrich Koch-nolte,1 Gunther Zahner,1 Gabriele M. Rune,1 Gerard J. Lambeau,1 Catherine Meyer-Schwesinger,1 Rolf A. Stahl,1 Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 2Charité-Universitätsmedizin Berlin, Berlin, Germany; 3Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: Membranous nephropathy (MN) is an autoimmune disease and a frequent cause of nephrotic syndrome in adults. Autoantibodies against the polypeptide proteins phospholipase A2 receptor 1 and thrombospondin type-1 domain-containing 7A (THSD7A) have been identified in about 75% of patients with MN. However, it is unclear whether these autoantibodies are causative for the development of MN.

Methods: Mice from two patients with anti-THSD7A autoantibody positive MN and control serum were injected into male BALB/c mice. We then analyzed the pathological and clinical development of MN in these mice.

Results: Mice that received anti-THSD7A positive serum developed subepithelial deposits containing IgG (hdpG) and C3 and were exposed to human serum were found to have circulating mouse anti-hdpG, but only mice which received mouse anti-THSD7A autoantibody positive serum developed albuminuria starting day 3, while urinary albumin excretion of mice injected with control serum remained unchanged.

Conclusions: We conclude that anti-THSD7A autoantibodies are pathogenic and can induce MN in mice.

Funding: Government Support - Non-U.S.

FR-OR063 Epitope Spreading in PLA2R1 Is Associated with Bad Prognosis in Membranous Nephropathy Barbara Seitz-Polaki,1, 2, 3 Guillaume Dolla,2 Christine Payre,2 Sylvia Benzaken,2 Ghislaine Bernard,1 Vincent L.M. Esnault,1 Germaine Lambeau,1 Immunologie, Nice Univ Hospital, Nice, France; 2Inst de Pharmacologie Moléculaire et Cellulaire, CNRS and Univ de Nice, Valbonne, France; 3Nephrology, Nice Univ Hospital, Nice, France.

Background: The phosphoprotein A2 receptor (PLA2R1) is the major autoantigen in idiopathic membranous nephropathy, with two recently identified epitopes of unknown clinical significance.

Methods: Fifty PLA2R1-positive patients’ sera were screened by western blot on a series of PLA2R1 deletion mutants covering the ten extracellular domains. We identified epitopes in the Cy3R, CTLD1 and CTLD7 domains and confirmed the reactivity against these three domains with soluble forms of each domain using a new ELISA in 69 PLA2R1-positive patients.

Results: Domain-specific ELISAs allowed stratifying 69 PLA2R1-positive patients into three subgroups: 23 Cy3R, 14 CTLD1 + Cy3R and 32 Cy3R + CTLD1 + CTLD7. Median ELISA titers measured using the full-length PLA2R1 antigen were not statistically different between different patients’ subgroups. The 23 patients with anti-CysR restricted activity were younger (p<0.008), had less nephrotic range proteinuria (p<0.018) and exhibited more spontaneous remission (p<0.03), lower rate of renal failure progression (p<0.0025) and less end-stage kidney disease (p=0.01) during follow-up. Indeed, 31/69 patients had poor renal prognosis according to KDIGO (urinary protein/creatinine ratio over 4 g/g or eGFR <45 ml/min/1.73 m² at end of follow-up). High anti-PLA2R1 activity and epitope spreading beyond Cy3R epitope were independent risk factors of poor renal prognosis in multivariable cox regression analysis. Epitope spreading during follow-up was associated with disease worsening (n=3), whereas reverse spreading from CTLD7 profile back to Cy3R was associated with favorable outcome (n=1).

Funding: Government Support - Non-U.S.

FR-OR064 Intravascular Extensions Allow Renal DC to Capture Bloodborne Antigens and Mediate T Cell Migration into the Kidney Karim Yatim,1 Martin H. Oberbarnscheidt. Thomas E. Starzl Transplantation Inst, Univ of Pittsburgh, Pittsburgh, PA.

Background: We have previously shown that the kidney, a non-barrier, highly vascularized organ organizes an extensive monocye-derived DC network with around 25% of DC sampling intravascular antigens (Ag) by extending projections into the lumina of cortical postcapillary venules. Here, we hypothesized that renal DC have an active role in immune surveillance via (1) capturing intravascular antigens such as bacteria and immune complexes (IC) and (2) mediate Ag-specific T cell migration into the kidney.

Methods: 2-Photon Intravital Microscopy (2PIM) and flow cytometry was performed on CX3CR1 GFP/+ (DC express GFP) mouse kidneys. Ovalbumin immune complexes (OVA-IC) conjugated to PE-TxRed or E.Coli expressing Ovalbumin (OVA) and CFP were i.v. injected. For migration experiments, C57D2R1 OT-I effector T cells were injected i.v. Results: After systemic administration of fluorescent E. coli we observed (1) DC uptake of bacteria from the intravascular space immediately after injection (2PIM and flow cytometry) and (2) a 4±1 increase of DCs with intravascular processes after E.coli injection (2PIM). DC also took up i.v. OVA-IC, (2PIM). Furthermore, in the setting of a systemic CFP-OVA E.coli infection, OT-1 T cells migrated into the kidney (2PIM and flow) with 2PIM showing stable DC-T cell interactions and DC (green)-mediated T cell (red) migration into the kidney (figure 1) (blood-cyan).

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

Underlines represent presenting author.
The C5a Receptor Mediates Anti-Myeloperoxidase Auto-Immunity and Glomerulonephritis

Centre For Inflammatory Diseases, Monash Univ, Melbourne, Australia.

Background: C5ar inhibition is currently the subject of a clinical trial for treatment of ANCA associated vasculitis. C5ar is known to play an important role in neutrophil behaviour, however whether complement acting through the C5ar influences anti-myeloperoxidase (MPO) autoimmunity itself is unknown.

Methods: MPO autoimmunity was induced by injecting C5BL/6 (WT) or C5ar/-/- mice with MPO in Freund’s adjuvant. In separate experiments WT mice were injected with 1x10⁶ WT or C5ar/-/- MPO-pulsed bone marrow derived dendritic cells (DCs). Anti-MPO glomerulonephritis was triggered by a sub-nephritogenic dose of anti-GBM globulin.

Results: Anti-MPO at 10 days measured by anti-MPO IgG ELISA was significantly reduced in C5ar/-/- mice (0.64±0.05 vs 2.0±0.20OD450, p<0.001). This was associated with a lower proportion of splenocytes that were B220+ B cells (58±2 vs 32±2% p<0.001) and a higher serum BAFF (11.4±1 vs 6.6±1.4 ng/ml p<0.01) compared to WT. T cell immunity to MPO was significantly attenuated in C5ar/-/- mice measured by proliferation of recombinant MPO stimulated lymph node culture (3H]-Thymidine 1302±253 vs 574±123 counts per minute p<0.01). Th1 response was reduced measured by IFNγ ELISPOT (55±11 vs 276±13 cells p<0.03) and footpad DTH (0.16±0.02 vs 0.04±0.01bmm p<0.001). There was no difference in Th17 response IL17A ELISPOT (32±7 vs 31±8 cells).

The proportion of CD4+CD25+Foxp3+ T regulatory cells was significantly increased in WT mice compared to C5ar/-/- mice (11.6±0.2 vs 13.5±0.4% p<0.001). To determine whether C5ar expression of DC in infection and the pathogenesis of immune-complex mediated renal diseases.

Conclusions: Complement acting through the C5ar plays an important role in modulating both humoral and cellular anti-MPO autoimmunity in mice. This suggests an additional mechanism by which C5ar inhibition in ANCA associated vasculitis may be an effective treatment strategy.

Funding: Government Support - Non-U.S.

FR-OR065

T-Bet Activation in Regulatory T Cells Is Required for General Fitness, Antibody Production and Control of Th1 Responses in Crescentic Glomerulonephritis

Anna Nosko,1 Malte A. Kluger,1 Paul Dieffenhardt,1 Simon M. Morgen,2 Claudia Wegscheid,2 Gina Tregs,2 RoF A. Stahl,1 Ulf Panzer,1 Oliver M. Steinmetz.1 1Nephrology, Hamburg Univ Medical Center; 2Experimental Immunology, Hamburg Univ Medical Center.

Background: Mechanisms responsible for down regulation of pathogenic Th1 immunity remain widely unknown. Recently, it was proposed that activation of the Th1 characteristic transcription factor T-bet optimizes Foxp3+ regulatory T cell (Treg) function to counteract Th1 responses.

Methods: Nothing is known about the role of T-bet+ Treg cells in inflammatory disease. We studied their function in the NTN model of acute crescentic glomerulonephritis (GN).

Results: Kneys of nephritic wild type mice showed increasing percentages of Treg1 cells during the course of NTN, indicating their functional importance. Naive Foxp3+T-bet+/- mice (Treg1-/-), lacking Treg cells, showed spontaneous skewing towards Th1 immunity. In the absence of Treg1 cells, NTN was aggravated in terms of renal function, histology and inflammatory cell infiltration with selectively elevated renal and systemic Th1 responses. Analyses of Tregs from Treg1-/- mice revealed unaltered systemic numbers, activation of Th1 responses and in vitro suppressive function. However, expression of the Th1 characteristic trafficking receptor CXCR3 was absent on T-bet deficient Treg cells, resulting in significantly reduced renal Treg infiltration. In addition to diminished renal trafficking, overall fitness of Tregs from Treg1-/- mice was greatly impaired. In competitive co-transfer experiments into lymphopenic hosts, T-bet deficient Tregs were outcompeted by wildtype Tregs in terms of proliferation and expression levels of Foxp3. Furthermore, T cell dependent humoral immunity was impaired in Treg1-/- mice, indicating that T-bet activation in Tregs plays a hitherto unrecognized role for antibody production.

Conclusions: Our data indicate the importance of regulatory T cells in crescentic GN. These Treg1 cells are characterized by activation of the transcription factor T-bet, which enhances their overall fitness, directs antibody responses and optimizes their capacity to down-regulate Th1 responses by inducing CXCR3 expression.

Funding: Government Support - Non-U.S.

FR-OR068

Predicting the Lifetime Risk of End-Stage Renal Disease in Kidney Donor Candidates


Background: A tool to comprehensively evaluate the lifetime risk of ESRD in potential living kidney donors could help standardize transplant center acceptance criteria.

Methods: We developed statistical equations to predict the lifetime incidence of ESRD according to a person’s baseline demographic and health characteristics before kidney donation. Data sources included prevalence estimates from NHANES, ESRD incidence from USRDS, and ESRD risk associations in low-risk subgroups of 7 general population cohorts (N=4,580,454). Developed equations were applied to the general population (using NHANES) and the recent US donor population (using the OPTN registry) and made available in an online risk calculator (www.transplantmodels.com/lifetime).

Results: For the “base-case” potential donor (eGFR 90 ml/min/1.73 m²; urine ACR 10 mg/g, systolic blood pressure 120 mmHg, and no adverse health characteristics), the predicted pre-donation lifetime incidence of ESRD varied by age, race, and sex: 2.7%, 1.1%, 0.9%, and 0.6% in 20-year-old black men, black women, white men, and white women, respectively, and 0.6%, 0.5%, 0.3%, and 0.2% in the corresponding 60-year-old candidates. The lifetime incidence of ESRD was higher with additional risk factors, particularly low eGFR or high ACR in young persons (Figure). The predicted lifetime incidence of ESRD before donation was <1% in 88% of recent US donors.

Conclusions: We suggest consideration of pre-donation lifetime ESRD risk in the evaluation and counseling of potential living kidney donors. Our equations estimate a person’s lifetime incidence of ESRD in the absence of donation according to multiple demographic and clinical characteristics.
Post Donation Hypertension and Risk of Death and ESRD

**Background:** Prevalence of de novo hypertension after kidney donation appears to be similar to that in the general population. Factors associated with it development, however, have not been studied. Goals: 1) ascertain donors' risk of developing HTN, 2) describe the impact of its development on death and renal function and 3) develop a HTN risk prediction model using pre-donation parameters.

**Methods:** Our donors are followed indefinitely through surveys inquiring about HTN, renal disease and also serial laboratory testing. Risk factors for post donation new onset hypertension were determined using stepwise proportional hazards regression.

**Results:** HTN status was ascertained in 3638 donors with a mean follow-up of 13±11 years. In total, 972 (27%) developed new onset hypertension. Pre-donation risk factors for development included older age, higher BMI, SBP, and serum glucose at donation (Table 1a). White donors were 40% less likely to develop hypertension, p<0.001 for all. HTN development included older age, higher BMI, SBP, and serum glucose at donation (Table 1b).

**Conclusions:** Hypertension can be reasonably predicted in kidney donors using baseline data. Hypertension is a significant contributor to reduced GFR, ESRD and also death. **Funding:** Other NIH Support - NIH(5P01 DK013083)

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### Table 1. Pre-donation risk factors for HTN

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.03-1.04)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>1.06 (1.04-1.07)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>1.03 (1.02-1.04)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>1.01 (1.01)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>White race</td>
<td>0.6 (0.45-0.79)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 2. Post donation HTN and hard outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3.69 (2.88-4.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3.99 (2.62-6.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR &lt;30 or RRT</td>
<td>2.48 (1.38-4.46)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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**FR-OR070**

Effect of Changing African American Race to Apolipoprotein L1 Genotype on Kidney Donor Risk Index

Bruce A. Julian,1 Robert S. Gaston,1 Barry L. Freedman,2 William Mark Brown,2 Amber M. Reeves-Daniel,2 Ajay K. Israni,1,4 David P. Schladt,1 Stephen O. Panst,2 Sumit Mohan,3 Jasmin Divers,2 1 Univ of Alabama at Birmingham; 2 Wake Forest Univ School of Medicine; 3 Minneapolis Medical Research Foundation; 4 Hennepin County Medical Center, Univ of Minnesota; 5 Emory Univ School of Medicine; 6 Columbia Univ.

**Background:** Renal allografts from deceased African Americans (AAs) with 2 renal-risk variants in apolipoprotein L1 gene (APOL1) are lost sooner than kidneys from AAs with 0 or 1 variant. For the latter, allograft survival is similar to that for kidneys from European Americans. Kidney Donor Risk Index (KDRI) was developed recently, before APOL1 effect was described, to quantitatively estimate quality of deceased-donor kidneys; it assigns higher risk for all AA donors. We postulated that replacing AA race with APOL1 genotype in KDRI improves risk prediction for kidneys from deceased AA donors.

**Methods:** Using the effect size in retrospective studies, we calculated KDRI wherein only AAs with 2 APOL1 renal-risk variants received higher KDRI scoring. Weight of APOL1 risk variants was defined by 10-fold cross validation: 9/10 of available data was used to estimate parameter associated with APOL1 in Cox proportional hazard regression with other 9 KDRI variables as covariates. Revised KDRI scores were computed and tested on the last subset; predictive ability was measured by c-index. Cross-validation was done 100x for comparison with original KDRI.

**Results:** Retrospective analyses of 1,149 kidney transplantations from deceased AA donors (979 APOL1=0/1; 170 APOL1=2 renal-risk variants) showed mean donor age, serum creatinine, and KDRI of 35.4 yr, 1.25 mg/dL, and 1.45. Observed c-index with original KDRI tested with full data was 0.89; distribution of observed APOL1-revised KDRI c-indices had minimum 0.55 and maximum 0.98, median 0.87. APOL1-revised KDRI c-index was higher than observed KDRI c-index in 44% of cases.

**Conclusions:** For the 13% of general AA population with 2 APOL1 risk variants, KDRI did not change. However, for the other 87% of AAs, the revised KDRI improved by deleting AA race as a risk factor and better reflects the quality of these kidneys relative to current system. **Funding:** NIDDK Support

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**FR-OR071**

Racial Disparities in Perioperative Complications After Live Kidney Donation

Krista L. Lentine,1 Ngan Lam,2 David A. Axelrod,3 Mark Schnitzler,1 Amit X. Garg,1 Jesse D. Schold,4 Daniel C. Brennan,1 Dorry L. Segev,4 1 Saint Louis Univ; 2 Western Univ; 3 Dartmouth; 4 Cleveland Clinic; 5 Washington Univ; 6 Johns Hopkins.

**Background:** The frequency and severity of perioperative complications after contemporary live kidney donation are not well-described.

**Methods:** We integrated national U.S. donor registry data with administrative records from an academic hospital consortium (98 centers, 2008-2012) to identify predonation comorbidity and perioperative complications captured in diagnostic, procedure and registry sources. Complication severity was graded by Clavien scoring. Correlates (adjusted odds ratio, aOR) of complications were examined with multivariate logistic regression.

**Results:** Among 14,964 donors, 11.6% were African American (AA) and 72.6% Caucasian; 93.8% of nephrectomies began as laparoscopic, 2.4% as robotic, and 3.7%
as open procedures. Compared with Caucasians, AA donors experienced higher rates of any complication (18.2% vs 15.5%, P=0.005), and those exceeding progressive severity thresholds including Clavien >=4 (3.7% vs 2.2%, P=0.0002) (Figure).

After adjustment for demographic, clinical (including comorbidity diagnoses), procedure and center factors, AA race was associated with increased risk of any complication (aOR 1.26, P=0.001), and Clavien >=2 (aOR 1.39, P=0.0002), Clavien >=3 (aOR 1.56, P=0.0001), and Clavien >=4 (aOR 1.65, P=0.004) events. Other significant correlates of Clavien >=4 events included obesity (aOR 1.55), predonation hematologic (aOR 2.78) and psychiatric (aOR 1.45) conditions, and robotic nephrectomy (aOR 2.07), while annual center volume >50 (aOR 0.45) predicted lower risk.

Conclusions: AA race is independently associated with increased frequency and severity of perioperative complications after live donor nephrectomy. Future work should seek to identify underlying mechanisms and approaches to reducing outcome disparities.

Funding: NIDDK Support

FR-OR072

Risk Prediction of End-Stage Renal Disease in Living Kidney Donors


Background: Recent studies have shown increased risk of end-stage renal disease (ESRD) in living kidney donors compared with healthy non-donors. Accurate risk prediction is paramount for informed consent for donation, but individual ESRD risk is unknown.

Methods: Using national donor registry data, we modeled ESRD in 122,773 donors via Cox regression, censoring for mortality. We performed multiple imputation with 50 repetitions to impute body mass index (BMI), unavailable prior to 1999. We used baseline hazard and hazard ratios to calculate individual risk of ESRD at 5, 10, 15, and 20 years post-donation.

Results: Male sex, African-American (AA) race, and higher BMI were associated with greater ESRD risk (all p<0.01, Table 1). Older age was associated with increased risk in non-AA donors (HR per 10y = 1.12, 1.40, 1.60, p<0.001), but decreased risk in AA donors (HR = 1.06, 0.76, 0.66, p=0.02).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.35 (1.25 to 1.45)</td>
</tr>
<tr>
<td>AA race (at age 40)</td>
<td>1.30 (1.19 to 1.41)</td>
</tr>
<tr>
<td>Age per 10y (non-AA donors)</td>
<td>1.40 (1.32 to 1.49)</td>
</tr>
<tr>
<td>Age per 10y (AA donors)</td>
<td>0.76 (0.65 to 0.88)</td>
</tr>
<tr>
<td>BMI per 5 units</td>
<td>1.14 (1.07 to 1.22)</td>
</tr>
</tbody>
</table>

Overall cumulative incidence of ESRD at 5, 10, 15, and 20 years was 3.0, 11.6, 27.7, and 56.9 events per 10,000 donors, respectively (Figure 1). Predicted individual 20-year risk of ESRD ranged from 6.9 per 10,000 (0.07% chance) to 1240.4 per 10,000 (12.4% chance) of ESRD. Median (IQR) individual 20-year risk of ESRD was 49.8 (31.2-83.8) per 10,000 (Figure 1).

Conclusions: Male gender and higher BMI are associated with greater ESRD risk in kidney donors. Old age is associated with greater ESRD risk among non-AA donors, but younger age is associated with greater risk among AA donors, likely due to donor selection. Greater permissiveness may be warranted for older AA donor candidates; younger AA candidates should be evaluated carefully and counseled about long-term ESRD risk.

Funding: NIDDK Support

FR-OR073

Factors Influencing Decision About Kidney Transplant: A Survey of Dialysis Patients

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Background: Kidney transplant (KT) is the treatment of choice for end stage renal disease (ESRD). The decision to pursue KT involves a complex interplay of disease-related, socioeconomic and ethnic factors. We explored factors influencing patients’ decision about KT.

Methods: We sent flyers to 1,283 dialysis units. Of 2,536 interested participants who fulfilled inclusion criteria, we randomly selected and invited 1,400 to complete the questionnaire. Independent variables were demographic factors, distance to dialysis unit, and modes of education about options. In multivariate analysis, we calculated odds ratios (OR) and 95% confidence intervals (CI) for the probability of pursuing KT.

Results: Of 673 participants, 401 had been referred and 201 were listed for KT. Positive predictors of pursuing KT (n=268) included: ‘received 3 or more modes of education about KT (OR=3.08; CI: 1.62 to 5.87); nephrologist discussed the option of KT at least twice in previous year’ (OR=2.49; CI: 1.43 to 4.32). The 2 most common reasons for not pursuing KT included satisfaction with current treatment (18%) and inadequate finances (14%). Urban residence (OR: 2.64; CI: 1.33 to 5.23) and >5 years on dialysis (OR: 1.75; CI: 1.09 to 2.81) were associated with likelihood of indicating satisfaction with current treatment as a reason not to pursue KT. Age >60 (OR: 2.18; CI: 1.21 to 3.94) and proximity to dialysis unit (OR: 2.30; CI: 1.27 to 4.17) were associated with higher likelihood of indicating inadequate finances as reason not to pursue KT. Of those pursuing KT, 36% would not consider LDKT, most commonly citing unavailability of potential donor (28%). Positive predictors of pursuing LDKT were: ‘nephrologist discussed the option of transplant at least twice in last year’; and married status. Negative predictors of considering LDKT were regular attendance at religious service, age >60, being on dialysis >5 years.

Conclusions: Nephrologist-related factors (delivering diverse education) and patient characteristics (age, gender, race, health status perception, marital/socioeconomic status, duration/comfort with dialysis) are important drivers of the decision making process for choice of KT.

Funding: NIDDK Support

FR-OR074

A Propensity-Matched Analysis Comparing Rates of Post-Transplant Diabetes Mellitus (PTDM) in South Asian and Caucasian Renal Transplant Recipients

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Background: South Asians have increased risk for type 2 diabetes but the risk of post-transplantation diabetes mellitus (PTDM) is unknown. The aim of this study was to compare PTDM risk in South Asian versus Caucasian kidney allograft recipients in a propensity matched analysis.

Methods: In this retrospective analysis, data was extracted from electronic patient records at a single-centre (2004-2014). 354 Caucasian and 121 South Asians met the inclusion/exclusion criteria for this study. Caucasians were more likely to be older, male and have higher BMI compared to South Asians. Propensity score matching was therefore undertaken to remove their bias effect.

Results: Propensity matching resulted in 102 pairs of kidney allograft recipients. Median follow up was 51 months (range 3-130 months). Both groups had similar baseline characteristics but South Asians were more likely to have diabetes (9/102 vs 8/102, p=0.84) and GFR at 3 months post-transplant was lower in South Asians (21 vs 26 ml/min/1.73 m², p=0.01). In multivariate analysis, South Asians were 3.5 times more likely to develop PTDM than Caucasians (OR 3.57, 95% CI 1.53 to 8.36, p=0.003). Increased risk was also found for older age group (OR 3.09, 95% CI 1.26 to 7.60, p=0.01) and for those from the north of England (OR 3.25, 95% CI 1.19 to 8.88, p=0.02).

Conclusions: South Asians have increased risk for PTDM compared to Caucasians, independent of BMI or GFR at 3 months post-transplant. However, further work is required to determine whether this excess risk is due to genetic or environmental factors.

Funding: NIDDK Support
characteristics, although South Asians compared to Caucasians received more deceased-donor kidneys (74% vs. 43% respectively, p<0.001) and were more likely to be CMV positive (77% vs. 43% respectively, p=0.001). Five-year PTDM was higher in South Asians versus Caucasians (34% vs. 11% respectively, hazard ratio 4.3 [95% CI: 2.0–9.4, p=0.001]).

Donor type had significant interaction with ethnicity. While no difference in PTDM was observed in recipients of live kidneys, 5-year PTDM risk was 42% versus 5% for South Asian versus Caucasian deceased kidney recipients respectively (p<0.001). No difference was observed in allograft function, rejection episodes, adverse cardiovascular events or patient graft survival.

Conclusions: South Asian kidney allograft recipients have increased risk of PTDM, especially in the context of deceased kidney donation. It is important to recognize South Asians as high risk for PTDM to allow targeted screening and management strategies.

FR-OR075
Increased Circulating T-Lymphocytes Expressing HLA-DR in Kidney Transplant Recipients with Microcirculation Inflammation
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Background: Despite the clinical impact of microcirculation inflammation (MI) and T-lymphocyte on antibody-mediated rejection in kidney transplant recipients (KTRs), the association between MI in allograft biopsy and activity of T-lymphocyte in the peripheral blood is not known. This study aimed to compare the histologic grading of renal allograft acute cellular rejection (ACR) and activity of serum T-lymphocyte subsets and HLA-DR positive monocytes in KTRs.

Methods: A total of 137 indication biopsies from renal allografts were performed from 117 KTRs. Among them, 24 biopsy specimens from KTRs who have data of serum T-lymphocyte subsets and HLA-DR positive monocytes at the time of biopsy were included in this study. The frequencies of serum HLA-DR+, CD4+, CD8+, and CD25+ T cells, and CD16+CD56+ NK cells were assessed in patients with MI sum score ≥1 (n=13) compared to KTRs with MI sum score=0 (n=11) (all p<0.05). Among four subsets, CD4+HLA-DR+/CD4+ T cells were positively correlated with MI sum score (P=0.013). However, no significant differences were observed between two groups categorized based on the sum score of HLA-DR, CD4+, CD8+, and CD25+ T cells, and HLA-DR+CD8+ T cells significantly increased in KTRs with MI sum score ≥1 (n=13) compared to KTRs with MI sum score=0 (n=11) (all p<0.05). Of four subsets, CD4+HLA-DR+/CD4+ T cells were positively correlated with MI sum score (P=0.013). However, no significant differences were observed between two groups categorized based on the sum score of HLA-DR, CD4+, CD8+, and CD25+ T cells. Analysis using the receiver-operating-characteristic curve showed that antibody-mediated rejection could be predicted with a sensitivity of 89.3% and a specificity of 53.3% using a cutoff value of 12.25% frequency of CD4+HLA-DR+/CD4+ T cells.

Conclusions: MI was significantly associated with increased frequency of activated T-lymphocyte expressing HLA-DR in KTRs. Further large-scale studies are needed to confirm circulating CD4+HLA-DR+/CD4+ T cells as a useful noninvasive immunologic monitoring tool for prediction of antibody-mediated rejection.

FR-OR076
Monitoring of Calcineurin Inhibitors by NFAT-Regulated Gene Expression in De Novo Renal Allograft Recipients
Claudia Sommerer,1 Martin G. Zeier,2 Stefan Meuer,2 Thomas Giese.2 1Nephrology, Univ Hospital, Heidelberg, Germany; 2Immunology, Univ Hospital, Heidelberg, Germany.

Background: Calcineurin inhibitors are critical-dose drugs with a narrow therapeutic range and the optimal monitoring strategies are discussed in terms of safety and efficacy. A new pharmacodynamic monitoring tool – assessing the expression of nuclear factor of activated T cells (NFAT)-regulated genes – has been established to measure directly the functional activity of cyclosporine A (CsA) in an individual patient. Until now, only sparse data on NFAT-regulated gene expression within the early post-transplant period are available.

Methods: Altogether 80 de novo renal transplant patients were enrolled in this prospective observational trial. The immunosuppression consisted of IL-2 receptor antagonism induction, CsA, mycophenolic acid and steroids. The expression of the NFAT-regulated genes (interleukin 2, granulocyte-macrophage colony stimulating-factor, Interferon γ) was determined by qRT-PCR at CsA C0 and C2 at regular follow-up visits within 6 months after transplantation.

Results: The median age of all patients was 47.9±13.7 years (54 male). Residual NFAT-regulated gene expression showed a high interindividual variability. Inversely to reduction of CsA doses expression of NFAT-regulated genes increased from 1.78±1.33% to 8.04±7.36% in month 1 to month 6. Despite of comparable CsA C0 levels NFAT-regulated gene expression was significantly less inhibited in patients without acute rejection (2.9±2.2% vs. 2.01±1.7%, p=0.047). Patients with very low residual expression on NFAT-regulated genes were on increased risk of early infectious episodes. Residual expression of IFNy and GM-CSF genes correlated most significantly with clinical outcome.

Conclusions: NFAT-regulated gene expression is highly inhibited in the early post-transplant period in renal allograft recipients on CsA treatment. High residual NFAT-regulated gene expression was related to acute rejection episodes but low residual expression with infectious complications. Thus, NFAT monitoring has the potential to support pharmacokinetic monitoring in the early post-transplant period.

Funding: Pharmaceutical Company Support - Novartis Germany

FR-OR077
Proteomics of Urinary Exosomes to Identify Biomarkers of BK Virus Infection and Acute Rejection
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Background: Acute cellular rejection (ACR) and BK virus associated nephropathy (BKV AN) are frequent causes of graft dysfunction after renal transplantation with similar symptoms but requiring different treatments. We investigated whether patients with an ACR episode or BKV AN could be distinguished based on proteins present in urine exosomes.

Methods: Urine samples (50 mL) were collected from renal transplant patients with ACR, BKV AN or stable graft function. Urinary exosomes were isolated from urine samples by ultracentrifugation (110’000×g) for 2 h. For each group (ACR, BKV AN, controls) we pooled equivalent amounts of exosome proteins of 4 patients (first set) and repeated this with 4 different patients in each group (second set). Subsequently, exosomes were lysed and the resulting protein expression was analyzed by 4-12% SDS-PAGE. After electrophoresis, gel lanes were cut into five pieces according to molecular mass. Proteins were in-gel digested with trypsin, and peptide mixtures were analysed using LC-MS/MS. Proteins were identified using the NCBI database. Partial least squares enhanced discriminant analysis was used to classify the patient groups based on exosomal protein content.

Results: A total of 340 individual proteins was detected in the first set of samples and 385 proteins in the second set, with 204 proteins overlapping between both sets. Our preliminary findings show 20 proteins for which the exosome content differed between ACR and BKV AN. Specific candidate proteins that can serve as urinary biomarkers include acid ceramidase, low density lipoprotein-related protein 2, copepeptide, alpha-1-acid glycoprotein 1, syndecan 4, and lactate dehydrogenase.

Conclusions: In this study we show that profiling of urinary exosomes is a promising tool to identify urinary proteins which allow differentiation between ACR and BKV AN in renal transplant patients.

FR-OR078
Identification of Signature Long Non-Coding RNAs in the Development of Diabetic Nephropathy
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Background: Long noncoding RNA (lncRNAs) have emerged as potent regulators of multiple cellular processes relevant to cellular homeostasis and differentiation. More recently, lncRNAs have also been implicated in the pathogenesis of a myriad of diseases, including cancer and heart diseases. However, the role of lncRNAs in diabetic nephropathy (DN) remains unknown.

Methods: Total RNA-Seq analysis was performed on glomeruli from Type 2 diabetic, db/db mice to explore differentially expressed lncRNAs. Following identification of a candidate lncRNA, Tug1 (Taurine-upregulated gene-1) we employed CRISPR/Cas9 genome editing to delete Tug1 in cultured podocytes. Tug1 overexpression in podocytes was used for gain of function analysis. To understand the functional role of Tug1 in vivo and because Tug1 is reduced in diabetic podocytes, we generated podocyte-specific, Tug1 transgenic, db/db mice.

Results: The RNA-Seq analysis revealed that expression of Tug1, a predicted antioxidant-responsive gene, is significantly reduced in the podocytes of db/db mice. Analysis of in vivo isolated podocytes from db/db mice demonstrated that downregulation of Tug1 over time is correlated with the progression of DN. To interrogate the functional relevance of Tug1, we performed transfection and transgenic analysis from CRISPR/Cas9 genome editing to delete Tug1 in cultured podocytes. Tug1 overexpression in podocytes was used for gain of function analysis. To understand the functional role of Tug1 in vivo and because Tug1 is reduced in diabetic podocytes, we generated podocyte-specific, Tug1 transgenic, db/db mice.

Conclusions: Tug1 is critical for podocyte survival and function. In DN, Tug1 is downregulated in podocytes which may contribute to the development and progression of DN.
We generated triple transgenic, podocyte-specific, tamoxifen-inducible miR-93 transgenic mice, which lack miR-93 in podocytes but express it in the proximal tubules in the diabetic kidney. Aberrant expression of PXR may be maintained by changes in obesity and diabetes. In this study, we investigated the expression of PXR in proximal tubules and demonstrated that Tug1 is a mediator of the transcriptional response to high glucose. We also found that activated Smad3 then bound directly to mTOR as determined by a ChiP assay and stimulated fibrosis in response to CRP and high glucose, which was blocked by a Smad3 inhibitor (SIS3) and a mTOR inhibitor (rapamycin). Our data suggest that CRP may promote T2DN by impairing the mTOR pathway via the Smad3-dependent mechanism.

Methods: Human CRP-tg-db/db mice and their littermate controls including db/db, db/m and CRPtg-db/m mice were generated by crossing db/db mice with CRPtg mice that overexpress human CRP. Blood glucose, intraperitoneal glucose tolerance test (IPGTT), intraperitoneal insulin tolerance test (IPTT), 24-hour urinary microalbumin levels were measured every 4 weeks in 8 groups of mice over the 36-week period. To study the signaling mechanism, intrarenal TGF-beta/Smad3 and mTOR signaling were also studied in vivo and in vitro in HK-2 tubular epithelial cells.

Results: Compared with littermate db/db mice, CRP-tg-db/mice developed higher levels of blood fasting glucose and enhanced insulin resistance. This was associated with a marked increase in microalbuminuria and the development of more severe renal fibrosis compared to the wild type collagen I and IV within the diabetic kidney. Enhanced renal fibrosis in CRP-tg-db/mice was associated with a marked activation of TGF-beta/Smad3 and mTOR signaling. Further studies in cultured HK-2 TEC revealed that CRP acted through its receptor CD32b to promote high glucose-induced activation of Smad3 as well as TGF-beta-dependent Smad3 and Smad2/3/4 signaling. The finding that addition of an neutralizing antibody against CD32 or TGF-beta1 and an inhibitor to ERK or p38 was capable of inhibiting CRP-induced Smad3 signaling. Furthermore, we also found that activated Smad3 then bound directly to mTOR as determined by a ChIP assay and stimulated fibrosis in response to CRP and high glucose, which was blocked by a Smad3 inhibitor (SIS3) and a mTOR inhibitor (rapamycin). Conclusions: CRP promotes renal fibrosis in T2DN via the CD32b-Smad3-mTOR signaling pathway.

NRCL4 Knockout Ameliorates the Development of Diabetic Nephropathy in Mice  Fangyun Yang, Yinchong Liu, Ryan Kolb, Fu-You Liu, Weizhou Zhang, 1 Department of Nephrology, the Second Xiangya Hospital, Central South Univ, Changsha, China; 2 Department of Pathology, Univ of Iowa, USA.

Background: Diabetic nephropathy is a growing health concern with characteristic sterile inflammation. An association of diabetic nephropathy with inflammasome activation has recently been shown, but the pathophysiological relevance of this finding remains unknown. In the current study, we aimed to study the role of NRCL4 inflammasome in the development of diabetic nephropathy in mice.

Methods: The expression of NRCL4 inflammasome and macrophage infiltration in renal tissues of patients with DN were detected by immunohistochemistry. Then, we used NRCL4 knockout mice to test the hypothesis that diabetic nephropathy is associated with re-expression of the NRCL4 inflammasome activation. We used the STZ-induced diabetes model, and followed the mice for up to 8 weeks. The mice were randomly divided into 3 groups: the normal control group; the wild-type diabetic group; NRCL4−/− diabetic group.After 8 weeks, serum biochemistry and urine albumin were measured. The kidneys were collected to test the macrophage by flow cytometric analysis and the renal pathologic changes were observed by light microscopy. We also detected the level of IL-1β, IL-18 and CRP in the renal tissues of patients with DN.

Results: Compared with littermate db/db mice, CRPtg-db/db mice developed higher levels of fast glucose and enhanced insulin resistance. This was associated with a marked increase in microalbuminuria and the development of more severe renal fibrosis compared to the wild type collagen I and IV within the diabetic kidney. Enhanced renal fibrosis in CRPtg-db/db mice was associated with a marked activation of TGF-beta/Smad3 and mTOR signaling. Further studies in cultured HK-2 TEC revealed that CRP acted through its receptor CD32b to promote high glucose-induced activation of Smad3 as well as TGF-beta-dependent Smad3 and Smad2/3/4 signaling. The finding that addition of an neutralizing antibody against CD32 or TGF-beta1 and an inhibitor to ERK or p38 was capable of inhibiting CRP-induced Smad3 signaling. Furthermore, we also found that activated Smad3 then bound directly to mTOR as determined by a ChIP assay and stimulated fibrosis in response to CRP and high glucose, which was blocked by a Smad3 inhibitor (SIS3) and a mTOR inhibitor (rapamycin). Conclusions: NRCL4 promotes renal fibrosis in T2DN via the CD32b-Smad3-mTOR signaling pathway.

Mitochondrial Lipid Overload in the Proximal Tubules Leads to Fibrosis Kristian Stanler, Claudia Kruger. Oxidative Stress and Disease Lab, Pennington Biomedical Research Center, Baton Rouge, LA.

Background: While there is ample evidence for defective lipid metabolism in diabetes and insulin sensitive tissues, the role of lipid metabolism in renal disease is underappreciated. Mitochondrial lipid overload – overburdening β oxidation – is an important phenomenon in mitochondrial flexibility. This metabolic disturbance in the kidney has not been studied.
Proximal tubules almost exclusively use fat as their energy source, therefore it is important to understand how they are damaged when they are overloaded with lipids. Tubular fibrosis seems to be a common pathway where all chronic kidney diseases culminate.

**Methods:** To test the relationship between mitochondrial lipid overload and tubular damage, we have developed a proximal tubule specific (GtG Cre) mouse strain lacking carnitine acetyl transferase - crAT (CrATGgt-/-). CrAT is essential for the removal of excess fatty acid products from mitochondria. In its absence, incompletely oxidized fatty acids accumulate, pyruvate oxidation is compromised and a reducing environment conducive to superoxide formation created. This can lead to hydroxyl radical production which will then induce mitochondrial apoptosis. By deleting CrAT an ideal system can be created to specifically model lipid radical formation due to metabolic sources.

**Results:** Knockout mice developed fibrosis, protein casts and tubular injury as they aged when compared to the GtG Cre controls. This was accompanied with increased TGFβ expression, an increased serum creatinine level, increased expression of vimentin, collagen IV, Bax, and caspase-3. Similarly to other mice models of kidney disease, CrATGgt-/- mice displayed phenotypic variations from minor to more severe injury. Kim-1 expression in CrATGgt-/- mice correlated with the severity of fibrosis. Interestingly, mice also developed glomerular injury and FSGS-like lesions, suggesting tubulo-glomerular interactions when tubular mitochondria are overloaded. Challenging mice with high fat diet or uninephrectomy accelerated this phenotype.

**Conclusions:** Our studies suggest that mitochondrial lipid overload (deletion of CrAT) in the proximal tubules may lead to metabolic/redox disturbances and tubular apoptosis and fibrosis. Funding: NIDDK Support

**FR-OR084**

**Role of Neuropilin-1 in Glomerular Function and Disease**

*Christina S. Bartlett,* 1 Monika Lucyna Wnuk, 2 Vera Eremina, 2 Chengjin Li, 2 Yashpal S. Kanwar, 2 Jeffrey H. Miner, 1 Maria Pia Rastaldi, 3 Susan E. Quaggini. 1

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**Background:** Neuropilin-1 (NP-1), a co-receptor for a variety of growth factors (e.g. VEGF, PDGF, and TGF-b), is critical for development and patterning of vascular and nervous systems. Mesangial cells strongly express NP-1 yet the physiological relevance of this is unclear. To date, onset of proteinuria in humans following antibody blockade of NP-1 hints at the importance of NP-1 in glomerular function.

**Methods:** NP-1 expression was assessed by immunofluorescence in biopsy samples from diabetic (DN) and IgA nephropathy (IgAN) patients. To further investigate the role of NP-1, we analyzed mice with perivascular cell specific deletion of NP-1. Intrinsically, cell behaviors affected by NP-1 were examined in primary human mesangial cultures.

**Results:** DN and IgAN biopsies have notably elevated mesangial expression of NP-1 indicating that NP-1 may have a role in glomerular dysfunction. In mice, deletion of NP-1 in the mesangium restricts glomerular maturation and causes dramatic mesangial expansion, marked GBM thickening and tubular dilatation. NP-1 deficient mutants develop severe proteinuria and succumb to renal insufficiency. In mutant glomeruli lacking NP-1 in the mesangium, VEGFR2 phosphorylation is increased while podocyte ERK signaling is hyperactivated. In vitro, we showed that NP-1 mediates direct migration of mesangial cells towards PDGF. Inducible gene targeting of NP-1 is currently underway to delineate developmental versus maintenance functions of NP-1 in the glomerulus particularly within the context of DN.

**Conclusions:** NP-1 expression in the mesangium is needed for glomerular development. NP-1 regulates matrix production and its absence compromises glomerular filtration. Increased expression of NP-1 in DN and IgAN further suggests that glomerular function relies on a finely tuned level of NP-1 signaling. Accordingly, NP-1 may be suitable targets to ameliorate glomerular disease.

**Funding:** Other NIH Support - 5T32 DK007169

**FR-OR085**

**Protein S Protects Podocyte from Injury in Early Diabetic Nephropathy**

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**Background:** Elucidating mechanisms that mediate the early stage of diabetic nephropathy (DN) may help us identify novel preventive and therapeutic measures for patients with DN. Protein S (PS), a vitamin K-dependent protein, functions mainly as a cofactor for the formation of activated protein C (APC). APC is known to have podocyte protective effects in DN. However, the role of PS in DS has not been studied.

**Methods:** Proteomic analysis was performed in glomeruli isolated from STZ and control rats. The podocyte cell-specific Pros1 homozygous knockout mice (KO) were developed to determine the role of PS in DS. Immortalized human podocytes (HPC) were used for in vitro studies. The expression of TMA receptors and podocyte-specific genes were examined by western blot and RT-PCR. The Protein S expression was examined in human kidney biopsies by immunostaining.

**Results:** Proteomic analysis of glomeruli revealed higher expression of PS in diabetic glomeruli. Then, we confirmed an increase of PS expression in the glomeruli of diabetic rats by RT-PCR and immunostaining. Interestingly, PS expression also increased in human kidneys with early DN but decreased in those with advanced DN. As a control, plasma concentrations of PS were not significantly different between diabetic and non-diabetic rats.

**Conclusions:** PS was more prominent in the podocytes of human diabetic kidney, we determined the role of PS in cultured human podocytes. We found that Knockdown of Pros1 enhanced high glucose-induced apoptosis while overexpression of Pros1 inhibited TNFα-induced pro-inflammatory gene expression in podocytes likely through modulation of the TMA receptors. To further determine the role of PS in DN, we developed podocyte-specific Pros1 knockout mice (KO) and found that diabetic KO mice (KO-STZ) developed more proteinuria, mesangial expansion, and foot process effacement than diabetic wide-type mice (WT-STZ).

**Conclusions:** Our data support a protective role of PS against podocyte injury in early DN.

**Funding:** Other NIH Support - NIH R01DK078897, NIH R01DK088541, NIH P01-DK-56492

**FR-OR086**

**Deletion of SHP-1 in Podocytes Prevents Diabetic Nephropathy**

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**Background:** Both clinical and experimental data suggest that podocyte injury is involved in the progression of diabetic nephropathy (DN) in the patients with type 1 diabetes. Although the mechanisms underlying the development of podocyte loss are not completely understood, insulin and nephrin actions have been shown to play a major role in the podocyte survival and function. We have reported that SHP-1, a protein tyrosine phosphatase, is increased in podocytes of diabetic mice and inhibited insulin and nephrin actions. However, the precise role of SHP-1 in the development of diabetic nephropathy remains to be investigated.

**Methods:** We have generated a non-diabetic (NDM) and diabetic Akita (DM; INsD2bKO) conditional podocyte specific SHP-1 knockout (podo-SHP-1KOlKO) mice using the TetO-NCre fox system. Mice received or not doxycycline at 4 weeks of age and renal function (albuminuria and GFR) and pathology were examined at 7 months of age.

**Results:** Elevated albumin/creatinine ratio and GFR showed in DM mice are prevented by 86% and 100%, respectively in DM mice that lack SHP-1 gene specifically in podocytes. Mesangial cell expansion and glomerular hypertrophy is increased by 1.8 and 4.9 fold in DM mice and reduced by 78% and 72%, respectively in DM podo-SHP-1KO mice. Moreover, the expression of collagen type IV and TGF-ß that is enhanced in DM mice compared to NDM was not increased in DM podo-SHP-1KO mice. Transmission electron microscopy analysis demonstrated podocyte foot process effacement in DM mice that is not observed in DM podo-SHP-1KO mice. Furthermore, inhibition of insulin-induced Akt and ERK phosphorylation showed in DM mice is completely prevented in DM podo-SHP-1KO mice. Similar to insulin, nephrin phosphorylation is restored in DM podo-SHP-1KO mice compared to DM mice.

**Conclusions:** Our data indicate that the deletion of SHP-1 specifically in podocytes restored insulin and nephrin actions and prevented renal pathology and dysfunction in diabetic mice.

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

**FR-OR087**

**Targeted Proximal Tubule Injury Promotes Progression of Diabetic Kidney Disease in Akita Mice**

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**Background:** Increasing evidence suggests that the kidney tubulointerstitial injury plays an important primary role in the pathophysiology of diabetes.

**Methods:** In the present studies, a mouse containing several epithelial cell-specific Sic2Cre allele was crossed with a mouse transgenic for a Cre-inducible simian diphtheria toxin receptor (DTR). The diphtheric mouse was then bred with Akita mice as a genetic model of type 1 diabetes. Targeted tubule injury was induced in these animals (Akita DTR+/-; Akita DTR+/- (DTR+) with injection of diphtheria toxin (DT).)

**Results:** Male Akita mice developed sustained hyperglycemia. A single sublethal dose of DT in Akita DTR+/- mice resulted in an acute two-fold rise in urinary albumin excretion and progression of albuminuria over the study period. By 19 weeks after DT injection, Akita DTR+/- mice developed an almost five-fold increase in albuminuria, 40% increase in urinary creatinine, and more than two-fold increase in blood urea nitrogen (BUN) level, and reduced kidney size when compared with Akita controls. Moderate glomerular mesangial expansion, and increased interstitial fibrosis and tubular atrophy (IFTA) and glomerulosclerosis were observed in Akita DTR+/- mice 20 weeks after DT injection. These pathologic changes were accompanied by increased levels of the molecular marker of proximal tubule injury, kidney injury molecule (KIM)-1, in both kidneys and urines of Akita DTR+/- animals. Increased proximal tubule DNA damage response (DDR) activation, pro-inflammatory and pro-fibrotic cells infiltration, and peritubular capillary rarefaction were observed in kidneys of DT-treated Akita DTR+/- mice.

**Conclusions:** In diabetes, proximal tubule injury, perhaps from glyco-toxins, can drive interstitial inflammation and fibrosis, capillary rarefaction, and secondary glomerular injury leading to progression of diabetic nephropathy. Our findings suggest novel therapeutic targets for the prevention and treatment of diabetic kidney disease.

**Funding:** Private Foundation Support
Pax8-Positive Epithelial Organs

DGCR8-Dependent MicroRNA Biogenesis Is Essential to the Function of Pax8-Positive Epithelial Organs

Background: Normal nephron endowment requires a balance of nephron progenitor (NP) self-renewal and differentiation during kidney development. Wnt11, a non-canonical Wnt signal produced by ureteric tip (UT) UT, has been shown to positively regulate the Gdfn-Ret signaling axis and branching morphogenesis. Our current data identifies a new role for Wnt11 in organization of the NP niche.

Results: We examined mice harboring a conditional knockout allele of Dgcr8. Dgcr8-/- mice show an increased apoptosis of nephron progenitors in kidneys that were analyzed the survival and proliferation of nephron progenitors. The loss of DGCR8-Dependent microRNA biogenesis is essential for both renal and thyroid function and can thus be the basis to future experiments addressing the role of specific microRNA sequences. Nonetheless, some aspects of the phenotype differ from the Dicer knockout model pointing towards microRNA-independent contributions of Dicer and Dgcr8 regarding the pathogenesis of these two organs in our mouse model.

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

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Conclusions: Taken together, these data suggest a model in which Trb2a/b are essential for patterning the distal IM from which the distal nephron segments and CS arise, and thus provide novel insights into the regulatory networks that influence renal ontogeny.

Funding: NIDDK Support, Other NIH Support - Office of the Director

FR-OR093

Dot1l Deficiency Leads to Increased Intercalated Cells and Up-Regulation of V-ATPase B1 in Mice

Saifudeen, Samir S. Center, Nashville, TN; 4 Center for Structure Biology, Vanderbilt Univ Medical School at Houston, Houston, TX.

Background: The collecting duct in the mammalian kidney consists of principal cells (PCs) and intercalated cells (ICs), which regulate electrolyte/fluid and acid/base balance, respectively. The repertoire of ICs and their function remains largely unexplored. We previously reported that mice with histone H3 K79 methyltransferase Dot1l disrupted in Aug-2-expressing cells (Dot1lfl/fl) vs. Dot1lfl/wt possessed ~20% more ICs and a similar decrease in PCs.

Methods: In this study, we performed multiple double immunofluorescence staining using various PC and IC markers to assess the relative abundance of PC and IC in Dot1lfl/fl and Dot1lfl/wt. Real-time RT-qPCR, luciferase assay, and chromatin immunoprecipitation assays were conducted to determine if Dot1l regulates the transcription of Atp6v1b1 in vivo in mouse kidney and in vitro in IMCD3 cells.

Results: Dot1lfl/wt had more IC and less PC, with expanded both a-IC and b-IC populations. These changes were associated with significantly upregulated V-ATPase B1 and B2, but not Aqp2, AE1, and Pendrin. Decreased V-ATPase B1 mRNA expression was coupled with a significant reduction of Dot1l and H3K79 di-methylation bound at the Atp6v1b1 5’ flanking region. Overexpression of WT Dot1l, but not the methylationtransferase-dead mutant Dot1a significantly downregulated a stably-transfected luciferase reporter driven by the Atp6v1b1 promoter in IMCD3 cells.

Conclusions: Dot1l is an epigenetic regulator of PC and IC differentiation and Atp6v1b1 is a new transcriptional target of Dot1l.

Funding: NIDDK Support

FR-OR094

DNp63 Progenitor Cells Pattern the Ureretic Bud Stem Cell Niche and Give Rise to b-Intercalated Cells


Background: 1. Ureteric Bud (UB) tip cells constitute a stem/progenitor cell niche with bipotential properties enabling them to self-renew or differentiate, giving rise to all cell types in the collecting duct. Understanding how the UB tip cell commits to the Principal Cell (PC) or Intercalated Cell (IC) fate is essential for the design of strategies to re-build a kidney from stem cells and for hastening epithelial cell regeneration after injury. 2. The N-terminus-truncated p63 isoform, DNp63, is a master transcriptional regulator of epithelial stem cells in skin. 3. Here, we document expression of DNp63 in the UB tip and assess the progenitor cell identity, fate and regenerative potential of DNp63 cells.

Methods: 1. Ret-GFPTg mice were used to demonstrate expression of DNp63 in Ret-IC populations of cortical nephrons. 2. A fraction of cortical H-ATPase+/AE1+ cells are also DNp63 lineage+. We assessed embryos for ureteric induction defects and for aberrations in candidate downstream targets mediating induction defects. We assessed postnatal mice for VUR with euthanized cystograms and ureter insertions into the bladder via three dimensional (3D) reconstruction.

Results: 1. Embryonic day (E) 11.5 Fgfr2α-/- embryos exhibit nearly random ureteric bud induction sites (several cranially or caudally displaced sites along the Wolffian duct) versus controls; moreover, apoptosis and proliferation rates were unchanged in Fgfr2α-/- Wolffian duct segments between the ureteric bud base and cloaca (common nephric ducts) versus control littermates. E11.5 Fgfr2α-/- mice had significantly lower Bmp4 mRNA stromal expression, which is known to cause abnormal ureteral bud induction. Postnatal day 1 (P1) and P30 Fgfr2α-/- mice had significantly higher rates (worsening with age) and grades of VURverse aged-matched controls. Refluxing ureters in Fgfr2α-/- mice had improper ureteral insertion locations into the bladder and significantly shortened intravesical tunnel lengths versus controls.

Conclusions: Deletion of Fgfr2α in peri-Wolffian duct stroma leads to aberrant ureteric bud induction sites resulting in improper ureteral insertion and shortened intravesical length versus controls.

Funding: Other NIH Support - T32 DK091202

FR-OR097

HCN3 Positive Urinary Pacemaker Cells Arise from the Neural Crest

Norman D. Rosenblum,1,2 Meghan M. Feeney,1,2 1Dev and Stem Cell Biology, Hosp Sick Children; 2Dept Lab Medicine and Pathobiology, U Toronto; 3Div Nephrology, Dept Paediatrics, Hosp Sick Children, Toronto, Canada.

Background: Coordinated proximal to distal ureteric peristalsis is mediated by HCN3(+) pacemaker cells (PMCs) in the pelvis-kidney junction (PKJ). Perturbations in HCN3(+) cell number and function are associated with congenital hydronephrosis. The molecular signature of these cells during development is unknown.

Methods: To determine the lineage of the origin of HCN3(+) PMCs, we genetically labeled five distinct lineages of the urogenital system via Cre-mediated expression of ROSA26tatTomato (tdTomato) fluorescent protein and analyzed for co-localization with HCN3, using antibodies, in mouse embryonic kidney tissue. To investigate the molecular signature of the PMCs, HCN3(+) cells were isolated using HCN3 antibodies and fluorescence activated cell sorting (FACS). RNA was prepared from sorted samples and gene expression was analyzed in isolated HCN3(+) PMCs via qRT-PCR and genome-wide RNA sequencing.

Results: tdTom expressed downstream of promoters specific for metanephric or tailbud mesenchyme, ureteric bud or renal stroma failed to co-label with HCN3-marked PMCs. In contrast, tdTom, expressed downstream of the neural crest (NC) specific Wnt1 promoter, co-localized with HCN3 in the PKJ, demonstrating that HCN3(+) PMCs arise from the NC. HCN3(+) PMCs were FACS isolated from mouse embryonic kidneys with >94% purity and >8,000 HCN3(+) cells per litter. Genetic analysis of HCN3(+) PMCs via qRT-PCR demonstrated enrichment of both Hcn3 and Sox10, a NC marker.
Further outlining the NC origin of these cells. Analysis of isolated PMCs, compared to adjacent cells in the PKI, via RNA sequencing, revealed a 3-7-fold upregulation of genes associated with neuronal function.

Conclusions: We conclude that HCN3(+) urinary PMCs arise from the NC and express genes associated with neuronal function. These results provide a basis to identify molecular mechanisms that control PMC development. Funding: Government Support - Non-U.S.

FR-OR100

Tubulogenesis After Acute Kidney Injury Is Limited and Only Driven by Tubular Progenitors

Elena Lazzeri, Anna Julie Peired, Maria Lucia Angelotti, Francesca Becherucci, Duccio Lombardi, Laura Lasaghi, Paola Romagnani. Excellence Centre DENOTHE, Univ of Florence, Italy.

Background: Traditionally, AKI was considered as reversible because of the high regenerative capacity of the tubule. Despite this, AKI is associated with increased risk to develop CKD, suggesting an incomplete repair of the tubules. In addition, it is debated whether regeneration is mediated by differentiated tubular cells or a population of tubular progenitors.

Methods: We developed inducible transgenic Pax8-rtTA/tetO-cre;ROSA26-Confetti (Pax8/Confetti) mice to track all tubular cells and the PAX2-rtTA/tetO-cre;R26.2.Confetti mouse model (Pax2/Confetti) to track putative tubular progenitors. Administration of doxycycline at the 5th week of age drove the stochastic expression at single cell level of CFP, GFP, RFP, YFP, allowing to track Pax8+ or Pax2+ cells and their progeny. After 1 week of washout, mice underwent 30 min of unilateral ischemia followed by a 30 day repARATION period. PAX2, Pax8 and Pax7 mice were used to study repARATION with retinoic acid, Pax2+/Pax8- Fucci Cre-2Fucci (Pax2/Fucci) and Pax2/Pax8 tet-cre;R26.Fucci2 (Pax2/Fucci2) mouse models were used to study cell-cycle (mCherry in G1 cells and mVenUS in S/G2/M cells).

Results: Comparison of clonal analysis in confetti mice demonstrated that Pax2+ progenitors is the only population that undergoes clonal expansion after tubular injury, excluding involvement of other tubular cells. However, regeneration was limited, and the majority of lost tubular cells was not replaced. In addition, confocal microscopy and DNA content analysis by flow cytometry in Pax8 and Pax2/Fucci mouse models demonstrated that only Pax2+ progenitors complete mitosis, while other tubular cells that entered the cell cycle do not complete cytokinesis and undergo death or arrest.

Conclusions: In summary: 1. The tubule displays limited regenerative capacity; 2. Differentiated tubular cells enter the cycle but do not complete mitosis; 3. Only tubular progenitors undergo a complete cell division providing regeneration after injury. Taken together, these results provide an innovative explanation of the mechanisms of tubular repair and a suggestive hypothesis to explain the occurrence of CKD after AKI.

FR-OR101

Mitochondria-Targeting Peptide (SS-31, Bendavia®) Prevents Progression of Chronic Kidney Injury After Acute Ischemia

Hazel H. Szeto, Shaoyi Liu, Yi Soong, Surya V. Seshan. Pharmacology and Pathology, Weill Cornell Medical College, New York, NY.

Background: It has been suggested that about 15% of patients who survive acute kidney injury (AKI) will advance to chronic kidney disease (CKD) characterized by tubulointerstitial fibrosis and glomerulosclerosis. We recently reported that mitochondria protection by SS-31 during ischemia mitigates microvascular rarefaction, inflammation and fibrosis (Am J Physiol 306:F970-F980, 2014). Here we report that delayed treatment with SS-31 can halt the progression of CKD.

Methods: Sprague-Dawley rats (n=40) were subjected to bilateral renal ischemia for 45 min followed by 4 weeks of reperfusion. Surviving animals (n=27) were then randomized to SS-31 (2 mg/kg/day) or saline by osmotic pump for 6 weeks. Kidneys were harvested for histopathology. Sham animals did not undergo ischemia.

Results: Despite recovery of renal function within 1 week after ischemia, pronounced tubulointerstitial fibrosis, interstitial inflammation, glomerulosclerosis, and tubulointerstitial fibrosis was seen at 4 weeks. Further increase in inflammation and fibrosis, accompanied by increase in TGFβ and TGFβ, were observed by 10 weeks in saline-treated rats. Pronounced changes were observed in glomeruli, with extensive fibrosis and peri-glomerular infiltration of inflammatory cells. Glomerular endothelial injury is suggested by the large increase in vWF expression. Electron microscopy revealed stressed vacuoles in podocytes and flattened foot processes. Rats that were treated with SS-31 from 4 weeks did not show any progression of glomerular or tubular injury, and prevented the upregulation of TGFβ and TGFβ.

Conclusions: These results show that SS-31 can halt the progression of chronic kidney disease even when administered 4 weeks after the acute ischemic injury. (Bendavia®) represents a novel paradigm for the treatment of CKD beyond approaches targeted at TGFβ.

Funding: Private Foundation Support

FR-OR102

Early Activation of Fibroblasts Is Required for Renal Protection and Early Reparative Regeneration After Acute Kidney Injury

Dong Zhou, Haiyan Fu, Roderick J. Tan, Youhua Liu. Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Acute kidney injury (AKI) is responsible for about 2 million deaths each year worldwide, and its incidence is rising. While the role of vascular, tubular and interstitial injury in the pathogenesis of AKI is well characterized, whether interstitial fibroblasts play any role in this process is poorly characterized.

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

Underline represents presenting author.
Methods: To address this issue, we established moderate (20 min) and severe (30 min) ischemia-reperfusion injury (IRI) models and tubular epithelial cells were generated and mice were subjected to IRI.

Results: In both moderate and severe IRI, interstitial fibroblasts became activated, as illustrated by vimentin and collagen expression, as early as 1 hour after AKI. Fibroblast proliferation, as assessed by Ki67 staining was detected in renal interstitium at 4 hours and reached the peak at 12 hours. This early activation of fibroblasts was mediated by Shh signaling, as Shh protein was rapidly induced at 1 hour after IRI and Shh induced fibroblast activation and proliferation. In mice with Shh deletion in mediating fibroblast activation and injury repair, we generated tubule-specific Shh conditional knockout mice (Ksp-Shh−/−) by mating Shh-floxed mice with Ksp-Cre mice. Mice with ablation of Shh in renal tubules exhibited normal phenotype under physiologic conditions, but displayed an increased level of serum creatinine and morphological injury at 1 day after IRI, compared with controls. This aggravated AKI in Ksp-Shh−/− mice was associated with a decreased vimentin and desmin expression, suggesting a beneficial role of fibroblast activation in this setting. Similarly, pharmacological blockade of Shh signaling by cycloপamine also aggravated serum creatinine and histological damages through inhibiting fibroblasts proliferation.

Conclusions: These studies suggest that fibroblast activation is an early event mediated by Shh signaling and plays an essential role in conferring renо-protection and injury repair in the setting of AKI.

Funding: NIDDK Support

FR-OR105

Select ADAM17 Substrates Released from Proximal Tubular Cells Promote Progressive Fibrotic Kidney Disease

Funding: NIDDK Support

FR-OR104

IL-4/13-Mediated Polarization and Proliferation of Renal Macrophages Are Essential for Recovery from Acute Kidney Injury

Funding: NIDDK Support

FR-OR103

Endothelial Sphingosine-1-Phosphate Receptor 1 (S1P1) Is Necessary for Early Recovery from Ischemia-Reperfusion Injury (IRI) and Prevention of Fibrosis

Background: Progression after AKI may result from maladaptive repair processes and can potentiate kidney dysfunction. The endothelium is the keystone of vascular homeostasis and vascular insufficienty after AKI may result in progressive fibrosis. S1P1, a G-protein coupled receptor, is important for endothelial function and we previously showed that endothelial cell (EC) S1P1 is necessary for recovery from AKI and prevention of fibrosis.

Methods: Tamoxifen inducible, EC specific, S1P1 knockout mice (ItiCreERT2S1pr1fl; S1P1 ECKO) or control (ITie2CreERT2S1pr1wt/wt) mice were subject to unilateral IRI or sham procedure for 24 h and mice were allowed to recover for 3 days. Tamoxifen was then administered i.p. daily for 5 days by a nephrectomy of the un-operated kidney and mice were euthanized on day 9. Plasma was collected for creatinine (PCr) measurement and kidneys were prepared for histology to assess renal repair, fibrosis, by picro-sirus red, detection of aSMA-PDGFRβ+ myofibroblasts by IF, and neutrophils and macrophages by flow cytometry. Total kidney tissue mRNA was measured by RT-qPCR.

Results: S1P1 ECKO mice had higher PCr levels compared to control mice (1.24 vs. 0.88 mg/dl; p < 0.001 n = 5–6) on day 9 post IRI. S1P1 ECKO mice had increased tubular atrophy, a higher proportion of fibrotic area in the medulla and cortex (1.57 vs. 0.68% p < 0.05 n = 4–5), and increased density of interstitial myofibroblasts expressing COL1 and COL3 in IRI kidneys compared to controls. Leukocyte adhesion molecules Pecam-1, Icam1, E-selectin, and Vcam1 expression and the number of neutrophils and Ly6Clo macrophages were increased in IRI kidneys of S1P1 ECKO mice compared to control mice.

Conclusions: During recovery from IRI, S1P1 suppresses endothelial cell activation of leukocyte adhesion molecules and subsequent inflammation to prevent maladaptive repair and tubular and vascular protection against fibrosis. This data suggests that pharmacological activation of EC S1P1 receptor during recovery can preserve EC function during a critical period of recovery after AKI may prevent the progression to fibrosis.

Funding: NIDDK Support

FR-OR106

Pericyte Ablation Leads to Acute Kidney Failure

Funding: NIDDK Support

Background: Pericytes (PCs) are tissue-resident mesenchymal progenitor cells embedded within the basement membrane of blood vessels. We recently showed that during nephrogenesis pericytes are critical in both vascular and epithelial maturation and patterning. Those data indicate that PCs are important for the maintenance of kidney homeostasis postnataIIy.

Methods: Diphtheria toxin was delivered in vivo, via intraperitoneal injection. Kidneys were collected and processed for histology. Urine albumin was measured using Albuwell M kit (Biorad, Philadelphia, PA). Urine and plasma creatinine levels were measured using creatinine Liquid reagents Assay (DIAZYMEx, San Diego, CA). Plasma albumin was measured using an Olympus au640 Chemistry Analyzer. Gene expression was measured by Taqman PCR, using pre-made assays (Life Technologies, Palo Alto, CA).

Results: PDGFβR+ pericytes present in the adult kidney derive from FoxD1+ mesenchymal progenitor cells. Here we created a FoxD1-Cre; R26v-iDT mouse to study the effect of pericyte ablation in kidney homeostasis. We observed virtually complete depletion of PDGFβR+ cells in the kidney, compared to the control group, after two days of daily intraperitoneal diphtheria toxin (DT) delivery without detectable variations in podocyte numbers or glomerular structure. Significant decrease in vascular density, increased vascular cell proliferation and endothelial swelling was detected. This was associated with aberrant vascularity, lipid accumulation, and injury of the proximal tubules, indicative of epithelial cell dysfunction. These observations were supported by finding elevated levels of plasma creatinine, increased urine nitrogen and albuminuria, markers of organ failure. Mice lacking pericytes progressed to rapid health deterioration and death by three days. Importantly, neither the number of macrophages nor the levels of inflammatory cytokines changed significantly during the treatment, ruling out a role for inflammation-induced damage as the cause for progressive loss of kidney integrity.

Conclusions: Our data show that by supporting homeostasis, pericytes are essential for proper kidney function.
FR-OR107
Preferential Proliferation in Response to Injury by an Interstitial-Derived Collecting Duct Subpopulation
Joan Li, Jinjin Guo, Jill A. Memmoh, Andrew P. McMahon, Melissa H. Little1,4  
Univ of Queensland, Brisbane, QLD, Australia; 2Keck School of Medicine of the Univ of Southern California, Los Angeles, CA; 3Mordoch Children Research Inst, Melbourne, VIC, Australia; 4Univ of Melbourne, Melbourne, VIC, Australia; 5Univ of Southern California Keck School of Medicine, Los Angeles, CA.

Background: We have reported the incorporation of Wnt4-expressing interstitial cells into the developing collecting duct (CD) during early postnatal development. These cells, representing a distinct CD subpopulation, may play a specific role in CD repair.

Methods: Time-mated Wnt4CreERT−R26lox-stop−lox− females received Tamoxifen injection (25mg/kg bw) at E17.5. Male offspring (8-12 wks) were subjected to Unilateral Ureteral Obstruction (UUO) for 3 or 7 days. Mice were euthanized 3 or 7 days after UUO. Kidneys were collected and processed for immunofluorescence studies. Confocal images were analyzed and quantified using Imaris software.

Results: At 7 days after UUO the cortical CDs were severely disrupted. This was accompanied by up-regulation of Wnt4-expressing cells present at E17.5. At 7 days after UUO the percentage of Tdtomato+ cells within the CD increased significantly compared to control (37% vs 14%, p= 0.00001), while pH3 positive was significantly higher in these cells at 7 days after UUO compared to control (4.6% vs 0.2%, p=0.03). The number of Tdtomato+ cells within the CD and the proliferation rate were not significantly different at 3 days after UUO compared to control.

Conclusions: In response to UUO damage, CD epithelial cells underwent Wnt4 expression accompanied by up-regulation of Wnt4 expression. An interstitial-derived, Wnt4 expressing CD subpopulation showed preferential proliferation capacity compared to ureteric bud-derived CD epithelial cells. These observations support previous work suggesting the presence of possible stem/progenitor cells within this compartment and CD plasticity derived CD epithelial cells. These observations support previous work suggesting the presence of possible stem/progenitor cells within this compartment and CD plasticity.

FR-OR108
Net Acid Excretion and Progression of CKD: Results from the Chronic Renal Insufficiency Cohort Study Julia J. Scialla,1 John R. Asplin,2 Mirela A. Dobre,1 Alex R. Chang,1 James P. Lash,2 Chi-yuan Hsu, Radhakrishna Reddy Kallam,1 Lee H. Hamm,1 Harold I. Feldman,1 Jing Chen,1 Lawrence J. Appel,1 Cheryl A. Anderson,10 Myles S. Wolf.12  
1Duke Univ; 2Lithostat Corp; 3Case Western Reserve; 4Geisinger Health System; 5Univ of Illinois Chicago; 6Univ of Pennsylvania; 7Tufts Univ; 10Johns Hopkins Univ; 11Univ of California San Diego; 12Northwestern Univ.

Background: Higher diet-dependent acid load has been associated with faster CKD progression, but not using gold-standard measurements [net acid excretion (NAE)].

Methods: We measured NAE in 24h urines from 1000 CKD participants as urinary bicarbonate (HCO3−) due to macroalbuminuric hypertension-associated nephropathy have acid retention despite no metabolic acidosis but the contribution of reduced eGFR to acid retention is unknown.

Results: We explored the role of reduced GFR in acid retention by re-assessing it after further GFR decline. Acid retention was determined by comparing observed to the expected increase in plasma [HCO3−] in response to administered HCO3− (dose - urine excretion) eight hours after an oral NaHCO3 bolus (0.5 meq/kg bw), assuming 50% body weight HCO3− space of distribution. Specifically, acid retention = [(retained HCO3−/0.5 x body weight) – observed increase in plasma [HCO3−] x 0.5 x body weight]. CKD 2 (n=40) and CKD 1 (n=26) patients had blood pressure controlled with regimens including ACE inhibitors and aldosterone blockers. Among both groups, eGFR declined in both groups, eGFR declined in both groups, eGFR declined in both groups, eGFR declined in both groups, eGFR declined in both groups, eGFR declined in both groups, eGFR declined in both groups.

Conclusions: The data show that GFR reduction exacerbates acid retention in CKD patients with less well preserved eGFR but not in CKD patients whose eGFR was better preserved, supporting the importance of reduced eGFR in mediating the acid retention of CKD.

### Table: Adjusted hazard ratio of ESRD or 50% decline in eGFR in patients with and without diabetes

<table>
<thead>
<tr>
<th>Overall (n=218)</th>
<th>No Diabetes (n=441)</th>
<th>Diabetes (n=647)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA E</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>NEAP</td>
<td>1.0</td>
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<td>NAE</td>
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NEAP estimated from urine biomarkers

| Quartile 1 | (42.5-5.2 mg/dL) | 1.0 | 1.0 | 1.0 |
| Quartile 2 | (25.5-30.7 mg/dL) | 0.91 (0.61-1.36) | 1.24 (0.73, 2.10) | 0.90 (0.55, 1.53) |
| Quartile 3 | (30.8-41.9 mg/dL) | 0.75 (0.54-1.05) | 1.01 (0.57, 1.77) | 0.65 (0.45, 0.99) |
| Quartile 4 | (42.0-6.0 mg/dL) | 0.75 (0.49-1.03) | 0.99 (0.51, 1.92) | 0.61 (0.37, 0.99) |
| P-value from continuous model | 0.04 | 0.06 | 0.01 |

P-interaction with diabetes | 0.02 |

P-values from urine biomarkers

| Quartile 1 | (42.5-5.2 mg/dL) | 1.0 | 1.0 | 1.0 |
| Quartile 2 | (25.5-30.7 mg/dL) | 1.13 (0.87-1.47) | 1.04 (1.04, 3.68) | 0.87 (0.67, 1.16) |
| Quartile 3 | (30.8-41.9 mg/dL) | 1.07 (0.76-1.55) | 1.58 (0.82, 3.03) | 0.92 (0.59, 1.43) |
| Quartile 4 | (42.0-6.0 mg/dL) | 1.10 (0.79-1.55) | 1.64 (0.87, 3.09) | 0.90 (0.60, 1.35) |

P-values from continuous model | 0.4 | 0.08 | 0.6 |

P-values from diabetes | 0.08 |

*Adjusted for age, sex, race, diabetes, cardiovascular disease, eGFR, proteinuria, 24 hour urine creatinine, BMI (body mass index)
FR-OR11

**Urinary Sodium and Potassium Excretion and Risk of Developing Chronic Kidney Disease**

Lyanne M. Kienekent,1 Ron T. Gansevoort, 1 Rudolf A. de Boer,2 Gerjan Navis,3 Stephan J.L. Bakker,1 Michel M. Joosten.1 1Internal Medicine, UMC Groningen, Netherlands; 2Cardiology, UMC Groningen, Netherlands.

**Background:** It is unclear whether dietary sodium and potassium intake are relevant to the development of chronic kidney disease (CKD) in the general population. Our aim was to examine the associations of urinary sodium and potassium excretion (UNaV and UKV, respectively) as estimates of intake, with risk of developing CKD in the general population.

**Methods:** We studied 5,315 subjects free of CKD at baseline of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study; a prospective, population-based cohort of Dutch men and women aged 28-75 years. UNaV and UKV were measured in two 24-hour urine specimens at baseline (1997-1998) and midway during follow-up (2001-2003). Incident CKD was defined as the new development of creatinine or cystatin C-based estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² and/or albuminuria >30 mg/24h.

**Results:** Baseline UNaV and UKV were 135 mmol/24h (interquartile range [IQR]: 106-169 mmol/24h) and 70 mmol/24h (IQR: 57-85 mmol/24h), respectively. During a median follow-up of 10.3 years (IQR: 6.2-11.4 years), 872 subjects developed CKD. After multivariable adjustment for important covariates, no association was observed between UNaV and risk of CKD (hazard ratio per 50 mmol/24h increment [1 standard deviation], 1.03; 95% confidence interval, 0.93-1.13). Each 21 mmol/24h (1 standard deviation) decrement in UKV was significantly associated with a 16% higher risk of developing CKD (multivariable adjusted hazard ratio, 1.16; 95% confidence interval, 1.05-1.29; Figure 1). Sensitivity analyses in which CKD was defined by either eGFR or albuminuria alone, rendered essentially similar results.

**Conclusions:** Low potassium intake and not high sodium intake was associated with an increased risk of developing CKD in the general population.

**Funding:** Private Foundation Support

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**FR-OR12**

**Sedentary Behavior as a Risk Factor for CKD**

Dominique Ferranti,1 Kate Lyden,1 Xiaorui Chen,1 Robert E. Boucher,1 G. Wei,1 Srinidhi Beddhu.1 1U of Utah; 2VA SLC; 3UC Denver.

**Background:** Sedentary behavior (engaging in activities in the seated or lying position that barely raise the energy expenditure above resting level) is commonly confused with physical inactivity (lack of moderate/vigorous physical activity [MVPA]). Sedentary behavior is an important risk factor for DM, HTN and obesity. It is unclear whether sedentary behavior is an independent risk factor for CKD. Therefore, we examined this in 5873 participants in whom intensity and duration of physical activities were measured objectively with an Actigraph accelerometer in the 2003-2006 National Health & Nutrition Examination Survey (NHANES) data.

**Methods:** Based on the number of counts/min recorded, sedentary (<100/min) and moderate/vigorous (> 2020/min) activity durations were defined and normalized to 60 min. Logistic regression models adjusted for age, gender, race, education, smoking, alcohol use, lung disease and mobility limitations were used to examine the associations of sedentary and MVPA durations with the presence of CKD (defined as CKD-EPI eGFR < 60 ml/min/1.73 m²).

**Results:** The mean age was 49 ± 13 yrs. 52% were women and 9.5% were black. 7.4% had CKD. The mean sedentary duration was 34.0 ± 5.6 min/hr. MVPA duration was highly skewed with median (25th - 75th percentile) of 1.2 (0.5 – 2.3) min/hr. Prevalence of CKD by sedentary and MVPA durations are summarized in the figure.

**Conclusions:** Low sedentary behavior is an independent risk factor for CKD and interventions that target sedentary behavior might slow the progression of CKD.

**Funding:** NIDDK Support

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**FR-OR113**

**The Metabolically Healthy Obesity Phenotype and Risk of Incident Kidney Failure**

Alex R. Chang,1 Morgan Grams,2 Amanda Young,1 Molly J. Kramer,1 H. Lester Kirchner,3 1Geisinger Health System; 2Johns Hopkins Bloomberg School of Public Health; 3Loyola Univ Medical Center.

**Background:** Little data exist on the association between obesity in the absence of metabolic abnormalities (metabolically healthy obesity) and renal outcomes.

**Methods:** Using data from 86,004 patients in the Geisinger Health System from 2004-2014, we examined the risk of kidney failure (dialysis, transplant, or eGFR < 15 ml/min/1.73m²) and eGFR decline ≥30% by categories of body mass index (normal 18.5-24.9, overweight 25-29.9, obesity ≥30) and metabolic health (<2 of the following : triglycerides >150, HDL cholesterol <40 in men, <50 in women; blood pressure >130/85, and glucose >100). Cox regression analyses were adjusted for demographics, smoking status, history of cardiovascular disease, and baseline eGFR.

**Results:** Only 10.6% of patients had normal BMI with 54.3% overweight, and 54.3% obese. Proportions of metabolically healthy individuals in normal, overweight, and obesity groups were 67.9%, 30.0%, and 20.0%, respectively. Over a median follow-up time of 6.0 years, 1,376 patients developed kidney failure and 17,688 developed eGFR decline ≥30%. Compared to metabolically healthy persons of normal BMI, metabolically healthy overweight and obese individuals had similar or lower risk for ESRD (overweight HR 0.75, 95% CI: 0.57-1.09; obesity HR 0.87, 95% CI: 0.64-1.17), but not kidney failure.

**Conclusions:** Metabolically healthy obesity is associated with eGFR decline ≥30% but not kidney failure.

**Funding:** Private Foundation Support

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

Underline represents presenting author.

59A
SA-OR002

Association Between Mitochondria DNA Copy Number and Incident Chronic Kidney Disease: The Atherosclerosis Risk in Communities (ARIC) Study


Background: Mitochondria play a key role in cellular energy production. Higher mitochondrial DNA copy number (mtDNA-CN) in peripheral blood has been associated with lower risk of diabetes and lower prevalence of microalbuminuria, both risk factors of chronic kidney disease (CKD). It is unknown whether mtDNA-CN is associated with incident CKD.

Methods: We estimated mtDNA-CN from 119 mtDNA single nucleotide polymorphisms (SNPs) genotyped using the Affymetrix 6.0 microarray. Incident CKD was defined as a composite outcome of (a) baseline estimated glomerular filtration rate (eGFR) ≥ 60mL/min/1.73m² with a 25% drop to < 60mL/min/1.73m², (b) CKD-related hospitalization, or (c) end-stage renal disease (ESRD) based on linkage to the US Renal Data System (USRDS). The association between quartiles of mtDNA-CN and incident CKD was evaluated using Cox regression.

Results: Among 9060 participants, those with higher mtDNA-CN had significantly lower prevalence of coronary heart disease and diabetes, and lower levels of C-reactive protein and white blood cell count. Baseline eGFR did not differ significantly by mtDNA-CN quartiles. Over a median follow-up period of 19 years, 1459 participants developed CKD. Higher mtDNA-CN was associated with lower risk of incident CKD adjusted for age, gender, and race (quartile 4 vs. 1: hazard ratio [HR] 0.76, 95% confidence interval [CI]: 0.66-0.87, p for trend < 0.0001). This association persisted with some attenuation after adjusting for body mass index, smoking, estimated glomerular filtration rate, hypertension, and coronary heart disease, smoking, high sensitive C-reactive protein and white blood cell count (quartile 4 vs. 1: HR 0.89, 95% CI: 0.76-1.03, p for trend 0.03).

Conclusion: Higher mtDNA-CN is associated with lower risk of incident CKD independent of known risk factors of CKD and inflammation biomarker levels. Further research on modifiable factors influencing mtDNA-CN may lead to insight on the pathogenesis and prevention of CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-OR003

Urinary EGF Predicts Composite Endpoints in Three Independent Chronic Kidney Disease Cohorts

Viji Nair, Li Zhu, Peter X.K. Song, Laura H. Mariani, Susan P. Steigerwald, Jicheng Lv, Jennifer Joyce Hawkins, Hong Zhang, Matthias Kretzler, Wenjun Ju, Medicine, Univ of Michigan, Ann Arbor, MI; 2Medicine, Parkland Health and Hospital, Dallas, TX; 3First Hospital, PKU Inst of Nephrology, Beijing, China; 4Biotestistics, Univ of Michigan, Ann Arbor, MI; 5Arbor Research Collaborative for Health, Ann Arbor, MI; 6St. John Hospital and Medical Center, Detroit, MI.

Background: The nephrology community is in need of non-invasive biomarkers that can predict CKD progression and identify patients for targeted treatment better than estimated glomerular filtration rate (eGFR) and proteinuria. Our previously identified and validated epidermal growth factor (EGF) as an intramural marker for eGFR. The significant reduction of baseline eGFR and albuminuria in CKD, including prevalent diabetes, hypertension, and coronary heart disease, smoking, high sensitive C-reactive protein and white blood cell count (quartile 4 vs. 1: HR 0.89, 95% CI: 0.76-1.03, p for trend 0.03).

Conclusion: Higher mtDNA-CN is associated with lower risk of incident CKD independent of known risk factors of CKD and inflammation biomarker levels. Further research on modifiable factors influencing mtDNA-CN may lead to insight on the pathogenesis and prevention of CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-OR004

Normalization of Biomarkers to Urine Creatinine: Impact on CRIC Study Findings


Background: There is no standard approach to the reporting of urine biomarkers; some studies normalize to urine creatinine concentration and others do not. Whether this influences findings is not well understood.

Funding: NIDDK Support, Pharmaceutical Company Support - Hoffmann-La Roche

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

Underline represents presenting author.
Methods: Urine kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-beta-D-glucosaminidase (NAG), and liver fatty acid-binding protein (LFABP) were measured in 2466 Chronic Renal Insufficiency Cohort participants. Cox models were used to examine the association between biomarkers and CKD progression, defined as halving of eGFR or incident ESRD. We compared results with and without normalization of biomarkers to UCr.

Results: Baseline mean eGFR was 44±18 mL/min/1.73 m²; median albuminuria was 53 mg/g UCr (6-503). After adjustment for eGFR, albuminuria, as well as socio-demographic and clinical covariates, non-normalized KIM-1 and NAG were independently associated with CKD progression by quintile (Table) and continuous biomarker value analysis [HR per SD 1.16 (1.05-1.28) and 1.14 (1.04-1.25), respectively] but KIM-1 Cr and NAG Cr were not. There were no independent associations between NGAL or LFABP and outcomes regardless of normalization.

Conclusions: Normalization for UCr influences the associations of biomarkers with CKD outcomes. In theory, normalization controls for differences in urine concentration, but more studies are needed to better understand the impact on a variety of clinical outcomes. At minimum, researchers should state their approach a priori, measure UCr, and perform sensitivity analyses where the alternate approach is tested.

Funding: NIDDK Support

SA-OR006

Underuse of Renin Angiotensin System Inhibitors and Other Medications in U.S. Patients with Advanced Chronic Kidney Disease Receiving Nephrologist Care: Results from the International CKDopps

Elodie Speyer,1 Laura H. Mariani,1 Charlotte Tu,1 Lindsay Zepel,1 Celine Lange,2 Brian Bieber,3 Christian Combe,2 Antonio Alberto Lopes,4 Izad Massy,1,2 Roberto Peccati-Filho,5 Ronald L. Pisoni,6 Helmut Reichl,1 Benedikt Stengel,1 Bruce M. Robinson.1 1Arbor Research Collaborative for Health, USA; 2Biomedicine Agency, France; 3CHU Bordeaux, Univ de Bordeaux, France; 4Federal Univ of Bahia, Brazil; 5Ambroise Pare Univ Hospital, UTSQ, France; 6Pontificia Univ Catolica do Parana, Brazil; 7Nephrological Center Villingen Schwenningen, Germany; 8InsERM UMR1108, France.

Background: In the US, ~86% of incident ESRD cases are attributable to hypertension or diabetes. Guideline-directed medication use may help to slow CKD progression and lower ESRD incidence. We report early findings on use of key medication classes by CKD stage in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps).

Methods: CKDopps is a prospective cohort study of patients with eGFR<60 in random national samples of nephrology clinics in Brazil, France, Germany, and the US. Early data from CKDopps (excluding Brazil and Germany for now) were used to characterize medication usage.

Results: 2,621 patients were included from 39 French, and 17 US clinics. The median number of prescriptions ranged from 7-9. Statin use was 52% and aspirin use was 31-48%. RASI (ACEI or ARB) use for CKD Stage 3 and 4 patients was 72% and 77% in France, and 51 and 55% in the US, respectively. Aldosterone blockade use was 3-6%. Among diabetics, insulin use was lower in US (32%) than in France (48 and 57% for stage 3 and 4 patients, respectively), as was metformin use which was 30 and 7%, and 10 and 1%. For stage 4 patients, sulfonylurea use was higher in the US (21%) than in France (6%).

Conclusions: These early results show large international differences in medication usage for diabetes and cardiovascular disease amongst CKD patients. Patients in US were much less likely to use RASIs, metformin or insulin than in France. Early data from Germany and Brazil will be available by mid 2015. Further investigation should determine the reasons for these practice variations and their impact on CKD progression, survival, and other outcomes.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHIC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGGN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

SA-OR007

Albuminuria Changes and Subsequent Risk of End-Stage Renal Disease and Mortality

Juan Jesus Carrero,1 Yingying Sang,2 Alessandro Gasparini,1 Abdul Rashid Tony Qureshi,1 Kunihiro Matsushita,2 Johan Amlod,3 Marie Evans,2 Peter F. Barany,2 Bengt Lindholm,1 Morgan Grames,2 Shoshana Ballwe,2 Carl Gustaf Elinder,1 Josef Coresh,2 Renal Medicine and Baxter Novum, Karolinska Inst, Sweden; 3Johns Hopkins Bloommg School of Public Health, Baltimore; 1Medical Sciences, Uppsala Univ, Sweden.

Background: Albuminuria is used to stage chronic kidney disease (CKD). Changes in albuminuria during the course of disease may serve as early indicators of CKD progression and complications beyond eGFR, but the risk implications are not well understood in large clinical studies.

Methods: Observational study from the Stockholm CREAtinine Measurements (SCREAM) project, a laboratory data extraction of all citizens from the region of Stockholm, Sweden, with at least one serum creatinine during 2006-2011; 39802 individuals with repeated albumin to creatinine ratio (ACR) measurements were followed up until 12/31/2012. ESRD risk after baseline (908 events) was related to fold-change in ACR during a baseline window of 1, 2 or 3 years. The secondary outcome was death (3890 events). Adjustment variables included demographics, comorbid history, laboratory assessments and medication, as well as first eGFR and ACR.

Results: The association between ACR changes and ESRD risk was strong and showed a largely linear dose-response relationship (Figure for 2-year baseline period). For example, 8-fold increase in ACR (e.g., from normal of 5 mg/g to microalbuminuria of 40 mg/g) conferred ~5 fold higher risk of ESRD compared to stable ACR. The association was weaker for mortality but significant for ACR increases. The observed risk estimates were similar and consistent at 1-, 2- and 3-year time-window.
Conclusions: Increases in albuminuria were strongly and consistently associated with the risk of ESRD and mortality, suggesting their usefulness as a kidney outcome in clinical studies of CKD progression.

SA-OR008

Prevalence of Chronic Kidney Disease, Diabetes and Hypertension in Rural Tanzania Based of Different Methodologies

David W. Plow, 1 Virginia Fonner, 2 Bruce Horowitz, 3 Philip Zagar, 1 Francis Fredrick, 4 Caroline M. West, 2 Michael D. Sweat. 2 Medicine, MUSC, Charleston, SC; 4Div of Family Services Research, MUSC, Charleston, SC; 6Medicine, Univ of New Mexico School of Medicine, Albuquerque, NM; 7Nephrology, Muhimbili Univ of Health and Allied Sciences, Dar es Salaam, Tanzania, United Republic of.

Background: Studies were conducted to explore the hypothesis that there are previously underappreciated and interrelated epidemics of chronic kidney disease (CKD), diabetes (DM), and hypertension (HTN) in rural Tanzania.

Methods: We initially assessed prevalence in a probability-based sample of 740 subjects randomly sampled from households in Kisinawa District, TZ. Prevalence of DM was obtained by measuring HbA1c. Blood pressure was measured by AHA guidelines, and kidney function by serum creatinine in blood samples obtained at home interview. Estimation of glomerular filtration rate (eGFR) was computed with the CKD-EPI equation. Prevalence of DM, hypertension, and kidney function by serum creatinine in blood samples obtained at home interview. Estimation of glomerular filtration rate (eGFR) was computed with the CKD-EPI equation.

Results:

<table>
<thead>
<tr>
<th>NCD</th>
<th>Criteria</th>
<th>Pre-Diabetes</th>
<th>CKD Stage 3-5</th>
<th>Pre-HTN</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>HbA1c &lt; 6.5%</td>
<td>30.5%</td>
<td>12.6%</td>
<td>40.0%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Pre-Diabetes</td>
<td>HbA1c ≤ 6.5%</td>
<td>30.5%</td>
<td>12.6%</td>
<td>40.0%</td>
<td>17.5%</td>
</tr>
<tr>
<td>CKD Stage 3-5</td>
<td>eGFR &lt; 60 ml/min/1.73 m²</td>
<td>120-300/80-90 mmHg</td>
<td>BP &gt; 140/90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HTN</td>
<td>HbA1c ≤ 6.5%</td>
<td>30.5%</td>
<td>12.6%</td>
<td>40.0%</td>
<td>17.5%</td>
</tr>
</tbody>
</table>

Following the probable basis screening of households, we assessed the same NCD’s in individuals who voluntarily presented for healthcare assessment in a community prevention center we established. We measured BP and assessed urine for glycosuria and proteinuria with dipsticks in 685 subjects self-selected from the community. We observed glycosuria in 3.6% proteinuria in 8.1% and proteinuria and glycosuria in 1.8%. Hypertension was observed in 23.6% and pre-hypertension in 34.9%. We observed a significant, direct relationship between increasing levels of BP and the prevalence of glycosuria and proteinuria (r = 0.05).

Conclusions: In summary we observed unexpectedly high and similar prevalence estimates for CKD, HTN and DM in a probability-based sample in rural Tanzania and from observations in a walk-in community clinic. The higher than expected prevalence of these NCD’s will likely contribute to rapidly accelerating rates of cardiovascular morbidity and mortality in these areas. Additional studies are desperately needed to address this problem.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc, Nashville, TN

SA-OR009

Race and the Association of Blood Pressure with Clinical Outcomes in U.S. Veterans with Chronic Kidney Disease

Csaba P. Kovesedy, 1,2 Miklos Zsolt Molnar, 1 Praveen Kumar Potukuchi, 1 Elvira Gosmanova, 1 Fridjof Thomas, 1 Jun Ling Lu, 1 Ebeny Bouweleur, 2 Keith C. Norris, 1 Kamyar Kalantar-Zadeh, 1 1Univ of Tennessee Health Science Center, Memphis, TN; 2VA Medical Center, Memphis, TN; 3Duke Univ School of Medicine, Durham, NC; 4UCLA, CA; 5UC, Irvine, CA.

Background: African American (AA) patients with CKD have poorer BP control, but it is unclear if the association of BP with outcomes is different in AA vs. white patients with CKD.

Methods: We examined the association of baseline SBP with mortality, slopes of eGFR, ESRD, incident coronary heart disease (CHD) and incident stroke in 308,920 US veterans (54,852 AA and 254,068 white) with CKD over a median follow-up of 4.9 years. We used Cox models and logistic regressions with interaction terms to explore race differences in associations of SBP categories (relative to SBP 130-139 mmHg in white patients) with outcomes, adjusted for demographic and socioeconomic characteristics, comorbidities, baseline eGFR, and medications.

Results: Compared to whites, AA patients were younger, less likely to be married, had lower income, more diabetes, but less CVD. Mean baseline SBP (SD) was 133 (17) in AA and 130 (16) mmHg in whites. Elevated SBP was associated with linearly higher risk of all outcomes in both race groups. Race and elevated SBP showed no interaction for the risk of mortality, ESRD, strokes, and CHD. The association of elevated SBP with steeper eGFR slopes was, however, 1.6 fold more pronounced in AA patients.

Adjusted hazard/odds ratios (95%CI)

<table>
<thead>
<tr>
<th>eGFR slopes (mL/min/1.73 m²/yr)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P Value</th>
<th>Age, sex, race-Adjusted HR (95% CI)</th>
<th>P Value</th>
<th>Fully Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ -10</td>
<td>0.67 (0.63-0.72)</td>
<td>&lt;0.001</td>
<td>1.17 (1.09-1.25)</td>
<td>&lt;0.001</td>
<td>1.26 (1.17-1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>-10 - ≤ -5</td>
<td>1.16 (1.08-1.25)</td>
<td>&lt;0.001</td>
<td>1.03 (0.98-1.08)</td>
<td>0.24</td>
<td>1.09 (1.03-1.15)</td>
<td>0.005</td>
</tr>
<tr>
<td>≤ -5</td>
<td>1.00 (reference)</td>
<td>N/A</td>
<td>1.00 (reference)</td>
<td>N/A</td>
<td>1.00 (reference)</td>
<td>N/A</td>
</tr>
<tr>
<td>0 - 0</td>
<td>1.42 (1.29-1.57)</td>
<td>&lt;0.001</td>
<td>1.53 (1.39-1.69)</td>
<td>&lt;0.001</td>
<td>1.04 (0.93-1.16)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Conclusions: Patients with rapid pre-dialysis eGFR decline have higher mortality risk in the first two years after dialysis start. The rate of eGFR decline in late CKD stages can be an additional predictor of mortality in incident dialysis patients.

Funding: NIDDK Support, Veterans Administration Support

SA-OR010

Association of eGFR Decline with Post Dialysis Mortality in Late-Stage CKD Patients Who Transitioned to ESRD

Keichi Sumida, 1 Miklos Zsolt Molnar, 1 Praveen Kumar Potukuchi, 1 Fridgjoj Thomas, 1 Jun Ling Lu, 1 Jennie Jing, 2 Vanessa A. Ravel, 1 Melissa Soohooh, 1 Connie Rhee, 1 Elani Streia, 2 Lawrence Agodoa, 1 Kevin C. Abbott, 1 Paul W. Egggers, 1 Kamyar Kalantar-Zadeh, 1 Csaba P. Kovesdy, 1,4 "Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of California, Irvine, CA; 3NIH, Bethesda, MD; 4VA Medical Center, Memphis, TN.

Background: The rate of eGFR decline is an independent risk factor for mortality in CKD. However, it is not known if pre-dialysis eGFR slopes are associated with outcomes after dialysis initiation.

Methods: We examined the association of pre-dialysis eGFR slopes with all-cause, cardiovascular (CV), and infectious mortality during two years after dialysis start in 19,254 U.S. veterans who transitioned to ESRD between October 1, 2007-September 30, 2011. eGFR slopes were categorized into four groups (≤-10, -10 to ≤-5, ≤-5 to ≤0, and 0 to 1.73 m²/yr). Associations were examined in Cox models with adjustment for age, gender, race, comorbidities, and last pre-dialysis eGFR.

Results: Patients were 68.7±11.4 years old, 98% male, 29% black, and 72% diabetic. There were 5,226 all-cause, 2,751 CV, and 613 infectious deaths. Compared to eGFR slopes of ≤-5, -10 to ≤-5, ≤-5 to ≤0, and >0 mL/min/1.73 m²/yr, the risk of all-cause and CV mortality decreased with steeper slopes of eGFR (95% CI: 1.00-1.30; 1.19-1.50; 1.19-1.50; 1.40-1.52). The risk of infectious death (95% CI: 1.00-1.25; 1.00-1.23; 1.00-1.22; 1.00-1.22) was similar across these groups.

Conclusions: The rate of eGFR decline is an independent risk factor for mortality in CKD. Additional studies are desperately needed to address this problem.

Funding: NIDDK Support, Veterans Administration Support

SA-OR011

A Randomized Controlled Trial of Rituximab for Severe Idiopathic Membranous Nephropathy (IMN)

Pierre M. Romeu, 1 Karine Dahan, 1 Hanna Deibech, 2,3 Emmanuelle M. Plaisier, 2,3 Marine Cachanado, 2,3 Alexandra Rousseau, 2 Laura Wakselman, 1 Pierre-Antoine Michel, 1 Fabrice Mihout, 1 Bertrand Dussol, 1 Marie Matignon, 1 Christiane I. Mousson, 1 Tabassome Simon, 1,2,3 "Nephrology and Dialysis, AP-HP, Hôpital Tenon, Paris, France; 2UMR S 1153, INSERM, Paris, France; 3Clinical Pharmacology and Unité de Recherche Clinique (URC), AP-HP, Hôpital Saint Antoine, Paris, France; 4Nephrology and Transplantation, AP-HM, Hôpital de la Timone, Marseille, France; 5Nephrology and Transplantation, AP-HP, Hôpital Henri Mondor, Créteil, France; 6Nephrology and Transplantation, Centre Hospitalier Univ, Dijon, France; 7UMR S1148, INSERM, Paris, France; 8UPMC, Sorbonne Univ, UPMC Univ Paris 06, Paris, France.

Background: IMN is a common cause of nephrotic syndrome. Anti-PLA2R antibodies occur in 70% of patients. No randomized controlled trial has evaluated rituximab efficacy and safety.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Patients with biopsy proven IMN and persistent nephrotic syndrome after 6 months despite Non Immunosuppressive Antiproteinemic Treatment (NIAT) were randomly assigned to 6-month therapy with TAC and 375 mg² of rituximab on days 1 and 8, or NIAT alone. At month 6, the primary end point was the rate of remission; the composite end point was defined as reduction of proteinuria > 50% and increase of serum albumin > 30%; secondary endpoints included serum creatinine, serum albumin, serum creatinine, and CP-therapy. Results: 37 and 38 patients received TAC with rituximab and NIAT alone. At month 3, rituximab decreased PLA₂R-Ab rate and titer (P=0.029), without difference in proteinuria. Number of SAEs was comparable and 8 (21%) in the NIAT group reached the primary end point (P=0.17); 15 (41%) patients in 56% of patients (P<0.001). At month 6, 13 (35%) patients in the NIAT-rituximab group rituximab decreased PLA₂R-Ab rate and titer (P<0.001), and induced PLA₂R-Ab depletion is inferior to MPR in maintaining remission of NS (The total follow-up of 70 cases will be helpful for the diagnosis of MN and when making treatment decisions in these patients. Background: The discovery of anti-PLA₂R antibodies provides options for individualized therapy in patients with idiopathic membranous nephropathy (IMN). We previously showed that the level of anti-PLA₂R antibodies (aPLA₂R) after 6-12 months of corticosteroid monotherapy predicted remission outcomes (Beck, CIUSN 2014). We present the first data of antibody guided therapy. Methods: CP-therapy (combined with steroids) is started in patients with aPLA₂R positive serum and prednisone is tapered. Otherwise, therapy is continued after 24 weeks with MMF and prednisone. Results: We treated 22 patients (characteristics in table 1). aPLA₂R were negative in respectively 15 (68%) after 8 weeks, 17 (77%) after 16 weeks and 17/20 (85%) patients after 24 weeks of treatment. A partial remission of proteinuria (P< 0.3 mg/day) was observed in 23% (5/22), 44% (8/18) and 67% (10/15) of patients after 8, 16 and 24 weeks respectively. Thus far, 4 of the 17 patients (24%) developed an immunological relapse after 3.4 (4.6-6.6) months. All 4 patients have persistent or recurrent proteinuria. Thus far, 6 of 22 patients (27%) needed additional treatment. Results: 12m (TAC*) (n=35) 12m (MPR) (n=35) 18m (TAC*) (n=35) 18m (MPR) (n=35) 24m (TAC*) (n=28) 24m (MPR) (n=26) Remission 71.4 77.1 62.8 85.7 64.2 88.4 CR 54.2 51.4 54.2 65.7 42.8 69.2 PR 17.2 25.7 8.6 20 21.4 19.2 Resistant 28.6 22.8 37.2 14.3 35.7 11.6

Conclusions: Preliminary analysis suggests that at 2 years post randomization, TAC* is inferior to MPR in maintaining remission of NS (The total follow-up of 70 cases will be presented at ASN).
Clinical Glomerular and Tubulointerstitial: Treatments and Outcomes of Nephrotic Diseases

SA-OR016
Melanocortin 1 Receptor (MC1R) Is Dispensable for the Proteinuria Reducing and Glomerular Protective Effect of Melanocortin Therapy Yingjin Oiao,1 Anna-lena Berg,2 Yan Ge,1 Zhangsuo Liu,1 Rujong Jin.1 Brown Medical School; 2 Lund Univ, Sweden.

Background: Evidence suggests that melanocortin therapy with using ACTH or non-steroidogenic melanocortin peptides attenuates proteinuria and podocyte injury in animal models of glomerular diseases and induces remission of nephrotic syndrome in patients with a variety of glomeropathies. The effect of ACTH therapy was evaluated.

Methods: The recessive yellow MC1R-mutant (MC1Rkn2) and wild type (WT) mice were injured by lipopolysaccharide (LPS) or adriamycin (ADR) to develop podocytopathy and the effect of NDP-MSH, a non-steroidogenic melanocortin pan agonist, was tested. In patients with steroid-resistant nephrotic syndrome and nonfunctional MC1R mutations, the effect of ACTH therapy was evaluated.

Results: Following LPS or ADR insult, NDP-MSH attenuated proteinuria in WT and MC1Rkn2 mice to the same extent and ameliorated signals of glomerular injury and podocytopathy, including loss of podocyte markers, de novo expression of podocyte damage markers, and podocyte foot process effacement. In vitro in primarily cultured podocytes, LPS or ADR elicited apoptosis and podocyte hypermotility, and impaired the filtration barrier function of podocyte monolayers. These injurious effects were mitigated by NDP-MSH to a similar degree in podocytes derived from WT and MC1Rkn2 mice. Moreover, two patients with congenital red hair and nephrotic syndrome due to idiopathic membranous nephropathy were enrolled and confirmed by gene sequencing to bear nonfunctional MC1R mutations. After failing multiple immunosuppressive regimens, including glucocorticoids, the patients were converted to synthetic ACTH monotherapy for 21 months and 8.5 months respectively (escalation and de-escalation included) and both achieved complete remission of proteinuria, denoting steroid independent effect.

Conclusions: Melanocortin therapy confers a proteinuria reducing and podoprotective effect in proteinuric glomerulopathies via a mechanism independent of MC1R.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

SA-OR017

Background: C3 glomerulonephritis (C3GN), dense deposit disease (DDD), atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) are rare diseases with phenotypic similarities and genetic commonalities. Variants in the CFH, CFI, CFB, C3, CFHR3, CD46, DGKE, ADAMTS13, THBD and PLG genes, and copy number variation of CFHR3-CFHR1 contribute to their pathogenesis and inform diagnosis and treatment options. To improve patient care, we developed a comprehensive genetic complement panel (GCP) to screen these genes. Herein we present our one-year experience using this panel in the clinical care of these patients.

Methods: 184 patients (37 with C3G and 147 with TMA) were studied using the GCP panel.

Results: Positive genetic diagnoses were provided in 43% of C3G patients and in 41% of TMA patients.

Conclusions: GCP panel provides a comprehensive and efficient genetic screen of complement genes. The observed differences in variant aggregation in patients with C3G and TMA refine our understanding of these diseases.

Funding: Private Foundation Support

SA-OR018
Amelioration of the Adverse Effects of Prednisolone by Rituximab Treatment in Adults with Steroid-Dependent Minimal Change Nephrotic Syndrome Yoei Miyabe, Takashi Takei, Yoko Iwabuchi, Takahito Moriyama, Kosaku Nitta. Tokyo Women's Medical Univ, Japan.

Background: We previously demonstrated the efficacy of single-dose 6-monthly rituximab infusions in 25 adults with steroid-dependent minimal-change nephrotic syndrome. Herein, we assessed the safety of rituximab treatment and its effect in ameliorating the adverse effects of prednisolone (PRED) in a larger study sample.

Methods: We treated 54 adult patients with four a single-dose 6-monthly infusions of rituximab (375 mg/m2 BSA per dose). We compared the adverse effects of PRED (osteoporosis, hypertension and diabetes mellitus) between the first rituximab infusion (baseline) and the end of the 24-month observation period. In addition, we examined the adverse effects of rituximab during the same period.

Results: The PRED dose was significantly lower at 24 months than at the baseline. The bone density was significantly higher at 24 months as compared to the baseline value (Z-score: -1.8 vs. -1.1, p < 0.05). Blood pressure at 24 months was significantly lower than that at the baseline (120.9/74.4 vs. 111.8/70.3 mmHg, p < 0.05). Eight patients with diabetes mellitus showed improved glycemic control at 24 months as compared to that at the baseline. There were no severe adverse effects of rituximab. However, mild infusion reactions occurred in 31 patients (57%). The frequency of the infusion reactions decreased significantly with every successive infusion.

Conclusions: Rituximab treatment was effective and safe in patients with steroid-dependent nephrotic syndrome, allowed reduction of the PRED dose, and ameliorated the adverse effects of PRED. It may be preferentially used in patients at a risk of the adverse effect of PRED.

SA-OR019
Determining eGFR Trajectory Clusters in the NEPhrtoic Syndrome STUdy Network (NEPTUNE) Laura H. Marianti,1,2 Jarcy Zee,1 Tony Wang,1 Vijji Nair,1 Wenjun Ju,1 Jonathan P. Troost,1 Debbie S. Gibson,1 Peter X.K. Song,1 Brenda W. Gillespie.1 1 Univ of Michigan; 2Arbor Research Collaborative for Health.

Background: Non-linear changes in eGFR over time are common in nephrotic syndrome. Traditional outcomes (e.g. 50% eGFR decline) may not capture these changes. We identified patient clusters via eGFR longitudinal trajectory and associated clinical characteristics with the groups.

Methods: NEPTUNE is a multi-center, prospective cohort study of children and adults with >500mg/day of proteinuria, enrolled at the time of renal biopsy. eGFR was calculated using the CKD-Epi formula for participants ≥18 yo and modified CKD-Schwarz formula for those <18 yo. 367 patients with ≥3 eGFR measurements were included. Each patient’s eGFR trajectory was estimated using Bayesian smoothing and a probability of non-linearity was calculated (Li, AJKD, 2012;59(4)). Quadratic regression coefficients from each trajectory were used in a clustering algorithm to identify distinct groups by minimizing within-cluster variance.

Results: Mean follow-up time was 26 mo. 25% (n=92) of the cohort had a trajectory with ≥50% probability of being non-linear and 10% (n=35) had a non-linearity probability >83%. The clustering algorithm produced five trajectory groups. Baseline mean eGFR (p=0.001) and median upcr (p=0.001) differed by cluster. Mean age was lowest in clusters 1 and 5 (28 and 25 vs. 39, 39, 31; p=0.002). Race and sex did not vary by cluster. MN composed 13-20% of each cluster whereas FSGS composed 40 and 35% of clusters 2 and 3, respectively (p=0.005).

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

Underline represents presenting author.

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Although not statistically significant, CNIs ± GC were associated with a lower likelihood of ESKD compared to GC alone [HR 0.42 (95% CI 0.15, 1.18)].

Conclusions: The use of CNIs as part of the early immunosuppressive regimen in primary FSGS may be associated with improved outcome, but their superiority over GC alone remains unproven.

SA-OR021
Living Donation Has a Greater Impact on Allograft Survival Than HLA Mismatching in Pediatric Renal Transplant Recipients

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Background: Living donor kidney transplantation accounts for around half of all paediatric (<18 years) renal transplant recipients (PRTR) and results in improved renal allograft survival, although there are no data comparing the effect of HLA-mismatching on outcomes. The UK 2006 Kidney Allocation Scheme prioritises children with good HLA matching (Level 1:2:000 A,B,DR or [0 DR & £1 B]). The aim of this study was to determine the effect of HLA mismatching on deceased and living donor renal allograft outcomes in paediatric recipients.

Methods: Data were obtained from the UK Transplant Registry on all PRTR who received a donation after brain death (DBD) or living donor (LD) kidney-only transplant between 2000 and 2011. HLA A, B and DR mismatch were categorised into four levels and two groups. Data were fully anonymised and ethical principles adhered to.

Results: 1,389 paediatric renal transplant recipients were analysed; 807 (58%) received a DBD donor kidney. Using Cox proportional hazard regression modelling of renal allograft survival, the risk of graft failure is 1.55 times as likely in children who receive a well HLA-matched DBD kidney compared to those that receive a poorly HLA-mismatched LD kidney (p=0.01, 95% CI 1.11-2.18). This analysis accounts for survival improvements across transplant years. In both DBD and LD grafts, there was no difference in renal allograft survival in children who received a good or poorer HLA-mismatched transplant (p=0.16 for DBD graft, p=0.55 for LD graft).

Conclusions: In children, well HLA-matched DBD renal transplants have inferior graft outcomes when compared with poorly HLA-matched LD grafts. It is difficult to justify preferentially waiting for an improved HLA-matched DBD kidney even when a poorer HLA-mismatched LD kidney transplant is available.

Funding: Government Support - Non-U.S.
In the DCD group the median time to astole was 12.5 minutes and the median standard warm ischaemia time was 13 minutes. In the DCD group there was 1 case of primary non-function and 5 cases of delayed graft function.

Conclusions: This is one of the largest studies reporting outcomes in children who receive DCD kidney transplants. In the post-2000 era children receiving a DCD kidney transplant have good graft survival at 3-year follow up, comparable to those receiving a kidney from a DBD donor or a living donor. This limited evidence encourages the use of selected DCD kidneys in paediatric transplantation as favourable graft outcomes can be achieved, and national DCD allocation algorithms may need to be amended in view of this.

Funding: Government Support - Non-U.S.

SA-OR023

Longitudinal Change in Neurocognitive Functioning in Pediatric Chronic Kidney Disease

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Background: Few longitudinal data exist on the cognitive functioning of children with mild to moderate chronic kidney disease (CKD). We report longitudinal findings for the neurocognitive functioning of participants with mild to moderate CKD from the 48-site CKD Study, with a particular focus on identifying CKD-related variables predictive of change in cognition over time and progression to renal replacement therapy (RRT).

Methods: The sample comprised 2,009 assessments over a span of approximately 12 years. Measures of IQ, attention, and parent ratings of executive functions were obtained. Joint longitudinal mixed models and time-to-event models with a shared random effect were used to examine the predictive value of CKD-related variables at study entry (glomerular diastolic blood pressure, age of CKD onset, iGFR, proteinuria, anaemia) and over time (duration of disease, iGFR annual percent change) adjusting for baseline covariates (e.g., gender, maternal education), while simultaneously examining the association of neurocognitive decline with RRT.

Results: Median chronological age at study entry was 11.3 yrs; 56% Caucasian; 62% male. 33% had maternal education of a college degree. The median duration of CKD was 7.9 yrs, with 62% of children having disease onset at birth. 21% had a glomerular diagnose; average iohexol-based GFR was 52.3 ml/min/1.73m². After adjusting, lower iGFR and elevated blood pressure at study entry were associated with declining Performance IQ. Lower GFR and annual percent change in iGFR were associated with worse parent ratings of executive functioning. The shared parameter associating declining neurocognitive abilities with RRT showed Attention Variability to be related to progression to RRT.

Conclusions: Findings suggest that selected disease-related variables should trigger referral for neurocognitive assessment as children with lower iGFR and elevated blood pressure, and those with larger annual iGFR change may be at greatest risk for neurocognitive declines. Attention variability also was significantly associated with CKD disease progression to RRT.

Funding: NIDDK Support

SA-OR024

Biomarkers and Urinary Tract Infection in Infants

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Background: Urine culture is needed to diagnose infants with urinary tract infection (UTI). Symptoms are nonspecific and urine biomarkers are a possible tool to improve the diagnostic accuracy minimizing the need for investigations and invasive procedures. The aim was to evaluate if urine biomarkers can aid in the diagnosis of UTI.

Methods: This is a prospective study of infants with first UTI. Urine biomarkers were measured in infants with UTI and in a control group of children with fever from other causes. Measured urine biomarkers were Kidney injury molecule 1, Clara cell protein, Retinol binding protein, Neutrophil gelatinase associated lipocalin, high sensitive C-reactive protein, Interleukin-1b, Interleukin-6 and Interleukin-8 (IL-8); all were adjusted for urine creatinine/ur. The area under the ROC curve (AUC) for each biomarker was compared for children with UTI versus children with fever without UTI; the optimal cutoff level for equal weight on sensitivity and specificity was determined.

Results: 108 infants with UTI, 59 boys (mean age 2.7 months) and 49 girls (mean age 4.0 months) and a control group of 64 patients with fever without UTI (23 girls and 41 boys) were included. The biomarkers NGAL/cre and IL-8/cre were superior in differentiating boys and girls. The biomarkers NGAL/cre and IL-8/cre were superior in differentiating boys and girls. The biomarkers NGAL/cre and IL-8/cre were superior in differentiating boys and girls. The biomarkers NGAL/cre and IL-8/cre were superior in differentiating boys and girls.

Conclusions: This prospective study shows that the urine biomarkers NGAL and IL-8 had high sensitivity and specificity for the diagnosis of UTI in infants. Infants with fever and a low NGAL/cre value were highly unlikely to have a UTI.

Funding: Government Support - Non-U.S.

SA-OR025

Phospholipase A2 Receptor Autoantibodies in Pediatric Membranous Nephropathy

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Background: Membranous nephropathy (MN) is the commonest cause of nephrotic syndrome in adults, with most cases being primary, or autoimune in nature. Understanding of MN advanced with the discovery of phospholipase A2 receptor (PLA2R) as the target autoantigen and with the detection of circulating autoantibodies in the sera of adult patients. In the pediatric population, MN is rare and often presents with persistent, steroid-resistant, proteinuria and is diagnosed by typical histological features on renal biopsy. In this study, we describe the clinical phenotype, renal histological analysis, anti-PLA2R status, and autoantibody binding in 6 children with biopsy-proven MN treated at the Royal Manchester Children’s Hospital over the past 7 years.

Methods: We carried out phenotypic characterisation of patients, determination of anti-PLA2R status by ELISA, anti-PLA2R Ig subclass analysis and histological characterisation of renal biopsies. Anti-PLA2R binding was determined by comparing autoantibody reactivity to recombinant fragments of the PLAR under denatured and native conditions.

Results: Determination of anti-PLA2R status revealed 50% of children were seropositive. Seropositivity was associated with a severe clinical phenotype with nephrotic syndrome with renal impairment and IgG4 was the predominant subclass. Seronegative patients presented with asymptomatic proteinuria. Autoantibody reactivity patterns to recombinant fragments of the PLAR, differed with clinical phenotype at presentation.

Conclusions: Here we report, for the first time, a series of 6 children with biopsy-proven MN. We demonstrate a correlation between clinical phenotype and anti-PLA2R status and evaluate autoantibody-PLA2R binding in the paediatric MN population. Our results suggest that minor, or alternative, epitopes exist within the PLAR which may be responsible for autoantibody binding in paediatric MN.

SA-OR026

APOL1-Associated Glomerular Disease in African-American Children in the CKiD and NEPTUNE Cohorts

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Background: Little is known about APOL1 associated nephropathy in children. This study aimed to describe characteristics and longitudinal outcomes in African-American children with glomerular disease, stratified by APOL1 risk genotype in the Chronic Kidney Disease in Children cohort (CKiD) & the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: Enrollment criteria for CKiD was age 1-16, diagnosis of CKD, & estimated glomerular filtration rate (GFR) of 30-90 ml/min. NEPTUNE subjects were enrolled with suspected primary nephrotic syndrome, proteinuria, >0.5g/day, & clinically indicated biopsy. 56 CKiD subjects with glomerular disease & 48 NEPTUNE pediatric subjects were included here (all African-American). APOL1 was directly genotyped and subjects were classified as low risk (LB, 0 or 1 risk alleles) or high risk (HR, 2 risk alleles). All analyses were performed under the recessive model; LR vs HR subjects. By APOL1 genotype, odds of prematurity and eGFR & proteinuria over time were modeled.
Results: All subjects were of similar age (12 to 15 yrs). HR subjects in both cohorts had a lower baseline HR <60 bpm and |±20 bpm/l/min. The combined cohort demonstrated a significantly increased odds of prematurity in HR subjects (OR: 4.57; 1.4-15.5). NEPTUNE HR subjects had 15% decline in GFR per year, comparable to that seen in all CKD subjects, independent of genotype. LR NEPTUNE subjects had no eGFR decline (3% per year).

Conclusions: HR genotype was associated with higher odds of prematurity, suggesting an interaction between the APOL1 HR genotype and prematurity in the development of pediatric glomerular disease and subsequent CKD. NEPTUNE children with the HR genotype had a similar decline in eGFR as CKD subjects.

Funding: NIDDK Support

SA-OR27

Comprehensive Approach to Understand Human Renal Development Based on the Identification of Responsible Genes for CAKUT

A Randomized Study of Cholecalciferol Supplementation in Incident Hemodialysis Patients – Preliminary Evaluation After 2 Years

Background: Although regenerative medicine using the pluripotent stem cells holds promise for the treatment of the renal failure, the complexity of the structure composed of diverse cell types makes the difficulty in the establishment of the differentiation protocol into renal nephron. Towards the comprehensive understanding of the molecular network underlying human renal development, this study aims to identify responsible genes for congenital anomalies and the kidney and urinary tract (CART) and reveal the molecular mechanism of pathogenesis.

Methods: Two hundred six CAKUT cases including 115 cases from 105 families of syndromic CAKUT and 91 cases from 82 families of non-syndromic CAKUT together with some patients who had the diagnosis of CAGS or CIRGS, who consented in agreement with parents, which was approved by the ethical committee at Kobe University. Genomic DNA samples were analyzed by the next-generation sequencing (Illumina exome and Agilent custom panels) in combination with the conventional Sanger sequencing and/or the DNA microarray subsequent to the phenotype classification based on the clinical manifestations.

Results: Responsible genes in 62 cases from 44 families were identified. The phenotype classification assisted to detect the reported responsible genes including PAX2, EYA1, HNF1B, UMOD, OFD1, SALL1 and CHD7 by Sanger sequencing, and the next-generation sequencing (Illumina exome and Agilent custom panels) was superior over the clinical manifestations in some indistinguishable cases from CAKUT, were collected in agreement with participants, syndromic CAKUT and 91 cases from 82 families of non-syndromic CAKUT together with some patients who had the diagnosis of CAGS or CIRGS.

Conclusions: These results would be significant to understand the network of disease-associated genes and the molecular mechanism underlying the human renal development, and might give us a future perspective for the regenerative medicine.

Funding: Government Support - Non-U.S.

SA-OR28

A Randomized Controlled Trial of LevoCarnitine in Hemodialysis Patients

A Randomized Controlled Trial of LevoCarnitine in Hemodialysis Patients

Background: Carnitine deficiency has been suggested as a factor of several cardiovascular risk factors, mortality and mobility in urinary patients. Our aim is to prospectively assess the safety and efficacy of vitamin D (cholecalciferol) supplementation with placebo.

Methods: We evaluated 108 (66% M) patients in group A (GA) under D 0-2000 U/kg/wk, and 95 (67% M) patients in Group B (GB) on placebo, matched in age, (mean 66 and 65 years), BMI (mean 25.7 and 26.3 kg/m2 respectively), etiology of renal disease and the presence of comorbidities such as HTN, arthromy, peripheral vascular disease and cancer. The prevalence of DM (42 vs 57%), ischemic heart disease (18 vs 32%) and cerebrovascular disease (16 vs 27%) was higher in GB. A follow-up of 12 and 24 months (m) was attained respectively in 67 and 18 pts in GA vs 60 and 21 pts in GB.

Results: The basal levels of 25(OH)D3 were similar in the two groups (median 11 ng/mL) and significantly increased at 12m in GA (30 vs 11 ng/mL in GB; p<0.001) and at 24m (38 in GA vs 15 ng/mL in GB; p<0.001). Laboratory evolution (Ca, P, PTH, Iap, Hb, CRP or albumin), was similar in both groups. There were differences in the Erythropoiesis Resistance Index (ERI) (mg/kg/gal/gl) at T0 (GA=0.034 vs GB=0.023, p<0.03) and at 24m (GA=0.010 vs GB=0.022, p=0.01). No differences in the evolution of pulse pressure, left ventricular mass index or vascular calcifications were observed. The leading causes of hospitalization were CV and infectious, similar in both groups. There were 18 (16.7%) deaths in GA and 12 (12.6%) in GB (Log rank=0.752, p=NS, Kaplan-Meier). Treatment with lipid-lowering drugs, phosphate binders, active vitamin D, or cinacalcet was similar in both groups.

Conclusions: Cholecalciferol administration at a dose of 20 000 U/week was safe and permitted a significant increase of vitamin D levels and a decrease of ERI in the supplemented group at 24M.

SA-OR029

Levodopa Improves Cardiac Function in Hemodialysis Patients with Left Ventricular Hypertrophy

Background: Left Ventricular Hypertrophy (LVH) is a major cardiovascular risk factor in end-stage renal disease (ESRD) patients on hemodialysis. LVH is an independent predictor of mortality. Doppler echocardiography can identify LVH in patients on dialysis. The secondary endpoints were clinical parameters and identification of factors that predict a favorable response to levodopa therapy. Echocardiographic parameters were measured at baseline and after 6 and 12 months of therapy.

Results: A total of 252 patients were randomly assigned, of whom 148 patients (levo group, n = 75; control group, n = 73) were analyzed. The ejection fraction values increased from 54.0±5.8% at baseline to 56.0±6.1% after 6 months (p<0.001) to 58.1±5.6% after 12 months (p<0.0001) in the levocarnitine group, while no significant changes in ejection fraction were observed in the control group. Furthermore, left ventricular mass index (LVMI) and N-terminal probrain natriuretic peptide levels were significantly decreased throughout the study in the levocarnitine group. Multivariate analysis revealed that LVMI was an independent predictor of improvement in ejection fraction following levodopa therapy. Subgroup analysis revealed that responders to levodopa therapy were patients with left ventricular hypertrophy (LVH).

Conclusions: Levodopa therapy is useful for hemodialysis patients with LVH; these patients may benefit from such therapy, with amelioration of cardiac function and mitigation of LVMI.

SA-OR30

Predictive Ability of Self-Rated Health and Symptom Burden for Mortality in Hemodialysis

Background: Little is known about the ability of self-rated health to predict mortality in hemodialysis.

Methods: A prospective cohort study in hemodialysis (n=362). The Euro Quality of Life Questionnaire (EQSD), the Palliative Care Outcome Scale Renal (POS-S Renal) and the participant self-rated health (EQ visual analogue scale: EQVAS) were used to assess HRQOL, symptom burden and self-rated health. Participants were followed from instrument completion to death or study end.

Results: Over a median (25th-75th centile) of 2.6 (1.4-3.3) years, 32% (N=116) of participants died. With competing risks survival analysis factors most notably associated with mortality were history of hospitalization (adjusted hazard ratio (95%CI) included: higher symptom burden 2.3 (1.3, 3.3) P=0.004 (highest tertile), lower HRQOL 2.6 (1.3, 5.3) P<0.001 (lowest tertile), lower self-rated health 2.7 (1.4, 5.2) P=0.004 (lowest tertile). Answering ‘Yes’ to the questions: “problems with mobility” 2 (1, 3.3) P=0.01, or “problems with usual activities” 2 (1.1, 4.0) P<0.001. 55% of those aged ≥ 60 years reporting problems with either self care, mobility or daily activities in this study died over a mean (SD) of 2.1 (1.1) years, compared to 18% over 2.5 (1) years in those reporting ‘no’ to these questions, P<0.001. After age adjustment area under the receiver operating curves (AUC) (95%CI) for mortality were: 0.71 (0.63, 0.79) for symptom burden, 0.76 (0.68, 0.84) for HRQOL and 0.71 (0.62, 0.79) for self-rated health.

Conclusions: Age adjusted participant-rated health and predictive models based on combinations of individual elements from the POS S Renal and EQSD instruments could possibly aid in mortality discrimination and subsequent advance care planning in hemodialysis.

SA-OR31

isonatric Dialysis Biofeedback in Hemodiafiltration with Online Renovation of Ultrafiltrate in Hypertensive Hemodialysis Patients: A Randomized Controlled Study

Background: Biofeedback in hemodiafiltration with online renovation of ultrafiltrate (HFR) could improve arterial hypertension by using an isonatric mode maintaining a natriemia equal between start and end of the dialysis session. We evaluated the impact of nonisotonic HFR (HFRISO) on hypertension compared to Conventional HFR.

Methods: 47hemodiafiltration patients having an arterial pressure > 140/90 mmHg were randomized (ratio 2/1) HFR iso versus HFR during 24 dialysis sessions. The course from S1 to S24 of the predialytic systolic (SBP) and diastolic (DBP) blood pressure, the defined

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
daily dose (DDD) of antihypertensive treatment and of the dry weight were compared by t-test and by mixed model for repeated measurements adjusted for treatment x time interaction. The impact of age, diabetes and cardiovascular co-morbidities on response to treatment was evaluated. Tolerance was evaluated by the number of sessions complicated by symptomatic hypotension.

Results: In the Isotonic HFR group (N=32), the predialysis SBP decreased from 81 to 79 ± 10 mmHg (p=0.02, 95% CI, 0.82-1.19), the DDD of antihypertensive treatment (HFRiso) was 0.2 ± 0.1 mmHg, p=0.9 did not vary during the study. Age increased the PAS course independently of the treatment group (interaction age*time, p=0.05). The number of symptomatic hypotension was significantly higher in the 2 groups.

Conclusions: Isotonic HFR improved blood pressure control without increasing dialysis hypotension episodes.

Funding: Pharmaceutical Company Support - Belloco

SA-OR032

Relevance of B-Lines on Lung Ultrasound in Volume Overload and Pulmonary Congestion: Clinical and Therapeutic Correlations in Hemodialysis Patients

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Background: Volume overload in patients on hemodialysis (HD) is an independent risk factor for death from cardiovascular events. The immediate role of B-Lines (BL) on ultrasound (US) in predicting physical performance, morbidity and mortality, raises interest in its utility for assessing volume status in patients on HD.

Methods: ESRD patients on HD at Island Rehab center older than 18 were screened. Those with chronic lung disease and pregnant women were excluded. Patients achieving their dry weight (DW) had a lung US in a supine position. Residents were trained to visualize BL and recorded scores in real time. Clips were reviewed by blinded certified physicians. Scores were classified as mild (0-14), moderate (15-30) and severe (>30) for pulmonary congestion, as validated by Zoccoli et al.

Results: 81 patients on HD were recruited. 58 were male, mean age 59.7 years, hemoglobin 10.6 g/dL. 44 had NYHA Class 1, 24 had class 2, and 13 had class 3. In univariate analysis, NYHA class had significant correlation with BL scores and classes (<0.001), and diastolic dysfunction (0.002). In multivariate analysis, NYHA grade strongly correlates with B-Lines classification (0.01) but not with heart function (0.95). The mean difference between physicians and residents scoring was 3.77 (0.048). However this difference was not significant after classification and scores were in agreement (Kappa 0.56).

Conclusions: At DW, NYHA grading tightly corresponded to BL classification irrespective of cardiac function. Pulmonary congestion is common among patients on HD; NYHA score is mainly driven by the extravascular water and not by heart dysfunction. These results render fluid overload estimated by BL a better predictor for ESRD patient’s performance and a reliable indicator for their volume status assessment. Moreover, moderate lung congestion noted in patients with NYHA class 1 outline the importance of lung US in identifying subtle lung congestion opening a new concept for achieving DW.

SA-OR033

Combined Target Ranges for Blood Pressure and Fluid Overload

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Background: Recent research has revealed areas of increased mortality risk in the combination of systolic blood pressure (BPsys) and fluid overload (FO) (Fig 1a). It was the aim of this retrospective analysis to assess whether classifying patients according to a dedicated flow chart taking into account BP, FO and antihypertensive therapy (AHT) may indicate improved survival compared with a BP target range alone.

Methods: Pre-dialysis FO and BPsys were measured monthly in 31,349 patients from the Fresenius NephroCare Clinic Network. Patients were classified as being on/off target in January 2013 according to the flow chart in Figure 1b, which combines a BPsys target range of 130 to 160mmHg with information about AHT and FO [L] (Target1). FO was measured by bioimpedance spectroscopy. Normohydration was defined as FO normalized to dry weight(DW) had a lung US in a supine position. Those who have lung disease and pregnant women were excluded. Patients achieving their dry weight (DW) had a lung US in a supine position. Residents were trained to visualize BL and recorded scores in real time. Clips were reviewed by blinded certified physicians. Scores were classified as mild (0-14), moderate (15-30) and severe (>30) for pulmonary congestion, as validated by Zoccoli et al.

Results: 81 patients on HD were recruited. 58 were male, mean age 59.7 years, hemoglobin 10.6 g/dL. 44 had NYHA Class 1, 24 had class 2, and 13 had class 3. In univariate analysis, NYHA class had significant correlation with BL scores and classes (<0.001), and diastolic dysfunction (0.002). In multivariate analysis, NYHA grade strongly correlates with B-Lines classification (0.01) but not with heart function (0.95). The mean difference between physicians and residents scoring was 3.77 (0.048). However this difference was not significant after classification and scores were in agreement (Kappa 0.56).

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SA-OR034

Volume Status Assessed by Bioimpedance in Hemodialysis Predicts Mortality

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Background: Mortality rates average over 20% in the End-Stage Renal Disease (ESRD) US population with cardiovascular disease being the leading cause of death. Accurate intravascular volume assessment is critical in the treatment of patients who receive chronic hemodialysis (HD) therapy due to its deleterious effects on the heart and blood pressure (BP). Clinically assessed dry weight and interdialytic weight gain (IDWG) are often used as surrogates of volume status. Bioimpedance has emerged as an effective tool for volume management but is not readily available in clinical practice. Thus we examined the association of volume status determined by bioimpedance with mortality, compared to the association of IDWG and BP with mortality in ESRD patients.

Methods: ACTIVITY/ADIPOSE (A Cohort Study to Investigate the Value of Exercise in ESRD/Analyses Designed to Investigate the Paradox of Obesity and Survival) was a multicenter study of prevalent HD patients coordinated by the United States Renal Data System in 2009-2011. The data collection sites were 14 outpatient dialysis clinics in Atlanta and San Francisco. Volume status by bioimpedance defined by calculation of extracellular fluid (ECF): total body water (TBW) ratio. Associations by quartiles of ECF:TBW, IDWG, and BP with 1-year mortality were estimated using Cox proportional hazards regression models.

Results: 660 patients were included in this analysis, with 36 total deaths at 1 year. After adjustments, each increase of 0.01 in ECF:TBW (range, 0.39-0.57) in quartiles was associated with a >30% increased risk of mortality, (HR=1.32,95% CI, 1.15-1.52)<p>.001. In comparison, quartiles of IDWG (HR: 0.96, 95% CI, 0.78-1.17) and BP (per 10 mmHg, systolic, HR=0.99, 95% CI, 0.82-1.19; diastolic HR=0.90, 95% CI, 0.64-1.25), were not associated with mortality. Further, the associations of ECF:TBW with mortality were independent of BP, IDWG, and BMI.

Conclusions: Volume status by bioimpedance, but not IDWG or BP, was significantly and independently associated with greater mortality in this HD cohort. These findings question the common clinical practice of using IDWG as a surrogate of volume status in the HD population as it may not correlate with clinical outcomes.

Funding: NIDDK Support

SA-OR035

Abnormal Global Longitudinal Strain Is Associated with All-Cause Mortality in Hemodialysis Patients

Diana Chu, Darren Green, Nik Abidin, Philip A. Kalra. Univ of Manchester, MAHSC, UK.

Background: Cardiovascular mortality is high in hemodialysis (HD) patients.Early detection of cardiac dysfunction is important.Left ventricular global longitudinal strain (GLS) measures the maximal shortening of myocardial longitudinal length during systole compared to the resting length in diastole.Reduced GLS may reflect abnormal systolic function before loss of ejection fraction (EF) becomes apparent.We aimed to determine the prevalence, clinical correlates and prognostic value of abnormal GLS in stable HD patients.

Methods: Clinical and echocardiographic data were obtained in a prospective study of HD patients at one centre.Survival analysis for GLS was performed using Cox regression adjusted for age, co-morbidities, dialysis chronicity, laboratory data, left ventricular mass index adjusted for height (LVMi) and echoloe EF.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: The mean age was 62±14 years, 69% were male, 39% had diabetes, 29% heart failure, 17% coronary artery disease. The mean GLS was −13.4±3.5% and LVEF = 0.53±0.12. 98% of patients had abnormal GLS (>−20%), compared with 14% with reduced LVEF (<50%) and 55% with LV hypertrophy. Factors associated with an abnormal GLS included LVMIIHt (OR 1.06, 95%CI 1.04-1.09, P=0.01), LVEF (OR 0.96, 95%CI 0.94-0.99, P=0.01) and diabetes (OR 2.04, 95%CI 1.08-3.9, P=0.03). Median follow-up was 24 (17-30) months, during which there were 41 deaths (21%). After adjustment for age, diabetes, coronary artery disease, LVEF, LVMIIHt, 3 month-averaged serum potassium and albumin, a less negative GLS remained an independent predictor of all-cause mortality (HR 1.18 for each 1% worsening change in GLS, 95% CI 1.03-1.35, P=0.02).

Conclusions: Abnormal GLS is highly prevalent amongst HD patients, and appears to be a better marker of all-cause mortality in stable HD patients than the “standard” echocardiographic parameters LVEF and LVMIIHt.

SA-OR036

Trimethylamine-N-Oxide (TMAO) and Cardiovascular Events in Hemodialysis Patients: The Retained Organic Solutes and Clinical Outcomes (ROSCO) Study

Tariq Shafi, Thomas H. Hostetter, Timothy W. Meyer, Seungyoung Hwang, Michali L. Melamed, Tanushree Banerjee, Josef Coresh, Neil R. Powe, Timothy W. Meyer, Seungyoung Hwang, Michali L. Melamed, Tanushree Banerjee, Josef Coresh, Thomas H. Hostetter, Johns Hopkins Univ; Univ of California San Francisco; Stanford Univ; Albert Einstein College of Medicine; Case Western Univ.

Background: Uremic toxins that contribute to cardiovascular (CV) disease and observed higher mortality in whites vs. blacks remain undefined. TMAO, a highly dialyzable metabolite, is associated with accelerated atherosclerosis and CV events in non-dialysis patients but previous studies in dialysis patients have been equivocal.

Methods: We measured TMAO in 1232 patients of the Hemodialysis (HEMO) Trial, 3-6 months after randomization and analyzed its association with CV mortality, sudden cardiac death (SCD) and first CV event, using Cox models adjusted for demographics, clinical characteristics, comorbidities, albumin and residual urea clearance.

Results: Mean age of the patients was 58 years, 34% white and 42% male. Median TMAO level was 88 µM (IQR, 62 to 124) and did not differ by race (p=0.9). The association of TMAO with outcomes differred by race (Figure) and was associated with outcomes only in whites. In whites, each 2-fold increase in TMAO was associated with 45% higher risk of CV mortality, 70% higher risk of SCD and 15% higher risk of CV events (Table). TMAO levels decreased in the higher Kt/VUREA group but did not have an effect on outcomes (p>0.1).

Conclusions: The association between TMAO and CV events differs among white and black hemodialysis patients.

Funding: NIDDK Support

SA-OR037

Serum Asymmetric (ADMA) and Symmetric (SDMA) Dimethylarginine and Morbidity and Mortality in Hemodialysis Patients: The Retained Organic Solutes and Clinical Outcomes (ROSCO) Study

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Background: ADMA, an endogenous nitric oxide synthase inhibitor, and SDMA, a promoter of oxidative stress, accumulate in dialysis patients and may contribute to uremic toxicity.

Methods: We measured predialysis levels of ADMA and SDMA in 1276 patients of the Hemodialysis (HEMO) Trial, 3-6 months after randomization and analyzed its association with all-cause and cardiovascular (CV) mortality, sudden cardiac death (SCD) and first CV event, using Cox model adjusted for potential confounders (demographics, clinical characteristics, comorbidities, albumin, residual urea clearance).

Results: Mean age of the patients was 58 years, 65% black and 42% male. Median (interquartile range) for ADMA was 0.9 µM (0.8, 1.0) and SDMA was 4.1 µM (3.3, 5.0). In fully adjusted models, ADMA was associated with all outcomes whereas SDMA was only associated with CV mortality (Table). Subgroup analyses did not show significant interactions with race or HEMO interventions.

Conclusions: ADMA and SDMA may play important roles in morbidity and mortality in hemodialysis patients. Further studies are needed to elucidate the mechanisms of these associations.

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

Underline represents presenting author.
Conclusions: ADMA and SDMA are uremic solutes associated with morbidity and mortality in hemodialysis patients.

Funding: NIDDK Support

SA-OR038

Gromeler on-a-Chip as a Model to Study the Glomerular Filtration Barrier In Vitro Stefano Da Sacco,1 Jos Joore,2 Paul Vulto,1 Roger E. De Filippo,1 Laura Perin.1,3 Urology, Children’s Hospital Los Angeles, Los Angeles, CA;4 IMMETAS.

Background: The glomerular filtration barrier (GFB) has three major components: the podocyte with the “slit diaphragms”, the glomerular basement membrane and the fenestrated glomerular endothelial cell (hGEC): each of them is essential for the correct blood filtration. Damage to any of these components often leads to a severe, irreversible GFB disruption with onset of chronic damage requiring drug treatment and eventually dialysis and transplantation. Development of alternative therapeutic approaches is limited by our poor understanding of the complex cell-matrix interactions and cellular cross-talk in vivo and the absence of in vitro GFB models. Therefore, an in vitro system that mimics the complex GFB architecture and that can be used to better study glomerular (patho-)physiology is urgently needed.

Methods: We have generated a population of renal progenitors from human amniotic fluid (hAKPC-P) that can differentiate into podocyte-like cells. Taking advantage of the peculiar characteristics of available microfluidic systems, we have developed an innovative Glomerulus-on-a-Chip system by co-culturing hAKPC-P and hGEC cells in OrganoplateTM microfluidic plates. Evaluation of culture conditions, immunostaining and qPCR were performed to characterize the 3D culture.

Results: We have successfully established the conditions for in vitro co-culture of hAKPC-P and hGEC in a microfluidic plate for up to 21 days. Apoptosis and proliferation were assessed by TUNEL and PCNA. Vessel formation by hGEC was confirmed along with expression of endothelial marker VE-Cadherin while hAKPC-P-derived podocytes were positive for nephrin and podocin. De-novo deposition of collagen IV in the 3D microfluidic plates was confirmed by immunostaining.

Conclusions: Our preliminary results suggest the feasibility of Organoplates for co-culture of podocytes and GFB in a 3D environment that more closely mimics the structure of the GFB. If successful this system might prove useful for the assessment of several aspects of cell-cell and cell-matrix interaction, thus helping to understand podocytes/endothelial crosstalk (or its perturbations) and how this might affects glomerular homeostasis.

Funding: Private Foundation Support

SA-OR039

Pharmacokinetic Model for Screening Nephrotoxicity Using Kidney on a Chip Se joong Kim,1 2 3 S aha Cai Les her-Per ez,1 By oung Ch oul C. Kim,1 C amer on Y amanishi,1 J osph M. Labu zig,1 Sh uichi Tak aya mana,1 4 U niversity of Michigan College of Engineering, A m A roor, M I; Int erna l M edicine, S ea o nal Un iv Bundang H ospital, Se o ngnam, K o rea.

Background: Animal renal clearance is usually higher than human renal clearance, which may underestimate nephrotoxicity. We developed a microfluidic device lined with kidney epithelial cells to mimic in vivo-like microenvironment. We evaluated the nephrotoxicity of two different gentamicin regimens using this kidney on-a-chip and human pharmacokinetic data.

Methods: The microfluidic device had top channels like luminal spaces and bottom channels like interstitial spaces. MDCK cells on the porous membranes between the two channels were exposed with a fluid shear stress (1.0 dyn/cm²). D1 regimen was 19.2 mM of gentamicin for initial dosage and reduction by half every 2 hours to mimic human renal pharmacokinetic models for evaluating nephrotoxicity.

Results: D1 regimen sustained the permeability, while D2 leaded to increase in the permeability (P < 0.05). In addition, D1 regimen exhibited less cytotoxicity than D2 (Dead cell 1.43 ± 0.30 % vs. 4.9 ± 0.20%, respectively, P < 0.05).

Conclusions: These data suggest that gentamicin may interrupt junctional protein complex and membrane permeability, and that single daily dose alleviate the nephrotoxicity, compared to the continuous infused regimen. Microfluidic devices can be one of novel pharmacokinetic models for evaluating nephrotoxicity.

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SA-OR040

Computational Prediction and Experimental Analyses of Proteins That Bridge Metabolite Markers of Human Diabetic Nephropathy Rintaro Saito,1 2 3 Anaí s Rocanín-A rjo,1 Mi nyu Pa,1 3 Simone Romoli,1 Lok i Natarajan,1 3 Wenjun Ju,1 Matthias Kretzler,2 Robert G. Nelson,1 Dana Thomasova,1 Shir i kant R. M ulay,1 Hans J. Anders,1 Kumar Sharma.2 2 3 3 Inst Metabol Med; 3 Center Renal Transl Med; Dept Med, UCSD, CA; 4 Medizinische Klinik und Poliklinik IV; Klinikum der Univ München, M unich, Germany; 5 Dept Family Med Epidem, UCSD; 6 Dept Internal Med, Nephrology & Dept Comput Med & Bioinf, Univ of Michigan, MI; NIDDK, AZ; 4 VA Health Systems, SD, CA.

Background: We have previously shown that thirteen metabolites are shown to be characteristic of human diabetic kidney disease (DDK) and linked to mitochondrial dysfunction. However, novel bioinformatic tools could indicate novel connections among these metabolites to identify new relevant protein targets for human disease.

Methods: We integrated publicly available human protein-protein interaction (PPI) networks with global metabolic networks onto a software (Cytoscape) to enhance the interpretation of metabolomic data. Validation was performed with gene expression data from Nephromine and experimental studies in mice.

Results: We found that all thirteen metabolites can be connected through a single subnetwork of PPIs. We focused on bridge proteins, which were predicted to potentially connect these metabolites through their associated enzymes and found that several proteins had a significant number of connections regulating the original 13 metabolites. These included MDM2 (BH corrected p < 0.005, 14 connections) and PEX5 (p < 0.005, 9 connections). Of these, MDM2 had the strongest regulation in its gene expression in glomeruli (p <0.01) and tubulointerstitium (p <0.01) from two different cohorts of diabetic kidney biopsies. In vivo studies with Nutlin3a, an inhibitor of MDM2 binding site, in both healthy C57Bl/6J mice and db/db type 2 diabetic mice resulted in a reduction of podocytes, an increase in proteinuria and higher levels of plasma urea levels in healthy and diabetic mice.

Conclusions: Our bioinformatics approach has been demonstrated to make biologically relevant interpretation of dysregulated metabolites, highlighting the significance of MDM2 dysregulation in DDD in both experimental models and patients with DDK.

Funding: NIDDK Support

SA-OR041

Mechanical Properties of Renal Tubules Measured Using Glass Microcantilevers Nicholas J. Ferrell, Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: The mechanical properties of tissues play an important role in maintaining tissue function, and altered biophysical properties affect disease progression. Measuring the mechanical properties of tissues play an important role in maintaining tissue function, and altered biophysical properties affect disease progression. Measuring the mechanical properties of isolated biological structures, including renal tubules can be challenging, especially in tension. We have developed a new method to measure the elastic modulus of renal tubules using glass microcantilevers as force measurement cantilevers.

Methods: Cortical tubules were manually dissected from normal mice. Elastic modulus was measured by clamping each tubule between a measurement microcantilever and applied force were determined my measuring the change in the tubule length and deflection of the measurement cantilever. Tubule stress was estimated assuming the resistance to deformation was imparted primarily by the tubular basement membrane. The cross-sectional area of each tubular basement membrane was calculated based on a basement membrane thickness of 0.24 µm. Elastic modulus was calculated from the slope of the stress-strain curve at a given strain.

Results: Stress-strain curves indicated a strain dependent increase in elastic modulus suggesting significant strain stiffening of renal tubules. At low strain (0-15%) elastic modulus was measured at 555±98 kPa. At higher strain (15-30%) elastic modulus was 1113±150 kPa and at even higher strain (30-50%) elastic modulus was 2161±173 kPa. Stain stiffening behavior was observed throughout the range of measurable strain.

Conclusions: These results indicate that renal tubules are highly deformable structures that exhibit increased stiffness as strain increases, a response typical of extracellular matrices such as collagen gels. This method provides a relatively simple means of determining renal tubular biophysical properties and may be a useful tool for evaluating renal tubule mechanical properties in a variety of kidney diseases.

Funding: NIDDK Support

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SA-OR042
Non-Invasive Measurement of Renal Blood Flow (RBF) in Rat by Magnetic Resonance Images (MRI)  Cesar A. Romero,1 Robert Knight,2 Oscar A. Carretto,1 1Hypertension and Vascular Research Div, Henry Ford Hospital; 1Henry Ford Hospital; 2Henry Ford Hospital.

Background: Quantitative measurement of RBF provides important information on renal physiology, nephropathies and kidney viability in different animal models. Arterial Spin Labelling–MRI (ASL-MRI) is a non-invasive method to measure blood flow without exogenous contrast media, using arterial water protons labeled by radiofrequency as an endogenous tracer. However, the low signal/noise ratio and the motion artifacts pose a challenge when acquiring RBF in small animals. Our objective is to evaluate the feasibility and reproducibility of the RBF measurement by ASL-MRI under basal conditions and in a high RBF state in rats.

Methods: ASL-MRI images were obtained in seven males Sprague-dawley rats (200-300g) under the inhalatory anesthesia (isoflurane 2%). Rectal temperature probe was used to control the body temperature. After 4 days, the MRI studies were repeated in 3 rats (6 kidneys) to evaluate reproducibility, using paired sample T-test and the test-retest reliability (TR) by the equation TR=(1-SDn/Mn)x100 were M and SD are the mean and standard deviation of the RBF in “n” different sessions. RBF was also measured in a set of animals that underwent unilateral nephrectomy 24 hours before and after the surgery. MRI was acquired using a 7 Tesla Varian MRI system with a spin echo imaging sequence using respiratory triggering and navigator correction to reduce motion artifacts. The sequence was averaged 16 times and the total scan time for the entire series of ~20 minutes. In house software was used to analyze the postprocessing imaging.

Results: The mean cortical RBF was 30±5.9 and 271.8±39 mll/min/100g tissue in right and left kidney, respectively. Re-test analysis showed no differences, with the means of differences 9.4±5.3mll/min/100g tissue (p=0.58). The TR was 92.4±6%. The RBF before and after the nephrectomy was 270±30 and 456.6±34 mll/min/100g tissue (p=0.004), respectively, showing a relative increase of 69.1%.

Conclusions: ASL-MRI performed with navigator correction and respiratory gating is feasible and reliable non-invasive method to measure RBF in rats.

SA-OR043
Intravoxel Incoherent Motion Analysis of Diffusion Weighted Imaging to Measure Glomerular Filtration Fraction – Proof of Concept René van der Bel,1 Oliver J. Gurney-Champion,2 Wouter V. Potters,2 Hein J. Verberne,3 Lifferg Vogt,4 Erik Stroes,4 Aart J. Nederveen,4 C.T.P. (Paul) Krediet.1 1Internal Medicine, AMC, Univ of Amsterdam, Netherlands; 2Radiology, AMC, Univ of Amsterdam, Netherlands; 3Nuclear Medicine, AMC, Univ of Amsterdam, Netherlands.

Background: Glomerular filtration fraction (FF) can be calculated from the fractional glomerular filtration rate (GFR) and the glomerular plasma flow (GPF). This technique is costly and time consuming. Intravoxel Incoherent Motion (IVIM) analysis provides an assessment of diffusion weighted imaging (DWI) for fractions of blood and pre-jurine within kidney tissue. This could serve as a surrogate for filtration fraction. With this study we a proof of concept for an MRI derived kidney function measurement.

Methods: After a baseline phase, 6 healthy volunteers (age 18-24 yrs) were subjected to continuous Angiotensin II (Ang-II) infusion at 3.0 ng/kg.min. Blood and (pre-)jurine fractions and renal blood flow (RBF) were assessed using DWI and phase contrast MRI (Ingenia 3.0T, Philips Healthcare). Fractions were calculated via tri-exponential IVIM analysis and renal blood flow (RBF) were assessed using DWI and phase contrast MRI as a surrogate for filtration fraction. With this study we a proof of concept for an MRI derived kidney function measurement.

Results: The mean cortical RBF was 30±5.9 and 271.8±39 ml/min/100g tissue in right and left kidney, respectively. Re-test analysis showed no differences, with the means of differences 9.4±5.3ml/min/100g tissue (p=0.58). The TR was 92.4±6%. The RBF before and after the nephrectomy was 270±30 and 456.6±34 ml/min/100g tissue (p=0.004), respectively, showing a relative increase of 69.1%.

Conclusions: ASL-MRI performed with navigator correction and respiratory gating is feasible and reliable non-invasive method to measure RBF in rats.

SA-OR044
Visualization of Kidney Fibrosis in Diabetic Nephropathy by DTI MRI Jun-Ya Kajimori,1 Yoshitaka Isaka,2 Masaki Hanatanka,2 Satoko Yamamoto,2 Hiroshi Shibata,2 Akira Fujimori,4 Akihiko Fujikawa,4 Sosuke Miyoshi,4 Naotsugu Ichimaru,3 Toshiki Mortyama,3 Hiromi Raugi,2 Shiro Takahara,1 1Dept of Advanced Technology of Transplantation, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Dept of Geriatrics & Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 3Osaka Univ Health Care Center, Osaka Univ, Toyonaka, Osaka, Japan; 4Drug Discovery Research Inst, Astellas Pharma Inc, Tsukuba, Ibaraki, Japan.

Background: Renal fibrosis (RF) is a well-known marker for chronic kidney disease (CKD) progression. However, an available examination for evaluation of RF is invasive biopsy. Diffusion MRI was once recognized as a promising option for RF. But now it is controversial and it could not be applied to diabetic nephropathy (DN).

Methods: To seek an optimal imaging method applicable even for fibrosis in DN, we tried series of MRI imaging methods, including proton density weighted imaging (PDWI), T1 weighted imaging (T1WI), T2 weighted imaging (T2WI), diffusion weighted imaging (DWI), and diffusion tensor imaging (DTI).

Results: We identified DTI/MRI by spin echo sequence plus a special kidney attachment as the best option for evaluation of UOU fibrosis, compared with normal kidney in the opposite side. To confirm these results, we applied this technique to rat UOU therapeutic model with anti-fibrotic reagent, Fasudil. FA values calculated form DTI MRI showed statistically significant linear correlation with RF area measured by Sirius Red or Masson trichrome staining positive area. Next, by using SHIR/3Dncmr-cpl(c/p) cartridge with or without telmisartan as a RF model of DN, we finally succeeded in visualization and evaluation of fibrosis accumulated in outer stripe of outer medulla region by FA map.

Conclusions: By DTI MRI with spin echo sequence, it may be possible to accurately evaluate RF in CKD including even DN.


SA-OR045
Super-Resolution Microscopy Reveals the Formation of a Mat of Contractile Fibers as Part of the Podocyte Foot Process Effacement Phenomenon Han Suleiman,1 Jeffrey H. Minner,2 Andrey S. Shaw.1 1Pathology and Immunology, Washington Univ in Saint Louis, Saint Louis, MO; 2Pathology and Immunology, Washington Univ in Saint Louis, Saint Louis, MO; 3Renal Devison, Washington Univ in Saint Louis, Saint Louis, MO.

Background: The ~200 nm resolution of traditional microscopes is limited by the wave-length of light. Imaging structures smaller than 200 nm, such as podocyte foot processes and slit diaphragms, has required electron microscopy (EM). New super-resolution imaging techniques can break the diffraction barrier of light, thus allowing us to easily image and resolve the molecular composition of structures in a nanometer range.

Methods: We used an array of antibodies for Stochastic Optical Resolution Microscopy (STORM) to study the spatial distribution of key molecules of the podocyte cytoskeleton and slit diaphragm in healthy and injured glomeruli. We also developed a novel technique that allows us to image podocyte actin cables by EM.

Results: In healthy glomeruli, synaptopodin, synaptopodin is localized to the center of each foot process, while nephrin is at the slit diaphragm. As foot processes efface, nephrin redistributes apically away from the base of foot processes. We confirmed this in 3 different injury models. After podocyte injury the positions of synaptopodin and α-actinin-4 clusters did not change, but there was robust recruitment of myosin IIa, normally only in primary processes, to the bases of foot processes. The pattern of myosin IIa staining, in alternating stripes with synaptopodin and α-actinin-4, indicates the formation of contractile actin fibers during effacement. Using our new EM method, we observed a dramatic change in the morphology of actin fibers during effacement.
Intravital and Organ Slice Imaging of Podocyte Membrane Dynamics

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Background: The elaborate network of podocyte foot processes, which is stabilized by the actin cytoskeleton, is one of the key components of the glomerular filtration barrier. The question of whether podocytes change their shape under physiological conditions or in response to injury has been vigorously debated. The Rho-family of small GTPases is at the center of this debate, as these molecular switches control assembly and disassembly of the actin cytoskeleton. Evidence as to whether and how small GTPases change podocyte shape and dynamics is largely circumstantial, as all studies to date have been conducted in vitro.

Methods: Here we use intravital two-photon imaging of fluorescently labeled podocytes to answer these questions. Rosa26-confetti/Podo-Cre mice were used as reference and compared with mice expressing eGFP-labeled, constitutively active Rac1 (gEFP-CaRac1) in podocytes. To achieve a higher resolution we also imaged freshly isolated kidney slices in an organ bath.

Results: Podocytes in Rosa26-confetti/Podo-Cre mice showed a stable network of foot processes with no significant membrane movement. gEFP-CaRac1 podocytes lost their characteristic shape and showed increased membrane dynamics and podocyte shedding. Shed podocytes seemed viable, as they were observed migrating in the tubular system. Organ slice imaging resembled the intravital results but yielded a higher temporal-spatial resolution, which complements the intravital imaging. With this approach, we were also able to show that increased membrane dynamics is a feature of injured podocytes in a glomerular disease model.

Conclusions: We show in vivo for the first time that Rac1 converts podocytes from a state of immobility to one with greatly increased membrane dynamics and blunted foot processes, which also occurs in a model of glomerular injury. This suggests that foot process effacement is the end result of a highly dynamic state, and that foot process instability could contribute to proteinuria itself.

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

SA-OR046

Intravital Multiphoton Imaging of Podocyte Ca2+ Confirms the Important Role and Mechanism of TRPC6 in Glomerular Pathology

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Background: TRPC6 channels in podocytes are important Ca2+ influx pathways involved in the modulation of the actin cytoskeleton and in the actions of angiotensin II (ANG II). TRPC6 overactivity by gain-of-function mutations and high ANGII leads to albuminuria and chronic kidney disease (CKD). However, the regulation of podocyte Ca2+ dynamics by TRPC6 and the mechanism of the resulting glomerular dysfunction in vivo and in response to injury have been elusive. We aimed to directly and quantitatively visualize and study the dynamic effects of TRPC6 on podocyte and glomerular function during the development of glomerular injury.

Methods: Serial multiphoton microscopy of the intact living kidney of the same wild type (WT), TRPC6 transgenic (TG), and TRPC6 knockout (KO) mice was performed over two weeks of high ANGII treatment (1000 ng/kg/min). All mice expressed the intensely green and calcium sensitive fluorescent protein GCaMP3 only in podocytes. Changes in single cell GCaMP3 fluorescence intensity were measured and served as readout for podocyte [Ca2+]i changes.

Results: Systolic blood pressure increased from baseline 106 ± 5 mmHg after ANGII treatment for two weeks in mice with ANGII phenotype, similarly in TRPC6 TG and KO mice. In WT mice, normalized GCaMP3 fluorescence intensity in podocytes (Ca2+ increase >2-fold) was increased to 1.2 ± 0.2 fold, while in TRPC6 TG and KO mice, respectively. Glomerular functional parameters after ANGII treatment were exacerbated in TRPC6 TG mice, while improved in TRPC6 KO mice. Podocytes with high GCaMP3 fluorescence appeared migrating to the parietal Bowman’s capsule after ANGII in WT and TRPC6 TG, but not in TRPC6 KO mice.

Conclusions: This study demonstrated in vivo direct visual evidence of the critically important pathogenic role of TRPC6 in the development and progression of glomerular disease. Podocyte TRPC6 is a promising therapeutic target for the prevention of CKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Amgen

SA-OR048

Mesangial Filopodial Invasion of Glomerular Capillaries in Alport Syndrome

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Background: Recent work shows mesangial cell filopodia invade the glomerular capillaries in Alport mice and humans. Filopodia progressively deposit laminin 211 and likely other mesangial matrix proteins in the GBM. Laminin 211 activates focal adhesion kinase in podocytes, which results in up-regulation of metalloproteinases and pro-inflammatory cytokines. These novel observations, which are key to glomerular disease initiation, have been met with some skepticism, which incentivized the current study.

Methods: Three color structured illumination microscopy (SIM, an ultra-high resolution endoscopy) was used to label mesangial cell filopodia and glomerular capillary cells, and the GBM. A mesangial cell culture bioassay was developed that allows induction of mesangial filopodia. RNAseq analysis of preproteinuric glomeruli identified novel candidates likely involved CDC42 activation in mesangial cells. These candidates were then validated in vivo.

Results: SIM analysis showed that integrin α8-immunopositive mesangial processes extend, contiguous with the mesangial angles, into the sub-endothelial spaces of the GBM. These processes are exclusive of CD31 immunopositive glomerular endothelium and the laminin α5 immunopositive GBM. Endothelin-1 (ET-1) activates CDC42 in mesangial cells and results in the formation of drebrin-immunopositive actin microspikes (filopodia). Of the six candidate proteins identified that may regulate endothelin A receptor (ET,R) mediated activation of CDC42, two have been tested by siRNA knockdown. MAL2 knockdown blocked ET-1 activation of filopodia, while BMP-7 knockdown had no effect. ET,R knockdown (a positive control) had no effect.

Conclusions: SIM analysis unequivocally proves mesangial filopodial invasion of the glomerular capillaries in Alport mice. The bioassay shows ET-1 mediated activation of CDC42 in mesangial filopodia and filopodial invasion. We identified one novel regulator of CDC42 activation, MAL2 which is critical mediator of CDC42 activation. This bioassay can thus be exploited to identify new therapeutic targets with the potential to prevent mesangial filopodial invasion of the glomerular capillaries.

Funding: NIDDK Support

SA-OR049

The DREADD Concept: A Novel In Vivo Tool for Kidney Research

Questioning the Role of Ca2+ on Actin Dynamics in Podocytes

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Background: The close homology between the slit diaphragm of the kidney glomerulus and the mechanosensor in C. elegans led to the hypothesis that the slit diaphragm is part of a conserved mechanosensor that is closely linked to an actin-based, contractile cytoskeleton regulated by Ca2+.

Methods: We generated a transgenic mouse line with specific expression of a mutated (Y149C/A239G) G protein-coupled human muscarinic type 3 receptor transgene (mMD) in the ROSA26 locus. This receptor is exclusively activated by the synthetic compound hM 3 -ligand acetylcholine. We mated the mMD,STOPhM3 mouse with the podocin:cre mouse to activate podocyte specific expression. We validated receptor expression and function both, in vitro and in vivo using immunofluorescence stainings, western blotting and live Ca2+ imaging using 2-photon microscopy of Ca2+2+.

Results: Here, we applied the DREADD (designer receptor exclusively activated by a designer drug, Conklin et al. 1998) concept to further test this hypothesis and to investigate the effects of an intracellular Ca2+ increase on the podocyte actin cytoskeleton. Even though we used a strong Ca2+ increase in podocytes after CNO administration no effects on the actin based cytoskeleton, glomerular perfusion or filtration were observed. Even administration of CNO over a prolonged period (4 wks) did not induce glomerular disease.

Conclusions: In conclusion, increasing Ca2+ levels in podocytes alone are not sufficient to induce podocyte rearrangements and to affect glomerular perfusion and filtration. Hence, these results challenge our current view on actin dynamics in podocytes and their role in glomerular perfusion and filtration.

Funding: Government Support - Non-U.S.

SA-OR050

Loss of Epithelial Membrane Protein 2 Aggravates Podocyte Injury via Uregulation of Caveolin-1

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Background: Nephrotic syndrome is a chronic kidney disease defined by proteinuria with subsequent hypoalbuminemia, hyperlipidemia and edema, due to impaired renal glomerular filtration barrier function. Glomerular podocytes have been proposed to play a critical role in the maintenance of glomerular filtration barrier and the pathogenesis of
nephrotic syndrome. We have previously identified mutations in EMP2 (epithelial membrane protein 2) in patients with nephrotic syndrome. These mutations are thought to cause clathrin-mediated endocytosis. They have not been found in patients with steroid-sensitive and steroid-resistant nephrotic syndrome.

**Methods:** To understand the pathogenic mechanism underlying EMP2 mutations, we have generated a zebrafish knockdown model of emp2 using TALEN and transgenic zebrafish. We have also characterized cultured human podocytes with shRNA-mediated EMP2 knockdown.

**Results:** We found that loss of emp2 in zebrafish up-regulated caveolin-1 (cav1), a major component of caveolae, in embryos and mesonephric glomeruli, and exacerbated podocyte effacement. These changes would be partially rescued by glucocorticoids. We also found that overexpression of cav1 in zebrafish podocytes was sufficient to induce the same phenotypes seen in emp2 homozygous mutants, which were treatable by glucocorticoids. Consistently, knockdown of EMP2 in cultured human podocytes resulted in an increase of cav1, and a decrease of podocyte survival in the presence of probucol, an immature aminocollidine. While glucocorticoid treatmentameliorated these phenotypes.

**Conclusions:** Taken together, we have established excessive CAV1 as a mediator of the predisposition to podocyte injury due to loss of EMP2, suggesting CAV1 could serve as a novel therapeutic target of nephrotic syndrome and podocyte injury.

_Funding: NIDDK Support, Private Foundation Support_

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**SA-OR053**

**The Spectrum of Nephrotic Syndrome from Minimal Change Disease to FSGS Correlates with Rac1 Activation**

**Richard Robins, Cindy Baldwin, Lamine Aoudjit, Indra R. Gupta, Tomoko Takano.**

_Nephrology, McGill Univ, Montreal, QC, Canada._

**Background:** Within podocytes, cytoskeletal organization is regulated by Rho-family GTPases including Rac1. Clinical and animal studies suggest that Rac1 activation within podocytes contributes to the pathogenesis of nephrotic syndrome (NS). We hypothesize that Rac1 activity is increased in clinical NS and podocyte-specific activation of Rac1 will result in NS in mice.

**Methods:** Kidney biopsies from patients with minimal change disease (MCD) and idiopathic focal segmental glomerulosclerosis (FSGS) were immunostained for active Rac1. Serum from FSGS patients was used to culture podocytes. Mice carrying the tetracycline-inducible constitutively active Rac1 mutant (L6I, CA-Rac1, Flag-tagged) were bred with mice with the podocin-driven reverse tetracycline trans-activator to generate double transgenic mice (DTG). Podocin was examined by the albumin/creatinine ratio (ACR). Renal histology was evaluated by light, immunofluorescence (IF) and electron microscopy.

**Results:** By IF, active Rac1 staining was increased in glomeruli (co-localized with nephrin) in patients with NS. FSGS patients sera activated Rac1 in cultured podocytes. DTG mice carrying 1 copy of the CA-Rac1 transgene; mice with 2 copies had significantly higher proteinuria upon 5 days Dox treatment (high responders), compared with those with 1 copy (low responders). Foot process effacement was more diffuse and pronounced in high responders compared to low responders. When Dox was withdrawn after 5 days, low responders returned to near baseline proteinuria while high responders remained high. When Dox was withdrawn after 2 weeks in high responders, podocin did not resolve. After 1 month, high responders displayed severe glomerulosclerosis.

**Conclusions:** Active Rac1 staining is increased in patients with NS. FSGS sera promote Rac1 activation in cultured podocytes. In mice, the amount of Rac1 activation within podocytes determines severity of foot process effacement, podocinuria, and degree of reversibility upon Dox withdrawal. The amount of Rac1 activation may be a critical factor determining whether MCD or FSGS arises within the NS spectrum.

_Funding: Government Support - Non-U.S._

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**SA-OR054**

Glomerular TNFα Expression Causes Free Cholesterol Mediated Podocyte Apoptosis in DKD and FSGS


**Background:** Tumor Necrosis Factor alpha (TNFα) levels predict the development of Diabetic Kidney Disease (DKD). TNFα inhibition may be efficacious in some patients with Focal Segmental Glomerulosclerosis (FSGS). Podocyte injury is observed in both diseases and glomerular cholesterol accumulation was associated with albuminuria and reduced ATP-Binding Cassette A1 (ABCA1) expression in experimental DKD. We hypothesized that TNFα causes lipid dependent podocyte injury in FSGS and DKD.

**Methods:** Caspase 3 activity and cholesterol efflux was determined in human podocytes treated with TNFα. Cyclohexatin (CD) was used for cholesterol depletion.

**Results:** DKD and FSGS sera treated podocytes showed increased TNFα expression. Glomerular TNFα expression correlated with reduced ABCA1 expression in FSGS. Podocytes treated with sera from patients with progressive DKD showed reduced ABCA1 expression compared to non progressive DKD. TNFα treatment increased apoptosis and cholesterol content, reduced ABCA1 mediated cholesterol efflux, increased lipid accumulation in podocytes treated with TNFα. ABCA1 lipids increased after treatment with TNFα. Treatment of ABCA1 knockdown cells with SOAT1 inhibitors caused apoptosis that was prevented by CD. TNFα treated mice showed albuminuria and kidney cholesterol accumulation, the former was prevented by CD.

**Conclusions:** Podocytes treated with FSGS or DKD sera showed increased TNFα expression compared to controls. TNFα expression correlates with reduced ABCA1 expression in patients with FSGS and reduced ABCA1 expression correlates with DKD progression. TNFα attenuates ABCA1-mediated efflux and reduces cholesterol esterification leading to free cholesterol mediated apoptosis. Our data suggest that targeting the TNFα-ABCA1 cholesterol axis may represent a new strategy to treat DKD or FSGS.

_Funding: NIDDK Support, Pharmaceutical Company Support - Hoffman La Roche_
SA-OR055
Novel Score to Predict Post-Transplant Outcomes  Miklos Zsolt Molnar,1 Danh V. Nguyen,2 Vanessa A. Ravel,2 Eliani Streja,2 Mahesh Krishnan,2 Yanjun Chen,2 Csaba P. Kovacsly,1 Kamyr Kalantar-Zadeh,2 1Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of California, Irvine, CA; 2DaVita Healthcare Partners, VA.

Background: Several previous studies have developed scoring tools to predict the allograft and patients’ survival in kidney transplant patients using information, which was not available at the time of transplantation. We developed a score to predict post-transplant outcomes using pre-transplant information including routine laboratory data available at the time of transplantation.

Methods: Linking the 5-year patient data of a large dialysis organization to the SRTR, we identified 15,125 hemodialysis patients who underwent first kidney transplantation. Prediction models were developed using Cox models for (a) mortality, (b) transplant failure (death censored) and (c) combined death or transplant failure. The cohort was divided into a two-thirds development set and a one-third validation set. We used backward-selection based on Akaike’s information criterion to avoid arbitrary and ineffective selection rules based on p-values. We used the bootstrap method to assess model overfitting and calibration using the development dataset. Model predictive discrimination was assessed using the index of concordance, or C statistic, which accounts for censoring in time-to-event (a-c).

Results: Patients were 50.1±13 years old and included 39% women, 15% African-American and 36% diabetics. For prediction of post-transplant mortality and graft loss 10-10 predictors were used (recipients’ age, cause and length of ESRD, hgb, albumin, comorbidities, race and type of insurance as well as donor characteristics such as donor age, diabetes, number of HLA mismatches). The new model showed the overall best C-statistics comparing to the currently used EPTS score.

<table>
<thead>
<tr>
<th>Current model</th>
<th>Model based on EPTS predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discrimination C (95%CI)</td>
<td>Discrimination C (95%CI)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.63 (0.62-0.65)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.70 (0.63-0.71)</td>
</tr>
<tr>
<td>Allograft failure</td>
<td>0.63 (0.62-0.65)</td>
</tr>
</tbody>
</table>

Conclusions: The new prediction tool, using exclusively data available prior to the time of transplantation, performs better to predict outcomes than currently used tool such as EPTS.

Funding: Other NIH Support - R21AG047306 and R01DK595668

SA-OR056
Long-Term Deceased Donor Kidney Graft Survival Has Improved in the Last Decade  Douglas Scott Keith, Gayle M. Vranic, Angie G. Nishio-Lucar. Medicine, UVA, Charlottesville, VA.

Background: Long-term graft survival did not improve significantly in the 1990s. We sought to determine if long-term graft survival is improving in the last decade.

Methods: All adults deceased donor renal transplant recipients in the SRTR database between 2000 and 2010 were included in the study. K-M survival analysis was carried out based on year of transplantation in all recipients who had at least 6 months of graft survival. Graft survival, death censored graft survival and death with graft function were analyzed. Cox modeling was carried out to determine if the year of transplant affected the outcomes.

Results: 92,616 deceased donor kidney transplants survived at least six months. The rate of graft failure has improved over the last decade.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-OR058

Identifying the Two Specific Types of Antibody-Mediated Rejection and Their Outcomes in Kidney Recipients

Olivier Aubert, 1 Alexandre Lopuy, 1 Luis G. Hidalgo, 2 Jeff Reeve, 3 Denis Glotz, 2 Christophe M. Legendre, 1 Carmen Lefaucheur, 1 Philip F. Halloran, 1 INSERM, 1 ATACG.

Background: Antibody-mediated rejection (ABMR) can be related to preformed/recurrent anti-HLA DFA or de novo anti-HLA ASA.

Methods: We included 965 kidney biopsies taken from two North American and five European centers and assessed patients with ABMR. We compared patients with preformed/recurrent DFA (Type-1 ABMR) to patients with de novo DFA (Type-2 ABMR). Microarray-based gene expression was assessed in biopsies. Patients with type-1 were managed in two centers with aggressive standardized treatment protocols; type-2 ABMR was managed as standard-of-care.

Results: We identified 278 patients with ABMR: 153 (55%) type-1 and 125 (45%) type-2. The mean time from transplantation to rejection was 10.1±8.8 vs 8.4±7.1 years for the type-1 and 2 ABMR. The mean eGFR at the time of biopsy was lower in type-1 ABMR (38±18) vs type-2 (46±20 mL/min/1.73m2) (p=0.0012). Kidney biopsies with type-1 ABMR presented with higher microcirculation injury (g−ptc score: 3.3±1.4 vs 2.4±1.5) and less transplant glomerulopathy score (0.5±0.9 vs 1.6±1.1) (p<0.0001). C4d PTC deposition was similar (32% vs 34%). Using the gene expression assessment, type-1 ABMR exhibited a higher expression of global disturbance transcripts, injury-repair response associated transcripts (IRRATS), endothelial cell associated transcripts (ENDAT), injury-induced transcripts (IRIT) (p<0.0001) but a lower expression of NK cell transcript burden (NK-B) (p=0.0147). Type-1 and Type-2 ABMR exhibited similar high expression of transcripts reflecting γ-IFN response (GRIT1), T cell transcript burden (TCB) and macrophage-associated transcripts (QCMAT). Kidney allograft survival at 4 and 8 years after rejection was superior in type-1 ABMR (72% and 58%) compared to type-2 (51% and 35%) (p<0.0001).

Conclusions: Type-1 and type-2 ABMR present with distinct phenotypes and outcomes. The fact that type-1 ABMR is treated with aggressive defined protocols and has superior outcomes despite lower GFRs and more molecular injury at the time of biopsy suggests that trials of structured aggressive therapy protocols in type 2 ABMR deserve study.

SA-OR060

Longitudinal Assessment of Cardiac Morphology and Function following Kidney Transplantation

Clark David Kensingter, 1 Antonio Hernandez, 2 Meagan Fairchild, 4 Guanhua Chen, 3 Loren Lipworth, 4 Talat Alp Ikizler, 4 Kelly A. Birdwell, 4 Dept of Surgery, Vanderbilt Univ Medical Center; 1 Dept of Anesthesiology, Vanderbilt Univ Medical Center; 2 Dept of Biostatistics, Vanderbilt Univ Medical Center; 4 Dept of Medicine, Vanderbilt Univ Medical Center.

Background: Despite improvement in traditional cardiovascular (CV) risk factors following renal transplantation, the death rate from CV disease remains high. Our aim was to evaluate the longitudinal change of cardiac morphology and function in a cohort of patients following renal transplantation, as well as to evaluate the association between Fibroblast Growth Factor 23 (FGF-23) concentrations and the evolution of cardiac morphology following transplant.

Methods: We performed a longitudinal prospective cohort study of 145 kidney transplant recipients, measuring left ventricular mass index (LVMi), left atrial volume index (LAVi) and ejection fraction (EF) by echocardiography at months 1 (baseline), 12, and 24 post-transplant. FGF-23 levels were measured at months 1 and 24 post-transplant. A linear mixed effects model was used to assess each outcome adjusting for age, race, gender, time on dialysis, CV disease, mean arterial pressure, glomerular filtration rate, diabetes, and body mass index.

Results: The cohort (mean age 49±13 years) was 74% male and 75% white. LVMi (P=0.001), LAVi (P<0.001), and EF (P=0.009) decreased significantly over time following transplant. Results from the multivariate models can be reviewed in Table 1. A one-unit decrease in FGF-23 was significantly associated with a 5.83 grams/meter2 decrease in LVMi (P=0.04).

Conclusions: LVMi, LAVi and EF improved significantly over 12 and 24 months post-transplant. There was also a significant association between FGF-23 and LVMi following transplant.

Table 1: Adjusted change in echocardiogram morphology and function following renal transplantation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>12 month effect</th>
<th>95% CI</th>
<th>P Value</th>
<th>24 month effect</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMi</td>
<td>-0.95</td>
<td>-16.34, -5.56</td>
<td>&lt;0.001</td>
<td>-14.77</td>
<td>-22.02, -7.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAVi</td>
<td>-3.11</td>
<td>-5.13, -1.49</td>
<td>&lt;0.001</td>
<td>-4.95</td>
<td>-7.38, -2.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>1.5</td>
<td>0.99, 2.91</td>
<td>0.04</td>
<td>2.75</td>
<td>0.87, 4.65</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Funding: NIDDK Support, Other NIH Support - UL1TR000445 from the National Center for Advancing Translational Sciences, K24 DK62849 (Ikizler) and P30 DK079341 from the National Institute of Diabetes, Digestive and Kidney Diseases; R01 HL070938 (Ikizler)

SA-OR061

Tolerance Induction versus Conventional Immunosuppression in HLA-Matched Kidney Transplantation: Comparison at Two Years Post-Transplant


Background: Over 10 years we have studied the safety and efficacy of tolerance induction using hematopoietic cell transplantation in combination with kidney transplantation.

Methods: Twenty-two patients underwent HLA-matched living donor kidney transplantation followed by a conditioning regimen of 10 fractions of total lymphoid irradiation (12 Gy total) and 5 doses of ATG. Infusion of purified donor CD4+ hematopoietic progenitor cells and T cells was on day 11 post-kidney transplant. Fifty-three patients contemporaneously underwent HLA-matched living donor kidney transplantation under conventional immunosuppression.

Results: Seventeen patients developed mixed chimerism of 6 months duration or longer and have now been off immunosuppression from 1 to 7 years. Their outcomes at two years post-transplant are compared to those of the 52 (one graft was lost to thrombosis on day 1) conventionally treated patients.

Funding: Pharmaceutical Company Support - The generation of the cohort was made possible by a grant from the Dutch Top Institute Food and Nutrition. M.H.J.B. and C.A.K. are supported by a consortium grant from the Dutch Kidney Foundation (NIGRAM consortium, grant no. CP10.11). This study was funded by a grant from De Cock-Hadders Foundation (grant no. 2015-44).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conventionally Treated, 2006-13 & Tolerance Induction, 2005-13

<table>
<thead>
<tr>
<th>Number</th>
<th>52</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplant (years)</td>
<td>38 +/- 11.2</td>
<td>40 +/- 10.5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>26/26</td>
<td>9/8</td>
</tr>
</tbody>
</table>

**ELEVATE Study** completed on study drug in EVR and CNI groups, respectively. The least squares (LS) rate (eGFR; MDRD-4) from RND to M12. 5–10 ng/mL, cyclosporine: 100–250 ng/mL); all received enteric-coated mycophenolate the ELEVATE Study; 2Novartis, Basel, Switzerland; 3Novartis Corporation, East Hanover, NJ, USA.

**Better Renal Function Preservation with Early Conversion to Everolimus** in De Novo Renal Transplant Recipients: 24-Month Results from the ELEVATE Study, Johan W. De Fijter, Hallvard Holdaas, Patricia M. Lopez, Cesar Escrig, Zailong Wang, Josep M. Cruzado, Markus van der Giet. 1 For the ELEVATE Study; 2Novartis, Basel, Switzerland; 3Novartis Corporation, East Hanover, NJ, USA.

**Background:** Long-term exposure to calcineurin inhibitors (CNIs) is one of the key factors contributing to progressive deterioration of renal function and graft loss. We present the 24 month (M) renal outcomes from the ELEVATE study which determined whether early CNI to everolimus (EVR) conversion in renal transplant recipients (RTxRs) provides better preserved renal function compared to continuation of standard CNIs.

**Methods:** ELEVATE (NCT01114529) was a 24M, multicenter, open-label study, in which de novo RTxRs were randomized (RND) at 10–14 weeks post-transplant to convert from CNI to EVR (n=360; C0 6–10 ng/mL) or continue standard CNI (n=357; tacrolimus: 5–10 ng/mL, cyclosporine: 100–250 mg/mL), all received enteric-coated mycophenolate sodium + steroids. 3 mo post Tx 499 pts were randomized: 1:1 to either a) continue standard (STD) CNI (100-180ng/ml) with EC-MPS (n=166), b) convert to a CNI-free regimen with everolimus (EVR, 5-10ng/ml) + EC-MPS (n=171) or c) convert to CNI-reduced regimen CNI (50-75ng/ml) with EVR(3-8ng/ml) (n=162).

**Results:** GFR (Nankivell, ITT) was similar at randomization 3 mo post Tx and had significantly improved at mo 12 by +5.6mL/min (95%CI:[+2.9;+8.3]; p<0.001) and remained significantly improved by +6.8mL/min in favor of CNI-free as well as reduced CNI in combination with EVR compared to STD in this randomized treatment group. However, CNI-free regimen was associated with better GFR maintained for 4 years post Tx. The results of this large trial confirm previous reports of improved GFR after CsA withdrawal with EVR in combination with EC-MPS.

**Conclusions:** Transplantation under this protocol is safe, achieves tolerance eliminating risk of acute rejection, and offers a better metabolic profile and better graft survival with time. **Funding:** Other NIH Support - NHLBI, Private Foundation Support

**SA-OR064**

Belatacept pts Had Superior Graft Survival versus CsA pts: Final Results from BENEFIT, Flavio Vincenti, 1  Jean Grinyo, 2  R. Bray, 1  L. Rostaing, 4  B. Bresnahan, 3  K. Rice, 4  S.M. Steinberg, 2  H. Gebel, 4  M. Polinsky, 4  U. Meier-Kriesche, 4  S. Munier, 2  R. Townsend, 3  C.P. Larsen, 1  Univ of California, San Francisco; 1  Univ Hospital Bellvitge, Barcelona, Spain; 2  Emory Univ, Atlanta; 3  Univ Hospital and INSERM U563, IFR-BMT, Toulouse, France; 4  Medical College of Wisconsin, Milwaukee; 2  Baylor Univ Medical Center, Dallas; 1  Sharp Memorial Hospital, San Diego; 2  BMS, Lawrenceville.

**Background:** At 3 and 5 yrs post-transplant in BENEFIT, renal function was improved in kidney transplant recipients administered belatacept (bela) vs CsA. We report final 7-yr results.

**Methods:**Pts were randomized to more (MI) or less intensive (LI) bela or CsA regimens. Outcomes were assessed for all randomized, transplanted pts at yr 7. In a prospective analysis, time to death or death-censored graft loss was compared using Cox proportional hazards. The presence of DSAs was established centrally (FlowPRA). Kaplan–Meier estimates for the cumulative rate of de novo (DN) DSAs were derived. Mean calculated GFR (cGFR) was estimated from mos 1–84 using a repeated measures model with an unstructured covariance matrix. Differences in cGFR at each timepoint were also estimated.

**Results:**In total, 153/219 of bela MI, 163/226 of bela LI and 131/221 of CsA pts were evaluable. HRs comparing time to death/graft loss were 0.573 for bela MI vs CsA (P<0.02) and 0.70 for bela LI vs CsA (P=0.02) — a 43% risk reduction in death/graft loss for bela MI or LI vs CsA. Cumulative event rates of DN DSAs at yr 7 for bela MI, bela LI, and CsA were 1.86, 4.64, and 17.81, respectively. Serious AE rate was similar (71%, bela MI; 69%, bela LI; 76%, CsA). Mean cGFR increased slightly over 7 yrs for both bela regimens but declined for CsA. Differences in mean cGFR at yr 7 were 25.6 mL/min/1.73 m² for bela MI vs CsA and 27.3 mL/min/1.73 m² for bela LI vs CsA differences favored bela regimen vs CsA at all time points (P<0.001).

**Conclusions:** In this 7-yr analysis, bela conferred statistically better graft survival and renal function vs CsA, with a reduced incidence of DN DSAs. The bela safety profile was consistent with previous reports.

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

**Underline represents presenting author.**

**SA-OR063**

Month 48 Follow-Up Results of the HERAKLES Study: Superior Renal Function After Early Conversion to an Everolimus-Based Calcineurin Inhibitor Free Regimen, Kiemens Biddle, Oliver Witzke, Thomas Rath, Peter Wiener, Johannes Jacobs, Beatrice Aebi, Wolfgang A. Arms, Claudia Sommerer,1 HERAKLES Study Group, Germany; HERAKLES Study Group, Switzerland; Novartis Pharma, Germany.

**Background:** To follow up on renal function (GFR) at month (mo) 48 after kidney transplantation (Tx) in patients (pts) on immunosuppressive regimen with different calcineurin inhibitor (CNI) exposures.

**Methods:**802 pts were included in this prospective, open-label, randomized multi-center study. After induction with basiliximab all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 mo post Tx 499 pts were randomized: 1:1 to either a) continue standard (STD) CsA (100-180ng/ml) with EC-MPS (n=166), b) convert to a CNI-free regimen with everolimus (EVR, 5-10ng/ml) + EC-MPS (n=171) or c) convert to CNI-reduced regimen CsA (50-75ng/ml) with EVR(3-8ng/ml) (n=162).

**Results:** GFR (Nankivell, ITT) was similar at randomization 3 mo post Tx and had significantly improved at mo 12 by +5.6mL/min (95%CI:[+2.9;+8.3]; p<0.001) and remained significantly improved by +6.8mL/min in favor of CNI-free as well as reduced CNI in combination with EVR compared to STD in this randomized treatment group. However, CNI-free regimen was associated with better GFR maintained for 4 years post Tx. The results of this large trial confirm previous reports of improved GFR after CsA withdrawal with EVR in combination with EC-MPS.

**Funding:** Pharmaceutical Company Support - Novartis Pharma
Nephrin Specific Deletion of the Prorein Receptor Modulates Blood Pressure and Urinary Na Excretion

Method: Since previous models of PRR knockout (KO) mice had early lethality and/or structural defects, we developed an inducible nephrin-wide PRR KO using the Pax8/Lc1c transgenes.

Results: Disruption of PRR at 1 month of age caused no renal histological abnormalities. On a normal Na diet, wild-type (WT) and PRR KO mice had similar BP and Na excretion. However, PRR KO mice had elevated PRC (KO-377±77 vs WT-127±19 ng Ang-I/ml/hr) and a 50% decrease in renal ENaCα protein. Protein levels of NHE3, NKCC2, NCC and ENaCβγ were similar between the two groups. Treatment with mouse nephrin (10 nM for 30 min) increased ENaCα channel number by 2-fold, but not open probability, in isolated split-open cortical collecting ducts (CCD) from WT mice; this was prevented by PRR inhibition (PR020) and Akt inhibition (A6730) but unaffected by blockade of AT-1 (losartan), ERK 1/2 (U0126) or p38 MAPK (SB203580). Addition of nephrin (10 nM) did not change isolated CCD (Ca2+), as assessed by Fura-2 loading (10 min exposure).

On a low Na diet, PRR KO mice had increased Na excretion (Day 2: KO-66±11 vs WT-42±6 mmol/day; Day 6: KO-39±4 vs ET-23±4 mmol/day) however, no differences in BP were observed. PRC remained elevated in PRR KO mice on a low Na diet. PRR KO mice had an attenuated hypertensive response to Angiotensin-II (Ang-II) infusion at 600 ng/kg/min for 2 weeks (MAP: KO-117±4 vs WT-133±4 mm Hg over 2 weeks). Urinary Na excretion was elevated in Ang-II treated PRR KO mice as compared to WT mice (KO-344±14 vs WT-268±30 mmol/day).

Conclusions: Taken together, these data indicate that nephrin, likely via direct prorein/renin stimulation of an Akt-dependent pathway, stimulates CCD ENaC activity. Absence of nephrin promotes Na wasting and reduces the hypertensive response to Ang-II.

Funding: This work was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (DK07656).

SA-OR066

Functional Testing of Human Epithelial Na+ Channel Missense Variants Identified in the GenSalt Study

Methods: Functional testing of human ENaC variants was performed in Xenopus laevis oocytes using co-expression with β1 and γ subunits. A total of 136 missense ENaC variants were identified in GenSalt participants with salt-sensitivity hypertension. Using the Xenopus oocyte expression system, we assessed the functional properties of these variants.

Results: Of the 136 missense ENaC variants, 11 were found to conferred a significant increase in channel activity compared to wild type. However, when expressed in an adrenal gland and in Xenopus oocyte models, these variants had a range of effects on channel activity. Some variants had a modest increase in channel activity, while others had a more dramatic effect. The results of these studies will help to better understand the role of ENaC variants in the development of hypertension.

Conclusions: These findings provide important insights into the functional consequences of ENaC variants and their potential role in the pathogenesis of hypertension.

Funding: This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (DK07656).
Methods: To determine the role of renal ADM on blood pressure in C57BL/6J mice (3 months old), males were fed a high NaCl diet while NIDDK and hypertension-induced high-salt consumption infused Adm mice (3 mg/day), via osmotic minipump, into the remnant kidney one week after unilateral nephrectomy. Mock Adm mice (3 mg/day) was used as control. The mice were placed in metabolic cages for 24 hr urine collection before blood pressure was measured via radiotelemetry. Renal function was assessed in metabolic cages. Blood pressure was measured via radiotelemetry. Vascular function was assessed by vascular relaxation assay.

Results: Body weight, water/food intake, and serum Na⁺, K⁺, Ca were similar in the two groups. Systolic blood pressure was measured in Adm mice (129.3±15.1 mm Hg) and NaCl diet, while NIDDK and hypertension-induced high-salt consumption mice (192.2±21.0) did not differ at baseline. In polarized human PCT cells, human ADM (1 hr, 5 mg/mL) inhibited apical sodium transport at 10 nm (84.6±5.4%) of vehicle and 100 nm (81.5%), similar to angiotensin II (100 nM).

Conclusions: Our data suggest that a renal-selective silencing of ADM gene increases blood pressure and impairs sodium excretion that is related, in part, to an increase in NHE3 abundance and functions in the RPT.

Funding: NIDDK Support

SA-OR070

Vascular AT1 Angiotensin Receptors Regulate Sodium Transporter Abundance in Kidney Epithelium

Matthew G. Sparks, Susan B. Gurley, Alicia A. McDonough, Thomas M. Coffman.

Background: Vascular constriction is a physiological action of angiotensin II (AngII) in the renal microvascular bed (AT1). Methods: In order to define the contribution of AT1R to vascular smooth muscle cells (VSMCs) to BP control, we generated mice with cell-specific deletion of AT1AR from VSMCs (SMKOs) using Cre-loxP technology. Results: Baseline BP was reduced by ~7 mmHg and responses to AngII-induced hypertension were blunted by SMKO mice compared to controls (16 ± 30 mm Hg; BP from baseline after 4 wks AngII, P = 0.02). Baseline renal flow (RBF) was higher, and renal vasoconstriction to AngII was impaired in SMKO mice. Moreover, SMKO mice displayed Na⁺ sensitivity and exaggerated natriuresis during chronic AngII. To investigate the mechanism of the lower baseline BP and the enhanced natriuresis during AngII infusion in SMKO mice by stimulating distal colonic oxalate secretion.

Of interest, we observed the WT and mutant luciferase constructs in the presence of ANS1 and a further increase in expression. Finally, gel electrophoretic mobility shift assays confirmed preferential binding of ANS1 to the mutant sequence.

Conclusions: Some children with hypercalciuria and kidney stones have a unique mutation in CLDN14 that introduces a novel INSM1 binding site.

Funding: Government Support - Non-U.S.

SA-OR073

Oxalobacter-Derived Bioactive Factors Reduce Urinary Oxalate Excretion in a Mouse Model of Primary Hyperoxaluria

Hatim A. Hassan, 1 Donna L. Arvans, 1 Yong-chul Jung, 1 Dionysios A. Antonopoulos, 1,2 John R. Asplin, 1 Ignacio Granja, 1 Jason C. Koval, 1 Mark W. Musch, 1 Eugene B. Chang, 1

1Univ of Chicago; 2Litholink Corporation; 3Argonne National Laboratory.

Background: Hyperoxaluria is a major risk factor for calcium oxalate kidney stones (COKS) and has no therapy. The probiotic bacterium Oxalobacter formigenes (OF) plays a critical role in maintaining the gut flora that metabolizes host dietary oxalate, leading to reduced intestinal absorption and urinary excretion. OF also interacts with colonic epithelium by inducing colonic oxalate secretion, leading to reduced urinary excretion, via an unknown secretagogue. Sustaining OF colonization in animals and humans in the absence of high oxalate diets remains problematic, underscoring the need for identifying OF-derived factors exerting effects similar to live OF.

Methods: We previously found that small molecular weight protein(s) and/or peptide(s) in OF-conditioned medium (CM) significantly stimulate oxalate transport (2-2-fold) by human intestinal Caco2-BBE cells. To evaluate the CM in vivo effects, CM or OM (control medium) was given rectally as enemas (100 µl twice daily ± 24 days) to PH1 mice (a mouse model of primary hyperoxaluria type 1).

Results: The CM significantly reduced urinary oxalate excretion by 32.5% while OM had no effect (µM/mg creatinine: OM = 51.50±3.32; CM = 32.04; CM = 47.27±3.43; 31.91±4.81; before and after treatment, respectively). To test our hypothesis that the observed reduction in urinary oxalate is due to CM-induced enhanced colonic oxalate secretion, colonic tissues were isolated and mounted in Ussing chambers. While a small short-circuit secretion flux (1.54) is observed in distal colonic tissues from OM-treated mice, a ~10-fold higher net oxalate secretion flux (16.34) is seen in distal colonic tissues from CM-treated mice (µmol/cm²/h: OM = 39.95±5.29; CM = 40.43±5.49; 31.91±4.81; before and after treatment, respectively).

Conclusions: We conclude that OF-derived bioactive factor(s) retain(s) its/their biological activity in vivo and significantly reduce(s) urinary oxalate excretion in PH1 mice by stimulating distal colonic oxalate secretion.

Funding: NIDDK Support; Other Support - Digestive Disease Research Center of the University of Chicago(NIH P30 DK42086); Private Foundation Support.
Hydroxyalyluria Requires TNF Receptors to Initiate Crystal Adhesion and Kidney Stone Disease

Background: Nephro- or urolithiasis involves intratubular mineral hypersecretation as well as lack of crystalization inhibitors to form crystal plugs obstructing renal tubules. Recently, NLRP3 inflammasome-related renal inflammation was added as a pathomechanism of acute oxalosis (Mulay et al, JCI 2013) as well as nephro-urolithiasis (Knauf et al, KI 2013). As TNF receptor (TNF-R) signaling is a major mediator of inflammation in several chronic kidney diseases (CKD), we speculated that TNF-Rs would also drive the progression of nephro lithiasis-related CKD.

Methods: In an independent experiment we did not see any direct binding of CaOx crystals to the tubular epithelial cells and CaOx crystals by atomic force microscopy. We observed that lack of calcium concentrations to WT mice. Further, we measured the adhesion forces between well as kidney immunostainings for CaOx, despite comparable hyperoxaluria and urinary CaOx nephrolithiasis and progressive CKD in WT mice. Surprisingly, KO mice showed type (WT) mice or mice deficient for Tnfr1, Tnfr2 or Tnfr1/2. Oxalate feeding induced consistent in mice kidneys. To test our hypothesis we fed an oxalate-rich diet to wild-Corporation, Chicago, IL; 4Dept of Internal Medicine, Yale Univ School of medicine.

Results: We observed that kidney immunostainings of hydroxyalyluria and mice with hydroxyalyluria-related CKD displayed strong tubular positivity for TNF-α, TNF-R1 and TNF-R2, which was absent in healthy kidneys. WB and mRNA expression analyses were consistent in mice kidneys. To test our hypothesis we fed an oxalate-rich diet to wild type (WT) mice or mice deficient for Tnfr1, Tnfr2 or Tnfr1/2. Oxalate feeding induced spontaneous CaOx nephrolithiasis and progressive CKD in WT mice. Surprisingly, KO mice showed absolutely no intratubal CaOx crystal deposits, as revealed by computed tomography as well as kidney immunostainings for CaOx, despite comparable hyperoxaluria and urinary calcium concentrations to WT mice. Further, we measured the adhesion forces between tubular epithelial cells and CaOx crystals by atomic force microscopy. We observed that lack of TLR4/1/2 impairs CaOx crystal adhesion to the tubular epithelial cell surface. However, in an independent experiment we did not see any direct binding of CaOx crystals to the soluble TNF-R1-IgG fusion protein. Instead, we observed that TNF-R signaling is indeed required for inducing the expression of known crystal adhesion molecules viz. osteopontin, CD44, annexin II on tubular epithelial cells in vitro and in vivo. Conclusions: We conclude that TNF-Rs are essential mediators of CaOx crystal adhesion at the luminal membrane of renal tubules as a fundamental mechanism of oxalate nephropathy.

SA-OR075
Critical Role of Toll-Like Receptor 4 in Crystal-Induced Inflammation and Renal Failure
Venkata Surya Narayana Murthy Durupadi,1, 2 Christoph Daniel,3 John All in vitro experiments were approved by the local government authorities. Immunohistochemistry, WB, RT-PCR and atomic force microscopy (AFM) were used for data analysis.

Results: We observed that kidney immunostainings of hydroxyalyluria and mice with hydroxyalyluria-related CKD displayed strong tubular positivity for TNF-α, TNF-R1 and TNF-R2, which was absent in healthy kidneys. WB and mRNA expression analyses were consistent in mice kidneys. To test our hypothesis we fed an oxalate-rich diet to wild type (WT) mice or mice deficient for Tnfr1, Tnfr2 or Tnfr1/2. Oxalate feeding induced spontaneous CaOx nephrolithiasis and progressive CKD in WT mice. Surprisingly, KO mice showed absolutely no intratubal CaOx crystal deposits, as revealed by computed tomography as well as kidney immunostainings for CaOx, despite comparable hyperoxaluria and urinary calcium concentrations to WT mice. Further, we measured the adhesion forces between tubular epithelial cells and CaOx crystals by atomic force microscopy. We observed that lack of TLR4/1/2 impairs CaOx crystal adhesion to the tubular epithelial cell surface. However, in an independent experiment we did not see any direct binding of CaOx crystals to the soluble TNF-R1-IgG fusion protein. Instead, we observed that TNF-R signaling is indeed required for inducing the expression of known crystal adhesion molecules viz. osteopontin, CD44, annexin II on tubular epithelial cells in vitro and in vivo. Conclusions: We conclude that TNF-Rs are essential mediators of CaOx crystal adhesion at the luminal membrane of renal tubules as a fundamental mechanism of oxalate nephropathy.

SA-OR076
ALLN-177 Oral Enzyme Therapy Reduces Urinary Oxalate in Patients with Secondary Hyperoxaluria (2° HO) and Recurrent Kidney Stones: Results of a Phase 2 Study
Gyan Desai, Julian A. Marschner, Santhosh Kumar Vr, Hans J. Anders. Ludwig Maximilian Un University, Germany.

Background: Oxalate excretion from diet and endogenous sources (adipose tissue and gut bacteria) can drive oxalate nephropathy. In this Phase 2 study, ALLN-177 significantly reduced urinary oxalate excretion and supersaturation index.

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

SA-OR077
Diet-Dependent Net Acid Load, Protein Intake, and Risk of Incident Kidney Stones
Pietro Manuel Ferraro,1, 2 Ernest I. Mandel,2 Gary C. Curhan,3 Giovannini Gambiro,3 Eric N. Taylor.4 Div of Nephrology, Catholic Univ of the Sacred Heart, Rome, Italy; 4Channing Div of Network Medicine, Harvard Medical School, Boston.

Background: Higher dietary acid load and protein intake may increase risk of kidney stones (KS). However, associations between net acid load and stone risk have not been explored in population-based studies, and it is not known whether stone risk varies according to protein type.

Methods: We prospectively examined the association between estimated net endogenous acid production (NEAP), protein intake (vegetable [VP], dairy [DP] and animal non-dairy [AP]) and risk of incident KS in three large ongoing cohorts, the Health Professionals Follow-up Study (n=82,919 men), Nurses’ Health Study 1 (n=60,128 older women), and Nurses’ Health Study II (n=90,629 younger women). We used Cox hazards regression models to generate hazard ratios (HRs) adjusted for age, BMI, dietary, lifestyle, and medical factors. We also analyzed multivariable associations between NEAP and 24-h urine composition in >6,000 study participants.

Results: During 3,133,014 person-years of follow-up, there were 6,347 incident KS. There was a significant association between NEAP and KS risk in all cohorts (pooled HR for highest vs lowest quintile 1.41, 95% CI 1.16, 1.72; p-value for trend < 0.001). There was no association between VP intake and risk of KS. There was a significant association between AP intake and risk of KS in HPFS (HR 1.14, 95% CI 1.07, 1.35; p-value for trend =0.04) and NHS I (HR 1.23, 95% CI 1.01, 1.49; p-value trend = 0.05) but not in NHS II. There was no association between DP and risk except in NHS II, where the HR was 0.83, 95% CI 0.72, 0.95; p-value trend =0.003. After multivariable adjustment, participants in the highest compared with lowest quintile of NEAP had 85 mg/d less urine citrate, 0.18 lower urine pH, 177 mL/d less urine volume, and higher urine supersaturations with respect to calcium oxalate and uric acid (all p-values ≤ 0.001).

Conclusions: In 3 large cohorts, higher NEAP is associated with higher risk of KS, as well as lower urine citrate and pH. In contrast with AP, VP and DP are not associated with the risk of KS.

Funding: Other NIH Support - NIH grants DK094910, DK94117, CA161071, CA176726 and CA167552

SA-OR078
Urologic Interventions for Urolithiasis and Risk of Incident Hypertension and Chronic Kidney Disease: A Population-Based Cohort Study
Michelle Denburg,1, 2 Thomas Jemielita,3 Gregory Edward Tasiian,3, 4 Kevin Haynes,5 Phillip Mucksavage,5 Justine Shults,6 Lawrence A. Copelovitch,7 The Children’s Hospital of Philadelphia; 5Perelman School of Medicine, University of Pennsylvania.

Background: We sought to determine if among individuals with urolithiasis, extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) are associated with a higher risk of incident hypertensive (HTN) and/or chronic kidney disease (CKD). Methods: A population-based retrospective cohort study using The Health Improvement Network comprised 11,570 participants (pts) with incident urolithiasis and a history of recurrent calcium oxalate KS.

Results: In 3 large cohorts, higher NEAP is associated with higher risk of KS, as well as lower urine citrate and pH. In contrast with AP, VP and DP are not associated with the risk of KS.

Funding: Other NIH Support - NIH grants DK094910, DK94117, CA161071, CA176726 and CA167552
SA-OR079

Anti-MicroRNA-21 Oligonucleotides Prevent Renal Fibrosis Progression by Blocking the Auto-Regulatory Loop of miR-21/PDCD4/AP-1 During Myofibroblasts Activation. Qi Sun, Jiewei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Renal fibrosis is a final common pathway of chronic kidney injury. During the injury, the resident fibroblasts are stimulated and trans-differentiated into myofibroblasts, which produce a large amount of extracellular matrix (ECM) components and ultimately lead to the loss of kidney function. Sustained activation of myofibroblasts is considered to play a key role in perpetuating renal fibrosis, but the driving force of myofibroblasts activation is only partially understood. Aberrant expression of miRNAs is associated with numerous pathologic processes including renal injury. To date, some investigations have identified specific overexpression of miR-21 in the progression of kidney fibrosis. Nevertheless, the precise role of miR-21 in myofibroblasts activation remains largely unknown.

Methods: To understand the role of miR-21 in the progression of kidney fibrosis, mouse, microarray and quantitative real-time PCR analysis were performed to examine the expression level of miR-21 in unilateral ureteral obstruction (UUO)-injured mice. Then, mice were administered with control or anti-miR-21 before or during surgery by tail vein injection, to determine whether blocking miR-21 in kidneys affects UUO-induced renal fibrosis.

Results: In this study, we identified miR-21 was instantly up-regulated after TGF-b1 stimulation, and maintained itself at constant high levels by employing a microRNA-21/proliferated cell death protein 4 (PDCD4)/AP-1 auto-regulatory loop during myofibroblasts activation. The persistent up-regulated miR-21 depressed Smad7 and PTEN expression and eventually enhanced TGF-b1/Smad pathway signaling in myofibroblasts activation. The persistent up-regulated miR-21 in the progression of kidney fibrosis. Nevertheless, the precise role of miR-21 in myofibroblasts activation remains largely unknown.

Conclusions: Altogether, these data suggest that miR-21 is a main driving force of myofibroblasts activation and keeps its high expression level by an auto-regulatory loop of miR-21/PDCD4/AP-1. Targeting this aberrantly activated feedback loop may provide a new therapeutic strategy in treating fibrotic kidneys.

Funding: Government Support - Non-U.S.

SA-OR080

Silencing of MicroRNA-132 Reduces Renal Fibrosis by Selectively Inhibiting Myofibroblast Proliferation. Reel Bierek,1,2 Ruben de Bruin,1 Coen van Solingen,1 Janine van Gils,1 Jacques Duijs,1 Eric P. van der Veer,1 Ton J. Rabelink,1 Benjamin D. Humphreys,2 Anton Jan Van Zonneveld.1 1 Dept of Nephrology and Eindhoven Laboratory for Vascular Experimental Medicine, Leiden Univ Medical Center, Leiden, Netherlands; 2 Renal Div, Brigham & Women’s Hospital and Harvard Medical School, Boston.

Background: Chronic kidney disease is associated with progressive renal fibrosis. Lineage analysis has shown that FoxD1-derived perivascular cells give rise to the majority of α-SMA positive myofibroblasts during renal fibrosis. We sought to identify pericytic microRNAs that could serve as a target to decrease myofibroblast formation.

Methods: To that end, we induced kidney fibrosis in FoxD1-GC/Z-R Red-mice by unilateral ureteral obstruction (UUO) followed by FACS sorting of CD10 Red-positive FoxD1-derived cells and profiled for differentially expressed miRNAs.

Results: MiR-132 expression selectively increased 21-fold during pericyte-to-myofibroblast formation whereas miR-132 was only 2.5-fold upregulated in total kidney lysates (both in UUO and ischemia-reperfusion injury). Antagomir-induced miR-132 silencing in the UUO model resulted in 35% decreased collagen deposition and decreased tubular apoptosis. Immunohistochemistry, Western blot and qRT-PCR analyses confirmed a similar decrease in o-SMA positive cells. Pathway analysis of differential gene expression in myofibroblasts identified a rate-limiting role for miR-132 in myofibroblast proliferation that was confirmed in in vitro studies with cultured fibroblasts. Indeed, UUO kidneys of antagonist-miR132 treated mice displayed a significant reduction in proliferating, ki67+ myofibroblasts. Interestingly, this reduction in proliferation was selective for the interstitial cells and did not impair the reparative proliferation of tubular epithelial cells, as evidenced by increased numbers of ki67+ epithelial cells, as well as increased p-RRB1 and Cyclin-A and decreased RASA1 and p21 levels in total kidney lysates.

Conclusions: Taken together, silencing miR-132 counteracts the progression of renal fibrosis by selectively decreasing myofibroblast proliferation and could potentially serve as a novel antifibrotic therapy.

SA-OR081

Characterizing the Molecular Identity of Pathogenic Fibroblasts Using Single Cell RNAseq. Yoonjong Chang,1 Kai-Hui Sun,1 Jan Driver,2 Andrew J. Kimpi,1 Magdalena Fragkou,1 Jason R. Rogall,1 Nilgun Reed,1 Dean Sheppard.1 1 Dept of Medicine, Univ of California San Francisco, San Francisco, CA; 2 Dept of Anatomy, Univ of California San Francisco, San Francisco, CA; 2 Abbvie Inc., Chicago, IL.

Background: Fibroblasts are the main effectors of organ fibrosis but their molecular identity is poorly understood. Using Collal1a1-GFP mice, we isolated pathogenic fibroblasts from 3 fibrotic organs and performed single cell RNAseq analysis.

Methods: We induced fibrosis in the kidney (unilateral ureteral obstruction), lung (intratracheal bleomycin) and liver (carbon tetrachloride injections). With fluorescence-activated cell sorting, we isolated collagen-expressing GFP positive cells from each organ. Single cell RNAseq was obtained via a fluidic system and libraries generated and sequenced. We performed hierarchical clustering (HC) analysis, principal component analysis (PCA) and targeted correlation assays on RNAseq data.

Results: We analyzed 130 kidney cells, 160 lung cells and 177 liver cells. HC and PCA analysis revealed 3 distinct groups of fibroblasts in fibrotic kidney and lung. Group 1 express high levels of collagen 1 and a set of fibroblast-related genes. Group 2 express low levels of collagen 1 and 3 express intermediate levels of collagen 1 as well as fibroblast-related genes and leukocyte markers. This group may represent circulating fibrocytes. In contrast, collagen-expressing cells in the liver are a mostly homogenous population that differs substantially in gene expression from those of the lung and kidney.

Conclusions: We characterized the molecular diversity of fibroblasts in 3 fibrotic organs. While pathogenic fibroblasts from the kidney, lung and, less so, liver share a core signature, they also each express unique sets of genes. This study may yield new biomarkers and therapeutic targets for treating fibrosis.

Funding: Pharmaceutical Company Support - Abbvie Inc., Private Foundation Support
Conclusions: Together, the results suggest that persistent activation of autophagy in kidney proximal tubules promotes renal interstitial fibrosis by regulating tubular cell death, interstitial inflammation, and the production of profibrotic cytokines.

Funding: NIDDK Support, Veterans Administration Support

SA-OR083

Macrophage Migration Inhibitory Factor Promotes Kidney Fibrosis in ADPKD Xia Zhou, 1, 2 Li Chen, 1, 2 Dorien J.M. Peters, 3 Mihaela Gadjeva, 4 Xiaogang Li, 1, 2 ‘Internal Medicine; ‘Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; ‘Leiden Univ Medical Center, Leiden, Netherlands; ‘Harvard Medical School, Boston, MA.

Background: Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine that functions to induce cell proliferation, inhibit apoptosis and regulate the inflammation. We found that MIF promoted renal cyst growth in different ADPKD mouse models (Chen et al., JCI, 2015). Renal cyst progression is accompanied by tubulointerstitial fibrosis which is associated with the renal function decline. However, whether MIF regulates fibrosis in ADPKD remains unknown.

Methods: To understand the role of MIF in regulating renal fibrosis in vivo, we generated Pkd1 flox/MIF -/ mouse. To explore the pathways mediated by MIF in regulating fibrosis process, we treated renal epithelial cells and fibroblasts with MIF or MIF inhibitor, ISO-1.

Results: We found that knockout of MIF or inhibition of MIF with ISO-1 not only delayed cyst growth but also decreased renal interstitial fibrosis as examined by Trichrome process, we treated renal epithelial cells and fibroblasts with MIF or MIF inhibitor, ISO-1.

Conclusions: MIF activates the renal fibroblasts and promotes renal interstitial fibrosis in ADPKD, which may be mediated by TGFβ, ERK, mTOR and Rb signaling pathways. Targeting MIF may be a viable new therapy for ADPKD.

Funding: NIDDK Support

SA-OR084

HGF/c-met Signaling in Macrophages Attenuates Kidney Fibrosis by Regulating Matrix Remodeling and Turnover Haivan Fu, 1 Dong Zhou, 1 Liangxiang Xiao, 1 Roderick J. Tan, 1 Youhua Liu, 1 ‘Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; ‘Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Kidney fibrosis results from an excessive accumulation and deposition of extracellular matrix (ECM). This is mainly due to an imbalance between matrix synthesis and degradation. While significant progress has been made recently on identifying the matrix-producing cells and elucidating how they are regulated, relatively little is known about the mechanism controlling matrix degradation and turnover.

Methods: We generated hepatocyte growth factor (HGF) receptor c-met conditional knockout mice in which c-met was deleted specifically in myeloid cells including macrophages (Mac-c-met/-). Mice were then subjected to tubular ischemia-reperfusion injury (UIR) or unilateral ureteral obstruction (UUO), respectively. Cultured bone-marrow-derived macrophages were also used.

Results: Mice with macrophage-specific ablation of c-met were phenotypically normal. We found that at different time points (3, 7, and 14 days after UUO), there was no difference in the mRNA levels of major fibrosis-related genes such as α-SMA, collagen I, collagen III and fibronectin in the kidneys between Mac-c-met/- and control mice, suggesting that HGF signaling in macrophages does not affect matrix synthesis. However, kidney fibrotic lesions as assessed by Masson’s Trichrome staining were more profound in Mac-c-met/- mice than controls. Comparable results were obtained after analysis of matrix proteins by Western blot. Similarly, in UIR model, loss of c-met in macrophage significantly aggravated renal lesions at 10 days, with elevated serum creatinine and increased deposition of matrix proteins, whereas renal mRNA expression of major matrix genes was not changed. In vivo, increased deposition of ECM was closely associated with the down-regulation of tissue-type plasminogen activator (tPA) in Mac-c-met/- kidneys. In vitro, HGF induced tPA, uPA and MMP-12 expression in cultured bone marrow-derived macrophages.

Conclusions: These results suggested that HGF/c-met signaling in macrophages plays a critical role in reducing kidney fibrosis by promoting matrix degradation and turnover.

Funding: NIDDK Support

SA-OR085

The Hippo-Salvador Signaling Pathway Regulates Renal Tubulointerstitial Fibrosis Yong kyun Kim, 1 Sun-ah Nam, 2 Wan-Young Kim, 3 Arum Choi, 2 Yumi Kim, 1 Jin Kim, 1 ‘Dept of Internal Medicine, Medical College, The Catholic Univ of Korea, Seoul, Korea; ‘Dept of Anatomy and Cell Death Disease Research Center, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: Renal tubulointerstitial fibrosis (TIF) is the final common pathway of various renal injuries. The mammalian Hippo-Salvador signaling pathway is a highly conserved network that cascades through contact inhibition, cell proliferation, and TGFβ plays a role in TIF development.

Methods: The expression of Hippo-Salvador pathway including WW45, Mst1/2, Lats1/2, Yap/Taz were examined. TEC-specific WW45 knockout mice (WW45 flox-/-;Ksp-Cre) were generated for in vivo experiments and Hippo-Salvador pathway were knocked down or overexpressed in HK2 cells. Unilateral ureteral obstruction (UUO) was used for in vivo model and TGFβ-target treatment. WW45 deficiency enhances TGFβ-signaling by the interaction of TAZ with Smads. WW45 deficiency also increases activated β-catenin dependent on TAZ.

Conclusions: Our data showed that Hippo-Salvador pathway regulate renal TIF and EMT, Hippo-pathway (Gbf/Smad and β-catenin signaling). Our experiments suggest that Hippo-Salvador pathway is a new mechanism in the pathogenesis of TIF development and indicate that regulation of Hippo signaling pathway may be a therapeutic target to reduce TIF.

Funding: NIDDK Support

SA-OR086

Cytosine Methylation Levels Determine Regeneration versus Fibrosis After Injury Krittik Gaur, 1, 2 Ae Seo Deok Park, Frank S. Chinga, Katalin Susztak. Renal Electrolyte and Hypertension Div, Univ of Pennsylvania.

Background: Cytosine methylation is an epigenetic mark that regulates gene expression, whereby increased methylation of promoter regions inhibits gene transcription by interfering with transcription factor binding. We previously showed that human CKD and DKD samples have differences in cytosine methylation levels. We hypothesized that these epigenetic modifications are functionally important in the pathophysiology of CKD.

Methods: The ten-eleven translocation (TET) family of proteins, regulate DNA methylation status by oxidizing 5-methylcytosine (mC) to 5-hydroxymethylcytosine (5hmC). In the absence of TET2, there is increased cytosine methylation and decreased hydroxymethylation. Here we examined the functional role of tubular epithelial cell (TEC) methylation levels in vivo by deleting TET2 in TECs.

Results: TET2 flox-/- and Cadenherin 16 Cre mice were crossed to generate animals with renal tubular epithelial cell deletion of TET2. Kidney injury was induced by administering 10% ethanol intra-peritoneally at a dose of 250 mg/kg body weight and sacrificed 1 or 12 weeks later. Mouse kidneys and primary epithelial cells were analyzed by quantitative RT-PCR, and immunohistochemistry to examine fibrotic changes.

Conclusions: Mice with TEC specific deletion of TET2 appeared histologically normal. We hypothesize that this may be due to a slow turnover rate of tubule cells in the kidney. Acute kidney injury and regeneration was induced through administration of folic-acid. Twelve weeks after folate administration control animals almost recovered, while fibrosis appeared more even severe in mice with TEC specific deletion of TET2. These TET2 null mice also had increased expression of collagen, activated myofibroblast and inflammatory markers. We believe that fibrosis developed as a secondary consequence of impaired epithelial cell differentiation, as TET2-deficient TECs remained undifferentiated and yet continued to proliferate.

Conclusions: TET2 is an epigenetic director of renal epithelial repair following injury. Increased TEC cytosine methylation levels interfere with epithelial cell differentiation and directs cells into a profibrotic phenotype.

Funding: NIDDK Support

SA-OR087

Roles of CCN2 and Caspase Activities in Tubular Epithelial Cells Involved in AKI Transition to CKD Takeru Kusano, Tsutomo Inoue, Hirokazu Okada. Saitama Medical Univ, Iruma-gun, Saitama, Japan.

Background: In AKI, severely injured tubular epithelial cells (TEC) are destined to be removed by apoptosis while a small part of them survive and transform, which then facilitate interstitial fibrosis (IF). (Nat Med 16;355, 2010) We previously reported that CCN2 and caspase activities in TEC are important for IF in CKD models (JASN 16;133, 2005; Clin Exp Nephrol (in press)) In this study, we investigate possible linkages between AKI and CKD, focusing especially on roles of CCN2 and caspase activities in TEC.

Methods: CCN2-haploinsufficiency mice (CCN2 +/-), mice transgenic for baculovirus pan-caspase inhibitor p35 (g-GT.Cre; p35) and control mice (g-GT.Cre) are used for generation of following mice; g-GT.Cre:p35, p35 is expressed in vivo.
TEC; g-GTC:Cre/CCN2-/-, CCN2 expression is defect in TEC; g-GTC:Cre:p35:CCN2-/-, defective CCN2 with p35 expression in TEC; and CCN2-/- as the control. We performed 1 hour ischemia and reperfusion injury (IRI) on these 4 groups of mice and evaluated renal fibrosis on day 14.

Results: The mRNA levels of collagen 1 (Coll), fibronectin EIIIA (FN) and TGF-b1 were significantly lower in g-GTC:Cre/CCN2-/- mice than the control mice (Coll: 7.2±0.62 vs. 63.5±1.67, FN: 1.29±0.98 vs. 9.96±2.83, TGF-b1: 0.83±0.12 vs. 4.35±0.98, p<0.05). The fibrosis area% in Masson trichrome stain was significantly narrower in g-GT.Cre/CCN2-/- mice than the control mice (7.4±1.36% vs. 34.8±3.16%, p<0.05). In the comparison between g-GTC:Cre/p35:CCN2-/- mice, the fibrosis area% was significantly wider in g-GTC:Cre/CCN2-/- mice (16.4±2.12 vs. 7.2±0.62, p<0.05). We also revealed that the number of phosphorylated histone H3-positive TEC were significantly higher in g-GT.Cre:p35:CCN2-/- mice. Thus, caspase activities and CCN2 in TEC are likely involved in AKI transition to CKD in the opposite direction, at least after IRI.

Conclusions: PEW is common across the entire spectrum of kidney diseases, but it exhibits the highest prevalence among dialysis and AKI patients. Its commonness, together with its well-documented impact on patient outcomes, deserves increased medical attention.

SA-OR090

A Novel Deleterious Role for Dietary Salt-Sugar Interplay in Metabolic Syndrome and Elevated Blood Pressure in Mice

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Background: High amounts and chronic salt intake are important risk factors for the development and progression of hypertension. Our group has described that also sugars, and in particular fructose, contribute to the pathogenesis of elevated blood pressure thus suggesting a potential interplay between both dietary components in hypertension and metabolic syndrome. Consistently, increased sodium excretion is observed in obese people. Here, we aim to determine whether dietary salt can play a deleterious role in the pathogenesis of other features of metabolic syndrome besides hypertension and if it is related to sugar metabolism.

Methods: Wild type and fructokinase deficient mice –that cannot metabolize sugar and fructose- were exposed to 1% salt in drinking water for 30 weeks and features of metabolic syndrome including elevated blood pressure, fatty liver, insulin resistance, leptin resistance and weight gain were determined.

Results: Exposure of mice to salt induced the hypertonic activation of aldose reductase and the endogenous production of fructose in liver, pancreas and fat. Consistent with increased fructose production and metabolism in these tissues, wild type but not fructokinase deficient mice demonstrated significantly higher fat deposition, fatty liver and blood pressure compared to controls. Furthermore, salt intake in wild type mice induced a significant increase in insulin resistance as determined by oral glucose and insulin tolerance test, hyperleptinemia, hypohalaminic leptin resistance, increased food intake and body weight gain compared to fructokinase deficient mice.

Conclusions: Our study indicates that dietary salt can induce multiple features of metabolic syndrome besides high blood pressure. It also suggests interplay between salt and sugar in which salt will induce the endogenous production of fructose. The metabolism of endogenous fructose by fructokinase would be the underlying factor for the reduced metabolic syndrome in mice. Thus, blockade of fructokinase could be a novel therapeutic approach for the prevention and treatment of hypertension and metabolic syndrome.

Funding: NIDDK Support

SA-OR088

Repeated Minor AKI Accelerates Renal Fibrosis and Dysfunction in Klootho Deficit Mice

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Background: It has been recognized that AKI and CKD are not independent disease but are related to each other. We previously reported that traumatic anuria in one kidney induces AKI and CKD in the contralateral kidney. Since chronic kidney injury by repetitive ischemic damage is a risk factor for the progression of CKD, it is likely that reducing the frequency of deterioration of renal function such as reduced Kltoho expression would attenuate advancing the kidney dysfunction, which is one possible strategies for preventing CKD progression.

Methods: We explored the effects of repeated minor AKI on the kidney in the rodent model of reduced Kltoho expression. Minor AKI was induced by short time clamping of renal artery, once a week for 3 weeks in kl(-/-) and wild type mice. Serum creatinine level was measured and the expression levels of fibrosis related marker, such alpha SMA, MCP, etc., by immunostaining and RTPCR was assessed. Internal expression of Kltoho was modified by gene delivery.

Results: Frequent AKI reduced the renal function much more (70% higher in Cr) in kl(-/-) mice than wild type mice. Kltoho expression quickly diminished after each ischemic maneuver. The expression of fibrotic markers increased (2.2 fold) in the kidneys comparing with wild type kidney. The reduction of renal function and tissue damage was attenuated by Kltoho gene delivery. Preliminary, gene screening suggested more down regulation of heat shock protein and ATP by AKI accumulation in kl(-/-) mouse kidney.

Conclusions: It is likely that reduction of Kltoho levels in the kidney, such as in aging or CKD, is a risk factor for accelerating the progression of CKD, resulting in sensitive status to various kinds and frequency of renal damage, and upregulation of the Kltoho may attenuate advancing the kidney dysfunction, which is one possible strategies for preventing the CKD progression.

Funding: Government Support - Non-U.S.

SA-OR091

Sodium Chloride Promotes Tissue Inflammation via Osmotic Stimuli in Subtotal Nephrectomized Mice

Fumiko Sakata, Yasuhiro Ito, Masashi Mizuno, Yasuhiko Suzuki, Takeshi Terabayashi, Takako Tomita, Mitsuhiro Tawada, Shoichi Maruyama, Eyu Imai, Yoshifumi Takei, Seichi Matsu, Nephrology and Biochemistry, Nagoya Univ, Nagoya, Japan; Nephrology, Nakayamadera Imai Clinic, Takarazuka, Japan.

Background: Chronic inflammation is prevalent in patients with end-stage renal disease, but the precise mechanisms remain unclear. Sodium is that reportedly stored in tissues after high salt intake induces lymphangiogenesis and autoimmune diseases via osmotic stimuli. We studied the effects and mechanisms of high salt loading on tissues and systemic inflammation (with a focus on macrophage infiltration) in sub-total nephrectomized (5/6Nx) mice and in cultured cells.

Methods: Mice underwent 5/6Nx or sham surgery (Sham), and were provided with either tap water (Water) or 1% NaCl (NaCl) for four weeks. Inflammatory changes in peritoneal wall, heart and paraaortic tissues were evaluated by immunohistochemistry, Western blot, ELISA and quantitative PCR. Inhibition studies were performed in vivo and in vitro.

Results: Significantly more macrophages infiltrated the peritoneal wall (p < 0.001), heart (p < 0.05) and paraaortic tissues (p < 0.001) of sub-total nephrectomized mice with salt loading (5/6Nx/NaCl) compared with 5/6Nx/Water. Tissue levels of IL-6, monocyte chemotactic protein-1 (MCP-1) and toxicity-responsive enhancer binding protein (TonEBP) were significantly increased in the peritoneal wall and heart of 5/6Nx/NaCl compared with 5/6Nx/Water. The administration of furosemide or tap water after NaCl for four weeks, indicating reversal of NaCl loading, reduced local macrophage infiltration and suppression of MCP-1 (p < 0.05) and TonEBP mRNA (p < 0.01). A high NaCl concentration...
in the culture media of mesothelial cells and cardiomyocytes induced MCP-1 protein, MCP-1 mRNA, and IL-6 and TNF-α. These effects were significantly higher for non-renal pathways (e.g. sweat or lower intestinal absorption) as kidney function declines.

Conclusions: 
- The study findings suggest that sodium excretion is reduced, possibly as a result of a greater fraction of sodium being excreted by non-renal pathways (e.g. sweat or lower intestinal absorption) as kidney function declines.
- Controlled balance studies in CKD patients are needed to confirm our findings.

Funding: NIDDK Support

SA-OR093
Lower Risk of ESRD Associated with DASH Diet in Adults with Moderate CKD and Hypertension

Tanshooe Banerjee,1 Deirda C. Crews,2 Meda E. Pavkov,1 Nilka Riis Burrows,3 Jennifer L. Bragg-Gresham,4 Rajiv Saran,4 Neil R. Powe.1 1UCSF; 2JHU; 3CDC; 4U Michigan, Ann Arbor.

Background: 
- Although the Dietary Approaches to Stop Hypertension (DASH) diet, rich in fruits, vegetables, and plant derived protein, has been shown to reduce blood pressure in individuals with normal and mildly impaired kidney function, it is not known whether the DASH diet impacts CKD progression among patients with moderate CKD.

Methods: 
- We determined a baseline diet adherence score (higher score=greater adherence) among patients with normal and mildly impaired kidney function, it is not known whether the DASH diet impacts CKD progression among patients with moderate CKD.

Results: 
- In AASK (n=1093) and MDRD (n=814), baseline mean(SD) age was 54.5(10.7) and 51.4(12.4) years; mean(SD) for g(m)/min/1.73m² was 46.8(14.1) and 33.5(12); and mean(SD) for sodium (g/day) was 3.7(2.0) and 3.5 (1.5), respectively. After adjustment, each SD reduction in g/day was associated with a 0.24 g/day (p=0.002) lower sodium excretion in AASK; and a 0.15 g/day (p=0.001) lower sodium excretion in MDRD.

Conclusions: 
- Our findings challenge the existing paradigm that the amount of sodium excreted in a 24-hour urine collection is roughly equivalent to intake in all persons. Further, the association of reduced sodium excretion with advanced CKD may help explain paradoxical risk relationships in studies that did not take into account concurrent kidney function.

Controlled balance studies in CKD patients are needed to confirm our findings.

Funding: NIDDK Support

SA-OR094
Normal Weight with Central Obesity Is Associated with the Highest Risk of Coronary Artery Calcification in Chronic Kidney Disease Patients

Mi Jung Lee,1 Shin-Wook Kang,1 Curie Ahn,2 Tac-Hyun Yoo.1 1Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; 2Dept of Internal Medicine, Seoul National Univ, Seoul, Korea.

Background: 
- In chronic kidney disease (CKD), body mass index (BMI) showed a U-shaped association with cardiovascular (CV) risk. In contrast, central obesity was directly associated with increased CV risk. This bi-directional relationship prompted us to evaluate the CV risk assessed by coronary artery calcification (CAC) based on a combination of BMI and waist-to-hip ratio (WHR) in CKD patients.

Methods: 
- We included 1,217 CKD stage 1 to 5 patients who enrolled in the KoreaN Cohort for Outcome in patients With Chronic Kidney Disease. Patients were divided into 3 groups by BMI (normal, 18.5 ≤ to <23.0; overweight, ≥23.0 to <27.5; obese, ≥27.5 kg/m²) and were dichotomized by sex-specific median of WHR (0.92 in male; 0.88 in female). CAC was defined as ≥10 Agaston using a multi-slice computed tomography.

Logistic regression analysis was used to assess the independent association of CAC with BMI and WHR, and cross-categorization of BMI and WHR, respectively.

Results: 
- CAC was observed in 501 patients (41.4%). Multivariate logistic regression analysis indicated that BMI was not independently associated with CAC (per 1 kg/m² increase, odds ratio [OR]=1.03, 95% confidence interval [CI]=0.98-1.08, P=0.24). However, WHR showed an independent linear association with CAC (per 0.01 increase, OR=1.04, 95% CI=1.02-1.07, P<0.001). Furthermore, when patients were categorized into 6 groups according to combination of BMI and WHR, normal BMI but increased WHR (OR=1.91, 95% CI=1.05-3.48, P=0.03) had the highest risk of CAC compared to others (normal BMI with lower WHR, as reference; overweight with lower WHR, OR=1.46, 95% CI=0.93-2.30, P=0.10; obese with lower WHR, OR=1.51, 95% CI=0.68-3.40, P=0.31; overweight with increased WHR, OR=1.45, 95% CI=0.95-2.22, P=0.06; obese with increased WHR, OR=1.49, 95% CI=0.88-2.53, P=0.14).

Conclusions: 
- In CKD patients, normal weight with central obesity was associated with the highest risk of CAC, suggesting that combining BMI and WHR could be more helpful to stratify CV risk than BMI alone.

Funding: Government Support - Non-U.S.

SA-OR095
MicroRNA-27a Is Decreased in Skeletal Muscle During Atrophy and Is Regulated by Calcineurin/NFAT Signaling: A Regulatory Mechanism for Myostatin Expression

Xiaoman H. Wang,1 Russ Price,1 Jill A. Rahnert,1 Matthew B. Hudson.1 1Medicine/Nephrology, Emory Univ, Atlanta, GA; 2Atlanta VAMC, Atlanta, GA.

Background: 
- Muscle atrophy occurs in chronic conditions like chronic kidney disease and diabetes. Production of myostatin by muscle plays a central role in the pathogenesis of atrophy during these conditions and research has recently focused on understanding how myostatin (MSTN) is controlled in muscle. MicroRNA-27a (miR-27a) can target MSTN mRNA and decrease MSTN protein in muscle; however, the mechanism(s) that control the mRNA and decrease MSTN protein in muscle; however, the mechanism(s) that control the expression of myostatin during muscle atrophy, some studies were conducted with C2C12 myoblasts and later, we found that CnA activity is reduced in skeletal muscle during CKD and STZ induced diabetes.

Methods: 
- In hindlimb muscles of STZ rats, miR-27a was decreased 40% and earlier, we found that CnA activity is reduced in skeletal muscle during CKD and STZ induced diabetes.

Results: 
- In hindlimb muscles of STZ rats, miR-27a was decreased 40% and earlier, we found that CnA activity is reduced in skeletal muscle during CKD and STZ induced diabetes.

Conclusions: 
- Our objective of this study was to investigate how miR-27a is regulated during muscle atrophy.

Funding: NIDDK Support, Veterans Administration Support

SA-OR096
Systemic Inflammation Affects Skeletal Muscle Protein Homeostasis in Maintenance Hemodialysis (MHD) Patients

Hung,1,2 Edward D. Siew,1,2 Xiaonan H. Wang,1 Russ Price,1 J. Ashley Booker,1,2 Serpil Muge Doger,1 Adriana Hung,1,2 Edward D. Siew,1,2 Cindy Bookor,1 Talat Alp Ikizler,1,2 1Hvard University, TN; 2VA, Nashville, TN.

Background: 
- Systemic inflammation is closely associated with protein energy wasting (PEW) in MHD. In order to understand its metabolic effects on skeletal muscle metabolism, we examined whole body and skeletal muscle protein turnover in MHD patients with varying degrees of PEW.

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

83A
SA-OR097

IL-1 Blockade Improves Adiponectin (ADPN) Levels in Patients with CKD Stages 3 and 4

Adriana Hung,1,2 Kristen L. Nowak,1 Talat Aly Bizzler,1 Natallie Salas,1 Heather Farmer,1,3 Rajit Chaudhry,1,3 Rafia J. Chaudhry,1 Michel Chonchol,1,3,4 Nashville VA, TN;1 Vanderbilt Univ, TN;1 Univ of Colorado Denver, CO.

Background: Adiponectin (ADPN), an adipose tissue-derived hormone, is known to have insulin sensitizing, anti-inflammatory, and anti-atherogenic properties in the general population. ADPN secretion is suppressed by systemic inflammation, a highly prevalent condition in chronic kidney disease (CKD), and may have cardiovascular health implications in this population. In this study, we evaluated whether short-term administration of a interleukin-1 (IL-1) blocker, improves ADPN levels and insulin sensitivity in patients with CKD stages 3&4.

Methods: This study was a pilot randomized placebo-controlled double-blind trial of administration of IL-1 blocker in patients with CKD stages 3&4. Forty-two patients were randomly assigned (1:1) to receive 160 mg of an IL-1 blocker (rilonacept) or placebo for 12 weeks; 37 completed the trial. The primary outcomes for this analysis were the effect of the intervention on the serum levels of ADPN, leptin, leptin adiponectin ratio (LAR) and HOMA-IR. Mixed effect models were used for all analyses.

Results: Mean age was 63.6 ±11 years, the median eGFR 37.9 (IQR 29.1, 46.7) ml/min, 76% were males and 24% were African Americans. The values for ADPN, leptin, leptin, HOMA IR at baseline were 78 ±17.4 μg/mL, 27.1±22.8 ng/mL, 2.63±2.76 and 5.6±5.35, respectively. IL-1 blockade resulted in an increase in serum ADPN in the intervention group compared to placebo (p=0.03). Leptin, LAR or HOMA IR levels did not change significantly [table 1].

Table 1. Metabolic indices at baseline and week 12

<table>
<thead>
<tr>
<th>IL-1 blockade</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (μg/mL)</td>
<td>Base: 21.0±17.7</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>Base: 28.4±23.7</td>
</tr>
<tr>
<td>Week 12</td>
<td>27.2±19.2</td>
</tr>
<tr>
<td>LAR</td>
<td>2.86±3.2</td>
</tr>
<tr>
<td>Week 12</td>
<td>2.02±2.4</td>
</tr>
</tbody>
</table>

Conclusions: Short-term administration of an IL-1 blocker significantly increased ADPN levels in patients with CKD stages 3&4. The intervention did not impact other insulin sensitivity parameters, including HOMA-IR, leptin and LAR. Results are consistent with those observed in dialysis patients.

Funding: Veterans Administration Support, Private Foundation Support

SA-OR098

Effects of Chronic Intradialytic Physical Exercises in NRf2 and NF-kB Expression and Antioxidant Enzymes in Hemodialysis Patients

Denise Mastra, Cinthia Da costa Abreu, Milena Barca Stockler-Pinto, Ludmila Fmr Cardozo. Post-Graduate Program in Cardiovascular Sciences, Fluminense Federal University (UFF), Niterói, Rio de Janeiro, Brazil.

Background: Oxidative stress and inflammation are cardiovascular risk factors in patients with chronic kidney disease (CKD) on hemodialysis (HD). Nuclear factor kappa B (NF-kB) plays a role in the coordinated expression of inflammatory genes. However, the role of nuclear factor erythroid 2-related factor 2 (Nrf2) increases the transcription of genes encoding enzymes of phase II detoxifying and antioxidant enzymes. Several studies have shown that Nrf2 expression can be modulated by some factors, such physical exercise. The aim of this study was to evaluate the effects of resistance exercise program on the NRf2 and NF-kB expression and antioxidant enzymes HD in patients.

Methods: This study included 44 patients on regular HD program, 25 patients (14 men, 46.1 ± 11.3 years and 71.2 ± 42.2 months HD) composed the exercise group and 19 patients (7 men, 46.8 ± 12.5 years and 67.4 ± 51.7 months HD) the control group. Strength exercise program was performed during HD sessions, 3 times a week (36 exercise sessions). The NRf2 and NF-kB expression were analysed by quantitative real time PCR. Superoxide dismutase (SOD) activity and glutathione peroxidase (GXP) levels were measured using ELISA commercial kits.

Results: The NRf2 mRNA expression increased significantly after intervention in exercises group (0.8 ± 0.4 to 1.7 ± 0.8, p<0.01). In both groups there were no changes in NF-κB mRNA expression after intervention. The SOD levels reduced in exercise group (from 45.1±6.1 U/mL to 31.9±4.6 U/mL, p<0.05) and in control group (from 45.1±6.1 U/mL to 31.9±4.6 U/mL, p<0.05). However, GXP levels increased in exercise group (from 24.7±12.4 nmol/mL/min to 53.4±20.4 nmol/mL/min, p<0.001) and in the control group there was tendency to decrease (from 26.0±5.3 nmol/mL/min to 20.6±3.7 nmol/mL/min, p=0.09). A negative correlation was found between the differences of NF-kB and GXP plasma levels (before and after 3 months) (R= -0.76, p<0.007).

Conclusions: Chronic intradialytic resistance exercises during 3 months seem to be able to modulate the NRf2 activation and increase the antioxidant protection in HD patients.

SA-OR099

Evaluation of Novel Urine Biomarkers for Diagnosis of Subclinical Acute Tubular Necrosis

Denis G. Moleoning, Isaac E. Hall, Mona D. Doshi, Peter P. Reese, Francis L. Weng, Bernd Schroppel, Heather Thiessen Philbrook, Joseph Fick, Chirag R. Parikh. TRIBE-AKI.

Background: Rise in serum creatinine (Scr) is currently accepted as the “gold-standard” for clinical diagnosis of acute kidney injury (AKI). However, acute tubular necrosis (ATN) may occur without evidence of AKI, a condition known as “sub-clinical AKI.” We evaluated the performance of Scr and urinary biomarkers of kidney injury for diagnosis of ATN on kidney biopsy.

Methods: This is a substudy of a multicenter prospective cohort of deceased donors and associated kidney transplants. A diagnosis of ATN was assigned if the kidney biopsy report (read at organ procurement) indicated acute injury in ≥25% of tubules. AKI was defined by AKIN criteria based on admission and terminal Scr. Urinary biomarkers were measured from stored samples collected at procurement.

Results: Of 581 donors who donated kidneys, 220 (38%) had ATN (Stage 1 or higher). Of the 57 donors with ATN on biopsy, 28 (49%) did not have AKI. Scr had an area under the ROC curve (AUC) for diagnosing ATN of 0.58 (95% CI 0.49, 0.67). Sensitivity and specificity for Scr were 51% and 64% using the AKIN stage 1 cut-off; 26% and 83%, respectively, using the AKIN stage 2 cut-off. In the 361 (62%) donors without AKI, Scr was higher if ATN was noted [79.0 (22.7-205.9) vs 30.1 (10.2-87.6) ng/mL for those without ATN, P=0.03]. Median L-FABP and YKL-40 were lower (though not significantly) in ATN compared to no ATN (L-FABP 25.6 (6.4, 64.0) vs 10.4 (3.4, 41.0) ng/mL, P=0.08; YKL-40 40.4 (31.6, 13.6) vs 6.0 (5.5, 2.5) ng/mL, P=0.11). IL-18, KIM-1 and MCP-1 concentrations were similar regardless of ATN. Adding NGAL to Scr correctly reclassified 26% of donors for ATN events. We noted a trend for lower 6-month recipient estimated glomerular filtration rate (eGFR) [-2.6 (95%CI -5.4, 0.2) ml/min] for worsening degrees of ATN, but 6-month eGFR was paradoxically better [+3.6 (95% CI 1.7, 5.4) ml/min] for each higher stage of Scr-defined donor AKI.

Conclusions: Scr lacks sensitivity and specificity for diagnosing ATN. Urinary biomarkers like NGAL, L-FABP and YKL-40 may help distinguish “subclinical AKI,” if not improve clinical prediction of biopsy-proven ATN over that of Scr alone.

Funding: NIDDK Support, Private Foundation Support

SA-OR100

The Epidemiology and Outcome of Worldwide Acute Kidney Injury in Critically Ill Children: A Prospective Multinational Study

Ahmad Kasdoun,1 2 1International Tubular Necrosis Initiative, 3Smart Group, 2 3International Tubular Necrosis Initiative, 4AKI, 5Acute Kidney Injury, 6Renal Angina and Epidemiology in Critically ill Children (AWARE) investigators; 2Cincinnati Children’s Hospital Medical Center.

Background: Epidemiologic data for pediatric acute kidney injury (AKI) is limited to retrospective single-center studies. We conducted a prospective observational study of critically ill children to provide an international epidemiological description of pediatric AKI and associated outcomes.

Methods: 12 centers from 5 continents collected data for 3 consecutive months in 2014 from children (aged 3 months to 25 years) admitted to a pediatric intensive care unit.
Severe AKI independently predicted mortality after adjustment for illness severity (OR 5.1, p<0.001). In a multivariate regression model, a 1-unit change in stage of AKI was associated with 1.28 days increase in illness-severity-adjusted length of stay (p<0.001). These prediction models are accurate for the prediction of progression of AKI to CKD.

Results: Seven variables were associated with a higher risk of progression to CKD: older age, female sex, higher baseline serum creatinine, higher urine albumin, greater AKI severity (KDIGO Stage), lesser recovery of kidney function by the time of discharge, and heart failure. The full model showed good discrimination in the derivation and validation cohorts (c-statistics of 0.85 and 0.82, respectively). A reduced model that included age, sex, baseline serum creatinine, AKI severity, and recovery of kidney function at discharge performed similarly to the full model, but better than a base model that included age, sex, and AKI severity alone (c-statistics: 0.82, 0.84, and 0.83, respectively). The full model had better discrimination (p<0.001) and was determined by KDIGO criteria, rhabdomyolysis was defined as a CK>5000 unit/L (by 429 ± 423 µmol/L; trace elements: IHD, 4156 ± 465; SLED-f 3732 ± 521; CVVH 3982 ± 465 µg/L). At RRT end, plasma amino acids and trace elements had significantly reduced compared to those without (1.3 years vs 1.0 years, respectively), eGFR was higher in patients with AKI (23.8% vs 12.3% p<0.01), and more patients in the low MAP category (24.0% vs 8.9%, p<0.01). Despite a longer median follow up time for patients with rhabdomyolysis compared to those without (1.3 years vs 1.0 years, respectively), eGFR was higher in rhabdomyolysis patients (23.8% vs 12.3%, p<0.01). The follow up period for assessing death and HTN was longer and not significantly different for those with and without rhabdomylosis (3.7 vs 4.0 years, respectively). While rhabdomyolysis was not associated with long-term mortality, it was associated with HTN (HR 1.32, 95% confidence interval 1.16-1.66, p<0.02) after adjusting for HTN. Conclusions: Rhabdomyolysis was not associated with a decline in eGFR or mortality after a median follow up of approximately 1 and 4 years, respectively. Rhabdomyolysis was independently associated with multiple deleterious outcomes. Our data will help guide future research to develop accurate and early diagnostic models of AKI.

Conclusions: These prediction models can stratify patients for risk of CKD following hospitalization with AKI. We developed and validated predictive models for progression of AKI to CKD.

Methods: We studied patients with baseline eGFR<45 mL/min/1.73m2 who survived>3 months following a hospitalization with AKI. We identified those with a sustained reduction in eGFR<30 mL/min/1.73m2 for >3 months. Data from 11,477 patients hospitalized with AKI in Alberta, Canada were used to develop the risk models. External validation was performed in a cohort of 9,387 similar patients from Ontario, Canada. Models were derived using logistic regression and evaluated based on discrimination, calibration, integrated discrimination improvement (IDI), and net reclassification improvement (NRI).

Results: Patient-Oriented Research in AKI Oral Abstract/Saturday

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

Underline represents presenting author.

85A
Renal Replacement Therapy Intensity for Acute Kidney Injury and Recovery to Dialysis Independence

Ying Wang, Serigne N. Lo, Martin P. Gallagher, Jiang Li, Alan Cass, John A. Myburgh, Robert Faulhaber-Walter, John A. Kellum, Paul M. Palevsky, Claudio Ronco, Patrick Saudan, Ashita J. Tolwani, Rinaldo Bellomo, John A. Kellum, 1 George Inst for Global Health; 2Hanover Medical School; 3Univ of Pittsburgh School; 4Bortolo Hospital; 5Univ Hospital; 6The Univ of Alabama.

Background: In acute kidney injury, randomized controlled trials (RCTs) have not found differences in survival with higher intensities of renal replacement therapy (RRT), but trials have not been powered for renal outcomes such as recovery of renal function.

Methods: Through an individual patient data meta-analysis we merged individual patient data from RCTs comparing high with standard intensity RRT. We assessed mortality at 28 days, 60 days and AKI recovery at 7, 14, 28, 60 & 90 days post randomisation. Renal recovery was assessed twice; by the proportion of patients RRT dependent and by time to RRT independence at these time points.

Results: Of the eight prospective RCTs assessing different RRT intensities, seven contributed individual patient data (n=5688) to the analysis. Mortality was not different between the high and standard intensity groups across these 7 studies at 28 days (775/1890 and 744/1798 respectively, 41% vs 41.4%, p = 0.24) after randomization, nor at any of the other time points. The proportion of patients RRT dependent at the 14 day point was greater in patients receiving high compared to standard intensity RRT (RR 1.36, 95%CI 1.12-1.65, p = 0.0016), but not at any other time point. Analysis by time to RRT independence suggested that patients receiving higher intensity therapy had less time independent of RRT (Day 28: HR 0.87, 95% CI 0.78 to 0.97, p=0.014, Day 60: HR 0.87, 95%CI 0.78 to 0.97, p=0.012, Day 90: HR 0.84, 95%CI 0.76 to 0.94, p <0.0022). This effect was more pronounced in trials that allowed the use of intermittent hemodialysis (IHD) to deliver higher intensity RRT. The robustness of these effects was confirmed in multiple sensitivity analyses.

Conclusions: Higher intensity RRT does not affect mortality but does appear to delay recovery to RRT independence. This effect appears to relate to the use of IHD to deliver higher intensity RRT.

Funding: Government Support - Non-U.S.

Outcomes of In-Hospital Cardiopulmonary Resuscitation (CPR) in Patients with Acute Kidney Injury

Fahad Saeed, 1 Jean L. Holley, 2 Sevag Demirjian, 1Cleveland Clinic; 2Univ of Illinois at Urbana-Champaign.

Background: There is paucity of data on the CPR-related outcomes in patients with AKI. Herein, we have analyzed the impact of AKI on the outcomes of in-hospital CPR.

Methods: We extracted data from the Nationwide Inpatient Sample (NIS, 2005-2011) including patients with and without AKI who had undergone in-hospital CPR. Baseline characteristics, in-hospital complications and discharge outcomes were compared between the two groups. We determined the effect of AKI on length of hospital stay, discharge destination, and hospital mortality in patients who underwent in-hospital CPR.

Results: 180,970 patients with primary or secondary diagnosis of AKI underwent in-hospital CPR compared to 323,620 patients without AKI. Unadjusted in-hospital mortality rates were higher in the AKI group (78.2 % vs. 71.8%, p <0.0001). After adjusting for age, sex, and potential confounders, patients in the AKI group had higher odds of mortality with odds ratio 1.3, 95% confidence interval 1.2-1.4, p<0.001. Survivors in the AKI group were more likely to be discharged to nursing home; odds ratio 1.3, 95% confidence interval 1.3-1.5, p<0.0001. Mean length of stay was significantly higher in patients with AKI, 11 ±34 days versus 7 ±26 days, p=0.0001.

Conclusions: AKI independently increases the odds of in-hospital mortality and nursing home placement after in-hospital CPR. These data may facilitate CPR discussions and decision-making.

Table-1

<table>
<thead>
<tr>
<th>Variables</th>
<th>AKI(n=114)</th>
<th>Control(n=114)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(SD)</td>
<td>73.4±11.3</td>
<td>73.4±11.5</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>63.2%</td>
<td>63.2%</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>34.2±11</td>
<td>31.3±7.6</td>
<td>0.02</td>
</tr>
<tr>
<td>CKD</td>
<td>49%</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR(KD/EPI)</td>
<td>64±1.7</td>
<td>77±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>28.1%</td>
<td>9.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34.2%</td>
<td>16.2%</td>
<td>0.002</td>
</tr>
<tr>
<td>HTN</td>
<td>87.7%</td>
<td>64%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE/ARB use</td>
<td>67.5%</td>
<td>44.7%</td>
<td></td>
</tr>
<tr>
<td>Diuretics use</td>
<td>64%</td>
<td>42.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAID use</td>
<td>51.8%</td>
<td>67.5%</td>
<td>0.015</td>
</tr>
<tr>
<td>NSAID+ACE/ ARB+Diuretics</td>
<td>36.8%</td>
<td>28.1%</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemoglobin (pre-op)</td>
<td>12.8±1.7 (8.7-17.1)</td>
<td>13.5±1.4 (8.4-16.4)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Hemoglobin (post-op)</td>
<td>9.9±1.3 (6.5-14.5)</td>
<td>18.6±1.3 (7.13-15.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>transfusion</td>
<td>61(53.5%)</td>
<td>23(20.2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: The incidence of AKI after THR is low. Several known risk factors were independently associated with AKI after THR, however, ACE/ARB, diuretics and NSAID exposure were not. A prospective study is needed to confirm these results.

SA-OR109

Discovery and Testing in Rat Models of UT-A1 Urea Transporters Cristina Esteva-Font, 1 Onur Cil, 2 Tao Su, 1 Sujin Lee, 3 Marc O. Anderson, 4 Alan S. Verkman, 5 Puay Wah Phuan. 1 Medicine and Physiology, Univ of California, San Francisco, San Francisco, CA; 2Chemistry and Biochemistry, San Francisco State Univ, San Francisco, CA.

Background: Ureas of ureter transport function have potential clinical applications as first-in-class salt-sparing diuretics for treatment of edema and hyponatremia (Nat Rev Nephrol 11, 113-123, 2015). Our goal is to develop small-molecule, UT-A1-selective inhibitors and demonstrate their diuretic efficacy in clinically relevant animal models.

Methods: Screening of ~250,000 drugs and synthetic small molecules was done using a cell-based fluorescence assay involving osmotic volume response to an urea gradient (Chem Biol 20, 1239-1244, 2013). Pharmacokinetics (PK) was measured in rats by liquid chromatography and mass spectrometry; diuretic efficacy was studied using metabolic cages and in a model of SIADH produced by chronic minipump infusion of dDA VP (5 ng/h) with liquid diet administration (NSAIDs) as the most promising compound.

Results: 22 distinct chemical classes of UT-A1 inhibitors were identified and optimized by structure-activity studies on >3,000 analogs. Compounds with high UT-A1 vs. UT-B selectivity were identified, some with nanomolar inhibition potency. In addition, analog and natural-product screening identified dimethylthiourea (DMTU) as a non-selective UT-A1 inhibitor.
inhibitor. Several classes of compounds gave good PK in rats with predicted therapeutic concentrations in blood and urine. Salt-sparing diuretic action was demonstrated in control hydrated rats and rats administered dDAVP acutely. Up to a 2.5-fold increase in hourly urine volume and 2-fold reduction in urine osmolality was found. Compounds also prevented hyponatremia in rats chronically treated with dDAVP.

**SA-OR110**

**Pathways for Urea Transport Across the Rat Inner Medullary Thin Limbs of Henle’s Loops**

Katsumasa Kawahara,1 Sebastian Bachmann,1 Kerim Mutig,1

**Background:** Transepithelial solute flows in thin limbs of Henle’s loops play critical roles in countercurrent exchange and the urinary concentrating mechanism; our goal is to identify the urea transport pathways in these segments. The rat inner medullary long-loop descending thin limbs (DTLs) consist of water permeable upper and water impermeable lower segments, positioned in the upper and lower 50% of the inner medulla, respectively. Mean transepithelial urea permeabilities of upper DTL are approximately 60 E-5 cm/sec and permeabilities of lower DTL and ascending thin limb (ATL) are approximately 350 to 450 E-5 cm/sec. A urea transporter, UT-A2, has been identified by immunohistochemistry only in a very limited region of the upper DTL, near the outer medullary-inner medullary boundary, and only in the presence of vasopressin.

**Methods:** Tubules were isolated without enzyme digestion and perfused with concentrated glass micropipettes by the method of Burg. The lumen-to-bath transepithelial urea flux was determined and permeabilities were calculated.

**Result:** Urea transport in isolated perfused upper and lower DTL is not inhibited by peritubular 0.25 mM phloretin and urea transport in lower DTL is not inhibited by 10 mM ouabain and is unaffected by a 125 mM lumen Na+ and 0 mM bath Na+ concentration gradient. The urea flux in upper and lower DTLs is almost completely and reversibly inhibited by peritubular 5 mM lmmannitin. Activation energy for transepithelial urea permeability measured at 37°C and 16°C in isolated perfused lower DTLs and ATLs is approximately 13 kJ/mol, a value that is consistent with channel-like activity.

**Conclusion:** The data suggest that a substantial fraction of the transepithelial urea flux occurs independently of known facilitated urea transporters such as UT-A1,3, is unlikely to be coupled to Na+ flux and occurs, in large part, by way of a plasma membrane or paracellular channel-like pathway.

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

**SA-OR111**

**Comparative Analysis of Vasopressin V1a and V2 Receptor Distribution in the Mammalian Kidney**

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**Background:** Vasopressin (AVP) promotes urinary concentration by activating the vasopressin V2 receptor (V2R). Parallel activation of the vasopressin V1a receptor (V1aR) may affect renal ion-electrolyte balance and stimulate the renin-angiotensin-aldoosterone axis. Analysis of the renal distribution of these receptor subtypes has been difficult owing to the lack of suitable, specific antisera. Here we have extended available data on their distribution and function using subtype-specific antibodies. Subtype-selective antisera were used for functional analysis.

**Methods:** Antibodies to V1aR- and V2R-specific peptides were generated. Segmental and cellular distribution of the subtypes along mouse and rat nephron were characterized by immunofluorescence and high-resolution immunocytochemistry. Functional studies were performed in AVP-deficient Brattleboro rats using subtype-specific agonists, A0-4-67 was used for V1aR, and desmopressin for V2R at short term.

**Results:** The V2R was localized basolaterally in mouse and rat kidney thick ascending limb (TAL), distal convoluted tubule (DCT), connecting tubule (CNT) and collecting duct (CD) epithelia; macula densa (MD) and intercalated cells were negative. Conversely, application of the anti-V1aR antibody produced basalolateral signal exclusively in MD cells and intercalated CNT/CD cells. Staining was controlled using V2R- and V1aR-deficient mouse kidneys, respectively. In line with the localization data, administration of desmopressin in Brattleboro rats induced the activation and trafficking of distal tubular NaCl transporters and of aquaporin 2 in the CNT/CD principal cells, whereas application of the anti-V1aR antibody produced basolateral signal exclusively in MD cells.

**Conclusions:** These data provide morphological support for the distinct epithelial effects of AVP mediated by V2R or V1aR and may improve our understanding of the pathophysiology of nephrogenic diabetes insipidus.

**Funding:** NIDDK Support, Other U.S. Government Support.
by renal prostaglandin E2 (PGE2), a metabolite of the cyclooxygenase (COX) pathway, by inducing osmotic diuresis and lysosomal degradation of AQP2. A decrease in microvascular (mRNAs) in the regulation of water and electrolyte balance remains virtually unexplored.

Methods: We generated antagonists to silence miR-132 function. Synthetic AVP (ddAVP) was administered with osmotic minipumps. Mice were housed in metabolic cages and sacrificed 1 day after i.v. or i.c.v. injection of the antagonists or scrambled controls.

Results: Silencing of miR-132 caused severe weight loss as a result of acute diuresis characterized by increased plasma osmolality and decreased urine osmolality. In addition, urinary PGE2 levels were elevated and hypothalamic AVP mRNA expression and blood AVP levels were decreased, suggesting a lack of transcription and subsequent less translation of AQP2 in CD cells. When ddAVP was administered after ILK inhibition, which colocalized with AQP2, we observed a decrease in urinary PGE2 levels, resulting in increased plasma osmolality and decreased urine osmolality. In contrast, levels of antagonism were increased, suggesting a PGE2 independent pathway. In conclusion, we have identified urinary PGE2 levels were elevated and hypothalamic AVP mRNA expression and blood AVP levels were decreased, suggesting a PGE2 independent pathway. In contrast, antagonism of antagonism resulted similarly in increased diuresis and decreased AVP production and we found miR-132 to target and increase hypothalamic MeCP2, which is known to block AVP transcription.

Conclusions: Taken together, silencing of miR-132 causes acute diabetes. Our data indicate that this is the result of a MeCP2 mediated decrease in hypothalamic AVP synthesis.

SA-OR115

Dephosphorylation at Ser-261 Is a Determinant for the Regulated AQP2 Apical Accumulation

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Background: AQP2 apical plasma membrane accumulation is crucial for vasopressin (VP)-regulated urine concentration. VP induces post-translational modification on AQP2 phosphorylation at several sites (S) in its C-terminus; however, the phosphorylated sites are unknown. We have previously shown that VP induces post-translational modifications on AQP2 phosphorylation at several sites (S) in its C-terminus; however, the phosphorylated sites are unknown. We have previously shown that VP induces post-translational modifications on AQP2 phosphorylation at several sites (S) in its C-terminus; however, the phosphorylated sites are unknown. We have previously shown that VP induces post-translational modifications on AQP2 phosphorylation at several sites (S) in its C-terminus; however, the phosphorylated sites are unknown. We have previously shown that VP induces post-translational modifications on AQP2 phosphorylation at several sites (S) in its C-terminus; however, the phosphorylated sites are unknown. We have previously shown that VP induces post-translational modifications on AQP2 phosphorylation at several sites (S) in its C-terminus; however, the phosphorylated sites are unknown. We have previously shown that VP induces post-translational modifications on

Methods: We hypothesized that dephosphorylation at S269 is crucial for regulated AQP2 apical accumulation during the initial phase of stimulation.

Results: In P262L-AQP2, a recessive NDI causing mutant, pS269 was greatly increased with continuous 256-phosphorylation after forskolin (FK) stimulation (20 µm, 10 min) as well as wild-type AQP2 (WT-AQP2). AQP2, whereas, pS269 was increased after FK treatment contrary to WT-AQP2 (20 µm, 10 min). Surprisingly, pS269-AQP2 was increased in the basolateral membrane after FK treatment (20 µm, 10 min). Stimulation with forskolin (FK) stimulation (20 µm, 30 min) decreased the phosphorylation of pS269 at Ser-261. Additionally, it took longer time (20 min) to dephosphorylate S261 in S269-AQP2 compared to WT-AQP2 (within 5 min).

Conclusions: These results demonstrated that pS269-AQP2 is greatly affected by phosphorylation status at Ser-261 and that pS269-AQP2 apical accumulation might be determined by Ser-261 phosphorylation, which is likely to be facilitated by lipopolysaccharide at Ser-269. Further investigation how VP-mediated dephosphorylation of Ser-269 phosphorylation mimics, accumulates in the apical membrane after FK treatment (20 µm, 30 min) with a striking reduction of phosphorylation at Ser-261. Interestingly, it took longer time (20 min) to dephosphorylate Ser-269 in S269-AQP2 compared to WT-AQP2 (within 5 min).

Funding: Other U.S. Government Support

SA-OR116

ILK Is Important for Recycling of AQP2 and Its Subsequent Entry into the Exocytotic Pathway

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Background: Within the past decade tremendous efforts have been made to understand the mechanism behind aquaporin-2 (AQP2) water channel trafficking and recycling, in order to open a path towards effective diabetes insipidus therapeutics. A recent study has shown that the heterotrimeric G protein Ga3, associated with AQP2 vesicles, is required for the water channel fusion to the plasma membrane. On the other hand, swelling of secretory vesicles has been implicated in exocytosis. Here we address the question of whether vesicle swelling is also a prerequisite for fusion of nonsecretory vesicles. The role of Ga3 in this process is investigated. AQP2 vesicles are chosen as paradigm of nonsecretory vesicles.

Methods: AQP2 vesicles isolated from rat kidney were analyzed by high resolution dynamic imaging using the atomic force microscope (AFM), allowing analysis of the fusion vesicles in a hydrated environment at nanoscale resolution. In parallel, a rapid fluorescence-based assay of vesicle or cell volume changes in a multwell format was applied to analyze real time fluorescence kinetic data.

Results: A subunits of PTX-sensitive G proteins, Ga3, was found associated to isolated AQP2 vesicles. Treatment of renal AQP2-transfected MDCD4 cells with pertussis toxin (PTX), which inhibits G proteins of the Ga family, inhibited CAMP-triggered increase in osmotic water permeability implicating a critical role of Ga3. Dynamic imaging of isolated AQP2 vesicles by AFM revealed that mastoparan, known to stimulate Ga proteins, caused a significant increase in vesicle swelling. This effect was confirmed by fluorescence-based assay of vesicle volume changes. Of note, mastoparan-induced vesicle swelling was abolished by anti-Ga3 antibodies or by anti-AQP2 antibodies.

Conclusions: Our results demonstrate that Ga3 localized in AQP2 vesicles mediates vesicle swelling regulating rapid water entry though AQP2, a potentially important prerequisite for vesicle fusion to the plasma membrane. We conclude that vesicle swelling is required also for nonsecretory vesicle fusion committed to insert a channel into the plasma membrane and depicts a general mechanism for vesicle fusion.

Funding: Government Support - Non-U.S.

SA-OR118

An Enzyme Immunoassay for Urinary Extracellular Vesicles

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Background: Urinary extracellular vesicles (uEVs) are derived from epithelial cells of the kidney and urinary tract. uEVs (also called exosomes) contain disease-related proteins and also transfer information to target cells. As such uEVs offer exciting opportunities for nephrology, but current isolation techniques rely on time-consuming ultracentrifugation hindering high-throughput clinical application.

Methods: To navigate this problem, we designed an enzyme-linked immunosorbent assay (ELISA) that isolates uEVs using a biotinylated CD9 antibody. uEVs are then lysed with a detergent and treated with an antibody targeting the protein of interest. The use of two conjugated antibodies allows quantification of the protein of interest and CD9. We tested the set-up using aquaporin-2 (AQP2) and the sodium chloride cotransporter (NCC).

Results: CD9 but not CD63 coated immunobeads isolated AQP2+ and NCC+ uEVs. Urinary creatinine and CD9 correlated strongly (n=20, r=0.9, P<0.001); thus CD9 can be also used for normalization in spot urines. Our uEV-ELISA sensitively detected AQP2
and NCC (coefficients of variance 5.6 and 3.3%). To verify whether expected effects of vasopressin on AQP2 and NCC were captured by our uEV-ELISA, we performed overnight thirsting followed by water loading in 4 volunteers. After water loading, similar 2-3 fold decreases in AQP2 and NCC were observed using either uEV-ELISA or immunoblotting after isolating uEVs with ultracentrifugation. The results by uEV-ELISA showed good correlations with immunoblot (r=0.8 for AQP2, r=0.6 for NCC, both P<0.001).

Conclusions: We successfully developed an ELISA to capture and quantify uEV-proteins and validated this technique for AQP2 and NCC. Our uEV-ELISA set-up does not require ultracentrifugation or measurement of urinary creatinine and may be used as a platform to examine other uEV proteins of interest in nephrology.
TH-PO001

The Long Non-Coding RNA Landscape in Hypoxic and Inflammatory Renal Epithelial Injury

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Background: Long non-coding RNAs (IncRNAs) are emerging as key regulators of disease processes. To identify IncRNAs involved in acute renal epithelial injury, we performed whole transcriptome profiling of human proximal tubular epithelial cells (PTECs) in hypoxic and inflammatory conditions.

Methods: Strand-specific RNA-seq (50 million paired-end reads per library) was performed on poly-adenylated RNA fraction of control PTECs and PTECs subjected to 12 hours of hypoxia or cytokine (IL6, TNF-α, and IFN-γ cocktail) stimulation. A transcript was considered differentially expressed (DE) between control and stimulation at >1.5 fold change with FDR-adjusted p < 0.05.

Results: 3,728 mRNAs and 69 IncRNAs were DE between cytokine-stimulated and control PTECs, while 2730 mRNAs and 70 IncRNAs were DE between hypoxic and control cells. Three IncRNAs were prioritized for further study based on abundance. Linc-ATPI13A-4 was specifically upregulated (8.1-fold at 12 hours, FDR p < 0.001) in PTEC hypoxia, peaked its expression 15-fold at 24 hours, is located in the nucleus and cytoplasm, and has high syntenic and conservation of a 206 bp sequence with the mouse genome. Linc-KIAA1737-2 was specifically upregulated after cytokine treatment (4.6-fold at 12 hours, FDR p < 0.001), was over 50-fold upregulated at 48 hours, is located primarily in the nucleus with an enhancer region (overlying H3K4me1/H3K4me3 overlying H3K27ac mark for adult kidney on NIH Epigenomics Roadmap), and is syntenic with nephrectomy kidneys previously micro-dissected and sequenced.

Conclusions: Transcriptome profiling of stimulated renal epithelial cells reveals different IncRNAs that may regulate the cellular response to distinct stressors relevant to acute kidney injury.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO002

Cortical Consequences of Ischemia-Reperfusion Injury: Computational Studies of the Renal Microvasculature

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Background: The acute injury of the ischemia-reperfusion (I/R) kidney model affects mainly the outer stripe (OS) of the outer medulla, but its long-term consequence is extensive cortical involvement. We were therefore interested in the long-term effects of such ischemic injury on the cortical capillary network.

Methods: Male C57BL/6 mice (n=11) were subjected to bilateral renal I/R for 25 min and sacrificed 2 weeks later. Untreated mice (n=5) were served as controls. Kidney sections were stained for MECA-32 to visualize the renal microvasculature. Vessel geometry was selectively quantified in damaged tissue regions by computer-assisted morphometric analysis.

Results: In the normal subcapsular cortex peritubular capillaries appeared elongated and formed an organized network. Although I/R initially affects the OS, 2 weeks after I/R, marked chronic tubular atrophy occurred in the cortex. Adjacent microvessels’ shape remarkably changed: capillaries were significantly smaller (perimeter, diameter decrease) and rounder (circle and roundness increased, see Figure, aspect ratio decreased) compared to control vessels.

Conclusions: If translatable from mice to human, these data have important therapeutic implications.

Funding: Pharmaceutical Company Support - ISIS Pharmaceuticals, Private Foundation Support

TH-PO003

Glomerular Injury Induces a Calcium Signal in Proximal Tubular Cells – A Multiphoton In Vivo Study

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Background: Recently it has been demonstrated that renal tubular cells undergo synchronized necrosis after ischemic injury, implying that the death of a single cell can induce a disastrous chain reaction. An early event in damage signaling is a massive increase in intracellular calcium levels. Therefore we investigated if a localized damage to glomerular cells can influence tubular calcium levels downstream of the damage site.

Methods: 4 weeks old mice expressing the calcium indicator GCaMP3 in proximal tubular cells (Pax8:cre) were anesthetized, an arterial catheter was placed into the right carotid artery and the left kidney was exteriorized for in vivo multiphoton microscopy. Blood vessels were labelled by injection of 70 kDa Texas Red dextrane. Acute glomerular injury was induced by focusing the laser beam on a podocyte to cause a localized injury. The resulting calcium response in tubular cells was recorded with in a time series of the glomerulus and the originating proximal tubulus.

Results: Upon laser induced injury of a podocyte, a strong calcium signal can be observed within seconds in the continuous stretch of proximal tubular cells downstream of the glomerulus. The signal lasts for a few seconds and then the calcium signal returns to baseline. The calcium response in proximal tubular cells is faster than the known calcium wave in podocytes after injury.

Conclusions: Glomerular injury induces a calcium signal in proximal tubular cells in vivo, linking glomerular injury to tubular damage signaling. The almost instantaneous calcium increase in tubular cells suggest that the release of podocyte cell content and most probably damage-associated molecular pattern molecules (DAMPs) affects tubular cells, unjured by the initial damage.

TH-PO004

Inhibition of Oxygen-Sensing Prolylhydroxylases 1 (PHD1) Protects from Acute Kidney Injury

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Background: Acute kidney injury (AKI) due to ischemia is associated with dramatic increases of morbidity and mortality. Conditions of ischemia with limited oxygen availability inhibit oxygen-sensing prolyl hydroxylases (PHD1-3) with subsequent stabilization of hypoxia-inducible factors (HIFs) resulting in a transcriptionally regulated response towards hypoxia adaptation. Thus, we hypothesize that a new pharmacological approach to inhibit PHD1 on a transcript level via specific antisense treatment before the onset of ischemic injury mediates protection.

Methods: Mice were studied in two ischemic models of AKI. With a hanging weight system we only compress the renal artery whereby we clamp the whole pedicle by using micro vessel clamps. Renal function was determined by inulin clearance, serum creatinine, BUN, renal NGAL and KIM-1.

Results: Our previous studies in gene-target mice (PHD1-3 KO mice) has shown that renal protection from ischemia was associated with PHD1. To pursue our hypothesis, we first treated wild type mice with PHD1 specific antisense inhibitors (ASO1 and ASO2). We tested the compounds over 2 to 6 week treatment periods in different doses. The optimal treatment length was 2 weeks before renal ischemia (30min ischemia and 24 hours reperfusion by utilizing the hanging weight system) in a dose of 100mg/kg per week. Treatment reduces renal PHD1 RNA by 90% and 60%, respectively and improved the glomerular filtration rate (GFR) by almost 300% in both treatment groups compared to untreated mice following 30min of renal ischemia. In a next step we used the clamp model to induce kidney ischemia. PHD1 specific antisense inhibitor treatment showed comparable kidney protection as in the hanging weight model demonstrated in GFR improvement, serum creatinine and renal tubular injury markers (NGAL, KIM1).

Conclusions: In conclusion, PHD1 oligo treatment before renal ischemia in two different ischemia models shows a tremendous attenuation from renal injury due to ischemia. If translatable from mice to human, these data have important therapeutic implications.

Funding: Pharmaceutical Company Support - ISIS Pharmaceuticals, Private Foundation Support

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

90A
Role of Thioredoxin-Interacting Protein (TXNIP) in Mitochondrial Function of Renal Tubular Cells in Ischemia Reperfusion Injury AKI Model


Background: Thioredoxin-interacting protein (TXNIP) has been found to regulate the cellular reduction-oxidation (redox) state by binding to and inhibiting thioredoxin in a redox-dependent fashion. However, little is known about the role of TXNIP in acute kidney injury (AKI) pathogenesis.

Methods: We evaluated the role of TXNIP in renal function in bilateral ischemia reperfusion injury (IRI) model using TXNIP knockout (KO) and wild type (WT) mice, cultured renal tubular cells (NRK-52E cells) and in an in vitro model. To elucidate the functional roles of TXNIP, we evaluated mitochondrial enzymes, morphology, and apoptotic change by transfection of siRNA for TXNIP in cultured renal tubular cells.

Results: TXNIP KO mice had significantly higher SCr (0.78±0.28 versus 0.45 ±0.20 mg/dl) and significantly decreased BUN (152.5±32.5 versus 75.3±18.2 mg/dl) at 24h post ischemia compared to WT mice. Immunohistological examination showed severer tubular injury in cortex and outer medulla in TXNIP KO mice compared to WT mice. The number of TUNEL positive tubular cells was increased in in TXNIP KO mice compared to WT mice. The protein expressions of mitochondrial enzymes (ATP5a, UCP2 and complex IV) were decreased in TXNIP KO mice at 24h post ischemia. In vitro experiments, protein and mRNA levels of ATP5a, complex IV, UCP2, PGC-1a were significantly decreased by H2O2, and siRNA for TXNIP amplify the reduction of these enzymes in NRK-52E cells.

Conclusions: These data demonstrate that TXNIP protects from IRI induced AKI. TXNIP changes mitochondrial function in oxidative conditions. These results indicate that TXNIP plays a key role in the pathophysiology of AKI.

TWEAK Decreases PGC-1α Expression in Renal Injury and Promotes Mitochondrial Dysfunction in Tubular Cells

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Background: There is currently no satisfactory therapy for acute kidney injury (AKI). Sustained decreases in mitochondrial targeted pro-and anti-apoptotic agents suggests a key role of mitochondrial injury in AKI. We hypothesized that an improved understanding of the regulation of factors responsible for mitochondrial biogenesis may provide clues to novel therapeutic approaches to AKI. Thus, we explored the interaction between inflammation and mitochondrial biogenesis regulators.

Methods: Transcriptomics databases from cultured murine tubular epithelial cells and follic acid-induced AKI in mice identified downregulation of PGC-1a and target genes regulated by the inflammatory cytokine TWEAK. Functional studies in vivo ad cell culture studies characterized the TWEAK–PGC-1α relationship.

Results: Transcriptomics identified decreased expression of PGC-1α mRNA and PGC-1α-dependent genes encoding mitochondrial proteins (Ndufs1, Sdhb and Tfm) as a shared feature between AKI and TWEAK-stimulated cultured tubular cells. Neutralizing anti-TWEAK antibodies prevented the decrease in kidney PGC-1α and its targets during AKI. TWEAK stimulation decreased kidney PGC-1α expression in healthy mice. TWEAK also decreased the expression of PGC-1α and its targets as well as mitochondrial membrane potential in cultured tubular cells. Adenoviral-mediated PGC-1α overexpression prevented TWEAK-induced downregulation of PGC-1α-dependent genes and the decrease in mitochondrial membrane potential. TWEAK promoted histone H3 deacetylation at the murine PGC-1α promoter. TWEAK-induced downregulation of PGC-1α was prevented by histone deacetylase (HDAC) or Nfkb inhibitors.

Conclusions: TWEAK decreases PGC-1α and target gene expression in tubular cells through NFκB activation and histone deacetylation. This information may be used to design therapeutic approaches that preserve mitochondrial function during kidney injury.

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

mir-21 Targets Prolyl Hydroxylase Domain Protein 2 in Renal Ischemia/ reperfusion

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Background: We previously reported that up-regulation of miR-21 attenuated renal ischemia-reperfusion injury, which was associated with increased hypoxia inducible factor (HIF)-1α expression. HIF-1α is mediated by prolyl hydroxylase domain protein 2 (PHD2) and regulate mir-668 transcription. To further examine the regulation mechanism of mitochondrial morphology by miR-21, we identified a list of potential miR-21 targets.

Methods: Luciferase reporter assay was performed to examine if miR-21 could target prolyl hydroxylase domain protein 2 (PHD2). We hypothesized that miR-21 regulated HIF-1α by inhibiting PHD2. The study suggested a new mechanism mediating the effect of miR-21 on HIF-1α and renal IRI.

Funding: Government Support - Non-U.S.
a crosstalk between gut microbiome and kidney, especially in relation with tryptophan metabolism and accumulation of uric toxins, 2) a beneficial role of AMPK, in reducing the level of uric toxins.

Funding: Private Foundation Support

TH-PO010
Suppressed Renal Mitochondrial Biogenesis After Liver Transplantation in Rats
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Background: Suppressed mitochondrial biogenesis (MB) contributes to acute kidney injury (AKI) after renal ischemia-reperfusion and sepsis. AKI occurs frequently after liver transplantation (LT), which substantially increases mortality. This study investigated whether MB is suppressed in AKI after LT.

Methods: Mice were culturally isolated from WT and PD-1 KO mice were adaptively transferred to naïve WT recipients 1 hr prior to ischemia reperfusion injury (IRI). WT and PD-1 KO Tregs were exposed to the pan-PPAR activator bezafibrate (BEZA) or vehicle (DMSO) overnight, then washed, prior to adoptive transfer in the IRI model.

Results: Suppressed MB in PD-1 KO Tregs, significantly decreased mitochondrial mass and mitochondrial membrane potential (TMRE mean fluorescence intensity: 45±10% of WT Tregs, p<0.05).

Conclusions: These results demonstrate that PD-1 must be expressed on Tregs in order for them suppress IRI and that PPAR activation ex vivo enhances subsequent Treg activity in IRI. Our findings suggest that enhanced OxPhos in Tregs promotes their ability to protect the kidney.

Funding: NIDDK Support

TH-PO011
TXNIP Is Involved in the Mitochondrial ROS Mediated NLRP3 Inflammasome Activation in Ischemia/Reperfusion Induced AKI
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Background: Renal ischemia reperfusion is a leading cause of acute kidney injury (AKI). TXNIP is a thioredoxin and ROS sensor, may have a role in NLRP3 inflammasome activation. In this study, we explored the relationship between TXNIP and NLRP3 inflammasome activation in ischemia/reperfusion induced AKI.

Methods: Ischemic mice models were built as previously reported. MitoTEMPO, a mitochondria-targeted antioxidant, was used to attenuate ROS production. Also, HK-2 cells were cultured for 8h with hypoxia-hypoglycemic plus 2 h normoxia/normal glucose incubation. SiRNAs of NLRP3 and TXNIP were applied to interrupt the signaling.

Results: In this study, we established an ischemia reperfusion induced-AKI model characterized by tubular necrosis and excessive mROS production. The renal expression of NLRP3 inflammasome, IL-1β and IL-18 were significantly increased in this animal model. However, kidney dysfunction and mitochondrial damage were attenuated obviously in NLRP3−/− mice compared with WT mice with ischemia AKI. In vitro study, oxygen-glucose deprivation injury time dependently increased the expression levels of NLRP3 inflammasome axis and TXNIP. The mitochondrial injury in damaged HK2 cells was suppressed by silence of NLRP3. Furthermore, MitoTEMPO could restore mitochondrial function and dissociate TXNIP from NLRP3 to inhibit NLRP3 inflammasome activation. Suppressed TXNIP siRNA significantly abrogated the mROS and NLRP3 inflammasome activation. TXNIP siRNA significantly abrogated the mROS and NLRP3 inflammasome activation.

Conclusions: TXNIP is involved in the mitochondrial ROS mediated NLRP3 inflammasome activation. TXNIP silencing suppresses AKI and also that this might be partially mediated by its immune modulatory effect.

Funding: Other NIH Support - National Natural Science Foundation of China

TH-PO012
PPAR Activation in Regulatory T Cells Enhances Protection from Kidney Ischemia Reperfusion Injury: Gilbert R. Kinsey, Didier Portilla, Liping Huang, Mana Yang, Michael N. Pham, Brian K. Stevens. Medicine, Univ of Virginia, Charlottesville, VA.

Background: Regulatory T cells (Tregs) are anti-inflammatory lymphocytes that protect the kidney from multiple types of injury. Our recent studies suggest that Tregs must express the surface receptor programmed death 1 (PD-1) to mediate protection. A metabolic program favoring mitochondrial oxidative phosphorylation (OxPhos) over glycolysis in Tregs is critical for Treg development and function in other models. PD-1 and peroxisome proliferator-activated receptors (PPARs) promote OxPhos in several cell types, but their role in Treg-mediated renal protection is not known.

Methods: Mitochondrial membrane potential (TMRE) and mass (Mitotracker) were assessed by flow cytometry. Tregs isolated from WT or PD-1 KO mice were adaptively transferred to naïve WT recipients 1 hr prior to ischemia reperfusion injury (IRI). WT and PD-1 KO Tregs were exposed to the pan-PPAR activator bezafibrate (BEZA) or vehicle (DMSO) overnight, then washed, prior to adoptive transfer in the IRI model.

Results: Suppressed MB in PD-1 KO Tregs, significantly decreased mitochondrial mass and mitochondrial membrane potential (TMRE mean fluorescence intensity: 45±10% of WT Tregs, p<0.05).

Conclusions: In contrast to WT Tregs, untreated PD-1 KO Tregs offered no protection from kidney IRI in terms of plasma creatinine levels, ATN scores and kidney neutrophil accumulation at 24 h of reperfusion. Treatment of WT Tregs with bezafibrate overnight significantly enhanced the ability of a sub-optimal number of Tregs to protect the kidney from IRI (24 h plasma creatinine (mg/dl): Sham 0.4±0.1; IR1 + saline 1.8±0.1; IR1 + WT Tregs (DMSO) 1.1±0.3; IR1 + WT Tregs (BEZA) 0.6±0.1*, N=7 per group; *P<0.01 vs. DMSO). Bezafibrate treatment also increased PD-1 KO Tregs with modest, but statistically significant, protective ability in the kidney IRI model.

Funding: Private Foundation Support

TH-PO013
Effects of Short Chain Fatty Acids on Inflammatory Process in Acute Kidney Injury
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Background: Short chain fatty acids (SCFAs) are the metabolic end products of normal bacterial fermentation of fibers in the large intestine. Emerging evidence suggest the role of gut-kidney crosstalk in regulating inflammatory processes. The purpose of this study was to elucidate the role of SCFAs in an acute kidney injury (AKI) in which the inflammatory process plays a major role.

Methods: Bilateral ischemia reperfusion injury (IRI) was induced in C57BL/6 mice. Sodium acetate were given to mice 30 minutes before ischemia and at the moment of reperfusion. Biochemical values, histological kidney damage and tissue inflammation were assessed. In in vitro analysis, immune cells harvested from mouse spleen were stimulated with LPS and the effect of sodium acetate on cytokine production was measured. Effects of SCFAs on T cell proliferation was also determined.

Results: Treatment with SCFAs attenuated IRI and reduced inflammation. Tubular cell apoptosis, determined by TUNEL stain also decreased by SCFAs. The anti-inflammatory effects of SCFAs persisted until IRI day 14, thereby attenuating renal fibrosis after injury. Significantly lower level of pro-inflammatory cytokines was observed in the supernatant of cells from spleen co-treated with LPS and SCFAs, compared with those treated with LPS alone. Especially, IL-12p70, major inflammatory cytokine of dendritic cells was also reduced, suggesting that SCFAs might modulate the function of dendritic subset. In addition, administration of SCFAs can dose dependently inhibit normal T cell proliferation induced by anti-CD3 Ab stimulation.

Conclusions: Thus, our findings provide evidence that the SCFAs have renoprotective effect in AKI and also that this might be partially mediated by its immune modulatory effect.

TH-PO014
The Renoprotective Effect of Abatacept in Ischemia/Reperfusion Injury in Mice
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Background: Although AKI is still an important complication in hospitalized patients, its prognosis remains poor, thus elucidation of the pathogenic mechanism and its effective treatment is urgently needed. Recently, a role for T cells in the renal ischemia/reperfusion injury (IRI) and also the renoprotective effect of abatacept, an inhibitor for CD28-CD80 T cell co-stimulation, have been reported, while its precise mechanisms are not fully understood. The purpose of this study is to determine the effect and mechanism of abatacept in the IRI model in mice.

Methods: Hemip nephrectomized mice were divided into three groups; the mice treated with ischemia/reperfusion (IRI) alone with normal saline or abatacept, and those treated with sham operation without renal ischemia as a control. Renal function (serum uro nitrogen and Cr, urine albumin excretion), pathology including T cell infiltration, expression of mRNA and protein for various parameters in the kidney were evaluated 1 day after ischemia reperfusion procedures.

Results: Compared with normal saline-treated mice, renal injury in the abactcept-treated mice were markedly attenuated both functionally and pathologically, with serum parameters improved to almost control levels. In addition, in abactcept-treated mice, apoptosis and expression of MCP-1 and PAI-1 were suppressed compared with normal saline-treated mice. Although the number of inflammatory cells and expressions of MCP-1 reduced by abatacept, the number of CD3-positive T cells, which was increased after ischemia/reperfusion, was not altered by abatacept.

Conclusions: We here showed that abatacept dramatically ameliorate IRI in mice, suggesting that it might be a new therapeutic option. It may be that abactcept, by blocking CD80-mediated signal in some cells responsible for the pathogenesis, exhibit anti-inflammatory effects, resulting in improvement of IRI, independently of T-cell-mediated acquired immune mechanisms.

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Underline represents presenting author.
TH-PO0015

Autophagy Is Activated to Protect against Kidney Injury following in Lipopolysaccharide Treatment

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Background: Sepsis, characterized by systemic inflammation, is a major cause of acute kidney injury (AKI) in hospitalized patients, especially in intensive care unit. The pathogenesis of septic AKI is poorly understood. Autophagy is a conserved, cellular catabolic pathway that plays crucial roles in cellular homeostasis including the maintenance of cellular function and viability. The regulation and role of autophagy in septic AKI remains unclear.

Methods: Lipopolysaccharide (LPS), an endotoxin, was injected in C57BL/6 mice to induce endotoxic/septic AKI. Autophagy reporter (CAG-RFP-EGFP-LC3) mice were used to monitor the dynamic changes of autophagy following LPS treatment. To determine the pathological role of autophagy, autophagy was inhibited pharmacologically with chloroquine or genetically by using proximal tubule-specific Aig7 (Autophagy gene-7) ablated mice. Blood area nitrogen (BUN) and serum creatinine were measured to evaluate renal function. HE staining and TUNEL staining were used to detect kidney injury. For in vitro study, cultured proximal tubular cells were treated with LPS in the absence or presence of chloroquine.

Results: LPS induced AKI in mice as indicated by increased in BUN and serum creatinine, and tubular injury, which was accompanied by an increase in LCHI expression. In CAG-RFP-EGFP-LC3 mice, LPS induced mRFP and EGFP-labeled autophagic puncta in renal tubular cells, further verifying the activation of autophagy. Chloroquine enhanced accumulation and P62 degradation after LPS treatment for 12 hours, which was consistent in renal tubular cells, further verifying the activation of autophagy. Chloroquine enhanced the presence of chloroquine.

Conclusions: Autophagy is activated in LPS-induced AKI and plays a renoprotective role.

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

TH-PO0016

Vascular Endothelial Growth Factor (VEGF) Contributes to Sepsis-Induced Acute Kidney Injury

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Background: Sepsis is the most common cause of acute kidney injury (AKI) in the ICU. However, we still have an incomplete understanding of the mechanisms that cause it, and consequently our therapies provide only suboptimal protection at best. Previous studies have shown that VEGF is upregulated in sepsis and plays a role in its associated morbidity and mortality. We recently found that sFlt-1, an endogenous VEGF inhibitor is upregulated in both sepsis and AKI; however, subsequently to normalize VEGF levels or neutralize its deleterious effects. We tested whether administering additional sFlt-1 protects against AKI and improves the balance between deleterious and protective cytokines and factors.

Methods: We used the cecal ligation and puncture technique (CLP) to induce sepsis. Male Sprague-Dawley rats were randomized into 4 groups: 1) Sham, 2) Sham + sFlt-1, 3) CLP, 4) CLP + sFlt-1. We administered sFlt-1 (12 μg/kg SQ) 6 hs after the CLP or sham procedure. At 24hs the rats were euthanized after collecting blood and kidneys for determination renal function and injury.

Results:

<table>
<thead>
<tr>
<th></th>
<th>VEGF pg/ml</th>
<th>SFlt-1 pg/ml</th>
<th>Creat. mg/dl</th>
<th>sKIM-1 pg/ml</th>
<th>TNF pg/ml</th>
<th>IL-6 pg/ml</th>
<th>HO-1 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAM</td>
<td>370± 10</td>
<td>30± 5</td>
<td>0.5± 0.07</td>
<td>135± 5</td>
<td>20± 0.8</td>
<td>1.8± 0.3</td>
<td>0.53± 0.01</td>
</tr>
<tr>
<td>CLP</td>
<td>790± 15*</td>
<td>330± 10*</td>
<td>2.2± 0.09</td>
<td>1900± 50*</td>
<td>265± 10*</td>
<td>13± 0.5*</td>
<td>3.0± 0.1*</td>
</tr>
<tr>
<td>CLP+SFlt-1</td>
<td>550± 10*</td>
<td>500± 15*</td>
<td>1.4± 0.1*</td>
<td>1100± 45*</td>
<td>130± 6*</td>
<td>6± 0.4*</td>
<td>7.5± 0.2*</td>
</tr>
</tbody>
</table>

Data: Mean ± SEM * p< 0.05 vs Sham /p<0.05 vs CLP

Conclusions: CLP causes AKI within 24hs and is associated with increased intra-renal expression of VEGF, IL-6, TNF and only a modest increase in renal HO-1. Administering SFlt-1 during sepsis attenuated the severity of AKI and blunted the increase in sKIM-1, VEGF and TNFα, while paradoxically causing a large increase in HO-1. Our data demonstrate a protective effect of SFlt-1 in sepsis-induced AKI, suggesting that excessive VEGF is deleterious in this condition, and that SFlt-1-associated induction of HO-1 may play a role in its beneficial actions.

Funding: NIDDK Support, Private Foundation Support

TH-PO0017

Up-Regulation of miR-98 in the Kidney with Ischemia Reperfusion Injury Protects Endothelial Cells against Apoptosis by Targeting Caspase-3

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Background: Endothelial dysfunction is one of the main pathophysiological processes involved in renal ischemia reperfusion injury. In our previous study, we screened the aberrantly expressed miRNAs in the kidney with ischemia reperfusion injury (IRI) by microarray assay, among which miR-98 was predicted to target caspase-3. The present study was performed to whether miR-98 was involved in the regulation of endothelial apoptosis under hypoxia and re-oxygenation (HR) conditions.

Methods: The level of miR-98 in IRI kidney and HR HUVECs was determined by real-time PCR. HUVECs were treated with HIF-1α siRNA to investigate the role of HIF-1α on miR-98 regulation. HUVECs were transfected with miR-98 mimics or antisense oligonucleotides against miR-98 to identify the effect of miR-98 on the expression of caspase-3, as well as the hypoxia-induced apoptosis. Finally, the relationship between miR-98 and caspase-3 was confirmed by dual-luciferase reporter assay.

Results: Both of IRI and HR induced significantly up-regulation of miR-98 in the ischemic kidney and hypoxic HUVECs, respectively (Figure 1A). HIF-1α siRNA remarkably down-regulated the expression of miR-98 in both normal and hypoxic HUVECs (Figure 1B). MiR-98 mimics significantly inhibited caspase-3 expression in HUVECs, while anti-miR-98 significantly up-regulated it (Figure 1C). Furthermore, miR-98 protected HUVECs against apoptosis induced by hypoxia, while anti-miR-98 had the reverse effect (Figure 1D). The dual-luciferase reporter assay showed that miR-98 decreased the luciferase activity when transfected with wild-type caspase-3 sequence, but not mutant sequence at the predicted binding site (Figure 1E).

Conclusions: Renal IRI induces up-regulation of miR-98 potentially dependent on HIF-1α, which protects endothelial cells against apoptosis by targeting caspase-3.

Funding: Government Support - Non-U.S.

TH-PO0018

Endothelial Caspase-8 Is a Key Mediator of Sepsis-induced Acute Kidney Injury

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Background: Acute kidney injury (AKI) is a frequent complication of gram negative sepsis. Prior work has demonstrated the importance of tumor necrosis factor (TNF) in endothiosis (LPS)-induced AKI. Caspase-8 is a key downstream effector of TNF, leading to apoptosis, and possibly facilitating inflammation. Mice genetically deficient in caspase-8 die in utero due to abnormal cardiovascular development.

Methods: To define the importance of caspase-8 activation in the endothelium in sepsis, we generated mice deficient in endothelial cell caspase-8 (EC-Casp8−/−), using Cre expressed in the endothelium under inducible control of the VE-cadherin promoter, activated after tamoxifen administration. After one week of tamoxifen followed by a washout period, mice were injected with 0.25 mg/kg E. coli LPS i.p. At baseline, EC-Casp8−/− mice showed an absence of caspase-8 staining in endothelium after tamoxifen. Mice were sacrificed at 24 h and blood collected for cytokines, BUN, and creatinine. Kidney tissue was analyzed for light microscopic and immunohistochemistry. A subset of mice underwent renal cortical blood flow measurement by laser Doppler.

Results: As expected, wildtype mice developed significant AKI with elevation of BUN and subtle pathologic injury. In contrast, EC-Casp8−/− mice had significantly less AKI (24 h BUN of 45.3 ± 11.2 vs. 114.9 ± 9.99 mg/dl, p < 0.01). LPS induced a decrease in renal cortical blood flow that was restored in EC-Casp8−/− mice (24 h renal blood flow of 1472 ± 61 perfusion units (BPU) in saline injected controls, 614 ± 89 BPU in LPS injected wildtype mice, and 1320 ± 159 BPU in LPS injected EC-Casp8−/− mice, p < 0.01). EC-Casp8−/− mice

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also had reduced evidence of pathologic injury on light microscopy (cortical injury score 0.9 ± 0.20 in LPS injected EC-Casp8⁻/⁻ mice vs. 1.7 ± 0.15 in wildtype, p < 0.05), and evidence of less vascular and tubular apoptosis on TUNEL staining.

Conclusions: These findings point to a key role of endothelial caspase-8 in sepsis-induced AKI. Further work will determine the relative role of caspase-8 in affecting renal microvascular perfusion, inflammation, and apoptosis in sepsis-induced AKI.

Funding: NIDDK Support

TH-PO019
Sepsis Reduces Kidney Function in Mice Before Hemodynamic Alterations or Clinical Symptoms Become Apparent
Jonathan Street, Yuning George Huang, Peter S. Yuen, Robert A. Star. NIDDK, Bethesda, MD.

Background: Acute kidney injury (AKI) increases the mortality and morbidity of sepsis. A rise in serum creatinine is used to detect AKI clinically and experimentally, but the slow kinetics prevents early detection of injury. To expand our understanding of the onset of AKI following sepsis we used a novel transcutaneous measurement of the plasma clearance of a fluorescent marker to directly measure GFR in near real-time.

Methods: Sepsis was induced in male CD-1 mice by cecal ligation and puncture (CLP). Blood pressure, heart rate, and activity/locomotion were simultaneously monitored by an implanted telemetry device. FITC-Sinistrin was injected at 0 and 90 min after surgery enabling GFR to be monitored for 5 hours via transcutaneous fluorescence, measured by a miniaturized fluorimeter attached to the mouse back.

Results: Log transformation of FITC-Sinistrin fluorescence decay allowed easy identification of when single pool kinetics applied, permitting calculation of GFR. GFR following CLP was similar to baseline during the first hour. During the second hour GFR fell by 30%, and dropped to 20% of baseline by 5 hours (p<0.01). In contrast, mean arterial pressure, and heart rate were stable immediately following CLP, but then began to decrease, and were statistically significantly different from sham 3, and 4 hours later, respectively (p<0.01). Activity/locomotion began to decline in the second hour, and was significantly different from sham 4 hours after CLP (p<0.01).

Conclusions: Transcutaneous fluorescence measurement of plasma clearance longitudinally enables greater temporal resolution in measured GFR than prior approaches, revealing novel pathophysiology during early AKI. GFR was initially stable after sepsis surgery, then fell rapidly 2 hours later. The fall in GFR preceded hemodynamic alterations and the appearance of clinical symptoms such as reduced activity.

Funding: NIDDK Support

TH-PO020
Urinary AIM/CDS Interacts with Kidney Injury Molecule-1 (KIM-1) and Promotes Recovery from Acute Kidney Injury via Enhancing Intraluminal Urinary AIM/CD5 Interacts with Kidney Injury Molecule-1 (KIM-1) and TH-PO020

**Background:** Acute kidney injury (AKI) is associated with prolonged hospitalization and high mortality, and may predispose patients to chronic kidney disease. To date, no effective treatments have been established for AKI. The apoptosis inhibitor of macrophage (AIM; also called CDS1) protein is a circulating protein that associates with IgM pentamers in blood, which protects AIM from renal excretion and maintains high levels of AIM (approximately 5 mg/mL in humans and mice) in blood.

**Methods:** By in vivo studies using AKI mouse models on a wild-type and AIM-deficient background, as well as in vitro experiments including phagocytosis assay focusing on the functional relationship between AIM and kidney injury molecule-1 (KIM-1). We here present that AIM is a ligand of KIM-1 and promotes prompt clearance of pathogenic dead cell debris by tubular epithelial cells, which is crucial for overall recovery from AKI.

**Results:** The blood AIM dissociates from IgM upon AKI attack and excreted in urine in AKI patients and mice. The urinary AIM accumulates on intratubular dead cell debris. The accumulated AIM binds to KIM-1 on injured tubular epithelial cells and induces the phagocytic removal of the debris by epithelial cells, facilitating kidney tissue repair. When subjected to ischemia/reperfusion-induced AKI, AIM-deficient mice exhibit abrogated bacteremia during sepsis and markedly higher mortality due to progressive renal dysfunction than wild-type mice. AIM administration promotes the rapid removal of the debris, thereby ameliorating AKI in both AIM-deficient and wild-type mice.

**Conclusions:** Our study demonstrates that the AIM/KIM-1 cooperation efficiently promotes recovery from acute kidney injury through rapid clearance of intraluminal debris. These findings could be the basis for novel AKI therapies.

Funding: Government Support - Non-U.S.

TH-PO021
Renal Handling of Circulating and Renal Synthesized Hepcidin and Its Protective Effects against Hemoglobin-Mediated Kidney Injury

**Background:** In multiple clinical observational studies it has been demonstrated that increased urinary hepcidin levels are associated with reduced risk of developing acute kidney injury (AKI) due to hemolysis in cardiac surgery patients. This study aimed to get more insight in renal hepcidin handling and its potential protective effects against heme-mediated AKI.

**Methods:** C57Bl/6 mice were treated with i) a single i.p. dose of 10 µg human hepcidin-25 (hhep25) to study renal handling of systemic hepcidin, ii) a single i.v. dose of 5 mg hemoglobin (Hb) to induce AKI, and iii) Hb combined with hhep25 to evaluate the protective effects of hhep25 on Hb-mediated kidney injury.

**Results:** Systemic hhep25 was rapidly cleared from plasma and excruted to urine. In addition to hhep25, we also detected the smaller isoforms hhep22 and hhep20 in urine, but not in plasma, showing that hhep25 is degraded in the tubular lumen. Urine hhep25 was 20-fold increased in megalin deficient mice compared to control (p<0.05) and immunofluorescence staining showed that hepcidin was present in tubules expressing megalin, but not in megalin-deficient tubules, demonstrating that megalin is responsible for hhep25 uptake in the proximal tubules. Administration of hhep25 simultaneously or 4h after Hb injection in wildtype mice significantly attenuated the Hb-induced rise in urinary NGAL and KIM1 levels, and renal IL6 and NGAL mRNA expression. Interestingly, simultaneous administration of Hb and hhep25, but not Hb or hhep25 alone, resulted in an increase in renal H-ferritin mRNA expression (15 fold, p<0.05). Administration of hhep25 to Hb-treated mice reduced renal mRNA expression of HO-1, DMT1, H-ferritin and L-ferritin (all p<0.05), possibly reflecting the mechanisms by which hepcidin exerts its protective effects.

**Conclusions:** Systemic hepcidin is filtered to the urine, partly reabsorbed via megalin in the proximal tubules and degraded in the tubular lumen. Moreover, our data suggest that both systemically delivered hepcidin and locally produced hepcidin are involved in renal protection against heme-induced AKI.

TH-PO022
The Lungs in Mice with Acute Kidney Injury Have an Exuberant Inflammatory Response to Endotoxin
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**Background:** Sepsis occurs in 40% of patients after the diagnosis of acute kidney injury (AKI) that may be related to impaired immune function. We sought to determine immune function specifically in the lungs in mice with AKI.

**Methods:** AKI was induced by bilateral renal pedicle clamping. Lung immune function was assessed by intrathoracic instillation of either endotoxin (LPS) or Pseudomonas bacteria to induce pneumonia.

**Results:** Intratracheal LPS was administered 4 hours or 7 days after Sham or AKI. 4 hours after intratracheal LPS, lung inflammation as judged by bronchoalveolar fluid TNF, lung myeloperoxidase (MPO) activity (a marker of lung neutrophils), and lung CXCL1 (a neutrophil chemokine) was greater after AKI+IT LPS versus Sham+IT LPS in both the 4 hour and 7 day group (P<0.05 for all endpoints n=4). To determine the role of alveolar macrophages, alveolar macrophages were recovered by bronchoalveolar lavage 4 hours after Sham or AKI, placed in culture, and exposed to endotoxin. Media TNF-α was significantly higher in alveolar macrophages from AKI mice compared to control (p<0.05) after induction of pneumonia, blood cultures were 0 colony forming units (CFU) in Sham and 61 CFU in AKI (n=10); notably, 0% of Sham were bacteremic (n=0 of 10) and 60% of AKI were bacteremic (n=6 of 10) at 7 days after induction of pneumonia, blood cultures were 0 colony forming units (CFU) in Sham and 12 CFU in AKI (n=10); notably, 0% of Sham were bacteremic (n=0 of 10) and 70% of AKI were bacteremic (n=7 of 10). We found that in mice with AKI, the lung immune response to bacteria or gram negative bacteria is characterized by an exuberant inflammatory response which leads to bacteremia during pneumonia.

**Funding:** Other NHLBI Support - NHLBI
Inhibition of MEK/ERK by Trametinib Attenuates Sepsis-Induced Systemic Inflammation and Multi-Organ Injury in Mice

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Background: MEK/ERK signaling is an essential component of the innate immune response in sepsis. We previously demonstrated that a potent and specific inhibitor of MEK1/2, trametinib, prevents endotoxin-induced renal injury in mice. Our goal was to further assess the efficacy of trametinib in a more clinically relevant model of sepsis induced by cecal ligation and puncture (CLP) in mice.

Methods: Male C57BL/6 mice (40 weeks of age) were subjected to CLP, and trametinib (1 mg/kg, i.p.) was administered at 6 h post-CLP. Serum cytokine levels were determined using a Luminex-based multiplex assay. Standard assays were used to measure clinical markers of organ/cellular injury including serum creatinine (SCr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), creatinine kinase (CK), and lactate dehydrogenase (LDH) in the serum. Renal microvascular perfusion was evaluated by intravital microscopy. Transcript levels of tubular injury markers and pro-inflammatory cytokines in the renal cortex were determined by qPCR.

Results: Delayed trametinib administration partially attenuated increases in circulating pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, GM-CSF) and development of hypothermia at 18 h post-CLP. In addition, MEK/ERK inhibition restored SCr to baseline levels and reduced other markers of organ/cellular injury (serum ALT, CK, LDH) in CLP animals. In the kidney, trametinib completely reversed the early deficits in peritubular capillary perfusion and decreased mRNA expression of tubular injury markers including KIM-1, NGAL, and HO-1. MEK/ERK blockade also attenuated CLP-mediated up-regulation of cytokines (TNF-α, IL-1β, IL-6) in the renal cortex.

Conclusions: These data reveal that the MEK/ERK inhibitor trametinib attenuates systemic inflammation and multi-organ injury in a clinically relevant model of sepsis, even with delayed administration. Since trametinib is FDA approved, this drug may represent a readily translatable approach to limit organ injury in sepsis.

Funding: Other NIH Support - NIGMS Support, Veterans Administration Support

TH-PO024

Chemokine Receptor 5 Blockade Modulates Inflammation and Immunity in Renal Ischemic Reperfusion Injury

Kyang Don Yoo, 1 Hajeong Lee, 1 Ran-hui Cha, 1 Jung Pyo Lee, 1 Yon Su Kim, 1 Seung Hee Yang. 1 Seoul National Univ College of Medicine; 2National Medical Center; 3Seoul National Univ Kidney Research Inst.

Background: The CC chemokine receptor (CCR5) is an important regulator of macrophage trafficking in the kidney in response to inflammation and immunity. Therefore, we investigated a role of CCR5 in the pathogenesis of experimental ischemic reperfusion injury (IRI).

Methods: Bilateral renal artery pedicles clamping for 30 min followed by reperfusion was performed on B6 wild type and CCR5 KO mice. We performed adoptive transfer of LPS treated RAW cells following depletion of macrophage by liposome chloride (LMC) in mice.

Results: CCR5 KO mice showed less aggravated IRI in terms of the apoptosis of tubular epithelial cells and creatinine compared to B6 wild type. CCR5 deficiency decreased mRNA expressions of pro-inflammatory cytokines but increased mRNA expressions of anti-inflammatory cytokines. CXCR3 positivity in CD11b+ cells and NOS were attenuated in CCR5 KO mice compared to that in B6 wild type mice. On the contrary, the CCR5 KO mice showed increased numbers of Arg1- and CD206-expressing macrophages. LC-treated wild type mice showed severe injury compared to CCR5 KO mice aftertransfer of M1 macrophage. Adoptive transfer of LPS-treated RAW cells, which constitutively express NOS, reverses the functional protection against IRI only in wild-type, not CCR5 KO mice. When CCR5 was knocked out in macrophages, bone marrow-derived macrophages showed M2 macrophage activation. The migration of Bone marrow-derived macrophage from wild-type mice towardsprimary tubular epithelial cell with CCR5 is increased. Moreover, blockade of CCR5 inhibited migration of macrophages. Renal tissue of patients with previous graft function frequently contained CCR5 cells, and the number of these cells tended to positively correlate with acute tubular necrosis severity.

Conclusions: These findings show that CCR5 deficiency favors M2 macrophages activation and provide a potential strategy for treating acute kidney injury through blocking CCR5.

TH-PO025

Early Activation of Inflammamome in Acute Kidney Injury After Renal Sympathetic Denervation in Pig

Il Younget Min Jung Kim, 1 Joo Hui Kim, 1 Dong Won Lee, 1 Soo Bong Lee, 2 Joo Min Jung, 2 Jong Min Park, 2 woo Jin Jung, 2 Harin Rhee, 2 Sang Heon Lee, 2 Eun Young Seong, 2 Ihm Soo Kwak. 2 Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea; 3Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea.

Background: Renal sympathetic denervation (RDN) is available and implemented as a strategy for the treatment of resistant hypertension. In the aspect of chronic safety, renal function, as assessed by serum creatinine, eGFR(MRD), and cystatin C was reported to be unchanged from baseline at 6 months. We investigated whether RDN might cause subtle inflammation and subclinical damage in the early phase of acute kidney injury (AKI).

Methods: Female pigs were divided into 6 groups; normal control (group A), Sham-operation control (group B), contrast media control (group C), and renal sympathetic denervation groups subdivided into 3 groups according to the time of sacrifice, immediately (group D), 1 week later (group E), and 2 weeks later (group F) after RDN. We checked IL-1α, IL-6, TNF-α, cystatin C, caspase-1, ASC, and NLRP3 as early biomarkers of inflammation and AKI.

Results: There were no significant changes in group B and C compared to group A. BUN, serum Na, K, Cl, CRP, urine protein/creatinine ratio, and urine albumin/creatinine ratio showed no significant changes between groups. Serum creatinine and cystatin C were increased from 1st week after RDN. Serum LDH was increased immediately after RDN, and then decreased at 2nd week. IL-1α, IL-6, and TNF-α were increased immediately after RDN, and then decreased at 2nd week. ASC and caspase-1 and ASC expression were increased from 1st week after RDN, and decreased at 2nd week after RDN. However NLRP3 expression showed no significant changes between groups.

Conclusions: RDN did not cause clinically significant damages on kidneys. However, RDN can induce the activation of pro-inflammatory cytokines, caspase-1 and then cause transient and self-limited acute kidney injury.
modulated ischemic AKI. Serum creatinine (Scr) was measured to assess kidney function and histology was studied. DNT cells from human peripheral blood was studied to lay the foundation for translational studies.

**Results:** Murine kidney DNT cell significantly (p<0.001) inhibited proliferation of CD4 T cell in vitro, using CD4+CD25− T cells as controls. Transfer of DNT cells significantly (p<0.001) improved kidney function (Scr=1.4±0.4) following IRI (n=3) in contrast with WT mice (Scr=1.3±0.4). Histological evaluation showed significantly reduced tubular necrosis (p<0.03) in mice that received DNT cells. This protection was lost in mice that received DNT cells with IL-10 antibody (Scr=1.0±0.01). DNT cells were found in normal subjects (n=3, 3.1±0.4 %) and higher in renal carcinoma patients (n=5, 3.3±0.1%, p<0.001).

**Conclusions:** Kidney resident DNT cells suppress CD4 T cell proliferation in vitro and protect WT mice from IR-induced AKI via IL-10. Furthermore, DNT cells are found in human peripheral blood and increase with kidney cancer. Future studies are warranted to better understand immunosuppressive properties of DNT cells and their clinical significance in AKI and other kidney diseases.

**Funding:** NIDDK Support

**TH-PO028**

**Interleukin-37 Diminishes the Inflammatory Response of Ischemia/Reperfusion-Susceptible Renal Tubular Epithelial Cells**

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**Background:** Renal ischemia and subsequent reperfusion (IR) induces excessive local inflammatory and fibrotic injury and renal dysfunction. Therapeutic strategies aiming to dampen inflammation might therefore provide new opportunities to diminish renal IR injury. The human cytokine Interleukin (IL)-37 inhibits inflammation via nuclear as well as cell-surface receptors. IL37 is expressed by different cell types, including renal epithelium and circulating monocytes. Cell type-specific effects of IL37 in renal IR remain however unknown.

**Methods:** Primary tubular epithelial cells (PTECs) and bone marrow-derived macrophages (BMDMs) were isolated from WT and transgenic mice expressing human IL37 (hIL37tg) and culture. In vitro, cells were pretreated with different concentrations of recombinant human IL37 protein (rhIL37) or vehicle and subsequently stimulated with LPS for 4 or 24hrs. Cytokine release (ELISA) and mRNA expression (quantitative RT-PCR) were determined.

**Results:** After 24hrs of LPS stimulation, the release of both CXCL1 and IL6 was reduced in hIL37tg PTECs as compared to WT PTECs. This was preceded by diminished CXCL1 and IL6 mRNA levels after 4hrs of LPS stimulation. rhIL37 pretreatment of WT PTECs reduced CXCL1 mRNA, but not IL6 mRNA expression after 4hrs. In hIL37tg BMDMs CXCL1 mRNA levels and protein release were both reduced after 4 and 24hrs of LPS stimulation, as compared to WT BMDMs. IL6 release was only diminished after 24hrs, whereas IL6 mRNA levels did not significantly differ. In contrast, rhIL37 pretreatment of WT BMDMs reduced IL6 mRNA expression after 24hrs of LPS stimulation, but neither affected CXCL1 nor IL6 release.

**Conclusions:** Our data indicate that both endogenous and exogenous IL37 diminishes inflammatory responses of renal epithelial cells and macrophages, both central players in the pathophysiology of renal IR injury.

**Funding:** NIDDK Support

**TH-PO029**

**Compensatory Induction of IL-17 during NKT Cell Deficient Rats Fed High Salt Diet**

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**Background:** Surviving AKI1 patients have a higher risk for developing chronic kidney disease (CKD) but the mechanism of AKI to CKD transition is unclear. Previous studies have shown inhibition of T-cell activity by mycophenolate blocked the proteinuria, fibrosis and hypertension in post-ischemic rats fed a high dietary salt and that T17 helper cells are dramatically increased in post ischemic rats on high salt diet. Therefore, we hypothesized that T-cell deficient athymic rats would manifest an attenuated salt sensitive progression of CKD following AKI.

**Methods:** Athymic rats (Foxn1rnu−/rnu−) or heterozygote control euthymic rats (Foxn1rnu−/+) were subjected to a model of AKI-to-CKD in which rats are allowed to recover from unilateral IR (40 min ischemia) for 5 weeks on standard salt diet (0.4% NaCl) and then subjected to contralateral UNX and 4% NaCl diet for 4 additional weeks.

**Results:** As expected we observed that MMF treatment in control-ethymic rats (day 35-63) lead to significant reduction in renal CD4+ inflammation (35±4.8, t0.05), Th-17 cells (78±5.2, p0.05%) and reduced fibrosis by 50% vs vehicle. T-cell deficient athymic rats showed an unexpected and similar level of renal fibrosis as compared to euthymic rats and MMF treatment did not alter this effect. The increased fibrosis could not be explained by enhanced initial injury in athymic vs euthymic rats, which was similar in 24 hours following bilateral I/R, indicating that athymic rats may operate an alternative pro-inflammatory pathway in the absence of T cells. Interestingly, athymic rats showed an increased population of IL-17+ NKT cells (126018±12656) as compared to euthymic rats (63892±12656), which was not sensitive to MMF treatment.

**Conclusions:** Taken together these data suggest that in the absence of T cells, compensatory NKT cell activity may mediate cytokine production and participate in salt diet induced fibrosis post AKI.

**Funding:** NIDDK Support

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

**Underline represents presenting author.**

**96A**

**TH-PO030**

**Chronic Kidney Disease and the Chromogranin A Pathway: From Pathogenic Molecular to Disease**

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**Background:** The chromogranin A gene (CHGA) variants are associated with autonomic blood pressure regulation and hypertension in the majority population, as well as hypertensive renal disease in African Americans. CHGA protein is the master switch for nucleation of catecholamine granules in neuroendocrine tissue. In this study we address the effect of CHGA in acute kidney injury.

**Methods:** Experimental chronic kidney disease (5/6 nephrectomized) mouse models were used to study susceptibility of mouse strains (wild type and Chga−/−) to kidney injury. Bisected issues of sham and nephrectomized mice were examined by immunohistochemistry. Kidney sections were stained using chromogranin A (anti CHGA antibody, 1:200) and different immunofluorescent approaches. The expression of CHGA was also profiled for genome-wide expression using NimbleGen microarray. The murine glomerular function was measured by LC-mass spectrometry based assay for creatinine. Array data was analyzed for differentially expressed genes using Bioconductor. The differentially regulated genes were analyzed by GO enrichment analysis using DAVID Bioinformatics Resources. The molecular function and biological process terminologies in the PANTHER database were considered during the GO analysis; the P-value cutoff was set at 0.01. The human study involved twin data set of European ancestry 129 monoyzotic and 58 dizygotic twin pairs.

**Results:** A significantly greater loss of GFR function was observed in nephrectomized mice expressing CHGA as compared to Chga knock out mice. Kidney injury resulted in far greater response of increased plasma CHGA, azotemia, catecholamine and systolic blood pressure in Chga−/− mice. Kidney biopsy also showed greater pathology and interstitial fibrosis associated with nephrectomized Chga−/− mice. In nephrectomized mice, the differentially up regulated genes in the Chga−/− strain include panoply of mitochondrial genes, oxidoreductases and extracellular matrix proteins, wound healing genes and transcription factors. In humans the plasma CHGA concentration has an inverse relationship with plasma creatinine.

**Conclusions:** CHGA expression is inversely correlated to glomerular function and is detrimental to kidney injury outcomes.

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

**TH-PO031**

**Inhibition of avß5 Integrin Protects against Renal Ischemia-Reperfusion Injury**

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**Background:** Ischemia-reperfusion injury is a leading cause of acute kidney injury (AKI), which is a common clinical complication that lacks effective therapies and can lead to life-threatening renal failure and progression to chronic kidney disease. Inhibiting avß5, a receptor for RGD-containing extracellular matrix proteins, has been suggested to be important in acute injury settings including septic shock and acute lung injury. To examine the in vivo function of this receptor in AKI we tested the impact of inhibiting avß5 in a rat model of renal ischemia reperfusion injury (IRI).

**Methods:** IRI was induced by removing the right kidney and clamping the renal artery of the left kidney for 30 minutes. Rats were administered avß5-blocking antibody or an isotype control antibody subcutaneously at various doses and times prior to ischemia. C57BL/6N rats were pretreated with different concentrations of avß5 (havcr1) antibody-treatment significantly reduced serum creatinine levels with a single administration 6 hours prior to ischemia. avß5 inhibition led to significantly reduced renal damage by 3 days after ischemia as assessed by histopathological scoring of fixed kidneys. Antibody blockade of avß5 also resulted in significantly fewer apoptotic tubular cells, and significant reductions in renal KIM-1 and serum MCP-1 levels in IRI rats. Global gene expression profiling of kidneys identified several established injury markers that were impacted by avß5 inhibition including reduced levels of haver1 (KM1-1), iNOS and adamas1 transcripts after ischemia. Finally, a single dose of avß5 antibody 8 hours post-ischemia was shown to significantly reduce creatinine levels at 24 hours, suggesting protection from injury with therapeutic dosing is possible.

**Conclusions:** This study identifies a novel role for avß5 integrin biology in the pathogenesis of renal ischemia-reperfusion injury. Inhibition of avß5 integrin with antibody administration may hold therapeutic promise for the treatment of acute kidney injury.

**Funding:** Pharmaceutical Company Support - Biogen
or an isotope control was administered 6, 12 or 18 hours pre-ischaemia or 4, 8 or 12 hours post-ischaemia. Serum creatinine (Scr) was evaluated 24, 48 and 72 hours post-injury and gene expression and histology in kidneys evaluated at 72 hours.

**Results:** 3G9 treatment significantly reduced Scr levels at all time points evaluated whether administered pre- or post-induction of ischaemia. Equivalent effects were detected when 3G9 was administered 12, 18 or 12 hours pre-ischaemia and maximal effects observed when administered 4 to 8 hours post-ischaemia. 3G9 reduced kidney damage as assessed by histopathological scoring of tubular necrosis, dilatation and casts. Gene expression profiling of kidneys identified transcripts impacted by avβ6 inhibition suggesting promotion of repair. This included reduced levels of cell death and necroptosis markers such as GADD45, AIF3, and RIP3K, and an upregulated cell growth signature including cyclins, cyclin-dependent kinases, and epidermal growth factor.

**Conclusions:** The combined role of avβ6 in regulating IRI and fibrosis highlight the potential for therapeutic intervention with BG00011 in acute kidney injury, a common clinical complication that lacks effective therapies and can lead to the development and progression of chronic kidney disease.

**Funding:** Pharmaceutical Company Support - Biogen Idec

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**TH-PO035**

Suramin Protects from Cisplatin-Induced Acute Kidney Injury

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**Background:** Acute kidney injury (AKI) resulting from cisplatin administration remains an obstacle in chemotherapy treatments. Suramin, an FDA approved drug for the treatment of trypanosomiasis, has been previously shown to speed recovery from multiple models of AKI and chronic kidney disease and is currently in clinical trials for combination therapy with cisplatin for the treatment of lung cancer.

**Methods:** In this study we examined the efficacy of the prolylhydroxamate use of suramin in a murine model of cisplatin-induced AKI. Nine-week old male mice were pre-treated with 10mg/kg suramin via tail vein injection 72h prior to cisplatin administration (20mg/kg, ip) and sacrificed 72h after cisplatin treatment.

**Results:** Our data indicate that pre-treatment with suramin protects the kidney from cisplatin injury according to markers of kidney function (BUN, Serum Creatinine), kidney injury (urinary Kim-1, and NGAL), Assessment of renal histology also indicated that suramin pre-treatment significantly protects mice from cisplatin-induced injury. The expression of many pro-inflammatory chemokines and cytokines (TNF-α, IL-1β, IL-6, MCP-1, and CXCL-1) involved in the response of cisplatin-induce AKI were examined via qRT-PCR. Mice pre-treated with suramin had significantly reduced expression of all the above inflammatory markers. Western blot analysis indicated that mice pre-treated with suramin were protected from death receptor-mediated apoptosis. We also utilized the same experimental design using 10-month old FVB mice expressing mutant KRAS driven lung tumors. The assessment of both renal and pulmonary histology and markers of kidney function (BUN and Serum Creatinine) indicate that suramin protects mice from cisplatin-induced kidney injury and more importantly does not inhibit cisplatin’s anti-tumor efficacy.

**Conclusions:** Thus, data presented suggest that suramin shows great potential as a renoprotective agent for the treatment and prevention of cisplatin-induced AKI.

**Funding:** NIDDK Support

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**TH-PO034**

ATIII Attenuates Acute Kidney Injury following Acute Severe Pancreatitis

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**Background:** Antithrombin III (ATIII) is the major anti-coagulation molecule in vivo and has anti-inflammatory effects. Acute kidney injury (AKI) is the most common organ failure following acute severe pancreatitis (ASP), which often results in death. Herein, we hypothesized that ATIII could protect against AKI following ASP.

**Methods:** Acute severe pancreatitis was induced in rats by retrograde pancreatic duct infusion of 3.5% sodium taurocholate. Intravenous injection of ATIII (500mg/kg) was carried out 30 min before induction of ASP. Animals were sacrificed 24 hours later. Renal tubular injury and renal function were assessed. Serum amylase, glutamic-pyruvate transaminase (ALT), and serum Ca2+ were also measured.

**Results:** Renal tubular injury scores were increased from 0.5±0.2 in control rats to 4.2±0.5 in the ASP group and to 2.7±0.3 in the ASP+ATIII group 24 hours after ASP induction (P<0.05, one-way ANOVA, n=5). Serum creatinine was increased from 23.2±1.6 mmol/L to 92.3±8.6 mmol/L in the ASP group and to 34.8±3.2 mmol/L in the ASP+ATIII group (P<0.05, n=6). Blood urea nitrogen was increased from 5.2±0.3 mmol/L to 47.0±1.3 mmol/L in the ASP group and to 30.0±1.9 mmol/L in the ASP+ATIII group (P<0.05, n=6).

There were no significant differences between ASP group and ASP+ATIII group in serum amylase, ALT, serum Ca2+ and pancreatic injury.

**Conclusions:** ATIII ameliorates AKI following ASP.

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

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**TH-PO036**

Caspase-3 siRNA and CHBP Ameliorate Renal Ischemia Reperfusion Injury in Mice

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**Background:** Ischemia/reperfusion (IR) is a main cause of acute kidney injury (AKI). Up-regulated caspase-3, a key enzyme involved in inflammation and apoptosis, was revealed in renal IR injury and reversed by a novel cyclic helix B peptide (CHBP), derived from erythropoietin. Here, caspase-3 small interfering RNA (C3siRNA) and/or CHBP were applied in a mouse model to further explore underlying mechanisms.

**Methods:** Bilateral renal occlusion for 30 min was performed in male C57BL/6 mice and followed by 48 h reperfusion. 0.03 mg/kg C3siRNA or its negative control (NC) was injected intravenously 2 h before ischemia. 24 mmol/kg CHBP was injected intraperitoneally post reperfusion. Serum and kidney samples were collected for renal function, histology and molecular biology analyses.

**Results:** Serum creatinine and tubulointerstitial damage (TID) score were increased by IR injury, but decreased by C3siRNA and/or CHBP (P<0.01). In addition, the expression of 17-kD active caspase-3, active caspase-3+ cells and apoptotic cells were raised by IR injury, but reduced by C3siRNA and/or CHBP (P<0.01). More interestingly, there was a significant reduction in TID in the kidneys treated with both C3siRNA and CHBP compared with its sole treatment.

**Conclusions:** TRPM7 was significantly correlated with LDLH and HMGB1; and serum creatinine, blood urea nitrogen, inflammation, apoptosis and tubulointerstitial damage in these in vitro and/or in vivo models.

**Funding:** THPT7 is involved in renal IR-related injuries and CHBP renoprotection, which might be a biomarker for diagnosis and intervention.

**Funding:** Government Support - Non-U.S.
Conclusions: C3siRNA and CHBP ameliorated IR injury, both of which might have certain synergetic effects. CHBP might reduce active caspase-3, subsequently affects apoptosis, and improve renal function and structure.

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

**TH-PO037**

Resveratrol Ameliorates Contrast-Induced Nephropathy Through Activation of SIRT1-PGC-1α-FoxO1 Signaling in Murine Model

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**Background:** Contrast-induced nephropathy (CIN) is a common cause of acute kidney injury among patients, but the pathogenesis has not been clearly defined. We aimed to investigate whether upregulation of sunitin (SIRT1)-dependent signaling by resveratrol could attenuate CIN through modulation of renal oxidative stress and tubular apoptosis.

**Methods:** CIN were established in vivo and vitro models by administration of iohexol in male C57BL/6J mice and rat tubular cells (NRK-52E). Resveratrol (30mg/kg in vivo/10 and 50µM in vitro) was treated with iohexol or saline as an activator of SIRT1. SIRT1 expression was reduced by siRNA treatment in vitro study. Tubular cell injury caused by iohexol was examined.

**Results:** Increase of serum creatinine and tubular injury measured by histologic examinations after iohexol administration was significantly attenuated by resveratrol treatment (creatinine 1.79±0.48 vs 0.72±0.59 mg/dL, p<0.001). It resulted in reduction of oxidative stress which were demonstrated by reduced malondialdehyde (MDA) levels and increased Mn superoxide dismutase (SOD). Increased apoptosis in CIN was also reduced by resveratrol treatment examined with caspase 3 expression and TUNEL staining. Attenuation of pro-inflammatory cytokines and the HIF-1α - HO-1 cascade.

**Conclusions:** Our results suggest that resveratrol attenuates CIN by modulation of renal oxidative stress and apoptosis through the activation of SIRT1-PGC-1α-FoxO1 signaling, and SIRT1 provides a potential therapeutic target to minimize CIN.

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

**TH-PO038**

Loss of Alpha(E)-Catenin-Fscn2 Signaling Increases Cisplatin-Induced Apoptosis in Aged Kidney

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**Background:** Aging patients are highly susceptible to acute kidney injury. Previous studies in our laboratory demonstrated a dramatic decrease of α(E)-catenin expression in proximal tubular epithelium in the aged kidney.

**Methods:** We created stable α(E)-catenin knock-down NRK-52E (C2) cells (NT3 is the non-targeted control) and observed a significant loss of viability in C2 cells as compared with NT3 cells after cisplatin challenge. In this study, we aimed to delineate the pathway by which loss of α(E)-catenin increases cisplatin injury.

**Results:** Increased caspase-8 and -9 activation, BID cleavage and cytochrome C release were observed in C2 cells after cisplatin treatment. Blocking apoptosis, using caspase-8 or -9 inhibitors, completely abolishes the increased susceptibility of C2 cells. Interestingly, the expression of fascin actin bundling protein 2 (Fscn2) is decreased in α(E)-catenin knock-down cells. Re-expression of Fscn2 in C2 cells attenuates the increased apoptosis following cisplatin challenge. Furthermore, our in vivo study showed a significant increase in serum creatinine, KIM-1 and in situ apoptosis level at 72 hr after a single dose of cisplatin in 24-month-old rats, but not in 4-month-old rats. The expression of Fscn2 was also decreased in aged kidney.

**Conclusions:** Taken together, these results suggest that loss of α(E)-catenin-Fscn2 signaling increases cisplatin-induced apoptosis in aged kidney.

**Funding:** Other NIH Support - Research reported in this publication was supported by the National Institute of Aging of the National Institutes of Health under award number ROI AG034154.

**TH-PO039**

Adenosine A1 Receptors Alleviate Cisplatin-Mediated Acute Kidney Injury

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**Background:** We have observed the incidence of acute kidney injury (AKI) in 479 lung cancer patients using platinum is 10.39% and AKI is the independent risk factor of in-hospital mortality. The results of previous studies about adenosine A1 receptors (A1ARs) in cisplatin-mediated AKI are controversial. In this study, we aimed to investigate the role of A1ARs in AKI induced by cisplatin and the involvement of mitochondria-mediated cell apoptosis.

**Methods:** 8- to 10-week-old male C57BL/6J wild type (WT) and A1AR-/- mice were given a single intraperitoneal injection of either vehicle (saline) or cisplatin (25mg/kg, 1mg/ml). Weight, blood pressure and heart rate were monitored. Mice were euthanized 24h/72h after cisplatin. Blood samples were collected to measure serum creatinine and urea. Acute tubular necrosis assessments were done through PAS staining. Western Blot and RT-PCR were used to study the expression change of CD73, A1AR and mitochondria-mediated apoptosis markers.

**Results:** 1) 72h after cisplatin injection, serum creatinine and urea were substantially elevated (85.9±65.9 vs 8.5±1.1 mmol/L, 63.3±33.84 vs 6.7±1.24 mmol/L, p<0.05) in WT mice which suggested AKI happened. The systolic blood pressure, heart rate and body weight remarkably declined (64±4 mmHg vs 105±2± mmHg, 412±16 bpm vs 721±48 bpm, p<0.05) compared with control mice. 2) 24h after cisplatin, the expression of A1AR in WT mice was significantly higher than control mice. Cisplatin also induced the expression of A2B AR and Bax, targets of mitochondria-mediated apoptosis. 3) Compared with WT mice, serum creatinine elevation and tubular injury were more obvious in A1AR-/- mice (25.8±19.28 vs 11.4±0.43 mmol/L, p<0.05). But contrast to WT mice, A2B AR and Bax expression were not elevated in A1AR-/- mice. The expression of CD73 was up-regulated significantly.

**Conclusions:** A1AR may be involved in cisplatin-mediated AKI and could alleviate the cisplatin nephrotoxicity. But it doesn’t work through mitochondria-mediated apoptosis pathway. A1AR agonists are potential to protect the kidney in cisplatin-mediated AKI.

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

**TH-PO040**

Testosterone Upregulates Heme-Oxygenase-1 – A Potential Mechanism to Protect against Acute Kidney Injury

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**Background:** Sex hormones modulate renal injury during ischemia-reperfusion-induced AKI. We reported that testosterone is reduced during I/R-AKI and that supplementing this hormone ameliorates the renal injury. This protective effect is dependent on the chronicity of therapy and dose (chronic exposure and high doses may exacerbate injury). In this study, we investigated a possible mechanism by which acute administration of low-dose testosterone propionate (A-LD-TP) can protect against I/R-AKI. Because we found that A-LD-TP increased hoxypox inducing factor-1α (HIF-1α), which in turn induces heme oxygenase-1 (HO-1), we hypothesized that the protective effect of A-LD-TP during I/R-AKI is mediated by HIF-1α dependent upregulation of HO-1.

**Methods:** SD rats were randomized into 4 groups; 1) Sham, 2) I/R-AKI, 3) I/R-AKI+TP, 4) I/R-AKI+A-LD-TP+2-ME. I/R-AKI was induced by 40 min bilateral renal pedicle clamping. A-LD-TP was given a single intraperitoneal injection of either vehicle (saline) or cisplatin (25mg/kg, 1mg/ml). Weight, blood pressure and heart rate were monitored. Mice were euthanized 24h/72h after cisplatin. Blood samples were collected to measure serum creatinine and urea. Acute tubular necrosis assessments were done through PAS staining. Western Blot and HIF-1α expression and HO-1 expression. Acute tubular necrosis assessments were done through PAS staining. Western Blot and HIF-1α expression and HO-1 expression.

**Results:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine (mg/dl)</th>
<th>KIM-1 (pg/ml)</th>
<th>TNFα (pg/ml)</th>
<th>HIF-1α (pg/ml)</th>
<th>HO-1 (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>0.5±0.06</td>
<td>450±120</td>
<td>30±8</td>
<td>0.45±0.05</td>
<td>0.55±0.1</td>
</tr>
<tr>
<td>I/R-AKI</td>
<td>2.4±0.07*</td>
<td>4500±190*</td>
<td>190±15*</td>
<td>5.6±0.3*</td>
<td>5.8±0.3*</td>
</tr>
<tr>
<td>I/R-AKI+TP</td>
<td>1.4±0.008</td>
<td>1700±200</td>
<td>115±60</td>
<td>10.6±0.80</td>
<td>11.7±0.60</td>
</tr>
<tr>
<td>I/R-AKI+TP+2-ME</td>
<td>2.2±0.1</td>
<td>4400±350</td>
<td>175±12</td>
<td>3.95±0.4</td>
<td>6.2±0.4</td>
</tr>
</tbody>
</table>

**Conclusions:** A-LD-TP supplementation ameliorated I/R-AKI-induced renal dysfunction, inflammation and tubular injury. These beneficial changes were associated with further upregulation of HO-1. Blocking HIF-1α attenuates the cytotoxic effects correlated by A-LD-TP. This data supports the hypothesis that A-LD-TP supplementation activates the renal HIF-1α pathway and its downstream cytoprotective factor (HO-1), which protects against I/R-AKI, thus providing a potential therapeutic target.

**Funding:** Private Foundation Support
Endothelial Preconditioning Induces an Effective Immune Response That Avoids Collateral Tissue Damage

**Backround:** Endothelial preconditioning is a powerful model of renoprotection against a variety of insults. Harnessing these protective pathways has important therapeutic potential in sepsis. However, the protective molecular pathways remain unknown. Here we examined the metabolic profile of urine in response to preconditioning.

**Methods:** Mice were divided into 3 groups: control, endothelial injury (LPS 5 mg/kg ip) and preconditioning (0.25 mg/kg following by 5 mg/kg LPS). Renal injury was assessed by serum creatinine and tissue KIM1. Cecal ligation and puncture (CLP) was used to evaluate mortality and bacterial load. Tissues and sera were examined using cytokine assays, 2DGE, proteomics and metabolomics.

**Results:** Preconditioning improved survival after CLP (75% vs. 25% in non-preconditioned mice). This protection was accompanied by reduced bacterial load in solid organs (23% ± 2.0 vs 1.200 ± 52 gram; LPS). Macrophages harvested from preconditioned mice exhibited robust phagocytic activity. Preconditioning also resulted in renal protection after toxic dose LPS (mean serum creatinine 0.08 ml/dl vs. 0.40 mg/dl in non-preconditioned mice; tissue KIM1 mRNA fold changes 110 ± 2.960). 2DIGE analyses revealed upregulation of molecules required for the activation and maintenance of phagocytosis in the preconditioned group. These molecules include elastin, serum amyloid P-component, neutrophil gelatase-associated lipocalin, and complement factor B. Despite the activation of these efficient cleaning pathways, serum and tissue proinflammatory cytokine levels were broadly downregulated in preconditioned animals. Tissue metabolic analysis revealed that preconditioning increased metabolites involved in tissue repair (proline and spermidine), antimicrobial activity (itaconate) and cell death (sulfate, 3-indoxil sulfate, pseudouridine).

**Conclusions:** Preconditioning confers tissue protection and increases survival through an organized upregulation of a modified innate immune response characterized by enhanced bacterial clearing and yet lacking the proinflammatory tissue damage frequently observed with ordinary immune injury.

**Funding:** NIDDK Support

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**TH-P0042**

Myeloid Cell Specific Nr2f2 Activation Protects Elderly Mice from Acute Kidney Injury

**Background:** Transcription factor Nr2f2 confers protection against ischemia-reperfusion (IR)-induced acute kidney injury (AKI) in mice by upregulating anti-inflammatory and cytoprotective genes, but the specific cell types where Nr2f2 is working is unknown. We recently demonstrated that T cell Nr2f2 activity is a major modulator of IR-induced AKI in mice with increased T cell Nr2f2 (J Am Soc Nephrol, in press). In this study we tested the hypothesis that Nr2f2 activation in myeloid cells (neutrophils, macrophages) is protective against IR-induced AKI. We tested our hypothesis in young and elderly mice with genetic deletion of Nr2f2 inhibitor, keap1 in myeloid cells (Lysm keap1-/-).

**Methods:** Young (7-8wks) and old (32-48wks) male Lysm keap1-/- and keap1f/f control mice were used. T cell-depleted bone marrow-derived DCs (BMDC) were used to achieve bilateral kidney ischemia. Serum creatinine (Scr) was measured at 0, 24, 48 and 72h post ischemia. Histological and inflammatory changes in kidney were examined at 72h.

**Results:** We observed significantly reduced Scr levels in young (0.6±0.1 vs 1.3±0.2, p<0.02, 24h) and elderly (0.4±0.2 vs 1.3±0.3, p<0.02, 48h and 0.2±0.03 vs 0.9±0.2, p<0.02, 72h) Lysm keap1-/- mice as compared to age-matched keap1f/f mice. Histological examination of corticomedullary region of kidney tissue revealed a significantly lower necrotic debris (24±8 vs 54±3, p<0.01), regeneration (22.1±0.8 vs 41±4.0, p<0.004) and higher percent of normal tissue (53.8±15.7 vs 5.0±0.6, p<0.01) in elderly Lysm keap1-/- mice. Young Lysm keap1-/- mice did not show any significant difference in kidney histology post AKI compared to young keap1f/f mice. Cytokine analysis showed significantly (p<0.04) higher levels of TGF-β, IL-1β, IL-2, IL-6, IL-10, IL-13, IL-17 and TNF-α in elderly Lysm keap1-/- kidneys. These cytokines were comparable in young Lysm keap1-/- and keap1f/f kidneys post AKI.

**Conclusions:** These data demonstrate that enhancing Nr2f2 activity in myeloid cells can provide protection against IR-induced AKI, which is markedly enhanced in elderly mice. These findings could be exploited to identify myeloid cell oxidative stress responses as a mechanism by which elderly are more susceptible to AKI.

**Funding:** NIDDK Support

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**TH-P0043**

Sphingosine-1-Phosphate-3 Deficient Dendritic Cells Modulate Splenic Responses to Ischemia-Reperfusion Injury

**Background:** The plasticity of dendritic cells (DCs) permits phenotypic modulation ex-vivo by gene expression or pharmacological agents, and these DCs can exert therapeutic effects in vivo through direct interactions with T cells or indirectly through T regulatory (Treg) cells or causing anergy. Sphingosine 1-phosphate (S1P), a sphingolipid that is the natural ligand for five G-protein coupled receptors (S1P1-5R), and S1P agonists reduced kidney ischemia-reperfusion injury (IRI) in mice. S1pr3-/- mice are protected from AKI, likely due to the induction of dendritic cells to mature. We tested the therapeutic advantage of S1pr3-deficient bone marrow-derived DC (BMDC) transfers in kidney IRI.

**Methods:** Renal injury was assessed by plasma creatinine (Pcr; mg/dl). 8-wk old C57BL/6 WT and S1pr3-/- male mice were used for generating highly pure BMDCs from wild type or S1pr3-/- precursors.

**Results:** IRI produced a rise in plasma creatinine (Pcr) in naïve mice, no cell (NC) and in mice pretreated with WT BMDCs. However, S1pr3-/- BMDC-pretreated mice were significantly protected from kidney IRI. S1pr3-/- BMDC-pretreated mice had significantly lower serum creatinine levels than NC and WT BMDC-pretreated mice. S1pr3-/- BMDC-pretreated kidneys of recipient mice showed a significant reduction in a dense fibrinoid necrosis (p<0.01) as compared to WT BMDC-pretreated mice.

**Conclusions:** S1pr3-/- BMDC-dependent protection requires CD169+ (marginal zone) macrophage-dependent CCL2/macrophage-derived-chemokine (MDC) signaling to increase Treg.

**Funding:** This work was supported by American Heart Association grant 17SDG33800168 to H. Wang and National Institute of Diabetes and Digestive and Kidney Diseases grant K12DK117315 to H. Wang.

**TH-P0044**

Spleen Plays a Critical Role in Hepcidin-Mediated Protection against Renal Ischemia-Reperfusion Injury

**Background:** We showed previously that pretreatment with hepcidin mitigates kidney injury by acting on hepatosplenic iron compartments. In these studies we observed that changes in the spleen iron content and ferroportin expression far exceeded that in the kidney and liver. We therefore hypothesized that hepcidin-mediated protection is through its immunosuppressive effect on the spleen, and that splenocytes are necessary in preventing renal injury following kidney IRI.

**Methods:** Mice (C57Bl/6, n=6-8) were splenectomized 1 week prior to treatment with saline or 50 mg of hepcidin and 24 hours later were subjected to bilateral renal IRI (26 min). In some experiments, splenocytes (1×10⁷ from 24 hour saline or hepcidin treated animals were adoptively transferred and the recipient mice were subjected to similar IRI regimen. Outcomes (renal function, injury markers, histopathology and inflammation) were examined after 24 hours of reperfusion.

**Conclusions:** We showed previously that pretreatment with hepcidin mitigates kidney injury by acting on hepatosplenic iron compartments. In these studies we observed that changes in the spleen iron content and ferroportin expression far exceeded that in the kidney and liver. We therefore hypothesized that hepcidin-mediated protection is through its immunosuppressive effect on the spleen, and that splenocytes are necessary in preventing renal injury following kidney IRI.

**Funding:** NIDDK Support

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**TH-P0045**

Endothelial Krüppel-Like Factor 4 Mediates the Protective Effect of Statins against Ischemic Acute Kidney Injury

**Background:** Endothelial cells participate in the pathophysiology of ischemic acute kidney injury (AKI) by increasing the expression of cell adhesion molecules and by recruiting inflammatory cells. Results of our previous studies showed that endothelial Krüppel-like factor 4 (KLF4) regulated Vcam1 expression and neonatal formation following carotid injury. The aim of the present study was to determine if endothelial KLF4 is involved in ischemic AKI.

**Methods:** Endothelial KLF4 knockdown (KLF4-knockout) mice were generated by breeding Tg-Cre mice and Klf4 floxed mice, and their phenotype was analyzed after bilateral renal ischemia.

**Results:** Klf4-knockout (Klf4-cKO) mice were phenotypically normal before the surgery. However, endothelial KLF4 deletion exacerbated renal ischemia-reperfusion injury, as indicated by elevated serum levels of urea nitrogen and creatinine and aggravated renal histology. Moreover, Klf4-cKO mice exhibited the enhanced accumulation of neutrophils and the recruitment of cell adhesion molecules including Vcam1 expression in leukemic injured kidneys. Interestingly, statins ameliorated renal ischemia-reperfusion injury in control mice, but not in Klf4-cKO mice, suggesting that the protective effect of statins against ischemic AKI is mediated by endothelial KLF4. Mechanistic analyses in cultured endothelial cells revealed that statins increased expression and that KLF4 mediated the suppressive effect of statins on tumor necrosis factor-a induced Vcam1 expression through the binding of NF-κB to the Vcam1 promoter.

**Conclusions:** These results provide evidence that endothelial KLF4 is a mediator of statins and plays a protective role in ischemic AKI by regulating the expression of cell adhesion molecules with concomitant recruitment of neutrophils.

**Funding:** National Institutes of Health - National Heart, Lung, and Blood Institute
Kidney Endothelial Progenitors Play a Critical Role in Susceptibility to Acute Kidney Injury

**Background:** Acute Kidney Injury (AKI) is characterized by an abrupt decrease in renal function leading to renal failure, and contributing to high percentages of morbidity and mortality. Kidney formation involves the production of nephrons each with a rich vascular infrastructure. This complex and high vascularization makes the kidney especially susceptible to ischemic injury. We hypothesize that malformations of the vascular system during kidney development compromise its ability to cope and recover from AKI.

**Methods:** We generated mice with a conditional deletion of Vegfr2 (flx/flox) in the Foxd1 cre cells (Vegfr2ST-/-), and evaluated the formation of the vascular system via histology, immunohistochemistry and fluorescent microangiography. Furthermore, we performed ischemia reperfusion injury (IRI) on control and mutant mice and determined their ability to recover 1 injury phase) and 7 days (repair phase) post injury. Lastly, we performed a lineage tracing study where Foxd1 cre mice were bred with a Tdg/Tdm reporter (permanently labeling all Foxd1 derived cells) and performed IRI and interrogated the percentage of Foxd1 derived endothelial cells that were present in the IRI and contralateral control kidneys.

**Results:** We determined that the Vegfr2ST-/- mice had dilated microvasculature embryonically and post-natally. Furthermore, when we stressed the Vegfr2ST-/- animals with IRI they had an increased injury compared to controls (both histologically and inflammatory markers). This increased susceptibility in the mutants continued to be observed 7 days following the injury. Lineage tracing experiments showed the Foxd1 derived endothelial cells are highly plastic during the repair phase of IRI and their deletion in the Vegfr2ST-/- is likely the reason for the increased susceptibility to injury.

**Conclusions:** From this we determined that Foxd1 derived endothelial cells are highly permissive to normalization of the renal vasculature and their risk of AKI. Patients that have an underlying perturbation of the renal microvasculature are likely at higher risk of suffering long term renal damage following AKI.

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**Diadenosine Pentaphosphate Reduces Glomerular Filtration Rate**

**Background:** Diadenosine polyphosphates are released by the action of contrast media and may act on glomerular arterioles thereby reducing GFR. Methods: Rat tubules were freshly isolated using a modified iron oxide sieving technique and treated with iodixanol (47 mg iodine/ml) at 37° for 20 min. The supernatant was analyzed regarding the content of ApnA (n=3-5) by using reversed phase chromatography, affinity chromatography and Maldi-MS. Concentration response curves for ApnA (n=3-5, 10^-10^-3 mol/l) were measured in isolated perfused glomerular arterioles. The GFR was obtained in conscious mice by inulin clearance.

**Results:** Treatment of tubules with iodixanol increased the concentration of ApnA (n=3-5) significantly in the supernatant. ApnA (n=3-5) reduced afferent arteriolar diameters dose dependent, but did not influence efferent arterioles. ApnA acted strongest; its effect weakened with time. Suramin blocked the ApnA effect. Further, application of ApnA in conscious mice significantly reduced the GFR.

**Conclusions:** The data indicate that contrast media induced release of ApnA act differentially on glomerular arterioles resulting in the reduction of the GFR. This mechanism may add to the reduced GFR in CI-AKI.

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**Effect of Anakinra on Inflammome Markers in Hepatorenal Syndrome**

**Background:** Hepatorenal syndrome (HRS) type I is a life threatening complication of cirrhosis with limited therapeutic options. We hypothesize that Inflammome plays a major role in HRS type I and we investigated this in a mouse model by blocking IL-1β, an end product of inflammome pathway by Anakinra, so that it could serve as a potential therapeutic agent in patients at risk for HRS type I.

**Methods:** C57BL/6 mice received 1ml/kg of carbon tetrachloride (CCl4) biweekly for 12 weeks induce liver cirrhosis. A 6 mg/kg of Lipopolysaccharide (LPS) was given intraperitonially to mice to induce acute kidney injury by simulating the inflammatory structure seen by acute intake amount of 30 mg/kg of Anakinra was given intraperitonially 3 hours before and 1 hour after LPS to CCH4 and LPS treated mice. Four mouse populations were studied. (1) control mice (2) CCH4 treated mice (3) CCH4 treated mice with LPS (4) CCH4 treated mice with LPS and Anakinra (N=6 per group). Renal function was monitored by measuring creatinine, urea and sodium content measured by RIA. Inflammatory markers were measured using western blot for the presence of inflammome markers: IL-1β, caspase 1, and apoptosis- associated specte like protein (ASC) and the therapeutic effect of Anakinra on the inflammatory markers.

**Results:** Control and CCH4 treated mice showed no change in renal function. The CCH4+LPS treated mice had a significant decrease in urine volume (p<0.05) and urinary Na (p<0.05) and marked increase in serum creatinine (p<0.05) compared to the other 3 groups. In CCH4+LPS+Anakinra treated mice IL-1β, caspase 1, and ASC expression significantly decreased (p<0.05) compared with CCH4+LPS treated mice.

**Conclusions:** In the CCH4-induced cirrhotic mouse model, simulating HRS type I by administration of LPS, accompanied by an increase in the expression of IL-1β, caspase-1, and ASC in mouse kidney. Anakinra resulted in down regulation of these markers and improvement in renal function. This suggests that agents like Anakinra could be a potential therapeutic option for patients at risk of HRS type I.
A Comparison of Three Prediction Models for Acute Kidney Injury Requiring Renal Replacement Therapy After Coronal Artery Bypass Graft Surgery

Background: Acute kidney injury (AKI) following cardiac surgery is associated with increased post-operative morbidity and mortality. Scoring systems to predict acute kidney injury requiring renal replacement therapy (RRT) among patients undergoing cardiac surgery have been developed to assess risk pre-operatively and give necessary prophylactic agents and also assist clinicians in the management post-operatively.

Methods: Cross sectional analytic study of 427 patients who underwent coronary artery bypass graft (CABG) surgery from January 2009 to October 2014. The following were excluded: a) on hemodialysis b) with missing data. Primary outcome: acute kidney injury requiring RRT after CABG. Risks were calculated using the three models: Cleveland scoring by Thakar, Simplified Renal Index by Wijeysundera, and the Bedside Tool for Predicting Risk of Postoperative Dialysis by Mehta. The area under the receiver operating curve (AUROC) was determined for each model.

Results: AKI was documented in 25.5% (n=109), 13.3% (n=57) underwent post-operative RRT. Discrimination for the prediction of RRT was good for the three scoring models using AUROC: Mehta: 0.94 (95% CI, 0.91 to 0.96), Thakar: 0.92 (95% CI, 0.89 to 0.94), and SRI: 0.90 (95% CI, 0.867 to 0.926). Mehta showed the highest predictive value, with significant difference with SRI (P = 0.0053). However, it was not significantly different with Thakar (P=0.23).

Conclusions: The Bedside Tool for Predicting Risk of Postoperative Dialysis by Mehta showed the highest predictive value but with no significant difference with the predictive value of the Cleveland scoring system. The advantages of the Cleveland scoring over Mehta are the applicability in cardiac surgeries other than CABG and the less number of variables.

Effect of Off-Pump and On-Pump Coronary Artery Bypass Graft Surgery on Acute Kidney Injury

Background: Acute kidney injury (AKI) is one of the serious complications of cardiac surgery. AKI is associated with increased mortality and morbidity. Coronary artery bypass graft (CABG) surgery can be done with a beating-heart (off-pump) or with a cardiopulmonary bypass machine (on-pump). There are conflicting studies regarding the reduction of acute kidney injury with the use of the Off-pump CABG vs. On-pump CABG.

Methods: Adult patients who underwent CABG using Off-pump and the On-pump technique from January 2005 to October 2014 were included in this retrospective cohort study. The following patients were excluded: a) chronic hemodialysis b) creatinine eGFR <15ml/min/1.73m2 c) missing data. The outcomes were: AKI defined as absolute increase in the serum creatinine concentration of ≥0.3 mg/dL from baseline within 48 hours after CABG and AKI requiring renal replacement therapy. Odds ratio were calculated between the use of Off-pump and On-pump CABG with the respective outcomes.

Results: Postoperative Acute Kidney Injury The incidence of acute kidney injury with off-pump group was lower (4/28 [14.3%]) vs on-pump group (10/427 [25.5%]) with OR 2.05 [95% CI, 0.69 to 6.59]; however, it was not significantly different at p-value 0.19. Postoperative Acute Kidney Injury with Renal Replacement Therapy Out of the 109 patients who had acute kidney injury after On-pump CABG, 53 (48.6%) patients underwent hemodialysis. While in the Off-pump CABG group, no one underwent hemodialysis out of the 4 patients who had acute kidney injury postoperatively (OR 8.8 [95% CI 0.537 to 146.9], P=0.1283).

Conclusions: There was a lower incidence of AKI and AKI requiring renal replacement therapy in the Off-pump CABG group, however, it was not statistically significant with the On-pump CABG group. There is still insufficient evidence to say that the use of Off-pump CABG technique reduces incidence of AKI. Limitations of this study are: small sample size, confounding variables since this study is a retrospective study, off-pump CABG populations may not have been represented accurately. A multi-center study to increase sample size is recommended.
TH-PO055
The Jelliffe Method for GFR Estimation with Non-Steady State Creatinine
Performs Better for Subjects with Higher Weight and Baseline Chronic Kidney Disease
Rejees Stephen, Sevag Demirjian, Steve Campbell. Nephrology; Cleveland Clinic, Cleveland, OH.

Background: The Jelliffe method is used to estimate the glomerular filtration rate (GFR) when creatinine is in a non-steady state, such as in patients with acute kidney injury (AKI). We explored the agreement between iohalumate-measured renal function (gGFR) and estimated GFR by the Jelliffe method (eGFR) in subjects after undergoing partial nephrectomy.

Methods: gGFR was measured within a week of partial nephrectomy in subjects who sustained AKI (≥0.3 mg/dl rise in serum creatinine from baseline) after partial nephrectomy. gGFR was standard on creatinine drawn at the time of gGFR measurement, were compared using Pearson’s correlation (r) in subjects grouped by weight (above and below median weight; 86 Kg) and baseline chronic kidney disease status (CKD; GFR: <60 ml/min.1.73m2).

Results: 69 of 90 subjects undergoing partial nephrectomy sustained AKI. Mean age was 61±11 years, and 55 were male. gGFR had a high correlation with eGFR (r=0.97, p<0.001). Correlation of gGFR with iGFR was shown and significant except in the group with both CKD and lower weight (Table). Subgroup analysis showed that subjects with lower body weight and no CKD had lower correlation (r=0.54) than those with both CDK and the higher weight (r=0.96). The group with no CKD but higher weight had a strength of correlation in between these extremes.

Conclusions: GFR estimated by the Jelliffe equation correlates well with measured GFR in the AKI setting. Higher body weight and CKD at baseline are associated with higher creatinine levels, which may account for the better performance of the Jelliffe method in these states.

TH-PO056
Development of a Multicenter Ward-Based Acute Kidney Injury (AKI) Prediction Model
Jay L. Kovner, Richa Adhikari, Dana P. Edelson, Matthew M. Charpke. Dept of Medicine, Univ of Chicago.

Background: Early identification of those at risk for the development of AKI on the general wards prior to increases in serum creatinine (SCR) would enable preemptive evaluation and intervention to minimize the risk and severity of AKI. We aimed to develop an AKI risk prediction algorithm using electronic health record (EHR) data in non-ICU patients.

Methods: All hospitalized ward patients who had SCR measured in 5 hospitals were included. Patients with a first measured SCR ≥3.0 mg/dl or who developed inpatient AKI outside the general ward were excluded. Using a discrete-time survival model, demographics (age, sex), continuous variables (respiratory rate, pulse, temperature, pulse pressure index, oxygen saturation, systolic and diastolic blood pressure, complete blood count, hepatic panel and blood chemistries) were modeled as restricted cubic splines with 4 knots. The algorithm was derived in 60% of the data and prospectively validated in the remaining 40%. Area under the curve (AUC) was calculated for the prediction of SCr-based KDIGO AKI within 12 or 24 hours. Subgroup analyses were conducted across baseline glomerular filtration rate (eGFR) groups and severity of AKI stage.

Results: Among the 206,192 included patients, 17,522 (8.5%) developed KDIGO AKI. We explored the agreement between iothalamate-measured renal function (iGFR) in subjects with AKI after undergoing partial nephrectomy. (AKI). We explored the agreement between iothalamate-measured renal function (iGFR) in subjects with AKI after undergoing partial nephrectomy.

Conclusions: Surrogate curves for multiple admissions (dashed lines) fell above the curve for single admissions, demonstrating survivor bias. Combining random selection and adjustment for Med# resolved the survivor bias, permitting inclusion of patients with multiple admissions in risk models for inpatient mortality.

TH-PO057
Survivor Bias: Utilization of Multiple Admissions for Evaluation Risk of Inpatient Mortality Associated with Hospital-Acquired (HA) Acute Kidney Injury (AKI)
David G. Warnock, T. Clark Powell, John P. Donnelly. Univ of Alabama at Birmingham, Birmingham, AL.

Background: Inpatient deaths censored the cohort at risk, introducing survivor bias favoring those with <1 admission. Analysis of first admissions this bias, but also loses information about those who survive multiple admissions. We evaluated inpatient mortality associated with AKI for adult admissions to UAB Hospital for FY2010-FY2013.

Methods: We used ICD9 codes and all inpatient serum creatinine (sCr) values for 109,456 adult patients with 5,452 inpatient deaths. We excluded patients with patients with <2 sCr values, ESRD, post-transplant renal failure, eGFR (<5 or >500 ml/min.1.73 m2), length of stay <1 and >28 days, and patients with community-acquired AKI. Minimum sCr for each admission was used as baseline, and HA-AKI was defined by peak sCr > (0.3 mg/dL + minimal sCr) and date-time for minimal sCr < date-time peak sCr. No-AKI was defined as (peak Scr - minimal sCr) <0.3 mg/dL. Survivor functions included HA-AKI, median age, black race, male gender, Deyo-Charlson comorbidity score, and median admissions for each patient (Med#).

Results: For 40,471 patients with 1 admission, there were 7,594 cases of HA-AKI (19%) with 1,290 deaths (17%). For 14,860 patients with 23,633 admission, there were 6,633 cases of HA-AKI (22%) with 732 deaths (11%). Figure shows survival curves for 1 versus >1 admissions (A); 1 versus >1 admissions adjusted for Med# (B), 1 versus selected >1 random selected admission (C), and 1 versus >1 random selected admission adjusted for Med# (D).

Conclusions: GFR estimated by the Jelliffe equation correlates well with measured GFR in the AKI setting. Higher body weight and CKD at baseline are associated with higher creatinine levels, which may account for the better performance of the Jelliffe method in these states.

TH-PO058
Validation of the Acute Renal Failure Trial Network (ATN) Study Risk Model for Predicting Mortality in Critically Ill Adults with Acute Kidney Injury
Ridhmi P. Rajapakse,1 Christopher M. Keener,2 Paul M. Palevsky,1,3 John A. Kellum,2 Emily Folds,1 1Medicine, Univ of Pittsburgh, Pittsburgh, PA; 2Critical Care Medicine, Univ of Pittsburgh, Pittsburgh, PA; 3Renal Section, VA Pittsburgh HCS, Pittsburgh, PA.

Background: Disease specific severity of illness scoring systems have been developed to predict survival of patients with acute kidney injury. Performance of these scoring systems outside the population in which they have been generated has been poor. We therefore evaluated the performance of the recently developed ATN Study risk model predicting 60 day all-cause mortality in intensive care unit (ICU) patients at initiation of dialysis for acute kidney injury (AKI).

Methods: We evaluated the performance of the ATN Study risk model using the High Density Intensive Care (HiDenIC) Database which contains data on all adult patients admitted to any of the eight ICUs at UPMC between July 2000 and October 2008. Clinical data and physiologic variables were closely matched with the original study model; missing data were imputed by either assuming clinical normality or viewing these data elements following similar rules used to build the original model. Model discrimination was assessed via area under the receiver operating characteristic curve (AUROC). Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Results: 1747 patients were initiated on renal replacement therapy (RT) for AKI during this interval; full data for model testing were available for 1300 patients (74%). The AUROC for the model was 0.78 (95% CI: 0.75-0.80) with a Hosmer-Lemeshow goodness-of-fit test p-value of 0.59 (Figure).

Conclusions: Readily available EHR data can be used to predict impending AKI on the general wards with good to excellent accuracy across different patient subgroups. Real-time use of this model, prior to changes in SCR, would allow early diagnostic and therapeutic interventions for those at high risk of AKI and may improve cost and outcomes.
Conclusions: The ATN score demonstrated good discrimination and calibration for predicting 60-day all-cause mortality in ICU patients initiating RRT for AKI in a population separate for the population in which it was developed.

TH-PO060

A Multifaceted Quality Improvement Programme for Tackling Acute Kidney Injury in a Large Teaching Hospital


Background: Acute kidney injury (AKI) is now widely recognised as a serious health care issue. Up to 25% of hospital patients have been reported to develop it, often with worse outcomes compared to those without AKI. AKI care in hospitals has been shown to be substandard. This study aimed to use quality improvement methodology to improve AKI care and outcomes in a large teaching hospital.

Methods: Several areas of documented poor AKI care were identified and specific improvement activities implemented through sequential Plan-Do-Study-Act (PDSA) cycles. An electronic alert system for AKI was developed, a ten point Priority Care Checklist (AKI PCC) was tested with the aid of specialist nurses and pharmacists whilst targeted education activities were carried out. Impact on key AKI care processes and patient outcomes was studied.

Results: The electronic alert had a sensitivity of 99% for the detection of new cases of AKI. Nine aspects of the PCC saw significant improvements in their attainment: Baseline creatinine 66% to 84%, identification of a cause for AKI 62% to 77%, fluid balance assessment 77% to 92%, appropriate investigations 61% to 77% catherisation 92% to 99% ultrasound scans 79% to 95% renal or intensive care referrals 80% to 100%, fluid charts 64% to 71% after, and appropriate drugs review 57% to 87%. The intervention led to a significant reduction in variability of delivered AKI care. AKI incidence showed a trend towards reduction; 9.9% of all hospitalisations before any intervention to 7.8% after.

Conclusions: This study demonstrates the success of an AKI care checklist implemented with the aid of a nurse/pharmacist in improving key processes of care and showing an early improvement in key patient outcomes.

TH-PO061

Prognosis of Contrast Induced Nephropathy After Outpatient Computed Tomography in Chronic Kidney Disease Patients

Suehon Park, Seokwoo Park, Eunjeong Kang, Hajeong Lee, Jung Pyo Lee, Kwon Wook Joo, Yon Su Kim, Dong Ki Kim. Dept of Internal Medicine, Seoul National Univ Hospital.

Background: Most studies regarding contrast induced nephropathy (CIN) were done in angiography era but computed tomography (CT) is more common cause of contrast exposure in general population. There were few prognosis data concerning CIN after outpatient CT.

Methods: Patients with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² underwent outpatient CIN prophylaxis program for contrast CT from 2008 to 2014 in Seoul National University Hospital. Patients received intravenous isonitrate saline and oral N-acetylcysteine. Baseline blood sample was done within 2 weeks before CT. Basic data was collected retrospectively by medical chart review. Prognosis was surveyed from death registry of National Statics Korea and dialysis registry of The Korean Society of Nephrology. CIN was defined by 0.5mg/dl or ≥25% increase of serum creatinine (sCr) from baseline within 48-96 hours after CT. Primary outcome was event of renal replacement therapy (RRT), duration from CT to RRT and survival period after CT. Results: 12179 cases of CT were performed with CIN prophylaxis protocol and 2816 cases of CT had baseline eGFR<60 without RRT history and follow up sCr ≥48-96 hours after CT. 84 (3%) cases of CIN were found and 99 (3.5%) cases went RRT, 551 death reported after CT. Prognosis was analyzed after adjustment with age, sex, baseline eGFR, history of diabetes and hypertension. No relationship between death, RRT incidence, doubling of sCr and CIN was shown. However, we found shorter period from CT to RRT in CIN cases. So we performed analysis with RRT within 6 months as outcome with subgroup devided by eGFR. CIN was risk factor for RRT within 6 months in cases with baseline eGFR<30 (aOR 4.70, 95% CI 1.39-15.90, P=0.013). However, in cases with eGFR≥30, start of RRT in acute period was not increased by CIN.

Conclusions: CIN due to CT contrast after appropriate prophylaxis was not related to long term renal prognosis. CIN was a risk factor for start of RRT within 6 months after CT in cases with baseline eGFR<30, but even this relationship was not seen in patients with relatively preserved renal function.

TH-PO062

Outcomes following Intra Arterial Contrast in Chronic Kidney Disease Patients

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Background: Contrast Induced Nephropathy (CIN) is a recognised complication of angiography. Risk factors include chronic kidney disease (CKD), advanced age, diabetes and cardiac insufficiency. Although incidence in the general population is 2-5%, reported patient and system characteristics independently associated with higher quality DC communications (greater number of quality elements out of 10 possible) in a multivariable model.

Results: Among 75 randomly selected hospitalized patients with AKI stratified by KDIGO stage 1 to 3 (n=25 per stage), mean age was 56 years, 48% were African American, 15% had known CKD, median length of stay was 9 days and 65% were discharged from medical (vs. surgical) services. Less than half of DC communications included key elements about AKI.

Conclusions: Few hospital DC communications provided information or recommendations for AKI care in sufficient detail to facilitate adequate follow-up. Improvements in this important aspect of care for patients with AKI are urgently needed.

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

Underline represents presenting author.

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incidence of CIN in CKD is 15-27%. The risk of CIN may have been over-estimated in
published risk factors. Any AKI, demographic data, specialist nephrology input, length of
stay and overall outcomes were recorded.

Results: Of 158 patients, 35 (22%) had AKI during their hospital stay. Most had AKI1
(24/35), vs AKI2 (7/35) and AKI3 (4/35). 28 had AKI on admission vs 7 after admission.

Conclusions: Pre procedure optimisation of CKD patients may reduce incidence of
CIN. In our study, incidence of CIN in CKD patients was low and did not lead to death or
progression of chronic kidney disease.

TH-PO063
AKI Risk Scores in Acute Admissions: Selecting the High-Risk or Missing the Vulnerable?
Amy Jeanne Riddell, Christopher J. Mulgrew. Renal Unit, Royal Devon and Exeter Hospital, Exeter, Devon, United Kingdom.

Background: AKI commonly complicates acute illness. 2014 UK NICE AKI guidelines stress early identification of those at high risk. In patients with many co-morbidities, while risk scores in select groups have been studied, there remains debate as to the effective use of AKI risk scoring in 1e2 care populations (currently being investigated by the UK National AKI Programme). If correctly identified, steps could be taken to minimise risk and manage AKI earlier. Alternatively, should we not treat all acutely ill patients as ‘at risk’?

Methods: Review of acute admissions to the AMU on 4 weekdays between Mar’14Mar’15. 158 cases were reviewed and risk scored based on NICE/KDIGO published risk factors. Any AKI, demographic data, specialist nephrology input, length of stay and overall outcomes were recorded.

Results: Of 158 patients, 35 (22%) had AKI during their hospital stay. Most had AKI1 (24/35), vs AKI2 (7/35) and AKI3 (4/35). 28 had AKI on admission vs 7 after admission. Patients with AKI (at any time) had higher median scores (4, 0-9) than non-AKI (2, 0-7).

Conclusions: Risk scores on arrival, with high scores correlating with AKI and LoS, the majority with AKI arrive from primary care with high scores. A validated risk score for use in 1e2 care, aiming to prevent admission, may be more more useful than stratifying all acute hospital admissions - are they not all ‘high risk’ anyway?

TH-PO064
Acute Kidney Injury Care Bundle Compliance in a Large District General Hospital in UK
Preetham Boddala, Shiva Sreenivasan, Israr Baig, Nerys Conway. Renal Unit, Gloucestershire NHS Foundation Hospitals, Gloucester, Gloucestershire, United Kingdom.

Background: AKI is a common and harmful condition, which is often treatable and avoidable. The incidence of AKI in patients admitted to a hospital is approximately 3 – 7%. Gloucestershire Hospitals NHS Foundation Trust sees about 500 cases of acute kidney injury (AKI) monthly from a catchment population of 612,000.

Research Question: Does an AKI flag, care bundle and electronic alert system reduce AKI in hospital?

Methods: An audit of patients with AKI showed deficiencies in care. We created an AKI care bundle (senior review, medication review, fluid balance, and repeat creatinine within 24 hours) for those patients with AKI, prompted by an AKI sticker for the case notes.

Results: For patients receiving an AKI flag, case notes were audited for appropriate use of the care bundle. We reviewed audit results over a 2-year period to see if the AKI bundles were being used appropriately and if patient care had improved. There has been improvement in AKI care bundle compliance. Figures up to August 2014 show that compliance for AKI care bundle use is 87%.

The compliance since its launch has generally exceeded the Commissioning for Quality and Innovation (CfQI) targets set in place by the project.

Conclusions: We have shown an improved care in patients with acute kidney injury by using an electronic alert system prompting early management. AKI can easily be identified and managed early and appropriately through the implementation of an AKI alert system.
Overall cumulative survival and 28-days survival rates were higher in early initiation group (Log-rank P < 0.001 for both). Furthermore, early CRRT treatment was associated with lower mortality rate after adjustment for age, sex, mean arterial pressure, Charlson comorbidity index, Sequential Organ Failure Assessment score, hemoglobin, serum C-reactive protein, serum albumin level and prothrombin time (hazard ratio, 0.752; 95% confidence interval 0.595-0.951, P = 0.008).

Conclusions: Early initiation of CRRT was associated with a better prognosis in critically ill elderly patients with AKI.

TH-PO067
Outcomes in Patients with Persistent Dialysis-Dependent AKI: Meganathan, 1,3
Daniel Tseytlin, Hope Kincaid, Sharon E. Maynard. Lehigh Valley Health Network, Allentown, PA.

Background: We sought to describe clinical characteristics & outcomes in patients with persistent dialysis-dependent AKI at the time of hospital discharge.

Methods: We performed a retrospective descriptive study of patients requiring dialysis for AKI at the time of hospital discharge in Lehigh Valley Health Network Subacute Dialysis Program between October 2012 & July 2014.

Results: Of 55 patients enrolled in the program, 26(47.3%) recovered renal function & 29(52.7%) developed ESRD. Clinical characteristics of these patients are shown below. The median duration of dialysis in the renal recovery group was 3.5 weeks. Although 75% of patients who recovered renal function did so by 5.1 weeks, 22(67.7%) recovered ≥3 months after dialysis initiation.

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Renal Recovery (n=26)</th>
<th>No renal recovery (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64</td>
<td>74</td>
</tr>
<tr>
<td>Comorbidities - % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>18 (69)</td>
<td>23 (82)</td>
</tr>
<tr>
<td>CHF</td>
<td>5 (19)</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>CAD</td>
<td>6 (23)</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>DM</td>
<td>16 (61)</td>
<td>10 (34.5)</td>
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<tr>
<td>Cerebrovascular dis</td>
<td>3 (11.5)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>PVD</td>
<td>4 (15.4)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dl)</td>
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<tr>
<td>Creatinine on admission (mg/dl)</td>
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<tr>
<td>Creatinine on dialysis initiation (mg/dl)</td>
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<td>5.5</td>
</tr>
<tr>
<td>Change in creatinine between week 3 &amp; 4 after dialysis initiation</td>
<td>-0.8*</td>
<td>+0.13</td>
</tr>
<tr>
<td>Etiology - % (n)</td>
<td></td>
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<tr>
<td>ATN</td>
<td>15 (57)</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>0 (0)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>CIN</td>
<td>2 (7.7)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>AIN</td>
<td>1 (3.8)</td>
<td>1 (3.4)</td>
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<tr>
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<td>1 (3.8)</td>
<td>1 (3.4)</td>
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<tr>
<td>CRS</td>
<td>3 (11.5)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Acute renal allograft rejection</td>
<td>1 (3.8)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Other</td>
<td>2(7.7)</td>
<td>5 (17.2)</td>
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</tbody>
</table>

* Among those who recovered renal function but were still dialysis dependent at 4 weeks.

Conclusions: This study indicates that patients who did not recover renal function were older & had higher creatinine levels at each time point than those who recovered renal function. While there was a decrease in serum creatinine from week 3 to week 4 in patients with renal recovery, there was an increase for those who did not recover. More patients who did not recover renal function had HTN, HF & CAD. Additionally, more patients who had ATN recovered renal function, while all patients with multiple myeloma did not. Hypothesis-testing studies are needed to explore whether or not these clinical characteristics may be used to predict which patients are likely to recover renal function and which are not.

TH-PO068
Acute Kidney Injury Episodes Accelerates Rate of Loss of Renal Function in Diabetes Mellitus: Charulatha V. Thakar,1,2 Anthony C. Leonard,1,2 Karthikoyian Meganathan,1,3 V. Shane Pankratz,4 Internal Medicine, University of Cincinnati, Cincinnati, OH; Medicine, Cincinnati VAMC; Cincinnati, OH; Family Medicine, University of Cincinnati, OH; Internal Medicine, University of New Mexico, Albuquerque, NM.

Background: Although acute kidney injury (AKI) is a risk factor for chronic kidney disease (CKD), whether it accelerates the rate of loss of estimated glomerular filtration rate (eGFR) is not known.

Methods: In a de-identified cohort of 3,678 type 2 diabetes patients we studied the impact of AKI on the rate of decline in eGFR. Patients with an entry eGFR of >30 ml/min and at least two creatinine (Cr) values at least one month apart were followed until their eGFR was <15 ml/min, death, or the end of the study. Cr measurements spanned over an average of 65 months. Estimated rates of linear eGFR decline were compared between those with and without AKI. We assessed the effect of AKI on the outcome of a rapid decline in eGFR (defined as >5 ml/min/year) adjusting for demographics, proteinuria, and baseline CKD status (initial eGFR greater or less than 60) in a multivariable logistic model, and expressed this as odds ratios (OR) and 95% confidence limits (95% CI).

Results: Patients’ mean (standard deviation) age was 62 (11) years at study entry with an average (95% CI) of 79 (72, 85) years. In 3,055 non-AKI patients the mean eGFR decline was 2.7 ± 4.2 ml/min/yr in the 623 AKI patients (P < 0.001). For 499 AKI patients with both pre and post-AKI eGFR slopes, the mean decline pre-AKI was 2.7 ± 4.2 ml/min/yr versus 6.3 ml/min/yr post-AKI (p = 0.03; paired t-test). In the non-AKI group 23.4% met the rapid decline outcome, compared with 36.0% in AKI group (p < 0.001); within AKI patients, rapid decline occurred in 37% of patients pre-AKI and 46% post-AKI (paired OR = 1.4; 95% CI, 1.1-1.8, McNemar p = 0.008). AKI was associated with rapid decline (OR 1.8; 95% CI, 1.5-2.2; p < 0.001), adjusted for age, gender, race, proteinuria, and CKD status.

Conclusions: Compared to no-AKI, diabetic patients with AKI experience an accelerated rate of decline in eGFR; and it occurs at twice the pace in the pre- vs post-AKI periods. Biological and process of care factors may be responsible for this effect.

Funding: Veterans Administration Support, Clinical Revenue Support

TH-PO069
Impact of Transient or Persistent Acute Kidney Injury on Chronic Kidney Disease Progression and Mortality After Gastric Surgery: Chang Seong Kim, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. Dept of Internal Medicine, Chonnam National Univ Hospital, Gwangju, Republic of Korea.

Background: Acute kidney injury (AKI) was common after gastric surgery for gastric cancer and associated with adverse outcomes. However, impact of transient or persistent AKI on clinical outcomes after gastric surgery for gastric cancer has not been described. The objective of this study was to determine the incidence, factors, and clinical outcomes associated with transient or persistent AKI after gastric surgery.

Methods: We performed a retrospective study of 4,886 patients with normal renal function who underwent partial or total gastrectomy for gastric cancer between June 2002 and December 2012. Transient AKI was defined as return of serum creatinine to the no-AKI range at discharge after gastric surgery. Our outcomes included occurrence of new-onset chronic kidney disease (CKD), and long-term kidney function and mortality.

Results: AKI occurred in 638 (13.3%) after gastric surgery. Of these, transient AKI was documented in 556 (87.1%). Length of intensive care unit (ICU) and hospital stay, and ICU admission rate (5.8% versus 1.0%) were higher in patients with transient AKI than in those without AKI. Male, use of diuretics and postoperative vasopressor, and lower baseline creatinine were common risk factors for persistent and transient AKI after gastric surgery. After adjusting for confounding factors, patient with transient and persistent AKI had a significantly higher new-onset CKD (odds ratio [OR], 1.62; 95% CI, 1.16–2.26, P = 0.005; OR, 3.60; 95% CI, 1.77–3.74, P < 0.001, respectively) and 1-year mortality (OR, 1.75; 95% CI, 1.15–2.66, P = 0.009; OR, 12.79; 95% CI, 7.57–21.31, P < 0.001, respectively) compared with no-AKI.

Conclusions: Not only persistent AKI but Transient AKI is associated with increased hospital complications and a significantly higher risk of CKD progression and long-term mortality than patients without AKI after gastric surgery.

TH-PO070
Use of Non-Tunneled Versus Tunneled Catheters for Renal Replacement Therapy in Acute Kidney Injury: Mallika L. Mendu, Sushrut S. Waikar. Div of Renal Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background: Treatment of severe acute kidney injury requiring renal replacement therapy (AKI-RRT) requires vascular access, with either temporary, non-tunneled dialysis catheters (NTDC), or tunneled dialysis catheters (TDC). The relative risks and benefits of these two vascular access options have not been well studied.

Methods: We conducted a 1-year prospective cohort study in an academic medical center to compare outcomes between TDC and NTDC for AKI-RRT. We collected information about catheter placement including reasons for type of catheter used, number of insertion attempts, duration of use, and infectious and mechanical complications.

Results: Over one year we collected information on 140 NTDC and 80 TDC placement procedures on 154 patients with AKI-RRT. Compared to NTDCs, TDCs required fewer insertion attempts (1.0 vs. 1.5), had longer median duration of use (58.5 vs. 6.5 days), and had fewer infectious and mechanical complications (6% vs. 25%) (all p<0.001). The most common reasons for NTDC over TDC placement were immediate need for use (74%), infection (11%) and catheter not working (7%) were the most common reasons for NTDC removal. Infection (4%) was the most common reason for TDC removal.

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

105A
Nonapnea Sleep Disorders and the Risk of Acute Kidney Injury: A Population-Based Retrospective Cohort Study

Background: From 2000 to 2010, 9,316 newly diagnosed NASD cases compared with 27,948, 1.5 times higher than that of the cohort without sleep disorders. Elder age, lower monthly income, hypertension, DM, cerebrovascular disease, CKD status, depression and higher psychological stress as reflected by ECG changes, and renal dysfunction is associated with AKI development with NASD (HR=2.23; 95% CI = 1.57-3.16, p<0.001 ).

Methods: Retrospective data collection from 71 living kidney donors presenting between 2006-2011. We calculated serum creatinine (sCr) changes defined as stage 1 AKI as per the KDIGO guidelines (sCr increase by 26.5 umol/L within 48 hours or 1.5-1.9 times baseline increase) and stage 2 AKI (2.0-2.9 times baseline increase).

Results: 54.9% of patients developed AKI. 52.1% AKI stage 1 and 2.8% AKI stage 2. The median age was 53 years (IQR 21-66 years) in the group of patients that developed AKI and 52 years (IQR 27-71 years) in the non-AKI group. 39.7% were males (26.8% with AKI) and 60.6% females (28.2% with AKI) (p=0.07). The AKI group had a lower mean sCr at baseline: 71±22.3 umol/L vs 84±18.0 umol/L (p<0.01). However, there was no difference in the CKDepi at baseline (91.6±18.6 ml/min in the AKI group vs 89±17.3 ml/min, p=0.14) as well as the raw and adjusted for surface area isotopic EDTA-GFR at baseline (101±38.2 ml/min in the AKI group vs 96±22.9 ml/min (p=0.31) and 89±20.2 ml/min in the AKI group vs 86±16.2 ml/min (p=0.41) respectively). Post nephrectomy there was no difference in absolute renal function (CKDepi in the AKI group 62.8±15.4 ml/min vs 60.2±10.7 ml/min, p=0.06) or change in renal function (33.4±16.5% decrease in CKDepi in the AKI group vs 35.4±14.0%, p=0.25) at 6 months.

Conclusions: Although 54.9% of patients fulfilled the diagnostic criteria for AKI as reported by the laboratory AKI screening algorithm this might not reflect actual kidney injury, and there were no differences in renal function measured after 6 months.

Fluid Overload and Mortality in Neonatal Intensive Care Unit Patients Requiring Continuous Renal Replacement Therapy

Background: Continuous renal replacement therapy (CRRT) has emerged as a favored modality in the management of the high risk neonates with acute kidney injury (AKI) and with inborn errors of metabolism. Recently, there are some reports that lesser degrees of fluid overload (FO) at CRRT initiation was associated with improved outcomes in children in pediatric intensive care unit (PICU). However, there has been little data that have analyzed the fluid status, risk factors, and outcome of neonates who receiving CRRT. The aim of this study is to evaluate the factors including FO associated with the outcome of neonates with CRRT.

Methods: A retrospective medical record review was performed 34 hemodynamic unstable neonates with AKI who underwent at least 48 hours of CRRT in neonatal intensive care unit (NICU) at Samsung Medical Center between January 2007 and December 2014. We divided into two groups with survivor (N=15) and non-survivor (N=19). Data were collected regarding demographic characteristics, fluid overload, CRRT parameters, and duration of CRRT. There was no significant difference in mean daily effluent volume between survivors and non-survivors. Adjusted regression analysis revealed that FO at CRRT initiation was associated with mortality, duration of CRRT, and hospitalization period.

Conclusions: Fluid overload might cause mortality, prolonged hospitalization period, and duration of CRRT in neonates. Early initiation of CRRT before severe fluid overload might improve the outcome of neonates requiring CRRT.
TH-PO075
Survival and Renal Outcomes following Transjugular Intrahepatic Portosystemic Shunt Placement in Hepatorenal Syndrome: A Case Series

Background: Few effective treatment options are available for hepatorenal syndrome (HRS). There may be a role for the placement of a transjugular intrahepatic portosystemic shunt (TIPS) in reversing the pathophysiologic changes in HRS.

Methods: We performed a multicenter, retrospective review of patients who underwent TIPS placement concurrent to having HRS from 1995 to 2014 using a centralized clinical data warehouse. Two clinicians adjudicated HRS diagnosis and classified cases as Type 1 (T1-HRS) or Type 2 (T2-HRS) based on review of medical records. Estimated glomerular filtration rate (eGFR), survival, and other parameters were assessed immediately before and after TIPS, and 90 days pre- and post-procedure.

Results: We identified 17 cases. Mean age was 54±12 years, 12 (71%) were male, 7 (41%) had T1-HRS and 10 (59%) had T2-HRS. Median MELD score at time of procedure was 21 (quartile 1, quartile 3: 14, 33). TIPS significantly reduced portal pressure gradient above 120 mcmol/L. We separated this cohort based on the year of admission (< or > to 2008). Secondary outcomes were length of ICU stay and total in-hospital mortality. Most cases are mild and can be managed on an outpatient basis with close monitoring. We present an intriguing and rare case of severe OHSS with acute renal failure secondary to obstructive nephropathy. The patient is a 38 year old black female stimulated with beta-human chorionic gonadotropin (b-HCG) prior to transfer of fresh embryos resulting in a diastolic dichorionic twin gestation. She presented to the OB-GYN service with progressive ascites, gaining 17 kg in 1 week, and also acute renal failure due to mechanical obstruction of both ureters from bilaterally enlarged fluid-filled ovaries. Initial ultrasonography estimated the dimension of the left ovary at 22 cm, containing 1.7 L of fluid volume. Her baseline creatinine of 0.8 mg/dL peaked at 5.8 mg/dL prior to placement of bilateral nephrostomy tubes, which led to rapid and effective relief of obstruction and normalization of kidney function within days. At follow-up, patient had spontaneously undergone an intrauterine demise of one fetus at 9 weeks; however, she successfully delivered the other fetus preterm at 35 weeks gestational age via C-section. The nephrostomy tubes remained in place for the duration of her pregnancy. This case highlights a rare presentation of a well-known, but potentially life-threatening complication of ovarian induction, which has become an increasingly popular treatment for infertility.

Methods: Clinical course of the patient during the entire pregnancy and the outcome.

Results: Successful fetal outcome.

Conclusions: Patient presented with severe obstructive urethrophy from very large kidneys from hyperstimulation resulting in acute renal failure and bilateral nephrostomy tube placements. This resulted in release of obstruction, normalization of renal function, and a successful delivery.

TH-PO078
Obstructive Nephropathy in Ovarian Hyperstimulation Syndrome and Successful Delivery


Background: Ovarian hyperstimulation syndrome (OHSS) is a well-described iatrogenic complication of exogenous gonadotropin administration preceding in vitro fertilization (IVF). Underlying pathophysiology stems from influx of reproductive hormones and inflammatory vasodilatory mediators that increase capillary permeability and cause intravascular volume depletion due to large fluid shifts into the interstitial space. Most cases are mild and can be managed on an outpatient basis with close monitoring. We present an intriguing and rare case of severe OHSS with acute renal failure secondary to obstructive nephropathy. The patient is a 38 year old black female stimulated with beta-human chorionic gonadotropin (b-HCG) prior to transfer of fresh embryos resulting in a diastolic dichorionic twin gestation. She presented to the OB-GYN service with progressive ascites, gaining 17 kg in 1 week, and also acute renal failure due to mechanical obstruction of both ureters from bilaterally enlarged fluid-filled ovaries. Initial ultrasonography estimated the dimension of the left ovary at 22 cm, containing 1.7 L of fluid volume. Her baseline creatinine of 0.8 mg/dL peaked at 5.8 mg/dL prior to placement of bilateral nephrostomy tubes, which led to rapid and effective relief of obstruction and normalization of kidney function within days. At follow-up, patient had spontaneously undergone an intrauterine demise of one fetus at 9 weeks; however, she successfully delivered the other fetus preterm at 35 weeks gestational age via C-section. The nephrostomy tubes remained in place for the duration of her pregnancy. This case highlights a rare presentation of a well-known, but potentially life-threatening complication of ovarian induction, which has become an increasingly popular treatment for infertility.

Methods: Clinical course of the patient during the entire pregnancy and the outcome.

Results: Successful fetal outcome.

Conclusions: Patient presented with severe obstructive urethrophy from very large kidneys from hyperstimulation resulting in acute renal failure and bilateral nephrostomy tube placements. This resulted in release of obstruction, normalization of renal function, and a successful delivery.

TH-PO079
Analysis of the VA/NIH Acute Renal Failure Trial Network Data: Comparison of Outcomes in Nutrition Delivery in Acutely Dialyzed Patients

Youngho Kim, V. Shane Pankratz, Eduardo A. Alas, Christos Argyropoulos, Mark L. Unruh. Div of Nephrology, Univ of New Mexico School of Medicine, Albuquerque, NM.

Background: The optimal nutrition management for acute kidney injury (AKI) is not well-defined and recommended for nutritional support in acute ill patients who undergo renal replacement therapy (RRT) are largely based on expert opinion.

Methods: In order to better understand associations between nutrition and outcomes of critically ill patients with AKI requiring RRT, we analyzed data available from the ATN study. Patients were classified by nutritional support provided at the time of enrollment.

Results: We retrospectively collected clinical and biological data of 135 patients admitted to the University Hospital of Marseille from 1999 to 2014 with a diagnosis of multiple myeloma. We compared two cohorts of patients according to the period of treatment: before or after 2008. Secondary outcomes were length of ICU stay and total in-hospital mortality. Ninety-day survival was 53%; 1 subject (6%) received a liver transplant during follow-up. Conclusions: TIPS improves eGFR in HRS post-procedure and at 90 days follow-up. Further study is needed to identify those who would benefit from the procedure.
into the following groups: NPO, Tube feed (TF), Total parenteral nutrition (TPN), and Oral (PO). Two competing outcomes were considered: mortality and continued dialysis dependency among survivors.

**Results:** Characteristics among groups were similar. ICU predictive scoring systems and disease etiology were strongly associated with mode of nutrition delivery. High ICU predictive scores were and a surgical primary treating service were associated with a higher percentage of patients treated with TPN. There were significant differences in 60-day outcomes among nutrition groups (p<0.011) [Figure 1]. Notably, PO group had better survival and RRT independency. After adjustment for patient characteristics, the strength of association between mode of nutrition delivery and outcomes weakened and was no longer statistically significant (p=0.106), although the patterns of association were similar to the unadjusted analyses with TPN having the highest and PO the lowest adjusted risks of death and continued dialysis dependency.

**Conclusions:** There was no significant global association between baseline nutrition modalities and 60-day mortality or 60-day dialysis dependence. Further investigation could be performed to prospectively elucidate the benefit of enteral vs. TPN feeding in AKI.

**TH-PO080**

**Pilot Trial of Dietary Restriction for Protection from Acute Kidney Injury in Cardiac Surgery**

Franziska Grundmang1, Torsten Kubacki, Roman-Ulrich Mueller, Maximilian Scherner, Michael Faust, Ingrid Becker, Martin Späth, Marc Johnsen, Thomas Benzing, Volker Rolf Burst. Univ of Cologne, Cologne, Germany.

**Background:** Even small acute changes in kidney function as a result of acute kidney injury (AKI) can result in short-term and long-term complications including chronic kidney disease, end-stage renal disease and death. However, despite an increasing incidence of AKI, few preventive and therapeutic options exist. Short-term reduction of calorie intake has been shown to provide effective protection from ischemic AKI in mice.

**Methods:** In this single-center randomized controlled trial (ClinicalTrials.gov Identifier: NCT01534364) 82 patients with at least one risk factor for postoperative AKI scheduled for cardiac surgery (CABG, valve replacement) were randomly assigned in a 1:1 ratio into a diet group (DG; 60% of calculated energy expenditure for 7 days prior to surgery) or an ad libitum food intake control group (CG). The intention-to-treat population encompassed 76 patients. The primary endpoint was defined as the change in serum creatinine from baseline to 24 hours after surgery, secondary endpoints included incidence of AKI (KDIGO criteria).

**Results:** Demographic and surgery associated characteristics were similar in both groups (DG; 80% male vs. CG 77.5% male; age: DG 72y[63-76] vs. CG 75y[70-77], body weight: DG 84.6kg[72.-91.7] vs. CG 79.1kg[75.0-72.7], crossclamp time: DG 59min[52-82] vs. CG 59min[44-82]). Average calorie intake in the DG was 1323 kcal and a 3 kg[-4.0 to -2.2] weight loss was observed (no weight change in the CG). With respect to the primary outcome measure there was no difference between the groups. Overall incidence of AKI was similar in both groups with considerably less patients with stage 1 AKI in the primary outcome measure there was no difference between the groups. Overall incidence of AKI was similar in both groups with considerably less patients with stage 1 AKI in the DG (n.s.). Length of stay, need for renal replacement therapy and mortality did not differ.

**Conclusions:** Dietary restriction is safe and feasible in patients awaiting cardiac surgery. Dietary restriction in animal studies restriction of calorie intake did not alter serum creatinine dynamics or AKI incidence after cardiac surgery. Funding: Pharmaceutical Company Support - Resmed

**TH-PO081**

**Minute Ventilation-Targeted Adaptive Servo Ventilation Reduces Kidney Injury in Patients with Acute Decompensated Heart Failure**

Matt Kawahara,1 Boris Arbitt,1 Elizabeth Lee,2 Trenton Gluck,2 Kathleen Sarmiento,2 Atul Malhotra,3 Alan S. Maisel.1 1Div of Cardiovascular Medicine, Univ of California, San Diego, La Jolla, CA; 2Div of Pulmonary and Critical Care Medicine, Univ of California, San Diego, La Jolla, CA; 4Cardiac Research, VA San Diego Healthcare System, La Jolla, CA.

**Background:** Acute kidney injury (AKI) is a frequent comorbidity in patients admitted for acute decompenated heart failure (ADHF). Minute ventilation targeted adaptive servo ventilation (MV-ASV) relieves anapnea, pulmonary congestion, and renal hypoxia. Kidney injury molecule (KIM-1) is a marker of AKI and could be used to detect early injury and monitor the improvement of kidney function. MV-ASV may mitigate AKI in patients admitted of ADHF compared to standard care.

**Methods:** This is a pilot study in which twenty-one consecutive patients with ADHF were randomized to receive either MV-ASV therapy (S9 VPA/Adapt, RespMed Corp.) with standard care, or standard care alone. MV-ASV therapy was administered for a minimum of six hours per day for up to 5 days, or until discharge. Daily measurements of plasma KIM-1 were obtained with SMC™ technology (Singulex). Daily serum creatinine levels were measured and used to calculate eGFR.

**Results:** Median baseline KIM-1 levels in the MV-ASV and standard groups were 312pg/mL and 361pg/mL, respectively. In the control group KIM-1 increased 18 % to 426pg/mL while the group with MV-ASV demonstrated a mitigation of kidney injury with a 7% decrease to 290pg/mL. These changes correlated with subsequent changes in serum creatinine and eGFR.

**Conclusions:** The use of MV-ASV therapy resulted in mitigation of kidney injury typically seen in patients with ADHF during hospitalization. Funding: Pharmaceutical Company Support - Resmed

**TH-PO082**

**Early Volume Expansion Improves the Outcome of Shigatoxin-Associated Hemolytic Uremic Syndrome – Data from the North Italian HUS Network**

Giullugi Ardissoni,1 Francesca Tel,1 Ilaria Possenti,1 Sara Testa,1 Dario Consomni,2 Stefania Saradì,3 Rosaria Colombo,1 Erminio Torresani.1 1Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca’ Granda, Ospedale Policlinico, Milan, Italy; 2Unit of Epidemiology, Fondazione IRCCS Ca’ Granda, Ospedale Policlinico, Milan, Italy; 3Unit of Microbiology, Fondazione IRCCS Ca’ Granda, Ospedale Policlinico, Milan, Italy.

**Background:** Shigatoxin-associated hemolytic uraemic syndrome (STEC-HUS) is a severe disease which has no specific treatment and among supportive care, fluid management is concentrated on preventing fluid overload because of oligo/anuric AKI. Volume expansion is associated with more severe disease, but it is unknown whether volume expansion (VE) can improve disease outcome. A network of pediatric hospitals has been operating in Northern Italy with the aim of early diagnosis and referral of STEC infections and to investigate the efficacy of VE to minimize disease severity.

**Methods:** All children with STEC-HUS referred to our centre in 2012-2014 received intravenous saline targeting at inducing a moderate VE (+10% of working weight) on the basis of the hypothesis that prompt restoration of circulating volume can limit thrombi formation and ischemic tissue damage. Their short- and long-term outcomes were compared with those of 38 patients (pts) referred to our centre during the years immediately before the network was established, when their fluid intake was routinely restricted.

**Results:** The pts undergoing VE showed a mean increase in body weight of 12.5%±0.0% in their predecessors and had significantly better short-term outcomes with a reduced rate neurological involvement (7.9%±2.7%, p=0.009), less need for dialysis (26.3%±9.9%, p 0.005) or intensive care support (median 8.5 IR, 3.5-15.5 days, p=0.02), and required fewer days of hospitalisation (median 12.0, IR 7.0-18.0 vs.0.0, IR 7.0-12.0 days, p=0.025). Long-term outcomes were also significantly better in terms of renal and extra-renal sequelae (13%vs.39.5%, p=0.000).

**Conclusions:** PVs with STEC-HUS benefit greatly from VE. Early and generous fluid infusions can reduce thrombi formation and ischemic organ damage, and thus have positive effects on both short- and long-term disease outcomes.

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

Underline represents presenting author.
Role of Statins on Contrast-Induced Nephropathy in Patients Undergoing Percutaneous Coronary Intervention
Nephrology, Hospital Juan A Fernandez, Buenos Aires, Argentina.

Background: The occurrence of contrast-induced kidney injury (CIKI) increased and is responsible for ~10% episodes of hospital-acquired AKI. The mechanism of renal dysfunction is incompletely understood; vasoconstriction, hyperosmolarity, free radicals and direct toxicity may play additive roles. Statins reduce O2 stress, increase renal NO and may prevent AKI. The aim of this retrospective study was to analyse the association between statin and the development of RCIN, defined by an increase in Scr >25% 48–72 h after the administration of low osmolar contrast agents, in high risk patients (Ps) undergoing percutaneous coronary intervention (PCI).

Methods: Data from 165 consecutive adults with Scr >1.25 mg/dl undergoing non-emergent PCI during a 24- mo period were assessed. All had received prophylaxis for RCIN (volume expansion + NAC). 31 Pts were removed due to absence of follow up Scr data or lack of information on statin use. Continuous variables are expressed as mean ± SD (adjusted) and categorical variables as frequency. Unpaired t-test, chi2 or Fisher’s exact test were used as appropriate. Those variables resulting significantly related to RCIN on univariate analysis, were included in a multivariate logistic regression model. P-values <0.05 were considered significant.

Results: 134 Pts met the admission criteria; 67 were on statins prior PCI. Both groups had similar clinical, and laboratory baseline conditions. 18% (13.4%) developed RCIN. There was a lower incidence of RCIN among Pts on statins (4.47%) vs. those not on statins (22.4%) (OR: 0.16, 95% CI: 0.04–0.59; P = 0.004). Multivariate logistic regression revealed that, after adjusting for covariates with significant association with RCIN in the univariate analysis, were included in a multivariate logistic regression model. P-values <0.05 were considered significant.

Conclusions: Our data suggest that statin use before PCI reduces the risk of RCIN. Further prospective, well designed, randomized clinical trials in a larger number of individuals are necessary to confirm these findings.

Risk of new AKI in patients without AKI at enrollment (n=511) OR (Rosuvastatin vs Placebo) p

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Potential Neoprophilic Effects of Carnitine and Phosphodiesterase-5 Inhibitor Therapy in Contrast-Induced Nephropathy
Zaher Anis Armaly,1 Suhail Artul,2 Adel Rafik Jabbour,3 Raymond Farah,4 Amir Abd Elkadir,2 Bishara Bishara.1 1Dept of Nephrology, E.M.M.S. Hospital, Bar Ilan Univ, Nazareth, Israel; 2Dept of Radiology, E.M.M.S. Hospital, Nazareth, Israel; 3Dept of Biochemical Laboratory, E.M.M.S. Hospital, Nazareth, Israel; 4Internal Medicine “B”, Ziv Medical Center, Faculty of Medicine, Bar Ilan Univ, Safed, Israel.

Background: Contrast induced nephropathy (CIN) is connected with prolonged hospitalization, need for dialysis and increased mortality and morbidity. The current available prophylactic measures are not sufficient to protect against CIN. Therefore, there is unmet need for novel therapeutic agents to prevent the development of CIN. This study examines whether phosphodiesterase type 5 (PDE-5) inhibitor or carnitine exert neoprophilic effects in individuals undergoing imaging that involves radiocontrast media (CM) administration as compared with N-acetyl Cysteine.

Methods: The study included 31 cases of patients with CKD (stage 3–4) as follows: 1- Control group (n=14), who were treated with Acetylcysteine of 600 mg twice daily, day before and on the day of CM administration; 2- Carnitine group (n=10), where the patients were infused with 20 mg/kg carnitine over 10 minutes 2 h prior to the CM administration and 24 hours post CT; 3- Phosphodiesterase type 5 inhibitor group (n=12), where patients were given orally 20 mg tablets of PDE5 inhibitor-Tadalafil 2 h prior to the administration of the CM and in the subsequent day. Urine and blood samples were collected before and at the following time sequence: 2, 6, 12, 24, 48, 120 hours after the contrast administration, for creatinine and NGAL determination.

Results: Administration of CM to CKD patients who were pretreated with Acetyl cysteine caused a significant increase in urinary NGAL, but not of plasma NGAL and Scr. In contrast, pretreatment with carnitine prior to CM prevented the increase in urinary NGAL throughout the follow up period and reduced Scr below basal levels. Similarly, tadalafil administration attenuated the elevation in CM-induced urinary NGAL, but did not affect neither plasma NGAL nor Scr.

Conclusions: These results suggest that carnitine and PDE-5 inhibition may comprise novel neoprophilic approaches against CIN.

TH-PO087
Acute Interstitial Nephritis: Case Series, 1998-2015
Yuu-me Li,1 Nephrology, Peking Union Medical College Hospital, Beijing, China.

Background: Acute interstitial nephritis (AIN) is an important cause of acute kidney injury. The time and effectiveness of steroids for treatment of AIN is debated.

Methods: Study Design: Case series. Study population: 40 cases with acute interstitial nephritis (secondary AIN) was excluded) conformal by renal biopsy in PUMC hospital between 1998 and 2015 years were analysed. Outcomes: The complete recovery was defined as improvement in serum creatinine level to 124/150 mL/L; partial recovery as a 50% decrease in serum creatinine level from its peak value, but not reaching to 124/150 mL/L; and no recovery as failure to meet criteria for complete or partial recovery or remaining on renal replacement therapy.

Results: The causes were not available in most cases (63%), 15% were identified due to drugs. Infectious causes were 13%. Idiopathic AIN were 10%. 68% patients had no records of baseline serum creatinine levels, which were available for 13 patients only (200–7.0 umole/l), and 5(38%) patients had CKD as defined by baseline eGFR <60 mL/min/1.73 m2. 30% patients had hematuria. 33% patients had glycosuria. Some degree of proteinuria (less than 1g/L) was present in 75% of patients. 60% patient had anemia.
The cause of AIN may be different. Steroid treatment may be effective in recovery of kidney function of AIN.

**Conclusions:**

Method: We present a prospective study involving 122 patients (48 male and 74 female) who had an elective MRI performed. Subjects have been fasting for at least 8 hrs prior to the imaging. We collected a blood sample 1 hr prior to the imaging and followed up with a repeat blood sample collection 48 hrs after completion of the imaging procedure.

**Results:**

We analyzed these samples for serum creatinine and BUN levels. Preliminary data shows that 46.43 % (52 out of 112) of the study subjects exhibited worsening of renal function while 53.57 % (60 out of 112) had normal or slightly improved renal function.

**Conclusions:**

Preliminary data analysis suggests gadolinium induces nephrotoxicity in a population including patients with chronic kidney disease. We appreciate the limitation of the study which are mainly the number of subjects and the fasting status of subjects. Since there was no exclusions, patient who are on diuretics and ACEI inhibitors could display a higher base line creatinine which might explain the improvement of renal function post study in some subjects.

**TH-PO088**

**Causality Assessment in Determining Drug-Induced Renal Injury**

**Authors:** Celina D. Cepeda; Linda Awduish; Etienne Macedo; Ravindra L. Mehta.

**Nephrology, Univ of California San Diego, San Diego, CA.**

**Background:**

Drug induced renal injury (DIRI) accounts for 18-27% of cases of acute kidney injury (AKI) and is usually recognized based on the timing and duration of drug exposure. The Naranjo (NJ) and Liverpool (LP) causality assessment tools (CAT) are validated for identifying adverse drug reactions and serious skin reactions, respectively. We hypothesized that inter-rater and inter-tool agreement using the two CAT would not be specific to identify DIRI.

**Methods:**

The drug induced renal injury (DIRECT) study is an ongoing prospective multicenter study evaluating genetic determinants of DIRI. Each enrolled case was adjudicated for causality by two independent nephrologists. We analyzed the first consecutive 86 adult (n > 69) and pediatric (n = 17) AKI cases. Two nephrologists adjudicated each case and used both CAT to determine likelihood of AKI due to a particular medication(s). We determined inter-rater and inter-tool agreement using percent agreement and kappa scores.

**Results:**

Adjudicators agreed 87.2% (n = 75) had DIRI. A single drug was involved in 54.7% (n = 47), 2 drugs in 37.2% (n = 32), and 3 drugs in 8.1% (n = 7) of cases. The inter-rater agreement was better with the NJ vs LP tool (61.6% vs 48.8%) and was significant for adults (p = 0.038) however the inter-tool kappa score was slight (0.181) and was fair (0.250) for pediatric patients (p = 0.006).

**Conclusions:**

For most categories, inter-rater percent agreement and kappa scores were superior using the NJ tool. Neither tool had better than moderate inter-rater agreement. Agreement between the tools was at best fair in determining likelihood of DIRI. Better causality assessment tools need to be developed for DIRI.

**Funding:** Private Foundation Support

**TH-PO089**

**Gadolinium Nephrotoxicity**

**Authors:** Kamllesh Reddy Kurre; Ashraf El-Meanaawy; Sameer Gupta.

**Nephrology, Zablocki VA Medical Center, Milwaukee, WI.**

**Background:**

Gadolinium-based contrast (GBC) agents are widely used as contrast agents for magnetic resonance imaging (MRI) and have generally been considered to be safe. Early on, Phase III trials and small studies in low-risk patients suggested a benign renal profile; however, more recent studies raised the possibility of nephrotoxicity. In the US, approximately 34.9 million MRI scans were performed in 2014 and in 45% of these cases a gadolinium chelate was administered. As with iodinated radiocontrast agents, concern for contrast-induced nephropathy existed with gadolinium-contrast as it possessed many similar qualities (hyperosmolar, renal excretion via glomerular filtration). Gadolinium-based contrast agents have recently been reported to induce a usually reversible decrease of glomerular filtration rate in a high-risk population group, especially in patients with altered baseline renal function. The lethal dose of gadolinium in animals is increased by 100 folds when gadolinium is in the form of a chelate. This raise a concern that the leaching of free metal from the chelate can pose health risk.

**Methods:**

We performed a retrospective observational study, including patients 18 years old admitted from 2008 and 2010 at Montefiore Medical Center. All patients had at least two serum creatinine values during their admission and a baseline creatinine within 6 months prior to admission. AKI was defined as a 50% increase in baseline serum creatinine. One year mortality data was from the Social Security Death Index.

**Results:**

Of 46,580 admissions, 2,102 developed AKI (4.7%). 7,889 patients (17%) had exposure to vancomycin, 1,172 patients (2.5%) had exposure to aminoglycosides and vancomycin, 3,700 patients (7.9%) had exposure to fluoroquinolones and vancomycin and 3,994 patients (8.6%) had exposure to cephalosporins and vancomycin. Those developing AKI were more likely female (70% vs 63%; p < 0.001), had GFR < 60 (37% vs 22% p = 0.001) and vancomycin exposure (31% vs 16% p = 0.001). The AKI risk associated with vancomycin alone was 1.55 (1.37, 1.76), combining vancomycin and gentamicin the risk was 1.95 (1.56, 2.45) while vancomycin with fluoroquinolones was 1.38 (1.17, 1.63) and vancomycin with cephalosporins was 1.37 (1.16, 1.62). The risk of mortality associated
with vancomycin alone was 2.27 (2.06, 2.49), combining vancomycin and gentamicin the risk was 2.52 (2.36, 4.74). Using vancomycin alone with the quadrivalent vaccine, the risk was 3.42 (3.05, 3.84), and combining vancomycin with cephalothin the risk was 2.62 (2.34, 2.95).

Conclusions: Our data suggests that vancomycin exposure is associated with a high risk of AKI and mortality, especially in combination with aminoglycosides. Further studies should be conducted to evaluate whether aminoglycosides should not be used in combination with vancomycin in order to prevent AKI.

TH-PO092
Adverse Renal Effects of Targeted Anti-Cancer Therapies: A Systematic Review of Data from the FDA Adverse Event Reporting System

Background: Novel molecular targeted anti-cancer therapies have shown improvement in patient survival compared to standard chemotherapy. Renal toxicities of novel targeted therapies are limited to case reports.

Methods: We reviewed the FDA Adverse Event Reporting System’s (FAERS) quarterly legacy data file (2011-2014). We queried the database for medications listed below. The adverse events queried were: hypokalemia, hyponatremia, hypophosphatemia, proteinuria, renal failure acute. To compare what has been published, we searched PubMed for each medication plus each adverse event.

Results: Total number of adverse events reported were 1,657. Ipilimumab had the highest number of events (341) and these were mostly acute renal failure (126) and hyponatremia (112). In PubMed review all case reports were diagnosis of renal failure. To compare what has been published, we searched PubMed for each medication plus each adverse event.

Conclusions: Our data elucidate previously unknown adverse renal events in targeted therapies. Older males are at higher risk for renal failure and females are at higher risk for electrolyte disorders from certain targeted anti-cancer therapies.

TH-PO093
Vemurafenib and Dabrafenib Related Renal Toxicities
Kenan D. Jhaveri, Rimda Wanchoo, Vipulbhai Sakhiya, Steven Fishbane. Nephrology, Hofstra NSLIJ School of Medicine, NY.

Background: Vemurafenib and dabrafenib, selective BRAF inhibitors have shown significant improvement in patient survival compared to standard therapy in V600 mutation metastatic melanoma. No cases of AKI have been reported with dabrafenib use. AKI has been recently reported in few case series with vemurafenib use. One case series included a patient who had a kidney biopsy demonstrating acute tubular necrosis as a potential mechanism of renal injury.

Methods: We reviewed the FDA Adverse Event Reporting System’s (FAERS) quarterly legacy data file from 3rd quarter of 2011 to 2nd quarter of 2014 for vemurafenib and 2nd quarter of 2013 to 2nd quarter of 2014 for dabrafenib. Vemurafenib and dabrafenib related renal adverse event data were extracted through formation of a query using FAERS assigned unique case identifiers. Search terms utilized were “renal insufficiency, elevated creatinine, renal failure, renal injury, proteinuria, renal impairment, blood creatinine increase, renal failure acute, low phosphorus, hypophosphatemia, hypercreatinemia, hypotension, hypokalemia, renal damage”.

Results: 132 cases of AKI were reported secondary to vemurafenib to the FAERS in the time frame reviewed. Eighty five patients were men and 47 women (p = 0.01). Average of the men was 65 years and 59 years for the women (p = 0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from the time frame reviewed.

Conclusions: While the FAERS reporting system is a crude database with scant demographic information, the number of cases reported of AKI is still alarming with the BRAF inhibitors. Vemurafenib appears to be more nephrotoxic than dabrafenib. This renal toxicity seems to be more prominent among male patients with melanoma. Dermatologists, oncologist and nephrologists need to be made aware of this important toxicity.
Creatinine Changes After Contrast: Chloride Poor versus Chloride Rich Solutions

Asish Thakkar, Rima Kang, Salem Almaani, Udayan Y. Bhatt.
Nephrology, The Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: There has been recent emphasis on utilization of chloride poor solutions for the prevention of acute kidney injury (AKI). The purported mechanism is the potential for chloride rich fluids to possibly impair renal blood flow. Similarly, exposure to intravenous radiographic contrast is known to induce renal vasoconstriction. Given these findings, the objective of this project was to examine the effect of chloride rich versus chloride poor intravenous (IV) fluids on the change in serum creatinine occurring after IV contrast administration.

Methods: This project was performed under an IRB-approved Honest Broker Protocol. Retrospective data was obtained from patients receiving IV contrast over a 4 week period. Variables collected included: age, race, gender, type of contrast procedure, baseline creatinine, creatinine at days 1 and 2, and all intravenous medications. Chloride rich solutions (normal saline) and chloride poor solutions (sodium bicarbonate, Plasmalyte, and Lactated Ringers) were identified. Multivariate linear modelling was used to examine the primary endpoint of change in creatinine at day 2 relative to baseline (delta creatinine).

Results:

<table>
<thead>
<tr>
<th>Cl Poor(N=22)</th>
<th>Saline(N=220)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62±21.6</td>
<td>58±36.5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66 (27.3%)</td>
<td>120 (54.5%)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 (81.8%)</td>
<td>172 (78.2%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Heart Catheterization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5±2.1%</td>
<td>56.5%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Baseline Creatinine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3±0.68</td>
<td>0.9±0.49</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Delta Creatinine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09±1.00</td>
<td>0.06±3.37</td>
<td>NS</td>
</tr>
</tbody>
</table>

Multivariate analysis: Delta Creatinine-Chloride rich vs Cl poor

| Saline | p-value | 0.000 |

The change in creatinine after IV contrast in the chloride rich group, after adjusting for all variables including baseline creatinine, was 0.37±0.09 lower than in the chloride poor group (p=0.000).

Conclusions: Patients receiving chloride rich IV solutions appeared to have a significantly lower change in serum creatinine after administration of IV contrast compared to patients receiving chloride poor solutions. On this basis, more investigation is needed for all variables including baseline creatinine, was 0.37±0.09 lower than in the chloride poor group.

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

112A
CHALLENGES TO IMPACT MORTALITY IN SIMILAR FASHION. WE HOPE TO GAIN INSIGHT INTO MORE PROSPECTIVE RESEARCH ON CRRT WITH AKI.

129 PATIENTS WERE WEANED FROM ECLS, 92 OF WHICH SURVIVED TO DISCHARGE. SURVIVAL WERE THESE WERE VA ECMO (41 PATIENTS) AND THE REST WERE VV ECMO (20 PATIENTS). A TOTAL OF MEASUREMENTS WE LOOKED AT WERE OVERALL SURVIVAL, ABILITY TO WEAN FROM ECLS OR BRIDGE TO KIDNEY INJURY BY RIFLE CRITERIA AND NEED FOR RENAL REPLACEMENT THERAPY. SPECIFIC OUTCOME PATIENT DEMOGRAPHICS, TYPE OF ECLS, INDICATION, LOCATION, COMORBIDITIES, INCIDENCE OF ACUTE KIDNEY INJURY BY RIFLE CRITERIA AND NEED FOR RENAL REPLACEMENT THERAPY. MACHINE ALARMS WOULD HAVE TO BE INTERPRETED IN LIGHT OF CIRCUIT POSITION, MODALITY WERE BASED ON PHYSICIAN DISCRETION REGARDING OTHER PATIENT COMORBIDITIES, TYPE OF EXTRACORPOREAL LIFE SUPPORT. OF THESE CASES, 61 REQUIRED RENAL REPLACEMENT THERAPY.

RESULTS: THIS STUDY REPRESENTS AN ANALYSIS OF 73 OF A PLANNED 90 SUBJECTS. WE FOUND THAT 14% SUBJECTS ACHIEVED 100% OF PRESCRIBED DOSE, 53% ACHIEVED 80%-99% AND 33% ACHIEVED < 80%. MEAN PRESCRIBED DOSE WAS 25 ML/KG/HR AND ACHIEVED DOSE WAS 20 ML/KG/HR. ACCESS/FILTER PROBLEMS WERE PRESENT IN 63.4%, IMAGING/PROCEDURE 12%, ELECTROLYTE IMBALANCE 2% AND NO CLEAR REASON DOCUMENTED IN 19.2% WHEN GOAL DOSE WAS NOT ACHIEVED. SUBJECTS IN WHOSE CVVH WAS NOT INTERRUPTED ACHIEVED G= 96% OF PRESCRIBED DOSE WHICH WAS STATISTICAL SIGNIFICANT (P=0.001) COMPARED TO 76.5% ACHIEVED IN SUBJECTS THAT HAD INTERRUPTIONS.

CONCLUSIONS: IN A NON-STUDY POPULATION THE PROPORTION OF PATIENTS WHO DO NOT ACHIEVE PRESCRIBED DOSE IS VERY LARGE. IN ORDER TO ACHIEVE A DOSE OF 20 ML/ KG/HR EFFLUENT VOLUME THE PRESCRIBED DOSE MAY NEED TO BE SIGNIFICANTLY HIGHER IN A NON-STUDY POPULATION. TIMELY CORRECTION OF ACCESS/FILTER PROBLEMS IS ANOTHER AREA OF FOCUS WHICH MAY NEED ATTENTION FOR BETTER DOSE ACHIEVEMENT.

TH-PO102
PRESCRIBED VERSUS DELIVERED DOSE OF CONTINUOUS VENO-VENOUS HEMODIALYSIS IN A NON-STUDY POPULATION
AUGA R FRAHMAN, MAJID A KHAN, AKSHAR N PATEL, KRISTAL HUNTER, LAWRENCE S. WEISBERG, WILLIAM D. SIROVER, CHRISTOPHER B. MCFADDEN. NEPHROLOGY, COOPER UNIV HOSPITAL, CAMDEN, NJ.

BACKGROUND: CRITICALLY ILL PATIENTS REQUIRING CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT) EXPERIENCE HIGH MORTALITY RATES. IN RANDOMIZED STUDIES, INTENSIFICATION OF CRRT BY INCREASING EFFLUENT VOLUMES FROM 20 TO 35 ML/KG/HR DID NOT IMPROVE SURVIVAL. THESE STUDIES ESTABLISHED ACHIEVEMENT OF PRESERVED DOSE. WE EVALUATED HOW OFTEN A SUBJECT ACHIEVES THE PRESCRIBED DOSE IN A NON-STUDY POPULATION.

METHODS: WE CONDUCTED A RETROSPECTIVE, OBSERVATIONAL CROSS SECTIONAL STUDY AND EXAMINED THE ELECTRONIC MEDICAL RECORDS (EMR) OF SUBJECTS RECEIVING CRRT. AN AUTOMATED, REAL TIME WIRELESS LINK FROM THE DIALYSIS MACHINES TO EMR, CONTAINED DATA ON THE CRRT SETTINGS AND HOURLY EFFLUENT VOLUMES. WITH THIS DATA WE CALCULATED PERCENTAGES OF PRESCRIBED DOSAGES ACHIEVED AND COMPARED SUBJECTS WHO DID OR DID NOT ACHIEVE THE PRESCRIBED DOSE. ACCESS PROBLEMS, PROCEDURES, ELECTROLYTE DISTURBANCE OR NO CLEAR REASON DOCUMENTED WERE INVESTIGATED AS VARIABLES IN SUBJECTS NOT ACHIEVING PRESCRIBED DOSES. PEARSON CHI SQUARE OR FISHER EXACT TESTS WERE USED TO COMPARE DICHTOMOUS, AND INDEPENDENT T TEST OR MANN WHITNEY U TESTS WERE USED TO COMPARABLE CONTINUOUS VARIABLES.

RESULTS: THIS STUDY REPRESENTS AN ANALYSIS OF 73 OF A PLANNED 90 SUBJECTS. WE FOUND THAT 14% SUBJECTS ACHIEVED 100% OF PRESCRIBED DOSE, 53% ACHIEVED 80%-99% AND 33% ACHIEVED < 80%. MEAN PRESCRIBED DOSE WAS 25 ML/KG/HR AND ACHIEVED DOSE WAS 20 ML/KG/HR. ACCESS/FILTER PROBLEMS WERE PRESENT IN 63.4%, IMAGING/PROCEDURE 12%, ELECTROLYTE IMBALANCE 2% AND NO CLEAR REASON DOCUMENTED IN 19.2% WHEN GOAL DOSE WAS NOT ACHIEVED. SUBJECTS IN WHOSE CVVH WAS NOT INTERRUPTED ACHIEVED G= 96% OF PRESCRIBED DOSAGE WHICH WAS STATISTICAL SIGNIFICANT (P=0.001) COMPARED TO 76.5% ACHIEVED IN SUBJECTS THAT HAD INTERRUPTIONS.

CONCLUSIONS: IN A NON-STUDY POPULATION THE PROPORTION OF PATIENTS WHO DO NOT ACHIEVE PRESCRIBED DOSE IS VERY LARGE. IN ORDER TO ACHIEVE A DOSE OF 20 ML/ KG/HR EFFLUENT VOLUME THE PRESCRIBED DOSE MAY NEED TO BE SIGNIFICANTLY HIGHER IN A NON-STUDY POPULATION. TIMELY CORRECTION OF ACCESS/FILTER PROBLEMS IS ANOTHER AREA OF FOCUS WHICH MAY NEED ATTENTION FOR BETTER DOSE ACHIEVEMENT.

TH-PO103
A PREDICTIVE MODEL FOR SUCCESSFUL CONVERSION OF CONTINUOUS RENAL REPLACEMENT THERAPY TO INTERMITTENT HEMODIALYSIS FOR ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS
JI HYEON PARK, JEE EUN PARK, SUBIN HWANG, HYE RYOUN JANG, WOOSEONG HAH, DAOJONG KIM, YOON-GOO KIM, HA YOUNG OH, JUNG EUN LEE. Nephrology, Samsung Medical Center, Seoul, Korea.

BACKGROUND: CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT) IS PREferred MODALITY OF RENAL REPLACEMENT THERAPY (RRT) IN CRITICALLY ILL PATIENTS WITH ACUTE KIDNEY INJURY (AKI). HOWEVER, IT HAS SEVERAL DISADVANTAGES SUCH AS HIGH COST AND RISK OF CONTINUOUS ANTIcoagulation. THEREFORE, INITIAL APPLICATION OF CRRT AND SUBSEQUENT CONVERSION TO intermittent hemodialysis (IHd) COULD BE PRACTICAL. HOWEVER, THERE HAS BEEN NO STANDARD CRITERIA FOR optimal timing of conversion to IHd IN patients receiving CRRT. THE AIM OF THIS STUDY WOULD BE TO DEVELOP A PREDICTIVE MODEL FOR successful conversion of CRRT TO IHd.

METHODS: THIS CASE-CONTROL STUDY WAS CONDUCTED BY RETROSPECTIVE chart review. WE IDENTIFIED 513 ADULT PATIENTS WHO RECEIVED CRRT AT LEAST 24 HOURS AND THEN IHd SUBSEQUENTLY IN ICU BETWEEN APRIL 2009 AND FEBRUARY 2014. FAILURE IN CONVERSION TO IHd WAS DEFINED WHEN CRRT WAS RE-APPLIED WITHIN 72 HOURS AFTER CRRT STOP, AND 83 OUT OF 513 PATIENTS CORRESPONDED FAILURE CRITERIA: failure group. Equal number of patients were selected randomly from remaining 430 patients: success group.

RESULTS: CARDIOVASCULAR (CV) SOFA score and neurologic (NR) SOFA score at CRRT stop day were only two independent predictors of conversion failure. The risk of failure was determined between score 0.1 and score 2.4 for both CV and NR SOFA. CV SOFA score 2.4 was associated with 15 fold increased Odds ratio for failure (95% CI. 4.6 - 38.3, OR 15.0). NR SOFA score 2 was associated with poor survival for failure (95% CI. 2.6 - 11.4, Ref 0.1). Final prediction model included CV SOFA and NR SOFA weighting CV SOFA (≥ 2) as 2 points and NR SOFA (≥ 2) as 1 point. Risk score ranged from 0 to 3 points (0; 47%, 1; 29%, 2; 13%, 3; 11%). The performance of this model was acceptable with area under the receiver operating characteristic curve of 0.79 (95% CI. 0.77-0.86).

CONCLUSIONS: THE PREDICTION MODEL MIGHT PROVIDE AN OBJECTIVE CRITERIA FOR CONVERSION OF CRRT TO IHd IN patients receiving CRRT and contribute to establish cost-effective protocol of RRT for AKI in critical ill patients.
Mortality Factors in Septic Shock Patients Requiring Continuous Renal Replacement Therapy and Timing Effect Based in Urine Output

Xosé Luis L. Perez-Fernández, Florentina E. Sileanu, Joan Sabater Riera, Kathleen D. Liu, John A. Kellum, 1,2 Servei de Medicina Intensiva, Hospital Universitari de Bellvitge, L’Hospital de Llobregat, Barcelona, Spain; 3 Critical Care, University of Pittsburgh Medical Center, Pittsburgh, PA; 4 Nephrology & Critical Care, Univ California San Francisco Parnassus MC, San Francisco, CA.

Background: Our primary objective was to identify factors associated with mortality in patients with septic shock and severe acute kidney injury (AKI) in order to design future interventional trials.

Methods: Observational retrospective study conducted in two tertiary care hospitals with more than 100 intensive care unit (ICU) beds each. Data were from 2000-2008 at UPMC (Pittsburgh, USA) and 2006-2012 at HUB (Barcelona, Spain). The final cohort included 938 patients who received CRRT and presented with septic shock. Cox models were used to identify variables associated with 90 day mortality. Timing analyses were performed in patients with severe AKI at ICU admission who were started on RRT within the first 5 days of ICU stay.

Results: Overall 90-day mortality was 62.9%. Independent risk factors for death included: age, SOFA score at ICU admission, days from hospital admission to ICU admission, days from ICU admission to CRRT initiation, and medical (vs surgical) admission. Both lower creatinine at CRRT start and lower urine output in the 24 hours before start of CRRT were associated with lower survival. ROC curve analysis identified urine output less than 500 mL in the 24 hours prior to CRRT initiation as the best variable to discriminate between survivors and non-survivors.

Conclusions: In patients with septic shock and advanced AKI (KDIGO stage 3), survival is lower when CRRT is started in the setting of low urine output. However, whether this finding represents differences in severity of illness between study subjects or is a useful tool to CRRT initiation needs to be evaluated in a future randomized controlled trial.

Funding: Government Support - Non-U.S.

Outcomes in Acute Kidney Injury Patients Undergoing Continuous Venovenous Hemodiafiltration and Regional Citrate-Based Anticoagulation: A Comparison Between Individuals with and without Liver Dysfunction

Thais OC Santos, Marisa S. Oliveira, Henrique Pinheiro Konigfeld, Virgilio Gonçalves Pereira, Marcelo Costa Batista, Oscar Santos, Julio M. Monte, Marcelino Souza Durão, Univ Federal de São Paulo, Brazil; 2Hospital Israelita Albert Einstein, Brazil.

Background: Regional citrate-based anticoagulation (RCA) has been widely used in intensive care unit (ICU) to treat subjects with acute kidney injury (AKI). Patients with liver failure (LF) have citrate metabolism impairment and are likely to experience citrate toxicity.

Methods: A prospective observational study was performed in a private hospital comparing clinical and laboratory data including citrate (C) plasma concentration from patients with and without LF. DF was defined as an International Normalized Ratio (INR) ≥2.5. Trisodium-citrate 4% was infused in the dialysis system to keep post-filter ionized calcium between 0.25-0.35 mmol/L. Patients with LF had a fixed-set infusion of 17 mmol/h (120 ml/h) regardless of the post-filter ionized calcium value.

Results: Two hundred patients were evaluated. LF group patients showed a higher mortality rate (70.5% vs 51.8%, p=0.014). CI was significantly higher in the LF group (median 2.68 vs 1.42, p<0.001), lactate levels (median 34 vs 16 mmol/L, p=0.001) and lower serum bicarbonate (median 15.8 vs 19.4 mmol/L, p=0.001) at baseline, as well as throughout the study period. There was no significant difference regarding systemic ionic calcium levels. LF group patients also underwent more red blood cell transfusions (median 3 vs 1, p=0.001). LF group showed higher mortality. Despite the LF group have presented higher citrate levels, there were no signs of toxicity, especially ionized hypocalcemia. There was a poor correlation between CaT/Cai ratio, a predictor of citrate toxicity, and Ci levels. LF group patients also underwent more red blood cell transfusions (median 3 vs 1, p=0.001) and total dialysis time. Analyzing the relationship between serum levels of citrate and total calcium/ionic calcium ratio (CaT/Cai), we found a weak positive correlation, with a correlation coefficient of 0.354.

Conclusions: LF group showed higher mortality. Despite the LF group have presented higher citrate levels, there were no signs of toxicity, especially ionized hypocalcemia. There was a poor correlation between CaT/Cai ratio, a predictor of citrate toxicity, and Ci levels.

Funding: Government Support - Non-U.S.

Outcomes in a Cohort of Patients with Acute Kidney Injury Submitted to Continuous Venovenous Hemodiafiltration: The Role of Negative Fluid Balance and Early Dialysis

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Background: Several factors are associated with adverse outcomes in acute kidney injury (AKI). These include some comorbidities, sepsis, high prognosis scores, positive fluid balance, and delay in beginning dialysis.

Methods: In a prospective and observational study, we evaluated risk factors for death in 183 patients with AKI requiring continuous venovenous hemodiafiltration (CVVHDF).

Results: Sepsis was the main cause of AKI (57%). Overall mortality was 58%. The median body weight (51 kg) and fluid balance (361 mL) during dialysis was -4 mL/hr for survivors and +1646 mL among the survivors. There were 114 oliguric independent. Risk factors for death in multivariate analysis were chronic obstructive pulmonary disease (COPD) (OR 3.07, 95% CI 1.06 to 1.50, p=0.047), liver cirrhosis (OR 4.47, 95% CI 1, 77 vs 0.002), hemodynamic hypotension (OR 6.19, 95% CI 1.83 to 20.93, p=0.003), oliguria (OR 3.01, 95% CI 1.43 -6.32, p=0.004), positive cumulative FB during dialysis (OR 1.13, 95% CI 1.06 to 1.20, p=0.001) and time between ICU admission and beginning of CVVHDF (OR 1.13, 95% CI 1.01 to 1.25, p=0.039). Among survivors, nearly 30% were discharged on warfarin for other indications. Poor APACHE II scores were associated with highest mortality at 81.06 % vs. 67.02 % in patients who underwent CVVH.

Conclusions: We identified 1240 (3.4%) patients who received dialysis treatment within 28 days of a diagnosis of myeloma. In Kaplan-Meier analysis patients who did not receive dialysis had better median overall survival (3 years; interquartile range [IQR] 0.7-8.1) than patients who received dialysis (1.4 years; IQR 0.2-4.8). From 2006 to 2010 survival improved from 2.6 years [IQR 0.6-7.7] to 3.3 years [IQR 1.0-6.2] for patients who did not receive dialysis and 0.6 [IQR 0.1-2.7] to 1.2 years [IQR 0.4-4.0] for those who received dialysis respectively. Compared to patients who did not receive dialysis, those who received dialysis were more likely to be older, male, and less socio-economically deprived.

Conclusions: Dialysis is a major independent risk factor for increased mortality in patients with myeloma; the overall survival of patients with myeloma requiring dialysis is improving.


Background: In the ICU setting, Acute Renal Failure is a part of multiple organ dysfunction syndrome with mortality in these patients ranging from 28%-90%. Continuous Venovenous hemofiltration (CVVH) is most commonly used for renal replacement therapy in ICUS. The objective of this study is to describe demographic characteristics and to establish an association between these characteristics and variables that define the severity of illness and in-hospital mortality outcomes of patients undergoing CVVH.

Methods: Medical records of patients who underwent CVVH from January 2007 to December 2013 in the intensive care at our institution were analyzed. Chi square test was done for categorical variables. Descriptive analysis was used to identify demographic data.

Results: 233 patients underwent CVVH from January 2007 to December 2013. The overall mortality was 75.22%. 49.3% of patients required ventilatory support. Acute respiratory failure requiring mechanical ventilation was associated with significantly increased mortality, 76.74% vs 40.0% (p=0.04) in patients who did not require mechanical ventilation. Septic Shock was the most common reason for ICU admission, 71.2% followed by non-operative admissions at 18.8%. The most common indication for CVVH was ATN (63.5%) followed by hyperkalemia (57.0%). However, CVVH for metabolic acidosis was associated with highest mortality at 81.06 % vs. 67.02 % in patients who underwent CVVH for other indications. Poor APACHE II scores were associated with higher mortality. Scores ranging from 0-24 were associated with an overall mortality of 49.9% whereas scores between 25-30 were associated with a small mortality of 19.7%.

Conclusions: This observational study in patients undergoing CVVH in an ICU setting revealed that patients presenting with worse baseline APACHE II scores had poor in-hospital outcomes. CVVH initiation for metabolic acidosis and use of mechanical ventilation was associated with higher mortality. There are no established guidelines for use of CVVH. This study may aid in delineating the group of patients who may benefit the most from use of CVVH and help us in more judicious use of health care resources. .
TH-PO109
Clinical Effectiveness of Diuretics following Continuous Renal Replacement Therapy
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Background: There is no consensus regarding diuretics administration in acute kidney injury (AKI) in patients weaning from continuous renal replacement therapy (CRRT). The effect of diuretics on the clinical course of critically ill patients with AKI was analyzed focusing on urine output and renal recovery following CRRT. In addition, we tried to identify the most optimal administration method of diuretics.

Methods: Data of 1231 adult patients who survived more than 3 days after discontinuing CRRT between September 2009 and December 2014 were included. Changes in renal function and urine output as well as the prescription of diuretics during the 3 days after discontinuation of CRRT were retrospectively analyzed. Patients were categorized depending on re-initiation of RRT within 3 days.

Results: There was no difference in baseline characteristics among all groups. CRRT cessation group had greater urine output after discontinuation of CRRT compared with other groups. Overall, patients who were treated with diuretics (diuretics subgroup) showed greater urine output than patients without diuretics (control subgroup) after cessation of CRRT and there was no difference in the degrees of serum creatinine elevation between control and diuretics subgroups. In CRRT cessation group, continuous infusion of furosemide showed greater urine output compared to other administration methods. However, serum creatinine increased significantly compared to other methods when the infusion was continued for more than 1 day.

Conclusions: Diuretic therapy following CRRT increases urine output significantly without causing significant deterioration of renal function. Compared with other methods using diuretics, continuous infusion of furosemide increases urine output significantly, but also increases serum creatinine for more than 1 day. Our study suggests that diuretics in patients who had received CRRT may be clinically useful.

TH-PO110
The Prognostic Value of Volume Status Assessment by Bioelectrical Impedance Analysis and Lung Ultrasound on Mortality in Septic Acute Kidney Injury Patients Undergoing Continuous Renal Replacement Therapy
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Background: Volume overload affects clinical outcome in patients with acute kidney injury (AKI). However, the significance of various methods to evaluate volume status has not been fully evaluated. Therefore, the prognostic value of volume status assessment measured by bioelectrical impedance analysis (BIA) and lung ultrasound (US) on mortality was investigated in septic AKI patients requiring continuous renal replacement therapy (CRRT).

Methods: Septic AKI patients requiring CRRT between April 2014 and February 2015 at Yonsei University Health System were included. Surrogates of volume status were 1) percent of body weight change between CRRT initiation and admission day, 2) over-hydration (OH)/extracellular water (ECW) measured by BIA, and 3) B-lines measured by lung US. Prognostic values of surrogates of volume status for 28-day mortality were evaluated.

Results: Among the 36 enrolled patients, 19 (52.8%) patients died during the follow-up duration. The mean percentage of weight change and OH/ECW measured by BIA was 5.3±20.7% and 0.3±0.1 L/L. The median number of B-lines counted by lung US was 6 (interquartile range, 4-10). OH/ECW was significantly correlated (r=0.39, P=0.02) with 48-hour fluid balance before CRRT initiation, while the number of B-lines was not. Kaplan-Meier analysis showed that 28-day mortality was higher in patients with the highest OH/ECW tertile compared to patients with lower OH/ECW values (P=0.02). Percent of weight change and the number of B-lines were not significantly associated with 28-day mortality (P=0.04 and P=0.45, respectively). Multivariate Cox proportional hazard regression analysis showed that higher OH/ECW was an independent risk factor for 28-day mortality after adjustment of confounding factors (HR=3.83, 95% CI=1.04-14.03, P=0.04).

Conclusions: Higher OH/ECW measured by BIA was an independent risk factor for 28-day mortality in septic AKI patients undergoing CRRT. Determining fluid status by BIA could be a useful method to stratify mortality risk in this patient group.

TH-PO111
Effect of Fluid Overload on the Outcome Among Acute Kidney Injury Patients Receiving Renal Replacement Therapy After Cardiac Surgery
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Background: We explored the effect of fluid overload in different periods on the outcomes among acute kidney injury (AKI) patients receiving renal replacement therapy (RRT) after cardiac surgery in order to guide the fluid management strategy.

Methods: Clinical data of patients who developed AKI requiring RRT after cardiac surgery from January 2009 to April 2014 in our hospital were prospectively analyzed.

Results: The total 1800 phosphate measurements in day 0, 1 and 2 were evaluated. With 49 patients (8%), 93 patients (15%) and 142 patients (23%) with hypophosphatemia, the prevalence of total and free phosphate were significantly increased with time on RRT. At baseline, 26.6% and 40% of patients were TC and FC deficient. Within 48-hour fluid balance before CRRT initiation, while the number of B-lines was not. Kaplan-Meier analysis showed that 28-day mortality was higher in patients with the highest OH/ECW tertile compared to patients with lower OH/ECW values (P=0.02). Percent of weight change and the number of B-lines were not significantly associated with 28-day mortality (P=0.04 and P=0.45, respectively). Multivariate Cox proportional hazard regression analysis showed that higher OH/ECW was an independent risk factor for 28-day mortality after adjustment of confounding factors (HR=3.83, 95% CI=1.04-14.03, P=0.04).

Conclusions: Carnitine is significantly and rapidly depleted with longer time on CRRT, and degree of deficiency is associated with increased mortality. Consequences of deficiency and benefits of supplementation in the pediatric CRRT population should be investigated.

TH-PO112
Carnitine Deficiency in Children Receiving Continuous Renal Replacement Therapy
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Background: Carnitine deficiency is known to occur in chronic hemodialysis, however the effect of continuous renal replacement therapy (CRRT) on carnitine homeostasis has not been studied. The purpose of this study was to investigate carnitine deficiency in critically ill patients with acute kidney injury undergoing CRRT in the pediatric intensive care unit. We hypothesized that patients receiving CRRT are at risk for deficiency due to continuous removal of carnitine and comorbidities related to critical illness.

Methods: Records of patients with acute kidney injury receiving CRRT at Children’s National between 2011 and 2015 were reviewed for total carnitine (TC), free carnitine (FC), Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score indicators, and survival outcome. PELOD-2 score was calculated to measure of severity of illness on a scale from 0 to 33 (maximum severity of illness). The proportion of carnitine deficient patients at baseline, 1, 2, and ≥ 3 weeks on CRRT were compared by Chi square, and relationships with other variables assessed by Pearson’s correlation and linear regression.

Results: The study group included 44 CRRT patients, age 8.1 ±1.1 years. Severity of illness of the population determined by PELOD-2 score ranged from 2 to 19 (mean 11.2 ± 0.43). Of 44 patients, only 14 (31.8%) survived. The prevalence of total and free carnitine deficiency, according to age-and-sex- specific reference values, significantly increased with time on CRRT. At baseline, 26.6% and 40% of patients were TC and FC deficient. Within 1 week, 65.6% (p=0.01) and 71% (p=0.04) were TC and FC deficient, and prevalence of deficiency increased to 80% (p=0.008) and 98% (p=0.01) by 2 weeks; 100% of patients were deficient 3 weeks (p=0.002 and p=0.01, respectively, vs. baseline). TC and FC deficiency was positively correlated with days on CRRT (r=0.4, p=0.001 and r=0.37, p=0.03). Lower TC and FC levels significantly associated with higher mortality (β=1.0, p=0.03 and β=8.6, p=0.02 respectively).

Conclusions: Carnitine is significantly and rapidly depleted with longer time on CRRT, and degree of deficiency is associated with increased mortality. Consequences of deficiency and benefits of supplementation in the pediatric CRRT population should be investigated.

TH-PO113
The Relationship Between Hypophosphatemia and Outcomes During Two Different Intensities of Continuous Renal Replacement Therapy
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Background: To identify risk factors for development of hypophosphatemia in patients treated with two different intensities of continuous renal replacement therapy (CRRT) and to assess the independent association of hypophosphatemia with major clinical outcomes.

Methods: We performed retrospective analysis of data collected from 620 patients. We allocated patients to two different intensities of CRRT (more than or less than 40 mL/kg/hour of effluent generation) and obtained daily measurement of serum phosphate levels. We obtained total 1000 phosphate measurements in day 0,1 and 2 and identified 49 patients (8%), 93 patients (15%) and 142 patients (23%) with hypophosphatemia. With lower intensity CRRT, there were 23 episodes of hypophosphatemia/1000 patient days, compared with 83 episodes/1000 patient days with higher intensity CRRT (P < 0.01).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only.
Of multivariable logistic regression analysis, higher intensity CRRT and hypokalemia were independently associated with an increased odds ratio (OR) for hypophosphatemia. The annual prevalence of such therapy per 1,000,000 human exposures was evaluated. The top 30 substances reported among all deaths were characterized among patients receiving HD.

Results: There were 18,252 patients who received ECT, of which 17,900 (98.0%) received HD, 257 received RP, and 214 received other ECT. The patient population was predominantly 40–59 years of age (45.0%). Poisonings were acute in 56.7% of patients. The prevalence of ECT (per million human exposures) was 865 in 2006 versus 1,140 in 2013. The most substances frequently identified among patients receiving HD included ethylene glycol (n=3,828), lithium (n=3,385), sedatives (n=2,711), salicylates (n=2,352), and opioids (n=1,783). Overall, 9.4% of patients receiving ECT for poisoning died. The three leading substances reported among all deaths included acetaminophen (22.1%), opioids (18.3%), and sedatives (15.3%).

Conclusions: The use of HD in the management of poisoning has continued to increase. While ethylene glycol, lithium, and salicylates remain frequent indications for dialysis, HD seems to be used more often in a supportive role as well given the number of patients treated for opioid and sedative poisoning. We were not able to distinguish the use of intermittent HD versus continuous renal replacement due to database limitations. Hemoperfusion has continued to be rarely used.

TH-POI116

Nationalwide Use of Hemodialysis and Other Extracorporeal Therapies in Poisoned Patients, 2006-2013

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Background: Nationwide use of extracorporeal therapies (ECT) in poisoned patients has not been characterized since 2005. The purpose of this study was to review the use of hemodialysis (HD), hemoperfusion (HP), and other ECT in poisoned patients throughout the United States from 2006 until 2013.

Methods: The National Poison Data System (NPDS) was queried for all poisoning cases reported to U.S. poison centers between 2006 and 2013 where HD, HP, or other ECT was performed. Data analyzed included demographics and geography, clinical characteristics, exposure chronology, and reported substances used by patients. The annual prevalence of each therapy per 1,000,000 human exposures was evaluated. The top 30 substances reported among all deaths were characterized among patients receiving HD.

Results: There were 18,252 patients who received ECT, of which 17,900 (98.0%) received HD, 257 received RP, and 214 received other ECT. The patient population was predominantly 40–59 years of age (45.0%). Poisonings were acute in 56.7% of patients. The prevalence of ECT (per million human exposures) was 865 in 2006 versus 1,140 in 2013. The most substances frequently identified among patients receiving HD included ethylene glycol (n=3,828), lithium (n=3,385), sedatives (n=2,711), salicylates (n=2,352), and opioids (n=1,783). Overall, 9.4% of patients receiving ECT for poisoning died. The three leading substances reported among all deaths included acetaminophen (22.1%), opioids (18.3%), and sedatives (15.3%).

Conclusions: The use of HD in the management of poisoning has continued to increase. While ethylene glycol, lithium, and salicylates remain frequent indications for dialysis, HD seems to be used more often in a supportive role as well given the number of patients treated for opioid and sedative poisoning. We were not able to distinguish the use of intermittent HD versus continuous renal replacement due to database limitations. Hemoperfusion has continued to be rarely used.

TH-POI117

Dialysis Treatment Options for Acute Kidney Injury in the Canadian Intensive Care Unit: A Systematic Review and Cost-Utility Analysis

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Background: Up to 67% of all patients admitted to the intensive care unit (ICU) will develop acute kidney injury (AKI). Treatment for these patients is very expensive. For example, in the United States, the incremental health care costs attributed to AKI care are upwards of $10 billion USD per year. In this health economic analysis, we simulate the cost per quality-adjusted life year (QALY) gained comparing three dialysis treatments for patients with AKI in a Canadian ICU setting: continuous renal replacement therapy (CRRT), intermittent hemodialysis (IHD), and sustained low efficiency dialysis (SLED).

Methods: A decision analytic model, with a 1-year time horizon, was developed to compare the incremental cost per QALY gained for the three dialysis modalities. The model used a public payer perspective, with Canadian costs and relevant utility values obtained through a systematic review of the literature. A systematic search of the literature was performed to determine the clinical parameters for the model, including the probability of in-hospital death, dialysis dependence and death at one year post-discharge. One-way sensitivity analyses were performed by varying all parameters by +/- 10%.

Results: The incremental cost per QALY gained for SLED compared to IHD was $68,501. Compared to IHD and SLED, CRRT was extendedly dominated (i.e. it is more
cost-effective to provide SLED to some of the eligible patients and IHD to the remaining patients than to provide CRRT. The sensitivity analyses showed that the results are generally robust across a wide-range of parameter values.

Conclusions: Similar to previous economic evaluations, these results suggest that CRRT is not cost-effective compared to IHD. A novel finding is that SLED may be cost-effective depending on the willingness-to-pay threshold.

TH-PO118
Efficacy of Acute Peritoneal Dialysis (PD) Over Sustained Low Efficiency Dialysis (SLED) in Critically Ill ICU Patients with Acute Kidney Injury – A Comparative Study
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Background: Acute peritoneal dialysis (PD) has largely been replaced by continuous renal replacement therapies (CRRT) and sustained low efficiency dialysis (SLED) in critically ill ICU patient.

Methods: Patient admitted in the ICU with acute kidney injury and multiple organ dysfunction were included in the study irrespective of the etiology of renal failure. Patients were randomly divided into two groups. Group A received acute PD and group B received SLED. Primary outcomes were correction of uremia, metabolic acidosis, fluid overload, dys-electrolytemia, and mortality. Secondary outcomes were improvement in sensorium, hemodynamic stability, ICU length of stay, cost of treatment and duration of mechanical ventilation.

Results: 116 were enrolled in this study. The mean age was 41.23±11.56 years in group A where it was 45.87±13.45 years in group B. Average duration of dialysis was 72.80± 67.90 and 19.07±11.08 hours in PD and SLED group respectively. Correction of uremia [Urea 24.78±10.31 ml/min vs 26.23±9.34 ml/min, creatinine 8.89±3.78 ml/min vs 9.98±7.09 ml/min, p value <0.001] were similar. Significant acidosis was present in 36 patients in Group A (92%) and in 23 patients (28%) in Group B. SLED had a better correction of acidosis in comparison to PD. Correction of fluid overload was faster in SLED and net ultrafiltration was significantly higher in group A (22.21±6.17 L vs 4.87±5.09 L in group A, P=0.001). No significant differences were seen in correction of hyperkalemia, altered fluids and electrolytes, and mortality. Sensorium, hemodynamic stability, ICU length of stay, cost of treatment and duration of mechanical ventilation.

Conclusions: Acute PD still remains as a viable alternative to SLED in critically ill patients in low cost setting. Advantages are its low cost, ease of administration, needs less expertise and its metabolic and clinical outcomes are not inferior to SLED.

TH-PO119
Measurement of Adequacy of Intermittent Hemodialysis in Acute Kidney Injury: Is There a Simpler Approach?
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Background: The KDIGO Guideline for Acute Kidney Injury (AKI) recommends a minimum single pool Kt/Vmin of 1.3 when intermittent hemodialysis (IHD) is delivered thrice weekly. However, Kt/V in AKI is complicated by uncertainty regarding volume of distribution of urea and non-steady state rates of urea generation. In the Acute Renal Failure Trial Network (ATN) Study, adequacy of IHD was assessed using Kt/V. Using data from the ATN Study, we assessed whether the simpler urea reduction ratio (URR) does not require assessment of volume status, would provide sufficient correlation with Kt/V to provide a reliable assessment of adequacy of hemodialysis in AKI.

Methods: Using data from IHD in the ATN Study, values of URR were plotted against Kt/V. Kt/V in AKI is complicated by uncertainty regarding volume of distribution of urea and non-steady state rates of urea generation. The Acute Renal Failure Trial Network (ATN) Study, adequacy of IHD was assessed using Kt/V. Using data from the ATN Study, we assessed whether the simpler urea reduction ratio (URR), which does not require assessment of volume status, would provide sufficient correlation with Kt/V to provide a reliable assessment of adequacy of hemodialysis in AKI.

Results: There was tight correlation between URR and Kt/V (figure).

Conclusions: A URR ≥0.67 provides a specificity of 0.999 that the corresponding value of Kt/V is ≥1.4. Therefore, this URR threshold provides a simplified means of assessing adequacy of IHD provided for management of AKI in the acute care setting.

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TH-PO120
A Novel Treatment for Edema and Fluid Overload: Transdermal Removal of Intestinal Fluid
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Background: Fluid overload is highly prevalent in kidney and heart failure, contributing to worse outcomes. Diuretics are the mainstay of treatment, they can become ineffective requiring intravenous treatment and/or invasive approaches to fluid removal such as dialysis. Transdermal fluid removal from intestinal fluid (ISF), the main fluid reservoir in these overloaded patients presents a potentially attractive elegant solution to fluid removal in these patients.

Methods: Plastic solid microneedle arrays and standard hypodermic needles were tested as methods of accessing epidermal ISF whilst vacuum pressure and superabsorbent wound dressings were investigated as fluid flow enhancers.

Results: 144 interventions were performed, with 71 (49%) resulting in the extraction of at least 1ml of ISF and 36 (25%) at least 5ml. Microneedle access was superior with spontaneous significant flow of ISF in 56% of cases compared to 10% for hypodermic needles (p<0.0001). Vacuum pressure correlated with extracted ISF volume (r=0.42, p=0.03). ISF volume also increased linearly with time (r=0.0085) by the equation volume(ml)=5.78t(hrs)-4.5. Of the patient characteristics, edema grade (r=0.46, p=0.003), edema refill time (r=0.28, p=0.01) and serum albumin (r=0.23, p=0.004) were significantly correlated to ISF volume extracted. ECFV/TBW was the strongest correlate of ISF volume extracted (r=0.50, p=0.001). With a Bio-ratio of 0.50 or higher, the OR for extracting 5ml of more was 10.4 [3.4-31]. Microneedle access with suction and a high Bioratio could achieve ISF extraction rates of 2ml/cm2/hr which equates to 800ml over 4 hours using a 10 by 10cm skin surface. The microneedle interventions were safe, painless and bloodless.

Conclusions: Microneedle access with vacuum pressure seems promising as a potential safe, minimally invasive transdermal treatment of significant fluid overload. Further evaluation to refine device characteristics and clarify patient stratification may lead to a potential clinical utility of such a device.
Conclusions: PD is a viable treatment modality in low-resource settings and decreases mortality rates in the course of AKI to the levels seen in developed countries. The frequency of PD-related peritonitis is low and does not affect treatment outcomes.

Funding: Private Foundation Support

TH-PO122
Pulse High Volume Hemofiltration versus Coupled Plasma Filtration Adsorption in Septic Shock – A Pilot Randomized Study Paolo Lentini,1 Luca Zanolli,2 Massimo de Cal,3 Stefania Rastelli,2 Andrea Contestabile,1 Antonio Granata,4 Roberto Dell’Aquila.1 1Nephrology, St. Bassiano Hospital, Bassano Del Grappa, Italy; 2Univ of Catania, Italy; 3St. Giovanni di Dio, Italy.

Background: Acute kidney injury (AKI), a frequent complication in critically ill septic patients is an independent risk factor for increased mortality, particularly when patients require renal replacement therapy (RRT). High Volume Hemofiltration (HVHF) and Coupled Plasma Filtration Adsorption (CPFA) have shown potential improvement in hemodynamics; however, no studies have compared these two methods. Our aim was to compare the hemodynamic effects of HVHF and CPFA in septic shock patients undergoing Continuous Renal Replacement Therapy (CRRT).

Methods: A cross-over study enrolling pts with septic shock undergoing CRRT. Pts were treated with pHVF+CVVH on Day 1 and CPFA+CVVH on Day 2. HVHF was performed for 8-10 hrs with a replacement fluid rate (Qr) of 85 ml/kg/hr. CPFA was performed for 8-10 hrs using Mediasorb (Bellco, Italy) with a maximum plasma flow rate of 15%. CVVH was performed for the rest of the day with a Qr of 35 ml/kg/hr. Both HVHF and CVVH used polysulfone filters. The primary endpoints were changes in vasopressor requirement (expressed as vasopressor score, VS), in noradrenaline (NA) dose (mg/kg/min), and in mean arterial pressure (MAP) before and after pHVFH and CPFA. These values were compared using nonparametric paired tests.

Results: 8 pts were included. VS and NA dose were compared using nonparametric paired tests. There was no significant change in VS and NA dose becomes NS (p=0.22). There was no significant change in MAP values were compared using nonparametric paired tests.

Conclusions: The data provide no evidence for a difference in hemodynamic effects between pHVFH and CPFA in patients with septic shock undergoing CRRT.

TH-PO124
Effect of Polymyxin B Hemoperfusion on Septic AKI: A Systematic Review Dinna Cruz,1 Deepthi Mundkur, Ravindra L. Mehta.1 UCSD, San Diego.

Background: Septic acute kidney injury (AKI) is common in the ICU, and associated with high mortality. Polymyxin B fiber column (PMX) is a medical device that reduces blood endotoxin levels in sepsis. A prior metaanalysis, PMX hemoperfusion was shown to improve blood pressure and reduce vasopressor requirement, which could help renal perfusion. PMX possibly reduces proapoptotic activity of septic plasma on renal tubular cells. A systematic review was performed to assess renal outcomes when PMX is used in sepsis.

Methods: We searched MEDLINE, PubMed to identify studies on PMX hemoperfusion in sepsis. Full-text articles were screened for renal-related outcomes. The primary endpoint was need for acute RRT after enrollment. Secondary endpoints included development of AKI, change in Cr, BUN, urine output, urine protein and biomarkers after PMX.

Results: A total of 18 studies (n=591 pts) with renal outcomes were identified. In 6 RCTs & 1 non-RCT, patients were treated with either PMX+standard medical therapy (SMT) (n=188) or SMT alone (n=136). In 10 cohort studies 267 pts were treated with PMX+SMT. The following renal outcomes were reported: need for RRT (n=4 studies), serum Cr &/or CrCl (n=10), BUN (n=4), urine output (n=5), urine protein/biomarkers (n=6). One study reported severe AKI (Failure) in 0/8 PMX and 1/8 SMT patients at 72h. Pooled analysis showed a non-significant trend for reduced need for RRT with PMX (OR 0.44, 95%CI 0.19,1.04). Figure 1 shows Cr and urine output before and after PMX. Weighted mean difference for Cr after PMX was not significant but there was an increase in urine output by 45 ml/hr (95%CI 15,74) after PMX.

Conclusions: Based on published studies, PMX has no significant effect on RRT need or Cr in patients with septic shock when added to SMT, although urine output appeared to improve post-PMX. These data provide evidence for scientific equipoise for a randomized clinical trial to address this question.

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

Underline represents presenting author.

118A
**TH-PO125**

Four Hour Infusion Piperacillin-Tazobactam in CRRT Patients Is Associated with Improved Target Attainment Compared to 30 Minute Infusion

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1School of Pharmacy, Cleveland Clinic, Cleveland, OH; 2School of Medicine, University of Alabama Birmingham (2 gm q6h or q8h, 3g q6h SI; n=29) University of Alabama Birmingham (2 gm q6h or q8h, 3g q6h SI, n=25) and Vanderbilt University (3 gm q8h q3h, IE, n=14). A two-compartment pharmacokinetic model was fitted simultaneously to all data using nonlinear mixed effects regression in R. Target attainment was quantified as the fraction of the dosing cycle wherein piperacillin concentration was greater than 64 µg/mL. Target attainment for a typical patient was estimated using the population mean (fixed-effect) for each pharmacokinetic parameter.

**Results:** For EI versus SI in the two most common dosing patterns, 2g q6h and 3g q8h, target attainment was improved by 27% (95% CI: 19, 35) and 23% (95% CI: 18, 28), respectively.

**Conclusions:** Limits of the study include that it is solely observational, and that subjects in Cleveland and Birmingham were enrolled earlier than subjects in Nashville. These results characterize the typical patient in this population. Additional analysis is warranted to examine the sensitivity of our findings to population pharmacokinetic heterogeneity.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Gambro Renal Systems

**TH-PO126**

Effects of Complement Factor H and Factor I Deficiency on Anti-MPO Induced Crescentic Glomerulonephritis in Mice

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**Background:** Complement alternative pathway (AP) activation plays a critical role in the pathogenesis of anti-neutrophil cytoplasmic autoantibodies (ANCA) crescentic glomerulonephritis (CGN). AP is negatively regulated by complement factor H (CFH) and factor I (CFI). Deficiency of either of these regulators results in uncontrolled AP activation with secondary depletion of C3, factor B and properdin. In this study, we investigate the effects of CFH and CFI deficiency in anti-MPO induced CGN in mice.

**Methods:** 9-11 wk-old CFH-/- and CFI-/- mice were injected with anti-MPO IgG. Animals were sacrificed at day 6 and kidney tissue was obtained for pathologic examination and IF staining with anti-C3 antibodies. Circulating C3 levels were determined by ELISA. In vitro neutrophil function was assayed.

**Results:** At day 6 of anti-MPO treatment, all CFH-/- mice (n=5) developed much more severe CGN (mean 85% glomeruli with crescents) compared to the WT control mice (n=8, 11% crescents). In contrast, no CGN developed in CHI-/- mice (n=8). Glomerular C3 staining showed strong (score 4+) linear capillary wall staining in CFH-/- mice, whereas CHI-/- mice had weak (1.5+) mesangial staining. On day 0 and day 6 after anti-MPO treatment, the circulating C3 level had no significant differences in WT and CHI-/- mice (p=0.05) and substantially reduced in CHI-/- mice (p<0.001). In vitro neutrophil function assay showed that anti-MPO IgG caused similar activation of neutrophils from CFH-/-, CHI-/- and WT mice.

**Conclusions:** Absence of the CHI causes more severe anti-MPO induced CGN. This is probably because they have uncontrolled alternative pathway activation and sufficient glomerular capillary wall deposition of complement activation fragments to synergistically attract and amplify anti-MPO activated neutrophils. 2) CHI deficiency protects from anti-MPO CGN. This might be because of no glomerular capillary wall C3 deposits and consumption of circulating AP components, such as factor B and properdin, as a consequence of uncontrolled AP activation.

**Funding:** NIDDK Support

**TH-PO127**

Can a Bacterial Protein Rescue Disease-Linked Mutations in Complement Factor H?

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**Background:** Can a bacterial protein rescue disease-linked mutations in complement factor H (CFH)? The protein PspC from Streptococcus pneumoniae hijacks host-derived FH in a complement-evasion strategy. We hypothesized that PspC(N-terminal region of PspC) to wild-type (WT) FH was shown to enhance complement regulation implying that PspC might restore useful levels of regulatory activity to disease-linked variants of FH.

**Methods:** Overcoming technical hurdles to recombinant full-length FH production, two mutations, R53H and R57H, R53H and R57H, were created in Pichia pastoris. Expression of plasma surface plasmon resonance (SPR), binding of mutants to C3b, and their C3bBb decay-accelerating activities (DAA), were compared with WT FH. Mutants were also compared to WT FH in erythrocyte DAA and co-factor lysis assays. Measurements were repeated in the presence of PspC.

**Results:** R53H decreased FH affinity for C3b and impacted negatively on both assays used to measure DAA as well as the haemolysis-based assay of co-factor activity. The mutant had WT-like abilities to bind C3b and decay C3b convertase on an SPR chip, but was defective in cell-based assays, and especially in co-factor activity. PspC enhanced both C3b binding and DAA on the SPR chip by both mutants and WT. The effects on PspC on cell-based assays were less clear.

**Conclusions:** These studies with full-length FH imply that disease-linked substitutions in its C-terminal surface-recognition region (unique in the functionally critical C1r/C1s, OVL, and K4 region) have little effect on SPR-based assays performed on a non-native and, hence, in effect, foreign surface. Whether the enhancing effects of PspC in SPR-based assays can be replicated on host-cell surfaces has therapeutic implications and will be discussed in the light of ongoing measurements.

**TH-PO128**

Recombinant Complement Factor H in a Model of C3 Glomerulopathy

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**Background:** C3 glomerulopathy (C3G) is an inflammatory renal disorder that is associated with abnormal complement alternative pathway activation. This includes deficiency of complement factor H (FH), the negative regulator of the alternative pathway. FH gene-targeted (FH-/-) mice are a model of C3G and spontaneously develop reduced plasma C3 levels and abnormal deposition of C3 within the glomerulus. We tested the efficacy of recombinant murine FH (mrFH) to restore C3 regulation in FH-/- mice.

**Methods:** MrFH was produced in Pichia pastoris. Plasma-purified mFH or hrFH (human) was used as a control. In experiment 1, mice received an injection of mrFH or mfH and were culled at 24 hours. In experiment 2, mice received a daily injection of mfH or hrFH for 10 days and were culled at 24 hours.

**Results:** A single injection of mfH resulted in increased plasma FH and C3 levels peaking at 6 hours. In mice receiving mfH, plasma FH and C3 levels remained elevated at 24 hours. Glomerular deposition of C3 at 24 hours showed a decrease in glomerular C3 staining both for mice receiving mfH and mrFH. In experiment 2, mice receiving daily injections of either mrFH or hfH exhibited elevated levels of both plasma FH and C3 at 24 hours, but these decreased to baseline within five days. All mice showed reduced C3 glomerular staining at 11 days. Mice receiving hfH showed strong glomerular IgG staining at 11 days. We tested the efficacy of recombinant murine FH (mrFH) to restore C3 regulation in FH-/- mice.

**Conclusions:** The effectiveness of treatment with plasma-purified FH may be due to glycosylation differences between plasma-purified and recombinant FH. Administration of recombinant FH may be a potential treatment choice for patients with C3G associated with deficiency or dysfunction of FH. However, the challenges of this approach include plasma half-life, immunogenicity and large scale production.

**TH-PO129**

Reduced Renal Infiltration of Inflammatory Cells following Selective Endothelial Injury in Mice Deficient for C3, C3ar or C5ar


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**Background:** Complement dysregulation leads to kidney specific diseases such as C3 glomerulopathy and thrombotic microangiopathy. However, data on the specific role of the complement system for local inflammation after endothelial cell injury (ECI) is limited. We here investigated the inflammatory response following site selective renal ECi in mice deficient (-/-) for C3, C3ar or C5ar.

**Methods:** Renal ECi was induced by intra-arterial injection of Concanavalin(A/m) anti-Cona in C3-/- (day 2) d=5; d4=4, C3ar-/- (d=2; d=5; n=4), C5ar-/- (d=2; d=4; n=3) deficient and C57Bl/6 wild-type (wt) mice (n=5; n=4). Six wt mice served as sham control (ctrl). Kidneys were harvested on day 2 or day 4. Multicolor FACS analysis was used to analyze macrophages and neutrophils (N) in C3, C3ar and C5ar deficient mice with the following antibodies: CD11b+ F4/80+ GR1- CD11c- (M), GR1+ CD11b+ (N) and CD4+ CD8+ (T). Histology was used to analyze macroages (MAC2, F4/80) and the IF (CD31).

**Background:** Inflammation was increased in C57Bl/6 mice 2 days after C57Bl/6: M=1.3±0.4; N=2.9±1.8; T=1.0±0.3 vs. sham: M=0.1±0.4; N=0.15±0.09; T=0.2±(0.2; p<0.01). Compared to C57Bl/6 wt mice a reduced influx of macrophages (C3-/- 0.3%±0.05; C3ar-/- 0.4%±0.2; C5ar-/- 0.5%±0.3) and neutrophils (C3-/- 0.9%±0.74; C3ar-/- 0.7%±0.9; C5ar-/- 0.5%±0.3) was detected in C3-/- mice. C3ar-/- mice showed a reduction in kidney infiltration of neutrophils (p<0.01). CD8+ cells were reduced in C3-/- mice (C3-/- 0.3%±0.03 vs C3ar-/- 0.7%±0.9).

**Conclusions:** Restoration of complement regulation is the goal of treatment for C3G.
Investigating a Pathogenic Role of C5a-C5aR1 Signaling in Diabetic Nephropathy

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Background: Complement 5a is a potent pro-inflammatory effector molecule. Although previous studies indicate a link between activation of the complement pathway and diabetic nephropathy (DN), the role of C5a and its receptor C5aR1 in DN has yet to be determined.

Methods: Complement signaling was characterized in type 1 diabetic (T1D) human, rat and mouse kidneys. C5a-C5aR1 signaling axis was inhibited by using the highly selective and potent C5aR1 antagonist, Ac-FLu(ChaW) (PMX35), in streptozotocin (STZ) induced diabetic mice. C5aR1 expression was upregulated in the renal cortex of STZ-induced diabetic rats (1.0 ± 0.1 fold change; p=0.05) and spontaneously diabetic Ins2-Akita mice (1.0 ± 0.1 vs 1.4 ± 0.1 fold change; p=0.85) compared to controls. Urinary C5a was increased in the diabetic rats (181.5±11 vs 115±57 pg/24hr; p<0.05) and Ins2-Akita mice (50.9 ± 31.3 vs 13.3 + 3.5 pg/kg/day; p=0.01) after 16 and 26 weeks of diabetes, respectively and was associated with albuminuria (p=0.05). Blockade of C5aR1 signaling with PMX35 attenuated albuminuria in STZ-induced diabetic mice when compared to vehicle-treated diabetic controls (1.4 ± 0.4 vs 0.08 ± 0.07; p=0.001).

Conclusions: The C5a-C5aR1 signaling is activated in human and experimental DN. A pilot study using PMX35 indicates that pharmacological blockade of C5aR1 is renoprotective in DN. Further studies are required to validate C5aR1 as a therapeutic target in DN.

Funding: Private Foundation Support

Identification of Glycosaminoglycans That Inhibit Specific Complement Pathways

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Background: Complement has been shown to play a role in renal diseases, such as hereditary urogenital syndrome, C3 glomerulonephritis and renal transplantation. It is well known that heparin and other glycosaminoglycans (GAGs) reduce complement activation. However, no studies have yet compared the complement pathway specific inhibitory properties of a library of GAGs. We have tested over 70 different GAGs for their complement inhibitory potential and their specificity for either of the complement pathways.

Methods: 72 GAG-based polysaccharides were tested for their complement inhibitory potential in the Wieslab complement screening assay. To pinpoint the inhibitory effect of GAGs on the lectin pathway (LP), the interference of GAGs on the binding of MBL to mannan and further C4 activation was tested. GAGs were also tested in the Wieslab-ficolin 3 screening kit to evaluate their effect on ficolin based LP activation. Direct binding of LP components to heparin was assessed by detecting MBL and MASp 1 & 2 after serum incubation to immobilized heparin-albumin.

Results: Unfractionated regular and partially desulfated heparin exhibit dose-dependent inhibitory potential of all three complement pathways, while small heparin and heparan sulfate (HS)-derived oligosaccharides show specific LP inhibition. These small heparin/HS derivatives do not interfere with the binding of MBL to mannan, but do inhibit the MBL-dependent activation of C4 and ficolin-3 mediated LP activation. We also find a dose-dependent binding of the MBL/MASp 1k2 complex to immobilized heparin-albumin, but not to albumin.

Conclusions: A large number of heparinoids/oid blocks all three pathways of complement, although small heparin/HS oligosaccharides inhibit the LP of complement specifically, according to our data via the inhibition of the MASp enzymes. Our data also suggest that HS on cell surfaces and in basement membranes act as a docking platform for the MBL-MASp complex. We speculate that GAG-derived polysaccharides may be useful as MASp specific LP inhibitors.

Funding: TH-PO130

Anti-GBM Antibody-Mediated Glomerular Injury Depends on Neutrophil Degranulation

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Background: Acute proliferative glomerulonephritis (GN) induced by ANCA or by anti-GBM antibodies is neutrophil (PMN) dependent. In vitro studies suggested that endothelial injury induced by ANCA was dependent on PMN granule enzymes, not release of reactive oxygen species. To test the hypothesis that PMN degranulation is required for acute GN, degranulation was inhibited in an in vivo model of heterologous anti-glomerul inflammation in mice.

Methods: After collection of urine for baseline protein excretion, two groups of 10 C57BL/6 mice received an intravenous injection of anti- rat GBM (1.5 mg/25 g body weight) at time 0. One group also received an intravenous injection of a TAT-fusion protein, TAT-SNAP-23 (0.5 mg/kg body weight) at time 0 and 6 hr later. We showed previously that TAT-SNAP-23 inhibited PMN degranulation in vitro and in vivo. At 24 hr urine was collected to measure protein excretion, and then mice were sacrificed and kidney tissue prepared for histology. Urine protein was measured as the protein:creatinine (ug/mg). Glomerular proliferation and mesangial expansion were graded on a 0 to 4+ scale.

Results: Baseline urine protein:creatinine did not differ between groups (18 ± 3.3 vs 13 ± 2.5, untreated vs TAT-SNAP-23 treated). Anti-GBM induced a significant increase in proteinuria, and that increase was significantly inhibited by TAT-SNAP-23 treatment (376 ± 108 vs 73 ± 15, untreated vs TAT-SNAP-23 treated). By light microscopy there was no difference in proliferation (2.2 ± 0.2 vs 2.0 ± 0.2) or mesangial expansion 1.3 ± 0.2 vs 1.2 ± 0.2) between the two groups. By electron microscopy the degree of podocyte foot process effacement was reduced by TAT-SNAP-23 treatment.

Conclusions: We conclude that PMN degranulation plays a critical role in acute glomerular injury induced by anti-GBM antibody deposition. We postulate that proteinuria may result from direct podocyte injury by PMN granule enzymes.

Funding: Other NIH Support - NIAID, Veterans Administration Support

Shared and End Organ Specific Transcriptional Networks in Skin versus Kidney Biopsies in Systemic Lupus

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Background: Patients with subacute cutaneous (sCLE) lesions have higher risk of lupus nephritis (LN) compared to those with discoid (DLE) lesions. We hypothesized that renal flares may be triggered via a crosstalk between skin and kidneys. To determine the potential factors contributing to this increased risk, we used systems biology approaches to integrate the regulatory events occurring specifically in sCLE and DLE and compared with those in LN.

Methods: Formalin-fixed paraffin-embedded tissue from 8 normal, 22 DLE and 24 sCLE rash biopsies were analyzed via microarrays. Gene expression profiles from 22 class III + IV LN and 14 healthy microdissected human renal biopsies (ERCB) were compared. The 85 genes regulated only in the LN glomeruli and DLE rashes showed a mainly up-regulated network with ITGB2, CD40 and TAT as the main nodes. Top pathways were epithelial adherens junction signaling. The 105 genes specific to LN glomeruli and sCLE showed a mainly up-regulated network with ITGB2, CD40, SYK, TIMP1 as major nodes. Ingenuity pathway was crosstalk between dendritic cells and natural killer cells, both of which may play a role in cutaneous and renal lupus pathogenesis.

Conclusions: DLE and sCLE have overlapping and unique transcriptional expression signatures which may guide therapeutic decisions and predict renal involvement. Further analysis of these specific profiles may identify the molecular crosstalk mechanism between skin and kidneys, as well as targets for novel therapy of cutaneous lupus lesions which could help to prevent or delay the renal disease. Our data suggest an inflammatory cell crosstalk between skin and kidneys in sCLE, which may not happen in DLE.

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Molecular Determinants of Myeloperoxidase-ANCA Glomerulonephritis:

Transcriptomic Analysis Across Three Species

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Background: Human myeloperoxidase (MPO)-ANCA vasculitis causes crescentic GN that results in glomerular degranulation. This has been modelled in rats (EAE) and mice (MEV), although it tends to resolve spontaneously in these models with little glomerular scarring. To investigate conserved and divergent molecular pathways involved in glomerular injury we analysed the glomerular transcriptome in EAV, MEV and humans with MPO-ANCA vasculitis.

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

Underline represents presenting author.

120A
Methods: Glomeruli were microdissected from WKY rats immunised with MPO (EAN) or human albumin (control), from mice receiving anti-MPO (MEV) or BSA (control) antibodies raised in MPO−/− mice (n=5/group), and from patients with MPO-ANCA GN (n=7) and healthy controls (n=18). RNA expression was analysed by Affymetrix arrays. Differential regulation was assessed by ChipInspector and rodent/human orthologs identified using HomoloGene. A restriction of gene lists using co-citation at sentence level, the human network was used to overlap with mouse and rat networks using TALE. In 74 selected genes, regulation was confirmed by nPCR.

Results: 3512, 1725 and 783 glomerular genes were significantly associated with GN in humans, mice and rats respectively. We observed overlap between human and mouse in 675 (12.9%), human and rat in 134 (3.1%) and across all 3 species in 179 (2.9%) genes. Of these 179 genes, 135 (75.4%) were differentially regulated in the same direction and 44 (24.6%) in opposite directions. We identified 12 canonical pathways (p value <0.001) conserved between human, mouse and rat, 5 between human and rat.

Conclusions: The transcriptomic profile in MEV was more similar to human disease than EAV. 2.9% of differentially regulated genes were conserved across all 3 species, with a quarter of these regulated in opposite directions between rodent and human. These data provide insights into both shared pathophysiology and mechanisms underpinning the divergent clinical phenotype between rodent and human MPO-ANCA GN.

Funding: Government Support - Non-U.S.

TH-PO135

PRTN3 and MPO Expression Correlates with Disease Activity in a Large Inception Cohort with Longitudinal and Serial Measurements Among Patients with ANCA Disease

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Background: We demonstrated up-regulation of autoantigenic genes, PRTN3 and MPO, in mature neutrophils and monocytes from patients with ANCA disease (J Am Soc Nephrol 2004, 15:2103-14). Here, we performed a longitudinal and serial analysis of PRTN3 and MPO expression following their disease course.

Methods: A total of 1063 leukocyte samples were collected from 152 ANCA-patients during various stages of disease activity and compared to 152 healthy controls. These patients were followed serially every 3 months over the past 5 years. Q-PCR was used to measure mRNA levels.

Results: PRTN3 (155±506; p=0.0001) and MPO (384±940; p=0.0001) mRNA levels were significantly up-regulated in leukocytes from patients with ANCA disease compared to healthy controls.

Conclusions: Our longitudinal and serial analysis of PRTN3 and MPO expression following their disease course.

TH-PO136

Galactose-Deficient IgA1-Containing Immune Complexes Induce Proliferation of Human Mesangial Cells and Activate PDGF/PDGFR Signaling Pathway

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Background: The murine model of glomerulonephritis (GN) is induced by an ultrasound-mediated microbubble/shRNA gene transfer method and shown to correlate with the progression of IgAN. NLRP3 inflammasome, a multiprotein complex, positively regulates caspase-1 activity and the maturation and release of IL-1β. NLRP3 inflammasome plays an important role in inflammatory response and controls the development of various inflammatory diseases. However, the potential pathogenic role of NLRP3 inflammasome on IgAN is unclear.

Methods: The pathogenic role of NLRP3 inflammasome and molecular mechanisms on IgAN progression using NLRP3 deficient mice and NLRP3 deficient kidneys were specific knockdown by an ultrasound-mediated microbubble shRNA gene transfer method.

Results: NLRP3 deficient and blockage resulted in attenuation of aluminuria, improved renal function, and blocking of renal progressive lesions, including glomerular proliferation, and periglomerular monocle neurone leukocyte infiltration. These findings were associated with (1) inhibiting ROS production and NF-κB activation in the kidney, (2) reducing NLRP1 inflammasome activation in the kidney, (3) inhibiting effect/memory T-cell activation and IL-17 expression, and (4) inhibiting maturation and activation of dendritic cells.

Conclusions: These results indicate that activation NLRP3 inflammasome is involved in the development of IgAN, and a kidney-specific knockdown of NLRP3 may have therapeutic potential for IgAN.

Funding: NIDDK Support

TH-PO137

The Pathogenic Role of NLRP3 Inflammasome in IgA Nephropathy and Establishment of a Therapeutic Strategy

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Background: IgA nephropathy (IgAN) is the most common cause of primary glomerular diseases induces chronic kidney disease. Tandem mass analysis has been shown to correlate with the progression of IgAN. NLRP3 inflammasome, a multiprotein complex, positively regulates caspase-1 activity and the maturation and release of IL-1β. The NLRP3 inflammasome plays an important role in inflammatory response and controls the development of various inflammatory diseases. However, the potential pathogenic role of NLRP3 inflammasome on IgAN is unclear.

Methods: The pathogenic role of NLRP3 inflammasome and molecular mechanisms on IgAN progression using NLRP3 deficient mice and NLRP3 deficient kidneys were specific knockdown by an ultrasound-mediated microbubble shRNA gene transfer method.

Results: NLRP3 deficient and blockage resulted in attenuation of aluminuria, improved renal function, and blocking of renal progressive lesions, including glomerular proliferation, and periglomerular monocle neurone leukocyte infiltration. These findings were associated with (1) inhibiting ROS production and NF-κB activation in the kidney, (2) reducing NLRP1 inflammasome activation in the kidney, (3) inhibiting effect/memory T-cell activation and IL-17 expression, and (4) inhibiting maturation and activation of dendritic cells.

Conclusions: These results indicate that activation NLRP3 inflammasome is involved in the development of IgAN, and a kidney-specific knockdown of NLRP3 may have therapeutic potential for IgAN.

Funding: Government Support - Non-U.S.

TH-PO138

Effects of DPPIV Inhibitor on Renal Function in Mice Model of ADR-Induced Nephropathy

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Background: The murine model of adriamycin(ADR) induced nephropathy is characterized by severe proteinuria, development of podocyte injury and glomerulosclerosis. The aim of our study was to investigate the mechanism and preventive effect of fibrosis in glomerular, tubular and interstitial tissue associated with DA1229 treatment in ADR-induced nephropathy.

Methods: 6-week-old balb/c mice were divided into 4 groups as follows: 1) untreated after injection of ADR (control of group 2), 2) immediately treated with DA1229 for 3 weeks after injection of ADR(preventive protocol), 3) untreated after injection of ADR(control of group 4), 4) treated with DA1229 for 2 weeks after 3 weeks from injection of ADR(therapeutic protocol).

Results: Treatment with DA1229 showed preventive effect on weight gain and renal hypertrophy after 5 weeks of injection of ADR. Plasma DPPIV activity was significantly decreased in treatment with DA1229. DPPIV activity in kidney was significantly increased after injection of ADR and was decreased with DA1229. Notably, both preventive and therapeutic protocol significantly decreased proteinuria and albuminuria induced by ADR injection. Urinary excretion of neprin was significantly decreased and inflammatory and fibrotic molecules in kidney tissue were significantly inhibited with DA1229 treatment. Additionally, infiltration of macrophages and fibrosis in the kidney were attenuated with DA1229 treatment in ADR groups.

Conclusions: Our data suggest that DA1229 might protect renal injury from podocyte injury in ADR-induced nephropathy, via antiinflammatory and antifibrotic effects. DA 1229 might be a potential therapeutic agent in a variety of glomerular disease inducing proteinuria.
**TH-PO139**

**Effects of Highly Selective Adenosine 3 Receptor Antagonist on Renal Function in Mice Model of Adriamycin Induced Nephropathy**

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**Background:** Concentration of adenosine in normal kidney increases markedly during renal hypoxia and ischemia. Previous studies have reported that mice lacking renal A3 adenosine receptor (A3AR) show significant protection against acute kidney injury, such as ischemia-reperfusion injury and myoglobinuria-induced injury. Moreover, A3AR antagonist blocked the development and attenuated the progression of renal fibrosis. The aim of this study was to investigate the effects of highly selective adenosine 3 receptor antagonists (LJ1888) treatment in ADR-induced nephropathy.

**Methods:** We designed three animal groups as following: 1) 6-week-old balb/c mice (control), 2) untreated with LJ1888 after injection of ADR (10mg/kg), 3) treated with LJ1888(10mg/kg) for 2 weeks after 5 weeks of injection of ADR.

**Results:** Body weight was significantly decreased in both ADR injection groups. ADR injection significantly induced proteinuria and albuminuria, which were notably reduced after treatment of LJ1888. Urine 8-iso-prostane and kidney lipid peroxidase level were also decreased with LJ1888. Urinary excretion of nephrin was significantly reduced and kidney nephrin stain showed increased nephrin expressions in the glomeruli of LJ1888 group. Less glomerular injury and macrophage infiltration were observed in LJ1888 treated kidney. Moreover, protein expressions of Nox4, TGF-β1, NF-κB were attenuated with LJ 1888.

**Conclusions:** These reprotective effects of LJ1888 on ADR-induced nephropathy may be associated with protective effect on podocyte injury. LJ1888 might be a potential therapeutic agent for glomerulonephrophy inducing proteinuria.

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**TH-PO140**

**Innate Immunity Is Activated Early in Adriamycin Nephropathy and Is Strongly Associated with Lymphocyte Infiltration**

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**Background:** Protein overload promotes interstitial injury by unclear mechanisms that may involve innate immunity (INIM). Here we investigated the time course of INIM activation in Adriamycin nephropathy (AN), and the participation of lymphocytes (LY) in this process.

**Methods:** AN (5 mg/kg iv) was induced in 30 Munich-Wistar rats. Control rats (C, N=10) received saline only. At 2 (AN2), 4 (AN4) and 20 (AN20) ANx, wks, albuminuria (ALB, mg/day), interstitial macrophages (MΦ) and LY (cells/mm²), α-SMA and collagen (COL). Renal INIM was assessed by gene expression (NLRP3 and IL-6, 2 and 4) and protein content (IL-1β, Casp1, TLR4). Four additional AN rats received r mutate (MMF, 10 mg/Kg/day, vo), and their ALB, LY, α-SMA, COL and renal content of IL-1β, Casp1 and TLR4 were assessed at 30 days.

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>ALB</th>
<th>LY</th>
<th>α-SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>4±2</td>
<td>33±14</td>
<td>10±0.2</td>
<td>19±3.6</td>
</tr>
<tr>
<td>30</td>
<td>4±2</td>
<td>33±14</td>
<td>10±0.2</td>
<td>19±3.6</td>
</tr>
<tr>
<td>60</td>
<td>5±0.1</td>
<td>10±0.3</td>
<td>8±1.0</td>
<td>9±1.9</td>
</tr>
</tbody>
</table>

**Conclusions:** LY correlated strongly with INIM parameters. All parameters were increased with time. MMF treatment significantly reduced LY (81±0.6, p<0.05 vs C, p<0.05 vs AD2wk).

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**TH-PO141**

**Inhibition of NF-κB Signaling in Podocytes Ameliorates Albuminuria in Adriamycin-induced Nephropathy**

Tadashi Yoshida, Maho Yamashita, Matsuhiko Hayashi.1 Apheresis and Dialysis Center, Keio Univ School of Medicine, Shinjuku, Tokyo, Japan.

**Background:** Inflammation involving the activation of the NF-κB signaling has been shown to contribute to proteinuria in chronic kidney disease. NF-κB is expressed not only in inflammatory cells, such as lymphocytes and macrophages, but also in podocytes. We herein examined the role of NF-κB in podocytes in adriamycin-induced nephropathy.

**Methods:** Podocyte-specific truncated IkBα expressing (Pod-IκBDN) mice, in which the NF-κB signaling was inhibited selectively in podocytes, were generated and analyzed their phenotype following the intravenous injection of adriamycin. Expression of nephrin and podocin was examined by immunostaining.

**Results:** Pod-IκBDN mice did not exhibit any abnormalities in body weight, blood pressure, and the heart rate before the treatment. Following the administration of adriamycin, albuminuria was observed in both Pod-IκBDN mice and control mice. However, in Pod-IκBDN mice, the amount of albuminuria in Pod-IκBDN mice (473±122 mg/creatinine) was significantly lower than control mice (992±230 mg/g creatinine) 14 days after adriamycin injection. Serum concentrations of urine nitrogen were not different between these mice. Expression of nephrin and podocin in the glomeruli was decreased in adriamycin-treated control mice, but not in Pod-IκBDN mice.

**Conclusions:** Results suggest that NF-κB in podocytes plays an important role in proteinemic renal disease by regulating the expression of podocyte-specific proteins.

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

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**TH-PO142**

**Apoptosis Signal Regulating Kinase 1/38 Signalling Promotes Renal Inflammation in a Rat Model of Crescentic Glomerulonephritis**

Liv A. Amos,1,2 Yingjie Han,1,2 John T. Liles,1,2 David J. Nikolic-Paterson,1,2 1 Dept of Nephrology, Monash Medical Centre, Clayton, Victoria, Australia; 2 Dept of Medicine, Southern Clinical School, Monash Univ, Clayton, Victoria, Australia; 3 Gilead Sciences Inc, Foster City, CA.

**Background:** Apoptosis signal-regulating kinase 1 (ASK1) is required for p38 mitogen-activated protein kinase (MAPK) signaling in tubular cells in response to angiotensin II and oxidative stress, but not to IL-1 or LPS. However, it is not known whether ASK1 is required for p38-dependent glomerular injury. The aim of the study was to determine whether blockade of apoptosis signal-regulating kinase 1 (ASK1) can suppress renal injury in a rapidly progressive glomerulonephritis (RPGN) model.

**Methods:** Accelerated anti-glomerular basement membrane (GBM) disease was induced in groups of 6-8 rats. Treatment with ASK1 inhibitor GS-444217 (30mg/kg/po bid) or vehicle began 1hr before anti-GBM serum injection and continued until animals were killed on day 1 or 14.

**Results:** Compared to normal controls, anti-GBM disease showed a 3-fold increase in phosphorylated (activated) p38 in glomeruli on day 1 which was prevented by ASK1 inhibition. In addition, the 20-fold increase in urine protein/creatinine ratio at day 1 was prevented by ASK1 inhibitor treatment. In a separate study, vehicle treated anti-GBM disease exhibited 30±3% (mean±SD) crescents on day 14, which was reduced to 10±2% by ASK1 inhibitor (P<0.001). ASK1 inhibitor treatment reduced proteinuria by 50% compared to the vehicle group (P<0.01), and prevented an increase in serum creatinine (4/5/5±0/L vs. 27±5±0/L, P<0.005). Glomerular macrophage and T cell infiltration was also attenuated by the ASK1 inhibitor (P<0.05), with an associated reduction in macrophage M1/M2 markers (iNOS, CD206). Finally, immunostaining and PCR analysis showed a reduction in renal fibrosis with ASK1 inhibitor treatment.

**Conclusions:** This study suggests that ASK1 is involved in activating p38 MAPK signalling in glomerular inflammation. In addition, treatment with GS-444217 decreased glomerular inflammation and crescent development. Further studies are required to investigate potential effects of therapeutic intervention in established anti-GBM disease.

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

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**TH-PO143**

**Transforming Growth Factor β-Activated Kinase 1 (TAK1) Attenuates Experimental Glomerulonephritis**

Liv A. Amos,1,2 Elyce Ozols,1,2 Yingjie Han,1,2 John T. Liles,1,2 David J. Nikolic-Paterson,1,2 1Nephrology, Monash Medical Centre, Clayton, Victoria, Australia; 2Medicine, Southern Clinical School, Monash Univ, Clayton, Victoria, Australia.

**Background:** Activation of p38/JNK signalling promotes glomerular inflammation. TAK1 is an upstream kinase in the p38/JNK pathway. TAK1 regulates the response to a range of stimuli which promote glomerular inflammation (TNF-a, IL-1 and TLR ligands). Therefore, we investigated whether TAK1 activates p38/JNK signalling in acute glomerular inflammation.

**Methods:** Global Taki gene deletion was induced in Tak1f/fER Cre mice via tamoxifen, while Tak1f/fER Cre mice have conditional Tak1 deletion in podocytes. Accelerated anti-glomerular basement membrane (GBM) disease was induced in Tak1f/fER Cre mice by intravenous injection of anti-GBM. We examined renal inflammation and crescent development. Further studies are required to investigate protective effects of therapeutic intervention in established anti-GBM disease.

**Funding:** Government Support - Non-U.S.
Absence of Osteopontin Accelerates Oxidative Stress-Induced Fibrosis in Glomerulonephritis

Gabriela E. Garcia, Jessica Helen Trostel, Luan D. Truong, Richard J. Johnson.

Background: Osteopontin (OPN) is a pro-angiogenic and profibrotic molecule that simultaneously attenuates oxidative stress in the inflammatory milieu. Evidence suggests that oxidative stress plays a significant role in the progressive fibrosis by upregulating fibrosis related genes. Moreover, elevation of biomarkers of increased oxidative stress has been demonstrated in patients with chronic kidney disease. OPN is highly induced in nephritic kidney and inactivation of macrophages (MΦ) by an ApoA-I agonist, attenuated OPN expression and protected from progressive kidney injury.

Methods: To further characterize the role of OPN in kidney injury we use OPN-/- mice in anti-glomerular basement membrane glomerulonephritis (anti-GBM GN), an inflammatory and progressive model of kidney disease.

Results: Wild type and OPN-/- mice did not show histological differences in the glomeruli and the tubulointerstitium. However, nephritic kidneys from OPN-/- mice showed severe kidney damage compared with those in WT mice. Fibrinoid necrosis, crescent formation, and tubulointerstitial injury were significantly higher in OPN-/- mice compared to WT mice. In addition, collagen (CoI) I, CoI III, and CoI IV deposition were increased in nephritic kidneys from OPN-/- mice compared with WT mice. MΦ and T cell infiltration in nephritic kidneys was not different between WT mice and OPN-/- mice. Elevated expression of the reactive oxygen species (ROS)-generating enzyme NOSx 4 was observed in nephritic kidneys from OPN-/- mice. In contrast, MΦ isolated from WT mice and OPN-/- mice did not show difference in the expression of NOSx4. Importantly, the antigen-specific humoral immune response and the glomerular immunoglobulin G deposition were not affected in OPN-/- mice.

Conclusions: These findings suggest that in global OPN-/- mice elevated NOSx4 creates a redox imbalance with increased oxidative stress induced-fibrosis. Targeting MΦ OPN could be protective to attenuate inflammation and inflammation-associated fibrosis without affecting the anti-oxidative stress of OPN.

Funding: NIDDK Support

TH-PO145

Investigating Connective Tissue Growth Factor as a Critical Mediator of Cryoglobulinemia

Gavathiri K. Rajakaruna, Charles E. Alpers, Alan D. Salama.

Background: Cryoglobulinemia are immunoglobulins that precipitate at temperatures below 37°C. Cryoglobulinemia vasculitis (CV) is commonly associated with hepatitis C (HCV) infection and causes a membrano proliferative glomerulonephritis (MPGN) in the kidney. Through a serendipitous finding we have previously established the development of CV in Connective tissue growth factor (CTGF) over expressing transgenic mice. CTGF, a matricellular protein involved in cell proliferation and key regulatory pathways, is elevated in patients with HCV-induced CV. Thymic stromal lymphopoetin (TSLP) transgenic mice also develop CV and have high serum CTGF levels. Higher TSLP levels have been shown in patients with HCV-induced CV. We hypothesized that CTGF overexpression is the key driver for cryoglobulin formation, and represents and potential therapeutic target.

Methods: TSLP Tg animals were used for this pilot study. We investigated whether CTGF anti sense oligonucleotides (ASO) attenuated CV, in comparison to control ASO. 14 TG and 12 WT animals were studied over a 10 week period.

Results: There were 2 deaths amongst CTGF ASO group whilst one control animal died. The incidence of ulcerative ear and neck lesions was 50% lower in the CTGF ASO group compared to the controls.(p=0.0549). The CTGF ASO cohort had lower proteinuria compared to the controls, this was significant between treatment arms and the duration of treatment (p=0.0092 and p=0.0034 respectively).

Conclusions: These preliminary pilot study suggests that antagonism of CTGF ASOs may attenuate CV in TSLP Tg animals. Larger studies are required to confirm this observation.

Funding: University of Kentucky, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Support

TH-PO146

The Toll-Like Receptor Signaling Pathway Is Activated Before the Development of Renal Injury in the 5/6 Nephrectomy Model


Background: Mechanisms of activation of inflammation in Chronic Kidney Disease (CKD) are unclear. We examined the participation of innate immunity in the 5/6 nephrectomy model (Nx) from its beginning to advanced phases.

Methods: Munich-Wistar rats underwent Nx (N=40) or Sham (N=10) operation. Tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/24h) glomerulosclerosis index (GSI) and cortical interstitial (%INT) were assessed. 7, 15, 60 and 120 days after Nx. Gene and protein content of Tlr4, Casp1, Il1b and Nlrp3 were also evaluated. PCR-Array and gene enrichment analysis (GEA) by z-score evaluated gene expression of innate and adaptive immunity components.

Results:

<table>
<thead>
<tr>
<th>S</th>
<th>Nx7</th>
<th>Nx15</th>
<th>Nx60</th>
<th>Nx120</th>
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<tbody>
<tr>
<td>TCP</td>
<td>142±1</td>
<td>168±5a</td>
<td>188±5ab</td>
<td>209±3abc</td>
</tr>
<tr>
<td>ALB</td>
<td>8±2</td>
<td>44±11a</td>
<td>108±15ab</td>
<td>112±18ab</td>
</tr>
<tr>
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<td>0±0</td>
<td>0±0</td>
<td>29±8abc</td>
</tr>
<tr>
<td>%INT</td>
<td>0±0</td>
<td>1±0</td>
<td>1±0</td>
<td>4±1ab</td>
</tr>
<tr>
<td>Cytokine Cytokine-Receptor Interaction</td>
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</tr>
<tr>
<td>Hematopoietic Cell Lineage</td>
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<td>-1.8a</td>
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<tr>
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<td>Cell Adhesion Molecules</td>
<td>-1.6a</td>
<td>-1.7a</td>
<td>-1.7a</td>
<td>-1.4a</td>
</tr>
</tbody>
</table>

Mean±SE: p<0.05 vs S, p<0.05 vs Nx7, p<0.05 vs Nx15, p<0.05 vs Nx60

In addition, Tlr4, Th9, Il1m3, Lbp2 and Ifn7 genes were twice as high in Nx7 vs S. Tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/24h) glomerulosclerosis index (GSI) and cortical interstitial (%INT) were assessed. 7, 15, 60 and 120 days after Nx. Gene and protein content of Tlr4, Casp1, Il1b and Nlrp3 were also evaluated. PCR-Array and gene enrichment analysis (GEA) by z-score evaluated gene expression of innate and adaptive immunity components.

Conclusions: These preliminary pilot study suggests that antagonism of CTGF ASOs may attenuate CV in TSLP Tg animals. Larger studies are required to confirm this observation.

Funding: University of Sao Paulo.

There was less severe histological injury in the CTGF ASO cohort (mean mesangial expansion score 1.85±5 SD 0.54 vs. 2.24±8 SD 1.16, p=0.0458).

Conclusions: These preliminary pilot study suggests that antagonism of CTGF ASOs may attenuate CV in TSLP Tg animals. Larger studies are required to confirm this observation.

Funding: University of Sao Paulo.

TH-PO147

Evidence suggests that oxidative stress plays a significant role in the progressive fibrosis by upregulating fibrosis related genes. Moreover, elevation of biomarkers of increased oxidative stress has been demonstrated in patients with chronic kidney disease. OPN is highly induced in nephritic kidney and inactivation of macrophages (MΦ) by an ApoA-I agonist, attenuated OPN expression and protected from progressive kidney injury.

Methods: To further characterize the role of OPN in kidney injury we use OPN-/- mice in anti-glomerular basement membrane glomerulonephritis (anti-GBM GN), an inflammatory and progressive model of kidney disease.

Results: Wild type and OPN-/- mice did not show histological differences in the glomeruli and the tubulointerstitium. However, nephritic kidneys from OPN-/- mice showed severe kidney damage compared with those in WT mice. Fibrinoid necrosis, crescent formation, and tubulointerstitial injury were significantly higher in OPN-/- mice compared to WT mice. In addition, collagen (CoI) I, CoI III, and CoI IV deposition were increased in nephritic kidneys from OPN-/- mice compared with WT mice. MΦ and T cell infiltration in nephritic kidneys was not different between WT mice and OPN-/- mice. Elevated expression of the reactive oxygen species (ROS)-generating enzyme NOSx 4 was observed in nephritic kidneys from OPN-/- mice. In contrast, MΦ isolated from WT mice and OPN-/- mice did not show difference in the expression of NOSx4. Importantly, the antigen-specific humoral immune response and the glomerular immunoglobulin G deposition were not affected in OPN-/- mice.

Conclusions: These findings suggest that in global OPN-/- mice elevated NOSx4 creates a redox imbalance with increased oxidative stress induced-fibrosis. Targeting MΦ OPN could be protective to attenuate inflammation and inflammation-associated fibrosis without affecting the anti-oxidative stress of OPN.

Funding: NIDDK Support
TH-PO147
TLR2/TLR4-MyD88-NF-κB Pathway Is Involved in Tubulointerstitial Inflammation Caused by Proteinuria | Linhong Ding, Dan Liu, Hong Liu, Kunling Ma, Bi-Cheng Liu. Inst of Nephrology, Zhong Da Hospital, Southeast Univ, Nanjing, Jiangsu, China.

Background: Proteinuria, an independent risk factor for progression of chronic kidney diseases (CKD), has been suggested to initiate or aggravate tubulointerstitial inflammation (TI). While the potential mechanism is still to be clarified. In this study, we hypothesized that activation of the TLR2/TLR4-MyD88-NF-κB pathway might be involved in proteinuria induced TI.

Methods: We established an albumin-overload nephropathy rat model, and the expression of TLR2, TLR4, MyD88, NF-κB and IL-6 were detected by western blotning, real-time PCR and Western blot. In vitro, we investigated the impact of albumin stimulation on these parameters in HK-2 cells. Furthermore, siRNA for TLR2, TLR4 and BAY 11-7082, the inhibitor of NF-κB, was applied to study their influence on the expression of TNF-α and IL-6 expression caused by proteinuria.

Results: In vivo, rats treated with albumin-overload induced a significant increase of proteinuria, proteinaceous casts and tubulointerstitial inflammation. The expression of TLR2, TLR4, MyD88 and NF-κB in the proximal tubular cells significantly increased as well as TNF-α and IL-6 expression. In addition, the expression of TNF-α and IL-6 was significantly correlated with proteinuria. Albumin-overload induced TNF-α and IL-6 expression by TLR2/TLR4-MyD88-NF-κB pathway activation, which could be attenuated significantly by siRNA for TLR2, TLR4 or NF-κB inhibitor BAY 11-7082 in HK-2 cells.

Conclusions: This study demonstrated that proteinuria might play as an endogenous danger-associated molecular pattern (DAMP) that induced renal TI via the TLR2/TLR4-MyD88-NF-κB pathway activation.

Funding: Government Support - Non-U.S.

TH-PO148
Targeting Integrin CD11b/CD18 Reduces Inflammation and TLR-Mediated IFN Responses Implicated in Lupus Nephritis | Samina Khan, Shreyar J. Khaliqidina, Mohd Hafeez Faridi, David J. Cimbaluk, Mariana Kaplam, Vineet Gupta. 1 Internal Medicine, Rush Univ Medical Center, Chicago, IL. 2 Systemic Autoimmunity Branch, National Insts of Health (NIH), Bethesda, MD.

Background: GWAS studies show strong associations between single-nucleotide polymorphisms in the ITGAM locus, which encodes for the α-subunit (CD11b) of the b2 integrin CD11b/CD18 and susceptibility to lupus nephritis. CD11b/CD18 is a leukocyte adhesion receptor that modulates their biological functions and negatively regulates TLR-mediated pro-inflammatory signaling. Insufficient activity of CD11b/CD18 drives disease pathogenesis, hence making it a promising therapeutic target.

Methods: We tested whether activation of CD11b/CD18 with small molecule agonist, leukadherin-1 (LA1), suppresses pro-inflammatory TLR and IFN signaling pathways in vitro and in vivo. Since stimulation of TLR-induced overproduction of inflammatory cytokines drives lupus nephritis, we also tested whether dampening of these pathways with LA1 treatment reduces kidney injury in lupus prone MLR/lpr mice.

Results: Treatment of macrophages or neutrophils with LA1 and TLR4 agonist LPS or TLR7/8 agonist R848 induced a significant decrease in IL-6, TNFα and MCP-1, as well as type I IFN pathways, as compared to controls. In a murine model of severe sepsis, LA1 treatment significantly prolonged survival and reduced serum IL-6 and IL-1β levels as compared to controls. In a murine model of lupus nephritis (MRL/lpr), renal pathology of mice treated with LA1 was significantly improved in terms of proteinuria, urine cell count, and histological features as compared to controls.

Conclusions: LA1-mediatedCD11b/CD18 activation suppresses TLR-induced production of pro-inflammatory cytokines and IFN pathways. LA1 treatment also dampens TLR-stimulated overproduction of cytokines in vivo, which drives lupus nephritis. These findings indicate a crucial role for CD11b/CD18 in suppressing inflammation and identify LA1 as a promising therapeutic agent for human autoimmune diseases.

Funding: NIDDK Support

TH-PO149
Allopurinol Attenuates Innate Immunity Activation and Renal Injury in the Nx Model, Despite Low Urine Acid Levels | Orestes Foresto-Neto, Victor F. Avila, Simone CA Arias, Camilla Fanelli, Lizieny CT Rempel, Denise M. Malheiro, Hugo Alho, Mário Nils OS Camara, Roberto Zata, Cláriane K. Fujihara. Univ of Sao Paulo, Brazil.

Background: Allopurinol (Allo) attenuates renal damage in experimental CKD. It is unclear whether this protection is due to inhibition of uric acid (UA) synthesis or to a direct action on oxidative stress and innate immunity (INIM). We studied the effect of Allo in the 5/6 nephrectomy model (Nx) in rats, in which UA degradation by uricase allows its effect on renal injury and INIM to be studied without its confounding action on UA levels.

Methods: Munich-Wistar rats (N=33) underwent Nx or sham operation (N=33), 2 weeks later they were divided in: Nx, untreated; and Nx+Allo, given Allo 36 mg/kg/day vs. Taul-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/24h), glomerulosclerosis (GS), urinary NGAL (uNGAL, mg/24h), interstitial collagen 1 (COL) and macrophages (MΦ, cells/mm²), renal proteinuria (rXO, mg/24h), renal delivery of angiopoietin 2 (Ang2, pg/mg), blood pressure (TCP, mmHg), and renal content of IL-1β (pg/g) and TLR4 (fold increase vs C) were assessed on Day 60.

Results: Mean ± SE: *p <0.05 vs S; #p<0.05 vs Nx.

As expected, pUA was only slightly (though significantly) elevated in Nx, remaining far lower than previously seen with uricase inhibition. Allo normalized rXO activity and cancelled the slight increase of pUA observed in Nx. Despite the low pUA, Allo attenuated hypertension and prevented selective tubulointerstitial protection, reducing uNGAL, COL and MΦ. In addition, Allo lowered the renal content of TLR4 and IL-1β, which correlated positively with both TCP and ALB.

Conclusions: In the Nx model, Allo exerts a renoprotective effect even in the context of low UA levels, which is associated, at least in part, with inhibition of innate immunity. FAPESCP/NPq.

TH-PO150
Meganin/Cubulin-Lysosome-Mediated Albumin Reabsorption Is Involved in the Tubular Cell Activation of NLRP3 Inflammation and Tubulointerstitial Inflammation | Dan Liu, Bi-Cheng Liu. Inst of Nephrology, Zhong Da Hospital, Southeast Univ School of Medicine, Nanjing, Jiangsu, China.

Background: Albuminuria contributes to the development and progression of chronic kidney disease (CKD) by inducing tubulointerstitial inflammation (TI) and fibrosis. However, the exact mechanisms of TI in response to albuminuria are unresolved. We previously demonstrated that NLRP3 and inflammasomes mediate albumin-induced lesions in tubular cells. Here, we further investigated the role of endocytic receptors and lysosome rupture in NLRP3 inflammation.

Methods: We established an albumin-overload induced rat nephropathy model. The adult male Wistar rats that were uninephrectomized or sham operated under anesthesia 5 days before starting BSA injection. In vitro, tubular epithelial cell line (HK-2) was cultured with or without megalin/cubulin gene siRNA transfection and then stimulated with BSA for different time durations (6h, 12h, 24h, 48h) and concentrations (5, 10, 20, 40 μg/ml). Cell lysates and supernatants were collected and determined by western blotting and ELISA. Catepsin B and Catepsin D with or without their inhibitors were detected by western blotting and immunofluorescence staining.

Results: The priming and activation signals for inflammasome complex formation were evoked simultaneously by albumin excess in tubular epithelial cells. The former signal was dependent on albumin-triggered NF-κB pathway activation. This process is mediated by the endocytic receptor, megalin and cubulin. However, the silencing of megalin or cubulin inhibited the albumin-induced NLRP3 signal. Notably, subsequent lysosome rupture and the corresponding release of lysosomal hydrolases, especially Catepsin B, were observed in the cells exposed to albumin. B release and distribution is essential for NLRP3 signal activation, and inhibitors of Catepsin B suppressed the NLRP3 signal in TECs.

Conclusions: Taken together, our findings suggest that megalin/cubulin and lysosome rupture are involved in albumin-triggered tubular injury and TI.

TH-PO151
Targeted Inhibition of Protein Kinase C-a Ameliorates Nephrotic Nephritis | Nino Kyvirkvelia,1 Maggie McNeminin,1 Vanessa Iris Gutierrez,1 Istvan Czikora,1 Shehryar J. Kaplam,2 David J. Cimbaluk,1 Mariana Kaplam,1 Vineet Gupta.1 Medicine, Georgia Regents Univ, Augusta, GA; 2Pharmacology and Toxicology, Georgia Regents Univ, Augusta, GA.

Background: Protein kinase C (PKC) is a ubiquitous phospholipid-dependent enzyme, with multiple isoforms that differ in their structure, biochemical properties, tissue distribution, subcellular localization, and substrate specificity. Since PKC-a-a expression was shown to be increased in patients with chronic kidney disease and in podocytes in renal biopsies of patients with diabetic nephropathy, we investigated the effect of specific PKC-a inhibition on renal injury in a murine model of acute kidney inflammation.

Methods: Mice were divided into four groups. 1) controls, 2) NTN, 3) NTN + PKC-a inhibitor Ro-32-0432 given i.p. after induction of nephritis on day 2, and 4) NTN group + PKC-a inhibitor conjugated to glomerular specific antibodies (i.e. a well-defined, human mAb (F1.1) directed against a3(IV) collagen) on day 2 to achieve kidney targeted drug delivery.

Results: On day 7, all NTN mice had severe nephritis, as evidenced by increased BUN, proteinuria and histology, whereas mice that received PKC-a inhibitors in either form had minimal evidence of kidney injury. BUN levels were reduced from 99.8±4.33mg/
Circumstances. The mechanism exerts sympathoinhibitory effects being impaired under pathophysiological conditions. Under resting conditions RSNA was higher, ARNA lower in nephritis as compared to controls. Some nephritic rats were pretreated with tachykinin receptor antagonists to prove the abnormality in kidney. Treatment of nephritic rats with genotoxic agents.

**Conclusion:**
- Circumstances and conditions are important mediators of the nephron, and that glomerular target inhibition of this enzyme is feasible. This methodology has the advantage of diminishing systemic side effects while limiting and/or reversing ongoing damage associated with severe inflammation. This approach has potential therapeutic implications for the treatment of human kidney diseases.

**Funding:** NIDDK Support

**TH-PO152**

**Renal Sympathetic Nerve Activity Controlled by Renal Afferent Sympathoexcitatory or Inhibitory Nerves?**

**Tilmann Ditting,** 1 Kristina Rodionova,2 Sonja Heinlein,1 Karl F. Hilgers,1 Christian Ott,1 Roland E. Schmieder,1 Martin Haagendam,1 Kerstin U. Amann,1 Roland Veelken,1

1Nephrology & Hypertension, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany; 2Pathology, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany.

**Background:** Renal sympathetic nerve activity (RSNA) is important in hypertension, volume disorders or disease. It is unclear if increases of RSNA in disease are due to sympathoexcitatory or impaired sympathoinhibitory renal afferent nerves. We present data from nephritic rats suggesting the latter.

**Methods:** Nephritis due to OX7-antibodies in male Sprague-Dawley rats. Methylene blue-stained nephritic rats & controls were instrumented to stimulate renal afferent nerve activity (ARNA) in order to influence RSNA: ipsilateral renal arterial catheter for intrarenal administration (IRA) of the TRPV1 agonist capsaicin to stimulate ARNA (CAP 6.6 x 10^-7M) and induce the release of the tachykinin receptor agonist SP from renal afferents; contralateral stainless steel electrode for RSNA recording; before and after IRA CAP the tachykinin-receptor blocker RP67580 was given. Baseline RSNA & ARNA were assessed. Some nephritic rats were pretreated with tachykinin receptor antagonists to prove increased SP effects.

**Results:** IRA CAP decreased RSNA from 67.5 ± 12.0 mV sec to 14.8 ± 4.2 mV sec (p<0.05) over 60 minutes while in nephritis RSNA suppression was abolished. Suppressed RSNA in controls was transiently reversed by the tachykinin inhibitor. Under resting conditions RSNA was higher, ARNA lower in nephritis as compared to controls. Tachykinin receptor antagonist ameliorated damage in nephritis suggesting increased SP release from renal afferent nerves despite lack of the tachykinin dependent sympathoinhibition seen in controls.

**Conclusion:** Our data suggest that a tachykinin dependent renosympathetic reflex mechanism exerts sympathoinhibitory effects being impaired under pathophysiological circumstances.

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

**TH-PO153**

**Fan1-/- Mice Develop Karyomegalic Interstitial Nephritis**

**Rannar Airik,** 1 Markus Schueler,2 Merlin Airik,1 Jonathan Porath,1 Friedhelm Hildebrandt.12

1Division of Nephrology, Dept of Medicine, Boston Children’s Hospital, Boston, MA; 2Howard Hughes Medical Inst, Chevy Chase, MD.

**Background:** Karyomegalic interstitial nephritis (KIN) is a chronic interstitial nephropathy, characterized by tubulointerstitial nephritis and formation of enlarged nuclei in kidneys and other tissues (1). We recently reported that recessive mutations in the gene encoding FANCD2/FANCI-Associated Nuclease 1 (FAN1) cause KIN in humans (2). In order to study the function of Fan1 in kidneys we generated a Fan1 knockout mouse model.

**Methods:** Targeted Fan1^12/12 ES cells were obtained from EUCOMM and injected into blastocysts to generate Fan1^-/- mice. Abrogation of Fan1 expression in the mutant mice was confirmed by qRT-PCR. Renal histology was studied using hematoxylin/eosin, PAS and Masson’s trichrome staining. Tubular damage was induced with intraperitoneal cisplatin injection. Cell culture experiments were performed using mouse embryonic fibroblasts or mesenchymal stem cells isolated from Fan1^-/- and wild type animals.

**Results:** Fan1^-/- mice were born at Mendelian ratio and appeared healthy with no gross abnormality in kidney. Treatment of Fan1^-/- and wild type mice with 10 or 20 mg/kg cisplatin caused severe tubular injury with cast formation and tubular dilation in Fan1^-/- animals (n=5), accompanied with dramatic weight loss and lethality. Chronic injection of cisplatin at 2 mg/kg induced karyomegalic interstitial nephritis that lead to renal failure within 5 weeks in Fan1^-/- animals, but not in wild type mice. Cell culture studies demonstrated decreased survival and reduced colony formation of Fan1^-/- cells in response to treatment with genotoxic agents.

**Conclusions:** Fan1^-/- mice provide a new model to study the pathomechanisms of chronic kidney disease. We demonstrate that Fan1^-/- mice are highly sensitive to genotoxic insults that lead to kidney failure. Our data indicate that Fan1 is involved in the physiological response of the kidney cells to DNA damage, which has been recently acknowledged to contribute to the pathophysiology of the chronic kidney disease (2,3).

**Funding:** NIDDK Support, Private Foundation Support

**TH-PO154**

**Down Regulation of Vitamin D Receptor (VDR) Expression Determines Initiation and Progression of HIV-Associated Nephropathy (HIVAN) with Variable Angiotensinogen (Agt) Copies**

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1Nephrology, Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

**Background:** Agt transgenic mice have achieved renin angiotensin system (RAS). On the basis of our recent findings we hypothesized that mice with enhanced expression of Agt would display accelerated progression of HIVAN. We evaluated the effect of different copies of Agt in the initiation and progression of HIVAN in genetically engineered HIVAN mice (Tg26).

**Methods:** Control and Tg26 mice with 2 (Tg26/Agt-2) and 4 (Tg26/Agt-4) copies of Agt were evaluated for severity of renal lesions, arteriosclerosis and hypertension at 8 weeks and 16 weeks. Renal cortical sections were stained with sinus red and PAS. RNA was extracted from renal tissues and probed for AT1, AT2, VDR and molecules involved in profibrotic and epithelial mesenchymal transition (EMT) pathways.

**Results:** Tg26/Agt-4/8wks showed lower blood pressure (P<0.01) vs. Tg26/Agt-2/8 wks, while Tg26/Agt-4/16wks displayed higher blood pressure vs. Tg26/Agt-2/16wks. Tg26/Agt-4/8wks displayed attenuated expression of PAI-1 vs. Tg26/Agt-2/8wks; however, Tg26/Agt-2/16wks showed 3-fold greater PAI-1 expression than to Tg26/Agt-2/16wks. Tg26/Agt-2/16wks displayed attenuated expression VDR and enhanced production of Ang II vs. Tg26/Agt-4/16wks, however this pattern reversed at 16 wks. Tg26/Agt-4/8wks displayed attenuated expression of AT1 and AT2 and down regulation of TGF-β, Snail, and vimentin when compared to Tg26/Agt-2/8wks. However, all these markers were comparable between these groups at 16 wks of age. Tg26/Agt-2/16wks developed renal lesions which were more advanced than fibroblast-like cells.

**Conclusions:** Tg26/Agt-2/4 displayed slower progression of HIVAN initially at 8 weeks associated with enhanced renal tissue VDR expression and attenuated expression of PAI-1, Tert and EMT markers. However, Tg26/Agt-4/16wks displayed accelerated growth due to attenuated VDR expression leading to high blood pressure, upregulation of EMT and profibrotic molecules.

**TH-PO155**

**Egr1 Deficiency Abolishes Inflammatory and Fibrotic Responses of Renal Tubular Cells**

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1Inst of Clinical Medicine, National Cheng Kung Univ, Tainan, Taiwan; 2Internal Medicine, National Cheng Kung Univ Hospital, Tainan, Taiwan.

**Background:** Early growth response-1 (Egr-1) is a transcription factor that has been found to regulate inflammation and fibrosis in non-kidney tissues, but its role in renal failure has not been well established.

**Methods:** Wild type and Egr1^-/- mice were fed with adenine-enriched diet to induce tubulointerstitial nephritis (TIN), and primary tubular epithelial cells (PTECs) were treated with pro-inflammatory and pro-fibrotic cytokines. In addition, human kidney tissue samples were obtained from diabetic patients with renal failure and from non-diabetic patients without renal failure. The cell-type in which Egr1 was activated was assessed using immunofluorescence and immunohistochemical stain. The levels of inflammatory and fibrotic markers were analyzed using RT-PCR and Western blotting. Kidney sections were also stained with H&E and Masson’s trichrome to assess immune cell infiltration and fibrotic area.

**Results:** In mouse kidneys with TIN as well as in human kidneys with renal failure, tubular epithelial cell is the primary site for Egr-1 activation and undergoing nuclear translocation. Egr1^-/- mice were protected from renal failure, reflected by lower levels of serum urea and creatinine. This is consistent with Egr-1 deficiency-related reductions of immune cell infiltration, NF-kB activity, and expression of cytokines and chemokines in the kidneys. In addition, Egr1^-/- mice with TIN had less fibrotic area and attenuated TGFβ signaling than wild-type mice with TIN. Egr1 deficiency also abolished the ordinary responses of PTECs to TNFα and TGFβ.

**Conclusions:** Egr-1 activation in the renal tubular cell plays an integrative role for renal inflammation, fibrosis and the subsequent renal failure. Thus, Egr-1 may serve as a therapeutic target for human kidney diseases.

**TH-PO156**

**Angiopoietin-1 Overexpression Attenuates Renal Fibrosis Through Decreasing Inflammation**

**Fan-Chi Chang,1 Ming-Hsuan Tsai,2 Yu-Ihsiang Chou,1 Shuei-Liong Lin.3**

1Internal Medicine, Taipei Medical Univ Hospital, Taipei, Taiwan; 2Graduate Inst of Physiology, College of Medicine, National Taiwan Univ, Taipei, Taiwan; 3Renal Div, Dept of Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.

**Background:** Our previous studies have found dysregulated angiogenic growth factors in fibrotic kidney. We thus hypothesized that dysregulated angiopoietin-Tie system is related to microvascular destabilization and inflammation in the injured kidney.

**Methods:** We use unilateral ureteral obstruction (UUO) and 5 to 6 subtotal nephrectomy (5/6Nx) as animal models of progressive renal fibrosis. Specific overexpression of angiopoietin-1 (Angpt1) is induced in Fan1^-/- mice overexpressing mouse Fan8 (with C57BL/6 background) and TRE-hAngpt1 (with ICR genetic background). Under the control of mouse Fan8 promoter, docyline administration directs high levels of expression of the reverse tetracycline-dependent transactivator (rtTA) to all proximal, distal tubules and

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

125A
the entire collecting duct system of both embryonic and adult kidneys. Double transgenic mice inheriting Pax8/TA and pTRE-3×Angpt1 responder. Littermates that inherited one or no transgenes serve as experimental controls.

**Results:** In animal model of UUO and 5/6Nx, Angpt1 decreases whereas Angpt2 and Angpt2/2Angpt1 ratio increase as renal fibrosis progresses. Cross-bred of pTRE-3×Angpt1 (with ICR geriatric background) and Pax8/TA (with C57BL/6 background) lines is conducted for conditional overexpression. Overexpression of Angpt1 by tubule cells, include all proximal, distal tubules and the entire collecting duct system is induced after doxycycline administration in offspring with two transgenes. Compared to littermate control, transgenic mice with Angpt1 overexpression attenuate interstitial fibrosis in UUO kidney demonstrated by picrosirius red staining. Further analyses demonstrate decrease of inflammatory cell infiltration in UUO kidney of mice with Angpt1 overexpression.

**Conclusions:** These studies indicate that Angpt1 supplement may provide a novel therapy to attenuate renal fibrosis through reduction of inflammatory cell infiltration in UUO kidney.

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

**TH-PO157**

Benidipine Targets Leukocyte Kv1.3-Channels and Slows the Progression of Renal Fibrosis in Rats with Advanced Chronic Renal Failure

**Authors:** Stefan Wawersik,1

**Affiliation:** Physiology I, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.

**Background:** Leukocytes, such as lymphocytes and macrophages, predominantly express delayed rectifier K+-channels (Kv1.3) in their plasma membranes. In our previous study, the overexpression of these channels in leukocytes was strongly associated with their proliferation in kidneys and the progression of renal fibrosis in the advanced stage chronic renal failure (CRF). Since benidipine, a long-acting 1,4-dihydropyridine Ca+-channel blocker, is also highly potent as a Kv1.3-channel inhibitor, it could exert therapeutic efficacy in advanced CRF.

**Methods:** Male Sprague-Dawley rats that underwent 5/6th nephrectomy followed by a 14-week recovery period were used as the model of advanced CRF. Benidipine hydrochloride (5mg/kg) was started at 8 weeks after nephrectomy and orally administered daily for 6 weeks. The histopathological features of the kidneys were examined in vehicle-treated and benidipine-treated CRF rat kidneys. Cellular proliferation of leukocytes and the cortical expression of pro-inflammatory cytokines were also examined.

**Results:** In CRF rat kidneys, Kv1.3-channels began to be overexpressed in leukocytes as early as 8 weeks after nephrectomy. In the cortical interstitium of benidipine-treated CRF rat kidneys, both immunohistochemistry and real-time PCR demonstrated decreased expression of fibrotic markers. Benidipine treatment significantly reduced the number of proliferating leukocytes within the cortical interstitium and decreased the expression of cell cycle markers and pro-inflammatory cytokines.

**Conclusions:** This study demonstrated for the first time that benidipine slowed the progression of renal fibrosis in rat kidneys with advanced CRF. Kv1.3-channels overexpressed in leukocytes were thought to be the most likely therapeutic targets of benidipine in decreasing the number of proliferating leukocytes and repressing the production of inflammatory cytokines.

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

**TH-PO158**

Renoprotection by Treatment with CXA10, an Endogenous Nitro-Fatty Acid Cynichta M. Arbeeny,1 Hong Ling,1 Mandy M. Smith,1 Stephen O’Brien,1 Stefań Wawersik,2 Steven R. Lederer,2 Diane J. Jorkasky,2 Genzyme, a Sanofi Company, Framingham, MA; 2Complexa, Inc., Pittsburgh, PA.

**Background:** CXA10 is an electrophilic nitro-fatty acid that modulates anti-oxidant and anti-inflammatory pathways through activation of NRF2 and reduction of NFkB. In mesangial proliferative glomerulonephritis (MesPGN), tissue inhibitors of metalloproteinases (TIMPs) can regulate transcription factors and cytokines and participate in immune and inflammation reactions in an MMP-independent way.

We found that in the anti-Thy-1 nephritis model, TIMP-1 and monocyte chemotactic protein 1 (MCP-1) were significantly increased at the mesangial dissolved phase and peaked at the mesangial proliferative phase, finally backed to normal at the recovery phase. Our hypothesis is that TIMP-1 can regulate MCP-1 expression through NF-kB in mesangial cells.

**Methods:** (1) We established the anti-Thy-1 nephritis model. Animals were sacrificed at day 0, 1, 2, 3, 5, 7, and mRNA levels of TIMP-1 and MCP-1 were detected at separate time points by Taqman probe technique. (2) TIMP-1 over-expression rat mesangial cell model was established by GFP-TIMP-1 lentivirus transfection and siRNA interference. (3) The cells of TIMP-1 over-expression were harvested at day 5, 6, 7, and low-expression cells at 48h. Then we detected the mRNA and protein levels of TIMP-1, MMP2, MMP9, NF-kB and MCP-1 by Taqman probe technique and Western blot. (4) TIMP-1 over-expression cells were treated with NF-kB inhibitor BAY 11-7082 (2mmol/L) at 4th day. After 48h-culture, mRNA level were detected.

**Results:** (1) In rat anti-Thy-1 nephritis, the expression levels of TIMP-1 and MCP-1 was increased gradually and peaked at day 5, then began to decrease. MCP-1 followed the same trend but peaked at day 2. (2) We established the TIMP-1 over-low-expression model successfully. (3)When TIMP-1 presented over-expression, MMP9, NF-kB and MCP-1 were up-regulated (P<0.05). When TIMP-1 presented low-expression, these were down-regulated. (P=0.001) The change in expression of MMP2 was not obvious. (4) At 48h after inhibition with NF-kB inhibitor, the expression level of MCP-1 in the TIMP-1 over-expression cells was down-regulated (P<0.01).

**Conclusions:** TIMP-1 could participate in the immune and inflammation reactions of MesPGN by up-regulating the expression of MCP-1 through NF-kB in rat mesangial cells.

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

**TH-PO159**

Selective Knock-Out of Glycogen Synthase Kinase 3-β in Proximal Renal Tubular Epithelial Cells (RTE) Attenuates Inflammation and Tubular Injury After Unilateral Ureteral Obstruction (UUO)

**Authors:** Josef Bautista, Eman Mohammad Shaban, Evelyn Tolbert, Rujun Gong, Lance D. Dworkin.

**Affiliation:** Medicine, Brown Univ, Providence, RI.

**Background:** Glycogen synthase kinase 3-β (GSK-3β) is a ubiquitous serine/threonine protein kinase that regulates a large number of processes in diverse cell types including RTE. Systemic administration of small molecule inhibitors of GSK-3β reduces inflammation and fibrosis and lessens acute and chronic kidney injury. However, the extent to which the beneficial effects of GSK-3β inhibition depend on blocking the enzyme specifically in kidney cells is unknown. We investigated whether gene deletion of GSK-3β in RTEs alone would reduce inflammation and progression of CKD.

**Methods:** The GSK-3β gene was selectively deleted in the renal tubular cells by crossing mice in which exon 2 of the GSK3b gene was “floxed” with mice expressing CRE recombinase under a YGT promoter expressed only in adult proximal RTE (KO). Injury was induced by UUO in wild type (WT), KO, and WT mice given low-dose (1 mg/kg) thiadiazolidinone (TDZD), a specific GSK3β inhibitor. After 7 days, kidneys were weighed and examined for tubular and glomerular injury, interstitial edema, and macrophage infiltration. Groups were compared by ANOVA.

**Results:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Kidney Wt (gm/100g body wt)</th>
<th>Injured Tubules (%)</th>
<th>Glomerular Injury Score</th>
<th>Interstitial edema score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KO (n=7)</td>
<td>0.74 ± 0.09</td>
<td>35% ± 0.15 *</td>
<td>2.14 ± 0.94</td>
<td>1.47 ± 0.32</td>
</tr>
<tr>
<td>WT (n=11)</td>
<td>0.79 ± 0.16</td>
<td>57% ± 0.09</td>
<td>1.54 ± 0.66</td>
<td>1.59 ± 0.35</td>
</tr>
<tr>
<td>TDZD (n=11)</td>
<td>0.69 ± 0.12</td>
<td>46% ± 0.12</td>
<td>1.52 ± 0.82</td>
<td>1.77 ± 0.28</td>
</tr>
</tbody>
</table>

**P<0.01 KO vs. WT**

Macrophage infiltration assessed by immunohistochemistry also declined by about 40% in KO vs. WT mice.

**Conclusions:** Selective deletion of GSK-3β in RTE attenuated macrophage infiltration and reduced tubulo-interstitial, but not glomerular injury after UUO. Elimination of GSK-3β signaling in RTE was more effective than systemic, low dose GSK-3β inhibition. Our data suggest that GSK-3β dependent pathways in RTEs play a critical role in promoting interstitial inflammation and tubular injury in CKD.

**Funding:** NIDDK Support, Clinical Revenue Support
TH-PO161
Calcitriol Protects against Renal Tubular Cell Apoptosis by Promoting M2 Macrophage Polarization in Diabetic Nephropathy Rats Yinfeng Guo, Zhixia Song, Min Zhou, Ying Yang, Xiaoliang Zhang. Zhong Da Hospital, Southeast Univ, School of Medicine.

Background: Renal tubular apoptosis is a key event in initiating kidney damage in DN. Heterogeneity of macrophage phenotype and function ultimately determines the outcome of DN. Therefore, we sought to investigate whether calcitriol, known as an important renoprotective drug, is sufficient to protect against tubular cell apoptosis by promoting M2 macrophage in DN rats.

Methods: DN model rats were established by intraperitoneal injection with streptozocin (STZ). The rats were subsequently receiving either calcitriol (0.1 mg/kg/d) or vehicle by gavage twice a week for 8 weeks. The rats were killed at 10 weeks for histological and molecular analyses. In addition, we performed in vitro study using Raw264.7 cells cultured with either high glucose or high glucose followed by 1,25-dihydroxyvitamin D3 medium to assess macrophage phenotype.

Results: Calcitriol significantly improved renal function and ameliorated renal histology in DN rats. The increased tubular cell apoptosis in DN rats was attenuated by calcitriol. Calcitriol up-regulated the expression of anti-apoptotic protein Bcl-2, down-regulated the expression of pro-apoptotic protein such as Bax and caspase-3. Interestingly, calcitriol significantly enhanced M2 macrophage polarization in vitro in elevated expressions of M2 markers, including CD163, Arg-1 and MR. Moreover, the ratio of CD163/CD68 considered as the proportion of M2 macrophage was about 2.9 fold higher after calcitriol treatment. In vitro, 1,25-dihydroxyvitamin D3 also promote high glucose-induced pro-inflammatory M1 macrophage toward anti-inflammatory M2 polarization.

Conclusions: Calcitriol protects against renal tubular cell apoptosis by promoting M2 macrophage polarization in STZ-induced DN rats.

Funding: Government Support - Non-U.S.

TH-PO162

Background: Apolipoprotein L1 (APOI) is an innate immune protein and its risk variants are strongly associated with kidney disease. We investigated the effects of APOI variants on monocyte monocyte differentiation and eicosanoid production in macrophages, as activated tissue macrophages in kidneys might contribute to injury.

Methods: THP-1 cells, a human monocyte/macrophage line, were transiently transfected with APOI-A isoform G0 (ancestral allele) or the renal risk variants G1 and G2 and cultured for 36 hr before RNA was obtained for gene expression studies.

Results: APOI-1-transfected THP-1 cells manifested a 6-8 fold increase in CD14 and CD68 gene expression, similar for all three variants, and similar to that seen with phorbol-12-myristate acetate treatment. Furthermore, APOI risk variants induced activated monocytes into atypical M1 macrophages with increased RNA encoding M1 markers CD80, TNF, IL-1β, and IL-6 (all vs EV p <.005, G1 vs G2 p <.005), modest increase in M2 markers CD163, CD206, and TGFβ1 with G1 transfection (all RNAs vs EV p <.005) and CD204 and TGFβ2 with G2 treatment (both RNAs vs EV p <.005). Gene expression for eicosanoid generating enzymes was increased as well: cyclo-oxygenase-2, G0, 1.3±0.9 fold over empty vector (EV), G1, 4.1±0.5 and G2, 4.5±0.5 (both G1 and G2 vs G0 p <.001) and thromboxane synthase, G0, 2.1±0.8 fold over EV, G1, 5.2±0.8 and G2, 4.5±0.5 (both G1 and G2 vs G0 p <.005). Thromboxane A2 receptor (TXA2R) gene expression was unchanged with G0, 1.8±0.4 fold over EV (p>0.05), and increased with G1, 6.1±1.0, and G2, 4.1±0.5 (G1 vs G0 p = 0.001, G2 vs G0 p = 0.001). Higher levels of thromboxane B2, a stable metabolite of thromboxane A2, were present in the supernatant of cultured THP-1 cells transfected with G1 (10.0±1.3 pg/mL/10⁶ cells, p<0.05 vs G0) and G2 (15.1±3.0 pg/mL/10⁶ cells, p<0.01 vs G0) compared to G0 (6.0±1.0 pg/mL/10⁶ cells), which was similar to EV (6.7±1.0 pg/mL/10⁶ cells, p<0.05 vs EV).

Conclusions: These results demonstrate a novel role of APOI variants in the regulation of monocyte monocyte differentiation and eicosanoid metabolism, which could modify the immune response and promote inflammatory signaling within the kidney and elsewhere.

Funding: NIDDK Support

TH-PO163
Purification and Analysis of Exosomes Derived from Primary Human Proximal Epithelial Cells (PTEC) Helen G. Healy, Xiangiu Wang, Andrew J. Kassinios,1 Ray Wilkinson.2,3,4 Renal Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia; 2Conjoint Kidney Laboratory, Pathology Queensland, Brisbane, Queensland, Australia; 3School of Medical Sciences, Queensland Univ of Technology, Brisbane, Queensland, Australia; 4Medical School, Univ of Queensland, Brisbane, Queensland, Australia.

Background: Exosomes are extracellular vesicles secreted by multiple cell types in the body which contain a tissue-type signature courtesy of their incorporated RNA and protein cargo. Exosomes have crucial roles in extracellular communication and are implicated in kidney inflammation and disease progression. Human PTEC play a central role in renal disease yet their extracellular vesicle expression remains virtually unknown. Here we characterize exosomes from primary human PTEC cultured under normal, hypoxic and inflammatory conditions.

Methods: Exosomes were purified from normal, hypoxic (1% O₂) and inflammatory (IFN-γ/TNF-α treated) PTEC cultures using ultracentrifugation and density gradients and analyzed for morphology (electron microscopy), size/concentration (qNano) and cytokine expression (Western blot). Protein and microRNA content were analyzed by mass spectrometry (MS) and sequencing respectively.

Results: Exosomes from all three culture conditions displayed the same size range (50-120nm) and morphology (spherical doughnut shape) with a similar expression of CD9 (occcludin) and CD63 (TSG-101). However, exosomes from normoxic and inflammatory conditions contained more protein compared to normal conditions. MS analysis demonstrated exosomes from hypoxic cultures contained 134 proteins not expressed in those from normal cultures, whilst inflammatory exosomes contained 152 unique proteins. A number of these proteins have been implicated in development of chronic kidney disease.

Conclusions: Collectively, our data indicate that exosome secretion is increased under ‘diseased’ conditions, and importantly, there is condition specific differential protein expression. Further investigation of exosome protein/microRNA cargo will identify novel targets whose utility in therapies and disease biomarkers warrant analysis.

Funding: Government Support - Non-U.S.

TH-PO164
HIIF-2a in Dendritic Cells in Renal Injury Soeren Schuchow,1 Joanna Kalucka,2 Gunnar Schley,1 Bernd Klanke,1 Kai-Uwe Eckardt,3 Alexander Weidemann.1 1Nephrology and Hypertension, Univ of Erlangen-Nurnberg, Erlangen, Germany; 2Laboratory of Angiogenesis & Neurovascular Link, Univ of Leuven, Leuven, Belgium.

Background: Hypoxia-inducible transcription factors, HIF-1α and -2α play key roles in cellular adaptation to hypoxia and have been linked to immune responses. In macrophages they are non-redundant and are expressed depending on polarization. However, in other innate immune cells, such as dendritic cells (DCs), the differential role of HIFα isoforms is less clear. DCs are abundant in the kidney and have been implicated in renal (patho)physiology. As shown previously, HIF-1α in DCs affects maturation and T cell stimulation, but whether HIIF-2α plays a specific role is elusive. The aim of our study was therefore to elucidate the functional properties of HIIF-2α in DCs in vitro and in vivo during renal injury.

Methods: Murine primary DCs (BMDC) were generated from bone marrow of tissue specific conditional knock-out mice (C11c-Cre-HIIF-2α-/-). BMDCs were then stimulated with hypoxia and LPS followed by mRNA, FACS and protein analysis. Bilateral renal ischemia and reperfusion injury (IRI) was used as a model of acute renal injury. To induce chronic kidney injury, mice were subjected to either a 3 week adenine rich diet or to unilateral ureteral obstruction (UUO), followed by the above mentioned analyses.

Results: HIIF-2a protein is detected in BMDC after LPS treatment and with hypoxic stimulation. Loss of HIF-2a does not affect expression of maturation markers such as CD86 or MHCI following LPS and the ability of T cell activation. In vivo during acute or chronic renal injury, loss of dendritic HIIF-2α does not affect renal function, inflammatory cell responses or the expression of fibrotic or inflammatory markers.

Conclusions: Taken together, our data indicates that loss of HIIF-2a in BMDC does not affect maturation in vitro and leukocyte infiltration or renal function in models of acute and chronic renal injury in vivo. Thus, in contrast to macrophages, HIIF isoforms in DCs do not seem to play functional opposing roles. This might have important implications for the development of pharmacologic agents targeting HIFFs in DCs to modulate immune responses during renal injury.

Funding: Government Support - Non-U.S.

TH-PO165
Fecal Transplantation from Uremic Mice Aggravates Kidney Fibrosis Myung-yeou Kim, Young Ju Na, Sung Yoon Lim, Sang-Kyung Jo, Won-Yong Cho. Dept of Internal Medicine, Korea Univ Anam Hospital, Seoul, Republic of Korea.

Background: Emerging evidence showed the important role of kidney-gut crosstalk in diverse pathological processes. Alterations in intestinal barrier or microbiota has been implicated in chronic kidney disease (CKD) and thought to be associated with increased cardiovascular risks or progression of CKD. The purpose of this study was to investigate the effect of gut microbiota in the animal model of kidney fibrosis with using fecal transplantation.

Methods: Unilateral ischemia/reperfusion injury (IRI) for 45min was performed in C57/BL6 mice for fibrosis model. Supernatants of centrifuged feces from 5/6 nephrectomized mice (8wks) or age matched control mice were administered 3 times per wk for 3 wks after gut decontamination and degree of fibrosis was compared (CKD feces vs control feces). Compared to mice with fecal transplantation from control mice, mice who were transplanted with CKD feces showed aggravated fibrosis at 2 wks after unilateral ischemia in the analysis of the Masson's trichrome staining and Western blot for type 4 collagen. Ex vivo analysis of immune cells showed increased number of mature CD80+ CD11c+ cells in mesenteric lymph node whereas percentage of splenic Tregs increased in mice transplanted from uremic mice. Immune cells from these mice showed significantly suppressed cytokine release upon LPS stimulation compared mice with WT feces.

Conclusions: This study showed the possible effect of kidney-gut crosstalk on the progression of CKD and this effect is thought to be partially mediated by immune modulatory effect.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
A Novel Mineralocorticoid Receptor Blocker Protects the Remnant Kidney Better Than Eplerenone as an Add-On to Late Losartan

Clarice K. Fujihara,1 Mark Kowala,2 Matthew D. Breyer,2 Claudia R. Sena,3 Victor F. Avila,3 Vivian L. Viana,3 Denise M. Malheiros,3 Jose E. Krieger,3 Roberto Zatz.3 1Univ of São Paulo, Brazil; 2Eli Lilly.

Background: Aldosterone (Ald) worsens MR blockers, e.g. eplerenone (E), slow CKD, but cause hyperkalemia, especially with RAS inhibitors, e.g. Losartan (L). LY2180176 (LY) is a novel, nonsteroidal, high-affinity MR blocker (Ki: 1.6 nM vs 124 for E). We tested LY as an add-on to L in 5/6 ablation (Nx) rats.

Methods: Male Munich-Wistar rats underwent Nx (N=89) or sham (N=24) surgery, being divided in all drugs in mg/kg/d, from Day 60 to 150 post Nx: Untreated, Untreated + L, Untreated + E, Untreated + L + E, L, E, L + E, 50 + 150; ALB, albuminuria, mg/g; TCP, tail-cuff pressure, mmHg; PR, plasma renin, ng/mL/h; plasma Ald, pg/mL; Serum K, mmol/L; GS, Glomerulosclerosis; COL, cortical collagen; intestinal Ald+, cells/mm²; Genes (italic): RT-PCR (x increase).

Results:

|          | L      | L + E   | E      | ALB     | TCP     | PR     | Ald    | K     | %GS    | %COL    | AngI+   | AngII   | Renin   | SGK1   | NHE3   | NKCC2  | WNK1   | SGLT1  | NLRP3   | IL6    | NLRP3   | IL6    | TCP     | PR     | Ald    |
|----------|--------|---------|--------|---------|---------|--------|--------|-------|--------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|--------|---------|--------|---------|--------|--------|
| S        | 4±1    | 4±1     | 4±1    | 4±1     | 4±1     | 4±1    | 4±1    | 4±1   | 4±1    | 4±1     | 4±1    | 4±1    | 4±1    | 4±1    | 4±1    | 4±1    | 4±1    | 4±1    | 4±1     | 4±1    | 4±1     | 4±1    | 4±1    | 4±1     |
| Nx       | 1±1    | 1±1     | 1±1    | 1±1     | 1±1     | 1±1    | 1±1    | 1±1   | 1±1    | 1±1     | 1±1    | 1±1    | 1±1    | 1±1    | 1±1    | 1±1    | 1±1    | 1±1    | 1±1     | 1±1    | 1±1     | 1±1    | 1±1    | 1±1     |

Conclusion: LY may become a new asset in the therapy of CKD.

TH-PO167

Role of Innate Immunity in a Model of CKD following Brief Dietary Adenine Overload

Gizely CS Moreira,1 Ricardo P. Mazzonetto,1 Lisienni CT Rempel,2 Orestes Foresto-Neto,1 Camilla Fanelli,1 Simone CA Arias,2 Viviane D. Faustino,2 Claudia R. Sena,2 Victor F. Avila, Vivian L. Viana,2 Denise M. Malheiros, Niels OS Camara, Clarke K. Fujihara,2 Roberto Zatz.3 1Univ of São Paulo, Brazil; 2Eli Lilly.

Background: Adenine (ADE) excess leads to accumulation of crystals (Crys) at the renal interstitium (INT) through NF-κB activation (AJPRenal:F155,2013). After ADE cessation, INT nephritis progresses even as Crys disappear. Here we verified whether AngII inhibition of T-cell activation. Since inflammation is an important feature of diabetes, we hypothesized that Abatacept protects the kidneys during DN primarily by blocking T-cell activation.

Results: We investigated B7.1 expression in 42 DN kidney biopsies using immunohistochemistry. B7.1 expression was not detected in podocytes but predominantly localized in a limited number of macrophages, with no differences found between control and DN patients (0.15±0.23 vs. 0.19±0.22cells/mm²). In situ hybridization confirmed these results. In cultured human podocytes, B7.1 was found at relatively low levels when assessed by qPCR, and treatment with high-glucose (30mM for 3, 5, 10 and 14 days) or LPS (20 and 50ug/ul for 24 hrs) did not enhance B7.1 expression. Western blotting analysis confirmed these results. LPS-induced F-actin re-organization was not prevented by Abatacept (10-100mg/ml). We then tested Abatacept in the STZ-induced DN model (high fat-diet-C57Bl6). After 3 weeks of diabetes induction, Abatacept was dosed s.c. at 50mg/kg every 2 days for 12 weeks. At 3 weeks of dosing, urinary albumin:creatinine ratio increased from 3±0.8 to 8.3±0.9ug/umoles in the diabetic animals (p<0.05) while in the Abatacept group UACR was 4.0±0.2ug/mmol (p<0.05 vs. DN group). Glucose or HbA1c were unaffected across groups and throughout the study.

Conclusions: B7.1 is a valid target for DN where the mechanism of action is more likely inhibition of T-cell activation rather than podocyte protection.

Funding: Pharmaceutical Company Support - Medimmune; AstraZeneca

TH-PO169

Systemic Overexpression of Endogenous Secretory RAGE Attenuates Diabetic Kidney Injury Through TLR4 Not TLR2 Signaling

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Background: Endogenous secretory RAGE (esRAGE) is a soluble decoy receptor that can competitively bind ligands for TLRs/RAGE, including HMGB1. Here we test whether: 1) esRAGE after the induction of diabetes can prevent the development of diabetic nephropathy(DN) in mice with streptozotocin-induced diabetes; 2) the protective effects of esRAGE are attributable to interruption of signaling via the HMGB1 receptors (TLR2, TLR4 and RAGE). Methods: DN was induced in WT, TLR4-/- and TLR2-/- mice by intraperitoneal injection of streptozotocin. At 2 weeks after STZ injection, mice received an IP injection of 5x10¹⁰ vector genome copies rAAV encoding either esRAGE or HSA, or saline-control. Samples were collected at week 12 post-induction of diabetes.

Results: Diabetic mice that received rAAV-esRAGE, rAAV-HSA or saline developed equivalent degrees of hyperglycemia. Diabetic WT-mice given rAAV-HSA or saline developed significant albuminuria versus non-diabetic WT-mice ACR=309±213 & 313±215 versus 55±10, p<0.05-0.01) while rAAV-esRAGE-treated diabetic-mice were protected(118±42, p<0.05). WT diabetic-mice developed histological damage including glomerular hypersecretory, podocyte injury, macrophage accumulation and interstitial fibrosis. These changes were significantly attenuated in diabetic mice given rAAV-esRAGE versus rAAV-HSA (p<0.05-0.01). While both TLR2-/- mice and TLR4-/- mice were partially protected against DN, rAAV treatment provided additional protection to TLR2-/- mice, but not TLR4-/- mice. A further study of esRAGE treatment in RAGE-/- mice is underway.

Conclusions: High-level expression of esRAGE during the induction of diabetes provided partial protection against the development of DN in STZ-induced diabetic mice, which may operate through the TLR4 pathway.
Calcitriol Inhibits Advanced Glycation End Product (AGE)-Elicited Mesangial Cell Damage by Sequesterated RAGE-NF-κB Signaling

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Background: Active vitamin D3 (Calcitriol) can effectively slow the progression of chronic kidney disease and its mechanism is not very clear. The advanced glycation products (AGEs) accumulate in the kidney disease through RAGE receptors. The aim of this experimental study was to explore the effect and mechanism of Calcitriol on the inflammatory changes of mesangial cells by AGEs and to further expand the clinical application of active vitamin D3.

Methods: AGE-HSA was prepared and human glomerular mesangial cells were cultured and treated with AGE-HSA. The purpose of the present study was to investigate the efficacy of calcitriol on AGEs-induced inflammatory in human mesangial cell. Pretreatment or not with calcitriol, the human mesangial cell was treated with various concentrations and time period of AGEs. IL-6 and MCP-1 were determined by real-time PCR and ELISA. The expression of vitronectin (VDR), receptor of advanced glycation end products (RAGE), NF-κB p65 and phosphorilated p65 was measured by Western-blot. NF-κB p65 translation was determined by immunofluorescence. Cellular oxidative stress was measured by reactive oxygen species (ROS) production.

Results: (1) AGE-HSA induces IL-6 and MCP-1 expression in human mesangial cells, and calcitriol inhibits this effect. (2) Not AGE-HSA but calcitriol induces Vitamin D receptor (VDR) expression in human mesangial cells. And calcitriol inhibits this effect through VDR. (3) AGE-HSA induced Receptor for advanced glycation end products (RAGE) expression, and effects was blocked by calcitriol. (4) Effect of Calcitriol on AGEs production of mesangial cells. (5) NF-κB activation in ren, mesangial cells was induced by AGE-HSA, and the effect was inhibited by calcitriol.

Conclusions: Calcitriol could attenuate the AGE-induced up-regulation of IL-6 and MCP-1 though VDR by suppressing RAGE expression and subsequent ROS generation and reducing NF-κB activation.

Funding: Government Support - Non-U.S.

TH-PO173
Renal Protection by Atorvastatin in Sickle Cell Nephropathy
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Background: Sickle Cell Disease (SCD) affects approximately 100,000 people in the USA. Renal involvement begins early commonly manifested as hyposthenuria with microalbuminuria occurring in ~25% of SCD patients <18 years. Clinical markers or guidelines for sickle cell nephropathy include ACE inhibitors or ARBs to prevent progressive proteinuria. Statins have pleiotropic effects in addition to their lipid lowering properties. Here we investigated the functional effects of Atorvastatin treatment on the development of nephropathy in a murine model of sickle cell disease.

Methods: Cohorts (n=10) of 8-12 week homozygous sickle cell mice were treated with atorvastatin (10mg/kg) or vehicle daily for 8 weeks by oral gavage. We assessed effects of atorvastatin on albuminuria, maximum urine concentrating ability and GFR at baseline and week 8. Urine was collected in metabolic cages for 24hrs and albuminuria quantified by ELISA. GFR was measured by plasma clearance of FITC-Insulin. Mice were water deprived for 12hrs and spot urine for maximum urine concentrating ability. Kidneys were prepared appropriately for light microscopic analysis and glomerular morphometry.

Results: After 8 weeks of daily treatment mice receiving atorvastatin were found to have statistically significant improvement in urine concentrating abilities and improvement in GFR (p < 0.01 and p < 0.001 respectively). Urine protein excretion was unchanged by treatment with atorvastatin. Under light microscopy there were no gross changes in appearance of glomeruli or glomerular vascular structure. In addition we did not find significant statistical changes in glomerular tuft size.

Conclusions: We assessed the pleiotropic effects of atorvastatin in SCD. While we did not find differences in urine albumin excretion and glomerular tuft size we found that atorvastatin reduced urine protein excretion and improved renal concentrating abilities in sickle cell mice. These complications of are found both in animal and human models. Further studies will examine microscopic examination of podocyte and endothelial structures and look at biomarkers of renal injury.

Funding: Other NIH Support - R01HL11659

TH-PO174
Endothelin Receptor Antagonism Protects from Sickle Cell Nephropathy

Background: Sickle-cell disease (SCD) is characterized by chronic hemolysis and recurrent episodes of vaso-occlusive events that affect the microcirculation and lead to cell injury with multi-organ dysfunction. Sickle cell nephropathy, a major hallmark of glomerular lesions. We investigated the effects of chronic mixed ET receptor antagonism in a model of SCD-mediated FSGS.

Methods: We used SAD Hbbsingle/single hemizygous mice on the C57BL/6J background. At 3 months of age SAD mice displayed little evidence of chronic renal damage but significant glomerulomageny compared to controls. Glomerulomageny persisted, and was worse, at 6 months of age (average glomerular section area: 2372 ± 207 vs. 1519 ± 180 mm², p<0.001). In addition, SAD mice had significant glomerulosclerosis. Based on these data we treated SAD mice and controls aged 3 months with the dual ET receptor antagonist bosentan for 9 months in a preventative study, and 6 months old SAD mice for 6 months in a therapeutic study. We assessed blood pressure, kidney structure and function after 6 and 9 months of continuous treatment.

Results: In the preventative study, 6 months of bosentan therapy was associated with ~4-fold reduction in glomerulosclerosis compared to untreated SAD mice (22.8± vs. 86.4±, p<0.001). Additionally, there was an 80% reduction in mean glomerular surface area (p<0.05). In the therapeutic study, there was a significant reduction in glomerulosclerosis (p=0.01) and...

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glomerulonephrye (p<0.01) compared to untreated mice but this was less effective than in the in vivo study (p<0.05). Furthermore, chronic ET-1 receptor antagonism alleviated the development of tubulointerstitial fibrosis in both groups and limited the rise of blood urea nitrogen levels that characterized untreated aged SAD mice.

**Conclusions:** ET receptor antagonism is a potentially useful preventative or therapeutic approach in SCN. Based on these data clinical trials are warranted.

**TH-PO175**

**Erythropoetin and Its Carboxylated Derivative Protected against Chronic Cyclospermine Nephropathy**

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**Background:** Erythropoietin (EPO) is known to raise hemoglobin and protect tissues and its carboxylated derivative (CEPO) has no effect on hemoglobin but could induce tissue protection. The aim of this study is to determine the effect of EPO and CEPO on the animal model of chronic cyclospermine nephropathy.

**Methods:** We evaluated therapeutic effects of EPO and CEPO using a rat model of chronic cyclospermine nephropathy. Rats were randomly divided into five groups: (1) the saline treatment group (control group, n=12); (2) EPO treatment group at low dose (low EPO group, 100U/kg, n=12); (3) CEPO treatment group at low dose (low CEPO group, 100U/kg, n=12); (4) EPO treatment group at high dose (high EPO group, 500U/kg, n=12); (3) CEPO treatment group at high dose (high CEPO group, 500U/kg, n=12).

**Results:** In control group, the levels of sodium, protein and NAG enzyme of urine, the values of serum creatinine and urine nitrogen, the concentration of MDA and GSH-PX of kidney tissue were significantly increased. Those of EPO and CEPO treatment groups were significantly lower than low dose of control group. EPO and CEPO could promote to produce new endothelial cells and promote microvascular formation by analysis of CD31+/CD34+ cell number of blood and kidney tissue. EPO and CEPO decreased collagen fibers, tubular apoptosis and expression of TGF-b1, Caspase-3 and u-SMA in kidney tissue. The higher doses of EPO and CEPO showed more protection effects. But EPO treatment increased hemoglobin concentration and induced infarction.

**Conclusions:** EPO and CEPO could effectively antagonize cyclospermine nephrotoxicity through anti-fibrosis, anti-inflammatory cell infiltration, anti-apoptotic, anti-oxidant, promotion new growth of renal tubular epithelial and endothelial cells, and the promotion of release and proliferation of endothelial progenitor cells.

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

**TH-PO176**

**Glucose Promotes Secretion-Dependent Renal Cyst Growth**

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**Background:** ADPKD is characterized by continuous cyst growth which is highly based on transepithelial Cl− secretion into the cyst lumen. Since ADPKD is a long-lasting, chronic disease, there is a significant number of patients suffering from both, ADPKD and type 2 diabetes mellitus. Recently, ADPKD patients with type 2 diabetes mellitus were shown to have kidneys with almost double the volume compared to non-diabetic ADPKD patients. Therefore, we wanted to test for the impact of glucose on renal cyst growth.

**Methods:** We examined the effect of different glucose concentrations ranging from 5.6 mmol/l to a maximum of 25.0 mmol/l on cyst growth of MDCK cells within a collagen matrix as well as in ex vivo cultured embryonic mouse kidneys treated with forskolin. In addition, we analysed changes in expression of potentially relevant ion channels and transporters at different glucose levels. Furthermore, we performed Ussing chamber experiments with MDCK cells in order to detect alterations of transepithelial Cl− secretion upon changes in glucose concentration.

**Results:** Cyst expansion highly correlated with the levels of glucose in both cyst models, revealing already significant increase of cyst growth by elevating glucose concentration from 5.6 mmol/l to 11.1 mmol/l. These effects were neither referable to changes in pH or lactate, nor due to osmotic changes demonstrated by the use of equivalent doses of mannitol. However, elevated levels of glucose resulted in significantly increased transcription of the Ca2+-activated Cl− channel Anoctamin (ANO) 1 which we have previously shown is involved in renal cyst growth. In line with these data, CaCl2/CaCl2-AO1, a specific inhibitor of ANO1, inhibited glucose-dependent cyst expansion in both models. In addition, Ussing chamber experiments revealed a significant increase of Ca2+-dependent Cl− secretion at elevated glucose levels which could be inhibited by the use of CaCCInh-AO1.

**Conclusions:** Elevated glucose levels could augment secretion-dependent cyst growth in ADPKD. Therefore, tight glucose control might be beneficial in ADPKD to reduce cyst growth and preserve renal function.

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

**TH-PO177**

**Kidney Stones Provide a “Third Hit in Autosomal Dominant Polycystic Kidney Disease”**

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**Background:** The progression of autosomal-dominant polycystic kidney disease (ADPKD) exhibits high inter- and intrafamilial variability suggesting the possibility that additional environmental factors may play an important role. Work on mouse models has led to the idea that renal injury is required as a so-called “third-hit trigger” for the initiation of renal cysts. We hypothesized that a much more frequent and prevalent form of renal insult may determine the speed of progression in ADPKD. We report here that chronic or acute hyperglycemia leads to very rapid dilation of renal tubule diameters in response to CaOx crystal deposition.

**Methods:** Mice and rats were challenged with intraperitoneally administered oxalate to rapidly produce calcium oxalate crystals or were fed oxalate producing compounds to form oxalate stones inside the kidney. To test the effect of the mTOR pathway, mTOR was inhibited with the administration of rapamycin prior to oxalate administration.

**Results:** The mTOR and STAT3 signaling pathways are rapidly activated in dilated tubule cells. Fast tubule dilation can be prevented by mTOR inhibition. Once crystals are cleared, mTOR and STAT3 signaling is inhibited and tubule diameters return back to normal. Our results suggest that tubule diameter dilation is an active mechanism employed by the kidney to clear lodged crystals. Both, mTOR and STAT3 have previously been shown to be aberrantly activated in cyst-lining cells in ADPKD and drive cyst growth. Therefore, we wanted to test for the impact of glucose on renal cyst growth.

**Conclusions:** These results suggest that cilia are required for reestablishing normal tubular diameters after crystal clearing. Furthermore, these results suggest that renal crystal clearance can be influenced by environmentally controlled “third-hit trigger” that affects disease progression in ADPKD. This suggests that dietary changes or treatments to reduce renal crystal burden may be effective in slowing ADPKD progression.

**Funding:** Private Foundation Support

**TH-PO178**

**Soluble RAGE Alleviates Disease Progression in Autosomal Dominant Polycystic Kidney Disease by Down-Regulation of Cell Proliferation**

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**Background:** Autosomal polycystic kidney disease (ADPKD) is one of the common genetic renal diseases in which epithelial-lining fluid-filled cysts appear in kidneys. It is accompanied by hyper-activation of cell proliferation, interstitial inflammation and fibrosis around the cyst lining cells, finally reaching end-stage renal disease (ESRD). Previously, we found high expression of ligands stimulating the receptor for advanced glycation endproducts (RAGE) in ADPKD mice. Furthermore, gene silencing of RAGE was revealed to reduce cystogenesis via down-regulation of cell proliferation in vitro, while intravenous administration of anti-RAGE adenosine in vivo also displayed alleviation of the disease.

**Methods:** Using either mice primary cells or human ADPKD cell line WT9-12, both sRAGE treatment and over-expression of sRAGE with cloned construct we established here was tested in vitro. In vivo test via intraperitoneal injection using ADPKD mice model jck, and confirmed the in vitro results in this study.

**Results:** Here, we attempted to identify the role of soluble RAGE (sRAGE) in inhibiting the progression of ADPKD, in vivo. sRAGE is an endogenously expressed form of RAGE which has no membrane-anchoring domain, thereby being able to neutralize the ligands that stimulate RAGE signals. Both over-expression of sRAGE and sRAGE treatment blocked RAGE-mediated cell proliferation in vitro. In addition, sRAGE-injected ADPKD mice showed reduced cysts accompanied by enhanced renal function, inhibition of cell proliferation, inflammation and fibrosis.

**Conclusions:** These positive therapeutic effects of sRAGE displayed little liver toxicity, suggesting it as a new potential therapeutic target of ADPKD with low side effects.

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

**TH-PO179**

**Metformin Inhibits Cyst Formation in a Zebrafish Model of Polycystic Kidney Disease**

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**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is characterized by enhanced fluid secretion and abnormal cell proliferation in renal tubular epithelial cells. Recent research has proposed that activation of AMP-activated kinase (AMPK) is a novel treatment strategy to examine the effects of treatments on the initiation of pronephric cysts in a PKD2 zebrafish model.

**Methods:** Morpholino-mediated knockdown of pkd2 was performed in wt-1b pronephric-specific GFP-expressing zebrafish embryos to induce visible pronephric cysts for observation. Pkd2 morphants were incubated with metformin (2.5 to 10 mM) in the embryo medium until 48 hours post fertilization.

**Results:** Metformin significantly reduces the frequency of cyst formation and pronephric tubular cell proliferation in pkd2 morphant embryos. Whole mount in situ hybridization for L-plastin mRNA showed significantly reduced macrophage infiltration

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in metformin-treated pkd2 morphants. RT-PCR showed that P2X7, IL-1β and IL-10 mRNA expression were significantly inhibited by metformin. Simultaneously morpholino knockdown of AMPK α1 prevents the rescue effect of metformin on cystogenesis. 

Conclusions: We showed that metformin decreases cyst formation through inhibiting cell proliferation and macrophage accumulation in a pkd2 zebrafish model. These results indicate that metformin reduces the earliest cyst formation in polycystic kidney disease, and its effect on progression of disease remained to be investigated.

Funding: Government Support - Non-U.S.

TH-PO180
Cardiac Hypertrophy and Cardiac mTORC1/2 Signaling in Rodent Models of PKD
Kameswaran Ravichandran, Qian Wang, Charles L. Edelstein. Univ Colorado Denver.

Background: Cardiac disease is the commonest cause of death in ADPKD patients. Young normotensive ADPKD adults and children have higher LVMi compared to controls. Aim of study was to determine in rodent PKD models: 1) whether there is cardiac hypertrophy and increased mTORC1/2 signaling in the heart 2) the effect of mTOR kinase inhibitor on cardiac hypertrophy.

Methods: Heart weight was determined in Pkd1 +/-, mice, Pkd1+/-+ Pkd2+/- mice and Han:SPRD (Cy/) rats. p66 and p4E-BP1, markers of mTORC1 and pAktSer473, marker of mTORC2, were determined by immunoblot analysis of 3 separate experiments. Pkd2 +/- mice were treated with an mTOR antagonist oligomycin (ASO) that inhibits mTORC1 and Pkd2 from 4-16 wks of age. Cy/+ rats were treated with the mTOR kinase inhibitor, PP242, that inhibits mTORC1/2 and PKD from 3-8 wks of age.

Results: There was increased heart weight in 150 d old Pkd1 +/- mice, 16 wk old Pkd1 +/-/+; Pkd2 +/-/+ (without PKD) and Pkd2 +/-/ mice that are haplo-insufficient for Pkd2 and do not have hypertension. There was increased p66, p4E-BP1 and pAkt in Pkd1 +/- hearts and increased p4E-BP1 and pAkt in Pkd2 +/- and Pkd2+/- hearts. mTOR ASO resulted in less p4E-BP1 and pAkt and less cardiac hypertrophy in Pkd2 +/- mice. mTOR kinase inhibitor, PP242, resulted in less cardiac hypertrophy in mTORC1 deficient Cy/+ rats HW/TBW(%) was 0.4 in +/-, 0.52 in Cy/^+/+ (P<0.05 vs +/-) and 0.44 in Cy/+PP242 (P<0.05 vs Cy/+).

Conclusions: There was increased heart weight in normotensive Cy/+ rats and Pkd2+/- mice. There was increased mTORC1 and 2 signaling in Pkd1 +/-, Pkd2+/- (without PKD) and Pkd2 +/ mice, that are haplo-insufficient for Pkd2 and do not have hypertension. In Pkd2 +/-/+; Pkd2 +/-/+ (without PKD) and Pkd2 +/- mice that are haplo-insufficient for Pkd2 and do not have hypertension. There was increased p66, p4E-BP1 and pAkt in Pkd1 +/- hearts and increased p4E-BP1 and pAkt in Pkd2 +/- and Pkd2+/- hearts. mTOR ASO resulted in less p4E-BP1 and pAkt and less cardiac hypertrophy in Pkd2 +/- mice. mTOR kinase inhibitor, PP242, resulted in less cardiac hypertrophy in mTORC1 deficient Cy/+ rats HW/TBW(%) was 0.4 in +/-, 0.52 in Cy/^+/+ (P<0.05 vs +/-) and 0.44 in Cy/+PP242 (P<0.05 vs Cy/+).

TH-PO181
Polycystic Kidney Disease – A Case of Suppressed Autophagy? 

Background: Autophagy is a normal physiological process that involves the degradation of cellular components. Autophagy in general promotes cell survival while apoptosis that promotes cell death. We have reported (Edelstein et al, AFP, 2011) that there are features of autophagy like autophagosomes, mitophagy and autolysosomes in normal tubules and tubular cells lining cysts in Cy/+ rats with PKD and that there is suppression of autophagic flux in cpk mice with PKD.

Methods: 150 day old mice with PKD due to a kidney specific Pkd4 knockout were studied. MDCK cells with a stable knockdown of PC1 was achieved by lentiviral-mediated delivery of a specific SiRNA for PKD1 were studied. MDCK cells that form tubules were studied. MDCK cells with a stable knockdown of PC1 was achieved by lentiviral-mediated suppression of autophagic flux in cpk mice with PKD.

Results: We showed that metformin decreases cyst formation through inhibiting cell proliferation and macrophage accumulation in a pkd2 zebrafish model. These results indicate that metformin reduces the earliest cyst formation in polycystic kidney disease, and its effect on progression of disease remained to be investigated.

Funding: Government Support - Non-U.S.
Periostin Regulates Polycystic Kidney Cell Proliferation and Cyst Formation via CFTR and JAK2/STAT3 Signaling Pathway

Young Isaline Rowe, The Possible Role of mTORC1 and TCA Cycle in Renal Cyst Formation via CFTR and JAK2/STAT3 Signaling Pathway

Periostin expression was analyzed using immunohistochemistry and western blot analysis in ADPKD cells and normal human kidney (NKH) cells. Cell growth and western blot analysis for related molecular levels were assayed after suppression of periostin by small interfering RNA (siRNA). In three-dimensional culture, addition of recombinant periostin enhanced cyst formation, whereas periostin depleted cells showed lower level of cystogenesis.

Conclusions: Periostin stimulated cyst formation via CFTR and JAK2/STAT3 signaling pathway in ADPKD.

Effect of Simvastatin on Cell Adhesion in ADPKD

Wei Wang, Michel Chonchol, Melissa A. Cadnapaphornchai, Berenice Y. Gitomer. Dept of Medicine, Univ of Colorado, aurora, CO.

Background: We have previously shown that statin treatment reduced the rate of cyst growth in children and young adults with autosomal dominant polycystic kidney disease (ADPKD) suggesting that this may be an effective intervention to slow progression of renal disease in ADPKD, however the mechanisms are unclear. Treatment of cultured cystic renal tubular cells with simvastatin significantly reduces cell viability in cystic epithelial cells (WT 9-12) in a time and dose dependent manner but had minimal effect on normal tubular epithelial cultures (HK-2). We hypothesized that loss of viability was associated with reduced cell adhesion due to reduced expression of cell adhesion proteins.

Methods: In normal tubular cells simvastatin significantly increased integrin β1 expression while a significant decrease in expression was observed in the cystic tubular cells.

In untreated cystic tubular epithelial cells E-cadherin expression was significantly lower compared to normal control cells. Expression of E-cadherin was slightly reduced in the cystic cells after treatment with simvastatin. This cytotoxic effect on cystic cells was increased with simvastatin compared to pravastatin.

Conclusions: Simvastatin may have pleiotropic effects on cystic epithelial cells including an effect on cell adhesion. The lack of effect on normal tubular epithelial cells indicates that simvastatin may have specific therapeutic benefits in human ADPKD. Future clinical trials will be necessary to test the benefits of simvastatin in slowing cyst growth.

Funding: NIDDK Support

Identification of a Renal Pkd1/Pc1 Self-Amplification Mechanism via c-Myc in Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic disorder associated mainly with Pkd1 mutations. One of the most extensively studied dominant polycystic kidney disease (PKD) mouse model is the transgenic Sbm mice produced by specific targeting of c-Myc expression in the kidneys. All mice reproducibly developed tubular and glomerular cysts leading to renal insufficiency with high similarities to the orthologous Pkd1 dosage-reduced mouse models.

Methods: The cystogenic mechanisms of Sbm and Pkd1 orthologous models were investigated concomitantly by molecular and cellular analyses.

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Results: We first determined that Pkd1 dosage-increased and -reduced mouse models lead to stimulation of renal cyst growth (5-10-fold) as in ADPKD renal tissues, identifying a key downstream effector and the high relevance of SBM mice. This prompted analysis of SBM mice that showed enhanced protein expression of C-Myc full length and lack-Myc in tubular epithelial cells. C-Myc immunostaining determined intense nuclear signals throughout the tubulointerstitial compartment of cystic kidneys. SBM renal epithelial cells displayed a marked activation of β-catenin in renal epithelium that was stimulated as well in both Pck1 dose-increased and reduced mouse models. Importantly, SBM caused striking upregulation of polycystin-1/Pck1 and Pkd1→6-17-fold over endogenous levels in kidneys. SBM and Pkd1 mouse models uncovered a reciprocal cystogenic targeting and an inter-regular network of C-Myc and Pck1 in PKD.

Conclusions: Together our data support a regulatory positive Pck1/C-Myc amplification loop via C-Myc that governs ADPKD.

Funding: Government Support - Non-U.S.

TH-PO191

Resveratrol Delayed Disease Progression in Polycystic Kidney Disease Through Attenuating P50/p65 Induced Inflammation

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Background: The natural anti-inflammatory compound resveratrol displayed beneficial effects in a variety of diseases. The current study aimed to study the efficacy of resveratrol in polycystic kidney disease (PKD) and reveal its underline mechanism.

Methods: Five weeks resveratrol treatment reduced BUN and creatinine level by 20% and 24% respectively in cystic Cy/+ Hsd:SPRk rats. Administration of resveratrol decreased the two kidney weight/total body weight ratio and cystic volume density in Cy/+ rats by 15% and 24% respectively. The proliferation index and the macrophage infiltration index were reduced by 40% and 43% respectively in resveratrol treated cystic kidneys in comparison to vehicle treated cystic kidneys. Resveratrol reduced protein levels of pro-inflammatory factors such as MCP-1, TNF-α and CBF in Cy/+ kidneys, which was correlated with decreased activity of NF-κB (p50/p65). Resveratrol and NF-κB specific inhibitor NQZ inhibited the expression of MCP-1, TNF-α and CBF and reduced NF-κB activity in ADPKD cells. Moreover NF-κB blockage minimized the reduction but not completely abolish the inhibition of inflammatory factor production by resveratrol treatment.

Conclusions: NF-κB signaling pathway is activated in PKD and partly responsible for PKD inflammation. Targeting inflammation through resveratrol could be a new strategy for PKD treatment in the future.

Funding: Government Support - Non-U.S.

TH-PO192

Increased Hedgehog Signaling in jck Mice and in Human ADPKD

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Background: Increased Hedgehog (Hh) signaling correlated with cyst growth in PKD. However, in polycystic kidney disease (PKD) and reveal it’s underline mechanism.

Results: In jck mice, expression of Hh target genes, Gl1, Gl3 and Pch2, were elevated at seven weeks of age and increased further at 18 weeks of age. Immunohistochemistry for GLI1 revealed increased expression in renal epithelial and interstitial cells, suggesting both paracrine and autocrine signaling mechanisms. Further, jck/Gl2 double mutants showed decreased renal cystogenesis compared to single mutant littermates, suggesting a causal role for increased Hh signaling in increased disease progression. In human PKD, cilia and cells, Hh target gene expression was elevated and Gl1 protein expression was increased in both cystic epithelial cells and interstitial cells. Additionally, even in the absence of an Hh agonist, ADPKD cells showed localization of the Smoothened signal transducer to primary cilia, reflecting increased basal pathway activity.

Conclusions: Increased Hh signaling appears to play a role in renal cystogenesis and could represent a novel therapeutic target for ADPKD.

Funding: Other NIH Support - NIGMS

TH-PO193

The Development of a Clinically Relevant Mouse Model for Autosomal Dominant Polycystic Kidney Disease

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Background: To perform pre-clinical studies for Autosomal Dominant Polycystic Kidney Disease (ADPKD), it is desirable that the models have an adult onset of PKD with cysts derived from all tubular segements, but within a time-window that is suitable for therapeutic testing. As described previously, Pkdl deletion in neonatal mice leads to rapid PKD and Pkdl deletion in adult mice leads to slow PKD. The differences in rate of PKD progression are largely explained by a rather sharp developmental switch that occurs for therapeutic testing. As described previously, Pkd1 deletion in adult mice leads to slow PKD. The differences in rate of PKD progression are largely explained by a rather sharp developmental switch that occurs in PKD.

Results: P16 mice developed PKD within 3 to 4 weeks, with large distal and collecting duct cysts and few proximal tubular cysts. The progression rate in P16 mice was highly variable. By contrast, P18 mice developed end-stage PKD at an age of 14-17 weeks, with...
cysts derived from all tubular segments that contributed equally to the phenotype. P40 mice developed end-stage PKD at an age of approximately 22 weeks with predominantly proximal cysts.

Conclusions: Despite a sharp developmental switch at P13 that has been proposed previously (Piontek et al. 2007) it is possible to generate multiple models with different progression rates and different origins of cyst. Notably, Pkd1 deletion at P18 reproducibly led to adult onset PKD within a time-window that is highly suitable for therapeutic testing. In addition, since cysts were derived from all tubular segments, this model will contribute to finding a clinically relevant therapy for ADPKD patients.

TH-PO194
Identification of New Signaling Pathways Related to Polycystic Kidney Disease: From Animal Models to Treatment
Olaya Lamas-Gonzalez,1 Susana Bravo,1 Ana Belen Sanz,2 Ana Barca de la Iglesia,1 Alberto Ortiz,2 Terry J. Watnick,3 Gregory G. Germino,2 Candido Diaz Rodriguez,2 Miguel A. Garcia-Gonzalez,1 Health Research Inst of Santiago de Compostela, Spain;2 Fundacion Jimenez Diaz, Spain;3 Univ of Maryland School of Medicine;4 National Inst of Diabetes and Digestive and Kidney Disease National Inst of Health.

Background: Pathogenesis of Polycystic Kidney Disease (PKD) has been related to a number of different mechanisms that make it very complex and there is no therapy for complete inhibition of cystogenesis, although there are advances in controlling cyst volume and cyst progression.

Methods: Taking advantage of the identified developmental window in PKD using the Pkd1 conditional KO mouse, we have identified the differential proteome of the cystic and non-cystic Pkd1 mutant kidneys. We identify TWEAK as a window dependent modulator of cystogenesis, inhibiting cystic progression in the cystic window, and promoting cystogenesis in the non-cystic window. We perform an exhaustive proteomics analysis of each cyst developmental stage by MALDI-TOF/TOF analysis of peptides and proteins separated either by LC or 2-D PAGE.

Results: We stabilized the proteomics fingerprint of each pathophysiological condition and refined new therapeutic targets to a very short list of 12 candidate targets. During progression of cystogenesis, inhibiting cystic progression in the cystic window, and promoting cystogenesis in the non-cystic window. We perform an exhaustive proteomics analysis of each cyst developmental stage by MALDI-TOF/TOF analysis of peptides and proteins separated either by LC or 2-D PAGE.

Conclusions: Here, we first describe the proteome related to the developmental cystic window as well as those pathways associated to the cystic progression under inflammatory respond, triggering new possible targeting pathways for both controlling origin and progression of cystogenesis.

TH-PO195
Cytokine Tweak as an Intermediary in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Olaya Lamas-Gonzalez,1 Ana Belen Sanz,2 Maria D. Sanchez-Niño,2 Ana Barca de la Iglesia,1 Adrian Cordido-Eijo,1 Alberto Ortiz,2 Miguel A. Garcia-Gonzalez,1 Health Research Inst of Santiago de Compostela, Spain;2 Fundacion Jimenez Diaz, Spain.

Background: The pathogenesis of Polycystic Kidney Disease (PKD) remains unclear, but appears to involve altered tubular cell proliferation, cell death, differentiation and polarity as well as inflammatory and pro-fibrotic factors. It has been reported that acute kidney injury (AKI) and inflammation accelerate cystogenesis. TWEAK is a TNF-like cytokine that has a key role in AKI since anti-TWEAK antibodies prevented experimental loss of kidney function and renal inflammation, cell death and proliferation.

Methods: We hypothesize that response to treatment and cyst progression depend on a particular developmental window, so the correct dose and timing of a drug may prevent cystogenesis and make chronic treatment unnecessary. Here, we use a mouse model in which conditional inactivation of the Pkd1 gene by Cre-mediated recombination results in cystogenesis at different ages depending on when Pkd1 is inactivated.

Results: PKD1 inactivation at day 12 resulted in massive cyst growth by day 30. Under these conditions systemic TWEAK administration at 10 days significantly reduced kidney cystogenesis. By contrast, PKD1 inactivation at day 14 did not result in cyst growth by day 30. Under these conditions systemic TWEAK administration for 10 days significantly promoted kidney cystogenesis. Inflammation background, tissue remodeling and immune response to kidney injury could be playing a key role in the development and progression of ADPKD. Interestingly, liver appeared to present a different developmental pattern than kidney since TWEAK had mild effects in its cystogenesis.

Conclusions: These results demonstrate a developmental impact of PKD1 inactivation and TWEAK in cystogenesis and are pointing out the antagonistic effects of the same molecule in different cyst developmental stages. Under the conditions of early PKD1 inactivation of the cystic window, TWEAK may protect from cystogenesis if administered early in the disease course. However, detailed time course are needed before human extrapolation given that TWEAK induce cystogenesis in some settings.

TH-PO196
Defects in Epithelial Morphogenesis of Fibrocytostin-Deficient Cells Are Associated with Disturbed Cell Adhesion
Wolfgang H. Ziegler, Birga Soetje, Lisa P. Marten, Dieter Haffner. Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.

Background: Mutations of the Phdal gene cause autosomal recessive polycystic kidney disease (ARPKD). Phdal encodes fibrocytostin (FCP), a type 1 transmembrane protein of largely unknown function, which has been suggested to affect adhesion signaling of epithelial cells. In this study, we focus on the correlation of epithelial cell adhesion to the disease process of ARPKD remain to be defined. Having established a link between loss of FCP function and epithelial morphogenesis in 3D cell culture, we now aim to determine FCP-mediated parameters of (i) cell contact formation and (ii) the function / orientation of the actin cytoskeleton and microtubule networks.

Methods: We analyze FCP function in Madin-Darby canine renal collecting duct epithelial cells (MDCK) based on Phdal silencing. Cells are being studied on micro-patterned chips in 3D cell culture conditions, which induce formation of epithelial spheroids. To determine epithelial differences, we performed quantitative IMVIM-FR analysis of each MDCK cell line in their one and 2-4-D cell stages after seeding on chips with fluorescent microscopy.

Results: Based on defined adhesion conditions, we quantified the impact of FCP deficiency on size / density of adhesion sites, cell shape characteristics and initiation of an apical surface. In cells deficient for FCP, cell culture conditions supporting correct epithelial morphogenesis induced significantly reduced cell area and number of cell adhesion sites per cell, with differences originating from defects in cytoskeletal organization rather than reduced cell size. Further insight is expected from ongoing analysis of centrosome dynamics and the epithelial developmental cascade. Using a cell-based model system, we can address molecular consequences of and analyze rescue strategies for FCP deficiency in collecting duct epithelia.

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

TH-PO197
Identification of FUBP1 as a PKD2 mRNA 3'UTR Binding Protein That Suppresses Its Translation
Wang Zheng, Xing-Zhen Chen. Dept of Physiology, Univ of Alberta, Edmonton, AB, Canada.

Background: PKD2, also called polycystin-2, a Ca2+-permeable non-selective cation channel that is mutated in around 15% autosomal dominant polycystic kidney disease (ADPKD). Increasing evidence indicates that the PKD2 protein level is important for embryonic development, cell response to ischemic renal injuries, and cyst formation, but there are limited studies so far about how PKD2 protein level is regulated.

Methods: Here, with dual luciferase assays, western blotting, biotin-RNA pull down, gene knockdown in zebrafish, co-immunoprecipitation and GST-pull down, we studied how PKD2 mRNA translation is regulated by its 3' untranslated region (3'UTR).

Results: First, by dual luciferase assays, we identified a fragment in PKD2 3'UTR, named 3F1 (3' fragment inhibitory), that negatively regulates luciferase activity. Western blotting with a luciferase antibody confirmed the data obtained from the luciferase assays. By 3F1 RNA pull down and mass spectrometry, we identified a 3F1-binding protein, called far upstream element binding protein 1 (FUBP1) that was originally found to promote transcription of oncogene c-Myc. Over-expression and knockdown of FUBP1 decreased and increased the PKD2 protein level, respectively, without altering the mRNA level. More interestingly, tail curvature induced by PKD2 morpholino (MO) knockdown in larval zebrafish was rescued by FUBP1 MO co-injection. Further, by co-IP and GST pull-down, we showed that FUBP1 directly binds with 4EBP1, a translational repressor that binds with eIF4E. Interestingly, 3F1 RNA was shown to strengthen this binding.

Conclusions: Therefore, our data indicate that FUBP1 inhibits PKD2 translation through anchoring to PKD2 mRNA 3F1 and interacting with 4EBP1. Funding: Government Support - Non-U.S.

TH-PO198
Towards Understanding the Structure-Function Relationships of Polycystin-1
Robin L. Masey,1 Brenda S. Magenheimer,1 Aaron Matthew Smaller Hall.1 Univ of Kansas Med Ctr, Kansas City, KS;2 Univ of Kansas, Lawrence, KS.

Background: Appropriate levels of functional polycystin-1 (PC1), product of the Pkd1 gene, are the key determinant preventing the development of renal cysts in ADPKD. Recent work revealed the existence of hypomorphic missense mutations of Pkd1 and the positioning of these particular biofunctions and trafficking of PC1, and the cell types that use specific effects could potentially be designed to correct the biofunction of mutant PCK. These advances underscore our lack of knowledge regarding PC1 structure and emphasize the importance of understanding PC1-structure-function relationships. As such, we seek to generate a plausible tertiary structure model of human PC1.

Methods: A combination of comparative protein structure modeling along with validation by biochemical analyses is being used to predict and refine a human PC1 structure model. Our initial goal is to generate a 3D model of the arrangement of the 11 transmembrane eIF4E. Interestingly, 3FI RNA was shown to strengthen this binding.

Conclusions: Therefore, our data indicate that FUBP1 inhibits PKD2 translation through anchoring to PKD2 mRNA 3F1 and interacting with 4EBP1. Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
prediction of transmembrane domain bundling, and experimental biochemical analyses to validate predicted models. Use of the predicted secondary structure or template-modeled tertiary structure of loops is used to constrain and refine TM segment arrangement.

Results: Initial work has focused on TM segments connected by shorter loops. Thus far, N-linked glycosylation scanning experiments have confirmed the de novo modeling results for TM segments 9 and 11. Glycosylation analyses for TM segment 10 are not entirely consistent with the predicted model, due to an extension of the length of the domain. Such discrepancy may result from the inherent membrane-associated property of this loop region of PC1, as described in earlier published work.

Conclusions: Preliminary, proof-of-concept work has resulted in a coarse model of the last 3 TM segments of PC1. These analyses will provide important knowledge for understanding structure-function relationships of PC1 and for the development of new ADPKD treatments.

Funding: Other NIH Support - KU-NIH Center of Biomedical Research Excellence in Protein Structure and Function

TH-PO201
Activation of the Polycystin Complex by WNT Ligands Seeokho Kim,1 Hongguang Nie,1 Vasyl Nesin,2 Uyen Tran,2 Patricia Outeda,2 Chang-Xi Bai,3 Jacob Keeling,1 Dipak Maskey,2 Terry J. Watnick,3 Oliver Wesely,2 Leonidas Tsiokas,1 1Cell Biology, Univ of Oklahoma HSC, Oklahoma City, OK; 2Cellular and Molecular Medicine, Cleveland Clinic, Cleveland, OH; 3Medicine/Nephrology, Univ of Maryland School of Medicine, Baltimore, MD.

Background: PKD1 (Polycystin 1) is considered an orphan, atypical G protein coupled receptor complexed with TRPP2 (Polycystin 2 or PKD2), a Ca2+-permeable ion channel. Inactivating mutations in their genes cause autosomal dominant polycystic kidney disease (ADPKD), one of the most common genetic diseases. However, the molecular identity of the extracellular ligands activating the Polycystin complex is unknown. WNT proteins induce Ca2+ signaling on target cells. Here, we tested whether WNTs can bind and activate the Polycystin complex.

Methods: Experimental approaches include electrophysiology, protein-protein-interactions using co-immunoprecipitations, directed cell migration assays, and embryological experiments in Xenopus laevis.

Results: Our data show that secreted WNTs bind to the extracellular domain of PKD1 and induce large whole cell currents and Ca2+ influx dependent on TRPP2, but independent of Frizzled (FZD) receptors. Pathogenic PKD1 or PKD2 mutations that abrogate complex formation, compromise cell surface expression of PKD1, or diminish TRPP2 channel activity suppress activation by a WNT protein. PKD2 fibroblasts lack WNT-induced Ca2+ currents and are unable to polarize during directed cell migration. In Xenopus embryos, PKD1 acts independently of FZD8, but within the same pathway with Dishevelled 2 to preserve normal kidney tubulogenesis.

Conclusions: These data define PKD1 as a new class of WNT (co)receptors and implicate defective WNT/Ca2+ signaling as one of the causes of ADPKD.

Funding: NIDDK Support

TH-PO202
Caffeine Consumption Contributes to Cyst/Kidney Enlargement and Progression of Polycystic Kidney Disease in a Pkd1-Deficient Mouse Model Renata Meca,1 Bruno E. Balbo,2 Milene Subtil Ormanji,1 Luiz F. Onuchic,1 Ita Pflefferman Heilberg,1 1Nephrology Div, Fed Univ of Sao Paulo, Sao Paulo, SP, Brazil; 2Nephrology Div, Univ of Sao Paulo, Sao Paulo, SP, Brazil.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic renal disease, characterized by progressive cyst formation and growth, and leading to kidney failure. In cultured cells from ADPKD patients, caffeine increased the levels of cyclic AMP and induced apoptosis and proliferation. We aimed to examine the in vivo effects of Caffeine on cyst growth and progression of renal disease using a murine model orthologous to human ADPKD.

Methods: Male and female Pkd1 heterozygous/Nestin+/cystic - CysCaf and Pkd1 knockout (NonCystic - NonCysCaf) mice consumed caffeine (3mg/day, in drinking water), from conception to 12 weeks of life. Caffeine was orally administered to the mother until puppy weaning (5 weeks) and thereafter directly supplied in drinking water.Cistric control animals consumed water (CysCtrl) for the same period.

Results:

<table>
<thead>
<tr>
<th>组别</th>
<th>CysCaf</th>
<th>CysCtrl</th>
<th>NonCysCaf</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCystatin(mg/ml)</td>
<td>5.95±1.14*</td>
<td>2.07</td>
<td>3.36</td>
</tr>
<tr>
<td>sUrea(mg/dl)</td>
<td>83.7</td>
<td>48.1</td>
<td>64.5</td>
</tr>
<tr>
<td>Renal Fibrosis Index(%)</td>
<td>0.84 (0.36-1.18)</td>
<td>0.37 (0.06-0.47)</td>
<td>0.30 (0.19-0.63)</td>
</tr>
<tr>
<td>Cell Proliferation Index - Ki67(%)</td>
<td>5.34</td>
<td>2.52</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* p<0.05 vs CysCtrl; † p<0.05 vs NonCysCaf

Data are mean±SD or median (interquartile range); NA-not applicable

Ultrasonographic analysis showed higher global renal cyst index and total kidney volume in the CysCaf group versus CysCtrl. CysCaf group presented higher serum Urea (sUrea) and Cystatin C (sCystatin) and lower maximum urine osmolality (data not shown) when compared to the NonCysCaf and CysCtrl groups. Renal fibrosis was higher in CysCaf than in the other groups and cell proliferation was higher in CysCaf than NonCysCaf kidneys.
**TH-PO203**

Changes in Urine Metabolites in PCK Rat Induced by dDAVP

**Administration**  Maria V. Irazabal, Tianyi Feng, Song Zhang, Fouad T. Chebbi, Xiaofang Wang, Hong Ye, Petras P. Dzeja, Slobodan Macura, Vicente E. Torres. Mayo Clinic.

**Background:** V2 receptor agonist 1-deamino-8-D-arginine vasopressin (dDAVP) aggravates the cystic disease of PCK rats by increasing renal cAMP without inducing cystic changes in wild-type rats (WT). We aimed to investigate the urinary metabolic changes in 1) PCK vs WT, and 2) response to dDAVP in PCK and WT rats.

**Methods:** PCK and WT rats were treated with 20 ng sc of dDAVP b.i.d. from p7 to p21, increasing to 40 ng sc b.i.d. from p22 to p35 inclusive or sc injections of isotonic (0.15 M) saline (S) at identical intervals. Abdominal MRI was performed at p10, p21 and p35 for kidney volume (KV). 1H-NMR-based metabolomics analysis was performed from 24h urine collections at p30. The urine spectra were normalized to creatinine.

**Results:** Administration of dDAVP significantly aggravated the disease in PCK rats as evidenced by KV at p10, p21 and p35 (p<0.04, <0.001 and <0.001), but did not increase significantly KV or generate a cystic phenotype in WT rats (Fig1A-B). BUN levels were evidenced by KV at p10, p21 and p35 (<0.04, <0.001 and <0.001), but did not increase significantly for Thirteen metabolites were significantly different between PCK (S) and WT (S) (Fig1C).

**Conclusions:** The role of miRNA-21 in ADPKD, miR-21 was inactivated in Pkd1(nl/mcw) mice, an orthologous mouse model of ADPKD. RNA-Seq was performed to elucidate the differential gene expression pattern between Pkd2-KO and Pkd2-mir-21 KO mouse kidneys.

**Results:** miR-21 expression was increased in multiple mouse models of PKD, including two orthologous models of PKD. Upregulation of miR-21 was primarily localized to mouse kidney cyst epithelial cells. Increased miR-21 expression was also seen in cysts of human ADPKD tissue samples. cAMP-CREB signaling transactivated the miR-21 promoter in kidney cells. Inactivation of miR-21 in Pkd2-KO mice reduced kidney size, cyst number, and prolonged survival. RNA-Seq and subsequent pathway analysis identified cell death as the main biological effect of miR-21 deletion. Accordingly, compared to Pkd2-KO mice, Pkd2-mir-21 KO mouse exhibited increased apoptosis of cyst epithelial cells without any change in proliferation. Expression of Pdcd4, a pro-apoptotic miR-21 target, was increased in cysts of Pkd2-mir-21 double knockout mice, indicating that miR-21 inhibits Pdcd4 in cystic kidneys.

**Conclusions:** Upregulation of miR-21 in a common feature of murine and human forms of PKD. Deletion of miR-21 attenuates cyst burden and prolongs survival. miR-21 may promote cyst growth in ADPKD by preventing apoptosis of cyst epithelial cells through direct suppression of Pdcd4. Our studies suggest that inhibiting miR-21 may be a useful therapeutic strategy for ADPKD.

**Funding:** NIDDK Support, Other NIH Support - NIH institutional T32 grant, Private Foundation Support

**TH-PO204**

Localized Changes in MicroRNAs Are Critical to the Development of Fibrosis in PKD

**Ameyra P. Patil, William E. Sweeney, Ellis D. Avner. Pediatric Nephrology, Dept of Pediatrics, Medical College of Wisconsin, Wauwatosa, WI.**

**Background:** ADPKD is characterized by proliferation and growth of tubular cysts and development of progressive interstitial fibrosis. These phases are consistently reproduced in the Pkd1(-/-) mouse, an orthologous model of PKD1. In this mouse model, as in human ADPKD, the progression of fibrosis, rather than cyst size, leads to ESRD. Our studies suggest that inhibiting miR-21 may be a useful therapeutic strategy for ADPKD.

**Methods:** Laser capture micro-dissection (LCM) of trichrome positive interstitium and adjacent cystic tubular epithelia were profiled separately for local miRNA expression with Qianqi miScript 384 HC miRNA PCR arrays at four distinct time points during which fibrosis is initiated and progresses. The miRNA profile was compared to age-matched whole kidney miRNA profiles, correlated with fibrosis pathway arrays, and immunohistochemical analysis.

**Results:** From PN21 to 28, interstitium and adjacent cystic epithelium demonstrated significant changes in miRNA expression (20 upregulated, 15 downregulated). These changes correlated with: a shift in the site of proliferation; a change in macrophage subtypes and number; significant increase in Tgf-b1,2,6, p21, p-smad2 and co3d1, and significantly decreased BMP7 expression. miRNA-21 expression exhibited a variable expression with initiation and then progression of the disease.

**Conclusions:** 1. Compartmental changes in miRNA expression seen with LCM were not seen in the whole kidney analysis, demonstrating the value of the approach. 2. Fibroproliferative and ADPKD specific microRNA predicted to regulate Tgf-b1,2 and BMP7 are significantly altered in peri-cystic interstitium. 3. We speculate that such compartment specific changes in miRNA expression are critical to development of fibrosis in ADPKD and may provide therapeutic targets to halt the progression of ADPKD.

**Funding:** Pharmaceutical Company Support - Taihso pharmaceutical ltd., Private Foundation Support

**TH-PO205**

miR-21 Promotes Cyst Growth in Polycystic Kidney Disease

**Ronak Lakhia, Sachin S. Hajaris, Darren Williams, Karam S. Aboudehene, Matan Yheskel, Vishal Patel. 1 Internal Medicine, UT Southwestern, Dallas, TX; 2 Internal Medicine, Univ of Minnesota, Minneapolis, MN.**

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the presence of numerous fluid-filled cysts in the kidney. MicroRNAs (miRNAs), short noncoding RNAs that regulate gene expression, have emerged as promising new therapeutic targets for many common diseases. The goal of this study was to identify miRNAs that represent new drug targets for ADPKD.

**Methods:** Microarrays, Q-PCR, and ISH were performed to determine miR-21 expression in PKD. ChIP and promoter luciferase reporter assays were performed to understand the mechanisms that underlie miR-21 regulation in cystic kidneys. To study the role of miR-21 in ADPKD, miR-21 was inactivated in Pkd1(Cre);Pkd2(+/-) (Pkd2-KO) mice, an orthologous mouse model of ADPKD. RNA-Seq was performed to elucidate the differential gene expression pattern between Pkd2-KO and Pkd2-mir-21 KO mouse kidneys.

**Results:** miR-21 expression was increased in multiple mouse models of PKD, including two orthologous models of PKD. Upregulation of miR-21 was primarily localized to mouse kidney cyst epithelial cells. Increased miR-21 expression was also seen in cysts of human ADPKD tissue samples. cAMP-CREB signaling transactivated the miR-21 promoter in cystic kidneys. Inactivation of miR-21 in Pkd2-KO mice reduced kidney size, cyst number, and prolonged survival. RNA-Seq and subsequent pathway analysis identified cell death as the main biological effect of miR-21 deletion. Accordingly, compared to Pkd2-KO mice, Pkd2-mir-21 KO mice exhibited increased apoptosis of cyst epithelial cells without any change in proliferation. Expression of Pdcd4, a pro-apoptotic miR-21 target, was increased in cysts of Pkd2-mir-21 double knockout mice, indicating that miR-21 inhibits Pdcd4 in cystic kidneys.

**Conclusions:** Upregulation of miR-21 in a common feature of murine and human forms of PKD. Deletion of miR-21 attenuates cyst burden and prolongs survival. miR-21 may promote cyst growth in ADPKD by preventing apoptosis of cyst epithelial cells through direct suppression of Pdcd4. Our studies suggest that inhibiting miR-21 may be a useful therapeutic strategy for ADPKD.

**Funding:** NIDDK Support, Other NIH Support - NIH institutional T32 grant, Private Foundation Support

**TH-PO206**

Macrophages Programmed by Polycystic Kidney Disease Cyst Cells Produce Soluble CXCR2 Ligands That Promote Cyst Cell Proliferation

**Sally M. Salah, Darren P. Wallace, Timothy A. Fields, Katherine Swenson-Fields. The Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.**

**Background:** The presence of renal macrophages in animal models of PKD has been shown to promote disease progression. The mechanisms underlying this phenomenon are incompletely understood but are likely due to reciprocal interactions between infiltrating macrophages and cyst epithelial cells: cyst cells stimulate macrophage differentiation to an M2-like, pro-proliferative phenotype and, in turn, these now “programmed” macrophages secrete unknown factors that promote cyst cell proliferation.

**Methods:** To identify macrophage-secreted factors that promote disease progression, macrophages were incubated for 48 h with conditioned media from primary human ADPKD cyst cells. These programmed macrophages were either collected and analyzed by RNASeq or were washed extensively and incubated for a further 24 h to allow production of secreted pro-proliferative factors, which were subjected to protein/peptide analysis and antibody array. Similar analyses of resting macrophages were carried out in parallel for comparison. Cytokine and co-culture of ADPKD cyst cell conditioned media with macrophages enhances macrophage production of protease-sensitive, pro-proliferative activity. RNASeq and cytokine array analysis revealed up-regulation of multiple candidate pro-proliferative factors in programmed macrophages, including several ligands of the CXCR2 receptor. The addition of a CXCR2 receptor antagonist (SB239022) to ADPKD cells significantly reduced proliferation stimulated by programmed macrophage conditioned media.

**Conclusions:** Efforts are underway to identify the specific CXCR2 ligands produced by programmed macrophages that are responsible for this pro-proliferative effect. These factors and their signaling pathways could provide new targets for the development of therapies to slow PKD progression.

**Funding:** Other NIH Support - NCATS and NIGMS
PKD2-Related Autosomal-Dominant Polycystic Kidney Disease (ADPKD): Mutation Spectrum, Clinical Presentation, and Diagnosis

Background: The milder severity of PKD2 related ADPKD (15% of the pedigrees) as compared to PKD1 is well acknowledged, but population-based studies, enabling to depict the exact burden of the disease, are currently lacking. In this study, we aimed to describe the clinical presentation and the mutation spectrum in a large cohort of PKD2 patients.

Methods: Genkyst is a cross-sectional cohort which aims to include all consenting ADPKD patients followed in 23 Nephrology centers from the western part of France. Clinical data were collected and a comprehensive molecular analysis of PKD1 and PKD2 genes was undertaken.

Results: A total of 70 different PKD2 mutations were identified in 248 patients from 172 pedigrees (i.e. 20.2% of the mutation-positive pedigrees from Genkyst). A recurrent 28-kb deletion involving exons 10-15 was identified in 45 patients from 23 pedigrees confined in an area of ~3500 km², which represents to our knowledge the first case of founder mutation in ADPKD. Median age at diagnosis in the total cohort was 41.5 yrs. At age 70, cumulative probability of ESRD obtained by Kaplan Meier analysis was 37.4%, whereas probabilities for hypertension, pain related to cysts and gross hematuria were respectively of 93.3%, 46.6% and 23.3%. Although there was no gender influence on renal survival, multiple linear regression demonstrated that men had significantly lower kidney function than women. Disease variability was observed in some patients harbouring the same mutation, suggesting that additional genetic or environmental factors may modulate the disease severity in PKD2 patients. In line with this hypothesis, familial study led to the identification of PKD1 hypomorphic alleles possibly acting as disease modifiers in 2 PKD2 pedigrees with marked intra-familial variability.

Conclusions: This large cohort confirms that PKD2 patients typically present with a mild disease and therefore a vast majority of them may not require emerging targeted therapies.

Funding: Government Support - Non-U.S.

Gene Discovery for Autosomal Dominant Polycystic Liver Disease (ADPLD)

Background: ADPLD involves identical polycystic liver disease to that seen in ADPKD, but without clinically relevant kidney cysts. While mutations in PKD1 lead to ADPKD, mutations in genes that indirectly affect Polycystin 1 (PC1) expression or function cause ADPLD. Study of two identified ADPLD genes, SEC63 and PRRKCH, has shown the importance of co-post-translational modifications in the ER for PC1 function, and demonstrated the critical role of PC1 dosage in cyst pathogenesis. We hypothesize that discovery of additional ADPLD genes in patients will identify other functional modulators of PC1.

Methods: We have established a cohort of 161 unrelated individuals and families with ADPLD. Those without known mutations (Discovery Cohort) underwent whole exome sequencing together with linkage analysis where sufficient family material existed. Initial evaluation focused on candidate genes with rare heterozygous loss of function mutations. We established an in vitro bioassay to test a subset of candidates by evaluating PC1 expression and cilia trafficking following knockout of the candidate gene by CRISPR in cell culture.

Results: We found that 65/161 (40%) of ADPLD probands have mutations in SEC63 (18%) or PRRKCH (22%). Initial analysis of exome sequencing of our Discovery Cohort identified three candidate genes that function in ER biogenesis pathways related to the known genes and explain a total of 10 unrelated cases. We have generated cell knockout of one of these new candidate genes and shown a decrease in PC1 expression and as well activation of XBP1s, similar to our earlier findings in sec63 knockouts.

Conclusions: ADPLD gene discovery using whole exome sequencing coupled with in vitro evaluation of PC1 function is an unbiased and achievable approach to identify necessary proteins and pathways for PC1 function, and thus help to better define cyst pathogenesis in ADPLD and ADPKD.

Funding: NIDDK Support

Morpholino and Mutant Studies of Pde3A and Pde1a in Renal Cystogenesis Using Zebrafish

Background: Numerous studies demonstrate the role of CAMP in cyst development and Polycystic Kidney Disease (PKD) progression. Studies in zebrafish using morpholinos show that Phosphodiesterase (Pde) 1A modulates renal cyst development and associated phenotypes, consistent with its hydrolysis of cAMP.

Methods: MOs were used to assess effects of Pde3A on renal cyst development and associated phenotypes, hydrocephalus and otolith defects. Additionally, we have generated 3 Pde1a mutant zebrafish lines using TALENs. Phenotypes were evaluated blinded, and data were analyzed using chi-square on embryos summed within treatments from 3-4 experiments.

Results: Depletion of Pde3A using two splice-blocking MOs increased the incidence of renal cysts at 2 days post-fertilization (dpf). Both MO targets exon 12 of pde3a, the first exon of the hydrolytic domain, encoding the conserved HD required for hydrolysis. Splice acceptor MO induced cysts with dose dependence at 5 ng (13%) and 10 ng (33%) vs. control MO (p=0.002, n=57 embryos/treatment). Splice donor MO induced cysts with dose dependence at 1 ng (13%), 2.5 ng (22%), and 5 ng (59%) vs. control MO (0%) (p<0.003, n=40 embryos/treatment). The splice-donor MO also induced hydrocephalus at 2.5 ng (25%) and 5 ng (60%), and otolith defects at 2.5 ng (38%) and 5 ng (79%) vs. control MO (0%) (p=0.001, n=60 embryos/treatment). Injection of 1 ng caused a non-significant trend toward induction of hydrocephalus (3%, p=0.3) and otolith defects (8%, p=0.06) (n=40 embryos/treatment). Sequencing of cystic embryos showed altered splicing at the targeted exon. Similar to MOs, Pde1a TALENs were generated targeting the exon encoding the conserved HD. We have obtained 3 unique mutant lines which disrupt the HD. In initial studies, Pde1a-/- fish are found at expected frequencies in adult populations, indicating survival equivalent to that of Pde1a-/- fish.

Conclusions: MO studies of Pde3A suggest its involvement in renal cystogenesis and associated phenotypes, similar to previous studies using Pde1A MOs. TALENs effectively induced function-blocking mutations in Pde1a, which will allow studies of Pde1a-/- fish.

Funding: NIDDK Support, Private Foundation Support
Transcriptional Repression of PKD1 by Gene-Body Hypermethylation Induces Renal Cyst Development in ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common human genetic disease characterized by the formation of multiple fluid-filled cysts in bilateral kidneys. Although mutations in polycystic kidney disease 1 (PKD1) are predominant, other loci for ADPKD, the sporadic and sporadic family history of individual cystogenesis suggests another molecular mechanism such as epigenetic alterations.

Methods: To determine the epigenetic alterations in ADPKD and their functional relevance, ADPKD and non-ADPKD individuals were analyzed by unbiased methylation profiling genome-wide and compared with their expression data.

Results: Intriguingly, PKD1 was hypermethylated in gene-body regions, and its expression was downregulated in ADPKD. Hypermethylation of PKD1 in vitro drug treatment with DNA methylation inhibitors retarded cystogenesis, suggesting another molecular mechanism such as epigenetic alterations.

Conclusions: These results are consistent with previous studies that knocking-down of PKD1 was sufficient for cystogenesis. Therefore, we reveal a critical role for hypermethylation of PKD1 and cystogenesis-related regulatory genes in cyst development, suggesting epigenetic therapy as a potential treatment approach for ADPKD.

Funding: Government Support - Non-U.S.

Sodium Intake versus Disease Progression in Experimental Polycystic Kidney Disease


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Background: Most forms of hypertension are influenced by gender and salt sensitivity. However, interplay of these two factors and their functional consequences in PKD-associated hypertension are incompletely understood. Thus, we tested the hypothesis that age and sex would influence the expression of PKD1 as well as cyst growth and risk of renal failure.

Methods: We used Pkd1−/− rats to study the sex difference in blood pressure in response to high salt (HS) diet. Two month and eight month-old male and female Pkd1−/− rats were surgically implanted with telemetry transmitters and allowed to recover for at least one week before obtaining baseline mean arterial pressure (MAP). Rats were then fed a high salt (HS: 4% NaCl) diet for 3 weeks. At the end of the diet, blood pressures were measured before obtaining cyst number and kidney weight.

Results: In the 2-month old Pkd1−/− rats, blood pressures were in a normal range and there were no differences between male and female rats. Female and male Pkd1−/− females, 3 weeks on a high salt diet had no effect on MAP. In 8-month old rats, again there were no differences between animals on normal rat chow. MAP was progressively increased in both male and female rats after 3 weeks of HS diet treatment. MAP increased from 127±6 to 171±6 mmHg in male and from 112±3 to 127±3 mmHg in female rats, both p<0.05. However, the MAP increase was significantly greater in male (p<0.05) rats. The blood pressure increase in male rats was associated with higher urinary protein excretion compared to female rats (1015±33 vs. 748±45 mg/d, p<0.05).

Conclusions: Our studies demonstrate that male Pkd1−/− rats with advanced cystic kidney disease are more vulnerable to salt sensitive hypertension and renal injury than age-matched females.

Funding: Other NIH Support - NHLBI

Kidney-Selective Inactivation of the Exocyst Gene Sec10 in Mice Leads to Primary Cilia Defects and a Cystic Kidney Phenotype


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Background: The primary cilium is a sensory organelle that projects from the apical surface of renal epithelial cells, and has been implicated in the pathogenesis of polycystic kidney disease. The exocyst complex is responsible for the polarized exocytosis of vesicles from the apical surface of secretory vesicles. Previous studies in cultured epithelial cells implicated exocyst activity, and particularly its Sec10 subunit, in primary cilia assembly. Our previous study revealed that Sec10 deficiency was associated with defects in ciliogenesis and kidney development.

Conclusions: Two month-old Pkd1−/− mice were polycystic kidney phenotype not seen in control littermates. Underline represents presenting author.

Funding: Veterans Administration Support

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

Underline represents presenting author.

138A
Whole Exome Sequencing (WES) Resolves ARPKD-Like and Meckel Syndrome (MKS)-Like Pedigrees Unresolved by Sanger/Chilopilagio Panel Screening Katharina Hopf, Sarah J. Koon, Christina M. Heyer, Vicente E. Torres, Peter C. Harris. Mayo Clinic.

Background: ARPKD and MKS have phenotypic and genetic overlap with other ciliopathies, with many unresolved pedigrees after Sanger sequencing of commonly mutated genes (ARPKD — ~10% of severe and ~50% of mild cases, MKS — ~45% of cases).

Methods: We performed WES (Agilent SureSelect, Illumina HiSeq 2000) of 18 Sanger screened, unresolved pedigrees, of which 13 were also assessed by targeted next-generation sequencing (NGS, 258 ciliopathy/cilia genes). Identified variants were filtered/scored based on quality, population frequency, segregation and substitution/gene significance.

Results: Screening for homozgyous, compound heterozygous, and de novo variants identified disease-alleles in 4 pedigrees. Ped 1, ARPKD diagnosis at 4y, was homozgous for a novel BBS9 mutation (c.437_438insA), although the proband lacked key Bardet-Biedl Syndrome (BBS) features (dysmorphia, obesity, polydactyly, learning disability). The variant was missed by the targeted NGS panel due to preferential WT allele enrichment. Ped 2, 2 MKS diagnosed fetuses with PKD, polydactyly, hepatic fibrosis, but no CNS abnormalities, inherited two novel BBS9 variants (c.1405_1406delAC and p.V266E [scored as pathogenic]). Of note, BBS rarely causes embryonic lethality. Ped 3, a 15w MKS-like fetus with occipital encephalocele, sloping forehead and bifid tongue, inherited two C2CD3 mutations (p.C1114>., caused ex18 skipping, and p.V899M [scored as pathogenic]). This verified findings of the targeted NGS panel and excluded additional genetic disease causes. C2CD3 is linked to oral-facial-digital syndrome 14 but the fetus lacked key associated features (polydactyly, microcephaly). Ped 4, a 16w MKS fetus with PKD, was initially diagnosed with a single C2CD2A variant (c.2182-2A>G). WES identified a second variant (c.3289-1delG) missed by Sanger sequencing.

Conclusions: We show here the value of WES for resolving Sanger/NGS panel unresolved ciliopathy pedigrees, although with low detection rates. In addition, we show BBS genes associated with a broad ciliopathy disease spectrum, reporting for the first time BBS9 mutations in an ARPKD-like case and BBS7 mutations in a MKS-like pedigree.

Funding: NIDDK Support, Private Foundation Support

TH-PO217

IFT81, Encoding an Intraflagellar Transport Protein, as a Rare Cause of a Ciliopathy Phenotype Jan Halbritter, Isabelle Pfeurts, Jonathan Porath, Xavier Gerard, Daniela A. Braun, Heon Yung Gee, Hanan Fathy, Richard P. Lifton, Jean-michel Rozet, Medicine, Boston Children’s Hospital, Boston, MA; 1Imagene Inst, Paris Descartes, Paris, France; 2Pediatric Nephrology, Univ of Alexandria, Alexandria, Egypt; 3Genetics, Yale Univ, New Haven, CT.

Background: Bidirectional intraflagellar transport (IFT) consists of two major protein complexes, IFT-A and IFT-B. In contrast to the IFT-B complex, all components of IFT-A have recently been linked to human ciliopathies when defective. We therefore hypothesized that mutations in additional IFT-B encoding genes can be found in patients with multisystemic ciliopathies.

Methods: We screened 1,628 individuals with reno-ocular ciliopathies by targeted-next-generation sequencing, including all IFT-B encoding genes.

Results: Consequently, we identified a homozygous mutation in IFT81 affecting an obligatory donor splice site in an individual with nephronophthisis and polydactyly. Furthermore, we detected a loss-of-stop mutation with extension of the deduced protein by 10 amino acids in an individual with neuronal ceroid lipofuscinosis-1 (CLN1). This proband presented with retinal dystrophy and brain lesions including cerebellar atrophy, a phenotype to which the IFT81 variant might contribute. Cultured fibroblasts of this latter affected individual showed a significant decrease in ciliated cell abundance compared to controls and increased expression of the transcription factor GLI2 suggesting deranged sonic hedgehog signaling.

Conclusions: This work describes identification of mutations of IFT81 in individuals with symptoms consistent with the clinical spectrum of ciliopathies. It might represent the rare case of a core IFT-B complex protein found associated with human disease. Our data further suggest that defects in the IFT-B core are an exceedingly rare finding, probably due to its indispensable role for ciliary assembly in development.

TH-PO218

Loss of Aatf in Murine Tubular Cells Leads to a Nephronophthisis-Like Phenotype Manaswita Jain,1 Heidi Irene Heine,1 Heike Goebel,2 Bernhard Schermer,1 Thomas Benzing,1 Katja Hoecker.1 1Internal Medicine II, Univ Hospital Cologne, Cologne, Germany; 2Dept of Pathology, Univ Hospital Cologne, Cologne, Germany.

Background: Genomic integrity is continuously being challenged by DNA damage of endogenous or exogenous sources. Aatf is a key regulator of the tumor suppressor p53 in the DNA-damage response signaling cascade. Aatf inhibits the ability of p53 to transactivate pro-apoptotic target genes. The conventional knockout of Aatf in mice is pre-implanationally lethal. A central role of DNA-damage signaling in tubular cells and cystic kidney diseases has been suggested. Here we show that deletion of Aatf in developing distal tubular and collecting duct cells leads to a degenerative, cystic phenotype, much alike juvenile nephronophthisis.

Methods: Conditional knockout mice, histology, phenotypic analysis.

Results: Aatf was knocked out using the Ksp/Cre mouse line in a floxed Aatf genetic background. The homozygous Aatf deletion results in weight loss and kidney failure at the age of 6-10 weeks. The mice show polyuria, polydipsia and have a reduced urine osmolarity. Their kidneys are small, pale and show small cysts predominantly at the cortico-medullary border. Histological examination shows tubular and glomerular cysts and interstitial fibrosis as well as an increased rate of apoptotic cell death.

Conclusions: Altering the outcome of the p53-driven DNA-damage response in the Ksp/Cre;Aatf knockout leads to clinical and histological signs of juvenile nephronophthisis that links DNA damage response signaling to cystic kidney disease.

Funding: Government Support - Non-U.S.

TH-PO219

Role for the Primary Cilium in Regulation Interstitial Macrophage Proliferation and Polarization During Kidney Maturaton and Injury Cheng 'Jack' Song,1 Kurt Zimmerman,1 Michal Mrug,1 Bradley K. Yoder.1 1Pediatric Developmental and Regenerative Biology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Induction of cilia loss in juvenile mice results in rapid cyst development while induction of cilia loss in adult mice causes a much slower rate of cyst progression. Rapid cyst formation can be initiated in the adult-induced IFT mutants by ischemic reperfusion (IR) injury suggesting a possible role for inflammation in cyst development. This study was to confirm that primary cilia deleterious deletion in adult mice is effective in inducing ciliated macrophage proliferation and that this proliferation is reduced in the absence of cilia.

Results: IR injury was capable of inducing ciliated macrophages in adult mice that reduced cyst severity and improved renal function. However, the crosstalk between primary cilia on epithelial cells and the interstitial macrophages during cyst progression is unknown. Here, we investigate potential connections between primary cilia associated cytokinesis and changes in macrophage populations.

Results: Our preliminary data suggest the presence of a kidney resident macrophage population, likely derived from the yolk sac, which are present in juvenile mice and re-immigrate in adult-induced cilia mutants following IR injury. Renal Resident macrophage demonstrates rapid proliferation following IR injury in adult-IFT88 mutant mice as early as 3 days following injury and persists for at least 21 days. In contrast, resident macrophages from control mice show peak proliferation 3 days following IR injury that then abates at days 7-21.

Conclusions: This work suggests communication between the cilia on epithelial cells and the resident macrophages is important for kidney maturation and repair after injury. Our prediction is that defects in this communication will result in persistent resident macrophage proliferation that contributes to the rate of cyst formation. This work will provide possible targets for therapeutic intervention.

Funding: NIDDK Support.

TH-PO220

Ciliary Trafficking of Polycystin-1 and Polycystin-2 Is Independent Chong Luo, Mingqiu Wu, Wasmim El-jouni, Jing Zhou. Harvard Center for Polycystic Kidney Disease Research and Renal Div. Dept of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background: Mutations in PKD1 account for over 85% cases of autosomal dominant polycystic kidney disease (ADPKD). About 30% of the PKD1 mutations are missense mutations which likely produce full-length proteins that are defective in trafficking to the primary cilia. We have recently shown that multiple sequences including a coiled-coil (CC) motif at the C-terminal tail of PC1 regulate full-length PC1 trafficking to primary cilia. PC1 remains to traffic to the primary cilium in cells depleted of PC2. The proteolytic cleavage at the GPS site of PC1 is not required for its ciliary trafficking.

Methods: A set of deletion/mutation constructs in mouse PC1 including those corresponding to ADPKD-associated mutations, as well as chimeric constructs with different mPC1 C-terminal motifs were developed. Transient transfection and immunostaining methods were used.

Results: We found that all pathogenic mutations we tested are defective in ciliary trafficking. Ciliary localization of full-length PC1 or its mutants is completely abrogated in PKD1-knockout cells. However, this defect can be rescued by co-expression of PC2 in a dose dependent manner. Overexpression of PC2 even drives the C-tail-less PC1 mutant to traffic to the primary cilium.

Funding: National Institute of General Medical Sciences.
TH-PO221

Anoctamin 6 Is Localized in the Primary Cilium of Renal Tubular Cells and Is Involved in Apoptosis-Dependent Cyst Lumen Formation

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Background: Anoctamin (ANO) 6 is a member of a novel family of Ca2+-activated Cl- channels. Although ANO6 is the most widely expressed paralogue, only little is known about its subcellular localization. Recently, we could show that ANO6 together with ANO1 is expressed in renal cyst-lining cells. Unlike ANO1, which was involved in cyst expansion, the role of ANO6 remained elusive. Therefore, we analyzed the localization of ANO6 in renal tubular cells and tested for a role in cyst formation.

Methods: We stained polarized MDCK cells for ANO6 in comparison to stably ANO6-deficient cells. In addition, we analyzed human collecting duct (HCD) cells and primary human tubular cells to test for species- and segment-specific expression. We also examined the effect of ANO6 deficiency on MDCK cyst formation and performed Ussing chamber experiments to test for changes in transepithelial Cl- secretion. Additionally, we stained kidney sections comprising healthy and cystic tissues from ADPKD patients for ANO6.

Results: ANO6 was localized in the primary cilium of all tubular cells irrespective of species or tubular origin. In addition, ciliary localization of ANO6 could be detected in human kidneys. ANO6 knockdown resulted in loss of cilary ANO6 signals but had no effect on ciliogenesis or MDCK cyst growth. In line with these data, ANO6-deficient MDCK cells revealed no alteration in Ca2+-dependent Cl- secretion. However, lumen formation was markedly disturbed in ANO6-deficient cells which could be referred to an increased number of cells situated within the cyst lumen which normally would get removed by apoptosis. However, ANO6-deficient cells showed a strong reduction of Ca2+-dependent phospholipid scrambling as well as TUNEL- and Caspase3 signals. In addition, apoptotic cyst cells in human ADPKD were characterized by strong co-expression of ANO6.

Conclusions: ANO6 is a ciliary protein and involved in apoptosis-dependent cyst lumen formation. 

Funding: Government Support - Non-U.S.

TH-PO222

Regulation of Cilia Function by Protein Palmitoylation

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Background: Cilia are microtubule-based protrusions of the plasma membrane which serve sensory and signaling functions. Abnormalities in cilia cause diseases known as ciliopathies, which include autosomal dominant polycystic kidney disease and nephropathies. Many ciliopathies involve abnormal trafficking of proteins to cilia. Trafficking of proteins may be affected by cysteine palmitoylation, the reversible post-translational attachment of the lipid palmitate to proteins. Since numerous cilia proteins are palmitoylated, here we have explored the role of palmitoylation in cilia function and protein trafficking. As a model, we used novel palmitoylation deficient (PD)- and wild-type (WT)-expressing cells. Introduction of a myristoylation site restored proper localization of palmitoylation-deficient Arl13b. In order to identify enzymes involved in Arl13b palmitoylation, we characterized localization and activity of all 24 ZDHHC family protein acyl transferases. Five were found to increase Arl13b in ADPKD. The others remained unaltered. In conclusion, we have identified a small number of enzymes which may regulate palmitoylation of cilia proteins.

Conclusions: These data collectively show that Arl13b is necessary for cilia formation in IMCD3 cells, and that palmitoylation is a key regulator of Arl13b localization. Further, these studies identify acyl transferase enzymes that may be novel regulators of Arl13b and thus cilia function. Given the large number of palmitoylated proteins in cilia, palmitoylation may be a general mechanism regulating localization of cilia proteins and thus controlling cilia function.

Funding: NIH Support, Other NIH Support - NHLBI, Private Foundation Support

TH-PO223

Cell Cycle-Dependent Ubiquitination and Destruction of NDE1 by CDK5-FBW7 Regulates Cilium Biogenesis

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Background: The primary cilium is an antenna-like organelle housing numerous signaling pathways. Loss of primary cilia can have opposing effects on ciliogenesis: in general, it induces ciliogenesis, but it suppresses cyst formation in mouse models of autosomal dominant polycystic kidney disease (ADPKD). Thus, inhibiting cystogenic pathways can be beneficial in treating ADPKD. Cilia are formed when cells exit the cell cycle and disappear as cells re-enter the cell cycle. We have previously identified NDE1 as a suppressor of ciliogenesis and showed that its expression is markedly reduced when cells exit the cell cycle. However, the mechanisms controlling its downregulation upon cell cycle exit are unknown.

Methods: Methods in the study included Western blotting and co-immunoprecipitations, sire-directed mutagenesis, ubiquitination assays, and indirect immunofluorescence.

Results: Focusing on the mechanisms mediating its downregulation, we have now discovered a pathway involving the CDK5 kinase and the FBW7 E3 ubiquitin ligase that controls ciliary function. Specifically, CDK5, which is active only in quiescent cells, phosphorylates NDE1 at a specific site, which is in turn recognized by the FBW7 E3 ligase and targets NDE1 for degradation through the Skp1, Cul1, FBW7 (SCEF/ubiquitin ligase. The destruction of NDE1 by SCEF/ubiquitin ligase allows ciliogenesis to proceed normally, cilia to reach their appropriate length and function properly. However, when this pathway is inhibited by depletion of FBW7, CDK5, or chemical inhibition of CDK5, NDE1 levels rise causing a reduction in ciliary length and function.

Conclusions: Our study furthers our knowledge on the mechanisms of ciliogenesis and function and helps develop new approaches to treat cystic diseases.

Funding: NIDDK Support, Other NIH Support - Oklahoma Center for the Advancement of Science and Technology

TH-PO224

Platelet-Derived PAI-1 Accelerates Podocyte Detachment in FSGS

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Background: Platelet activation has been shown to be involved in glomerular diseases by releasing cytokines and pro-coagulant factors. In FSGS, we have previously shown that PAI-1 is upregulated within the glomerular capillary, which accelerates detachment of remnant podocytes through up-regulated mediators of integrin endocytosis. Endothelial cells and platelets are the possible producers of intracapillary PAI-1. However, endothelial cells were involved in the early stage of our study, the role of platelet-derived PAI-1 in FSGS is unknown. Here we tested whether platelet-derived PAI-1 is involved in podocyte loss in FSGS mice.

Methods: We used an immunotoxin inducible FSGS model, NPE25 mice. NEP25 mice were injected with immunotoxin (LMB2, 4 ng/g body weight) on day 0 and treated with 2 mg of anti-mouse platelet antibody (Ab group, n=10) or PBS (C group, n=10) on day-1,4,9. Proteinuria, histology, and PAI-1 localization were examined on day 1 and 12.

Results: The platelet-positive cell number was increased on day-1,4,9. Analysis of day-1,4,9. Proteinuria, histology, and PAI-1 localization were examined on day 1 and 12.

Results: Platelet depletion decreased proteinuria (P = 0.05) with the protection of podocyte number on day 12 (3.15 ± 0.21 in Ab group vs. 1.55 ± 0.27 in C group, P < 0.05). Glomerular PAI-1 mRNA expression was increased on day 1 in both groups, but it was decreased back to normal on day 12 in Ab group (0.14 ± 0.02 in Ab vs. 1.0 ± 0.23 in C group, P < 0.05). Immunostaining showed glomerular PAI-1 was colocalized with CD31 (endothelial cell marker), but not with CD41 (platelets marker) on day 1 in both groups. PAI-1 was colocalized with CD41, and occasionally with synaptopodin, but not with CD31, on day 12 in C group.

Conclusions: In podocyte injury, PAI-1 was initially induced in the endothelial cells and shifted to the platelets later. Since intracapillary PAI-1 has been shown to promote additional podocyte detachment via integrin endocytosis, inhibition of platelets is a plausible strategy to slow progression of FSGS.

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

TH-PO225

Podocyte Knockdown of Plasminogen Activator Inhibitor-1 (PAI-1) Is Insufficient to Replicate Protective Effect of Systemic PAI-1 in Chronic Kidney Disease

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Background: Podocyte injury is a major trigger for glomerulosclerosis. PAI-1 is upregulated in injured podocytes and sclerosing glomeruli. We assessed the role of podocyte vs. systemic PAI-1 in a primary podocyte injury model.

Methods: We generated a podocyte injury model with intact (PAI-1+/−Nenp5, n=8) or systemic (PAI-1 deficiency) (PAI-1−/−Nenp5, n=8) by chemical inhibitors. As a model, we used Nefta13b, a palmitoylated monomer/P-cadherin epitope that is removed from day -7 to day 10. All mice received LMB2 at day 0, and were sacrificed at day10.

Results: These data collectively show that PAI-1 is necessary for cilia formation in IMCD3 cells, and that palmitoylation is a key regulator of Arl13b localization. Further, these studies identify acyl transferase enzymes that may be novel regulators of Arl13b and thus cilia function. Given the large number of palmitoylated proteins in cilia, palmitoylation may be a general mechanism regulating localization of cilia proteins and thus controlling cilia function.

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Results: Nep25 mice with systemic PAI-1 deficiency had less body weight increase, an increase of edema, but similar podocyteuria, when compared to those with intact PAI-1 and also had more preserved podocytes, as shown by higher synaptopodin expression and glomerular WT-1 density (PAI-1-/-/Nep25 5.07 ± 0.17 vs. PAI-1-/-/Nep25 2.59 ± 0.22x10^3/um^2, p<0.05). Total glomerular CD44 positivity, a marker for activated parietal epithelial cells, was also higher in PAI-1-/-/Nep25 vs PAI-1-/-/Nep25 (5.06 ± 0.35 vs 0.51 ± 0.15, p<0.05). In contrast, Nep25 mice with podocyte-specific PAI-1 knockdown had similar edema and podocyteuria as its control, and WT-1 density and glomerular CD44 positivity were not different between PAI-1floxed/Podocin Cre/Nep25 and PAI-1floxed/Nep25. However, synaptopodin was higher in mice with podocyte PAI-1 knockdown vs its control (3.82 ± 0.87 vs 1.96 ±0.23%, p<0.05).

Conclusions: We conclude that podocyte PAI-1 knockdown was insufficient to produce a similar protective effect as seen in systemic PAI-1 knockout in a podocyte-specific kidney injury model. We speculate that this may partially relate to PEC to podocyte transition.

Funding: NIDDK Support

TH-PO226
Reversal of Podocyte Loss in Mice with Membranoproliferative Glomerulonephritis (MPGN) by Imaiitchi, Neepgut Pattamacharwat, Masayuki Iyoda, Tomasz A. Wietecha, Kelly L. Hudkins, Charles E. Alpers. 
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Background: Mice transgenic for thymic stromal lymphopoietin (TSLP-Tg) develop cryoglobulinemia and MPGN. Platelet-derived growth factor (PDGF-D), expressed by podocytes in humans, with its receptor (PDGFR-β) are likely mediators of mesangial expansion in MPGN. Inhibition of PDGF-Dβ by imatinib, a tyrosine kinase inhibitor, reduces mesangial proliferation in TSLP-Tg mice. The importance of podocyte loss and PDGF-D expression in MPGN are currently unknown. This study sought to identify possible podocyte loss and investigate the effect of imatinib on podocyte density in mice with MPGN.

Methods: Three-week old female mice were assigned to three groups: TSLP-Tg mice treated with imatinib (50 mg/kg) daily by intraperitoneal injection for eight weeks; control TSLP-Tg mice treated with sterile water; and wild-type C57BL/6 control mice. TSLP-Tg mice were identified by immunohistochemical staining (for HIC) in p57, and their density morphometrically quantitated. Expression of PDGF-D and PDGFβ was detected by IHC. Albuminuria was measured from timed urine samples.

Results: Podocyte density in TSLP-Tg mice was significantly less than WT controls (182.67 ± 21.5 vs 278.6 ± 16.9 podocytes/10^6 μm^2, p = 0.005), and was markedly increased by imatinib (249.17 ± 14.9, p = 0.029). TSLP-Tg mice had significantly increased mesangial (but not podocyte) expression of PDGF-D (248.23 ± 40.75 μg/ml) and slightly increased PDGFβ (192.91 ± 17.3) compared to WT controls (124.17 ± 10.46, p = 0.028 and 175.55 ± 6.61, p = 0.388 respectively). The overexpression of PDGF-D was significantly reduced (129.02 ± 10.95, p = 0.025) whereas the expression of PDGFβ was increased after imatinib treatment (260.51 ± 18.62, p = 0.024). Albuminuria in TSLP-Tg mice was higher than WT controls (16.6 ± 4.66 vs 4.23 ± 0.76 μg/mg, p = 0.036), and was decreased by imatinib (4.97 ± 1.64, p = 0.049).

Conclusions: This study demonstrates podocyte loss in MPGN. Reversing podocyte density number may be a key to reversal of MPGN. Imatinib markedly reversed podocyte loss and reduced mesangial injury. PDGF-D overexpression and albuminuria in TSLP-Tg mice. Unlike humans, mesangial cells rather than podocytes express PDGF-D in mice.

Funding: NIDDK Support

TH-PO227
Role of Epithelial Membrane Protein 2 in Nephrotic Syndrome Michael D. Donnan, Rizaldy P. Scott, Tuncan O., Anna Woo, Susan E. Quaggin. Feinberg Cardiovascular Research Inst and Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.

Background: Mutations in the human gene EMMP2 (Epithelial Membrane Protein 2) have recently been linked to childhood-onset nephrotic syndrome. Its gene product, a tetraepitope integral membrane protein, affects various cell behaviors including regulation of cell adhesion, migration, proliferation, apoptosis and tumorigenesis. EMMP2 protein modulates the expression of GPI-anchored proteins, caveolin-1, and the integron, and the growth factor VEGFA. EMMP2 is also necessary for embryo implantation and chondral infecitvity. We studied the renal expression pattern of EMMP2 and generated a conditional Emmp2 knockout mouse. We investigated the role of EMMP2 in glomerular function.

Methods: We created a floxed Emmp2 (Emmp2fl/fl) mouse containing a LacZ reporter gene controlled by the endogenous Emmp2 promoter. We assessed Emmp2 expression in kidneys using whole-mount β-galactosidase (β-gal) histochemistry. To complement this analysis, we used an antibody against Emmp2 to assess localization by immunofluorescence (IF). Podocyte-specific KO mice (Emmp2fl/fl J2cre) were generated by breeding Emmp2fl/fl mice with the Nphs1-Cre driver strain and were assessed for proteinuria.

Results: β-gal staining reveals that Emmp2 is prominently expressed within major vascular bundles and a distinct band of cells within the cortex and renal papillae. Double-label IF using an Emmp2 antibody and Lotus lectin suggests that the Emmp2 expression within the renal cortex is in proximal tubules. The Emmp2 antibody did not stain the renal papilla or renal vascularity. Whether this disparity is due to cell-specific post-translational modification (glycosylation) remains to be addressed. However, in both β-gal and IF assays Emmp2 within the glomerulus was not seen. By 3 months of age, Emmp2fl/fl mice do not have proteinuria.

Conclusions: In contrast to a previous report, we did not observe Emmp2 expression in podocytes. Emmp2 may not be a major contributor to developing kidney disease. Genetic deletion of Emmp2 in tubular and endothelial compartments will provide additional insights regarding the etiology of renal dysfunction in patients with EMMP2 mutations.

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

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Glomerulonephritis models were developed. 2  In the chronic stages, podocytes proliferate in response to anti-HPA antibody and are Aglentin's RX66K microarray (n=12) and qRT-PCR (n=8).

Results: In a basal condition, microarray analysis revealed 5070 (9.1%) probes were significantly and more than 2-fold enriched in podocytes within the glomerulus, which include most known podocyte genes. qRT-PCR confirmed that Nphs1 and Nphs2 RNAs were concentrated in podocytes (15 and 8.6-fold), while mesangial and endothelial RNAs were diluted. Seven days after immunotoxin injection, 3130 (5.6%)/1938 (3.5%) probes were significantly and more than 2-fold up/down-regulated in podocytes from the basal condition. Podocytes and VIM were decreased (0.37, 0.39, 0.28 and 0.51-fold), and Des, Relb, Gadd45b and Cxcl1 were markedly upregulated (8.1, 6.9, 20 and 160-fold), which were confirmed by qRT-PCR. These changes were significantly correlated with those in Actn4 KO podocytes reported in TRAP study (R=0.520, p<0.001), suggesting that these changes are common pathogenic responses. Separately, we were reviewing 84 candidate genes identified by GWAS, thirteen, including Vegfa, were found concentrated in podocytes (15 and 8.6-fold), while mesangial and endothelial RNAs include most known podocyte genes. qRT-PCR confirmed that Nphs1 and Nphs2 RNAs significantly and more than 2-fold enriched in podocytes within the glomerulus, which provides a good fit for domain 1, connected to the other globular domain in an open conformation, in contrast with the tight closed conformation seen in crystal structures of the intact protein (isoform 1). msuPAR transgenic mice are fertile and they start to develop proteinuria 1 month after birth. With rising serum msuPAR level, progressive proteinuria was observed. The mouse secretive isoform uPAR 2 forms a dimeric protein with a circulating factor in focal segmental glomerulosclerosis (FSGS) by direct activation of podocyte aVb3 integrin. Mouse secretive uPAR isoform 2 (msuPAR) is an alternatively spliced uPAR variant. This study was aimed to evaluate the ability of this isoform to function as a circulating factor.

Methods: For structural study, msuPAR was cloned from podocytes, and expressed in HEK cells with a Flag tag. The recombinant msuPAR protein was purified with Flag beads and analyzed by electron microscopy (EM). For functional study, a transgenic mouse model was created that drives msuPAR expression from adipose tissue with consequent release into circulation.

Results: Negative-stain EM and single particle image analysis reveal that msuPAR protein forms a compact, well-defined structure in solution, which is formed by a dimer of two globular domains. The three-dimensional reconstruction shows two domains, which provides a good fit for domain 1, connected to the other globular domain in an open conformation, in contrast with the tight closed conformation seen in crystal structures of the intact protein (isoform 1). msuPAR transgenic mice are fertile and they start to develop proteinuria 1 month after birth. With rising serum msuPAR level, progressive proteinuria develops in most animals. By 7 to 8 months old, about 20% of msuPAR transgenic mice developed FSGS-type lesions, while 80% of mice showed mild glomerular damages. Transmission EM analysis showed variant degree of podocyte foot process effacement that correlated to the proteinuria and the light microscopy changes. Analysis of serum level of the inflammatory marker, CRP or IL-6 did not distinguish msuPAR transgenic mice from littermate control. Glomerular b3 integrin activity however was significantly increased in msuPAR transgenic mice.

Conclusions: The mouse secretive isoform uPAR 2 forms a dimeric protein with globular domains. Its expression in transgenic mice results in increased podocyte injury activation and progressive renal disease with a spectrum from minimal change to FSGS type kidney lesion.

Funding: NIDDK Support, Pharmaceutical Company Support - Therumo BCT

TH-PO234

Disparate Apolipoprotein E Expression in HIV-Associated Nephropathy Reflects Podocyte Injury Xinjuan Lan,1 Hongxiu Wen,1 Ashwani Malhotra,1 Karl Leon Skorecki,2 Pravin C. Singhal.1 1 Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; 2 Medicine, Ramham Health Care Campus, Haifa, Israel.

Background: Patients with ApoE1 variants carry 10 fold higher chance for the development of HIVAN if not on antiviral therapy. HIV is known to hijack autophagy in the host cells-enhancement of autophagosome formation (the site of viral replication) but inhibits the delivery of autophagosome cargo (AC) to the lysosomes and thus, prevents viral degradation. Since podocytes are terminally differentiated cells their protein homeostasis is tightly regulated by autophagy. We hypothesized that ApoE1 risk variants would also have potential for augmenting the initial phase but would inhibit the terminal phase of autophagy.

Methods: We used human podocytes (HPs) stably expressing ApoE1G0, G1, or G2 (Vec/HPs, G0/HPs, G1/HPs, and G2/HPs). Pseudo type HIV or empty vector (control) virus was transduced into Vec/HPs, G0/HPs, G1/HPs and G2/HPs. After 48 h, cells were harvested and assayed for vacuolar density (number of autophagosomes) by staining with acridine orange or monodansylcadaverine (MDC). Protein blot of HPs (Vec, G0, G1, and G2) were probed for mTOR pathway modulating autophagy (beclin-1 and LC3-II markers) and terminal phases of autophagy (p62, marker of degradation of AC) and reprobe for actin. HPs were co-labeled for ApoE1 and endosomal/lysosomal markers to delineate route of APOL1.

Results: G0/HPs, G1/HPs and G2/HPs displayed greater number of autophagosomes when compared to Vec/HPs. Protein blots of G1 and G2/HPs demonstrated enhanced expression of LC3II and beclin-1 and thus indicating enhancement of initiation of autophagy. Protein blot of G1 and G2/HPs also showed enhanced expression of p62, which indicated that AC did not reach to lysosomes. Additionally, G1/HPs and G2/HPs showed attenuated mTOR expression (pexpression by G1/HPs and G2/HPs further enhanced early markers of autophagy but displayed further attenuation of lack AC at lysosomal compartment. Co-labeling studies of APOL1 revealed decreased presence of APOL1 in lysosomal compartment. Conclusions: APOL1 risk variants enhance initiation but inhibit terminal phase of autophagy both in control and HIV stimulated states.

TH-PO235

Sildenafl-Dependent Reduction of TRPC6 Expression, Podocyte Injury and Proteinuria is Mediated via PPARY Ramon Sonneveld1, Jeost Horstman2, Carole Henrique3, Jo H.M. Berden1, Pierre-Louis Thuraux4, Johan Van der Vlag1, Tom Nijenhuis.,1 1Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands; 3Cardiovascular Research Centre, INSERM, Paris, France.

Background: Increased transient receptor potential channel C6 (TRPC6) activity in the podocyte leads to glomerular injury and proteinuria. Sildenafil (Viagra®) is used to treat erectile dysfunction and pulmonary arterial hypertension where it reduces TRPC6 activity and expression. The nuclear receptor PPARY is a downstream target of sildenafil via cGMP inhibition of the PKG axis (PPARY agonists include Pio and Glee cata). We hypothesized that sildenafil has renoprotective effects, with PPARY as central mediator modulating TRPC6 expression and activity in podocytes.

Methods: Using pharmacological compounds in cultured podocytes, rat and mouse models in which the role of PPARY in mediating TRPC6 expression/activity was tested. Results: TRPC6 expression was upregulated in adriamycin-injured podocytes, which was dose-dependently downregulated by sildenafil, the cGMP derivative 8-Br-cGMP or the PPARY agonist Pio. The PKG blocker KT8823 or the PPARY agonist GW9662 enhanced TRPC6 expression. cAMP or cGMP were found to increase when inhibition of PKG by KT8823 and PPARY by GW9662. The effect of Pio was negated only by GW9662. Similar results were shown for TRPC6 promoter activity and calcium influx. Chromatin immuno precipitation showed binding of PPARY to the TRPC6 promoter. Healthy rats treated with GW9662 showed proteinuria and upregulation of TRPC6 expression in the podocytes, which was also observed in podocyte-specific PPARY knock-out mice. Renal injury and increased TRPC6 expression in adriamycin induced nephropathy rats could be prevented by sildenafil and Pio treatment.

Conclusions: Amelioration of podocyte injury by sildenafil involves cGMP- and PKG-dependent binding of PPARY to the TRPC6 promoter, thereby inhibiting TRPC6 promoter activity, expression and activity. Our data identify sildenafil as a novel anantiproteinuric agent, which acts by inhibiting deleterious TRPC6-mediated intracellular calcium signaling.

TH-PO233

APOL1 Risk Variants Enhance Initiation but Retard the Terminal Part of Autophagy in Podocytes Höcker J.,1 Hongxiu Wen,1 Ashwani Malhotra,1 Karl Leon Skorecki,2 Pravin C. Singhal.1 1 Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; 2 Medicine, Ramham Health Care Campus, Haifa, Israel.

Background: proteinuria is mediated via PPARγ

TH-PO232

for understanding podocyte pathophysiology.

Background:

Conclusions: Thus, these comprehensive data provide potentially important insights for understanding podocyte pathophysiology.

Funding: Government Support - Non-U.S.
A Soluble Guanylate Cyclase Activator Is Superior to a Phosphodiesterase Type 5 Inhibitor and a Soluble Guanylate Cyclase Stimulator in Protecting from Diabetic Nephropathy in the ZSF1 Rat

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

**UNDERLINE** represents presenting author.

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**TH-PO235**

The Glomerular Parietal Epithelial Cell Phenotype Depends on SPARC Levels

**Levels** Shokichi Naito, Nephrology, Kitasato Univ School of Medical Sciences, Sagamihara, Kanagawa, Japan.

**Background:** Parietal epithelial cell (PECs) might play a critical role in a glomerular repair to their progenitor function. Conversely, PECs might paradoxically contribute to the deterioration of glomerular function by augmentation of scarring and crescent formation under certain conditions. The factors governing these PEC functions are not well understood. We have previously shown that SPARC (secreted protein acidic and rich in cysteine) plays a causal role in mediating podocyte detachment and accelerating glomerulosclerosis in experimental crescentic glomerulonephritis. However, the effect of SPARC levels on PECs is unknown.

**Methods:** Experimental glomerular disease was induced in aged-matched SPARC+/+ and SPARC−/− mice by intraperirenal injection of a sheep anti-rabbit glomerular antibody. Immunostaining methods were then employed on days 0 and 7 of disease.

**Results:** The number of PEC transition cells, defined as cells co-expressing a PEC marker (PAX2), and podocyte marker (Sytaptopodin) was higher in diseased SPARC−/− mice compared with SPARC+/+ mice (1.35 ± 0.18 vs. 0.46 ± 0.14, P < 0.01 vs. SPARC+/+ mice). WT1 staining along Bowman’s capsule was higher in diseased SPARC−/− mice (2.57 ± 0.30 vs. 1.37 ± 0.30, P < 0.01 vs. SPARC+/+ mice). This observation was accompanied by increased PEC proliferation (measured by Ki-67 staining, (4.56 ± 0.46 vs. 2.66 ± 0.49; P < 0.01) and an increase in immunostaining for a progenitor marker, neural cell adhesion molecule (1.35 ± 0.05 vs. 1.21 ± 0.05, P < 0.05 vs. SPARC−/− mice), in a subpopulation of PECs in increased SPARC−/− mice.

**Conclusions:** PECs have the potential to become glomerular epithelial transition cells. SPARC expression in PECs favors a decrease in the number of PEC transition cells.

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**TH-PO238**

Low Dose Hydralazine Augments Losartan Mediated Reversal of Epigenetic Alterations in Diabetic Nephropathy (DN)

**Himansu Vashistha,** Nirupama Chandel, 2 Xiqian Lan, 2 Anjali Maheshwari, 2 Nairuti H. Shah, 2 Ashwani Malhotra,2 Leonard G. Meggs,1 Pravin C. Singhal, 1, 2, Medicine, Ochsner Health System, New Orleans, LA; 1, 2Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

**Background:** Epigenetics has been demonstrated to play a role in the development and progression of DN. Recently, we observed that losartan reverses high glucose-induced podocyte epigenetic alterations. We therefore hypothesized that low (non-hypertensive) dose hydralazine (HYDZ) will further augment losartan-induced reversal of epigenetic alterations in DN.

**Methods:** Protein blot of renal tissues/renal cortical sections of 2, 4, and 6 month old control and Akita mice (n=3) were probed for methylation at histone (H)3 lysine (K)4 residue, acetylation at H3 lysine (K)9 residue, SNAIL, vitamin D receptor (VDR), and neprhin. In vitro studies, protein blot of control and high glucose (30 mM, HG) treated human podocytes (HPS) were probed for SNAIL, VDR, neprhin, H3K4me3, H3K9ac and actin. Podocyte VDR and neprhin gene methylation status (pyrosequencing)and SNAIL binding at VDR and neprhin promoter (ChIP assay) were determined. Control and Akita mice (n=4) were treated with losartan with/without HYDZ (10 mg/kg/day, 4 weeks) followed by evaluation of proteinuria and renal epigenetic alterations.

**Results:** Protein blots of renal tissues of Akita mice displayed enhanced expression of SNAIL and H3K4me3 but down regulation of VDR and neprhin. Podocytes in renal cortical sections also displayed similar profile; losartan not only decreased proteinuria but also partially reversed epigenetic alterations and associated SNAIL, VDR and neprhin expressions; HYDZ alone has similar effects on proteinuria and epigenetic markers and further enhanced these effects when combined with losartan. HG/HYDZ displayed enhanced expression of SNAIL and H3K4me3 and attenuated expression of VDR, neprhin, and H3K9ac. Both neprhin and VDR displayed more than 70% cytosine methylation. HG/HP displayed decreased cytosine methylation and neprhin degradation via ubiquitination. Chip assay revealed binding of SNAIL at VDR and neprhin promoter.

**Conclusions:** Optimal reversal of epigenetic alterations can be used as a therapeutic strategy in DN.

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**TH-PO239**

Klotho Ameliorates Proteinuria by Targeting TRPC6 Channels in Podocytes

**Jing Xin,? Ji-Hee Kim,? Kyu-Hee Hwang,? Yuezhi Lin,? Noell Oliver,? Chou-Long Huang,? Seung-Kya Chua,? Wonju College of Medicine, Yonsei Univ, Wonju, Korea; †Dept of Medicine, UT Southwestern Medical Center, Dallas, TX; Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT.

**Background:** Klotho is a type-1 membrane protein mainly produced in the kidney tubules. The extracellular domain of klotho is secreted into extracellular space. Whether klotho is expressed in podocytes and whether and how it may protect the glomerular filter is unknown.

**Methods:** TRPC6-mediated Ca2+ influx, cytoskeletal remodeling, and transphthalmic albumin flux were studied in cultured mouse podocytes. Klotho expression in cultured podocytes and the kidney was examined by immunostaining, in situ hybridization, and RNA sequencing. Effects of klotho on albuminuria were studied using mouse models with genetically altered expression of TRPC6 and klotho.

**Results:** Recombinant soluble klotho suppressed ATM-stimulated, TRPC6-mediated Ca2+ influx in cultured mouse podocytes. Cytoprotection by klotho in cultured podocytes is supported by the reduction in ATM-stimulated actin cytoskeletal remodeling

**Conclusions:**
and transepithelial albumin leakage. OVERexpression of TRPC6 by gene delivery in mice induced pathological albuminuria and solute loss. Heterozygous klotho-deficient sham-operated mice had no basal albuminuria vs WT sham mice, but het-klotho chronic kidney disease (CKD) mice had aggravated albuminuria compared to that in WT CKD mice with a similar degree of hypertension and reduced renal function. Klotho is expressed in podocytes of mouse and human kidney. Disrupting the integrity of glomerular filter increased urinary excretion of soluble klotho.

Conclusions: Klotho protects podocytes from injury by suppressing TRPC6-mediated Ca²⁺ entry. Cytoprotection of podocytes in the native state may be through membranous klotho presented on podocyte cell surface or soluble klotho present in Bowman’s space. Soluble klotho may be a treatment for proteinuria.

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

TH-PO240
Aminopeptidase A Is Up-Regulated in the Intact Areas of Segmentally Sclerotic Glomeruli in Advanced Focal Segmental Glomerulosclerosis
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Background: Angiotensin (Ang) II is involved in the pathology of focal segmental glomerulosclerosis (FSGS). We hypothesized that FSGS may be associated with adaptive changes in glomerular expression of Ang-converting peptides.

Methods: Using fawn-hooded hypertensive (FHH) rats as a model of FSGS, we examined the pattern of glomerular expression of Ang converting enzyme (ACE) and the robust Ang II-clearing enzyme aminopeptidase A (APA) by Western blot (WB) and immunohistochemistry (IHC).

Results: APA was absent in glomeruli by both WB and IHC. Overall expression of APA in glomerular extracts was found to gradually decrease over time, with 87% reduction at 60 weeks compared to 6 weeks of age (p<0.001). Glomerular extracts from 30 week-old FHH rats had lower APA expression and lower APA activity compared to age-matched Wistar rats (p<0.05).

Conclusions: In conclusion, podocyte marker GLEPP1 was not only absent in all sclerotic areas but also attenuated in the intact areas within the segmentally sclerotic glomeruli and in normal-appearing glomeruli, suggesting that APA increases during the late response phase to podocyte injury. To determine whether the APA augmentation corresponded to a feedback response to Ang II, cultured mouse podocytes were incubated with Ang II (100 nM) for 24-72 hours. No change in APA abundance was observed, nor could APA abundance be induced by incubating Ang II in 8 week-old FHH rats for 4 weeks.

Funding: Private Foundation Support

TH-PO241
Anti-VEGF Treatment by Transfection of the Natural Inhibitor sFlt-1 Increases Albuminuria in Type 1 Diabetic Mice
Pascal Bus, Jan A. Brujin, Hans J. Baele. Dept of Pathology, Leiden Univ Medical Center, Leiden, Zuid-Holland, Netherlands.

Background: It has been shown that VEGF-A is involved in diabetic nephropathy (DN). In diabetic mice, treatment with anti-VEGF antibodies reduced glomerular hypertrophy. On the other hand, women with pre-eclampsia develop proteinuria due to increased levels of soluble Flt-1 (sFlt-1) - a natural inhibitor of VEGF-A. In this study we investigated the effects of systemic VEGF-A inhibition by sFlt-1 transfection in type 1 diabetic mice.

Methods: Diabetic mice were transfected with an sFlt-1 construct at the onset of diabetes. After five weeks of treatment mice were sacrificed. Collection of urine and blood was performed at baseline, and week 1, 3, and 5. Albuminuria was measured using Rotor Electrothesos. Kidneys were sectioned and stained for PAS, FA-11 (macrophages) and WT1 (podocytes). Glomerular hypertrophy was measured using Philips Digital Pathology Solutions.

Results: Diabetic mice transfected with sFlt-1 had higher albuminuria levels than mice with diabetes alone (p<0.05). However, glomerular hypertrophy as well as the number of glomerular macrophages were reduced in the treated group (p<0.05).

Conclusions: In contrast to other studies investigating VEGF-A, we reduced VEGF levels with the use of a natural inhibitor. In line with previous findings we showed that sFlt-1 treatment reduced podocyte cell surface and soluble klotho present in Bowman’s space. Soluble klotho may be a treatment for proteinuria.

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

TH-PO242
Apolipoprotein C1 Transgenic Mice Develop Gomerulosclerosis: A Potential Role for Macrophages
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Background: Associations between an APOC1 polymorphism and the development of diabetic nephropathy (DN) have been identified and confirmed in several meta-analyses. In addition, patients with type 1 and type 2 diabetes have higher serum levels of APOC1 compared to healthy control subjects. APOC1 transgenic (APOC1tg) mice develop albuminuria and glomerulosclerosis at 15 months of age. In this study we investigated the role of macrophages in APOC1 induced glomerulosclerosis in APOC1tg mice.

Methods: APOC1tg and wild-type (WT) mice were sacrificed at various ages. Kidneys were sectioned and stained for APOC1, F4/80 (macrophages), CD11b (M1 macrophages), CD163 (M2 Macrophages) and TNF-alpha. RT-PCR was performed to measure APOC1 mRNA levels. To confirm data from APOC1tg mice, human autopied kidneys with DN and healthy controls were included, sectioned and stained for APOC1. Correlations were assessed using the Pearson’s correlation test.

Results: In APOC1tg mice, the number of glomerular macrophages were already increased at 15 weeks of age, long before the development of glomerular damage, and increased even further in time. A strong linear correlation was found between the number of glomerular macrophages and glomerular damage (p<0.001). These macrophages were to be of the M1 type and expressed high amounts of APOC1 and TNF-alpha. In patients with DN, glomerular APOC1 expression was significantly increased compared to healthy control subjects.

Conclusions: Both our mice and our human autopied data indicate that APOC1 could play a crucial role in the development of glomerular damage. We hypothesize that APOC1 expression by macrophages causes glomerular damage, potentially by increasing the inflammatory state of these macrophages.

TH-PO243
Decreased Renal α-Klotho Expression Is Associated with Urinary Calcium Excretion in Early Diabetic Nephropathy in db/dB Mice
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Background: Hypercalcemia is one of the early manifestations of diabetic nephropathy (DN). We surveyed the role of α-Klotho, a protein expressed predominantly in the distal tubules (DTs). α-Klotho is known to up-regulate receptor transient potential vanilloid type 5 (TRPV5) expression, involved in tubular calcium reabsorption.

Methods: We used db/dB mice, a type II diabetes mellitus (DM) model. We employed purinergic amaminoleucoside (PAN)-induced nephritic mice and db/m mice for control. PAN mice was induced by injecting 150 mg/kg PAN intraperitoneally for every 2 weeks.

Results: Animals were sacrificed at the age of 15 week. At 15 week, db/dB mice and PAN mice developed albuminuria (218 ± 33 mg/day and 68 ± 9 mg/day, respectively), while db/m mice were normoalbuminuric (1.4 ± 3 mg/day). Urinary calcium excretion (UCa/Cr) significantly increased in db/dB mice (0.91 ± 0.09 mg/mg Cr), compared to PAN (0.30 ± 0.02 mg/mg Cr) or db/m mice (0.29 ± 0.03 mg/mg Cr). mRNA and protein expression levels of α-Klotho in the distal tubule were markedly ameliorated. Urinary klotho levels were significantly decreased in db/dB mice (1.45 ± 0.02 mg/mg Cr) compared to PAN (10.77 ± 3.01 mg/mg Cr) or db/m mice (6.39 ± 0.40 mg/mg Cr). By immunohistochemistry and immunofluorescence staining, we also confirmed reductions of renal α-Klotho, FGFR receptor type 1 (FGFR1) and TRPV5 expressions in db/dB mice.

Conclusions: Thus, renal loss of α-Klotho may affect urinary calcium excretion via inhibition of TRPV5 expression in DTs in early diabetic nephropathy.

TH-PO244
NF-κB System Inhibition Attenuates Renal Injury in Diabetic Nephropathy
Orestes Foresto-Neto, Amanda H. Albino, Simone CA Arias, Lisetty CN Rempel, Gizeley CS Moreira, Victor F. Avila, Viviane D. Faustino, Camilla Fanelli, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Niels OS Camara, Clarice K. Fujihara, Roberto Zatt. Univ of Sao Paulo, Brazil.

Background: The NF-κB system may be involved in the pathogenesis of diabetic nephropathy (DN). We investigated whether NF-κB inhibition with pyrrolidinedithiocarbamate (PDTC) exerts renoprotection in experimental DN.

Methods: Diabetes was induced in 23 adult male Munich-Wistar rats through streptozotocin injection (65 mg/kg, iv) and maintained moderately hyperglycemic with daily insulin. Rats were divided in untreated (DM) and PDTC-treated, 60 mg/kg/day vo (DM-PDTC). Untreated nondiabetic rats (C, n=12) were also followed. Body weight, glycemia, serum glucose (BGS), blood pressure (BP), urinary albumin/creatinine ratio (UAlb/Ucr), kidney/body weight ratio (KW/BW), % glomerular albuminosis (Z0-1, %) were assessed after 12 months of follow-up.

Conclusions: In conclusion, podocyte-localized APA is up-regulated in the “surviving” non-sclerosed segmental areas in glomeruli of FHH rats. However, the mechanism of up-regulation does not appear to be directly mediated by Ang II. Understanding the mechanism of APA up-regulation may provide tools to enhance the actions of a potentially renoprotective peptide.
TH-PO245
Renin Accelerates Progression of HIV-associated Nephropathy (HIVAN) Through Kidney Cell HDL Gene Expression
Parthib Rai, Rivka Lederman, Shabirul Haque, Adowada Mallavarapu, Pravit C. Sangaiah. Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

Background: The activation of renin-angiotensin system has been demonstrated to play an important role for the development and the progression of HIVAN. However, the progression of HIVAN attributed predominantly to Ang II generation by kidney cells. Recently, HIV has been demonstrated to stimulate renin generation by kidney cells to play an important role for the development and the progression of HIVAN. However, the progression of HIVAN attributed predominantly to Ang II generation by kidney cells. HIV gene expression and production might also be enhancing kidney cell HDL gene expression, which may accelerate progression of renal lesions, independent of the effects of Ang II.

Methods: Human podocytes (HPs) were transduced with either empty plasmid (EV) or HIV (NU3-4, HIV). To increase endogenous renin production, EV-HPs and HIV-HPs were transfected with miRNA-targeting renin (miRNA-HIV/HPs) or scrambled (Scr-siRNA-HIV/HPs) siRNA; protein blots were probed for renin and actin. To evaluate the effect of renin in vivo, mRNA expressions of HIV genes from renal tissues of HIV (Tg26) mice with high endogenous renin (Tg26 mice either with 2, 3 and 4 copies of angiotensinogen [Arg] or lacking VDR) were quantified by qPCR. To down regulate renal tissue renin expression, Tg26 mice were treated with either vehicle or a VDR agonist (VDA) for 2 weeks and then renal tissues were evaluated for HIV gene expression. Additionally, gene expression and progression of renal lesions were compared in Tg26 mice and Tg26 mice lacking renin.

Results: HIV enhanced renin expression in HPs. Silencing of VDR in HIV/HPs further enhanced expression of Nef, Tat, and Vif. On the other hand, treatment of HIV/HPs with VDA downregulated HIV gene expression. Renal tissues of Tg26-Agi-1 displayed 2-4 fold increase in mRNA expression of gp120, Ypr, Tat, Nef and Vpu vs. Tg26-Agi-2. Similarly, Tg26 mice lacking VDR displayed greater HIV gene expression when compared with Tg26 mice with intact VDR. VDA treatment of Tg26 also down regulated renal tissue expressions of renin as well of HIV genes. Tg26 mice lacking renin, displayed attenuated renal tissue HIV gene expression and slowed progression of renal lesions.

Conclusions: Renin enhances progression of HIVAN through HIV gene expression.

TH-PO246
Podocyte and Tubule Injury Have Different Effects on Renal Handling of Apolipoprotein A-I (ApoA-I) and Its Receptors

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Background: Developing effective therapies for APOL1 nephropathies will require insights into the mechanisms of APOL1-associated cell damage. Disease-associated G1 and G2 mutations in the C-terminus of APOL1 increase toxicity through lysosomal membrane permeability (LMP). Vesicle-associated membrane protein (VAMP) 8, a lysosomal soluble NSF attachment protein receptor (SNARE) has been proposed to inhibit APOL1 function by binding the C-terminus, with the terminal G2 mutations abolishing the interaction. Co-expression of VAMP8 increased APOL1 toxicity. A non-toxic APOL1-A protein lacking the N-terminal signal peptide exhibited the greatest affinity to VAMP8.

Methods: APOL1-G1 and G2 variants increased ER stress and autophagy compared to the ancestral G0 variant. All APOL1 variants traffic to Rab7, LBPA+, and VAMP8-positive late endosomes and lysosomes. Deletion of the APOL1 C terminus abolished APOL1-induced autophagy and toxicity, but not trafficking to lysosomes. APOL1 bound all R-SNAREs with greatest affinity for lysosomal VAMP7 and VAMP8. There were no differences in affinity to VAMP8 among the APOL1 variants, and truncation of the APOL1 C terminus did not abolish the interaction. Co-expression of VAMP8 increased APOL1 toxicity. A non-toxic APOL1-A protein lacking the N-terminal signal peptide exhibited the greatest affinity to VAMP8.

Conclusions: APOL1 G1 and G2 toxicity may not be due to decreased VAMP8 affinity, as previously proposed. The APOL1 C terminus is required for toxicity but not for lysosomal trafficking, suggesting the increased toxicity of APOL1 risk variants is not due to altered APOL1 trafficking to lysosomes. Cellular stress pathways beyond LMP, such as autophagy and ER stress, may contribute to the increased toxicity of APOL1 risk variants.

Funding: NIDDK Support, Other NIH Support - NCI

TH-PO248
N-Acetylmuramomannosamine Mitigates Neuraminidase-Induced Podocyte Injury in Mice
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Background: Podocyte injury is present in many glomerular diseases. Current therapies do not achieve sustained remissions and often have adverse events. Recent findings suggest that a subset of patients with glomerular disease may have ongoing desialylation or impaired resialylation of certain renal glycans (glycoproteins and glycolipids), as detected by lectin histochemistry.

Methods: We induced podocyte injury in mice by a single intraperitoneal injection of Vibrio cholera neuraminidase (V cholera neuraminidase (NA), an enzyme that removes α2,6 linked sialic acid end-groups from glycans. The sialic acid precursor N-acetylmuramomannosamine (ManNAc) was administered in drinking water at a ~1 g/kg/dose, either prophylactic (starting 10 days prior to NA and continued for 4.5 days). Treatment of APOL1-A mice with ManNAc significantly reduced proteinuria and albuminuria as compared to untreated controls. ManNAc did not alter albuminuria in untreated mice.

Results: NA-injected wild type mice developed proteinuria and renal insufficiency in a dose-dependent manner. Podocalyxin and other glomerular glycans were hyposialylated. Histopathology showed acute renal injury predominantly in the cortical region, swollen podocytes, and glomerular mesangial cell hyperplasia and hypertrophy. Ultrastructural studies showed podocyte foot process effacement. Importantly, both prophyllactic and therapeutic ManNAc treatments decreased renal glacial sialylation and markedly reduced urinary albumin/creatinine ratio (ACR) and podocyte injury at Day 5 (N=14 per group).

Funding: NIDDK Support, Other NIH Support - NCI
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Underline represents presenting author.

### TH-PO249

A Mismatch Between Glomerular Volume and Podocyte Mass Is Associated with Albuminuria and Accelerated Podocyte Hypertrophic Injury in Leptin-Deficient Zucker Rats

**Background:** Glomerular hypertrophy is a well-established component of diabetic nephropathy. We previously reported that failure of podocytes to match glomerular tuft enlargement (in response to high glucose signaling through the mTORC1 pathway) can trigger proteinuria, glomerulosclerosis and progression to end stage renal disease in dominant negative AA-4E-BP1 Tg rat model. We therefore tested the hypothesis that a mismatch between glomerular volume and podocyte mass causes progression of diabetic nephropathy.

**Methods:** We used the leptin-deficient Zucker Diabetic Fatty (ZDF-fatty) rat model, a genetic model of type 2 diabetes. We transfected with GapmeR targeting human lncMGC. These parameters were also examined in human mesangial cells (HMC) transfected with GapmeR targeting lncMGC. These parameters were also examined in human mesangial cells (HMC).

**Results:** ZDF-fatty rats gained weight much faster than control rats over the first 15 weeks, but did not become hypertensive over the study period. ZDF-fatty rats became diabetic with increased blood glucose and glycosuria by 10 weeks. Albuminuria and urine podocin:aquaporin2 mRNA ratio were also significantly increased by 10 weeks. Sequential kidney biopsies at 15, 30, and 45 weeks revealed that by 15 weeks glomerular volume was significantly increased above control (1.5-fold, P<0.01) and podocyte density was significantly reduced (0.9-0.01), although podocyte number per tuft was not detectably decreased. By 45 weeks glomerulosclerosis was present and the Glep1+ peritubular positive podocyte tuft area was significantly reduced in the ZDF-fatty rats but not in controls.

**Conclusions:** These data indicate that a mismatch between glomerular volume and podocyte mass (reduced podocyte density) is associated with development of albuminuria and accelerated podocyte hypertrophic stress in this model of type 2 diabetes, compatible with data previously reported in Pima Indians.

### TH-PO250

An ER Stress-Regulated Transcript Hosting a MicroRNA Megachuster as Therapeutic Target in the Early Stage of Diabetic Nephropathy

**Background:** Glomerular epithelial cell injury and rescue are early features of DN, highlighting the GapmeR approach for targeting lncRNAs as a novel therapy for DN.

**Funding:** NIDDK Support, Other NIH Support - Nephrology

### TH-PO251

No Difference in Cytotoxicity of APOL1-G0 or Risk Variants G1 and G2

**Background:** The genetic evidence linking variation in the APOL1 gene to kidney disease in ancestral African populations is strong; however, the biological mechanisms that underlie the association remain uncertain. Autophagy and cell death has been observed after the expression of APOL1 and variant dependent cell death has been reported with the transient expression of APOL1. Therefore we sought to examine autophagy and cell death for variant dependent effects in stable expression systems.

**Methods:** Stable tetracycline inducible HEK293 cells were generated for the expression of APOL1-G0 (reference), the G1, and -G2 risk variants. We compared autophagy and apoptosis under conditions of autophagy induction induced by tetracycline and anoikis induction by treating cells with 4 μg/mL TNF. We also utilized stable cell lines of APOL1-KO and APOL1-G0 transduced with lentiviruses expressing a shRNA targeting human APOL1.

**Results:** We found no difference in autophagy induction and apoptosis induction between the different cell lines.

**Conclusions:** Our findings suggest that autophagy and apoptosis are not major contributors to the renal disease phenotype associated with APOL1.

### TH-PO252

NGAL Regulates TH17 Immunity in ANCA Vasculitis

**Background:** Neutrophil NGAL plays a pathogenic role in ANCA vasculitis. A diagnostic marker or participates mechanistically in renal damage is not known. We hypothesized that neutrophil NGAL plays a pathogenic role in ANCA vasculitis.

**Results:** Patients with active ANCA disease demonstrated increased NGAL serum levels by western blot analysis (47.3±13.1 OD) compared to patients in remission (19.4±8.1) and healthy controls (2.1±0.4). We then assessed ANCA-activated neutrophils as a potential source for upregulated serum NGAL. By ELISA, both PR-3-ANCA and MPO-ANCA stimulated NGAL release from human neutrophils (887±72 and 961±70 pg/mL), whereas control IgG induced much lower levels (105±21 pg/mL). Mice with anti-MPO-induced NCGN demonstrated significantly increased NGAL serum levels by ELISA (data not shown). To assess the role of neutrophil NGAL in vivo, we used a murine model of anti-MPO induced NCGN where neutrophils were depleted with anti-Gr1. Mice with anti-MPO-induced NCGN demonstrated upregulated NGAL serum levels by ELISA (data not shown).

**Conclusions:** Our findings indicate that neutrophil NGAL down-regulates inflammation in ANCA-induced NCGN by inhibiting TH17 immunity.

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TH-PO253

Streptococcus mutans Strains with Collagen-Binding Protein May Cause IgA-Like Glomerulonephritis in Rats

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Background: The precise pathological mechanisms of IgA nephropathy (IgAN) remain unclear. It is known that 10-20% of healthy subjects harbor strains of Streptococcus mutans, a known pathogen of dental caries, that possess Cnm, a cell surface collagen-binding protein encoded by the cnm gene. Furthermore, it is widely accepted that an association between S. mutans with Cnm protein and systemic diseases exists. We previously found that the rate of cnm-positive S. mutans organisms isolated in saliva specimens was significantly higher in an IgAN group as compared to the controls, and reported those findings at ASN Kidney Week 2014 and in Clinical and Experimental Nephropathy in 2014. The aim of this study was to investigate whether nephritis is induced by Cnm-positive S. mutans strains inoculated into the oral cavity of a rat model of dental caries.

Methods: Cnm-positive S. mutans strains (ID-17R, ID-32R, ID-74R) were isolated from the oral cavities of 3 IgAN patients. Those along a standard oral isolate, were inoculated into the oral cavities of 2-week-old Dawley rats fed a 56% sucrose-containing diet and then we confirmed that the strains were harbored in the oral cavity of each rat 1 week later. From 10 weeks of age, findings of severe dental caries were confirmed in all rats. They were euthanized at 24 weeks of age, then kidney tissues were extirpated and stained with PAS, and immunohistochemistry with the IgA antibody was performed for histopathological analysis.

Results: Dental caries in nearly all of the rats were found extending to the pulp space, which contains nerves and blood vessels. In rats harboring Cnm-positive strains in the oral cavity, mesangial cell proliferation was observed and immunohistochemical staining of the IgA antibody was seen in the para-mesangial area. However, no abnormal findings were observed in extirpated kidney tissues from rats harboring MT8148 in the oral cavity.

Conclusions: Our results indicate that Cnm-positive S. mutans strains harbored in the oral cavity may cause IgA-like glomerulonephritis.

TH-PO254

Prevention of Lupus Nephritis in the BXSB-Yaa Mouse by Metabolic Inhibitors

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Background: In a heavily Type II gamma interferon activated model of lupus nephritis (LN), we showed metabolic inhibition by chronic oral combination of 2 deoxycorticosterone (2DG) and metformin (Met) reversed LN. We now show 2DG + Met prevents LN in the heavy Type I alpha interferon driven BXSB-Yaa LN.

Methods: Mice were treated chronically with treatments in drinking water. At sacrifice blood and tissues were taken for analysis and correlation of renal histopathology with a LN classification modeled on the ISN-RPS classification of LN. For clarity of presentation, 5 animals with global proliferative glomerulonephritis (PG) will be given for each treatment group in results. All other animals were classified as normal to mesangiocapillary LN (data not shown).

Results: 2DG (Pg 0.0%), 2DG + Met (P<0.05) and rapamycin (P<0.001) all showed marked inhibition in LN. Dichloroacetic acid (P<0.001) and Met (single agent, P<0.05) showed moderate but significant reduction of LN compared to disease controls (P=0.76). Untreated C57Bl/6 mice were used as a normal (disease free) control (PG 0.0%). Target organ protection is supported by animal wellbeing and in vitro and in vivo determination of immunologic and metabolic parameters.

Conclusions: This study presents a second model of LN that responds favorably to metabolic inhibition and normalization by existing drugs utilized for other clinical indications.

Funding: Private Foundation Support

TH-PO255

Successful Treatment of a Mesangial Proliferative Glomerulonephritis by Foxd1+ Metanephric Mesenchymal Cells

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Background: Short hairpin RNA (shRNA) knockdown of Foxd1 by lentivirus vector infection in vitro and in vivo showed that Foxd1+ mesenchymal cells had good osteogenic and adipogenic differentiation capacity. 2 After intravenous injection of Foxd1+ cells could improve the pathological changes in the kidney and could reduce urinary protein significantly. 3,4 CK-R results showed that Foxd1+ cells condition medium could antagonize proliferation of mesangial cells activated by PDGF-BB from 48 hours. Transwell migration assay results showed that Foxd1+ cells could significantly inhibit active mesangial cell migration.

Conclusions: Foxd1+ metanephric mesenchymal cells could be isolated using transgenic mice and also are proved that they have the characteristics of stem cells. Foxd1+ mesangial mesenchymal cells could improve the renal pathological changes in anti-Thy1 mesangial proliferative glomerulonephritis, and inhibit the activation of mesangial cells.

Funding: Government Support - Non-U.S.

TH-PO256

Beyond HIF1α - Regulatory Genomic Insights into Renal Cell Carcinoma Revealed by DNasel-seq

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Background: Clear cell renal cell carcinoma (RCC) is the most common sporadic malignancy affecting the kidney. Inactivation of the VHL tumor suppressor gene and subsequent stabilization of the HIF1α transcription factor (TF) is very common in RCC. However, it is unclear how HIF1α and the closely related HIF2α (EPAS1) interact with each other and other TFs to produce and maintain the RCC phenotype. Here, we delineate the regulatory genomic landscape of RCC using DNasel-seq and define the transcriptional regulatory network of RCC.

Methods: Fresh normal human kidney tissue and RCC were disaggregated and cultured to generate primary tubular and renal cell carcinoma cultures. These were subjected to DNasel-seq and RNAsseq according to established protocols. HIF1α hypersensitivity profiling (DNasel-seq) allows for comprehensive mapping of regulatory DNA at a genomic scale and with single nucleotide resolution. Examination of footprinting-depth-DNasel-seq data identifies DNasel-protected transcription factor (TF) motifs within the promoter of other TFs. Mapping these TF footprints across all TFs with known motifs results in a TF interaction network (Cell. 150: 1274-1286).

Results: Even HIF1α plays an important role in RCC biogenesis, it does not prominently feature in the TF interaction network of RCC. Instead, several other TFs (e.g. FOX, CEBP, SMADs nuclear receptors, etc.) interact to control the transcriptional regulatory network of RCC with a relatively minor contribution from HIF2α (EPAS1).

Conclusions: While the HIF transcription factors play an important role in RCC oncogenesis, DNasel-seq reveals that other TFs are responsible for maintaining the RCC phenotype. Systematically testing this regulatory circuitry promises to identify novel TF pathways to intervene in the growth of this deadly cancer. These techniques/approaches are also being applied to other primary kidney cancers such as endothelial cells and podocytes.

Funding: Other NIH Support - NHGRI - U54HG007010-03, Private Foundation Support

TH-PO257

Uneven Reinnervation After Unilateral Renal Denervation: Afferents Dominate Efferents

Kristina Rudinova,1 Franziska Günther,2 Eric Groening,1 Michael JD-17R, JD-52R, JD-74R), were isolated S. mutans strains (JD-52R, JD-74R) were isolated from the oral cavities of 3 IgAN patients. Those along with MT8148, a standard oral infection model, were inoculated into the oral cavity of a rat model of dental caries.

Methods: We used Foxd1cre/GFP transgenic mice and Rosa-DTRflox transgenic mice to screen target embryonic kidney cells, and isolate Foxd1+ metanephric mesenchymal cells by adding diphtheria toxin. We detect Foxd1+ cell proliferation, cell surface markers and osteogenic adipogenic differentiation potential. 3. 24h after establishment of anti-Thy1 mesangial proliferative glomerulonephritis, Foxd1+ cells were injected via intravenous, and this group was set as group of treatment. We detect renal pathology and renal function at different time points on control, model and treatment group. 4. Mesangial cells were stimulated by PDGF-BB, we detect the influence of Foxd1+ cells at the different time points on control, model and treatment group. 4. Mesangial cells were stimulated by PDGF-BB, we detect the influence of Foxd1+ cells on the proliferation and migration of activated mesangial cells.

Results: 1. The results showed that CD90 positive rate was 0.96.05, CD 44 91.11%, CD34 0.53, CD34 0.53%, CD34 0.35%. After 72 hours, we found that Foxd1+ cells had good osteogenic and adipogenic differentiation capacity. 2. After intravenous injection of Foxd1+ cells could improve the pathological changes in the kidney and could reduce urinary protein significantly. 3. CK-R results showed that Foxd1+ cells condition medium could antagonize proliferation of mesangial cells activated by PDGF-BB from 48 hours. Transwell migration assay results showed that Foxd1+ cells could significantly inhibit active mesangial cell migration.

Conclusions: 1. Foxd1+ metanephric mesenchymal cells could be isolated using transgenic mice and also are proved that they have the characteristics of stem cells. 2. Foxd1+ metanephric mesenchymal cells could improve the renal pathological changes in anti-Thy1 mesangial proliferative glomerulonephritis, and inhibit the activation of mesangial cells.

Background: Renal nerve ablation is a beneficial, but controversial treatment for resistant hypertension. We found morphological evidence that intrarenal paravascular afferents reinnervate more thoroughly than efferent sympathetic nerves. We now measured the tissue content of the afferent and efferent neurotransmitters, calcitonin gene related peptide (CGRP) and norpinephrine (NE) within 12 weeks after denervation.

Methods: Tissue levels of CGRP and NE from 24 male SD rats (ELISA-test, mass spectrometry) were measured in denervated left (L) and non-denervated right kidneys (R) 1, 4 and 12 weeks after renal denervation.

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

Underline represents presenting author.
Results: CGRP decreased by 72% in denervated (L) kidneys compared to (R) kidneys in week 1 [W1_L: 0.19±0.16 vs. W1_R: 0.24±0.06; p<0.05]. In week 12 CGRP content in (L) kidneys did not differ from (R) kidneys. We observed a 78% decrease of NA tissue levels [pmol/mg kidney] in week 1 due to surgical denervation [W1_R: 1.09±0.16 vs. W1_L: 0.24±0.06; p=0.05]. In contrast to the CGRP tissue levels there was no complete recovery of NA in week 12. The commonly used addition phenol to the surgical denervation procedure did not influence these results significantly. All data are given as mean±SEM.

Conclusions: We could show that there is a complete reinnervation of CGRP positive perivascular nerves within 12 weeks after renal denervation. However, NA tissue content did not recover completely inspite of complete morphological regrowth of sympathetic nerve fibers. This might potentially result in a net surplus of affrent sympatho-inhibitory influence, adding to the beneficial effect of renal denervation in some cases of resistant hypertension.

Funding: Government Support - Non-U.S.

TH-PO258

An Aristolochic Acid-Induced Nephropathy (AAN) Model for Stable CKD in Mice

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Background: ACEi/ARB are standard therapy for progressive CKD but do not slow progression in ~50% of patients. To explore novel therapies of CKD in humans, better preclinical models are needed. A few mouse models for CKD have been developed, each with strengths and weaknesses. In humans, Aristolochic Acid (AA) causes Balkan nephropathy, with chronic interstitial fibrosis and slow progression to ESRD. However, published AAN mouse models have poorly characterized CKD outcomes.

Methods: CD-1 or C57BL/6 mice were injected i.p. with AA dissolved in DMSO using two regimens: R1: AA i.p. (3 mg/kg) every 3 d for 6 wk, then 6 wk of disease development. R2: AA i.p. (2.5 mg/kg) every 7 d for 3 wk, then 1 wk of disease development. Spot urine samples and non-invasive GFR by plasma disappearance of FTC-Sinistrin were obtained weekly: serum and kidney were collected at euthanasia. Using aged animals, or addition of salt-loading, uninephrectomy (UNx), or an adenine-rich diet were tested to increase the severity of the model.

Results: CD-1 mice (R1) had severe body weight (BW) loss at 3 wk and was discontinued. Both CD-1 and C57BL/6 (R2) showed moderate loss of BW. All R2 mice survived. Both CD-1 and C56BL/6 mice had elevated BUN, and developed severe tubulointerstitial injury. CD-1 mice showed higher injury score and fibrosis (%) than C57BL/6 mice. There was no elevation of blood pressure in CD-1 (R2). Neither regimen nor strain developed progressive CKD model as urinary albumin transiently peaked then fell, and GFR dropped by 60%, but plateaued within two weeks. Aging, salt-loading, UNx, or an adenine-rich diet did not increase injury or lead to progressive CKD.

Conclusions: AA caused a strain- and regimen-dependent severity of tubulointerstitial injury, with moderate but stable decreases in kidney function (~ human CKD stage 3). AAN may still be a foundation of a progressive CKD model, but additional renal insults might be needed to achieve a progressive CKD model.

Funding: NIDDK Support

TH-PO259

The Polymeric Immunoglobulin Receptor Is Expressed in Scattered Cells of Human Kidney and Increase in Expression following Kidney Injury

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Background: We have previously shown that the proximal tubules of human kidney contain a scattered cell (SC) population of importance for kidney regeneration, where the markers for SC are identical to those of the parietal epithelium of Bowman’s capsule. Using gene expression analysis of the SC we found that these may express the Polymeric immunoglobulin receptor (PIGR).

Methods: Biopsy material was procured from normal and diseased kidneys. Using gene expression analysis of the SC we found that these may express the Polymeric immunoglobulin receptor (PIGR).

Results: Colocalization studies showed that PIGR indeed localizes to the SC of human kidney. Furthermore, the tubular PIGR expression increases as an early response to both acute and chronic renal injury. ELISA measurements of secretory IgA levels in serum and urine samples from patients suffering from various kidney diseases show and increased urinary content of secretory IgA. In vitro, we show that primary renal epithelial cells perform vectorial transport of secretory IgA towards the apical compartment.

Conclusions: The human kidney uses PIGR to export secretory IgA into the tubular luminal contents, a function similar to the established secretion of dimeric IgA onto the mucosal surfaces of the respiratory and gastrointestinal tracts. The levels of urinary secretory IgA increase prominently in response to renal injury.

Funding: Government Support - Non-U.S.

TH-PO260

Establishment of Canine Remnant Kidney Model in Beagle Dogs

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Background: The remnant kidney model has been well established in the rodents, whereas it has not been fully understood in higher and bigger animals. Canine remnant kidney model is important for better medical applications. We aimed to establish 1/16 canine remnant kidney model.

Methods: Remnant kidney model was induced in beagle dogs by a two-step subtotal necrectomy. First, left kidney was exposed by flank incision. Among a total of eight branches of left renal arteries, seven-eighths of left renal arteries were ligated. Ischemia induction was confirmed by visual identification of topical cyanosis.

After 1 week, right kidney was removed and consequently 1/16 remnant kidney model was completed. A total of 20-weeks of subtotal nephrectomy, we sacrificed the animals and their renal histopathologic changes were examined.

Results: During 20 weeks, CKD dogs (n=12) and sham-operated dogs (n=2) were monitored. Blood pressure of CKD dogs had been maintained highly at 2 weeks. In spite of anti-hypertensive medication, 3 CKD dogs died from uremia and hypertension. After surgery, body weights were declined in both CKD and sham-operated dogs in first 2 weeks. Sham-operated dogs had recovered their body weight within 3 weeks, however, CKD dogs had recovered slowly until 3-months after surgery. Blood urea nitrogen, serum creatinine and proteinuria amount were significantly higher than those of sham-operated dogs during overall period. Renal function decline were accentuated during first 3 weeks after subtotal nephrectomy and last 2 weeks before sacrifice. Intra-renal infiltration of inflammatory cells, apoptosis of renal tubular cells, and renal fibrosis were prominent in CKD dog than in sham.

Conclusions: We successfully established 1/16 remnant kidney model by renal artery ligation in beagle dogs.

TH-PO261

Molecular Score of Acute Kidney Injury Identifies Discarded Kidneys That Are Potentially Transplantable

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Background: Many kidneys from older deceased donors are discarded due to uncertainty based on conventional features (clinical or histology). We previously showed that the molecular AKI score in implantation biopsies (Bx) predicts future graft function better than histology. Now we hypothesize that AKI scores in kidneys accepted for transplantation will be similar to some discarded kidneys when decision to transplant is based on conventional features.

Methods: Pre-implantation Bx from accepted and discarded kidneys were obtained from brain dead >90 years donors. Decision to discard was based on MAPI scores of wedge Bx in 20/28 discards. Molecular AKI scores and global gene expression were analyzed by microarrays.

Results: The molecular AKI scores in all kidneys were compared by principal component analysis (PCA).
TH-PO262

Characterization of Injury in Renal Proximal Tubules During Cold Incubation and Rewarming

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Methods: Male C57BL6 mice aged 8-12 weeks, were subjected to mouse kidney transplant. Donor kidneys were subjected to 3 hours of cold incubation followed by rewarming in an extracellular buffer (37°C). Underline represents presenting author.

Background: Cold ischemia and rewarming induce an essential component of preservation injury which is iron-dependent in many cell types. In rat hepatocytes a chloride-dependent component of injury has been described, while chloride-poor solutions accentuated damage in endothelial cells. This work examines the injury induced by cold incubation and rewarming in isolated renal proximal tubules.

Results: ATP content and resazurin reduction were measured as indicators of cellular integrity, energy content and metabolic activity.

Conclusions: The data provide evidence of mitochondrial disruption in mouse RTECs during CS/REW, resulting in caspase independent apoptosis mediated by AIF. One potential reason for the remarkable ability of hibernators to survive prolonged CS/REW far in excess tolerable by nonhibernators is mitochondrial preservation that prevents release of AIF. Understanding caspase independent pathways during CS/REW may lead to improved organ preservation, and novel therapies for DGF.

Funding: Other NIH Support - R03 DK96151-01 to Alkesh Jani

TH-PO264

Phenotype of Renal Tubular Cell Death During Delayed Graft Function


Methods: Male C57BL6 mice aged 8-12 weeks, were subjected to mouse kidney transplant. Donor kidneys were subjected to 3 hours CI in UW solution, and processed immediately or subjected to syngeneic mouse kidney transplant. Renal function was assessed by serum creatinine (SCr). Renal tubular cell (RTC) apoptosis and necrosis were quantified by an independent nephropathologist. TLR4, RIP3, cleaved BID, cleaved caspase-8 (CC8) and cleaved caspase-3 (CC3) were examined by immunoblot.

Background: Delayed graft function (DGF) independently predicts reduced 5 yr kidney transplant survival. Treatments of DGF are lacking. Cold ischemia (CI) is a significant risk factor for DGF but the mechanism by which CI leads to DGF is unknown. The aim of this study was to determine the effects of CI on donor kidneys alone versus CI followed by warm reperfusion after kidney transplant (CI+Txp). We hypothesized that CI alone would produce a different injury phenotype to CI+Txp.

Results: CI+ Txp resulted in a significantly increased SCr (1.9±0.15) vs. transplant without CI (0.3±0.05). CI alone results in increased RTC apoptosis and CC3 but did not result in necrosis. In contrast, CI + Txp led to: (1) increased CC8, cleaved BID, Bax and CC3, and (2) increased RTC apoptosis and also increased programmed necrosis; (2) increased RTC necrosis that was associated with increased RIP3 and TLR4.

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TH-PO265

Abstract Withdrawn

TH-PO266

Swine Leukocyte Antigens and Orthotopic Kidney Transplantation in Yorkshire Piglets and Yucatan Miniature Swine

Long Jin, Jian Sum in Yorks and YMS, allowing for predictable patterns of RJX/acceptance. For Yorks, Pig #7 showed hyperacute rejection (RJX) of LK8 (POD-2, Cr 12.1) and Pig #9 were removed. The same procedure was performed in Yorks. No immunosuppression was used; both animals were sacrificed (sac) on POD-2.

Results: Mean pre-op creatinine (Cr) was 1.05 mg/dL. For YMS, Pig #10 rejected LK9 and died on POD-6 (Cr 19.6). Pig #9 accepted LK10 with Cr 2.4 at sac on POD-9.

For Yorks, Pig #7 showed hyperacute rejection (RJX) of LK8 (POD-2, Cr 12.1) and Pig #8 had vascular rejection of LK7 (POD-2, Cr 4.4). All KT organs were well perfused at sac.

For YMS, sheep LK haplotype mismatch (Lr-4.5/6.7, blood type A, and Pig #9, SLA Lr-4.5/4.5, A) and 2 Yorks (Pig #7, SLA Lr-6.12.22.15b, non-A; and Pig #8, SLA Lr-4.40.12.14, A). Species couples were operated simultaneously. For YMS Pig #9, the left kidney (LK9) was resected, ex vivo perfused on ice, and stored in an ice bath. LK10 was then removed, perfused and stored while LK9 was transplanted into #10. Then LK10 was transplanted into #9. Both R kidneys were removed. The same procedure was performed in Yorks. No immunosuppression was used; both animals were sacrificed (sac) on POD-2.

Conclusions: Orthotopic DEAK and SLA typing with PCR-SSP are equally effective in Yorks and YMS, allowing for predictable patterns of RJX/acceptance. Yorks may offer an inexpensive approach to low-resolution (Lr) swine leukocyte antigen (SLA) genotyping.

Funding: Private Foundation Support

TH-PO267

Development of Experimental Model of Renal Thrombosis Microangiopathy in Rat Allogeneic Bone Marrow Transplantation

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Background: Renal thrombosis microangiopathy (TAM) after clinical hematopoietic stem cell transplantation (HSCT) is a well-recognized complication that carries a high risk of death. In TAM after HSCT, total body irradiation, use of immunosuppressants for prophylaxis against graft versus host disease (GVHD), viral infection, and GVHD have been proposed as risk factors. However, so far, experimental model of renal TAM after HSCT has not been reported.

Methods: In order to develop the experimental rat model of renal TAM after allogeneic BMT, we performed BMT from Lewis (RT1l) bone marrow cells (6×10^7 cells) to DA (RT1a) rats after 10G irradiation without immunosuppression. We examined the clinical and pathological characteristics of several organs, including the skin, liver, gut and kidney during 9 months after BMT.

Results: In syngeneic BMT and non-BMT control rats, acute or chronic GVHD and renal TAM did not develop by 9 months. In BMT rats after Lewis BM cell transplantation without immunosuppression, renal TAM in the kidney developed in 3 out of 6 rats 9 months after BMT with GVHD in the skin, gut, and liver. Renal dysfunction included the increased levels of the serum creatinine (0.33±0.1mg/dL), and urinary protein (0.4±0.1 g/day) developed at 9 months with skin rash, alopecia, decreased body weight, and liver dysfunction (AST: 231 mg/dL, ALT: 112 mg/dL, LDH: 987 mg/dL). Renal pathology showed collapsed and sclerotic glomeruli with endothelial cell injuries in all animals. Renal TAM findings were characterized by the glomeruli with mesangiosis, duplication of the GBM, and fibrin thrombus formation. Exudative lesions in small arteries were also seen. These renal findings were quite similar findings as renal TAM after HSCT in humans.

Conclusions: In 50% of animals, renal TAM associated with GVHD developed with renal dysfunction after Lewis to DA rat allogeneic BMT. Further studies are needed to assess the mechanism of renal TAM after BMT.

TH-PO268

Beneficial Effect of Exendin-4 on Autophagy Dysfunction During Tacrolimus-Induced Pancreatic Beta Cell Injury

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Background: Autophagy is a cellular degradation-recycling system for aggregated proteins and damaged organelles. Previously, we reported that chronic calcineurin inhibitors (CNIs)-induced nephropathy characterized by excessive autophagosome formation and decreased autophagic degradation rate. We suggested that lysosomal dysfunction may associate in the process of autophagic degradation. In this study, we evaluated the autophagic function in CNI-induced pancreatic beta cell injury, and combined treatment of exendin-4 (Exd), anti-diabetic agent has therapeutic effect by improving CNI-induced lysosomal dysfunction.

Methods: Rats were treated with tacrolimus (TAC, 1.5 mg/kg, s.c.) and Exd, (1 ug/kg, i.p.) for 4 weeks. The effects of Exd on TAC-induced pancreatic beta cell dysfunction were evaluated by IGTG, serum insulin level, HOMA-IR index, and islet size. Using an INS-1 cells, we examined the effect of Exd on TAC-induced lysosomal dysfunctions such as pH increase, reduced cathepsin B activity and LAMP-2A. Autophagosome formation and autophagic protein aggregates were confirmed by the expression of LC3-B and p62, respectively. Oxidative stress was measured by the concentration of 8-OhdG, MnSOD, catalase, and H2DCF-DA. The influence on apoptosis was examined by TUNEL assay, Annexin V, and active caspase-3.

Results: Four weeks of TAC treatment increased blood glucose levels and HOMA-IR index and decreased serum insulin level and islet size. But co treatment with Exd attenuated TAC-induced pancreatic beta cell dysfunction and islet size. TAC treatment improved TAC-induced pH increase, cathepsin B activity and LAMP-2A expression in INS-1 cells. These were accompanied by restored expression of LC3-B and p62 which are markers for autophagic degradation rate. The markers for oxidative stress and apoptosis were also recovered by cotreatment of Exd.

Conclusions: The results of our in vivo and in vitro studies demonstrate that Exd has an effective anti-diabetic agent that exerted antioxidative and antiapoptotic effects via restoring TAC-induced autophagic dysfunction.

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TH-PO269

Klotho Deficiency Is Associated with Chronic Tacrolimus-Induced Oxidative Injury

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Background: We previously demonstrated that experimental animal model of chronic calcineurin inhibitors (CNIs)-induced nephropathy showed down regulated Klotho in renal tissues. We suggested that Klotho deficiency is highly associated with prolonged treatment of CNI-induced oxidative injury and resultant apoptosis and renal dysfunction. To determine whether Klotho deficiency is closely associated with CNI-induced renal injury via oxidative stress, Klotho heterozygote mice were compared with wild type control.

Methods: Mice of wild type (+/+) and Klotho heterozygote (Kl/+) were daily treated TAC (0.25, 0.5 ,1 mg/kg, s.c.) for 4 weeks under the 0.01% sodium diet. The effects of varied dose of TAC and Klotho deficiency on renal function, fibrosis, and apoptosis were examined. The expression of Klotho was measured in renal tissue and serum. Oxidative stress was evaluated with measuring 8-OhdG and MnSOD. Using a HK-2 cells, we examined the protective effect of recombinant Klotho under TAC treatment by measuring oxygen consumption rate (OCR), ATP production, amount of ROS, mitochondrial membrane potential (MMP), and apoptosis.

Results: Four weeks of TAC treatment induced renal dysfunction, renal fibrosis, and apoptosis in a dose-dependently in +/+ mice. These changes were aggravated in Kl/+ mice receiving TAC. Reduced Klotho level in urine, serum, and renal tissue was accompanied by further increased 8-OHdG. The expression of Klotho was measured in renal tissue and serum. Oxidative stress was measured by the concentration of 8-OhdG, MnSOD, and autophagic protein aggregates were confirmed by the expression of LC3-II and p62, respectively. Oxidative stress was increased by the concentration of 8-OhdG, MnSOD, catalase, and H2DCF-DA. The influence on apoptosis was examined by TUNEL assay, Annexin V, and active caspase-3.

Conclusions: The results of our in vivo and in vitro studies demonstrate that Klotho has a renoprotective role against TAC-induced renal dysfunction and cellular injury by reducing oxidative stress. These results suggest that Klotho has therapeutic potential in CNI-induced nephrotoxicity.

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TH-PO270

Discrepant Effect of Metformin on Hyperglycemia in Rats with Tacrolimus- or Sirolimus-Induced Diabetes Mellitus

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Background: Metformin is the first choice used drug in the treatment of diabetes mellitus. However, the effect of metformin on immunosuppressant-induced hyperglycemia is not well known. In this in vivo study, we aimed to investigate the effects of metformin in tacrolimus- or sirolimus-induced diabetes mellitus.

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

Underline represents presenting author.
Methods: Six groups of Sprague-Dawley rats were studied: animals received tacrolimus (1 mg/kg or 0.5 mg/kg of body weight), metformin (200 mg/kg) or vehicle (0.9% NaCl) treatment. Body weight, water intake, and urine volume were measured before sacrifice. The effect of metformin on tacrolimus or sirolimus-induced hyperglycemia was evaluated by assessing intraperitoneal glucose tolerance test (IPGTT), islet size, and insulin level. For further analysis, isolated islet from normal rats were treated with tacrolimus (30 ng/ml) or sirolimus (90 ng/ml) and metformin (165 ng/ml) for 12 hr, then glucose stimulated insulin secretion (GSIS) were performed.

Results: After four weeks, tacrolimus or sirolimus-treated animals showed decreased body weight and increased water intake and urine volume compared with vehicle group. Treatment with tacrolimus or sirolimus caused elevated blood glucose level and reduced serum insulin level. Islet size by measuring insulin-positive area was significantly decreased in tacrolimus or sirolimus-treated group. Combined treatment of metformin did not improve tacrolimus-induced blood glucose level. On the other hand, metformin recovered these value compared with the sirolimus alone. In vitro study of GSIS, combined treatment with metformin and tacrolimus showed a reduction in insulin secretion ability compared with tacrolimus alone. But, sirolimus and metformin-treated group showed higher level of insulin secretion than sirolimus alone.

Conclusions: In this study, we found that metformin confers to the insulin secretion capacity during sirolimus treatment, but not in tacrolimus treatment. Therefore, use of metformin should be considered in transplant recipients receiving tacrolimus.

Funding: Government Support - Non-U.S.

TH-PO272

Use of D-Lactate for Therapeutic Immunosuppression

Ulf H. Beier, Zhonglin Wang, Wayne W. Hancock, Matthew H. Levine


Background: Current immunosuppressive therapies are limited by non-specificity and toxicity. Lactic acid is a carboxylic acid present as L- and D- optical isomers. In mammals including humans, lactate is present almost entirely as L-lactate. L-lactate can accumulate under conditions of ischemia and/or Warburg metabolism, and suppress T cell function.

Methods: We hypothesized that since D-lactate is more slowly eliminated than L-lactate. L-lactate, it may have immune modulatory effects similar to L-lactate that may be exploited for therapeutic immunosuppression, and tested both optical isomers in vitro and in vivo.

Results: We observed that while both D- and L-lactate (5-40 mM) markedly impaired murine and human CD4 and CD8 T cell proliferation in vitro, D-lactate had stronger effects than L-lactate. Neither D- nor L-lactate affected cell viability and apoptosis (7AAD, annexin V), and L- and IFN-γ cytokine production by CD4 and CD8 T cells were unaffected. However, adding 20 mM D-lactate to CD4/CD25-Foxp3- T-Fector cells (Teff) under polarizing conditions augmented T-Fector Foxp3+ Treg induction. Our data suggests that use of specific, defined metabolites may have important therapeutic value as novel immunosuppressive agents.

Funding: Other NIH Support - NIAID

TH-PO273

Environment and Graft Interaction Impact on Endothelium After Experimental Kidney Transplantation

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Background: At transplantation (TX) into a CKD recipient, the donor’s endothelium is exposed to uremic and oxidative stress that may negatively influence graft function and structure. We hypothesized that in CKD milieu, graft endothelial damage is determined by the uremic and oxidative stress until intrinsic or acquired injury. We also investigated whether healthy environment halts progressive endothelial loss in expanded criteria donor (ECD) graft.

Methods: Male inbred Lewis rats were used as donors and recipients. CKD developed in 7 weeks after bilateral ablation of 2/3 of kidney mass. Control rats (n=24) were age-matched. Orthotopic TX was performed: healthy kidney to healthy rat (HD-HR); CKD kidney to healthy rat (CD-HR); healthy kidney to CKD rat (HD-CR); CKD kidney to CKD rat (CD-CR). Right donor kidney served as reference for left graft (graft injury) at TX. Contralateral kidney of recipient was removed 10-14 days after TX. At wk 6, we evaluated graft function and morphology, and systemic oxidative (TBARS) and vascular damage (aorta calcification).

Results: Graft function (mullin & PAH clearance) at wk 6 after TX confirmed improved after and was not affected by environment (CD-HR vs. CD-CR and HD-CR vs. HD-HR, all NS). TX of healthy vs. CKD graft did not influence oxidative and vascular damage at wk 6 postTX (CD-HR vs. HD-HR and CD-CR vs. CD-CR, both NS). Grafts from healthy donors developed more glomerulosclerosis (GS) and tubulointerstitial injury (Tl), but did not show reduction in chronic allograft and interstitial endothelial cell loss (IG12 stain) compared to reference kidneys after TX in a CKD donor (all P>0.05). However, despite similar ischemia-reperfusion, TS and GS did not worsen in ECD grafts and TX of ECD grafts in healthy recipients did preserve glomerular and interstitial endothelium.

Conclusions: TX to CKD environment was less detrimental for ECD graft as shown by preserved endothelium compared to healthy graft, possibly due to preconditioning. In the reverse model, healthy environment halted progression of endothelial damage in ECD grafts. Thus, depending on environment, ECD grafts appear to maintain their structure.

TH-PO274

Heparan Sulfate in the Glyocalyx of Donor Renal Allografts Modulates Transplant Rejection

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Background: The molecular mechanisms underlying transplant allograft vasculopathy and chronic rejection are not fully elucidated. Glycosaminoglycans (GAGs) modulate inflammatory cell responses and Heparan sulfate (HS) is the predominant GAG in the vasculature. Binding to GAGs plays an important role in the function of chemokines. The role of donor heparan GAGs in renal transplant rejection is not well defined. In these studies, we investigated the effects of selective HS deficiency and interference with HS-chemokine interaction on renal allograft rejection in the mouse.

Methods: Donor renal allografts from C57BL/6 (WT) or Ndst1-/- mice were transplanted into Balb/C mice and then treated with either saline (control) or MT7. Results: Compared to the WT, the Ndst1-/- donor renal allografts had significantly reduced scores for lesions induced by rejection including infiltrates, tubulitis, peritubular cuffing, glomerulitis, vascularitis and mesangial matrix. M-T7 treatment of WT donor renal allografts significantly reduced the histologic markers of rejection. However, the M-T7 mediated decrease in rejection was not observed in the Ndst1-/- donor allografts.

Conclusions: Donor renal allografts, deficient in endothelial glyocalyx HS, reduces renal rejection. Although M-T7 reduced rejection in WT donor renal allografts, M-T7 treatment in Ndst1-/- donor renal allografts is inactive, and negates the reduction of rejection mediated by the Ndst1-/- donors. Donor kidney HS and HS/chemokine interactions may have a major role in reducing allograft rejection.

TH-PO275

Identification of Key Meta-Signatures Associated with Acute Rejection Post Kidney Transplant

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Background: Acute rejection (AR) is a major contributor to chronic allograft dysfunction and graft failure. Kidney biopsy expression datasets to identify key meta-signatures associated with acute rejection and the key drivers were validated in independent expression datasets of kidney transplant and kidney diseases.

Methods: Meta-analysis and Bayesian network analysis were performed on 6 kidney biopsy expression datasets to identify key meta-signatures associated with acute rejection and the key drivers that use of specific, defined metabolites may have important therapeutic value as novel immunosuppressive agents.

Funding: Other NIH Support - NIAID

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

Underline represents presenting author.
protein kinase cascade and NFkB signaling pathways were upregulated, while genes involved in cell cycle and DNA repair were downregulated. The expression data of metenkephalin was used to build a meta-expression network from which functional submodules were identified. 14 key driver genes were subsequently derived from these network submodules that had differential connectivity in AR compared to no AR patients. The differential modules and key differential genes themselves significantly correlated with HLA antibody and graft survival.

Finally, the differential expression of key drivers was validated in independent expression datasets from kidney transplants (N=839) as well as other kidney diseases (IgA and Diabetic nephropathy and Lupus nephritis).

Conclusion: We identified a set of AR-associated key drivers that may play a common and pivotal role for driving the inflammatory responses in acute rejection in kidney transplantation as well as other kidney diseases, which will help the better understanding of molecular mechanism of acute rejection post transplant and therefore improve the early diagnosis/treatment of acute rejection to prevent renal failure.

Funding: NIDDK Support

TH-PO276

SNPs ofSolvent Carrier Family Genes Associated with Acute Renal Allograft Rejection in Korean Population By Soonho Kim, Yeong Hoon Kim, Simg ho Loe, Sunwoo Kang.

Background: Solvent carrier family genes are often associated with acute rejection of kidney transplantation (KT) in Korean population. This study sought to investigate whether polymorphisms of solute carrier family genes are involved in the development of acute renal allograft rejection.

Methods: We firstly selected 349 solvent carrier family genes in NCBI gene database and searched the nonsynonymous SNPs on coding region in each gene. Finally we selected 420 common SNPs. The expression of these SNPs were performed using Affymetrix genome wide human assay. SNPStats and SPSS 18.0 were used for the analysis of genetic data. Logistic regression models were performed to determine odds ratio (OR), 95% confidence interval (CI), and P value.

Results: A total of 96 renal allograft recipients transplanted in Pusan Paik hospital. Acute rejection developed in 49 patients among them. Among 420 SNPs of 349 solvent carrier family genes, three genes (rs5306 in SLC4A1, rs11643718 in SLC12A3, and rs1047099 in SLCO4A1) only showed significant association with acute rejection (p<0.05).

Conclusions: These results suggest that significant SNPs (rs5306 in SLC4A1, rs11643718 in SLC12A3, and rs1047099 in SLCO4A1) may be associated with the susceptibility to the acute rejection in the KT patients of Korean population.

Funding: Clinical Revenue Support

TH-PO277

The Expression and Role of Human Cytomegalovirus-Induced Viral Chemokine Receptor US28 in Smooth Muscle Cells of Renal Allografts Wouter Loffinga, Raymond H. De Wit, Gwenda F. Vasse, Afsar Rahbar, Amelie Riebesz-brilman, Cecilia Süderberg-naaucer, Willem Van Son, Johanna van de Klashorst, Kaan van der Steen, Jacob van den Born.

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Background: Renal transplantation is the preferred treatment for end-stage renal disease. Human cytomegalovirus (HCMV) infection is associated with decreased renal graft function and survival. HCMV expresses US28, a chemokine receptor that enables HCMV to escape immune surveillance and affect microenvironment in the graft. Our aim was to localize the expression of US28 in renal biopsies and determine its effect on viral dissemination in vitro.

Methods: US28 and immediate early antigen (IEA) expression was semi-quantitatively scored in recipient renal transplant biopsies (n=49) from HCMV-seropositive donors. Expression in glomerular, endothelial, smooth muscle cells, epithelium and inflammatory infiltrates was analyzed. Primary vascular smooth muscle cells were infected (MOI 0.01) with HCMV WT and US28-deficient HCMV (US28) carrying a GFP-tag, to follow viral dissemination in vitro.

Results: IEA was uniformly distributed over the renal compartments. US28 was expressed during active infection and latency. It was expressed in all compartments, but prevalent (Kruskal-Wallis; P<0.001) in vascular smooth muscle (42% cells positive) and tubular epithelial cells (30%). It was also expressed in the neointima. Smooth muscle cells were permissive to HCMV and underwent lytic infection in vitro, but dissemination was delayed for US28-deficient HCMV.

Conclusions: In short, HCMV-induced US28 is expressed in smooth muscle cells of renal allografts. US28 expression here suggests a role in vascular disease following viral infection, especially given its presence in the neointima. Absence of US28 decreased HCMV dissemination in smooth muscle cells in vitro, yielding it an interesting target for intervention. The observation that HCMV may interfere with vascular function through the expression of chemokine receptor US28 is an intriguing finding worth further exploring.

TH-PO278


Background: Connective tissue growth factor (CTGF), a member of the CCN gene family, is an extracellular matrix (ECM)-associated heparin-binding protein involved in matrix production. CTGF has been shown to contribute to progression of fibro-proliferative diseases by modifying proliferation, migration, and adhesion of fibroblasts. CTGF has also been shown to play a role in ECM remodeling in normal physiological processes including embryogenesis, implantation, and wound healing. However recent new insights into the pathogenesis of fibrosing kidney diseases lead us to re-evaluate CTGF in the context of a cellular level. Here we therefore generated a mouse model expressing CTGF in a tissue specific, conditional over-expression of CTGF using homologous recombination.

Methods: We generated mice conditionally over expressing CTGF in pericytes only. We cloned domains of CTGF and the WNT inhibitor Dkk1 and tested their function on primary mesenchymal cultures.

Results: Overexpression of CTGF in pericytes has no impact on nephrogenesis or adult homeostasis but amplifies fibrogenic and inflammatory responses to kidney disease. CTGF domain IV activates Wnt/b-catenin signaling in pericytes, which is inhibited by recombinant Dkk1. CTGF Dom IV rapidly phosphorylates the co-receptor of Wnt/b-catenin signaling - LRP6. Dkk1-1 blocks CTGF domain IV mediated fibrotic responses in culture including fibroctic gene activation, pericyte morphology changes and migration in JNK MAP kinase dependent, WNT partially dependent pathway. CTG Dom 1 also activates pericyte migration which is also inhibited by DKK-JNK inhibition or Wnt ligand secretion.

Conclusions: CTGF over expression restricted to kidney stroma in vivo is sufficient to amplify cell activation and myofibroblast transition. Multiple domains of CTGF drive fibrogenic responses in pericytes as well as WNT and JNK signaling pathways.

Funding: Pharmaceutical Company Support - Bioenergetics

TH-PO279

Spingosine Kinase 2 Mediates Kidney Fibrosis Through Epigenetic Change Tsvoshi Inoue, Amandeep Bajwa, Heather M. Perry, Liping Huang, Hong Ye, Youichiro Wada, Diane L. Rosin, Mark D. Okusa, Univ of Virginia; The Univ of Tokyo.

Background: In numerous forms of organ injury, interstitial fibrosis is a final common pathway. Despite recent epidemiological studies, therapies to focus on fibrosis and to delay progressive renal failure are limited. We recently found that spingosine kinase 2 deficient-mice (SphK2KO) develop less fibrosis after folic acid (FA) - or ischemia-reperfusion-induced kidney injury. Spingosine 1-phosphate (SIP) is produced by two spingosine kinase isoforms (SphK1 and SphK2). SIP is involved in diverse functions, but the role of SIP produced by Spk2 is gathering attention as treatments focused on epigenetics have been developed. Sphk2 is primarily located in the nucleus, Sphk1 is cytoplasmic. Sip produced by Spk2 inhibits histone deacetylase (HDAC) and change in histone acetylation status, which can lead to an altered target gene expression. The aim of this study is to elucidate new mechanisms of kidney fibrosis through epigenetic changes.

Methods: Transcriptome analysis and ChiP-seq of H3K9ac and H3K27ac using primary renal tubular epithelial cells (SPL) were performed to find new target genes that regulate fibrosis through histone acetylation.

Results: Microarray analysis identified 135 down-regulated (<1/4) genes and 245 up-regulated (>4) genes in Sphk2 KO compared to Sphk1 KO mice. ChiP-seq (QuEST) revealed that 258 genes have H3K27ac and 589 genes have H3K9ac only in Sphk1 KO and not in Sphk2 KO. The combination of microarray and ChiP-seq analysis yielded 21 candidate genes. To determine the in vivo relevance of gene expression was evaluated using an in vivo fibrosis model (FA model and unilateral IR). We further applied Sphk2 knock down to WT fibroblasts and overexpression to fibroblasts from Sphk2KO to determine if the selected genes are regulated by Sphk2. Based on these strategies, candidate genes were identified that are regulated by Sphk2 through the change of histone acetylation.

Conclusions: The combination of microarray and ChiP-seq of H3K9ac and H3K27ac identified 21 candidate genes. A more detailed investigation is needed, but some genes regulated by Sphk2 appear to modulate kidney fibrosis through epigenetic changes.

TH-PO280

MCP-1 Directly Induces Renal Tubulointerstitial Fibrosis Independently of Monocytes/Macrophages Infiltration Meiran Wai, Hye-Young Kang, Mi Jung Lee, Shin-Wook Kang. Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Previous studies have demonstrated the importance of monocyte chemoattractant protein-1 (MCP-1) and its receptor, C-C chemokine receptor 2 (CCR2), in the pathogenesis of tubulointerstitial fibrosis via the recruitment and activation of monocytes/macrophages. However, recent in vitro evidence has suggested that MCP-1 may act directly on renal cells via CCR2. Therefore, the results of a number of former studies showing the impacts of MCP-1/CCR2 blockade on renal injury may be partly attributed to a direct inhibitory effect of MCP-1 on renal cells that have not been clarified in vivo to date.

Methods: Monocyte/macrophage-deficient mice were induced by either liposomes-clodronate or diphtheria toxin. These mice were treated with MCP-1 expressing lentivirus (LV) and/or RS102895, a specific inhibitor of CCR2. NRK-52E cells were treated with
recombinant MCP-1 or with or without RS102895, or CCR2 siRNA. The mRNA and protein expression of fibronectin and type I collagen in cultured NRK-52E cells and the whole kidney were evaluated by Western blot and real-time PCR.

Results: Fibronectin and type I collagen expressions were increased in NRK-52E cells exposed to MCP-1, which was then significantly abrogated by co-administration with RS102895 or CCR2 siRNA. LV-MCP-1 transfection in mice (n=6) resulted in significant increases in infiltrated macrophages, fibronectin, and type I collagen mRNA and protein expression in the kidney. However, LV-MCP-1 transfection in monocytic/macrophage-deficient mice (n=6) resulted in increases in fibronectin and type I collagen mRNA and protein expression in the kidney. This indicates that macrophage infiltration is crucial for the observed increases in fibronectin and type I collagen mRNA and protein expression.

Conclusions: The MCP-1/CCR2 system is directly involved in MCP-1-induced renal fibrosis. Blockade of the MCP-1/CCR2 system can be a promising approach to treat various kidney diseases such as diabetic nephropathy, of which MCP-1-induced renal fibrosis is involved in the pathogenesis.

TH-PO281

T-Type Calcium Channel Blocker Attenuates Unilateral Ureteral Obstruction-Induced Renal Inflammation and Fibrosis via Activation of the Nrf2 Antioxidant Pathway


Background: Besides the effect on high blood pressure, T-type calcium channel blocker has been reported to exert a renoprotective effect in experimental models with renal fibrosis. However, the exact mechanism of T-type calcium channel blocker on tubulointerstitial fibrosis has not been elucidated. In the present study, we investigated whether the renoprotective effect of T-type calcium channel blocker is associated with modulation of the signaling of oxidative stress-induced renal fibrosis.

Methods: Treatment with a nonhypotensive dose of efonidipine, a T-type calcium channel blocker, or an L-type calcium channel blocker, was initiated one day before unilateral ureteral obstruction (UUO) in C57BL/6j mice, and was continued until 3 and 7 days after UUO. Markers of renal fibrosis, inflammation, apoptosis and oxidative stress were evaluated.

Results: In the obstructed kidneys of UUO mice, treatment with efonidipine significantly attenuated interstitial fibrosis, collagen deposition and inflammation increased by UUO creation compared with treatment with nifedipine. Efonidipine significantly increased the expression of antioxidant enzymes such as HO-1, NQO1, catalase and SOD1. Increased apoptotic cell death and decreased Bcl-2 expression in the obstructed kidneys were also significantly ameliorated by treatment with efonidipine. The expression of the histone acetyltransferase p300/CBP-associated factor, which is known as a regulator of inflammatory molecules, was significantly inhibited by efonidipine. These beneficial effects of efonidipine were attributed to the increased nuclear expression of Nrf2 on UUO day 3 and the increased expressions of both total and nuclear Nrf2 with elevated Keap1 on UUO day 7, suggesting that efonidipine would promote activation of Nrf2 differently depending time course after UUO. Nifedipine had little effect on antioxidant enzymes, anti-apoptosis and Nrf2 signaling.

Conclusions: These results suggest that T-type calcium channel blocker exerts beneficial effects in renal interstitial fibrosis by activating Nrf2 and subsequent antioxidant enzymes.

TH-PO282

Fimasartan, the Novel Angiotensin Receptor Antagonist, Protects against Renal Inflammation and Fibrosis in Mice with Unilateral Ureteral Obstruction: A Possible Role of Nrf2

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Background: A newly developed angiotensin II receptor blocker, fimasartan, has effective blood pressure lowering effect via blocking renin-angiotensin system. Renal interstitial fibrosis is a final pathological process in the progression of chronic kidney disease, which is believed to be due to oxidative injury. Transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2) is known to regulate cellular oxidative stress and induce antioxidant genes. This study investigated the role of Nrf2 in fimasartan-mediated antioxidant effects in mice with renal fibrosis induced by unilateral ureteral obstruction (UUO).

Methods: Fimasartan was administered intraperitoneally (3mg/kg/day) from the day of UUO surgery in C57BL/6 mice and was continued for 7 days after operation.

Results: UUO-operated mice revealed renal inflammation and fibrosis as evidenced by the degree of fibrosis and inflammatory cell infiltration in histopathological findings, total collagen content in kidney tissues and the expression of fibrotic markers in immunoblot analysis, which were reversed in the obstructed kidneys of fimasartan-treated mice. Fimasartan treatment upregulated renal expression of Nrf2 and its downstream signaling molecules such as NQO1, HO-1, Nos 1, 2 and 4, GSTm2 and GSTT3 in both protein and mRNA levels. Furthermore, fimasartan increased the expression of antioxidant enzymes including CuSOD, MnSOD and catalase. Significantly less apoptosis in TUNEL staining, decreased pro-apoptotic protein, along with increased anti-apoptotic protein were observed in fimasartan-treated mice.

Conclusions: In conclusion, these results demonstrate that fimasartan has beneficial effects on renal oxidative stress, inflammation and fibrosis, which may be via upregulating of Nrf2 signaling, subsequently the induction of antioxidant pathways.

TH-PO283

The Na/K-ATPase Signaling and Oxidative Stress Contribute to PNx-Mediated Cardiac and Renal Fibrosis in Mice

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Background: We have shown that the Na/K-ATPase signaling regulates cardiac and renal fibrosis both in vivo and in vitro. We have also demonstrated that increases in oxidative stress activate Na/K-ATPase signaling. Here we report that administration of CoPP (an inducer of hemox gene expression-1, HO-1) and nPKide (a Na/K-ATPase signaling antagonist) attenuate 5/6 renal partial nephrectomy (PNx) mediated fibrosis in heart and kidney in C57BL/6j mice.

Methods: The C57BL/6j mice were randomly divided into six experimental groups. (1) Sham surgery (Sham), (2) PNx surgery (PNx), (3) Sham+CoPP, (4) PNx+CoPP, (5) Sham + nPKide, and (6) PNx+nPKide. CoPP (5mg/KG BW, ip) was given 5 day and one day before surgery as well as every 5 day after PNx surgery. nPKide (25mg/KG BW, ip) was given weekly 7days after surgery. All experimental mice were sacrificed 4 weeks after PNx surgery. Expression of collagen-1, HO-1, and protein carbonylation of heart and kidney was determined by western blot.

Results: Comparing with sham, PNx surgery significantly stimulates type 1 collagen expression both in heart and kidney assayed by western blot and histology analyses. Induction of HO-1 by CoPP significantly attenuates PNx-mediated collagen production and protein carbonylation. Administration of nPKide, which blocks Na/K-ATPase-mediated eNOS activation, also attenuates PNx-mediated collagen production. Theranostic PET/CT imaging analysis demonstrates that treatment with CoPP and nPKide restores PNx-induced changes in relatively wall thickness (RWT) and myocardial performance index (MPI).

Conclusions: Attenuating oxidative stress and blocking Na/K-ATPase signaling is capable of restoring PNx-mediated cardiac and renal fibrosis as well as cardiac function.

TH-PO284

Wnt4 Induces Renal Fibrosis by Activating p38 Mitogen-Activated Protein Kinase Pathway

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Background: Previous studies demonstrated that Wnt signaling pathway plays a key role in the pathogenesis of renal fibrosis and is related to various kidney diseases. However, although Wnt4 is abundantly expressed in renal tubule cells, the roles of these specific Wnt subfamilies in the pathogenesis of renal fibrosis have not been fully explored. Therefore, this study examined the effect of Wnt4 on renal tubulointerstitial fibrosis via p38 MAPK signaling.

Methods: In vivo, UUO was performed in C57BL/6 mice (n=12). The kidneys were harvested after 6 days of UUO. Immunohistochemistry was conducted with renal tissues. In vitro, renal proximal tubular cells (NRK-52E) and inner medullary collecting duct cells (IMCD) were each treated with recombinant TGF-β1 (with or without Wnt4 siRNA transfection). The effect of recombinant Wnt4 protein treatment was also examined in NRK-52E and IMCD cells. Real-time PCR and Western blot analysis were performed to evaluate Wnt4, fibronectin (FN), collagen type 1 (Col I), α-SMA, phos-p38 and p38.

Results: Wnt4 induced fibrosis in renal tubule (NRK-52E) and IMCD cells. Furthermore, in NRK-52E treated cells, the roles of these specific Wnt subfamilies in the pathogenesis of renal fibrosis have not been fully explored. Therefore, this study examined the effect of Wnt4 on renal tubulointerstitial fibrosis via p38 MAPK signaling.

Conclusions: These findings suggest that Wnt4 may play a role in renal tubulointerstitial fibrosis by activating the p38 MAPK pathway.

TH-PO285

Peroxiredoxin 5 Protects TGF-β1 Induced Renal Fibrosis by Modulating Stat3 Activation

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Background: Renal fibrosis is a common final pathway of end-stage kidney diseases which is induced by aberrant accumulation of myofibroblasts. This process is triggered by reactive oxygen species (ROS) and proinflammatory cytokines generated by various source of injured kidney cells. Peroxiredoxin 5 (Prdx5) is a thiol-dependent peroxidase that reduces reactive oxygen species (ROS) and proinflammatory cytokines generated by various source of injured kidney cells. However, physiological effects of Prdx5 in renal fibrosis have not been fully characterized and the underlying mechanisms remain poorly understood.

Results: UUO-operated mice revealed renal inflammation and fibrosis as evidenced by the degree of fibrosis and inflammatory cell infiltration in histopathological findings, total collagen content in kidney tissues and the expression of fibrotic markers in immunoblot analysis, which were reversed in the obstructed kidneys of fimasartan-treated mice. Fimasartan treatment upregulated renal expression of Nrf2 and its downstream signaling molecules such as NQO1, HO-1, Nos 1, 2 and 4, GSTm2 and GSTT3 in both protein and mRNA levels. Furthermore, fimasartan increased the expression of antioxidant enzymes including CuSOD, MnSOD and catalase. Significantly less apoptosis in TUNEL staining, decreased pro-apoptotic protein, along with increased anti-apoptotic protein were observed in fimasartan-treated mice.

Conclusions: In conclusion, these results demonstrate that fimasartan has beneficial effects on renal oxidative stress, inflammation and fibrosis, which may be via upregulating of Nrf2 signaling, subsequently the induction of antioxidant pathways.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Methods: As in vivo and in vitro model of renal fibrosis, Sprague-Dawley rats were subjected to unilateral ureteral obstruction (UUO) for 1 or 7 days. Fibroblast-like rat proximal tubule cells (NRK-49F) were treated with transforming growth factor β (TGF-β) for 0, 1, 3, or 5 days. To access the involvement of its peroxidase activity in TGF-β-induced renal fibrosis, wild type Prdx5 (WT) and double mutant Prdx5 (DM), converted two active site cysteines at Cys 48 and Cys 152 residue to serine, were transiently expressed in NRK-49F cells.

Results: The protein expression of Prdx5 was reduced in UUO kidneys. Upregulation of fibrotic markers, such as fibronectin, vimentin, and alpha-smooth muscle actin (α-SMA), were delayed in NRK-52E cells to caused the pathological conditions in GN.

Conclusions: In summary, fucoidan at adequate doses inhibits pressure-induced fibrotic responses in rat renal tubular cells. The investigation of the protective effect of fucoidan against renal fibrosis may provide a new therapeutic agent for CKD patients.

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TH-PO288

Fucoidan reduces Pressure-Induced Fibrotic Responses in Renal Tubular Cells Through Down-Regulating β-Catenin

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Background: Fucoidan is a kind of natural fucose-enriched sulfated polysaccharides found mainly in various species of brown algae and brown seaweed. In recent years, many studies show fucoidan reduces hypoxia nephropathy, and also inhibits liver fibrosis. However, the influence of fucoidan on renal fibrosis is not clear yet.

Methods: Rat renal tubular cells (NRK-52E) are applied in this study. We study the influence of low-molecular-weight fucoidan (50 Da) on renal fibrosis in a pressure-stressed cell model. Sixty mmHg of pressure will be applied on NRK-52E cells for different periods to induce EMT. The expression of EMT markers and β-catenin will be monitored by Western blotting.

Results: NRK-52E cells were subjected to 60 mmHg of pressure for the indicated periods. Cellular E-cadherin, TGF-β, CTGF, fibronectin, α-SMA and Snail were detected by Western blotting. We found sixty mmHg of pressure induces EMT markers expression in NRK-52E cells. Fucoidan (0.1 – 1 mg/ml) reduced pressure-induced α-SMA and fibronectin (NRF-52E cells). Fucoidan reduced pressure-induced CD44 and β-catenin, which may be a critical mechanism of anti-fibrosis effect of fucoidan. NRK-52E cells were pretreated with fucoidan for 30 min and then treated with TGF-β for 4 h. We found fucoidan could reduced TGF-β-induced α-SMA and fibronectin in NRK-52E cells.

Conclusions: In summary, fucoidan at adequate doses inhibits pressure-induced fibrotic responses in rat renal tubular cells. The investigation of the protective effect of fucoidan against renal fibrosis may provide a new therapeutic agent for CKD patients.

Funding: Government Support - Non-U.S.

TH-PO287

Indoxyl Sulfate Exacerbates Oxidative Stress and Impairs NF-κB/Nrf2 Levels in RAW Macrophages

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Background: Indoxyl sulfate (IS), a uremic toxin produced by intestinal bacterias, is accumulated in Chronic Kidney Disease (CKD) patients and exhibits potent inflammatory effects. However, no informed scientific evidence has evaluated the effects of this toxin on nuclear E2-related factor 2 (Nrf2) and nuclear factor-kB (NFkB) expression, which modulating Stat3 activation in a peroxidase activity dependent manner.

Methods: We evaluated the influence of IS in Nrf2, NF-κB and malondialdehyde (MDA) levels in RAW macrophages. We found sixty mmHg of pressure induces EMT markers expression in RAW macrophages. We found fucoidan at adequate doses inhibits pressure-induced fibrotic responses in rat renal tubular cells. The investigation of the protective effect of fucoidan against renal fibrosis may provide a new therapeutic agent for CKD patients.

Funding: Government Support - Non-U.S.
PKR in MSU mediated tubular cell inflammasome complex has not been investigated. We hypothesized that MSU triggers PKR pathway to activate NLRP3 inflammasomes in tubulointerstitial fibrosis.

**Methods:** Human renal proximal tubular cells (HRPTCs) were incubated with MSU (100 μg/ml) for either 24 or 48 hours and assayed for pyroptosis by a morphologic assay (through staining with H3342 and propidium iodide). To determine the involved mechanical protein blots of HRPTCs treated with MSU (100 μg/ml) for 48 hrs were probed for PKR and actin. Total RNA was extracted from HRPTCs treated under similar conditions and cDNAs were amplified with specific primers. To establish causal relationship between caspase-1 activation and pyroptosis, HRPTCs were pulsed with MSU in the presence or absence of caspase-1 inhibitor and then assayed for pyroptosis. To establish a causal relationship between NLRP3 mediated induction of K-efflux and inflammasome formation, HRPTCs were treated with MSU with or without glyburide.

**Results:** MSU exposure enhanced tubular cell pyroptosis. MSU promoted transcription of NLRP3, caspase-1, -3 and -1. MSU exposure augmented protein expression of PKR, NLRP3, -1β and caspase-1. MSU-induced pyroptosis was attenuated by caspase-1 inhibitor. Glyburide treatment showed downregulation of NLRP3, caspase-1 and -1β expressions in MSU treated HRPTCs.

**Conclusions:** MSU activates PKR which leads to NLRP3 inflammasome activation and pyroptosis in HRPTCs.

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**TH-PO290**

Hyperglycemia-Induced NLRP3 Inflammasome Formation Contributes to Podocyte Dedifferentiation via IL-1β and p38

**Background:** NLRP3 inflammasomes have been reported to play a role in hyperglycemia associated morbidities including diabetic nephropathy. Functionally active inflammasome pathway promotes the maturation of proinflammatory cytokines such as IL-1β and IL-18. We hypothesized that hyperglycemia induced NLRP3 inflammasome complexes would down regulate p38 pathway through the generation of IL-1β. These interactions would lead to dedifferentiation of podocytes in high glucose milieu.

**Methods:** Human podocytes (HPs) were incubated in media containing either control (CH-IP) or high glucose (35 mM, HG/IP) for variable time periods. High glucose (HG) and normal glucose (NG) conditioned media (CM) were collected. Total RNA was extracted from cellular lysates and cDNAs were amplified with specific primers for inflammasome molecular markers (IMMs, NLRP3, ASC, caspase-1, IL-1β, and IL-18). Protein blots of CH- and HG/IP treated HPs were used to examine protein expression regulatory mechanism and actin. To establish a causal relationship between HG and IMMs, HPs were incubated in media with or without HG in the presence or absence of caspase-1 inhibitor/glyburide (K-efflux inhibitor) for 48 hours followed by mRNA and protein analysis for IMMs. Effects of IL-1β alone and HG-CM were examined on podocyte dedifferentiation (loss of podocyte markers- nephrin and synaptopodin by Western blot analysis and immunolabeling).

**Results:** HG upregulated mRNA and protein expressions of NLRP3, caspase-1, -3 and -1β in HPs. Both caspase-1 inhibitor and glyburide inhibited mRNA and protein expression of IMMs in HG/IP. HG-CM not only downregulated p35 mRNA transcription but also induced dedifferentiation in HPs in the form of attenuated expression of nephrin and synaptopodin. IL-1β downregulated p35 mRNA and synaptopodin expressions in HPs.

**Conclusions:** Hyperglycemia induces dedifferentiation of HPs through inflammasome formation and downregulation of p35.

**Funding:** NIDDK Support

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**TH-PO291**

Human Renal Proximal Tubular Epithelial Cells: Effects of Primary Cilia Loss on Epithelial Phenotype and Function

**Background:** The primary cilium is a hair-like microtubule based structure, protruding from nearly all mammalian cells. Originally thought to be a vestigial organelle, it is now well established as a crucial signalling hub. The importance of the primary cilium in cell signalling has become clear with a range of diseases associated with its loss (ciliopathies). The primary cilium is a well established as a crucial signalling hub. The importance of the primary cilium in cell signalling has become clear with a range of diseases associated with its loss (ciliopathies).

**Methods:** Deciliating agents were used to induce loss of the primary cilium. Immunofluorescent labelling of the ciliary marker acetylated α-tubulin was used to detect the primary cilium in the RPTEC/TERT1 cells. Western blotting was used to assess epithelial marker expression and tight junction protein expression. Trans-epithelial electrical resistance (TEER) was measured to assess epithelial barrier function following cilia loss.

**Results:** Removal of cilia using deciliating agents was confirmed by acetylated α-tubulin staining. Deciliation was found to cause alteration of tight junction protein expression, in particular claudin family members. Cilia loss caused an increase in TEER, suggesting a decrease in tight junction permeability and a change in epithelial barrier function following deciliation.

**Conclusions:** Results suggest an altering of epithelial cell junctions and barrier function following deciliation. Further analysis is being carried out to understand the relationship between the primary cilium and the maintenance of an epithelial phenotype and function.

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**TH-PO292**

Development of a Novel Human Renal Proximal Tubule Epithelial Cell Culture Model That Retains Robust Mitochondrial Respiratory Capacity, and Critical In Vivo Renal Functional Attributes

**Background:** Renal mitochondrial dysfunction and oxidative stress are implicated in diabetic kidney disease, acute kidney injury, and the progression of chronic kidney disease. The renal proximal tubule is a mitochondria-rich nephron segment that relies on oxidative phosphorylation to carry out its multiple, metabolically demanding absorptive and buffering functions. However, mechanistic investigation of proximal tubule mitochondria in cell culture systems in vitro is challenging because available immortal proximal tubule epithelial cells exhibit a transformed, glycolytic metabolism concomitant with loss of key functional parameters.

**Methods:** In this study, primary human renal proximal tubule epithelial cells (PTEC’s) were immortalized (iPTEC) by retroviral transduction with hTERT and papilloma virus. To test their utility as a cell culture model of in vivo kidney function, we evaluated iPTEC’s for retention of mitochondrial respiratory capacity and key proximal tubule cell functional attributes.

**Results:** iPTEC’s maintained capacity for mitochondrial respiration and oxidative phosphorylation utilizing several substrates including pyruvate and glutamine. Furthermore, iPTEC’s retained critical proximal tubule functional characteristics, including monolayer formation with expression of E-cadherin, expression of proximal tubule cell transporters, and the ability to perform glomerulonephrosis and amogenicargenesis. iPTEC’s plated on micellc cell culture inserts developed transepithelial potential that was maximal on day 20 and mediated in part by polarized Na/K-ATPase expression in the basolateral membrane.

**Conclusions:** The development of an immortalized iPTEC line with broad retention of in vivo functional attributes, including robust oxidative phosphorylation, will enable the study of mitochondria biology in kidney health and disease.

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**TH-PO293**

Pangenomic Analyses of Hypoxia Inducible Factor (HIF) Pathway Activation in Human Primary Renal Tubular Cells

**Background:** In the kidney, epithelial integrity is crucial for organ function. Ischemic or toxic damage of tubular cells can cause acute kidney injury. Preconditional stabilization of hypoxia inducible factor 1 alpha (HIF-1α) in tubular cells is beneficial in animal models of acute kidney injury. The precise protective mechanisms and the relevance of the HIF system in human kidneys remain unknown. Therefore, the aim of this study was to characterize the hypoxic response and to investigate direct HIF effects in primary human tubular cells.

**Methods:** Healthy human kidney tissue from patients undergoing tumour nephrectomy was used for tissue studies and isolation of primary tubular cells. HIFs were stabilized using hypoxia (1%) or the hypoxia-mimetic dimethyl oxalylglycine. We used genome-wide analyses of open chromatin (FAIRE-seq) and HIF DNA-binding (ChIP-seq) in freshly isolated primary human tubular cells from several individuals to define conserved regulatory DNA elements and HIF-binding sites.

**Results:** Immunohistochexmixtio experiments using human kidney tissue revealed the presence of HIF-1α protein in tubular cells. Co-staining with 1β-hydroxy steroid dehydrogenase localized HIF-1α signals predominantly in the distal convoluted tubule and the collecting duct. Using ChIP-seq we identified over 500 high-stringency HIF-1 binding sites.

**Conclusions:** The importance of the HIF system for cell survival and integrity is well documented for rodent kidneys. We expand analyses of the renal HIF response to human kidneys and identify important mechanisms to potentially preserve tubular function in human kidney disease.

**Funding:** Government Support - Non-U.S.
TH-PO294

The Na-H Exchanger Regulator Factor Isoform 1 is a Critical Determinant of Renal Proximal Tubule Brush Border Composition

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Background: We recently showed that Tamm-Horsfall protein regulates granulopoiesis by inhibiting the expression of IL-23 in S3 segments and the resultant activation of the IL-23/IL-17 axis. The molecular mechanism of this observation is unclear.

Methods: We performed laser micro-dissection (LMD) of S3 segments from THP-/- and THP+/+ kidneys sections followed by 2 Dimensional –Differential Gel Electrophoresis (2D-DIGE) to identify pathways that are modulated by THP in vivo. We also used an unbiased, label free proteomics approach to understand the signaling of THP on human proximal HK-2 cells. Additional experimental methodology is described in Results.

Results: Bioinformatics analysis of differentially expressed proteins in S3 segments dissected from THP-/- compared to THP+/+ kidneys revealed that the free radical scavenging network had the highest score of clustering, suggesting that THP regulates redox balance in S3 segments. Using in vivo reporter dyes and by measuring enzymatic markers of oxidative stress in S3 segments, we observed a 50% decrease in total RNA levels and a near absence of Npx2a mRNA. We hypothesize that NHERF1 plays a defining role in BBM protein expression.

Conclusions: We conclude that the presence of NHERF1 defines renal BBM protein expression through post-transcriptional, trafficking, and anchoring mechanisms.

Funding: NIH Support - NIA, Veterans Administration Support, Clinical Revenue Support

TH-PO295

Tamm-Horsfall Protein (Uromodulin) Regulates IL-23 Expression in S3 Segments by Inhibiting the Rac-1-NOX2 Signaling Pathway of Oxidative Stress

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Background: We recently showed that Tamm-Horsfall protein regulates granulopoiesis by inhibiting the expression of IL-23 in S3 segments and the resultant activation of the IL-23/IL-17 axis. The molecular mechanism of this observation is unclear.

Methods: We performed laser micro-dissection (LMD) of S3 segments from THP-/- and THP+/+ kidneys sections followed by 2 Dimensional –Differential Gel Electrophoresis (2D-DIGE) to identify pathways that are modulated by THP in vivo. We also used an unbiased, label free proteomics approach to understand the signaling of THP on human proximal HK-2 cells. Additional experimental methodology is described in Results.

Results: Bioinformatics analysis of differentially expressed proteins in S3 segments dissected from THP-/- compared to THP+/+ kidneys revealed that the free radical scavenging network had the highest score of clustering, suggesting that THP regulates redox balance in S3 segments. Using in vivo reporter dyes and by measuring enzymatic markers of oxidative stress (OS), we found increased OS in S3 segments from THP-/- compared to THP+/+ kidneys. Label-free proteomic analysis of HK-2 cells revealed that incubation of WT and NHERF1 deficient (KO) mice and measured mRNA expression of selected transport proteins from WT and OK cells.

Results: We identified 148 proteins whose expression was downregulated at least two fold and 78 proteins whose expression was upregulated at least three fold in KO mouse BBM. 14 proteins were absent in KO. Integrity Pathway Analysis demonstrated that 113 of the downregulated proteins were involved in cellular assembly, assembly, function, or maintenance, specifically, microvillus and actin cytoskeleton structure (Shroom4, Fascin), protein trafficking (CLIC1 and 4), signaling (taperin, FGFR2), and repair. Immunohistochemistry of KO kidneys and scanning electron microscopy of OK cell showed no obvious defects in cell structure/polarity. The mRNA levels of Npx2a, SGLT1 and NHE3 in OKH cells were less than 50% of WT but promoter activity of SGLT1 was similar.

Conclusions: We conclude that the presence of NHERF1 defines renal BBM protein expression through post-transcriptional, trafficking, and anchoring mechanisms.

Funding: NIH Support - NIA, Veterans Administration Support, Clinical Revenue Support

TH-PO296

Abstract Withdrawn

TH-PO297

Hydrophobic Motif Site Phosphorylation of Protein Kinase CbetaII by mTORC2 Regulates High Glucose (HG)-Induced Mesangial Cell Hypertrophy

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Background: Protein kinase C beta II (PKCβII) has been implicated in diabetic nephropathy (DN). Mesangial cell (MC) hypertrophy is a pathologic feature of DN. PKCβII translocation to the hydrophobic motif site is regulated by HG in its activity. We have shown that mTOR complex 1 (C1) regulates MC hypertrophy. How activation of PKCβII by HG-660 phosphorylation fits into mTOR signaling to control MC hypertrophy is not known.

Methods: Human MCs, immunoblotting, siRNA and shRNA transfections, protein synthesis assays were used.

Results: HG significantly increased phosphorylation of PKCβII at Ser-660 in a PI 3 kinase-dependent manner. siRNAs against PKCβII, dominant negative PKCβII and nonphosphorylatable mutant of PKCβII, PKCβIII(S660A), blocked mTORC1 activity due to lack of PRAS40 phosphorylation, resulting in significant inhibition of HG-induced MC protein synthesis and hypertrophy. Also, PKCβIII(S660A) attenuated phosphorylation of Akt at Ser-473, a putative mTOR complex 2 (C2) site. Specific inhibition of mTORC2 by siRNAs against rictor or Sm1, two exclusive and required components for its activity, suppressed HG-induced phosphorylation of PKCβII Ser-660, PRAS40 and Akt Ser-473, resulting in attenuation of mTORC1 activity leading to inhibition of MC hypertrophy. Constitutively active (CA) Akt or CA mTORC1 reversed shRictor- or shSm1-mediated inhibition of HG-induced MC hypertrophy. Furthermore, CA PKCβIII reversed the shRictor- or shSm1-induced inhibition of HG-stimulated Akt Ser-473 phosphorylation and MC hypertrophy. Finally, we show increased phosphorylation of PKCβII Ser660, PRAS40 and Akt Ser-473 in association with activation of mTORC1 in renal cortices of OVE26 mice with type 1 diabetes.

Conclusions: These results provide the first evidence that HG-induced activation of mTORC2 phosphotyrosylates and activates PKCβII to increase the phosphorylation of Akt at Ser-473 to finally activate mTORC1 to induce MC hypertrophy. Thus, we uncover a specific role of mTORC2 for Akt/mTORC1 activation via PKCβII Ser-660 phosphorylation.

Funding: NIDDK Support, Veterans Administration Support

TH-PO298

Hyaluronan Mediated Motility Receptor regulates Cell Motility in Glomerular Endothelial Cells in Response to Shear Stress

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Background: Laminar shear stress (SS) is an important determinant of vascular health. The glycocalyx is a carbohydrate-rich layer that covers the endothelial cell surface. Hyaluronan (HA) motility mediated receptor (HMMR) promotes cell motility and invasion through interactions with HA on the cell surface in non-renal cells.

Methods: Human conditionally immortalized glomerular endothelial cells (GEnC) were exposed to SS (10 dyn/cm2) using an orbital rotator for 0, 24, 48 and 72h. Effects on expression of glycocalyx-related genes were analysed using a custom designed focused Taqman qPCR array. HMMR and CD44 (another hyaluronan receptor) and production of HA were measured using ELISA. HA fragments did not increase cell motility on its own. siRNA HMMR knockdown GEnC. HMMR expression was increased in isolated glomeruli from type 1 diabetic mice.

Results: HA on the cell surface in non-renal cells.

Motility assays (scratch assay, 2D chemotaxis and Transwell migration) were performed on GEnC and siRNA HMMR GEnC. HMMR expression was increased in isolated glomeruli from type 1 diabetic mice.

Conclusions: These results provide the first evidence that HG-induced activation of mTORC2 phosphotyrosylates and activates PKCβII to increase the phosphorylation of Akt at Ser-473 to finally activate mTORC1 to induce MC hypertrophy. Thus, we uncover a specific role of mTORC2 for Akt/mTORC1 activation via PKCβII Ser-660 phosphorylation.

Funding: NIDDK Support, Veterans Administration Support

TH-PO299

Cell Surface Expression of TRPC6 in Podocytes Depends on Syndopodin Stability

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Background: TRPC6 gain-of-function mutations and increased TRPC6 expression in podocytes were found in familial FSGS and acquired glomerular diseases. TRPC6 is expressed in syndopodin (synp) rich podocyte yet only a fraction is located on plasma membrane. Modulation of localization and function of TRPC6 harbors potential for treatment.

Results: There was a significant increase in versican expression, peaking at 24h. Thrombomodulin expression significantly increased and reached a plateau within 24h. CD44 expression peaked at 72h of SS. There was a dramatic decline in HMIR expression by 24h of SS (10-fold decrease p<0.0001) and levels remained suppressed over 72h. Furthermore, HMIR recovery to nearly pre-SS level after a period without SS for 24h. LSS increased release of HA into culture medium. What is more, HA fragments increased cell motility where LSS for 24h reduced it. HA fragments did not increase cell motility on siRNA HMIR knockdown GEnC with and without HA fragments. HMIR expression was assessed on freshly isolated and cultured glomeruli.

Conclusions: HMIR is exquisitely shear-sensitive in vivo and ex vivo and acts as a marker for LSS exposure in endothelial cells. Chronic LSS reduces cell motility. Our data suggest this is due to HMIR expression changes and that HMIR is likely to play important roles in glomerular physiology and disease.

Funding: Government Support - Non-U.S.
Methods: Immunogold and co-ip were performed to examine co-localization and interaction of TRPC6 and synpo. Cell surface biotinylation and high-throughput analysis were used for quantitative analysis of cell surface levels of TRPC6. Calcium imaging was performed to measure calcium influx mediated by TRPC6. Glomerular isolation, biotinylation and podocyte enrichment were performed to determine podocyte membrane TRPC6 expression in vivo.

Results: Co-localization of TRPC6 and synpo was observed in podocyte foot processes by immunogold double labeling in mouse kidney. Interaction of the two proteins was observed by co-ip in cultured podocytes and mouse glomeruli. TRPC6 levels on cell surface increased in synpo knockdown podocytes and decreased in synpo overexpressing podocytes. Consistent with the changes in expression levels, calcium influx mediated by TRPC6 was enhanced in synpo knockdown podocytes and reduced in synpo overexpressing podocytes. Mechanistically, we found both actin and microtubule cytoskeletons were involved in regulating membrane TRPC6 expression affected by synpo. Membrane TRPC6 expression in podocytes was elevated upon LPS treatment and was restored by cyclopamine (A CSa) in WT mice. Functionally, CsA treatment significantly reduced LPS proteinuria in WT mice (71%) and to a lesser extent in TRPC6-/- mice (45%).

Conclusions: Synaptopodin limits expression of TRPC6 on podocyte plasma membrane. CsA, a drug that stabilizes synpo, is shown to lower podocyte surface TRPC6 levels upon LPS treatment. The partial benefit of CsA in reducing LPS proteinuria in membrane. CsA, a drug that stabilizes synpo, is shown to lower podocyte surface TRPC6 expression affected by synpo. Membrane TRPC6 expression in podocytes was elevated upon LPS treatment and was restored by cyclopamine (A CSa) in WT mice. Functionally, CsA treatment significantly reduced LPS proteinuria in WT mice (71%) and to a lesser extent in TRPC6-/- mice (45%).

TH-PO300
APOL1 Risk Variants Enhance Podocyte Oxidative Stress Xinjian Lan, Hungxu Wang, Weiwei Malhotra, Karl Leon, Corrado, Pravin C. Singhal, Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

Background: APOL1 variants have been implicated for increased prevalence and accelerated rate of progression of kidney diseases amongst African Americans. Since oxidative stress has been demonstrated to play a role for loss of podocytes in both experimental animal and human kidney disease models, we hypothesized that APOL1 variants could be inducing podocyte injury through augmentation of oxidative stress.

Methods: Human podocytes (HPs) stably expressing Vector, APOL1G0, APOL1G1, or APOL1G2 were used. Pseudo type HIV or empty vector (control) virus was transduced into Vector/HPs, G0/HPs, G1/HPs, and G2/HPs. After 48 h, cells were collected and DCFDA and ROS generation was assayed every 10 min for 60 min by a fluorometer. Three sets of experiments were carried out in triplicate. Protein blots of HPs expressing Vector, APOL1G0, APOL1G1 and APOL1G2 were probed for molecular markers for oxidative stress and associated down stream signaling (phospho-p53, phospho-FoxO3A, p27, BAD, RIP3, MnSOD, and catalase). To evaluate the status of apoptotic pathway, protein blots of HPs expressing Vector, APOL1G0, APOL1G1, and APOL1G2 were probed for caspase-3 and then reprobed for actin. To determine the role the activation of Ang II type 1 (AT1R) and II (AT2R), protein blots of HPs expressing APOL1 and variants were probed for AT1R and AT2R.

Results: Both HP/G1 and HP/G2 displayed increased ROS generation when compared to Vec/HPs and G0/HPs. G1/HPs and G2/HPs displayed higher expression of pro-oxidant molecules, including RIP3, P27, BAD, phospho-FoxO3A, phospho-p53, phospho-3, HP/G1 and HP/ G2 also enhanced expression of cleaved caspase-3 when compared with vector/HPs and G0/ HPs. However, both G1/HPs and G2/HPs displayed lower expression of MnSOD and catalase. Both G1/HPs and G2/HPs displayed higher ROS generation and enhanced expression of pro-oxidant molecules in HIV milieu when compared to vector/HPs and G0/HPs.

Conclusions: These results indicate that APOL1 risk variants have potential to augment oxidative stress in podocytes and this effect is further exacerbated in HIV milieu.

TH-PO301
The SMAD2/3 Ratio Is Controlled by PLCE1 in Podocytes Carl J. May,1,2 Gavin Iain Welsh,1,2 Moein Salleh,

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Background: Podocytes are thought to be the target cell in nephrotic syndrome pathogenesis. Mutations in PLCE1 which encodes a lipid signalling enzyme, have been reported to cause the nephrotic syndrome in African Americans. However, the effects of PLCE1 mutations in podocyte function are not clear.

Methods: A conditionally immortalised human podocyte cell line was established from a patient, with nephrotic syndrome caused by a deletion of exon 32 at position 321 of PLCE1 which leads to a stop codon. This mutation severely truncates the protein such that no protein expression was detected. This cell line was characterised in order to investigate the deleterious effect of this mutation on podocyte phenotype and function.

Results: The PLCE1 mutant podocytes express lower levels of both epithelial and podocyte markers when compared to wild-type cells. Morphologically they appear more mesenchymal. They demonstrate a diminished response to TGF-B1 compared to the wild-type. Interestingly the PLCE1 mutant podocytes show no SMAD2 phosphorylation but a robust SMAD3 phosphorylation. Whereas, the wild-type podocytes which show marked SMAD2 phosphorylation show only low level SMAD3 phosphorylation. It is thought that the SMAD2 pathway is anti-fibrotic while the SMAD3 pathway is pro-fibrotic. The PLCE1 mutant podocytes had equal levels of SMAD2 and SMAD3 while the wild-type podocytes had twice the amount of SMAD2 compared to SMAD3. This biases TGF-B1 signaling along the anti-fibrotic SMAD2 pathway in the wild type. Despite the 1:1 ratio between SMAD2 and SMAD3 the lack of SMAD2 phosphorylation shows that the PLCE1 mutant podocytes are biased towards the pro-fibrotic SMAD3 signaling. Most interestingly, however, PLCE1 knockdown in wild-type podocytes increased the expression of SMAD3 relative to SMAD2. This changes the SMAD bias of the podocyte.

Conclusions: This work suggests that by altering the SMAD2/3 ratio within the podocyte, the PLCE1 mutant enhances the pro-fibrotic response to TGF-B1. This provides a novel therapeutic target to modulate the podocyte’s response to TGF-B1 and may prove to be protective against the development of fibrosis.

TH-PO302
Dynamin Oligomerization Plays a Catalytic and Structural Role with Regard to Actin Dynamics During Actin-Dependent Clathrin Mediated Endocytosis Chankyu Gu, Sanja Sever, Nephrology, Massachusetts General Hospital, Charleston, MA.

Background: The GTPase dynamin is essential for podocyte structure and function as it plays a role in regulating endocytosis and the actin cytoskeleton. Recently, using a combination of different dynamin mutants and Bis-T-23, we showed that it is possible to directly target actin cytoskeleton dynamics by targeting the dynamin oligomerization cycle of the whole organism. It has been shown that direct dynamin-actin interactions are required for the scission of the clathrin-coated pits in yeast. While actin is critical for endocytosis in yeast cells, data suggest that it plays a cell type specific role in endocytosis in mammalian cell. In this study, we aim to investigate the functional role for dynamin oligomerization in endocytosis.

Methods: Actin polymerization assay was performed to investigate dynamin oligomerization-driven actin polymerization using purified proteins or cytosolic extracts. Electron microscopy was used to explore the effects of dynamin on actin structures. Tfn uptake assay and cell surface expression were used to examine endocytosis and Clathrin coated pits profiles respectively. Total internal reflection fluorescence microscopy was used to monitor clathrin mediated endocytosis.

Results: Here we show, using a combination of diverse dynamin mutants and a small molecule that specifically promotes actin-dependent dynamin oligomerization named Bis-T-23, that dynamin provides a physiological link between gelsolin and Arp2/3 complex driven actin polymerization. Dynaminpromoted Arp2/3 complex driven nucleation by providing free barbed ends via gelsolin displacement in vitro, in cell extracts and in the cell. In addition, dynamin oligomers exhibited a structural role with regard to the actin cytoskeleton. More interestingly, these experiments suggest that a 1:1 ratio between SMAD2 and SMAD3 the lack of SMAD2 phosphorylation shows that the PLCE1 mutant enhancing the pro-fibrotic response to TGF-B1. This provides a novel therapeutic target to modulate the podocyte’s response to TGF-B1 and may prove to be protective against the development of fibrosis.

TH-PO303
Functional Characterization of β-Catenin in Podocyte Damage Michelle Duong, Beina Teng, Hermann G. Haller, Mario Schiffer, Nephrology, Medical School Hanover.

Background: β-Catenin plays a crucial role in the Wnt signaling pathway as well as in cell adhesion. In the kidney β-Catenin is critically involved in the development of proteinuria and podocyte damage. Here we investigated if the injury is associated with a change in subcellular localization of β-Catenin and is mediated by its binding partner o-Catenin.

Methods: We used the wheat germ model to express human β-Catenin mutants lacking the ability to bind o-Catenin or TCF. To examine the impact of β-Catenin acting in only one of its subcellular localization, we expressed β-Catenin either in the membrane or in the nucleus. Knockdown of endogenous β-Catenin was conducted by morpholino injection and co-expression of the mutants with injection of mRNA. After that the integrity of the glomerular filtration barrier was analyzed.

Results: Our analysis revealed that β-Catenin tethered to the membrane only seems to be able to partially retain the glomerular filtration barrier, whereas nuclear β-Catenin alone cannot abrogate the impact of the β-Catenin knockdown and leads to loss of high molecular weight proteins from the glomerular filtrate. The absence of β-Catenin missing the function of binding TCF have a normal glomerular filtration function, while the expression of β-Catenin unable to bind o-Catenin leads to proteinuria.

Conclusions: These results suggest that the cell-cell adhesion function of β-Catenin is of greater importance for the maintenance of the glomerular filtration barrier than its role as a transcription factor.

Funding: Government Support - Non-U.S.

TH-PO304
Vitamin D (V) Upregulates Nephrin in HIV-Induced Differentiated Podocytes Through Down Regulation of SNAIL Nirupama Chandel, Rivka Lederman, Ashwani Malhotra, Pravin C. Singhal, Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

Background: HIV infection of kidney cells plays a key role in the development of HIV-associated nephropathy (HIVAN). We recently observed that HIV-induced differentiations of podocytes regulated through SNAIL. We hypothesize that VD has potential to prevent

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
the Nephron downregulation through modulation of SNAIL expression. VD may be downregulated during inflammatory response. It can also downregulate transcription factors, including HUK4 (Huk4) trimethyltransferase) at snail promoter or at Nephrin promoter (H3 K27 trimethylation) or either through reversal of HIF-1α-induced stabilization of SNAIL.

**Methods:** Renal tissues were harvested from (FVB/N) and HIV-transgenic (Tg26) mice (3-4 months old), or with DEX treatment. Transgenic mice receiving TgFBV and Tg26 mice for two weeks (n=5, 4 wk old). In vitro studies, human podocytes (HPs) were transduced with either empty vector (EV) or NL-4-3 (HIV). EV/HPs and HIV/HPs were treated with EB1089 for 48 hours. Protein blots of renal tissues, EV/HPs and HIV/HPs with/without VD were performed for SNAIL, p62 (marker of endosomal cargo degradation), and histone trimethylation. Immunoprecipitation (IP) studies were carried in cellular lysates of EV/HPs and HIV/HPs with SNAIL antibody. Binding of SNAIL at VDR promoter was evaluated by ChiP assay. Additionally, we evaluated the effect VD on disruption of SNAIL repressor complex at nephrit promoter. Renal tissues of Tg26 mice (n=3) displayed increased SNAIL transcription as well as translation but downregulation of nephrit. VD does not downregulate SNAIL, but also upregulated nephrit expression in renal tissues of Tg26 mice as well as in HIV/ HPs. Chip assay revealed enhanced trimethylation at nephrit promoter and binding of SNAIL at nephrit promoter in HIV/HPs. VD also enhanced nephrit expression through disruption of SNAIL/SNAIL/MAD2 complex at nephrit promoter in HIV/HPs. HIV/HPs display of decreased levels of p62 which signifies increased HIV induced autophagy in vitro system.

**Conclusions:** VD has potential to upregulate nephrit expression in HIV-induced dedifferentiated podocytes through multiple ways including modulation of HIV-induced epigenetic alterations, autophagy, and disruption of SNAIL repressor complexes.

**TH-PO305**

Krüppel-Like Factor 15 Mediates Glucocorticoid-Induced Podocyte Dysfunction and Differentiation

**Background:** Glucocorticoids (GCs) are the initial and common, the primary target for various glomerulopathies such as MCD and FSGS. The mechanism by which GCs restores podocyte differentiation and improves cell survival is unclear. We previously demonstrated that Krüppel-Like Factor 15 (KLF15), a kidney-enriched zinc-finger transcription factor, was required for podocyte differentiation. Here, we hypothesize that KLF15 mediates GC-induced podocyte differentiation.

**Methods:** Human podocytes (HP) and primary mouse podocytes (MP) were treated with or without dexamethasone (DEX) (1μM, 10μM) for 3, 6, 12, and 24 hours. Initially, we generated podocyte-specific knockout mice, Podocin−/− (Klf15−/−) (Klf15−/−). Proteinuria was induced in Klf15−/− and wildtype mice with LPS (10mg/kg) and subsequently treated with or without DEX (1mg/kg). HP with stable overexpression of KLF15 (LentiORF-KLF15) were generated. Immunostaining for KLF15 was performed on kidney biopsies from patients with healthy donor nephrectomies (n=16), GC-responsive (n=20), and GC-nonresponsive to GCs in patients with MCD and FSGS.

**Results:** In primary glomerulopathies such as MCD and FSGS. The mechanism by which GCs restores podocyte differentiation and improves cell survival is unclear. We previously demonstrated that Krüppel-Like Factor 15 (KLF15), a kidney-enriched zinc-finger transcription factor, was required for podocyte differentiation. Here, we hypothesize that KLF15 mediates GC-induced podocyte differentiation. Human podocytes (HP) and primary mouse podocytes (MP) were treated with or without dexamethasone (DEX) (1μM, 10μM) for 3, 6, 12, and 24 hours. Initially, we generated podocyte-specific knockout mice, Podocin−/− (Klf15−/−) (Klf15−/−). Proteinuria was induced in Klf15−/− and wildtype mice with LPS (10mg/kg) and subsequently treated with or without DEX (1mg/kg). HP with stable overexpression of KLF15 (LentiORF-KLF15) were generated. Immunostaining for KLF15 was performed on kidney biopsies from patients with healthy donor nephrectomies (n=16), GC-responsive (n=20), and GC-nonresponsive to GCs in patients with MCD and FSGS.

**Conclusions:** VD has potential to upregulate nephrit expression in HIV-induced dedifferentiated podocytes through multiple ways including modulation of HIV-induced epigenetic alterations, autophagy, and disruption of SNAIL repressor complexes.
**TH-PO309**

The Redox Sensitive Glycogen Synthase Kinase (GSK) 3β Suppresses the Self-Protective Antioxidant Response in Podocytes upon Oxidative Glomerular Injury  

Changbin Devuyst, 1 Simone Lerner, 2 Geert Devuyst, 1 Hiroshi Bruni, 1 MedZed Therapeutics, Zug, Switzerland; 4 Christoph Brunati, 1 Simone Lerner, 2 MedZed Therapeutics, Zug, Switzerland

**Background:** GSK3β has been implicated as a crucial kinase controlling the balance between proinflammatory and self-protective responses in podocytes.

**Methods:** Podocytes were treated with 48h of hypoxia. The senescence was evaluated by β-galactosidase expression and telomere length measurement by real time PCR. The activity of the Wnt pathway aimed to examine a Wnt-reporter luciferase assay.

**Results:** Preliminary data showed CD133+ cells downregulated the stem-related gene Oct4A and acquired the differentiation marker marker AQP1. The activity of Wnt pathway in KO mice seemed to be reduced in CD133 silenced cells both in basal culture conditions as well as after oxidative damage, as shown by a Wnt-reporter assay. Functionally, CD133+ cells did not modify their response to cisplatin, cyclosporine or hydrogen peroxide, suggesting that CD133 may not be involved in resistance to damage. At variance, in CD133+ cells the senescence formation was slightly reduced, both in number and size. Interestingly CD133+ cells showed an increased expression of β-galactosidase, a marker of senescence, compared to CD133- cells, along with a telomere lengthening.

**Conclusions:** Our preliminary data suggest that CD133 may be involved in the maintenance of a stem-like phenotype in renal cells along with a delay of senescence.

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

**TH-PO310**

Vitamin D Receptor (VDR) Inversely Modulates Renin Angiotsensin System (RAS) Through MDM2 and p53 in Kidney Cells  

Hongxiu Yan Ge, 1 Changbin Devuyst, 1 Simone Lerner, 2 MedZed Therapeutics, Zug, Switzerland; 4 Christoph Brunati, 1 Simone Lerner, 2 MedZed Therapeutics, Zug, Switzerland

**Background:** Vitamin D has been reported to be a negative regulator of renin gene transcription. However, this concept is not able to provide a logical explanation for activation of the RAS in VDR knockout (KO) mice. We hypothesized that VDR inversely modulates the RAS through modulation of MDM2 and p53 expression.

**Methods:** Protein blots of control and siRNA/VDR treated HPTC were probed for MDM2, p53, Agt, renin, and AT1R. To evaluate the role p53, cells were transfected with either p53 or siRNA+p53. To evaluate relationships amongst VDR, MDM2, and p53, protein blots of VDR agonist treated p53/HP and p53/HPTCs and siRNA/p53/HP and HPTCs were evaluated for MDM2 and p53 expressions.

**Results:** Renal tissues of VDRKO mice displayed attenuated protein and mRNA expression of MDM2 but enhanced expression of p53, Agt, renin, and AT1R. Both podocytes and tubular cells lacking VDR also displayed attenuated expression of MDM2 but enhanced expression of p53, Agt, renin, and AT1R. HPS and HPTCs displayed enhanced expression of p53 also displayed down regulation of VDR but activation of RAS; on the other hand, HPS and HPTCs silenced for p53 displayed upregulation of VDR but down regulation of RAS. VDR agonist enhanced expression of VDR and MDM2 but down regulated expression of p53 and the RAS.

**Conclusions:** VDR determines the status of the RAS through modulation of MDM2 and p53 expression in kidney cells.

**TH-PO311**

The Role of CD133 Molecule in Renal Papillary Cells and Its Possible Involvement in Wnt Signaling and Cellular Senescence Prevention  

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**Background:** The nature of cells involved in homeostasis/repair of adult human kidney is unclear. In human tissue, using the AC133 antibody, recognizing a stem cell-specific glycosylation-dependent epitope of promin (CD133), CD133+ cells with phenotypic and functional properties were detected in all nephron segments as scattered distinct cells with a dedifferentiated phenotype that survive and proliferate after damage.

However, the role of the CD133 in the progenitor phenotype and its possible modulation is unknown. In the present study we aim to evaluate the role of the CD133 in the maintenance of cellular stem-like phenotype and its involvement in cellular senescence.

**Methods:** CD133+ progenitor cells were isolated from the inner medullary of human kidney biopsies. We generated CD133 knock-down (kd) cell lines by infecting them with lentiviral vectors carrying GFP-shCD133 plasmids. Cytotoxicity was evaluated by BrdU uptake or MTT assay. Spheroid formation was evaluated by sphere counting and MTT assay after 48h of hypoxia. The senescence was evaluated by β-galactosidase expression and telomere length measurement by real time PCR. The activity of the Wnt pathway was investigated using a Wnt-reporter luciferase assay.

**Results:** Preliminary data showed CD133+ cells downregulated the stem-related gene Oct4A and acquired the differentiation marker AQP1. The activity of Wnt pathway seemed to be reduced in CD133 silenced cells both in basal culture conditions as well as after oxidative damage, as shown by a Wnt-reporter assay. Functionally, CD133+ cells did not modify their response to cisplatin, cyclosporine or hydrogen peroxide, suggesting that CD133 may not be involved in resistance to damage. At variance, in CD133+ cells the senescence formation was slightly reduced, both in number and size. Interestingly CD133+ cells showed an increased expression of β-galactosidase, a marker of senescence, compared to CD133- cells, along with a telomere lengthening.

**Conclusions:** Our preliminary data suggest that CD133 may be involved in the maintenance of a stem-like phenotype in renal cells along with a delay of senescence.

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

**TH-PO312**

The Effect of Wnt5a/Ca2+ Pathway on High-Glucose Induced Fibrosis of Human Peritoneal Mesothelial Cells  

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**Background:** Fibrosis is the main reason of ultrafiltration failure. Human Peritoneal Mesothelial Cells (HPMC) expresses wnt5a, which induces noncanonical wnt signaling pathway to cause cytoskeletal fiber thickening and fibrosis in vitro. However, the role of the CD133 in the progenitor phenotype and its possible modulation is unknown. In the present study we aim to evaluate the role of the CD133 in the maintenance of cellular stem-like phenotype and its involvement in cellular senescence.

**Methods:** We used a comprehensive approach, ranging from biochemistry, molecular biology, and functional studies to reveal the role of CD133 in fibrosis generation. Western blot shows the expression of Wnt5a elevated in HG groups, which depended on concentration and action time.Wnt5a mRNA expression in HG group was upregulated in the Western blot and immunofluorescence microscopy. The Wnt5a mRNA was detected by RT-PCR.

**Results:** Western blot shows the expression of Wnt5a in HG groups, which depended on concentration and action time.Wnt5a mRNA expression in HG group was upregulated. Western blot and immunofluorescence microscopy showed the Wnt5a mRNA expression in HG groups, which depended on concentration and action time. Wnt5a mRNA expression in HG group was upregulated. Western blot and immunofluorescence microscopy showed the Wnt5a mRNA expression in HG groups, which depended on concentration and action time. Wnt5a mRNA expression in HG group was upregulated.

**Conclusions:** Western blot and immunofluorescence microscopy showed the Wnt5a mRNA expression in HG groups, which depended on concentration and action time. Wnt5a mRNA expression in HG group was upregulated. Western blot and immunofluorescence microscopy showed the Wnt5a mRNA expression in HG groups, which depended on concentration and action time. Wnt5a mRNA expression in HG group was upregulated. Western blot and immunofluorescence microscopy showed the Wnt5a mRNA expression in HG groups, which depended on concentration and action time. Wnt5a mRNA expression in HG group was upregulated.
MDCK cells and extensive analysis of urinary uromodulin processing in vivo in hepsin and prostanin knock-out mice, we demonstrate that hepsin is the enzyme responsible for the physiological cleavage releasing urinary uromodulin.

**Conclusions:** Our findings define a key aspect of the biology of uromodulin that could pave the way for future studies on the regulation of its secretion. Given the similar function of hepsin in the human, the conservation of cleavage site in ZP domain proteins, our results are likely relevant for other members of this protein family.

**Funding:** Private Foundation Support

**TH-PO314**

The Favorable Effect of AdipoRon on Diabetic Nephropathy through Improvement of Endothelial Dysfunction in db/db Mice

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**Background:** Adiponectin is one of the numerous adipocyte-derived adipokines that interplays with others to exert the milieu of metabolic syndrome. It binds to adiponectin receptors (AdipoR), AdipoR1 and AdipoR2 and exhibits anti-diabetic effects via activation of AMPK and PPAR-α. Oral active synthetic small-molecule AdipoRon agonist, AdipoRon binds to both AdipoR and ameliorates obesity-related disease. Therefore, we investigated the possible role of AdipoRon in renal physiology in the view of prevention and development of diabetic nephropathy in diabetic mouse model.

**Methods:** Male db/db mice were fed a diet containing AdipoRon (30 mg/kg/day) for 4 weeks from 17 to 20 weeks of age. Serum, urine and renal tissue were obtained to analyze for changes in metabolic parameters, molecular levels and renal structure.

**Results:** AdipoRon treatment showed decreased amount of albuminuria with no significant changes in production of serum adiponectin, glucose and creatinine and it seems to be weight neutral. Increased expressions of AdipoRon in the renal cortex and consistent up-regulations of phosphorylated AMPK and PPAR-α level were associated with AdipoRon treatment. AdipoRon treatment showed favorable effects on diabetes-induced GBM thickening, foot process widening and slit diaphragm space narrowing and further decreased glomerular matrix expansions and inflammation.

**Conclusions:** Increased expressions of renal AdipoRon, not AdipoR2, indicates that renal injury may cause a compensatory up-regulation of relevant receptors in kidneys to mitigate further renal injury. AdipoRon may control oxidative stress in glomerulus through AMPK and PPAR-α activated pathways and further contribute to prevent deterioration of renal function. The protective role of AdipoRon against the development of albuminuria seems to occur through a direct action on podocytes independently of systemic effects of adiponectin. Its reduction of oxidative stress provides protection against albuminuria and podocyte damage thereby ameliorating endothelial dysfunction in diabetic nephropathy.

**Funding:** Private Foundation Support

**TH-PO315**

Diabetes-Induced Impairments in Slit-Robo Signaling Augment Glomerular Angiogenesis

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**Background:** Diabetic nephropathy is characterized by glomerular endothelial cell (GEC) injury. One of the earliest manifestations of this injury is glomerular angiogenesis, a process that classically is thought of as being driven by increased glomerular VEGF production. Slit2 is a regulator of endothelial function, eliciting either pro- or anti-angiogenic effects through its Robo1 and Robo4 receptors, respectively. We have shown previously, that glomerular endothelial Robo4 expression is downregulated by high glucose exposure, whereas Robo1 expression is unchanged. Objectives: To determine whether high-glucose-induced alterations in Robo1 and Robo4 expression regulate VEGF-induced angiogenesis in the diabetic kidney.

**Methods:** GEC responsiveness to VEGF in angiogenesis assays was examined in both normal glucose (NG) and high glucose (HG) conditions, and following Robo1 knockdown. Using Robo4 knockout (KO) mouse, the effect of Robo4 deficiency on diabetic glomerular angiogenesis was also analyzed using fluorescence microangiography (FMA) and PECAM-1 immunohistochemistry.

**Results:** As compared to GEC grown in NG medium, GEC grown in HG medium expressed lower levels of the anti-angiogenic Robo4 receptor, but not the pro-angiogenic Robo1 receptor, and exhibited greater VEGF responsiveness. Loss of Robo eliminated VEGF-induced GEC network formation and migration in both normal and high glucose conditions. In contrast, Robo4 deficiency was associated with enhanced PECAM-1 density and glomerular capillary length in Robo4 KO mice (compared to their WT littermates) after 4 weeks of STZ-induced diabetes.

**Conclusions:** Our observations suggest that diabetic glomerular angiogenesis is driven not only by increased VEGF production, but also by enhanced glomerular endothelial VEGF responsiveness. Our data also suggest that this increased responsiveness is promoted by a shift in glomerular endothelial Slit2-Robo signalling, favouring more pro-angiogenic Robo1, and less anti-angiogenic Robo4 activity.

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

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

**Underline represents presenting author. 160A**
Methods: To test the therapeutic effects of SUL121 in diabetic and normal mice, db/db and lean control mice were subcutaneously injected with osmotic pumps delivering SUL121 or vehicle from age 10 to 18 weeks. Mice were placed in metabolic cages every two weeks until termination at which time endothelial mediated relaxation in aortic rings was assessed. ROS status and H2S levels were measured in plasma, and renal expression of H5 producing enzymes was determined.

Results: While treatment with SUL121 did not alter the glycemic state in db/db, it prevented albuminuria and diabetic kidney damage, as evidenced by an inhibition of the progression of albumin excretion rate, lower albumin creatinine ratio, decreased focal glomerulosclerosis severity score and normalization of kidney weight. In addition, S11121 normalized systemic ROS formation, increased renal expression of the H5 producing enzymes, cystathionine gamma lyase and cystathionine beta synthase (CSE and CBS), and prevented the development of endothelial dysfunction in db/db. SUL121 treatment in lean control mice demonstrated no observable side-effects, indicating that SUL121 is well tolerated.

Conclusions: Thus, SUL121 represents a novel compound inhibiting the progression of experimental diabetic kidney damage via a mechanism that inhibits both oxidative stress and preserves vasorelaxation.

Funding: Pharmaceutical Company Support - This study was partially financed by Sulfateq B.V., a company that owns patents on SUL121, and produces and markets similar compounds., Government Support - Non-U.S. -

TH-P0319
Coagulation Factor Xa and Protease-Activated Receptor 2 as Novel Targets for Treating Diabetic Nephropathy
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Background: Role of hypercoagulability in pathogenesis of diabetic nephropathy (DN) remains elusive. We have recently demonstrated that elevated coagulation factor III (tissue factor) exacerbates DN (J Thor Haemost 2010, PNAS 2011). Tissue factor activates factor X (FXa), which in turn stimulates protease-activated receptor 2 (PAR2). PAR2 causes inflammation and fibrosis. Accordingly, we hypothesized that activation of FXa-PAR2 signaling exacerbates DN.

Methods: To test this hypothesis, we used diabetic mice with reduced expression of endothelial NO synthase (Nos3) as a model of DN. We first tested whether inhibiting FXa ameliorates DN by administering an oral FXa inhibitor Edoxaban (50 mg/kg/day) for 3 months in diabetic mice lacking eNOS (Ins2Akita/+; Nos3-/-). We next tested whether lack of PAR2 ameliorates DN using diabetic mice lacking PAR2 (F2rl1-/-;Ins2Akita/+;Nos3-/-). Finally, the effects of FXa or PAR2 agonist (SLIGKV) on human endothelial cells (EA.hy926) and conditionally immortalized murine podocytes were evaluated.

Results: Renal expression of FX and PAR2 was up-regulated in DN, together with elevation of FXa activity in the urine. Edoxaban and lack of PAR2 both reduced renal expression of inflammatory and profibrotic genes, and ameliorated diabetic glomerulosclerosis and urinary albumin excretion. FXa or a PAR2 agonist (SLIGKV) increased IL-8 secretion and gene expression of MCP-1 and PAI-1 in human endothelial cells. These treatments also increased Mmp1/mRNA level in murine podocytes.

Conclusions: We conclude that FXa - PAR2 signaling exacerbates DN possibly through up-regulating inflammatory response. FXa - PAR2 signaling is a promising target for treating or preventing DN.

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

TH-P0320
Herniation of the Mesangium Together with Sprouting of Blood Vessels Out of the Glomerular Entrance Is a Frequent Feature of Diabetic Nephropathy
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Background: In contrast to diabetic retinopathy, where neovascularizations have a central pathogenetic impact, in diabetic nephropathy (DN) angio-proliferative processes are generally not considered as a major factor underlying disease progression. The studies by Osterby and Nyberg (J Diab Comp 1987, 1:122) and Min and Yamanaka (Vircows Arch A Panhol Anat 1993, 423:201) have shown neovascularizations in DN but have found little attention.

Methods: Re-evaluation of biopsies of DN (archive: Dep. of Molecular Pathology, German Cancer Research Center, Heidelberg) has revealed that the proliferation of newly formed blood vessels out of the glomerular entrance into the surroundings of the glomerulus is a frequent feature in DN.

Results: In a total of 437 biopsies (so far evaluated) 60.2% contained aberrant vessels at the vascular pole or in periglomerular position. 13% of these cases were associated with diffuse mesangial sclerosis (DMS), 35% with transitional stages from DMS to nodular glomerulosclerosis (NGLS) and 52% with NS. The Chinese plant medicine such as Huanglian, Letasiona S(Rhizoma corylifolia), and Gold Seal (hydrastis canadensis), was reported from an extracts from some Chinese plant medicine such as Huanglian Letasiona S(Rhizoma corylifolia) and Chinese Traditional Medicine, which play a pivotal role in the progressive of glomerulosclerosis or thickening of the glomerular basement membrane in DN. Berbine, an alkaloid from some Chinese plant medicine such as Houttuynia Cordifolia, is reported to ameliorate diabetic nephropathy, but the mechanism still need verified. This study was to investigate the changes of monolayer permeability in GEnCs caused by induced Glomerular Endothelial Cell Hyperpermeability
Nanmei Liu. Jinlin Hospital of Shanghai.

Background: Glomerular endothelial cells (GEnC) are important part of the glomerular filtration barrier. The dysfunction of glomerular endothelial cells (GEnCs) could be a characteristic of early stage diabetic nephropathy (DN). Accumulating evidence indicate that advanced glycation end products (AGEs) play a pivotal role in the progressive of glomerulosclerosis or thickening of the glomerular basement membrane in DN. Berbine, an alkaloid from some Chinese plant medicine such as Houttuynia Cordifolia, is reported to ameliorate diabetic nephropathy, but the mechanism still need verified. This study was to investigate the changes of monolayer permeability in GEnCs caused by high concentration glucose and AGEs, and the effects of Berbine.

Methods: GEnCs were cultured in growth medium causing cell proliferation, then seed in a Transwell culture system to form confluent monolayer. The cell was treated with ordinary glucose (5.5mM), or high glucose (25mM), AGE 100mg/ ml, berberine (3aH) respectively. The GEnC permeability was evaluated by measuring the diffusion of biotin-conjugated bovine serum albumin (biotin-BSA) across a cell monolayer. The changes of cytoskeleton was observed under Confocal laser scanning fluorescence microscopy after double staining of F-actin and G-actin.

Results: The protein leakage rate was increased slightly after treated with high glucose (25mM), but increased significantly in high glucose plus AGE 100mg/ml compared with low glucose control group. High glucose and AGE strongly affected orientation of F-actin fibers, induced rearrangement of F-actin fibers. While berberine intervention can reduce protein leakage rate (P<0.05), improved the F-actin cytoskeletal actin disorder significantly.

Conclusions: High glucose and AGE increased permeability of the GEnC monolayer and leads to long-term alterations of F-actin structures. Berbine has a protective effect. The mechanism may be related to inhibit endoplasmic reticulum stress and reduce the cytoskeleton injury.

Funding: Government Support - Non-U.S.
Arginase Inhibition: A New Treatment for Preventing Progression of Established Diabetic Nephropathy

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Background: Our previous publication showed that inhibition of arginase prevents the development of diabetic nephropathy (DN). However, identification of targets that retard the progression of established DN—which is more clinically relevant—is lacking. Therefore, we tested the hypothesis that arginase inhibition would prevent the progression of established DN. Effects of arginase inhibition were compared to treatment with the ACE inhibitor captopril, the current standard of care in DN.

Methods: Experiments were conducted in Ins2Akita mice treated with the arginase inhibitor S-(2-boronoethyl)-L-cysteine (BEC) or captopril starting at 6 wk of age for 12 weeks (early treatment) or starting at 12 wk of age for 6 wk (late treatment).

Results: Early and late treatment with BEC resulted in protection from DN as indicated by reduced albuminuria, histological changes, kidney macrophage infiltration, urinary TBARS, and restored nephrin expression, kidney nitrate/nitrite, kidney eNOS phosphorylation, and renal medullary blood flow compared with vehicle-treated Ins2Akita mice at 18 wk of age. Interestingly, early treatment with captopril reduced albuminuria, histological changes, and kidney macrophage infiltration without affecting the other parameters, but late treatment with captopril was ineffective.

Conclusions: These findings highlight the importance of arginase inhibition as a new potential therapeutic intervention in both early and late stages of diabetic renal injury.

Funding: NIDDK Support

Transgenic TGF-β1 Receptor Type I (TβRI) Overexpression in Podocytes Promotes STZ-Induced Diabetic Nephropathy in Rats

Sigrid C Hofmann, Sternad, M. Marianna Robert-Auger, Wilfried Kritz, Tamara Micakovic. Medical Faculty Mannheim, Univ Heidelberg, Mannheim, Germany.

Background: Glomerular TGF-β1 is increased early in the course of diabetic nephropathy. The podocytes are sources and targets of TGF-β1. This study addresses the hypothesis that increased TGF-β1 in diabetic rats stimulates the development of diabetic nephropathy via selective signalling in podocytes.

Methods: Transgenic rats carrying the TGR/TβRI driven by the podocin promoter were generated. Expression of TβRI was verified by Northern blotting, in-situ hybridization and Western blotting. Glomerular expression profiling was performed by real time RT-PCR. Western blotting and immunohistochemistry. Podocyte density was determined by counting WT-1 stained podocytes per glomerular area, which was determined morphometrically in 200 glomeruli per rat. At 2 months of age rats received STZ (40 mg/kg i.v.) or saline, respectively. Body weight and kidney function were evaluated by urinary albumin excretion in the glomeruli without affecting BW, BG or GTT.

Results: TGR expressed the transgenic receptor specifically in podocytes. Glomerular TβRI protein levels were almost twice that of WT. At 5 months of age 40 % of TGR exhibited moderately increased albumin excretion up to 2.2 mg/24hr vs. 0.11 mg/24hr in WT. 3 months after STZ, albumin excretion was significantly increased in 80% of TGR with an average of 4 mg/24hr (max. 7.3) but only slightly elevated in 40% of the WT with an average of 0.7 mg/24hr (max. 2.2). Expression profiling in isolated glomeruli revealed that in TGR PAI-1 was significantly upregulated and the survival marker bcl-2 and podocyte differentiation marker synaptopodin, podocin and nephrin were significantly down-regulated relative to WT. Podocyte number per glomerulus was significantly decreased in diabetic TGR vs. diabetic WT.

Conclusions: Podocyte-selective TβRI-overexpression contributes to the leakage of the glomerular filter in the course of STZ induced diabetic nephropathy which might be mediated by podocyte loss due to podocyte dedifferentiation, downregulation of bcl-2 and PAI-1 upregulation.

Funding: Government Support - Non-U.S.

Comparison of Glomerular and Podocyte mRNA Profiles in eNOS−/− Diabetic Mice Induced by Streptozotocin

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Background: Gene expression profiles have never been reported in primary podocytes isolated from the diabetic kidney. Here, we compared mRNA profiles in both isolated glomeruli and sorted podocytes between diabetic and control mice.

Methods: IRG mice carrying a two-color fluorescent reporter gene were first crossed with ENOS−/− mice and then with podocin-rtta and TetO-cre mice allowing us to permanently label podocytes. Then, mice were injected with either streptozotocin (STZ- eNOS−/− vehicle (CL-eNOS−/−) or STZ-eNOS−/− mice developed typical findings of diabetic nephropathy at 10 weeks after STZ injection. mRNA sequencing was performed in both isolated glomeruli and sorted podocytes from STZ-eNOS−/− and CL-eNOS−/− mice.

Results: Consistent with the previous reports, expression of podocyte-specific markers in the glomeruli were down-regulated in the STZ-eNOS−/− mice compared to CL-eNOS−/− mice. However, these differences disappeared when mRNA levels were corrected for podocyte number/glomerulus. Interestingly, expression of these markers in sorted podocytes did not differ between diabetic and non-diabetic mice. These data suggest that reduced expression of podocyte markers in isolated glomeruli is likely secondary to reduced podocyte number/glomerulus, rather than loss of differentiation markers. Analysis of the differentially expressed genes (DEGs) between diabetic and non-diabetic mice revealed distinct pathways between glomeruli and podocytes. The up-regulated DEGs in isolated glomeruli were involved mainly in the regulation of mitochondrial function and oxidative stress pathway, while the up-regulated DEGs in sorted podocytes were heavily involved in the actin organization.

Conclusions: In conclusion, our data suggest that podocyte-specific gene expression in transcriptionome obtained from glomeruli not represent those of podocytes in diabetic kidney.

Funding: Other NIH Support - JCH is supported by NIH 1R01DK087889, and NIH 1R01DK088541, and NIH P01-DK-56492; PYC is supported by NIH 1R01DK909126-01A1, Veterans Administration Support, Government Support - Non-U.S.

Tristetraprolin Overexpression Ameliorated Inflammation in db/db Mice and Mouse Podocytes

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Background: Tristetraprolin (TTP) is a well-characterized, zinc-finger-containing, RNA-binding protein, which plays a role in the regulation of inflammatory factors expression by targeting the 3’untranslated region (3’UTR). We investigated whether TTP modulates inflammation in high glucose-induced-podocytes and in db/db mice kidneys.

Methods: Differentiated mouse podocytes were treated by high glucose, and TTP expression and inflammatory factors was measured by quantitative real-time PCR, western blot or ELISA. TTP mRNA or silencing vectors containing TTP sequences were transfected into podocytes to down-regulate or up-regulate TTP expression. Db/db mice were used as the diabetic model in the in vivo experiment. At the age of 10 weeks, db/db mice were injected via tail vein with lentiviral vectors containing TTP sequences. At the age of 14 weeks, mouse kidneys were removed. Inflammatory factors and podocyte markers were examined in both podocytes and mice kidneys. Urine albumin to creatinine ratio and serum creatinine was also detected.

Results: TTP was down-regulated while IL-6, IL-18, TNF-α were up-regulated in high glucose-induced mouse podocytes. Silencing TTP by siRNA induced inflammatory factors expression. Overexpression of TTP reduced the expression of inflammatory factors in high glucose-induced podocytes. TTP expression was significantly decreased in db/db mice.
kidneys compared with db/db mice. Overexpression of TTP by lentivirus injection ameliorated insulin resistance in diabetic db/db mice. Urine albumin to creatinine ratio and urine inflammatory factors was also decreased in db/db mice overexpressing TTP.

**Conclusions:** TTP is involved in the regulation of inflammation in diabetic conditions. Targeting TTP might be effective in diabetic kidney disease.

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

**TH-PO328**

**CIN85 Deficiency Prevents Nephrin Endocytosis in Podocytes Under Diabetic Conditions**

**Heina Teng,** Hermann G. Haller, Mario Schiffer. Medical School Hannover, Hannover, Germany.

**Background:** Podocytes are important for the maintenance of the glomerular filter in the kidney. Podocyte damage is associated with ultrastructural changes and decreased expression of components of the slit diaphragm in many glomerular diseases. Nephrin, a podocyte-specific protein is crucial for the intact filtration barrier. Loss of nephrin has been observed in rodent models of experimental diabetes as well as in human diabetic kidney disease. CIN85, a homologue of CD2AP, was identified as a binding partner of nephrin and mediates the nephrin endocytosis via ubiquitination in podocytes.

**Methods:** Using STZ injection, we induced a type I diabetes in BLC57/N wild type and CIN85Dex2 mice to examine diabetes induced dysregulation of glomerular filtration barrier and alteration of extracellular matrix. We then generated immortalized cell lines of podocytes for the CIN85Dex2 and the CD2AP to examine nephrin endocytosis in both cell types on the molecular level. To inquire the impact of CIN85 and CD2AP on filtration barrier integrity in zebrafish, we examined proteinuria in zebrafish injected with capped mRNAs.

**Results:** We can demonstrate that the loss of nephrin expression and onset of the proteinuria in diabetic mice is associated with an increased accumulation of ubiquitinated proteins and expression of CIN85 in podocytes. The CIN85Dex2 deficiency leads to preserved nephrin surface expression, reduced proteinuria and Collagen-IV deposition in glomeruli under diabetic conditions. High glucose levels induced an increased CIN85 expression in contrast to a significantly reduced expression of CD2AP and nephrin in both murine and human podocytes. Furthermore, by high glucose stimulation, the CD2AP+/− podocytes, which express more full-length CIN85, showed an increased nephrin endocytosis compared to the CIN85 knockout podocytes. In addition, injection of capped CIN85 mRNA induced a severe edema and proteinuria in zebrafish embryos which could be rescued by co-injection of CD2AP mRNA.

**Conclusions:** Our findings suggest that CIN85 is involved in the endocytosis of nephrin in podocytes under diabetic conditions promoting the development of glomerulopathy. Therefore CIN85 might be a novel treatment target to prevent diabetic nephropathy.

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

**TH-PO329**

**Atrasantan Inhibits Diabetic Nephropathy and Restores Podocyte Number in BTBR/oH/ob Mice**

**Kelly L. Hieking,** Tomasz A. Wietecha, Floorjoe Steegh, Kristina M. Sorg, Noppnatit Pattanachawit, Minsewo Eom, Julia K. Shankland, Charles E. Alpers. Pathology, Univ of Washington, Seattle, WA.

**Background:** Leptin deficient BTBR/oH/ob mice develop type 2 diabetes and DN that closely mimics human DN, including mesangial expansion, podocyte loss, and proteinuria. This study tested the effect of atrasantan (A), an endostatin-1 receptor antagonist, with or without concurrent RAAS inhibition by losartan (L) on DN and whether this can restore podocyte number.

**Methods:** Cohorts of 18 week old BTBR/oH/ob mice and BTBR WT littermates were treated via drinking water with A (5 mg/kg/day), A plus L (25 mg/kg/day) or normal water for 6 weeks. Mice were analyzed for body weight, blood glucose, serum creatinine, proteinuria and morphometric measures of numbers of p57 expressing podocytes, collagen IV staining mesangial matrix.

**Results:** Treatment with A alone had no effect on body weight or blood glucose. Combined treatment with A and L also had no effect on body weight, but significantly decreased blood glucose levels in both BTBR WT (243 ± 18.6 vs 160 ± 5.6, p<0.005) and BTBR/oH/ob (595 ± 5.3 vs 382 ± 51.5, p<0.01) mice. Treatment with A and combined A and L decreased proteinuria in BTBR/oH/ob mice, although this did not reach statistical significance due to wide variations within the groups. Serum creatinine was elevated in BTBR/oH/ob compared to WT mice, and was decreased by treatment with A plus L (p<0.05). Mesangial collagen IV was increased both in A and A plus L treated mice (p<0.05). There were decreased podocytes (p57 expressing cells) in BTBR/oH/ob (149.7 ± 5.6) compared to WT mice (188.7 ± 9, p<0.05). Podocytes increased in BTBR/oH/ob mice receiving A (160.7 ± 7, ns, p=0.005) and were restored to WT numbers in mice receiving A plus L (190.4 ± 5.7, p<0.001).

**Conclusions:** Treatment with A plus L significantly increased podocyte number in diabetic BTBR/oH/ob mice. A treatment alone increased podocyte number, but to a lesser degree. Podocyte restoration correlated with decreased blood glucose, serum creatinine, and mesangial matrix with A plus L treatment. The benefit of combined A and L treatment in patients with DN may occur in part through a previously unrecognized restoration of podocytes.

**Funding:** Pharmaceutical Company Support - Abbvie Pharmaceuticals

**TH-PO330**

**Insulin Signaling in Glomeruli and Podocytes from Insulin Resistant db/ db DBA/2J Mice**

**Mette Viberg Østergaard,** Jesper Worm, Lisbeth N. Fink, Richard Coward. Global Research, Novo Nordisk A/S, Maaloev, Denmark; 2 Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.

**Background:** Impaired insulin signaling in the podocyte is altered early during development of insulin resistance and T2D due to altered insulin receptor (IGF-1 receptor (IGF-1R) or insulin/IGF-1 hybrid receptor (HR) expression levels.

**Methods:** The development of insulin resistance, T2D, albuminuria, and renal pathology was characterised in db/db DBA/2J mice and wild-type (wt) littermates from 6 weeks of age. Insulin-induced Akt phosphorylation, and IR, IGF-1R and HR expression levels were investigated in the glomeruli of insulin resistant db/db DBA/2J mice. The PodCre, ROSA26R reporter strain enriched in the DBA/2J background is crossed with the db/db DBA/2J strain to enable isolation of insulin resistant GFP podocytes by FACs and characterisation of podocyte IR, IGF-1R and HR expression levels.

**Results:** The body weight was >50% higher in db/db vs. wt mice (P<0.001) from 8 weeks. From week 9, db/db males were hyperglycaemic with non-fasting blood glucose ranging from 23.4-30.7 mM (wt range 6.3-7.7 mM, P<0.05). Insulin tolerance tests showed development of whole-body insulin resistance by 8 weeks in male and female db/db vs. wt mice (P<0.05). The urinary albumin-to-creatinine ratio was elevated in db/db vs. wt mice from 7-12 weeks of ages (range of means 2451-5997 vs. 75-479 µg/mg; P<0.001). GFP podocytes were successfully isolated from glomerular single cell suspensions from PodCre, ROSA26R mice and their purity validated by qPCR analysis of Npht2, Pcam1, and Pdgfrb. Podocytes are currently being isolated from 9-week-old insulin resistant db/db PodCre, ROSA26R DBA/2J mice to characterise IR, IGF-1R and HR expression levels.

**Conclusions:** The db/db mouse in the DBA/2J background show early signs of systemic insulin resistance and glomerular disease. Isolating podocytes from this model will allow us to further clarify the roles of IR, IGF-1R and HR in podocytes during the development of insulin resistance and diabetic nephropathy.

**Funding:** Pharmaceutical Company Support - Novo Nordisk A/S

**TH-PO331**

**PKC-α Triggers EGFR Ubiquitination, Endocytosis and MAPK/ERK Activation in Podocytes with High Glucose Stimulation**

**Hua Su, Yanhong Wei, Chun Zhang. Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.**

**Background:** PKCα and EGFR are both involved in diabetic kidney disease, however the association between these two proteins during high glucose induced podocyte injury is unclear.

**Methods:** Diabetes was induced in SD rats by a single intra-peritoneal injection of STZ at a dose of 55 mg/kg body weight in sodium citrate buffer. 14 days later the rats were sacrificed and the cortex of kidney was removed and subjected to plasma membrane isolation and lipid raft fraction. In vitro study human podocyte cell line was employed, and after differentiation it was treated with high glucose or osmotic control for 24 h. The membranous protein expression and endocytosis were assessed by biotinylation and MesNa treatment. G66976 and FyR-41 were used as an inhibitor for PKCα and ubiquitin inhibitor, respectively.

**Results:** By plasma membrane isolation and lipid raft separation we identified that in diabetic rat the abundance of PKCα in membranous fraction and lipid raft domain was elevated, whereas EGFR level was reduced in abovementioned compartments. Consistently, in high glucose treated podocyte the membranous EGFR was downregulated accompanying with the increased membranous PKCα expression which was examined by biotinylatation and plasma membrane isolation. Furthermore by immunoprecipitation, biotinylation and MesNa treatment experiments it showed that the ubiquitination and endocytosis of EGFR were enhanced in podocyte under high glucose stimulation which accompanied with MAPK/ERK signaling activation and the injury of podocyte which was proved by the reorganization of F-actin fibers and increased desnlin level. However above processes could be ameliorated by either PKCα or ubiquitin activating E1 enzyme inhibitor. Conclusion: Our observations demonstrate that in high glucose treated podocyte PKCα mediates EGFR ubiquitination, endocytosis from cell plasma membrane and eventually leads to the activation of MAPK/ERK signaling pathway which partially attributes to podocyte injury in diabetic kidney disease.

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

**TH-PO332**

**Activation of Protein Kinase C-β in the Podocyte by Diabetes-Associated Inflammatory Mediators**

**Brad Dieter, Rick L. Meck, Robert J. Anderberg, Sheryl K. Cosney, Katherine R. Tuttle. Providence Health Care, Spokane, WA; 2 School of Medicine, Univ of Washington, Seattle, WA.**

**Background:** Activation of protein kinase C-beta (PKC-β) is a key signal transduction mediator strongly implicated in development and progression of diabetic kidney disease (DKD). However, the potential role of PKC-β in podocyte mechanisms of DKD has not been previously studied. The aim of this study was to determine whether advanced glycation end-products (AGE) or serum amyloid A (SAA), inflammatory mediators in DKD, activate PKC-β and downstream consequences of inflammation and apoptosis in podocytes.

**Methods:** Podocytes were exposed to AGE (300 mg/ml) or exogenous SAA (10 mg/ml) for 1 hour. PKC-β activity was measured as the phosphorylated form and by membrane

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

**Underline represents presenting author.**
Podocyte SIRT1 Deficiency Contributes to Albuminuria and Renal Fibrosis in Diabetic Kidney Damage in Mice

**Background:** SIRT1 has been shown to play an important role in stress response, metabolic disorder and aging process, and is suggested to be involved in the pathogenesis of diabetic kidney damage. The study examines whether and how SIRT1 deficiency is involved in diabetic nephropathy.

**Methods:** Metabolic disorder and aging process, and is suggested to be involved in the pathogenesis of diabetic kidney damage. The study examines whether and how SIRT1 deficiency is involved in diabetic nephropathy.

**Results:** Increased PK-β activity is observed in podocytes, indicating that SIRT1 deficiency contributes to diabetic kidney damage. In diabetic mice, PK-β activity is increased in podocytes after exposure to diabetes-related inflammatory mediators. Consequently, podocyte inflammatory and apoptotic responses are mediated by the PK-β pathway.

**Conclusions:** Podocyte SIRT1 deficiency contributes to albuminuria and renal fibrosis in diabetic kidney damage in mice.
**Methods:** C57Bl/6 male mice were randomized to a low fat diet (LFD - 10% of total calories from fat) or a high-fat diet (HFD - 60% of total calories from fat) and treated with L-NIL, a specific INOS inhibitor (0.1 % in drinking water) for 16 weeks.

**Results:** Mice fed a HFD exhibited a significant increase in body weight, fasting blood glucose, plasma levels of NEFA, triglyceride and insulin. iNOS inhibition with L-NIL in the adipose tissue increased these effects. In mice fed a HFD, the infiltration of macrophages and the enhanced MCP-1 level, was also prevented by L-NIL in the adipose tissue.

**Conclusions:** These results suggest that inhibition of iNOS leads to beneficial effects in kidney and adipose tissue in mice fed a HFD. This study opens new areas of investigation on the involvement of iNOS in obesity-induced organ injury.

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

**TH-P0338**

The Impact of Diabetes on Total Glomerular Number and Size in Kidney Estimated by Synchrotron Radiation Micro-CT in Sprng-8

Yumi Takiyama,1 Toshihiro Sera,2 Masanori Nakamura,3 Ryuichi Bessho,4 Kentaro Uesugi,2 Naoto Yagi,2 Masakazu Haneda.3

**Background:** To investigate the impact of diabetes on the number and volume of glomeruli in the whole kidney, we explored CT imaging of male type 2 diabetic db/db mice and of nondiabetic db/m mice at 22 week of age using synchrotron radiation.

**Methods:** Perfused kidneys with contrast medium were removed and visualized using the synchrotron radiation micro-CT in Sprng-8. X-ray image was detected on the fluorescent screen camera coupled synchrotron camera detector with 15.5 mm in the pixel size. A segmentation algorithm was conducted to identify and count all glomeruli within the whole kidney, using image analyzing Amira® software.

**Results:** Db/db mice had larger kidney volume and more glomerular number in right kidney than left kidney. Intriguingly, diabetes abolished this laterality in db/m mice. Db/db mice had larger glomerular volume than db/m mice. Especially, the cortical glomerular size was remarkably increased. On the other hand, diabetes failed to affect the total glomerular number in kidneys. The mean glomerular volume was strongly correlated with fasting blood glucose, kidney volume, urinary volume and glomerular number in all mice, and urinary volume was a significant independent determinant of the mean glomerular volume, whereas the mean glomerular volume was associated with glomerular number.

**Conclusions:** Our study, for the first time, showed the impact of diabetes on total glomerular number and glomerular volume of the whole kidney by developing new imaging analyzing system, providing the possibility of glomerular hypertrophy in subjects before diabetes onset.

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

**TH-P0339**

NADPH Oxidase-Nox5 Plays a Delerious Role in Diabetic Nephropathy

Jay Chandra Jha,1 Stephen P. Gray,1 Claudine Banal,2 Harald H. Schmidt,2 Mark E. Cooper,1 Rhiannon Touyz,1 Chris R. Kennedy,3 Karin JandeLeit-Dahm.1

**Background:** Ins2Akita heterozygote (Akita; 10 weeks old) mice were used. Wild-type (WT) mice were used for control. Akita mice were treated with Top (3mg/kg/day), Feb (1mg/kg/day) or placebo for 4 weeks. Serum urea acid and urinary albumin excretion (UAE) were measured. Glomerular pathological changes were also examined by light microscope and electron microscope. Glomerular permeability was assessed using 2 photon microscopy and fluorescent labeling albumin.

**Results:** Serum urea acid levels showed no significant difference between all groups. Akita+Top or Akita+Feb groups showed significant reduction of UAE in comparison with Akita+Vehi group. Mesangial expansion, glomerular collagen IV deposition, and glomerular dysfunction both in vitro and in vivo RSV acted as a phosphodiesterase 4B inhibitor and SIRT1 activator, attenuated high glucose-induced mitochondrial network fragmentation and impaired oxidative phosphorylation capacity both in vitro and in vivo. Furthermore, it was shown that the protective role of RSV on early-stage DN was probably through AMPK-ACC pathway.

**Conclusions:** These findings suggested that RSV exhibited a strong ability to inhibit high-glucose-induced PTCs damage and may serve as a promising new therapeutic approach for treating early-stage DN.

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

**TH-P0340**

Resveratrol Exhibits Protective Effects on Early-Stage Diabetic Nephropathy by Restoring Mitochondrial Function of Renal Tubular Cells

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**Background:** Diabetic nephropathy (DN) is a progressive and irreversible renal disease. Mitochondrion plays an important role in the pathogenesis of DN. Resveratrol (RSV), a naturally occurring sirtuin-1 (SIRT1) activator, has been shown to promote mitochondrial function. The aim of the present study is to investigate the renoprotective effects of RSV and delineate its underlying mechanism in early-stage DN.

**Methods:** Diabetes was induced by streptozotocin (STZ) injection in male CD-1 mice. Two weeks after the onset of DM, the DM mice were further divided into three subgroups concomitantly treated with placebo, RSV 50mg/kg or RSV 100mg/kg for 28 consecutive days. At the end of RSV treatment course, the mice were sacrificed. Primary kidney proximal tubular cells (PTCs) were cultured in high glucose with indicated concentrations of RSV.

**Results:** In diabetic mice, RSV treatment postponed the progression of DN, as demonstrated by ameliorating the increases of urine albumin excretion, mean arterial pressure level, plasma blood glucose level and plasma triglyceride level. Meanwhile, the increases of plasma creatinine level, plasma BUN level, glomerular diameter, mesangial accumulation and renal fibrosis in diabetic mice were also reduced by RSV treatment. Moreover, orally administration of RSV partly restored the expression and distribution of neprilin, WT1 and podocin. We demonstrated that hyperglycaemia increased mitochondrial mass and mitochondrial DNA content, upregulated miRNA and protein expression of oxidative phosphorylation enzyme complexes in early-stage DN but led to mitochondrial dysfunction both in vitro and in vivo RSV acted as a phosphodiesterase 4B inhibitor and SIRT1 activator, attenuated high glucose-induced mitochondrial network fragmentation and impaired oxidative phosphorylation capacity both in vitro and in vivo. Furthermore, it was shown that the protective role of RSV on early-stage DN was probably through AMPK-ACC pathway.

**Conclusions:** These findings suggested that RSV exhibited a strong ability to inhibit high-glucose-induced PTCs damage and may serve as a promising new therapeutic approach for treating early-stage DN.

**Funding:** Government Support - Non-U.S.
TH-PO342
Effect of Mitochondria-Targeted Ubiquinone Q in Tubular Oxidative Injury of Diabetic Nephropathy Modulated by Mitochondrial ROS/NLRP3/IL-1β Biological Axis
Xiaoxuan Xu, Li Xiao, Chun Hu, Yachun Han, Yashpal S. Kanwar, Fuyou Liu, Lin Sun.
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**Background:** To understand the underlying mechanism by MitoQ attenuate the progression of DN.

**Methods:** 8 patients with DN or primary minimal changes disease were enrolled. Renal pathological changes were observed. MitoQ was intraperitoneally injected to the db/db mice for a week (5mg/kg), the injury of kidney and expression of NLRP3, IL-1β, Caspase-1, FN, Collagen I, Mitochondrial membrane potential (MMP), mt ROS and the mitochondrial translocation of NLRP3 were observed.

**Results:** The expression of NLRP3, IL-1β, IL-18 increased in kidney of DN patients, which were positively associated with the renal pathological change, oxidative injury in db/db mice. MitoQ ameliorated proteinuria, renal damage, mitochondrial dysfunction, oxidative stress, and apoptosis in the kidney of db/db mice, which was accompanied by decreased NLRP3/IL-1β biological axis related protein and Caspase-1, FN, Coll-1. MitoQ also decreased the expression of NLRP3, IL-1β, Caspase-1, FN, Coll-1 and attenuated mROS and apoptosis in HK-2 cells. It also recovered MMP and decreased mitochondrial translocation of NLRP3 induced by high glucose. These effect was blocking partially in transfection with lentiviral vectors expressing NLRP3 plasmid, while this effect was abolished by treated with NLRP3 siRNA.

**Conclusions:** This data indicated that MitoQ ameliorate injury of renal tubular of DN through mROS/NLRP3/IL-1β axis.

TH-PO343

**Background:** Xanthine oxidoreductase (XOR) inhibitor, has been approved as a medicine for hyperuricemia and gout in Japan, and showed a decrease of urinary albumin excretion (UAE) in hyperuricemic stage 3 chronic kidney disease patients in clinical trial. Meanwhile, the induction of oxidative stress and morphological changes known as the representative evidences of diabetic nephropathy (DN) has been reported. We aimed to test the hypothesis that XOR-induced oxidative stress was associated with progression of DN.

**Methods:** Nine-week-old male diabetic db/db mice were fed with diet containing topiroxostat 3 mg/kg (for 4-8 weeks). The levels of plasma uric acid, UAE concentration for 24 hours, and XOR activity of kidney were determined. PAS staining was performed in paraffin section of renal tissue, and then glomerular tuft area, diameter and cell height of proximal tubules were measured with image analysis software. In addition, immunohistochemical staining for nitrotyrosine was performed.

**Results:** Treatment with topiroxostat decreased the levels of plasma uric acid and UAE. XOR activity of kidney in db/db was significantly elevated compared with that in db/m, which was inhibited by treatment with topiroxostat (db/m: 47.1±12.6, db/db: 87.2±19.7, and 3 mg/kg: 16.6±6.4 pmol/min/mg protein; P<0.01, mean±SD). In morphometric analysis, glomerular hyper trophy in db/db control was significantly attenuated by treatment with topiroxostat 3 mg/kg (db/m: 2952±302, db/db: 4028±301, and 3 mg/kg: 3602±270 mm²; P<0.05). The diameter and cell height of proximal tubules in topiroxostat 3 mg/kg group were significantly decreased compared with those in db/db control (db/m: 3.6±2.7, 15.9±2.1, db/db: 43.8±2.0, 18.5±0.9, and 3 mg/kg: 41.7±1.8; P<0.01, 16.8±0.7 mm; P<0.05, respectively). As compared to db/m, glomerular nitrotyrosine positive area in db/db was increased 7.4-fold, which was reduced by 46% by treatment with topiroxostat.

**Conclusions:** Topiroxostat decreased UAE and attenuated renal morphological changes, at least in part, by inhibition of enhanced XOR-induced oxidative stress in DN.

TH-PO344
Knockout of Matrix Metalloproteinase 2 Attenuates the Progression of Renal Disease in Streptozotocin-Induced Diabetic Dhal Salt Sensitive Rat Model
Noriyuki Miyata, Richard J. Roman. Pharmacology and Toxicology, Univ of Mississippi Medical Center, Jackson, MS; Pharmacology Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, Japan; Pharmaceutical Business Planning, Taisho Pharmaceutical Co., Ltd., Tokyo, Japan.

**Background:** We have found that chronic blockade of MMPs with a broad spectrum inhibitor, XLT784, reduced renal injury in type 2 diabetic nephropathy rats. However, the isoforms involved in the development of diabetic nephropathy are unclear.

**Methods:** The present study examined the role of MMP2 in the development of diabetic nephropathy using a MMP2 knockout (KO) rat in the Dhal salt sensitive (DSST) rat model. NIDDK Support, Veterans Administration Support

**Conclusions:** These results indicate that telomerase deficiency promotes DN progression and accelerates glomerular endothelial senescence, implicating a role for the telomere shortening of aging as a predisposing factor for development of DN.

**Funding:** NIDDK Support, Veterans Administration Support
Interaction of the EGF Receptor and the Hippo Pathway in Diabetic Nephropathy  
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Background: Activation of both EGFR and the Hippo signaling pathway can control cell proliferation, apoptosis and differentiation, and their dysregulation may contribute to tumorogenesis. Previous studies have shown that activation of EGFR signaling in renal epithelial cells can exacerbate diabetic kidney injury. YAP is a transcriptional activator that is regulated by the Hippo signaling pathway, which is a kinase cascade in which Mst1/2 kinases and Sav1 form a complex to phosphorylate and activate LATS1/2, which phosphorylate and inhibit the downstream effector, YAP. Mst1/2 kinases are type I diabetes in proximal tubule EGFR deletion mice (EGFR\textsuperscript{−/−}) and their wild type littermates (WT) by (WT) by daily low dose streptozotocin injections for 5 consecutive days. A subset of wild type diabetic mice were administered the EGFR kinase inhibitor, erlotinib. Cell signaling studies were performed in a proximal tubule epithelial-like cell line (LLC-PK1).

Results: STZ injection induced similar levels of hyperglycemia in EGFR\textsuperscript{−/−} and WT mice. Both total and phosphorylated YAP (at Ser127) increased in diabetic WT mice, primarily in proximal tubule cells and these increases were inhibited in EGFR\textsuperscript{−/−} mice or by administration of erlotinib. Further studies demonstrated that EGFR-P38-Akt signaling pathway activation mediated YAP gene expression, YAP nuclear translocation and interaction with the TEAD transcription complex, which led to up-regulation of expression of TEAD-dependent genes, CTGF and AREG (amphiregulin). In a proximal renal tubule cell line, either pharmacologic or genetic inhibition of EGFR or Akt blunted YAP expression in response to high glucose treatment. In addition, knocking down YAP expression by specific siRNA inhibited cell proliferation in response to high glucose or exogenous EGF.

Conclusions: This is the first study to demonstrate that the Hippo pathway downstream effector YAP activation is a mediator of EGFR-mediated renal epithelial injury in diabetes.

Funding: NIDDK Support, Veterans Administration Support

Role of Histone Modification in 12-Lipoxygenase Related P21 Gene Regulation  
Helen Liu; Nyan Liu, 1  Fu Joon Zhong, 2  Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh.

Background: Glomerular hypertrophy is characteristic pathological changes of diabetic nephropathy, which is associated with p21 protein overexpression under diabetic condition. It has been demonstrated epigenetic histone modifications like acetylation (Ac) and methylation (Me) are involved in gene transcriptional regulation. We have certified 12-lipoxygenase (12-LO) and its metabolic product 12(S)-HETE can activate p21 expression, but the mechanism details are still unclear.

Methods: Mesangial cells (MC) from Rat were used for this study. Chromatin immunoprecipitation assay, qRT-PCR and Luciferase assay were used to detect transcriptional activity, enrichment of H3K Ac as well as Me in the promoter region (P) and (T) transcribe region. 12(S)-HETE induction was determined by overexpression of p300 to see changes of 12(S)-HETE related p21 regulation as well as epigenetic modifications.

Results: 12(S)-HETE enhanced p21 transcriptional activity and mRNA expression; in the promoter regions of p21, P1 and T1 transcribe region, 12(S)-HETE induced significant H3K9Ac as well as H3K4Me1 epigenetic modifications, but no changes were seen in T2 region; on the contrary, 12(S)-HETE treatment prevented H3K9Me3 at p21 promoter obviously, suggest complex Me involved in 12(S)-HETE associated p21 regulation; furthermore, overexpression of p300 obviously enhanced basal as well as 12(S)-HETE associated p21 transcriptional regulation in MC. At same time, 12(S)-HETE treatment also induced histone acetylation/fibers p300 occupancy at p21 promoter, reduced demethylase LSD1 nuclear expression and occupancy at p21 promoter.

Conclusions: 12(S)-HETE can induce p300 occupancy at p21 promoter, reduced LSD1 nuclear expression and occupancy at p21 promoter, therefore enhanced H3K9Ac as well as H3K4Me1 at p21 promoter and transcribe regions, decreased H3K9Me3 at p21 promoter, increased p21 expression.

Funding: Government Support - Non-U.S.

E-Box CpG Hypomethylation of NMN-Producing Enzyme Nampt in Proximal Tubules Enables a Constant Supply of NMN from Tubules to Glomeruli, which is Disrupted in Diabetic Nephropathy  
Hirokazu Murakoa, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. Keio Univ.

Background: Nicotinamide mononucleotide (NMN) producing enzyme nicotinamide phosphoribosyltransferase (Nampt) cooperates with a longevity gene, Sirt1, to exert the stress resistance. We previously reported that high expression levels of Nampt lead to NMN production in the proximal tubules (PTs), which contributes to the sufficient supply of NMN to glomeruli (Nat Med 2013). Downregulation of Nampt and NMN in PTs in diabetic nephropathy (DN) leads to glomerular damage. However, the underlying molecular mechanisms by which Nampt is regulated remain unknown. Here, we investigated how Nampt expression is consistently retained at high levels in PTs under normal conditions and decreased in DN.

Methods: Expression levels of Sirt1, TGF-β, and Nampt were measured in PTs of mice with DN. A promoter analysis was performed, and luciferase reporter and gel electrophoresis mobility shift assays were used to examine promoter binding. Methylation levels were investigated with methylation-specific PCR and bisulfite sequencing using laser-microdissected PT regions.

Results: Sirt1 expression in mouse PTs was decreased 8 weeks after DN onset. At 24 weeks, TGF-β production increased, which directly lowered Nampt expression in PTs. The hypermethylation of the E3 and E4 promoter regions by DN could induce transcriptional silencing of Nampt. The methylation levels of E3 and E4 were significantly higher in DN mice than in non-DN mice.

Conclusions: Although E-boxes are generally enhancer regions, Nampt-E-boxs is a conserved sequence with low CpG methylation and is easily bound by AhR/ARNT. This hypermethylation blocked AhR/ARNT binding and decreased Nampt expression. The methylation levels of E3 and E4 were significantly higher in DN mice than in non-DN mice.

Funding: Government Support - Non-U.S.

MicroRNA-21 Silencing as Novel Therapeutic Strategy in Diabetic Nephropathy  
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Background: Diabetic nephropathy (DN) is the main cause of end-stage renal disease. We therapeutically inhibited microRNA-21 (miR-21) in mice with DN.

Methods: We used miR-21 silencing in vivo analysis, qPCR, in situ hybridization, PCR, Western Blot, electrophoretic mobility shift assay and bioinformatic algorithms. Furthermore, we fused the 3’UTR of cell division cycle 25a (Cdc25a) and cyclin-dependent kinase 6 (Cdk6) to a Luciferase reporter gene. Luciferase activity was measured after overexpression of miR-21. 28 patients and 20 controls were included. Mesangial cells (MC) and renal fibroblasts were treated with TGF-β. F-Actin staining. Cell Cycle FACS, scratch migration and BrdU incorporation revealed functional changes. In vivo and in streptozotocin-induced diabetic mice, miR-21 was silenced by locked nucleic acid. Immuno-., PAS- and Sirius red stainings were performed.

Results: MiR-21 was among the most up-regulated miRs in kidneys of diabetic mice and was mainly increased in the glomerular and interstitial compartment. In kidney biopsies of patients, miR-21 correlated with the tubulointerstitial injury. Moreover, miR-21 was tightly associated withalbuminuria, hypertension and inflammation. Activator Protein-1 regulated miR-21 expression. Cdc25a and Cdk6 were identified as novel targets of miR-21 in MC. MiR-21 mediated repression of Cdc25a and Cdk6 resulted in G1-phase arrest and subsequent MC hypertrophy. In renal fibroblasts, we identified dual specificity phosphatase 8 (Dusp8) as novel target of miR-21, in association with extracellular-signal-regulated kinase signaling activation, increasing renal fibroblast proliferation, migration and extracellular matrix production. MiR-21 silencing in diabetic mice ameliorated various functional parameters including mesangial expansion, tubulointerstitial fibrosis, inflammatory cell infiltration, albuminuria and podocyte loss.

Conclusions: MiR-21 antigenism might be a viable therapeutic option in future clinical trials involving patients with DN.

The NMDA Receptor Antagonist MK-801 Reduces Progression of Nephropathy in Two Mouse Models of Type-1 Diabetes  
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Background: Podocytes express ionotropic NMDA receptors that can be activated by endogenous circulating agonists such as L-homocysteic acid and quinolinic acid. Sustained activation of NMDA receptors causes cytotoxicity and oxidative stress in podocytes. Here we report that the prototypical antagonist MK-801 can reduce nephropathy in mouse type-1 diabetes.

Methods: We examined two mouse models: the Akita mice on a DBA/2 background (with DBA/2 mice as controls), and the low-dose streptozotocin (STZ) protocol in DBA/2J mice. MK-801 or saline were administered by surgically implanting subcutaneous Alzet osmotic minipumps (protocol approved by local IACUC). Nephropathy was monitored by periodic analysis of 24-hr urinary samples, and by histology and electron microscopy at the end of the protocol. NMDA subunit expression in renal cortex was examined by immunoblot. MiR-21 was measured in 7-week Akita mice. Urine albumin secretion was already slightly elevated at that age. Over the next 28 days, albumin excretion increased 3-4 fold in saline-treated mice, but did now show a significant increase in the MK-801 group. At the time of sacrifice there was less foot process effacement in MK-801-treated mice. MiR-21 was silenced by locked nucleic acid. Immuno-, PAS- and Sirius red stainings were performed.

Results: MiR-21 was among the most up-regulated miRs in kidneys of diabetic mice and was mainly increased in the glomerular and interstitial compartment. In kidney biopsies of patients, miR-21 correlated with the tubulointerstitial injury. Moreover, miR-21 was tightly associated with albuminuria, hypertension and inflammation. Activator Protein-1 regulated miR-21 expression. Cdc25a and Cdk6 were identified as novel targets of miR-21 in MC. MiR-21 mediated repression of Cdc25a and Cdk6 resulted in G1-phase arrest and subsequent MC hypertrophy. In renal fibroblasts, we identified dual specificity phosphatase 8 (Dusp8) as novel target of miR-21, in association with extracellular-signal-regulated kinase signaling activation, increasing renal fibroblast proliferation, migration and extracellular matrix production. MiR-21 silencing in diabetic mice ameliorated various functional parameters including mesangial expansion, tubulointerstitial fibrosis, inflammatory cell infiltration, albuminuria and podocyte loss.

Conclusions: MiR-21 antigenism might be a viable therapeutic option in future clinical trials involving patients with DN.
Conclusion: These data support the hypothesis that sustained NMDA receptor expression and/or activation contribute to the progression of diabetic nephropathy, and suggest that targeting these receptors might be a useful therapeutic strategy.

Funding: Private Foundation Support

TH-P0352

Role of the N-Type Calcium Channel in a Mouse Model of Diabetic Nephropathy Shoko Ohno,1 Hideki Yokoi,1 Kiyoshi Morii,2 Masato Kasahara,3 Takashige Kuwabara,1,4 Moin Saleem,5 Kazuwa Nakao,2 Motoko Yanagita,1 Masashi Mukoyama,1,4 1Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 2Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 3Inst for Advancement of Clinical and Translational Science, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 4Dept of Nephrology, Graduate School of Medical Sciences, Kumamoto Univ, Kumamoto, Japan; 5Academic Renal Unit, Univ of Bristol, Bristol Children’s Hospital, Bristol, United Kingdom.

Background: Recent clinical studies have shown that an L- and N-type calcium channel blocker cilnidipine reduces urinary protein in hypertensive patients with proteinuria. In the present study, to explore the functional role of N-type calcium channel (Ca.2.2) in diabetic nephropathy, we investigated renal injury in Ca.2.2-deficient diabetic db/db mice.

Methods: We employed mice lacking the N-type calcium channel α1 subunit gene (Ca.2.2+) to generate db/db (diabetic), Ca.2.2-/- double mutant mice. Because the genetic background plays an important role in developing diabetic nephropathy, in this study, we backcrossed Ca.2.2-/- knockout mice on the C57BL/6J background to those on the C57BLKS background.

Results: Ca.2.2-/- was localized in glomeruli, including podocytes, and vascular walls. Diabetic Ca.2.2-/- mice showed lower BP than diabetic WT mice by ~20 mmHg, and exhibited ~50% reduction in urinary catecholamines. Compared with diabetic WT mice, both diabetic Ca.2.2+/- and Ca.2.2-/- mice revealed a significant reduction (by ~70%) in UAE. The increase in mesangial matrix and downregulation of nephrin in diabetic WT mice were alleviated in diabetic Ca.2.2-/- mice. There was an improvement in glycemic control in diabetic Ca.2.2-/- mice but not in diabetic Ca.2.2-/- mice. Furthermore, db/db mice receiving cilnidipine showed a significant reduction in UAE. In vitro, depolarization-dependent calcium entry was abolished by α-conotoxin, a Ca.2.2-specific inhibitor. The reduction of nephrin expression by TGF-β was abolished with α-conotoxin and cilnidipine in podocytes.

Conclusions: The inhibition of Ca.2.2 exerts renoprotective effects against the progression of diabetic nephropathy.

TH-P0353

D-Carnosine Prevents Diabetic Nephropathy in db/db Mice Giuseppe Pagliese, Carla Iacobini, Stefano Menini. Dept of Clinical and Molecular Medicine, La Sapienza Univ, Rome, Italy.

Background: The endogenous dipetide L-carnosine was shown to act as a quencher of reactive carbonyl precursors of advanced glycation end products (AGEs). However, in humans, it is rapidly inactivated by carnosinase. This study was aimed at evaluating the efficacy of the carnosinase-resistant compound D-carnosine (DC) in preventing diabetic nephropathy in db/db mice.

Methods: Adults male db/db mice and the corresponding db/+ controls were treated with a DC derivative (60 mg/kg body weight in the drinking water) or vehicle for 14 weeks. Glomerular sclerosis index (GSI), mean glomerular area (mGA), fractional mesangial area (mMA), and mean glomerular volume (mGV) were assessed morphometrically. Renal expression of inflammatory and damage progression markers were assayed by immunohistochemistry and/or RTPCR. Serum AGEs and immunoreactive-8-epi-PGF2α were measured by ELISA, pentosidine by HPLC and total carbonylated proteins (PCOs) by slot blot immunoassay.

Results: DC treatment induced a significant attenuation of renal disease in db/db mice, whereas it did not influence renal structure in db/+ control mice. Proteinuria (35%), GSI (31%), mGA (32.2 ± 0.27 vs. 35.2 ± 0.21 mm²/10⁴), mGV (137.5 ± 10.1 vs. 157.2 ± 13.7 mm²/10⁴, mMA (428.0 ± 82.5 vs. 588.5 ± 48.7 mm²) and mFA (13.2 ± 1.8 vs. 16.8 ± 1.7%) decreased significantly (P<0.001) in DC-treated db/db mice, as compared with untreated animals. Glomerular staining for HNE adducts (5.6 ± 1.7 vs. 12.8 ± 2.5 % glom area), fibronectin (11.7 ± 2.6 vs. 19.7 ± 1.8 % glom area) and collagen IV (13 ± 3.4 vs. 24.6 ± 3.1 % glom area) were also significantly reduced (P<0.001) in DC-treated vs. untreated db/db mice. The mRNA levels of F4/80, CXCR3, MCP-1, TNF-α, CHOP, RAGE, galecin-3 and CD36 were also significantly lower in db/db mice treated with DC. Finally, serum AGE, pentosidine, PCOs, and immunoreactive-8-epi-PGF2α levels were lower in DC-treated vs. untreated db/db mice.

Conclusions: DC is effective in reducing carbonyl reactive species and preventing renal damage in db/db mice, thus suggesting that carbonyl stress plays a major role in diabetic nephropathy and that DC derivatives might be useful for treatment of this complication.

Funding: Private Foundation Support, Government Support - Non-U.S.
Methods: db/db mice were uninephrectomized at week 6 and received vehicle (water) or PBI-4050 (100 or 200 mg/kg/day) by daily gastric gavage from 6 to 24 weeks of age.

Results: PBI-4050 treatment ameliorated the fasting hyperglycemia and abnormal glucose tolerance tests seen in vehicle-treated db/db mice. In addition, PBI-4050 led to higher serum insulin, C-peptide and GIP levels which correlates with the improvement of glucose tolerance observed by glucose and immunohistochemistry analysis. Kidney function was also improved by PBI-4050 treatment as shown by significant decrease in filtration, proteinuria and mesangial expansion lesions. Furthermore, expression of IL-6, Collagen I, MMP2 and Timp1 in kidney were downregulated by PBI-4050 treatment. Moreover, using human enhancer array in kidney panel, serum IL-6 and IL-9 levels were significantly reduced in PBI-4050-treated mice.

Conclusions: These studies suggest that PBI-4050 improves hyperglycemia, preserves insulin production and β-cell function and survival, and prevents renal fibrosis in association with pro-fibrotic and fibrotic biomarkers.

TH-P0357

Kallistatin Protects against Diabetic Nephropathy in db/db Mice by Suppressing AGE-RAGE-Induced Oxidative Stress

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Background: Kallistatin is a serine protease inhibitor that exerts anti-inflammatory, anti-apoptotic and anti-oxidative effects in regulating cellular dysfunction. As oxidative stress plays a critical role in the pathogenesis of diabetic nephropathy, we aim to investigate the effect and mechanisms of kallistatin gene transfer on diabetic renal injury in the db/db model of type 2 diabetes.

Methods: Plasmid with kallistatin gene was injected into the kidney of db/db mice using ultrasound-mediated microbubble-ioducible gene transfer. The therapeutic potential of kallistatin in diabetic kidney was evaluated by histopathology, renal function, oxidative and inflammatory pathways.

Results: Expression of induction was expressed in tubules of kidney after gene transfer compared with mice treated with empty plasmid. In db/db mice, kallistatin overexpression reduced serum creatinine and BUN levels, ameliorated glomerulosclerosis and tubulointerstitial injury and attenuated renal fibrosis by inhibiting TGF-β signaling and the downstream plasminogen activator inhibitor-1 and type IV collagen expression. Furthermore, kallistatin gene transfer significantly attenuated elevated oxidative stress in db/db mice as evidenced by suppressed levels of Nox4 and the oxidative maker (8-OHdG and MDA) in diabetic renal tissue. Finally, kallistatin inhibited expression of RAGE in both diabetic kidney and AGE-stimulated cultured proximal tubular epithelial cells, reflecting an anti-oxidative mechanism via AGE/RAGE axis.

Conclusions: Our results suggest a renoprotective role of kallistatin against progression of diabetic nephropathy via anti-oxidative properties. Kallistatin reduced AGE/RAGE-induced Nox4 expression, leading to suppression of oxidative stress and TGF-β-mediated renal fibrosis.

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TH-P0358

Kidney pSMAD2 in Type 1 and Type 2 Diabetic Nephropathy Patients and in Mouse Models of Diabetic Nephropathy

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Background: Fibrosis is a hallmark of diabetic nephropathy (DN) leading to chronic kidney disease. However, we lack good animal models resembling kidney pathology of human DN. Renal fibrogenesis has been suggested to be caused by dysregulation of SMAD proteins (CTGF, Gremlin, KCP, USAG1) promoting increased TGFβ activity in both models of diabetes patients. T1D patients showed elevated staining in distal tubuli. Increase in SMAD2 activation in the kidney of diabetes patients. T1D patients displayed elevated staining in proximal tubuli, whereas T2D patients showed elevated staining in distal tubuli. In addition, PBI-4050 ameliorated the fasting hyperglycemia and abnormal glucose tolerance tests seen in vehicle-treated db/db mice. In addition, PBI-4050 led to higher serum insulin, C-peptide and GIP levels which correlates with the improvement of glucose tolerance observed by glucose and immunohistochemistry analysis. Kidney function was also improved by PBI-4050 treatment as shown by significant decrease in filtration, proteinuria and mesangial expansion lesions. Furthermore, expression of IL-6, Collagen I, MMP2 and Timp1 in kidney were downregulated by PBI-4050 treatment. Moreover, using human enhancer array in kidney panel, serum IL-6 and IL-9 levels were significantly reduced in PBI-4050-treated mice.

Conclusions: These studies suggest that PBI-4050 improves hyperglycemia, preserves insulin production and β-cell function and survival, and prevents renal fibrosis in association with pro-fibrotic and fibrotic biomarkers.

TH-P0359

Role of Liver X Receptors in Diabetic Nephropathy and Obesity Related Glomerulopathy

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Background: Our recent human and rodent studies have associated ectopic lipid accumulation and abnormalities in lipid metabolism in the kidney with diabetic nephropathy (DN) and obesity-related glomerulopathy (ORG). Liver X receptors (LXR α and β) are nuclear receptors that are master regulators of cholesterol metabolism and also inhibit inflammation. Next-generation RNA sequencing data show downregulation of LXR pathways in DN. To obtain insight into the pathophysiology of obesity-induced renal lipotoxicity, we investigated the expression of LXRα and their target genes in human DN and ORG kidneys.

Methods: Renal lipid contents, inflammation genes involved in cholesterol and fatty acid metabolism, and LXRα target genes, were studied on amplified mRNA of laser capture microdissection (LCM) isolated glomeruli and tubules from kidney biopsies of patients with established DN (n=16), ORG (N=16), and normal kidneys (n=16).

Results: LXRα and LXRβ mRNA were higher in the glomerular compared to the tubular fraction. LXRα and β mRNA and protein were significantly decreased in DN and ORG kidneys. We found a significant relationship between LXRα mRNA and cGPR2, glomerulosclerosis, and inflammation. Furthermore, we studied the anti-inflammatory effect of different LXR agonists including DNL1CA, TO-901317 and GW3965 against oxLDL and palmitate-induced lipotoxicity in culture podocytes. Our results indicate that all LXR agonists induce cholesterol efflux while DMICA exhibited limited effect on SREBP1c. Furthermore treatment of diabetic db/db mice with the LXR agonist resulted in significant decreases in albuminuria and expression of the proinflammatory cytokines IL-6 and TNFα in the kidney.

Conclusions: Our results suggest that decreased glomerular and tubular expression of LXRα seems to have a role in DN and ORG. Consequently, decreased activity of LXR and related downstream pathway mediators may contribute to lipotoxicity, inflammation and GFR decline. We suggest that modulation of LXR receptors in the kidney may serve as a novel therapeutic target in DN and ORG.

Funding: NIDDK Support

TH-P0360

Dual Activation of FXR and TGR5 by INT-767 Mediates Protection from Diabetic Nephropathy and Retinopathy

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Background: bile acids are agonists for the nuclear hormone receptor, farnesoid X receptor (FXR) and the G protein-coupled receptor TGR5. We have found that TGR5 expression is decreased in human diabetic nephropathy and retinopathy.

Methods: We examined the effect of their combined activation by the dual FXR/TGR5 agonist INT-767 on diabetic nephropathy in DBA/2J mice fed a Western diet and streptozotocin (STZ) induced hyperglycemia.

Results: Diabetic mice developed marked albuminuria, increased glomerular area and mesangial expansion, decreased podocyte (WT-1) density. Diabetic mice also had increased renal triglyceride and cholesterol accumulation, increased NF-kB activity, and increased oxidized protein accumulation. Treatment with 30 mg/kg BW/day INT-767 for 8 weeks normalized albuminuria (ACR), glomerular area and mesangial expansion, podocyte density (WT-1), kidney cholesterol (CHOL), NF-kB transcriptional activity, oxidized proteins, and proinflammatory growth factors TGFβ-1 and CTGF and significantly decreased kidney triglycerides (TG). In addition, in the retina INT-767 also reduced the number of acellular capillaries, decreased the inflammatory infiltration into the retina, and corrected the diabetes-associated endothelial progenitor cell dysfunction, restoring cell migration to nondiabetic levels.

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TH-P0361
High Fat Diet and BCL2-Modifying Factor (Bmf) Overexpression Together Promote Tubular Apoptosis in BMF-Transgenic Mice via Reactive Oxygen Species Generation
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Background: We previously reported that the pro-apoptotic gene Bmf is up-regulated in renal proximal tubular cells (RPTCs) of diabetic obese mice (db/db) compared to normal lean mice (db/+) . We investigated whether high-fat diet (HFD) regulates Bmf expression and RPTC apoptosis and studied its underlying molecular mechanism(s) in RPTCs.

Methods: Non-transgenic (non-Tg) mice, catalase-Tg (Cat-Tg) and Bmf-Tg mice overexpressing Bmf in both rat and human BMF in RPTCs, respectively, were fed normal chow or HFD from 4 to 2 weeks of age. All animals were euthanized at 20 weeks. Blood glucose (BG), systolic blood pressure (SBP) and urinary albumin creatinine ratio (ACR) were monitored bi-weekly. Renal oxidative stress and ROS generation were quantified by dihydroethidium staining and lucigenin assay, respectively. RPTC apoptosis was evaluated by TUNEL assay, immunostaining for active caspase-3 and Bax expression. Pro-apoptotic protein and gene expression was assessed by Western blotting and quantitative-PCR. Rat RPTCs stably transfected with the plasmid pGL4.20 containing rat Bmf gene promoter were also studied.

Results: Non-Tg mice fed HFD had increases in BG, ACR, acetylated p53, renal oxidative stress and pro-apoptotic genes (Bax, Bmf) expression and RPTC apoptosis. Catalase overexpression prevented HFD-induced RPTC apoptosis and pro-apoptotic gene expression in Cat-Tg RPTCs. In contrast, overexpression of Bmf gene in RPTCs with or without HFD aggravated RPTC apoptosis , pro-apoptotic genes expression and ACR. In vitro, high glucose and palmitate attenuated SIRT1 expression, enhanced acetylated p53 expression and stimulated Bmf gene transcription.

Conclusions: We conclude that HFD and Bmf may act in concert to induce ROS-mediated tubular apoptosis, suggesting an important role for Bmf in tubular atrophy in diabetes.

Funding: Government Support - Non-U.S.

TH-P0362
Prevention of Diabetic Nephropathy and Other End Organ Damage by Stem Cell-Based Cure of Type I Diabetes Mellitus in Mice and Rats
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Background: Endogenous insulin replacement by pancreas or islet transplants is currently the optimal treatment to achieve insulin independence and end organ protection in patients with T1DM. However, the limited availability of cadaveric pancreas donors, and both the need for permanent antirejection therapy and repeated islet transplants continue to prevent the widespread use of these therapies. Auto- and allo-immune isolation of transplanted islet cells is currently tested with encapsulation technologies, several of which have failed early. Because β-Cells cannot be adequately expanded ex vivo, Embryonic stem cell-derived pluripotent Stem Cells are evaluated instead. In our present studies, we succeeded to cure T1DM in mice and rats by achieving both adequate culture expansion of islet cells and diabetes control, without altering the robust immune modulating and other trophic actions of Mesenchymal Stem Cells (MSCs).

Methods: Immune isolation of islet cells was accomplished by two methods: either by fusing islet cells and MSCs, creating heterokaryons (β-MSCs), or by generating islet-sized islet-mSC cell clusters (Pseudo islets) composed of islet cells and MSCs. Islet cell expansion was accomplished via reversible epithelial-mesenchymal transition.

Results: Streptozotocin (STZ) diabetic rats and mice and spontaneously diabetic female NOD mice were infused with either β-MSCs or Pseudo islets. STZ-diabetic NOD/SCID mice were identically treated with canine Pseudo islets. Long-term euglycemia and normal BG and normal p53 Glucose Tolerance Tests were obtained in all treated animals. No Xenograft responses were detected in allogeneic groups, no adverse events were observed and no evidence of diabetic nephropathy or other end organ damage was detected. Retrieval of administered cells resulted in prompt return of hyperglycemia.

Conclusions: We conclude that our pre-clinical data have significant translational utility for clinical T1DM. In further preparation for clinical trials, we are currently conducting a Phase I/II Trial in dogs with T1DM.

Funding: Veterans Administration Support

TH-P0363
High Glucose Modules Hedgehog Interacting Protein (Hhip) Gene Expression in Diabetic Related Proximal Tubular Cell Damage
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Background: Hedgehog Interacting Protein (Hhip) is a putative antagonist of hedgehog (Hh) signaling, since both the full length Hhip and its soluble form (sHhip) bind Hh ligands with nanomolar affinity to attenuate the Hh signaling. We previously reported that high glucose (HG) modulates Hhip gene expression and then, targets TGFβ signaling in embryonic renal cells, resulting in impaired kidney formation. Given our prior findings we hypothesized that Hhip might be involved in the evolution of kidney damage in diabetic conditions, such as proximal tubular injury during the development of diabetic nephropathy.

Methods: Two diabetic animal models-- the spontaneously diabetic Akita (T1DM) and db/db (T2DM) mouse models were used for in vivo studies. Renal morphology, immunohistochemistry (IHC), promoter activity analysis and gene expressions were assessed by standard methods. Rat immortalized renal proximal tubular cells (RPTCs) were used in vitro studies.

Results: As compared to non-diabetic Akita littermates and lean db/db animal (db/m), renal oxidative stress and/or sHhip levels were significantly increased in adult Akita and db/db mice at 20 weeks of age. There was strong Hhip- and TGFβ1-HIPC expression in diabetic kidneys, mostly localized to glomerular endothelial cells and renal proximal tubular cells. In vitro, high glucose significantly stimulated the activity of the plasmid containing mouse Hhip promoter in dose-dependent manner. HG stimulated intracellular Hhip and inhibited sHhip level protein expression in time-dependent manner. Hhip siRNA attenuated the stimulatory effect of HG on intracellular Hhip and TGFβ1 gene expression in IRPTCs.

Conclusions: Our data suggest that high glucose increases both Hhip and TGFβ1 gene expression acting in a paracrine fashion to promote renal tubulointerstitial fibrosis in DM, both in vivo and in vitro.

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TH-P0364
Development of Diabetic Nephropathy in Streptozotocin-Treated ID1 Knockout Mice
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Background: Cell injury induces expression of Id1, a BHLH transcription factor inhibitor that regulates cell cycle and differentiation. Id1 knockout results in increased tissue fibrosis in injury models. Since Id1 may have an important role in maintaining vascular stability during hyperglycemia and oxidative stress associated with diabetes, preliminary studies demonstrated the potential value of determining whether deleting Id1 knockout would result in kidney pathology in a diabetic nephropathy resistant strain of mice.

Methods: Id1−/− mice in a B6;129 background and WT littermates were treated with streptozotocin (STZ) 125 mg/kg i.p. for 2 doses to induce type 1 diabetes (DM). Mice with persistent blood glucose levels > 300 mg/dL (n = 10-genotype) were sacrificed at 3 months. Endothelial and perivascular cells from WT and KO mice were cultured in 2% FBS and used at passages 1 and 2.

Results: In WT B6;129 mice, ID1 levels were increased 15-fold at 3 months in response to STZ-induced DM with increased expression detected in glomerular capillary endothelial cells compared with normal mice. WT mice had no pathological changes despite severe hyperglycemia. In contrast, Id1−/− mice developed mesangial expansion and matrix deposition, focal capillary aneurysms and glomerular arteriolar hypertension and increased proteinuria (serum albumin: 0.61 ± 0.26 mg/ml vs. 0.30 ± 0.14 mg/ml, p = .05). KO mice showed a 5-fold increase in glomerular endothelial and tubular epithelial cell proliferation by Ki67 immunohistochemistry. These changes occurred despite no significant difference in average glucose between WT and KO mice. Comparison of primary co-cultures of WT and KO endothelial and perivascular cells demonstrated 10-fold decreased angiopoietin-1 expression by qPCR and decreased autophagy in response to TGFβ in KO cells. These results correlated with marked p62 accumulation in glomerular arterioles in normal and diabetic KO mice.

Conclusions: Glomerular endothelial Id1 expression is increased with type 1 DM. KO mice develop diabetic nephropathy suggesting a protective effect of endothelial Id1. Funding: Veterans Administration Support

TH-P0365
Heterogeneous Nuclear Ribonucleoprotein F Stimulates Sirtuin 1 Expression and Attenuates Renal Proximal Tubular Cell Apoptosis in Mice with Type 2 Diabetes
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Background: We hypothesized that overexpression of the transcription factor heterogeneous nuclear ribonucleoprotein F (hnRNP F) can stimulate sirtuin 1 (SIRT1, a NAD+-dependent deacetylase/lipase) expression and signaling in renal proximal tubular cells (RPTCs), subsequently attenuating RPTC apoptosis in type 2 diabetes. We made and studied db/db (BKS strain) transgenic (Tg) mice specifically overexpressing hnRNP F in their RPTCs. Blood glucose (BG), systolic blood pressure (SBP) and albuminuria were monitored bi-weekly in adult male non-diabetic db/+ littermates, diabetic db/db and/db F-Tg mice from 10 to 28 weeks of age. Background kidneys were processed for histology and apoptosis studies. Renal oxidative stress and reactive oxygen species (ROS) generation were quantified by dihydroethidium staining and lucigenin assay, respectively. Renal proximal tubular (RPT) gene expression was evaluated by real-time qPCR methods. Blotting Rat immortalized RPTCs stably transfected with hnRNP F-G or SIRT 1 gene promoter were also studied.

Results: Db/db mice developed higher BG, SBP, renal hypertrophy and albuminuria at week 20 as compared to db/+ littersmates; db/db hnRNP F-Tg mice did not have elevated SBP, renal hypertrophy or albuminuria. ROS generation, apoptosis, acetylated p53, Bax and active caspase-3 expression were significantly increased in RPT of db/db mice but not in db/db lnRNP F-Tg mice. In contrast, SIRT 1 and caspase-3 expression were significantly decreased in RPT of db/db mice but not in db/db lnRNP F-Tg mice.

Funding: Government Support - Non-U.S.
Finally, overexpression of hnRNPF stimulates SIRT1 protein, mRNA and gene promoter activity and reverses high glucose (35 mM D-glucose) and palmitate inhibition of SIRT1 expression in rat RPTCs in vitro.

Conclusions: Overexpression of hnRNPF attenuated RPTC apoptosis in type 2 diabetic mice via up-regulation of SIRT1 gene expression and signaling. Funding: Government Support - Non-U.S.

TH-PO366
Lack of CD2AP Disrupts Glucose Transporter 4 Trafficking and Attenuates Glucose Uptake

Background: Recent data indicate that adapter protein CD2AP is downregulated in diabetic conditions via PI3K/Akt signaling in podocytes. In this study we investigated the role of CD2AP in insulin-dependent glucose transporter 4 (GLUT4) trafficking and glucose uptake. Methods: Glucose uptake was measured using tritium-labeled 2-deoxyglucose. CD2AP-/- and wildtype (WT) podocytes were transiently transfected with HA-Glut4-GFP to quantify the amount of Glut4 on the plasma membrane and to study the trafficking of Glut4 by live cell imaging. Protein complexes were analyzed by coimmunoprecipitation and Duolink proximity ligation assay (PLA).

Results: The level of glucose uptake was 32% lower in CD2AP-/- podocytes compared to WT podocytes in the basal state. After insulin stimulation, glucose uptake in WT cells increased 19%, whereas CD2AP-/- podocytes failed to respond. Knockdown of Cd2ap in L6 myoblasts with siRNA lowered glucose uptake by 20% in the basal state and blunted insulin-induced glucose uptake in line with this, insulin stimulation increased HA-Glut4-GFP on the plasma membrane by 50% in WT podocytes, whereas no difference was observed in cells lacking CD2AP. Live cell imaging revealed dynamic trafficking of HA-Glut4-GFP in response to insulin in WT cells, whereas in CD2AP-/- podocytes HA-Glut4-GFP formed insulin unresponsive clusters in the perinuclear region. Subcellular fractionation indicated that CD2AP was found in intracellular membrane fractions together with Glut4, IRAP and sortilin, constituents of Glut4 storage vesicles (GSVs). Coimmunoprecipitation and PLA assays revealed that CD2AP forms a complex with GGA2, a clathrin adaptor which sorts Glut4 to GSVs. We further found that lack of CD2AP increases the interaction between GGA2 and clathrin. Insulin stimulation further increased GGA2-clathrin interaction and led to perinuclear accumulation of the complex in CD2AP-/- podocytes. Conclusions: Our results indicate that CD2AP facilitates glucose uptake into podocytes and muscle cells. Interaction of CD2AP with GGA2 suggests a role for CD2AP in sorting Glut4/GGA2 and clathrin. Insulin stimulation further increased GGA2-clathrin interaction and led to perinuclear accumulation of the complex in CD2AP-/- podocytes. Funding: Private Foundation Support

TH-PO367
Tauroursodeoxycholic Acid (TUDCA) Ameliorates Both Tubular and Glomerular Injury in Diabetic Nephropathy, Thus Providing an Added Value to ACE-Inhibition
Mohd Mohd Mohamad Ahmad Al-Dabadi, Andi Marquardt, Fabian Bock, Khurram Shahzad, Madhusudan Thati, Berend Heinrich Isermann. 1Inst of Clinical Chemistry and Pathobiochemistry, Otto-von-Guericke-University, 2Dept of Internal Medicine and Clinical Chemistry, Univ of Heidelberg, Heidelberg, Germany; 3Univ of Health Sciences, Khayaban-e-Jamia Punjab, Lahore, Pakistan.

Background: Therapeutic inhibition of the Ren-Angiotensin Aldosterone System (RAAS) is firmly established in diabetic nephropathy (dNP). Despite efficient RAAS inhibition dNP frequently progresses to end-stage renal disease, necessitating the need for additional and mechanistically distinct therapeutic approaches. We have recently demonstrated that amplification of endoplasmic reticulum stress using TUDCA protects mice from dNP (Madhusudan et al., Nat Comm 2015). To foster clinical evaluation of additional and mechanistically distinct therapeutic approaches. We have recently developed a mouse model of dNP Aggravated by Bridging Fibrosis in Mouse Lacking eNOS Gene
Shota Ozawa, Shuko Ueda, Kiyoshi Morii, Katsuhiko Asanuma, Motoko Yanagita, Takahiko Nakagawa. 1TMK Project, Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Japan; 2Pharmacore Research Laboratories II, Mitsubishi Tanabe Pharma Corporation, Japan; 3Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Japan.

Background: Insulin deficiency leads to an increase in serum free fatty acid concentration. Diabetic glomerular nodules often contain lipid droplet, suggesting that abnormal fatty acid metabolism might contribute to the development of diabetic glomerular injury. However, its precise mechanism remains unclear. Fatty acid binding proteins (FABPs) are currently considered as key molecules for lipid metabolism. Methods: Since diabetic eNOS knockout (KO) mouse is considered to be a good model for human diabetic nephropathy, we here investigated whether FABP could mediate glomerular and tubular injury in this model. Results: First of all, oil red O staining demonstrated that lipid droplets were accumulated in the injured glomeruli in diabetic eNOSKO mice, suggesting that lipid abnormality was involved in the injured process. Microarray assay with isolated glomeruli revealed that among 10 isoforms in FABP family, FABP3 mRNA was most highly expressed in diabetic eNOSKO mice compared to non-diabetic eNOSKO mice. We found that FABP3 protein was predominantly located in the mesangial cells while glomerular injuries were associated with inflammatory processes, such as macrophage infiltration and MCP-1 induction in the diabetic eNOSKO mice. Overexpression of FABP3 resulted in a greater response to palmitate, a saturated FA, to induce MCP-1 in the rat mesangial cells. Furthermore, tubular FABP3 was likely exclusively translocated from cytoplasm to basolateral membrane in proximal tubular epithelial cells under diabetic condition. In turn, the heart, a major organ for FABP3 protein in normal condition, did not show any significant changes in its expression level under diabetic condition in either wild type or eNOSKO mice. Conclusions: FABP3 likely mediates diabetic glomerular and tubular injury. Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma

TH-PO369
Cinchacalcet Ameliorates Diabetic Nephropathy Through Intracellular Ca++-CaMKβ-LKB1-AMPK Activation
Ji Hee Lim, Min Young Kim, Yaeni Kim, Eun Nim Kim, Soojeong Kim, Hyung Wook Kim, Cheol Whee Park. College of Medicine, Dept of Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: In cardiovascular system, the Calcium-sensing receptor(CaSR) simulates the production of NO in the endothelial cells. A decrement in NO bioavailability associated with AMPK inactivation and increased generation of reactive oxygen species are critical to the pathogenesis of diabetic vascular complications. Therefore, we evaluated the renoprotective effect of cinacalcet on glucotoxicity through AMP-kinase pathway (AMPK) in diabetic nephropathy (dNP).

Methods: Male C57BLKS db/db mice and db/db controls at 8 weeks of age were divided to receive either a regular diet or a diet containing cinacalcet (10 mg/kg, n=8, respectively). Mice were followed for 12 weeks and were evaluated for renal functions, pathologic phenotypes, and AMPK-eNOS-NO pathway. Results: Cinacalcet ameliorated albuminuria in db/db mice without influencing the changes in blood glucose and Ca ++ concentrations. The mesangial area expansion and inflammatory cell infiltration in the glomerulus were observed in db/db mice, which were all restored by cinacalcet treatment. Cinacalcet increased expression of CaSR, phosphorylation of CaMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and suppressed oxidized forms of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α. Conclusions: In conclusion, the results suggest that cinacalcet improves glucotoxicity through an increase in intracellular Ca ++-CaMKβ-LKB1-AMPK signaling in the kidney, especially GECs, and may be a potential therapeutic modality for type 2 diabetic nephropathy.

TH-PO370
Ectopic Expression of TIMP-1 and LTBP-2 in Proximal Tubule-Specific Nampt Conditional Knockout Mice Aggravates Bridging Fibrosis in Diabetic Nephropathy
Kazuhiro Hasegawa, Hirokazu Muraoka, Shu Wakinoto, Hiroshi Itoh. Keio Univ.

Background: Nicotinamide phosphoribosyltransferase (Nampt), the rate-limiting enzyme for nicotinamide adenine dinucleotide (NAD) synthesis, and Sirt1, an NAD-dependent histone deacetylase, exert protective effects in various tissues, leading to enhanced stress resistance and extended longevity. We previously reported that proximal tubule (PT) specific Sirt1 knockout mice are protected against diabetic nephropathy (DN), and that PT conditional knockout (CKO) aggravates DN (Nat Med 2013). However, the role of Nampt in DN remains unknown. In this study, we established PT-specific conditional Nampt-deficient mice to investigate the role of Nampt in DN initiation and progression.

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

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Methods: We generated PT-specific, Nampf-deficient mice by crossing Nampf-fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fox fo
Conclusions: Our findings underline that dialysis with a higher cut-off influences endothelial cell function in vitro.


TH-P0375
Pharmacological Inhibition of Prolyl-4-Hydroxylase Improves the Impaired Angiogenic Response to Ischemia in Chronic Kidney Disease

Background: Ischemia-induced angiogenesis is impaired in chronic kidney disease (CKD). Activation of hypoxia-inducible factors has been shown to improve angiogenesis. Here, we investigated whether activation of hypoxia-inducible factors can improve capillary supply in rats with CKD. Inhibition of prolyl-4-hydroxylase (PHD) was started a few hours after onset of hindlimb ischemia.

Methods: CKD was induced in rats by 5/6 nephrectomy; controls were sham operated. After 8 weeks, ischemia of the right limb was induced by ligation & resection of the femoral artery. Post-conditioning activation of hypoxia-inducible factors was induced by 2 intraperitoneal injections of the PHD inhibitor 2-(1-chloro-4-hydroxybenzeneamine-3-carboxamido) acetate (ICA), 12.5 mg/kg, 2 and 6 hours after onset of ischemia. Further animals received placebo injections. Rats were sacrificed 24 h or two weeks after the onset of ischemia. Computer-assisted integration of capillary area normalized for the number of muscle fascicles was performed after double staining for CD31 and laminin of sections of the gastrocnemius muscle.

Results: In control rats, capillary area increased in the ischemic vs. non-ischemic hindlimb by 38±3 % after 2 weeks (p=0.01, N=8). In contrast, there was no significant increase in the ischemic over the opposite limb in CKD (5±4%, N=8, p>0.1). ICA increased capillary supply of ischemic limbs of CKD rats by 45±5 % compared to CKD-placebo rats (n=8, p<0.01), and by 36±4 % (p=0.05) compared to non-ischemic limbs of CKD-ICA animals. After ICA treatment, capillary supply of ischemic limbs was no longer different between CKD and control rats. RT-PCR showed that the ischemia-induced stimulation of VEGF-A was doubled after 24 h by ICA in CKD. The short treatment with ICA did not affect hematocrit levels.

Conclusions: Transient PHD inhibition restores ischemia-induced angiogenesis in CKD rat hindlimb even if applied in a therapeutic approach after onset of ischemia.

Funding: Government Support - Non-U.S.

TH-P0376
Vascular Access Choice in Elderly ESRD Patients

Background: The number of elderly ESRD patients is rapidly increasing. Their high prevalence of comorbidity and short life expectancy result in substantial challenges for choice of vascular access. The aim of this study is to suggest optimal choice of vascular access in elderly ESRD patients who require hemodialysis (HD).

Methods: We included outpatients visiting vascular access clinic between January 2008 and March 2014, retrospectively. We divided these patients into 3 groups by age as follows: younger (<65yrs), elderly (65–79yrs) and very elderly (>80yrs). Various clinical and vascular access associated characteristics were compared among these groups. Cox proportional model was used to analyze the effect of vascular access type on maturation failure, access failure and all-cause mortality.

Results: Among a total of 1,109 patients, 59.1% was men and the mean age was 61±14 years. At the time of HD initiation, 56.4% of patients used central catheters, 38.9% used AVFs and 4.7% used AVGs. Of these, 87.4% (n=973) were chosen AVFs as their permanent vascular access and the proportion of AVF was increased with age. Compared with AVG, AVF was associated with better survival rate, require less intervention to maintain patency and have lower access failure. Very elderly patients had higher proportion of proximal vascular access and also required more preoperative surveillance and interventions. In total patients, the rate of mortality, access failure, maturation failure was 15.7%, 7.1% and 32%. The mortality benefit with RA AVF was superior to that with both BC AVF and AVG for all age. In elderly group, BC AVF has lowest access failure and highest 1yr patency rate compared with RA AVF or AVG. However, in very elderly group, there was no significant associations between access type and access failure or 2ndary outcomes when adjusted for confounding factors.

Conclusions: We concluded that AVF is the preferred form of vascular access for long term outcome in elderly patients. Nevertheless, BC AVF could be considered by individual characteristics in elderly patients who has complicated radiopaque site and a short life expectancy.

TH-P0377
Evaluation of Renal Perfusion in CKD Patients Using Arterial Spin Labelling (ASL) Magnetic Resonance Imaging (MRI)

Background: Evaluation of renal blood flow in chronic kidney disease (CKD) is beneficial for the determination of drug efficacy and prognostic expectations of CKD. At present, radiomolecule scanning or contrast agents are required for this purpose. In this study, we employed arterial spin labeling (ASL) MRI, which is a non-invasive method of measuring tissue perfusion using magnetized blood as an endogenous contrast agent, for the evaluation of CKD patients.

Methods: A total of consecutive 50 CKD patients (33 males and 17 females, 57±16.1 years old) were subjected to MRI, including T1-weighted images, ASL and blood oxygen level-dependent (BOLD) MRI. MRI was performed using a 3.0-T Image (Skyra; Siemens, Erlangen, Germany). MATLAB, a technical computing language for data analysis, was used for the production of a perfusion map, while OsiriX, image-processing software for digital imaging and communications in medicine (DICOM), was used for measuring the signal intensity on each map.

Results: The perfusion map showed that the signal intensity of the renal cortex is higher than that of the medulla. Similarly, T2* map obtained by BOLD MRI showed the same tendency. These findings appear to reflect the differences in the volume of blood flow and tissue oxygenation in each area. Mean cortical blood flow was 134±43.8 in G4 and 180.0±48.6 in G3a/b (ml/min/100g tissue weight, p<0.05), with significant differences observed between the two groups.

Conclusions: A reliable, non-invasive and repeatable system for monitoring renal blood flow is currently clinically available. ASL MRI at 3.0 Tesla provides a method of measuring renal perfusion in CKD patients as well as healthy subjects without the need for the administration of exogenous compounds.

Funding: Government Support - Non-U.S.

TH-P0378
In-vivo Studies of the Microcirculation in Experimental Uremia

Background: Endothelial dysfunction is a clinical hallmark of cardiovascular disease in patients with CKD. We analyzed morphology and function of the microcirculation in vivo in mice with experimental uremia.

Methods: In-vivo microscopy of the muscular cremaster capillary bed was performed in BAL/Bc mice with moderate to severe uremia due to 5/6 nephrectomy or adenine feeding (n=18), and in healthy controls (n=5). Morphological measurements included capillary length, capillary density, and the non-vascularized area. Functional parameters included the arterio-venous difference in oxygen saturation (avΔO2) and the change in diameter (ΔD) before and after application of acetylcholine, sodium-nitroprusside, papaverine and adenosine.

Results: Capillary length was inversely associated with the degree of experimental uremia, with a reduction of 15% per 100 mg/dl increase of serum urea. Overall, there was a heterogeneous pattern of capillary rarefaction, with areas of normal capillary density and capillary-free areas. The mean non-vascularized area in severely uremic animals (urea ≥ 400 mg/dL) was 19.8±10 mm² ± 50.5 x 10^2 mm² and 3.3±10 x 10^2 mm² in controls. The ΔD after pharmacological vasodilatation was 15.4% ± 3.7% in controls, 12.4% ± 4.2% in moderately uremic animals and 7.0% ± 3.5% in severely uremic mice. The avΔO2 was 13.1% ± 2.6% in controls, 11.8% ± 3.3% in moderately uremic and 9.8% ± 2.9% in severely uremic mice, indicating an arteriovenous shunt effect and a diminished oxygen delivery.

Conclusions: These in-vivo studies show a loss of microcirculation in the muscular cremaster of mice with experimental uremia, occurring in a heterogeneous ”wipe-out” pattern. Morphological changes (capillary rarefaction) and functional changes (ΔD, avΔO2) were associated with the degree of experimental uremia. These data suggest that a diseased microcirculation (uremic microangiopathy) contributes to endothelial dysfunction and precedes macrovascular disease in uremia.
Arterial Biopsies of Children with CKD Show Altered Morphology, Calcium Content and Gene Expression

Uwe Querfeld, Betti Schaefer, Aysun Bayazit, Ursula Schulz, Kerstin Sommer, Markus J. Kemper, Guido Laube, Francesca Mencarelli, Sandra Habbig, Franz S. Schaefer, Rainer Bässler, Peter Schmitt. 

Background: The prospective 4C study investigates cardiovascular comorbidity in children with CKD. We have studied arterial biopsies of 4C-patients and age-matched controls. Methods: Arterial biopsies were performed at the time of renal transplantation of patients aged 15.4 (8.8-21) years (n=21). Age-matched healthy control biopsies were obtained from a biobank (Deutsches Herzzentrum Berlin) collecting arterial biopsies from children undergoing elective cardiac surgery. Calcium concentrations were determined by the OCP/GC method. Intima-media thickness (IMT) was measured manually (Image J software) in H&E stained sections. Gene expressions were analyzed by a Custom RT® Profiler PCR Array. Statistical significances were determined using the Holm-Sidak method, with α=5.000%. Results: IMT was correlated with the calcium content of biopsies (r=0.41; P<0.05). Marked transcriptomic alterations were detected in the arteries of the CKD patients: Amongst 34 significantly regulated genes (P<0.05<0.001), SP7 (apoptosis; ratio 4C/controls: 2.75; 5Q2, RUNX2 (24.8), IL-10 (11.3), TNF (8.3) and TRPV6 (7.7) were upregulated, whereas COL1A2 (0.7), TIMP2 (0.26) and ENPP1 (0.31) were downregulated. Conclusions: Arterial biopsies from children with stage 5 CKD show an increased calcium accumulation on osteogenic proteins (VSMC and matrix), calcification transporting proteins, inflammatory cytokines, and downregulation of calcification inhibitors. These findings most likely reflect an early stage of a CKD-specific calcifying arteriopathy.

Capillary Rarefaction in Omental Biopsies of Children with CKD

Dorothea Burghardt, Betti Schaefer, Maria Bartosova, Hamoud Nasser, Birder Lahmann, Joan Nyarangi-Dix, Anja Lingnau, Claus Peter Schmitt.

Background: The omentum is a dynamic organ which is capable of macrophage infiltration and angiogenesis. It serves as a reservoir for mesothelial precursor cells. In chronic kidney disease (CKD), the omental adipose tissue may be a link between inflammation, atherosclerosis and thrombosis. The goal of this work is to study the evolution of atherosclerotic lesions, inflammation and mRNA profiling in an animal model of hypercholesterolemia after CD40 silencing. Methods: 35 APOE-/- mice of 8 weeks old were sequentially euthanized (at 8, 10, 14 and 24 weeks of age). We compared a group treated with a siRNA against CD40 with a control group treated with a scrambled siRNA. Atherosclerotic lesions (red-oil, HE), number of macrophages (F4/80) and degree of NFκB activation, in the aorta, were quantified. Furthermore, a mRNA profiling by microarray hybridization was performed. Results: Silencing CD40 reduced the number (Control-14w:13.7±3.3%, siRNA-14w:7.3±4%, Control-24w:13.7±8.5%, p<0.015) and the progression of lesions (Control-10w:0.10±0.09mm², siRNA-10w:0.01±0.02mm², Control-24w:0.27±0.21mm², siRNA-10w:0.18±0.12mm², Control-24w:0.68±0.06mm², siRNA-24w:0.33±0.16mm², p<0.002). siRNA group displayed lower numbers of infiltrating macrophages (p<0.04) and a lower NFκB activation than controls (p<0.026). mRNA profiling detected 1996 genes up-regulated and 1285 genes down-regulated associated with the progression of lesions. CD40 silencing showed 190 genes up-regulated and 403 genes down-regulated. The involvement of these genes detected the enrichment of biological processes related with tissue remodeling, macrophage differentiation and apoptosis. CD40 silencing was associated with IFN-γ production, chronic inflammation, endothelial cell migration and apoptosis. Conclusions: CD40 and NFκB were associated with the progression of atherosclerotic lesions in the APOE-/- model. Funding: Government Support - Non-U.S.

Diabetic Cardiomyopathy is Associated with Loss of Endothelial Glycocalyx in Coronary Microvessels

Vascular Biology: Atherosclerosis, Inflammation, Endothelium


Funding: Private Foundation Support

Monocyte Subpopulations of Hemodialysis Patients Exhibit Distinct Changes of Cold Shock Y-Box Protein-1 Expression

Lara Ewert, Florian Gunnar Scurt, Christos D. Chatzikyrkou, Sabine Brandt, Peter R. Mertens.

Background: Chronic kidney disease (CKD) and inflammation are risk factors for atherosclerosis. In inflammatory states NF-κB is frequently activated and the CD40/CD40L axis may be a link between inflammation, atherosclerosis and thrombosis. The goal of this work is to study the evolution of atherosclerotic lesions, inflammation and mRNA profiling in an animal model of hypercholesterolemia after CD40 silencing. Methods: 35 APOE-/- mice of 8 weeks old were sequentially euthanized (at 8, 10, 14 and 24 weeks of age). We compared a group treated with a siRNA against CD40 with a control group treated with a scrambled siRNA. Atherosclerotic lesions (red-oil, HE), number of macrophages (F4/80) and degree of NFκB activation, in the aorta, were quantified. Furthermore, a mRNA profiling by microarray hybridization was performed. Results: Silencing CD40 reduced the number (Control-14w:13.7±3.3%, siRNA-14w:7.3±4%, Control-24w:13.7±8.5%, p<0.015) and the progression of lesions (Control-10w:0.10±0.09mm², siRNA-10w:0.01±0.02mm², Control-24w:0.27±0.21mm², siRNA-10w:0.18±0.12mm², Control-24w:0.68±0.06mm², siRNA-24w:0.33±0.16mm², p<0.002). siRNA group displayed lower numbers of infiltrating macrophages (p<0.04) and a lower NFκB activation than controls (p<0.026). mRNA profiling detected 1996 genes up-regulated and 1285 genes down-regulated associated with the progression of lesions. CD40 silencing showed 190 genes up-regulated and 403 genes down-regulated. The involvement of these genes detected the enrichment of biological processes related with tissue remodeling, macrophage differentiation and apoptosis. CD40 silencing was associated with IFN-γ production, chronic inflammation, endothelial cell migration and apoptosis. Conclusions: CD40 and NFκB were associated with the progression of atherosclerotic lesions in the APOE-/- model. Funding: Government Support - Non-U.S.
Upon acetylation YB-1 is secreted via a non-classical pathway, influencing inflammatory processes. As acting by activating chemokines. In dialysis patients prone to inflammations, we investigated monocyte populations and their YB-1 content and degree of acetylation.

**Methods:** The monocytic phenotypes Mo1/Mo2/Mo3 were differentiated by flow cytometry with the surface marker CD14 and CD16. After permeabilisation and antibody staining, intracellular content of acetylated and non-acetylated YB-1 was measured.

**Results:** In dialysis patients (n=63; 63±17 years; in; 41; 22 leukocyte numbers varied markedly (6,500 +/- 2,000/µl) while monocyte fractions were equal among control (n=100; 43±11 years; m; 59; 41) and patient cohorts. An analysis of the monocytic YB-1 content showed that YB-1 was significantly lower in the dialysis cohorts (healthy control: MFI 18000; dialysis cohort: MFI 12000; p=0,001), whereas the amount of acetylated YB-1 was increased in all three monocytic subpopulations in comparison with healthy controls (healthy control: CD14+/YB-1ac 6,6%; n=8; dialysis cohort: CD14+/YB-1ac 8,3%; n=8). Higher amounts of acetylated YB-1 were seen in the dialysis cohort compared to healthy controls (healthy control: CD14+/YB-1ac 6,6%; n=8; dialysis cohort: CD14+/YB-1ac 8,3%). In dialysis patients monocytes belonging to the CD14++YB-1ac++ population were significantly more abundant. Notably, challenge with LPS (5 ng/ml for 2h) resulted in a major shift with loss of the CD14++YB-1ac++ population.

**Conclusions:** Monocytic populations and their YB-1 content are highly regulated and differ significantly between healthy controls and dialysis patients. The cold shock protein YB-1 undergoes acetylation in dialysis patients, which may causally linked to the pro-inflammatory state.

**TH-PO384**

Epoetin Beta Pegas Improves Endothelial Function in Diabetic Nephropathy Rats Even After Onset of Endothelial Dysfunction


**Background:** Endothelial dysfunction is a powerful surrogate marker of cardiovascular events and markers of early atherosclerosis. The development of a diabetic nephropathy (DM) is a useful indicator of endothelial dysfunction in clinical settings. Epoetin beta pegol (continuous erythropoietin receptor activator, C.E.R.A.) is a drug for the treatment of renal anemia. In this study, we examined the ameliorating effect of C.E.R.A. on vascular endothelial function as evaluated by flow-mediated dilatation (FMD) in diabetic nephropathy rats.

**Methods:** Male Spontaneously Diabetic Tori rats (SDT, 22 wks old) were used as type-2 diabetic rats. Male Sprague-Dawley rats (SDD) were used as age-matched controls. C.E.R.A. (0.6, 1.2 µg/kg) was administered subcutaneously once every 2 wks for 8 wks. At 1 wks after last administration (31 wks old), we assessed endothelial function by FMD in the femoral arteries of anesthetized rats.

**Results:** Blood glucose level was over 500 mg/dl in SDT rats. FMD was significantly decreased in SDT rats before the start of C.E.R.A. treatment (22 wks old; SD, 16.2 ± 1.3%; SDT, 10.0 ± 1.3%; n=8), and persisted to 31 wks old (SD, 17.8 ± 1.7%; SDT, 10.4 ± 1.8%; n=7–8). C.E.R.A. dose-dependently improved FMD in SDT rats (31 wks old; C.E.R.A. 0.6 µg/kg, 17.0 ± 2.0%; C.E.R.A. 1.2 µg/kg, 19.2 ± 2.1%; n=7–10) without lowering blood glucose. Endothelium-independent vasodilation by nitroglycerin and kidney function were not changed by C.E.R.A. treatment. Because long-term treatment with C.E.R.A. increased hemoglobin (Hb), we also examined the relationship between Hb up-regulation and FMD improvement in a separate experiment. We found FMD was not significantly improved 1 wk after single administration of C.E.R.A. (SD, 15.5 ± 1.6%; SDT, 10.8 ± 0.5%; C.E.R.A. 0.6 µg/kg, 17.0 ± 2.1%; C.E.R.A. 1.2 µg/kg, 19.5 ± 2.1%; C.E.R.A. 2.4 µg/kg, 20.6 ± 2.6%), whereas Hb levels were comparable with those in long-term C.E.R.A. treatment.

**Conclusions:** These results demonstrated that C.E.R.A. improved endothelial function as evaluated by FMD in type-2 diabetic rats, even after onset of endothelial dysfunction, and these effects were exerted independently of the increasing shear stress induced by hemopoiesis.

**Funding:** Pharmaceutical Company Support - Chugai Pharmaceutical Co., Ltd.

**TH-PO385**

Determinants and Progression of Intimal and Medial Arterial Changes in Children with CKD


**Background:** After kidney transplantation, and these changes are due to modifiable pathophysiology. Conventional ultrasound (CUS) for CA IMT was measured. Vascular Physiology, UCL, London, United Kingdom.

**Background:** To determine the development of atherosclerosis. Increased counts and priming of peripheral polymorphonuclear leukocytes (PMNLs) are associated with future or ongoing atherosclerosis, however, the role of PMNLs in the accelerated atherosclerotic process of hemodialysis (HD) patients is still unclear. We hypothesize that atherosclerosis is a circulatory disease, where circulating primed PMNLs activate monocytes and the endothelial layer, at the circulation. Our aims are to examine endothelial dysfunction, monocytes transmigration, post-transmigration activation and differentiation, induced ex-vivo by primed PMNLs (HD).

**Methods:** A unique ex-vivo co-cultivation system of 3 cells types was developed, enabling interaction among: primary endothelial cells (HUVEC), in-vivo primed PMNLs and monocytes (THP-1), mimicking the initiation of the atherosclerotic process. The interactions among these cells was examined at the cellular, protein and gene expression levels.

**Results:** THP-1 transmigration through pre-treated HUVEC with HD PMNLs showed a significant increase in transmigration.

**Funding:** Clinical Research Support, Clinical Revenue Support, Non-U.S. Private Foundation Support, Clinical Revenue Support, Government Support - Non-U.S.

**TH-PO386**

Is Polymorphonuclear Leukocytes’ Priming a Prerequisite for Monocyte Activation and Transmigration, Initiating the Atherosclerotic Process?

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**Background:** Endothelial dysfunction and monocytes transmigration underlie the development of atherosclerosis. Increased counts and priming of peripheral polymorphonuclear leukocytes (PMNLs) are associated with future or ongoing atherosclerosis, however, the role of PMNLs in the accelerated atherosclerotic process of hemodialysis (HD) patients is still unclear. We hypothesize that atherosclerosis is a circulatory disease, where circulating primed PMNLs activate monocytes and the endothelial layer, at the circulation. Our aims are to examine endothelial dysfunction, monocytes transmigration, post-transmigration activation and differentiation, induced ex-vivo by primed PMNLs (HD).

**Methods:** A unique ex-vivo co-cultivation system of 3 cells types was developed, enabling interaction among: primary endothelial cells (HUVEC), in-vivo primed PMNLs and monocytes (THP-1), mimicking the initiation of the atherosclerotic process. The interactions among these cells was examined at the cellular, protein and gene expression levels. A, post-transmigration activation, B compared to transmigration through HUVEC pre-treated with PMNLs from healthy subjects (HC). THP-1 transmigration correlates with the PMNLs counts and priming state. Pre-treatment with primed PMNLs induced higher MCP-1 expression (2-folds) in HUVEC.

**Results:** The higher levels of monocytes transmigration, post-transmigration activation and endothelial MCP-1 expression mediated by primed PMNLs suggest a novel mechanism for the initiation of the atherosclerotic process, emphasizing the pivotal role of PMNLs in the initiation of the atherosclerotic process.

**TH-PO387**

The Effect of End-Stage Renal Disease (ESRD) on Differentiation of Circulating T Cell Subsets

Hyun Yee Seo, Chae Ho Lim, Seunghyun Lee, Young-II Lee.

**Background:** Progressive loss of renal function is associated with a dysregulation of circulating T cells that may underlie their impaired T-cell immunity. However, it is not known how dysregulation of circulating T cells relates to the ESRD-related T-cell immunity. In this study, we investigated the ESRD-related changes in subsets and differentiation of circulating T cells in ESRD patients.

**Methods:** Adult ESRD patients on HD and healthy subjects were recruited. Peripheral blood was collected in heparin-containing tubes. Circulating of naive, central-memory(CM), effector-memory(EM), and terminal effector-memory(TEM) subsets of CD4 and CD8 T cells. The frequency of apoptotic cells was calculated by scoring annexin-V binding cells after back-gating of CD4/CD8 T cells. CD95(FAS) protein levels were confirmed by Western blot analysis and Flow cytometry.

**Results:** A total of 20 adult ESRD patients on HD (male:female 12:8, DM 65%), and 17 healthy subjects (male:female 6:11) were enrolled. The ESRD patients revealed an increased frequency of CD4+CD25+ Treg and CD4+CD8+ cell compared with healthy subjects. However, the frequency of CD4+CD8+ T cells decreased in ESRD patients. (Figure. 1-A). Circulating of naive, central-memory(CM), effector-memory(EM), and terminal effector-memory(TEM) subsets of CD4+ and CD8+ T cells. CD95(FAS) protein levels were confirmed by Western blot analysis and Flow cytometry.

**Conclusions:** In ESRD patients, the differentiation of effector memory CD8+ T cells increased (Figure 1-B). In ESRD patients, the differentiation of effector memory CD8+ T cells increased (Figure 1-B). In ESRD patients, the differentiation of effector memory CD8+ T cells increased (Figure 1-B).

**Funding:** Clinical Research Support, Clinical Revenue Support, Government Support - Non-U.S.
Cannabinoid Receptor Antagonist Attenuates Cardiac Hypertrophy and Fibrosis in Experimental Chronic Kidney Disease

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Background: Cannabinoid receptor type 1 (CB1R) has been shown to participate in the development of myocardial hypertrophy and fibrosis—two main pathological features of uremic cardiomyopathy. However, it remains unknown whether CB1R is involved in the pathogenesis of uremic cardiomyopathy. Here, we aimed to elucidate the role of CB1R in the development of uremic cardiomyopathy via modulation of Akt signalling.

Methods: The myocardial hypertrophy and fibrosis were evaluated by echocardiography and immunohistochemical staining, respectively, in 5/6 nephrectomy chronic kidney disease (CKD) mice treated with a CB1R antagonist. CB1R and fibrosis marker expression levels were determined by immunohistochemistry in cardiac tissue obtained from CKD mice and in H9c2 cells exposed to the uremic toxin indoxyl sulfate (IS), with an organic anion transporter 1 inhibitor or a CB1R antagonist or agonist. Akt phosphorylation was also assessed to examine the signaling pathways downstream of CB1R activation in both in vitro and in vivo models of uremic cardiomyopathy.

Results: CKD mice exhibited marked left ventricular hypertrophy and myocardial fibrosis, which were reversed by treatment with the CB1R antagonist. CB1R, collagen I, transforming growth factor (TGF)-β, and α-smooth muscle actin (SMA) expression showed time- and dose-dependent upregulation in H9c2 cells treated with IS. The inhibition of CB1R by either CB1R antagonist or small interfering RNA-mediated knockdown attenuated the expression of collagen I, TGF-β, and α-SMA in IS-treated H9c2 cells, while Akt phosphorylation was enhanced by CB1R agonist and abrogated by CB1R antagonist in these cells.

Conclusions: CB1R blockade attenuates LVH and Akt-mediated cardiac fibrosis in a CKD mouse model. Uremic toxic IS stimulates the expression of CB1R and fibrotic markers and CB1R inhibition exerts anti-fibrotic effects via modulation of Akt signaling in H9c2 myoblasts. Therefore, the development of drugs targeting CB1R may have therapeutic potential in the treatment of uremic cardiomyopathy.

Cannabinoid Receptor Antagonist Attenuates Cardiac Hypertrophy and Fibrosis in Experimental Chronic Kidney Disease

TH-PO390

A Novel Interacting Molecule with AT1 Receptor, ATRAP, Inhibits Ang II-Induced Proliferative Activity and Oxidative Stress in Vascular Smooth Muscle Cells

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Background: Ang II influences the structure and function of vascular smooth muscle cells, and plays an important role in reactive oxygen species production. Superoxide anions are recognized as mediators of intracellular signaling cascades and are known to participate in cardiovascular diseases such as arteriosclerosis and hypertension. Previous studies reported that the production of superoxide is modulated by many factors including Ang II - AT1 receptor signaling. One of the major sources of superoxide in the aorta is NADPH oxidase located in the smooth muscle cells.

Methods: We cloned a novel molecule interacting with carboxy-terminal domain of AT1 receptor, which we named ATRAP (for AT1 receptor-associated protein), using the yeast two-hybrid strategy. In this study, we tested the hypothesis that vascular smooth muscle cells express ATRAP and that ATRAP attenuates Ang II-induced proliferative activity and oxidative stress in vascular smooth muscle cells. We used rat smooth muscle cells and used adenoaviral gene transfer for ATRAP overexpression. We used real time PCR,ELISA of TGF-β,p22phox,Rac1,NOx1 and BrdU incorporation assay for cell proliferation.

Results: We identified that the ATRAP mRNA and protein were endogenously expressed in VSMC, and found a colocalization of ATRAP and AT1 receptor in Ang II-stimulated VSMC. The results of gain-of-function studies by adenoviral gene transfer demonstrated that overexpression of ATRAP significantly inhibited Ang II-mediated increases in c-fos gene transcription, BrdU incorporation, and mRNAs expression of NADPH oxidase complex .

Conclusions: These results indicate that ATRAP significantly attenuates Ang II-mediated proliferative activity and oxidative stress in vascular smooth muscle cells, and suggests a novel strategy to inhibit cardiovascular disease such as arteriosclerosis and hypertension.
Myostatin: A Playmaker in Chronic Kidney Disease and Vascular Damage

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Background: Patients with abdominal aortic aneurysms (AAA) have higher prevalence of chronic kidney disease (CKD), that may contribute to arterial deterioration in a mutual detrimental feedback. Myostatin (Mstn), a TGF-β family member with cell-cycle inhibitory effects, is up regulated by CKD, but its role in vascular remodeling is unexplored. We hypothesized that Mstn may play a role in the progression of vascular damage.

Methods: In human AAA (N=8), non atherosclerotic atherosclerosis-related lesions (NAAL) samples (N=7) and normal abdominal aortas (N=3): Rt-PCR for Mstn and Smoothelin, cell proliferation. In monocytes, AAAS upregulated Mstn and α-SMA and Mstn (p<0.05). Mstn colocalized with VSMC (aSMA) and leukocytes (CD45). In A7R5, aSMA. In vitro studies: A7R5 vascular smooth muscle cells (VSMC) and human monocytes exposed to normal sera (NS), sera from patients with AAA (AAAS) or Mstn (500 ng/ml) for 48 hours. VSMC: proliferation, rt-PCR for Mstn and Smoothelin. Human monocytes: rt-PCR for Mstn, α-SMA and MCP-1 dependent chemotaxis.

Conclusions: Our data suggest that Mstn is overexpressed in atherosclerosis lesions at sites of leukocyte infiltration and de-differentiated VSMCs. Unrecognized circulating Mstn, at sites of leukocyte infiltration and de-differentiated VSMCs. Unrecognized circulating Mstn, increases aSMA and chemotaxis (p<0.01).

TH-PO394 Vitamin D Analogs-Induced Ectodomain Shedding of Tumor Necrosis Factor Receptor 1 as an Anti-Inflammatory Action

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Background: 1,25-Dihydroxyvitamin D3 (1,25D3), causes a disintegrin and metalloproteinase 10 (ADAM10)-mediated ectodomain shedding of tumor necrosis factor receptor 1 (TNFR1) in human aortic smooth muscle cells (HASMCs) and thereby decreases responsiveness of the cell to TNF-α. In this study, we examined the potency of other vitamin D analogs, and analogs to induce ectodomain shedding of TNFR1 in HASMCs.

Methods: TNFR1 was measured by Western blot. Intracellular Ca2+ was measured using Fluo-4 AM. ADAM10 was localized by immunofluorescence staining. To examine platelet-HUVEC interactions, we isolated HUVECs, treated with or without FIR radiation, and investigated the expression and decrease platelet adhesion to endothelial cells. These data suggest that FIR irradiation reduced TBXA2R RNA and protein expressions with decreased platelet adhesion to HUVECs. Our result may provide further mechanisms of FIR in the prevention of thrombus formation.

Funding: Clinical Revenue Support

TH-PO395 Effect of Mycophenolate Mofetil on Cytokine Release and Cholesterol Transport in Different Subsets of Polarized Macrophages

Joseph Mattman, Nobuyuki (Bill) Miyawaki, Isaac Teboul, Iryna Voeloshyna, Allison B. Reiss. Medicine, Winthrop-Univ Hospital, Mineola, NY.

Background: Patients with systemic lupus erythematosus (SLE) have a 5-9 fold increased incidence of cardiovascular disease (CVD). Lupus nephritis is commonly treated with mycophenolate mofetil (MPA). We examined the effect of MPA on cytokine release and expression of the proteins involved in cholesterol transport in mononuclear cells (Mφ) in lupus patients treated with MPA.

Methods: THP-1 human monocytes were differentiated to a non-polarized phenotype (M0) (100nM PMA) and then incubated with or without MPA (0.5, 1, 5, 10 and 50 mg/ml). Supernatants were collected and level of IL-10, IFN-γ and TNF-α were analyzed. M0 were then incubated with mycophenolate mofetil (MPA). We examined the effect of MPA on cytokine release and the expression of the proteins involved in cholesterol transport in mononuclear cells (Mφ).

Results: MPA decreased the levels of IL-10 and TNF-α after 48 hours of incubation with MPA. Both M0 and M2 Mφ showed a significant decrease in the levels of IL-10 and TNF-α. MPA also decreased the levels of IFN-γ in both M0 and M2 Mφ.

Conclusions: MPA decreased the levels of IL-10 and TNF-α after 48 hours of incubation with MPA. Both M0 and M2 Mφ showed a significant decrease in the levels of IL-10 and TNF-α. MPA also decreased the levels of IFN-γ in both M0 and M2 Mφ.
Conclusions: MPA has effects on MΦ cytokine release and cholesterol handling which are dependent on MΦ subtype and concentration. These effects may be important in modifying atherogenesis in patients with SLE and may have relevance in kidney transplantation as well.

Funding: Other NIH Support - 5 NCCAM R21 AT00702 02 Allison B. Reiss

TH-PO396
Mitochondria Derived Reactive Oxygen Species and Microvascular Dysfunction in Chronic Kidney Disease

Background: Endothelial dysfunction in chronic kidney disease (CKD) is characterized by reduced nitric oxide bioavailability as a consequence of oxidative stress. Damaged and dysfunctional mitochondria as a result of CKD are likely a large contributor to reactive oxygen species. The aim of this study was to determine if mitochondria derived reactive oxygen species contribute to impairments in nitric oxide mediated microvascular function in CKD.

Methods: Cutaneous vasodilation in response to local heating was assessed in 8 CKD patients (age:67.7 ±7 years; eGFR:48±11 ml/kg/1.73m²) and 8 matched healthy individuals (age:60.6 ±6 years; eGFR:91±11 ml/kg/1.73m²). Participants were instrumented with 2 intradermal microdialysis fibers for the infusion of 1) Ringers solution and 2) mitochondria specific superoxide scavenger mitoTempo. Skin blood flow in response to local heating (42°C) was assessed at the microdialysis sites by laser-Doppler flowmetry. Cutaneous vascular conductance (CVC) was calculated as a percentage of the maximum CVC achieved during sodium nitroprusside infusion at 43°C.

Results: CVC was attenuated in CKD patients compared to healthy controls (86±5 vs 95 ±3 %; p<0.01). MitoTempo significantly improved CVC in CKD patients (CKD Ringers vs CKD MitoTempo: 86±5 vs 93±6, p=0.05) to levels similar to that of healthy controls (CKD MitoTempo vs Healthy Ringers: 93.6 ± vs 95.3 %; p=0.67).

Figure 1. Cutaneous vascular conductance in response to local heating. *p<0.05 vs Healthy Ringers and CKD MitoTempo.

Conclusions: MitoTempo improved cutaneous microvascular function in CKD patients suggesting that mitochondria derived reactive oxygen species play a role in microvascular dysfunction in CKD. Improving mitochondria health and reducing mitochondria derived oxidative stress may be a potential therapeutic target for improving endothelial function in CKD.

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TH-PO397
Indolic Uremic Solutes-Aryl Hydrocarbon Receptor-Tissue Factor: A Novel Antithrombotic Target
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Background: Indolic uremic solutes (IUOS) are a post-translational mechanism. AHR is known to interact with CHIP, a RING-finger E3 ubiquitin ligase, and thus was thought that CHIP regulates AHR. Binding and immunofluorescence studies supported an interaction of CHIP and TF in the cytosol. Deletion of the intracellular domain of TF substantially abrogated the interaction with CHIP suggesting that CHIP binds at the intracytosolic tail of TF. CHIP knock-out and silenced cells showed both significantly elevated TF expression and activity and prolonged TF half-life in uremic milieu supporting CHIP’s role as an E3 ligase of TF.

Conclusions: Our data suggest CHIP as a candidate E3 ligase of TF and raise a tantalizing possibility of aHRBs regulating TF ubiquitination and thrombosis through CHIP. While supporting a novel post-translational regulation of TF, this work in turn will reveal a potential mechanism of action of aHRBs, an emerging class of anti-thrombotics in CKD.

Funding: Private Foundation Support

TH-PO398
APOL1-B3 G2 Risk Variant Perturbs Cholesterol Homeostasis in THP-1 Macrophages
Alex Dinh, Hidefumi Wakahashi, Jurgen Heymann, Alessia Fornoni, Jeffrey B. Kopp. 1NIDDK, NIH, Bethesda, MD; 2Dept of Medicine, Univ of Miami, Miami, FL.

Background: Apolipoprotein L1 (APOL1) circulates in human plasma bound to high-density lipoprotein (HDL). APOL1 G1 and G2 variants increase the risk of developing chronic kidney disease. We examined differences in cholesterol homeostasis in THP-1 macrophages stably expressing G0 and G2 variants of the APOL1-B3 (intracellular) isoform.

Methods: THP-1 cells were stably transfected with the G0 or G2 APOL1-B3 variants or an empty vector, and activated with phorbol myristate acetate (PMA) for 3 days. For cholesterol efflux assays, cells were incubated with 1 µCi/mL [3H]-cholesterol for 24 h. Indolic uremic solutes were added to the media for 4 hr, after which media was collected and quantified. For amphotericin B (AmB), cells were exposed to amphotericin B for 5 h. Cell viability was assessed using the CellTiter-Glo luminescence assay. To generate foam cells, THP-1 cells were stimulated with PMA for 2-3 d and incubated with 20 mg/ml oxidized LDL for 18 h. Cells were stained with Oil Red O (ORO) and quantified.

Results: THP-1 macrophages expressing the APOL1-B3 G2 variant exhibited increased survival compared to cells expressing the APOL1-B3 G0 variant at amphotericin B concentrations of 10 mg/ml (93.2±2.6% vs 79.4%±2.6%), 100 mg/ml (52.4%±0.3% vs 30.8±0.5%), and 250 mg/ml (11.0±8.8% vs 8.0±1.1%), all p<0.01. Cells expressing the APOL1-B3 G2 variant had increased cholesterol efflux compared to cells expressing the APOL1-B3 G0 variant (25.2±3.5% vs 11.6±5.6%, p<0.05). Following incubation with oxidized LDL, APOL1-B3 G2 expressing cells had qualitatively less Oil Red O staining compared to APOL1-B3 G0 expressing cells, indicating a relative decrease in neutral lipid content.

Conclusions: Stable expression of the APOL1-B3 G2 risk variant in THP-1 macrophages increased cholesterol efflux and decreased neutral lipid content compared to APOL1 G0 cells, which could lead to cellular cholesterol depletion. This finding may explain the observed protective effect of APOL1 risk variants on cardiovascular mortality in African Americans with type 2 diabetes, a disease characterized by decreased cholesterol efflux and increased propensity to form foam cells.

Funding: NIDDK Support, Private Foundation Support

TH-PO399
Indoxyl Sulfate-Induced Endothelial Microparticles Stimulate Vascular SMC Proliferation and Neointimal Hyperplasia Formation Through TGF-β Induction
Jung-hwa Ryu, Shina Lee, Dong-Ryoo Ryu, Suk-Kee Kang, Kyu Bok Choi, Seung-Jung Kim. Internal Medicine, College of Medicine, Ewha Womans Univ, Seoul, Republic of Korea.

Background: Vascular access stenosis occurs frequently and predominantly as a result of neointimal hyperplasia formation caused by vascular smooth muscle cell (SMC) proliferation. Previous reports showed that endothelial microparticle (EMP) is closely associated with vascular dysfunction and atherosclerosis. In this study, we investigated the effects of EMP on TGF-β signaling and its association with proliferation of vascular SMC and neointimal hyperplasia formation.

Methods: To produce EMPs, HUVECs were stimulated by indoxyl sulfate (IS). IS-induced EMPs were collected by ultracentrifugation of culture media and sorted by flow cytometry. Human aortic SMCs (1x10^5) were treated with EMPs of 2x10^5 particles Western Blot analysis was done for Akt, ERK1/2, p38 MAPK, and Smad3. SMC proliferation was measured by BrdU cell proliferation assay. TGF-β1 production was measured by PCR and ELISA. Porcine internal jugular veins were cultured ex vivo in the presence of EMPs for 12 days, and immunohistochemistry for TGF-β1 and phospho-specific TGF-β1 signalings was also measured.

Results: EMPs stimulated the proliferation of aortic SMCs in a dose-dependent manner. EMPs induced TGF-β secretion from aortic SMCs as well as the phosphorylation of its down-stream signaling molecules including Akt, ERK1/2, p38 MAPK, and Smad3. The proliferation of aortic SMCs was dose-dependently regulated by the signaling molecules were significantly reduced by anti-TGF-β neutralizing antibody. In ex vivo culture of porcine internal jugular veins, neointimal hyperplasia was significantly developed in EMP-treated venous tissues. The expression of TGF-β1 and the phosphorylated signaling molecules were significantly up-regulated in the area of neointimal hyperplasia.

Conclusions: IS-induced EMPs stimulated the proliferation of vascular SMCs and the production of TGF-β by vascular SMCs, and the proliferation of these cells was mediated by TGF-β. Accordingly, EMPs induced neointimal hyperplasia formation and TGF-β expression in cultured venous tissue. Further investigation is needed to demonstrate the role of EMPs on vascular access stenosis.

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

178A
**TH-PO400**

**Inflammation, Apoptosis, Fibrosis and Vascular Calcification in a Model of Balloon Injury in Rats with Chronic Kidney Disease**

**Artur P. Mendes, ISNI, CHLO, Lisboa, Portugal.**

**Background:** Cardiovascular disease (CVD) is more prevalent and has a worse prognosis in chronic kidney disease (CKD) patients than in the general population and is the leading cause of morbimortality in those patients. Not only traditional risk factors of CVD but also uremia-related ones like inflammation, fibrosis and mineral disorder may contribute to the poor CVD prognosis.

**Methods:** We developed a model of accelerated vasculopathy in rats with CKD to study the vascular damage in CKD: inflammation, apoptosis, fibrosis and vascular calcification. The model consisted of inducing a balloon injury (BI) with an inflated balloon in the carotid arteries (CA) of 5/6 nephrectomy rats and compare the lesion with non-CKD rats (NR). We used 24 Wistar rats.

**Results:** We analyzed the normal and injured CA of NR and CKD rats with histology, immunohistochemistry (IHC) and PCR, 1 week after the BI. With HE, we saw similar intimal hyperplasia in the CA with BI in both groups. With Masson trichrome and sirius red we observed connective tissue mainly in adventitia layer. With IHC for fibronectin we saw abundant expression in hyperplasia areas of the intima of the CA submitted to BI. The expression in the media layer was higher in CKD than NR. In cellular proliferation studies with Mib1 Ab we also appreciated a higher expression of the Ab in the neo-intima of CKD rats. In IHC for activated caspase 3 no expression was noticed in both groups. In the anti-apoptosis marker bcl-xL expression was higher in the neo-intima of CKD than NR. In IH for activated caspase 3 no expression was noticed in both groups. In the anti-apoptosis marker bcl-xL expression was higher in the neo-intima of CKD than NR.

**Conclusions:** In a model of accelerated vasculopathy we have shown a more intense activation of the inflammation and fibrosis pathways in the CKD rats than in NR.

**TH-PO401**

**Post-Transcriptional Guidance of Monocyte to Macrophage Differentiation by the RNA-Binding Protein Quaking**

**Jurrien Prins, Ruben de Bruin, Janine van Gils, Ton J. Rabelling, Anton Jan Van Zonneveld, Eric P. van der Veen. Nephrology, Leiden Univ Medical Center; Leiden, Zuid-Holland, Netherlands.**

**Background:** Injury is associated with excessive recruitment and influx of monocytes to sites of tissue damage and their ensuing differentiation into macrophages. This differentiation is associated with a striking increase in protein expression levels of the RNA-binding protein Quaking (QKI). We therefore set out to investigate the role of QKI in monocyte and macrophage function.

**Methods:** Monocytes expressing an shRNA against QKI were studied for their capacity to adhere, migrate and differentiate into macrophages. RNA-seq and microarray analysis of human monocytes and macrophages, including those of a unique QKI haploinsufficient patient, was performed to identify QKI-mediated signalling events. Identified splice variants of the actin capping protein y-Adducin were validated using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay. Unilateral ureteral obstruction (UUO) on mice hypomorphic for QKI (QK−/−) was performed and analysed.

**Results:** Specific depletion of QKI protein significantly impaired monocyte adhesion, migration and differentiation into macrophages in vitro. RNA-seq and microarray analysis revealed 571 and 629 splicing events in monocytes and macrophages, respectively. One such event was the inclusion of a cassette exon in y-Adducin, which occurred after depletion of QKI protein, and was found to reduce monocyte migration when ectopically expressed. UUO in hypomorphic QKI−/− mice revealed a two-fold reduction in macrophage markers (F4/80 and CD115) and decreased interstitial collagen deposition compared to controls.

**Conclusions:** We show that QKI post-transcriptionally guides monocyte macrophage function in vitro and in vivo, by mediating alternative splicing of pre-mRNA targets of QKI such as y-Adducin. The reduced infiltration of monocytes and ensuing differentiation into macrophages, and deposition of interstitial collagen observed in this high-risk group.

**TH-PO402**

**Induction of Autophagy and Its Role in Endothelial Cell Injury in Response to Carboxylated Low-Density Lipoprotein (cLDL)**

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**Background:** We and others have demonstrated that plasma levels of carbamylated LDL (cLDL) rise in end-stage renal disease and DNA damage and death resulting from a single exposure to 5 mM 3-methyladenine (3-MA) and chloroquine. DNA fragmentation will be measured by a TUNEL assay.

**Results:** Carboxylated LDL treatment of human coronary artery endothelial cells (HCAEC) increased LC3-II 3-4 fold and punctate dots in a dose- and time-dependent manner. Autophagy induction in response to cLDL was observed by conversion of LC3-I to LC3-II by western blot. The formation of cLDL-induced LC3-II vesicles was markedly inhibited by 3-MA. These studies provide the first evidence that cLDL increases LC3-II protein and autophagy in human endothelial cell. The autophagy inhibitor 3-MA suppressed cLDL-induced LDH release, EndoG activation, and DNA fragmentation, suggesting that inhibition of cLDL-induced autophagy provides a cytoprotective role against EndoG activation and cell death in HCAECs.

**Conclusions:** HCAECs treated with cLDL by induction of autophagy in a dose- and time- dependent manner, and inhibition of cLDL-induced autophagy is cytoprotective against cLDL-induced cell death, DNA fragmentation, and EndoG activation.

**Funding:** Veterans Administration Support

**TH-PO403**

**Fractalkine Receptor CX3CR1 on Bone Marrow Derived Cells is Required for Excess Atherosclerotic Inflammation in Renal Impairment**

**Shuwan Gie, Johannes Nordlohne, Barbara Hertel, Hermann G. Haller, Sibylle Von Vichtighoff. Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.**

**Background:** Reduced kidney function is an important risk factor of aggravated atherosclerosis. Inflammatory leukocytes are attracted to the lesion and regulate lesion development by cytokine production. Fractalkine receptor CX3CR1 is highly expressed on peripheral blood leukocytes, but also resident vascular cells such as smooth muscle cells. This study investigated the role of CX3CR1 in atherosclerotic inflammation a mouse model with moderate renal impairment.

**Methods:** ApoE−/− mice without CX3CR1 were protected from increased atherosclerotic lesion size and macrophage accumulation in renal impairment. LDLr−/− mice were similarly protected. Renal impairment increased CX3CR1 expression on aortic macrophages. Conversely, in renal impairment, aortic macrophage numbers were significantly decreased in the absence of CX3CR1. In mixed chimeric mice, absence of CX3CR1 on bone marrow cells only sufficed to decrease atherosclerotic macrophage numbers and aortic root lesion size in renal impairment.

**Conclusions:** CX3CR1 was instrumental in enhanced atherosclerosis in renal impairment. This effect was beyond the CX3CR1 effect observed in normal renal function suggesting that CX3CR1 inhibition should be investigated as a targeted treatment approach in this high-risk group.

**TH-PO404**

**Afferent Arteriolar Endothelial-Dependent Dysfunction Precedes Radiation-Induced Nephropathy and Hypertension**

**John D. Irim, Eric P. Cohen.1,2 Medical College of Wisconsin; 1UNiv of Texas Southwestern.**

**Background:** Chronic kidney disease (CKD) occurs in 15% of hematopoietic stem cell transplant (HSCT) patients, and has been clearly linked to irradiation at the time of the HSCT. Radiation nephropathy is expressed in rats and in humans as azotemia and hypertension. There is a latent period of 6-8 weeks after irradiation to the development of proteinuria, azotemia, and hypertension in rats. We tested the hypothesis that afferent arteriolar responses to the endo-renal-dependent dilator acetylcholine are impaired prior to the development of azotemia and hypertension in rats exposed to total body irradiation (TBI).

**Methods:** Male Apoe−/−C57BL/6J rats were subjected to TBI (11 Gy) and afferent arteriolar responses to acetylcholine using the juxamedullary nephron technique determined at one, three, and six weeks.

**Results:**Systolic blood pressure (117 ± 6 vs. 119 ± 4 mmHg) and BUN (15.6 ± 1.4 vs. 15.8 ± 0.8 mg/dL) were different between control and TBI groups at 6 weeks. Afferent arteriolar diameters averaged 22.5 ± 0.8 mm (n=30) in controls and 21.7 ± 0.7 mm (n=27) in TBI rats and were not different between control and TBI groups at 1, 3, or 6 weeks. Acetylcholine dilator responses were progressively attenuated from one to six weeks in TBI vs control rats. There is a latent period of 6-8 weeks after irradiation to the development of proteinuria, azotemia, and hypertension in rats. We tested the hypothesis that afferent arteriolar responses to the endo-renal-dependent dilator acetylcholine are impaired prior to the development of azotemia and hypertension in rats exposed to total body irradiation (TBI).

**Conclusions:** Male WAG/RijCmcr rats were subjected to TBI (11 Gy) and afferent arteriolar responses to acetylcholine using the juxamedullary nephron technique determined at one, three, and six weeks.

**Funding:** This work was supported by the National Institutes of Health grants 1R01HL126003 and 1R01HL131910.
Elevated Lp-PLA2 Plasma Activity Is an Independent Predictor of Subclinical Atherosclerosis in CKD5-D Patients – No Correlation with Lp-PLA2 mRNA Expression in Isolated Monocyte Subsets

Elevated Lp-PLA2 plasma activity was measured by an enzymatic kinetic test and leucocytic Lp-PLA2 mRNA expression by real time PCR. Monocyte subsets were analyzed flow-cytometrically and defined as classical monocyte (CD14+/CD16-) intermediate monocyte (CD14+CD16-), and non-classical CD14+CD16+(Mo3) mRNA expression analysis for these subsets (N=24) was done after sorting of cells using ARIA II FACS-sorter.

Results: 60 CKD-D (62.3±15.5 years) patients and 39 healthy control subjects (54.0±18.4 years) were enrolled in a cross-sectional study. Lp-PLA2 mRNA expression in leucocytes and plasma Lp-PLA2 activity were significantly higher in CKD5-D-D patients diagnosed with subclinical atherosclerosis (A+) than the highest Lp-PLA2 activity values, which even remained significantly different compared to A- after adjustment for age and Hba1c. Among different monocyte subsets Mo1 and Mo2 had the highest Lp-PLA2 mRNA expression level, but it was Lp-PLA2 mRNA expression on “patrolling” Mo3 cells which was significantly elevated in A+ versus A-.

Conclusions: We conclude that Lp-PLA2 activity is an independent predictor of subclinical atherosclerosis in CKD5-D patients. Among monocyte subsets Mo3 cells appear to have an exceptional position within the setting of atherosclerosis. These vessel sorting cells may reflect a physiological response to vascular inflammation in CKD5-D patients.

Funding: Private Foundation Support

Atherosclerosis following Renal Injury Is Ameliorated by Pioglitazone and Losartan via Macrophage Phenotype

Background: Chronic kidney disease (CKD) amplifies atherosclerosis which involves renin-angiotensin system (RAS) regulation of macrophages. RAS influences peroxisome proliferator-activated receptor-γ (PPARγ), a modulator of atherogenic functions of macrophages, however, little is known about its effects in CKD related vascular pathology.

Methods: Apolipoprotein E knockout mice were uninecrophrornized (UNx) and treated with pioglitazone, losartan, or both (UNx+Pio/Los) for 10 weeks. Extent and characteristics of atherosclerotic lesions and macrophage phenotypes were assessed. Peritoneal macrophages and RAW264.7 cells were used to examine pioglitazone and losartan effects on macrophage phenotype and inflammatory response.

Results: UNx significantly increased atherosclerosis. Pioglitazone and losartan each significantly reduced the atherosclerotic burden by 29.6% and 33.5%, respectively; however the benefit was dramatically augmented by combination treatment (57.7%). Assessment of plaques revealed significantly greater macrophase area in UNx+Pio/Los with more apoptotic cells and an expanded macrophage-rich lesions of UNx+Pio/Los had more actively activated, Ym-1 and arginase 1-positive M2 phenotypes. There was no difference in plaque collagen content or calcifications. In vitro, pioglitazone alone and together with losartan was more effective than losartan alone in dampening lipopolyasarhichic-induced cytokine production, preserving M1 phenotype change while enhancing M2 phenotype change.

Conclusions: Combination of pioglitazone and losartan is more effective in reducing renal injury-induced atherosclerosis than either treatment alone. This benefit reflects mitigation in macrophase cytokine production, enhanced apoptosis, and a shift toward an anti-inflammatory phenotype.

Funding: NIDDK Support
Methods: To identify novel angiopoietins peptides, we isolated these peptides from a human angiopoietins library.

Results: Angiopoietin A (Ang A) is a potent endothelial cell growth factor and plays a role in angiogenesis. Peptides isolated from this library were tested for their ability to promote endothelial cell proliferation. One peptide, named VIF (Vasoconstriction Inhibiting Factor), was identified and characterized. VIF is a 13-amino acid peptide that inhibits vasoconstriction and promotes vasodilation.

Ang II, a key regulator of cardiovascular function, is a potent vasoconstrictor. VIF antagonizes the contractile actions of Ang II. These physiological actions of vasoconstrictor actions of Ang II by Angiopoietin is mediated by the Mas receptor. Angiopoietin has a stronger affinity to the Mas receptor than to Ang II receptors. Plasma concentrations of healthy humans were about 15% in Ang II and 28% in Ang A concentrations. Both Ang A and Ang II have the same affinity for the AT receptor as Ang II, but a higher affinity for the AT receptor. Ang II revealed a less vasocostrictive effect than Ang II in vitro, which is not modified in the presence of the AT2 receptor antagonist PD123319, suggesting a lower intrinsic activity at the AT receptor.

In healthy subjects, Ang A concentrations are less than 20% of the Ang II concentrations, but the ratio Ang A / Ang II is higher in CKD patients up to 50% of plasma Ang II concentrations. Ang A has the same affinity to the Mas receptor as Ang II.

Angiopoietin A is a novel human, vasoconstrictive angiopoietin-derived peptide. Due to stronger agonism at the MAS and AT receptor, respectively, and further-more their increased plasma concentration in CKD, Ang A may modulate the harmful effects of Ang II.

TH-PO410
Phosphate (Pi)-Induced Endothelial Microparticles Express Histone H2B which Supports Thrombin Generation
Nima Abbaasan,1 Karl Herbert,2 Janice Haynes,3 Niguel J. Barlow,2,3,1 Allen Bevington3

Background: Cardiovascular disease is common in patients with chronic kidney disease. Hyperphosphatemia is a well-known cardiovascular risk factor which we have recently shown can induce the formation of pro-coagulant endothelial microparticles (EMPs) through upregulation of tissue factor (TF) and phosphatidylserine (PSer) expression. EMPs express TF and PSer on their surface; however, a comprehensive characterization of the antigenic composition of PI-induced EMPs has been poorly defined.

Methods: EMPs were isolated from healthy human plasma. EMPs were probed by immunoblotting using anti-H2B antibody. The presence of DNA and RNA in EMPs was determined by using DAPI and RNase A, respectively. The presence of PI in EMPs was determined by using crystal violet staining.

Results: EMPs were isolated from healthy human plasma. EMPs were probed by immunoblotting using anti-H2B antibody. The presence of DNA and RNA in EMPs was determined by using DAPI and RNase A, respectively. The presence of PI in EMPs was determined by using crystal violet staining.

Conclusions: EMPs play a crucial role in the pathogenesis of thrombosis in vivo. In conclusion, EMPs are a novel platform to study kidney microvasculature in vitro while maintaining the structure and morphology observed in vivo.

Funding: Pharmaceutical Company Support - Biogen

TH-PO413
The Circadian Clock Provides Beneficial Effects against the Endothelial Dysfunction to Promote Atherogenesis by Regulating Plasma-Activator Inhibitor-1 and Cellular Adhesion Molecules Generation
Hidetaki Negoro, Medicine, Harvard Medical School, Boston.

Background: The circadian clock is a molecular mechanism that confers 24 hours variation in gene expression and function to regulate number of physiological functions in human. Dysregulation of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic cardiac circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence plasma-activator inhibitor-1 (PAI-1) and cellular adhesion molecules, such as monocyte chemotactic protein-1 (MCP-1) and intracellular adhesion molecule-1 (ICAM-1) which play an important part in the progression of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for further studies. We also knocked down Bmal1 to evaluate the protein levels of PAI-1, MCP-1 and ICAM-1 in the knocked down cells.

Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in MCP-1 and ICAM-1 expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include circulating fibrinogen and PAI-1, which are significantly elevated in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating PAI-1 and cellular adhesion molecules generation. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Other U.S. Government Support

TH-PO414
TNF-Alpha Receptor 1 Is Associated with Mortality in Persons with Coronary Artery Disease
Mary Whooley, Michael Shlipak. UCSF.

Background: Inflammation is a possible mechanism to explain the association between atherosclerosis and mortality. Chronic kidney disease is associated with high levels of inflammation. This study evaluated circulating tumor necrosis factor receptor type 1 (TNFR1A), a marker of inflammation, as a risk factor for mortality.

Methods: In the Heart and Soul Study, a cohort with established coronary artery disease (CAD), we measured TNFR1A from baseline serum samples and defined elevated levels of TNFR1A by the highest quartile (Q4, > 3.4 ng/ml). Our outcomes were myocardial infarction, hospitalization for heart failure, and death. The sequence of the peptide isolated from human plasma was HSGFEDSVLENQOSPSELKEVEAPSPKDVME. Both peptides diminished significantly the vasoconstrictive effect of Ang II in vitro. Therefore, we named the peptide “vasoconstriction inhibiting factor” (VIF). The vasoregulatory effects of VIF were observed in vivo and VIF impairs Ang II-induced phosphorylation of the p38MAPK-pathway but not of ERK1/2. The vasodilatory effects were confirmed in vivo.

Results: The plasma concentration in humans was quantified in chronic kidney disease patients, heart failure patients and healthy controls. The amino acid sequence of the peptide from bovine adrenal glands was HSGFEDSVLENQOSPSELKEVEAPSPKDVME, which is a degradation product of Chromogranin-A. The sequence of the peptide isolated from human plasma was HSGFEDSVLENQOSPSELKEVEAPSPKDVME. Both peptides diminished significantly the vasoconstrictive effect of Ang II in vitro. Therefore, we named the peptide “vasoconstriction inhibiting factor” (VIF). The vasoregulatory effects of VIF were observed in vivo and VIF impairs Ang II-induced phosphorylation of the p38MAPK-pathway but not of ERK1/2. The vasodilatory effects were confirmed in vivo.

Conclusions: VIF is a vasoregulatory peptide which modulates the vasoregulatory effects of Ang II by acting on the AT2 receptor. It is likely that the increase in VIF may serve as a counter-regulatory effect to defend against hypertension. The identification of this target may help us to understand the pathophysiology of renal and heart failure and may form a basis for the development of new strategies for the prevention and treatment of cardiovascular disease.
unadjusted analyses [incident rate ratio (IRR) 2.56 (95% CI 1.73-3.81)]. This was attenuated by adjusting for ESRD (IRR 1.82 (95% CI 0.92-3.60)). The higher rate associated with AHI was retained in all unadjusted and adjusted analyses [adjusted IRR 1.79 (1.12-2.86)] as well as with death [adjusted IRR 1.6 (1.22-2.1)].

**Conclusions:** Levels of TNFR1A are elevated in CKD. TNFR1A is independently associated with HF and mortality. These findings implicate inflammation as a potential contributor to the elevated mortality risk in persons with CAD.

**Funding:** NIDDK Support

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**TH-PO415**

**Blood Monocyte Profiles and P2X7 Receptor Expression in Chronic Kidney Disease and End-Stage Renal Disease**

Serika D. Naicker, Susan Logue, Deirdre Cotter, Matthew D. Griffin. REMEDI, School of Medicine, National Univ of Ireland, Galway, Ireland.

**Background:** Monocytes are innate immune cells with 3 subsets [Classical (CD14++CD16−), Intermediate (CD14+CD16+), and Non-classical (CD14+CD16−)] which have distinct pathogenic roles in chronic inflammation and atherosclerosis. We quantified blood monocyte subsets in a cohort of patients with CKD and ESRD/chronic hemodialysis (cHD) and evaluated their expression of the inflammasome-activating ATP receptor P2X7.

**Methods:** CKD stage 1-5 was assigned based on MDRD eGFR. PBMCs from healthy adults (CTRL, n=25), patients with CKD stages 1-5 (n=100) or ESRD prior to and after HD (n=32) were analyzed by 8-colour flow cytometry to quantify monocyte subsets and their surface expression of P2X7 receptor. PBMC stimulation cultures were carried out using optimized concentrations of TLK ligands ± ATP.

**Results:** Total monocyte numbers progressively increased from CTRL through CKD stages 1-5 and remained higher in the HD group. Among the subsets, Intermediate monocytes were most highly expanded in CKD in a stage-dependent manner. ESRD patients additionally demonstrated higher numbers of non-classical monocytes which diminished significantly following HD. Surface expression of P2X7 was readily detected on all monocyte subsets in CTRL. CKD Stages 1-5 and ESRD but was most highly expressed by Non-classical monocytes. Compared to CTRL, all stages of CKD were associated with higher monocyte expression of P2X7 but, in ESRD, this was further increased on Non-classical monocytes following HD. High-level interleukin (IL)-1 beta release by monocytes from CTRL and CKD/ESRD patients was observed upon brief exposure to the P2X7 ligand ATP following priming with ligands for TLR4 (highly expressed by Classical monocytes) or TLR7/8 (highly expressed by Non-classical monocytes) indicating active inflammasome response in multiple monocyte subsets.

**Conclusions:** CKD is associated with a stage-dependent increase in circulating monocytes that is greatest for the Intermediate subset. Non-classical monocytes are also expanded in ESRD and modulated by HD. The P2X7 receptor, which mediates inflammasome activation via extracellular ATP, is expressed by all monocyte subsets in ESRD. TNFR1A is expressed by all monocyte subsets in all stages of CKD and ESRD/cHD. Among the subsets, Intermediate monocytes were most highly expressed by Non-classical monocytes. This highlights the potential of P2X7 as a therapeutic target for monocyte mediated inflammation in CKD.

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

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**TH-PO416**

**Activation of CXCL16/CXC R6 Pathway by Inflammation Accelerates the Progression of Atherosclerosis in ESRD Patients**

Zebo Hu, Kun ling Ma, Yang Zhang, Bi-Cheng Liu. 1Inst of Nephrology, Southeast Univ, Nanjing City, Jiang Su Province, China; 1Inst of Nephrology, Southeast Univ, Nanjing City, Jiang Su Province, China.

**Background:** Objective Chronic inflammation plays a crucial role in the progression of atherosclerosis (AS). The current study aimed to observe the effects of inflammation on lipid accumulation in the radial arteries of end-stage renal disease (ESRD) patients with arteriovenous fistula (AVF). We investigated the expression of AS markers, including macrophage infiltration, foam cell formation, and lipid accumulation.

**Methods:** Forty-seven ESRD patients were divided into control group (n=20) and inflamed group (n=27) according to plasma C-reactive protein (CRP) level. Biochemical index and lipid profile of patients were measured. Surgically removed tissues from the radial arteries of patients receiving arteriovenous fistula were used for the experiments for preliminary evaluation of AS. Foam cell formation was observed by Hematoxylin-eosin (HE) and Filipin staining. CXCL16/CXC R6 pathway related protein expressions and the expression of Monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor α (TNFα), and CD68 were detected by immunohistochemistry staining and immunofluorescence staining.

**Results:** Immunohistochemical staining demonstrated that inflammation increased both protein expressions of MCP-1 and TNFα in the arterial areas of inflamed group accompanied with macrophage infiltration. Further analysis showed that there were significantly increased foam cell formation in continuous cross-sections of radial arteries of inflamed group compared to the controls, which were closely correlated with increased protein expressions of CXCL16, CXC R6, and decreased protein expression of ADAM10.

**Conclusions:** Inflammation contributed to foam cell formation in the radial arteries of ESRD patients via the activation of the CXCL16/CXC R6 pathway.

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**TH-PO417**

**Ablation of Pericytes Induces Capillary Rarefaction and Proximal Tubular Injury**

Janewit Wongboonsin, Rafael Kramann, Susanne V. Fleig, Flavia G. Machado, Benjamin D. Humphreys. Renal Div, Brigham and Women’s Hospital, Boston.

**Background:** We recently showed that Gli1+ cells in the pericyte niche are the predominant source of myofibroblasts in kidney fibrosis. One hypothesis for the mechanism of capillary rarefaction observed in fibrotic kidney disease is that injury induces pericyte detachment from endothelium, leading to capillary dropout. There is no direct evidence supporting this idea, however. In this study we measured pericyte detachment during injury, and asked whether ablation of pericytes in the absence of any other injury destabilizes capillaries and induces tubular injury.

**Methods:** We performed unilateral ischemia-reperfusion injury (IRI) in bigenic Gli1CreERT2;fTdTomato mice and performed fluorescence microangiography (FMA) at 2 weeks after injury to delineate the renal microvasculature and quantitate detachment of Gli1+ cells from capillaries. In a second set of experiments we ablated Gli1+ in Gli1CreERT2, iDTR mice by diphtheria toxin injection, performed FMA and analyzed peritubular capillary changes by automated software-based quantification over a time course of 56 days.

**Results:** After IRI, Gli1+ cells proliferate and detach from the renal microvasculature. Specific genetic ablation of Gli1+ cells triggers peritubular capillary rarefaction and induces focal cortical and tubular injury. While peritubular capillary number decreased, peritubular capillary perimeter and area remain unchanged. Injured tubules were characterized by focal Ki67 expression in cortical areas with decreased FMA+ perfored capillaries. Renal Ki67 and Hif1α mRNA expression increased early after Gli1+ cell ablation. Interestingly, while mice with collagen1a1 mRNA expression decreased early after ablation, confirming the role of Gli1+ cells as myofibroblast progenitors, we detected increased expression of both fibrinogen and von Willebrand reads at 56 days after ablation. Immunostaining for aSMA showed focal cortical areas with myofibroblast expansion and scar formation.

**Conclusions:** Ablation of Gli1+ pericytes in healthy kidney causes peritubular capillary rarefaction, focal tubular epithelial injury and focal fibrosis in the outer cortex most likely due to hypoxia.

**Funding:** NIDDK Support

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**TH-PO418**

**Activation of Tie2 by Deletion of VE-PTP Increases GFR in Mice**

Isabel Anna Carota,1,2 Chengjin Li,1 Vera Eremina,1 Tuncer Onay,1 Susan E. Quaggin. 1Div. of Nephrology/Hypertension and Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago; 2Eli Lilly and Company; 3Samuel Lunenfeld Research Inst, Mount Sinai Hospital, Toronto, Canada.

**Background:** With an increasing number of patients suffering from CKD, there is an urgent need for new therapeutic targets. The Angiopoietin-Tie2 signaling pathway has been implicated in the development of kidney disease. In CKD patients elevated levels of circulating Angpt2, the antagonist of the tyrosine kinase receptor Tie2, correlate with a decrease in glomerular filtration rate (GFR). Additionally it has been shown that loss of Angpt1, the Tie2 agonist, leads to enhanced glomerular scarring in diabetic Angpt1−/− mice. These findings suggest that an imbalance of Tie2 ligands is associated with progression of renal disease. Here we investigate the impact of Tie2 activation on baseline renal function by genetic deletion of its negative regulator the endothelial specific phosphataseVE-PTP in an inducible KO mouse model.

**Methods:** To study the effect of Tie2 activation following loss of VE-PTP, we generated inducible VE-PTP KO mice. Kidneys were examined histologically and phosphorylation level of Tie2 was quantified by IP from lung lysates followed by Western blot analysis. GFRs were measured using the FITC-Sinistrin clearance method (n=7 KO, 6 controls at 10 weeks).

**Results:** Knock-out of VE-PTP enhances Tie2 phosphorylation 2-fold resulting in enhanced Tie2 activity in a ligand-independent manner. Deletion of VE-PTP before embryonic day 13.5 leads to the formation of dilated glomerular capillaries, which are not observed in kidneys of mice when VE-PTP is deleted after E18.5. In contrast, mGFRs of VE-PTP KO mice (deletion after E18.5) were increased from 298.6±28.0 in controls to 458.1±27.9 ml/min in KO litter mates (p<0.016). Both groups showed no difference in blood pressure, albuminuria or renal histology.

**Conclusions:** Inhibition of VE-PTP leads to elevated Tie2 phosphorylation suggesting VE-PTP is a potential target to rescue the effects of increased Angpt2 levels that occur in CKD patients. The increased GFR observed in VE-PTP KO mice suggest that disrupting VE-PTP–Tie2 interactions may be a strategy to slow progression of CKD.

**Funding:** Other NIH Support - RC1HL124120, Pharmaceutical Company Support - Eli Lilly and Company

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**TH-PO419**

**Circulating VEGF-C Levels Are Associated with Insulin Sensitivity in End Stage Renal Disease Patients**

Sernil Mugo Deges,1,2 Adriana Hung,1 Edward D. Sorensen, Chang Sha,1,2 Charles D. Lim,1,2 Iain Titz,1 Talat Alpkilic,1,2 Vanderbilt Univ, Nashville, TN; 1VA, Nashville, TN.

**Background:** Insulin resistance (IR) is a common metabolic derangement in advanced kidney disease. We have previously demonstrated that inflammation is a key mediator of IR in end-stage renal disease (ESRD). Vascular Endothelial Growth Factor C (VEGF-C) is a key regulator of lymphangiogenesis that may contribute to IR. Recent experimental data suggest that the VEGF-C pathway may have important effects on adipose tissue IR by promoting macrophage recruitment. The relationship between VEGF-C and IR in humans
Lymphatics and Vascular Function in Renal Health and Disease
Poster/Thursday

TH-PO420
Disruption of Angiopoietin-Tie2 Signaling Leads to Cystic Kidney Disease
Yael Kenig-Kozlovsky,1 Rizaldy P. Scott,1,2 Benjamin R. Thomson,1,2 Shinji Yamaguchi,1 Christine Jiang Wu,1 Stefan Heinm,1 Susan E. Quaggin,1,2 1Div of Nephrology-Hypertension and Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago, IL; 2Lunenfeld-Tanenbaum Research Inst, Toronto, Canada.

Background: Angiopoietin ligands Angpt1 and Angpt2 and their cognate receptor Tie2/Tek are essential for development of the heart and systemic blood vasculature. While investigating their function in the shaping of the complex renal vasculature, we uncovered that mid-gestational inactivation of the Angpt1/Angpt2-Tie2 signaling axis remarkably impairs the development of lymphatic vasculature and specialized “hybrid” vessels and/or lymphatic drainage of interstitial fluid in the kidney. Our study highlights a hitherto unidentified role of angiopoietin-Tie2 signaling in the pathogenesis of renal cysts and suggests this pathway as a potential therapeutic target to alleviate cystic kidney disease.

Conclusions: Our data suggest that macrophage have a partial role in HD production and HA-induced renal lymphangiogenesis in UUO model.

TH-PO421
Role of Macrophage in Hyaluronic Acid-Induced Lymphangiogenesis in UUO Model
Won Kim, Jong-Hwan Jung, Yujin Jung, Kyung Pyo Kang, Sik Lee, Sung Kwang Park. Chonbuk National Univ Medical School.

Background: Hyaluronic acid (HA) is one of important component of extracellular matrix proteoglycan, has many biologic and pathologic effects such as inflammation, angiogenesis, wound healing and tissue remodeling. Renal lymphangiogenesis has been demonstrated in a rat remnant kidney model and in mouse unilateral ureteral obstruction (UUO) model. However, there is few data about role of macrophage in HA-induced lymphangiogenesis in UUO. We investigated the effect of macrophage in HA-induced lymphangiogenesis in UUO.

Methods: RAW 264.7 cells (RAW cell, macrophage cell line) were incubated with TGF-beta1 (1, 5, and 10 ng/mL) treated cells were evaluated by ELISA. LYVE-1-positive lymphatics, HA, vascular endothelial growth factor (VEGF)-C were evaluated by immunofluorescence and ELISA in UUO-induced fibrotic kidney treatment with or without clodronate (macrophage depleting agent).

Results: To evaluate the changes in HA expression in macrophages, RAW cell were treated with TGF-b1. We found that TGF-beta1 (1, 5, and 10 mg/mL) increased hyaluronic acid synthase (HAS1), HAS2 and HAS3 mRNA expression in the cells. ELISA data demonstrated that treatment of RAW cells with TGF-b1 (10 ng/mL) increased HA production in a time-dependent manner. In UUO model, renal HA level was higher in ureteral obstruction operated kidney than that of sham-operated kidney. Our immunofluorescence finding showed that HA is expressed on interstitial space in UUO kidney. HA accumulation is correlated with the number of LYVE-1-positive lymphatic vessels after ureteral obstruction. HA expression was also costained with F4/80-positive renal macrophages 7 days after ureteral obstruction. Depletion of macrophage with clodronate significantly decreased UUO-induced renal HA expression and UUO-induced increased density of LYVE-1-positive lymphatic endothelial cells. We also found that VEGF-C expression in the kidney was significantly decreased in UUO kidney after treatment with clodronate compared to that after treatment with control buffer.

Conclusions: These results suggest that macrophage may have a role in HA production and HA-induced renal lymphangiogenesis in UUO model.
Novel Mechanisms for Salt Sensitive Hypertension in Humans: Effects of Salt Loading on Skin Sodium, VEGF-C and Blood Pressure

Kvinne V. Selvarajah,1 Kaisa Maki-Petaja,1 Liliana Domingues Pedro,2 Sylvaine Fa Bruggerbauer,1 Carmel M. McEniery,1 Ian Wilkinson,3 ‘Div of Experimental Medicine and Immunotherapeutics, Univ of Cambridge, Cambridge, United Kingdom; 2MBF Human Nutrition Research Unit, Fulbourn, Cambridge, United Kingdom.

Background: Dietary sodium is an important trigger for hypertension. Animal studies show that the skin buffers dietary salt and salt-loading induces lymphangiogenesis mediated by VEGF C from macrophages, helping to maintain BP in response to salt load. The relevance of these mechanisms in humans is unclear.

Methods: We conducted a double-blind randomised crossover trial examining the effects of dietary salt loading on skin sodium, systemic haemodynamics, ambulatory BP and plasma VEGF-C in 48 healthy participants. Participants were placed on a low salt diet (70mmol sodium/day). Dietary compliance was checked using 24hr urine collections. Skin biopsies were taken after placebo and slow-sodium treatment (200mmol daily for 7 days). Skin Na and K concentrations (mg/g tissue) were analysed by ICPOES. Results were expressed as the ratio of Na:K to correct for variability in sample hydration. Plasma VEGF C was analysed by ELISA.

Results: Skin data was available for 47 individuals. Mean age was 29.9 ± 8.3 with mean baseline urinary sodium 98.8 ± 55.0 mmol/24h. 24hr urine sodium excretion increased from 71.4 ± 43.1 to 225.9 ± 89.0 mmol (p< 0.001) with salt loading. Ambulatory MAP showed a non-significant increase from 88.7 ± 7.0 to 89.7 ± 7.4 mmHg (p= 0.10). Office MAP was unchanged. Skin NaK increased from 2.91 ± 0.56 to 3.12 ± 0.62 (p=0.01). Percentage change in NaK was negatively correlated with baseline NaK (r=–0.40; p=0.007). Changes in ambulatory MAP correlated positively with baseline skin NaK (r=0.30, p=0.048). Stroke volume correlated with skin NaK post placebo (r=–0.42;p=0.002) and slow sodium (r=–0.53, p=0.0001) respectively. No significant change was noted in plasma VEGF C.

Conclusions: Skin NaK appears to increase with dietary salt loading and the degree of change correlates with baseline NaK levels. Ambulatory blood pressure change with dietary salt loading correlates with baseline skin NaK, supporting a possible role for the skin as a buffer for dietary salt.

Albuminuria Downregulates NKCC2 via Stimulation of COX-2/mPGES-1/PGE2 Cascade in Thick Ascending Limb

TH-PO425

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Background: The renal sodium handling defect in nephrotic syndrome patients is characterized by increased urinary and plasma sodium and a rise in plasma renin activity. Despite of the physiological importance of NKCC2 in NaCl homeostasis, the molecular mechanisms for its membrane trafficking have not been fully elucidated. In 2012, Carmosino et al. (Biol. Cell. 104(11): 658-676) reported that moesin, which is a member of ERM (Ezrin-Radixin-Moesin) family, plays an important role in the apical membrane trafficking of NKCC2 by in vitro experiments.

Methods: We examined the physiological impact of Moesin in the regulation of renal function in vivo by using male moesin-null (Msn−/−) mice. Wild-type (Msn+/+) and Msn−/− mice were treated with or without albumin (2 g/100 g body weight) for 12 days. The mouse kidney tissues and renal biopsy specimens from proteinuric patients with nephrotic syndrome patients. However, the pathogenic mechanisms remain elusive. Here we examined NKCC2 expression in kidney biopsy specimens of proteinuric patients via immunohistochemistry (IHC) and found a 50% downregulation of NKCC2 which was negatively correlated with COX-2 and mPGES-1 expression. By IHC, stimulation of COX-2 and mPGES-1 were localized in the thick ascending limb of Henle’s loop. Stimulation of COX-2 and mPGES-1 were significantly enhanced by 82% following albumin overload. Interestingly, inhibition of COX-2 and mPGES-1 was observed, which significantly decreased COX-2 and mPGES-1 expression. These novel findings highly suggest that albuminuria plays an important role in the regulation of renal salt handling.

Conclusions: Stimulation of COX-2 and mPGES-1 could play a pivotal role in the regulation of renal salt handling in the nephrotic kidney.

TH-PO426

Paracellular Cation Selectivity in the Thick Ascending Limb of Henle’s Loop Increases Under the Control of Vasopressin

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Background: The thick ascending limb of Henle’s loop (TAL) has the highest paracellular cation selectivity along the nephron. Transepithelial voltage as driving force for the paracellular reabsorption of cations can be generated either by transepithelial transport properties or by paracellular cation diffusion. Arginine vasopressin (AVP) has been shown to stimulate active transepiscopal NaCl transport and we hypothesize that paracellular permeability properties are co-regulated to support the increase in NaCl reabsorption.

Methods: To measure long term regulation 8-10 week old mice were kept for 4 days on low sodium diet, AD (0.256g NaCl/24h) or high (water diuresis WD, 0.78mg g NaCl/24h) water intake. Spot urine osmolality was determined as treatment indicator. For acute AVP experiments mice were kept at water ad libitum. mTAL were isolated perfused and transepiscopal electrone光学ic properties (transepiscopal resistance Rp, voltage Voc, equivalent short circuit current Isc) were assessed as well as paracellular properties (NaCl) dilution potential, ion permeabilities PNa, PCl).

Results: mTAL of AD mice showed a higher active transepiscopal transport compared to the WD group tubes, represented by a two-fold increase in Isc. Urine osmolality was positively correlated to Isc. NaCl dilution potential was increased in the AD group, indicating a higher PNa/Pi and a higher Rp compared to WD. PNa/Pi as a measure of paracellular cation selectivity was also positively correlated to urine osmolality. mTAL from untreated mice showed an increased activity. mTAL treated for 12 minutes by 100nM AVP (n=6), in paired experiments, Isc increased while it decreased in a time control group. At the same time, AVP induced an increase in PNa/Pi compared to time controls.

Conclusions: Acute application of AVP as well as water restriction increase paracellular cation selectivity and permeability in mTAL in parallel to the increase of active transepiscopal NaCl transport.

TH-PO427

Adult Nephron-Specific MR-Deficient Mice Develop a Severe Renal Pseudohypoaldosteronism Type 1 Phenotype

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Background: Aldosterone is the main mineralocorticoid hormone controlling sodium balance, fluid homeostasis and blood pressure by regulating sodium reabsorption in the ascending thick ascending limb of Henle’s loop (TAL). Increased urinary sodium excretion in adulthood is a common feature in patients with tubular sodium excretion (TAL) and is characterised by increased urinary and plasma sodium, increased renin activity and increased aldosterone production. Despite that, the precise mechanisms by which aldosterone promotes renal sodium reabsorption are currently not well understood. Two recent studies have shown that a novel sodium reabsorbing system present in TAL, named the mineralocorticoid receptor (MR) in humans and in mice lead to the “renal” form of type 1 pseudohypoaldosteronism (PHA-1), a case of aldosterone resistance characterized by salt wasting, dehydration, failure to thrive, hyperkalaemia and metabolic acidosis. In 2019, Schlosser et al. reported that PHA-1 phenotype could result from a reduction in MR expression in TAL. However, the exact mechanism by which MR expression is reduced in PHA-1 phenotype is unknown.

Objectives: To investigate the impact of MR in adult epithelial cells, we generated nephron-specific MR knockout mice (MRKO−/−) using a doxycycline inducible system.

Results: Under standard diet, MRKO−/− mice exhibit inability to gain weight and significant weight loss compared to control mice. Interestingly, despite failure to thrive, MRKO−/− mice were able to survive but develop a severe PHA-1 phenotype with higher urinary Na+ levels, decreased plasma Na+, hyperkalaemia and higher levels of plasma aldosterone. This phenotype further worsens and becomes lethal under a sodium-deficient diet. NCC protein expression and its phosphorylated form are downregulated in the MRKO−/− kidneys, as

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

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well as αENaC protein levels, whereas the expression of glucocorticoid receptor (GR) is increased. A diet rich in NaCl low in K+ does not restore plasma aldosterone to control levels, but is sufficient to restore body weight, plasma and urinary electrolytes.

Conclusions: In conclusion, MR expression along the nephron and in the collecting duct system during adulthood is crucial for Na+ and K+ homeostasis, and its deletion cannot be compensated either by sodium transporters including ENaC, nor by GR overexpression, but solely by a high Na+ and low K+ rescue diet.

Funding: Government Support - Non-U.S.

TH-PO428
The Suczyniec Receptor 1 Is a Physiological Regulator of the Renin-Angiotensin Aldosterone System
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Background: It has been shown that oxidative stress in diabetes type I (T1DM) induces tubular release of mitochondrial succinate and that subsequent activation of the SUCNR1 in the juxta-glomerular apparatus is needed for renin release and T1DM-induced hypertension. Here, we tested whether the SUCNR1 also has a physiological role in renal water and electrolyte handling.

Methods: Wild-type (wt) and SUCNR1-/- mice 10 weeks old were placed in metabolic cages and 24-hour clinical parameters were analyzed in order to assess physiologically relevant differences. After sacrifice, kidneys were weighed and collected for further analysis.

Results: Blood and urine analysis of wt and SUCNR1-/- mice showed that wt mice possessed higher plasma sodium and serum potassium concentrations, had a significant decreased plasma sodium concentration. KO mice develop a severe and lethal phenotype, characterized by severe body weight loss, hypertension, and low in K+ does not restore aldosterone to control levels, but is sufficient to restore body weight, plasma and urinary electrolytes.

Conclusions: Our data demonstrate that the single beta- and gamma-ENaC subunits are crucial for daily maintaining sodium and potassium balance in adulthood.

Funding: Government Support - Non-U.S.

TH-PO429
Adult Nephron-Specific Beta- and Gamma-ENaC Knockout Mice Develop a Severe Pseudohypoaldosteronism Type 1 Phenotype
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Background: The epithelium sodium channel (ENaC) consists of three subunits (alpha, beta and gamma ENaC) that are expressed at the apical side in tight epithelia in the kidney, and is limiting for sodium reabsorption. Mutations in ENaC subunits are causative for the human pseudohypoaldosteronism type 1 (PHA-1) syndrome. Here, we deleted beta- and gamma-ENaC from the adult kidney using an inducible and kidney-specific CreloxP-mediated recombination system.

Methods: We used 4-week-old doxycycline inducible nephron-specific beta- and gamma-ENaC knockout mice obtained by crossing the double transgenic mouse (PAX8- LCL), which expresses the reverse tetracycline transactivator under the control of a tetracycline response element (Traykova-Brauch et al., 2008) with the floxed Scnn1b and Scnn1g mice, respectively (Merillat et al., 2009).

Results: Already following 3-4 days of doxycycline treatment, beta- and gamma-ENaC KO mice develop a severe and lethal phenotype, characterized by severe body weight loss, severe hyperkalemia (beta-ENaC KO: 11.5 ± 1.0 mmol/l, n = 7; C57, 5:5, M/M, n = 21; p < 0.001; gamma-ENaC KO: 11.4 ± 1.0 mmol/l, n = 6; C57, 5:5, n = 7; p < 0.001), and dehydration. Beta-ENaC KO mice additionally suffer from severe hyponatraemia, while the gamma-ENaC KO present with significant decreased plasma sodium concentration.

Conclusions: Our data demonstrate that the single beta- and gamma-ENaC subunits are crucial for daily maintaining sodium and potassium balance in adulthood.

Funding: Government Support - Non-U.S.

TH-PO430
New Mechanistic Insights into the Regulation of ENaC by AMPK in Kidney Epithelial Cells
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Background: Renal collecting duct epithelial Na+ channels (ENaCs) play a key role in total body volume and blood pressure control. The metabolic sensor AMP-activated protein kinase (AMPK) inhibits ENaC currents in kidney and other epithelial cells, but the mechanisms involved are unclear. We hypothesized that AMPK regulation of ENaC could be mediated by modulation of ENaC degradation, ENaC subunit cleavage status, and/or ENaC protein synthesis.

Methods: Mouse polarized kidney cortical collecting duct (mpkCCD-14) cells were cultured on Transwells for immunoblot analysis and equivalent short-circuit current (Isc) monitoring after AMPK activity modulation and proteasomal or lysosomal inhibitor treatments. Apical domain biotinylation assays were performed to measure changes in ENaC apical membrane expression, and cycloheximide chase assays were performed to investigate ENaC stability.

Results: AMPK activation decreased cellular ENaC stability in cycloheximide chase assays. ENaC-dependent I(1) was inhibited by the AMPK activators AICAR and A769662 (Abbott), and these effects were blocked by the proteasomal inhibitor MG132, but not by the lysosomal inhibitor leupeptin. Western blot analyses revealed that AMPK activation decreased both mature and immature beta-ENaC expression as well as cleaved-gamma-ENaC expression, while increasing uncleaved-gamma-ENaC expression. Moreover, treatment of mpkCCD-14 cells with AMPK activators decreased p70S6K expression, suggesting decreased signaling of the mTOR pathway involved in protein synthesis and cell proliferation. Finally, AMPK activation decreased apical cell surface expression of both mature beta- and cleaved-gamma-ENaC, the active forms of ENaC, an effect that was blocked by MG132.

Conclusions: AMPK-dependent regulation of ENaC in mpkCCD-14 cells occurs by: 1) increased targeting of ENaC for proteasomal degradation, thereby decreasing cellular ENaC stability; 2) inhibition of g-ENaC cleavage and g-ENaC surface expression; and 3) inhibition of ENaC protein synthesis along with mTOR pathway inhibition.

Funding: NIDDK Support.

TH-PO431
Sodium Retention in Nephrotic Syndrome Occurs Independently of Proteinuria
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Background: Patients with nephrotic syndrome often present symptoms of volume retention, such as edema formation or hypertension. The primary dysregulation was localized to the renal cortical collecting duct and involves an inappropriate activation of the epithelial sodium channel (ENaC). Plasma renin levels passing the leaky glomerular filter were made responsible; however, clinical observation demonstrated signs of volume retention before the initiation of proteinuria.

Methods: To elucidate the relationship between sodium retention and proteinuria tamoxifen-soluble podocin (Nphs2)(-/-) and Nphs2(-/-) mice were infused via the jugular vein with either saline vehicle (V) or a 290 mmol/l solution of tamoxifen (T); podocin(-/-) Nphs2(-/-) demonstrated reduced sodium excretion on day 7 (Na+/creatinine: 24±10 vs. 22±8 mol/mg) while proteinuria occurred on day 11 (protein/creatinine: 13±1 vs. 6.5±0.8 mg/mg). Blood pressure started to increase on day 10 (BP: 120±12 vs. 74±10 mmHg) and remained high till the end of the treatment. In mice with nephrotic syndrome western blot analysis of kidneys harvested on the day 9 of the experiment demonstrated no change in the full length ENaC subunit abundance and a 3-fold increase in the 30 kDa ENaC cleavage product. Nephritic kidneys at the day 21 of the experiment demonstrate strongly increased abundance of full length and cleaved forms of alpha- and gamma-ENaC.

Conclusions: The IGF1 receptor can also bind IGF1. Here, we tested whether the SUCNR1 also has a physiological role in renal water and electrolyte handling.

Funding: Government Support - Non-U.S.

TH-PO432
Altered Renal Electrolyte Handling in Mice with Genetic Knockout of the Inulin-Like Growth Factor-1 Receptor (IGF1R) from the Collecting Duct Principal Cell
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Background: IGF1, produced predominantly in liver, can be increased in the circulation during metabolic disease (MetS) due to hyperinsulinemia. In addition to anabolic effects, IGF1 can increase sodium reabsorption in the renal collecting duct (CD); however, the role of IGF1 in these effects is uncertain, since the insulin receptor can also bind IGF1.

Methods: To address the role of IGF1R in the CD, we produced CD-principal cell-specific IGF1R knockout (KO) mice, by crossing mice with Cre recombinase driven by an aquaporin-2 promoter with mice with losp sites flanking IGF1R gene. Adult KO mice were of normal body weight and had no overt alterations in kidney structure/function. To test the impact of IGF1 infusion on urinary electrolytes, anesthesia infused male WT and KO mice were infused via the jugular vein with either saline vehicle (V) or a 290 µmol solution of IGF1 (1) in saline at a rate of 15 µl/min for 60 minutes (n = 5 genotype/treatment). Urine was collected via a cannulated bladder.

Results: Urine volume was reduced by IGF1 and the reduction was blunted in the KO versus WT mice (9.3±1.2 (WTV), 9.2±1.4 (KTV)) (P<0.05). Urine Na+ and K+ excretion were increased in the KO compared to WT in all genotypes (41±6 (WTV), 59±9 (KTV); 86±9 (WTV), 70±11 (KTV) µmol/mg) for treatment. In WT, IGF1 infusion led to a significant 42, 65, and 67% reduction in the concentration of Na+, K+, and Cl-, respectively in urine. Total urine Na+ in the WTV was 20% of WTV. In contrast, the excretion of electrolytes was relatively maintained in KO, i.e., IGF1 led to a 19, 21, and 17% reduction in Na+, K+, and Cl- concentrations, respectively, and means (KOV versus KOI) were not significantly different. The ratio of Na+ to K+ in the urine was also affected by genotype, i.e., increased by 76% in the WT, but reduced...
by 9% in the KO (p = 0.023 for interaction). A benzoil test (ENaC antagonist, 1.4 mg/ kg bw) was revealed 23, 34, and 27% (all significant) reduced total Na+, K+, and Cl- in the KO versus WT in 4-hour urine.

Conclusions: These results support a role for IGF1 via the IGF1R to increase Na+ and Cl- reabsorption in the CD, through activation of ENaC. Thus, IGF1 may play a role in sodium retention associated with MetS.

Funding: NIDDK Support

TH-PO433
ENaC Activity in the Cortical Collecting Duct of HKA, H-K-ATPase Knockout Mice Is Unaffected from Na Intake James D. Stockland, Elena V. Mironova, Vladimir V. Bugay, J. Jeanette Lynhe, Michelle L. Gumz, Elena V. Mironova, Vladimir V. Bugay, J. Jeanette Lynhe, Michelle L. Gumz, Charles S. Wingo,1,2 1Univ of Texas HSC, San Antonio, TX; 2NF/SG VHS, Gainesville, FL, 1Univ of Florida, Gainesville, FL.

Background: The renal HK-ATPases are integral membrane proteins of the collecting duct (CD), a segment that mediates Na reabsorption via the mineralocorticoid regulated epithelial Na channel, ENaC. ENaC activity is inversely related to dietary Na intake, a relationship essential to blood pressure (BP) regulation, and its dysfunction contributes to salt-sensitive hypertension. Mineralocorticoids stimulate the activity and expression of renal HK-ATPases. We hypothesized that HK, H-K-ATPase knockout (KO) would affect ENaC activity.

Methods: Na reabsorption was measured by in vitro microperfusion in CCD from KO and control mice fed a 0.2% Na diet. Single channel analysis of ENaC activity in split open CCD by cell-attached patch clamp and measurements of urinary ATP were performed on KO and control mice fed a 0.2, or 2.0% Na diet.

Results: Na reabsorption in the KO was significantly less than in controls and was not significantly inhibited by benzamil (ENaC activity in the KO is unscopled from Na intake). When fed a 2.0% Na diet ENaC activity is higher in the KO vs. controls, and is lower on a 0% Na diet in KO vs. controls with no difference in activity in the KO on any of the Na diets. Preliminary results suggest that purinergic regulation of ENaC by a local signaling system is abnormal in the KO contributing to inappropriate channel responses to changes in dietary Na. KO mice have lower urinary ATP than controls and show no dietary Na- effect on ATP in contrast to controls where ATP is proportionally related to dietary Na intake. The defect in the KO is likely upstream of the inhibitory purinergic receptor since ENaC in the KO responds normally to exogenous ATP.

Conclusions: These results implicate the HKa, HK-ATPase in the maintenance of Na homeostasis. The lack of response to Na intake implies that renal Na excretion and ENaC activity are inversely related to dietary Na intake, a relationship essential to blood pressure (BP) regulation, and its dysfunction contributes to salt-sensitive hypertension. The lack of response to Na intake implies that renal Na excretion and ENaC activity are inversely related to dietary Na intake, a relationship essential to blood pressure (BP) regulation, and its dysfunction contributes to salt-sensitive hypertension.

Funding: Veterans Administration Support

TH-PO434

Background: The apical BK channel in the CCD mediates flow-induced K secretion (FIKS) in vivo. BK channels possess multiple cholesterol recognition/interaction motifs in the subunit and, in non-renal cells, are inhibited by enhanced cholesterol content in the lipid membrane and hypercholesterolemia. Cholesterol determines membrane fluidity, and changes in membrane cholesterol are expected during postnatal development and in lipid membrane and hypercholesterolemia. Cholesterol determines membrane fluidity, and changes in membrane cholesterol are expected during postnatal development and in lipid membrane and hypercholesterolemia.

Methods: NIDDK Support

Results: In the present study, we used the whole-cell patch-clamp technique to examine the ROMK and ENaC activity in the late DCT (200-300 µm) of mice before and after IP injection of furo. Fluorescent immunohistochemistry (FIHIC) and western blotting were used to determine BK-α and Na-K-Cl cotransporter (NKCC2) expressions.

Conclusions: These results suggest that there is a furosemide-sensitive BKJα-dependent net K secretion in the thick ascending limb of mice on LNaHK diet.

Funding: NIDDK Support

TH-PO435
Net K Secretion in Thick Ascending Limb of Mice on Low Na High K Diet Bangchen Wang, Donghai Wen, Ryan J. Cornelius, Yang Yuan, Huaqing Li, Jun Wang-France, Steven C. Sansom. Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE.

Background: It has been long understood that thick ascending limb (TAL) reabsorbs Na+, Cl-, and K+ and high K diet inhibits NaCl reabsorption in TAL. In the present study, however, we found a persistent NaCl reabsorption and a net K secretion in TAL of mice on a low Na high K diet (LNaHK) that is dependent on β4 subunit of large Ca-activated K channels (BK). We hypothesized that K secretion in the TAL was the result of K recycling via BK-β4 from the medullary collecting ducts (MCD).

Methods: Wild-type (WT) and mice with a knock-out of BKβ4 (KO) were fed either a control LNaHK diet for 4 weeks. They received intraperitoneal (IP) injection of vehicle (veh), furosemide (furo), amiloride (amil), or furosemide + amiloride (furoami) and were placed in metabolic cages for 12 hours to collect urine. Urine and plasma [Na+] and [K+] were measured with flame photometry. Micro puncture was used to measure [K+] in the labyrinthine tubule (ELT) and medullary collecting duct (MCD) of WT and KO mice before and after IP injection of furo.

Results: In WT on a control diet, K clearance was higher in furo-treated mice compared to veh due to increased distal flow. However, in WT on LNaHK, K clearance was significantly lower in furo-treated mice despite increased distal flow, and furoami decreased K clearance more than either drug alone. In KO on LNaHK, K clearance was higher on a low Na diet compared to veh, indicating NKCC2 was still active. NCC2 expression in medullary TAL was higher in WT on LNaHK compared to control diet. FIBIC showed that BK-α was expressed in the apical membranes of MCD of WT on LNaHK, but not KO, which may mediate K recycling in MCD.

Conclusions: These results suggest that there is a furosemide-sensitive BKJα-dependent net K secretion in the thick ascending limb of mice on LNaHK diet.

Funding: NIDDK Support

TH-PO436
A Decrease in ENaC and ROMK Activity in the Late Distal Convoluted Tubule/Connecting Tubule May Contribute Hypertension in PHAI Mutant WNK4 Knockin Mice WenHui Wang, Pharmacology, New York Medical College, Valhalla, NY.

Background: Pseudohypoaldosteronism type II (PHAI) is caused by mutations in with-no-lysine kinase1 (WNK1) that lack an amino-acid-rich domain at the alpha subunit.

Results: Western blot confirmed that NCC expression is upregulated in TgWNK4 mice. Immunohistochemical staining for NCC and ENaCβ in the late distal convoluted tubule (CDCT) was performed on whole-mounted tissue. The whole cell microperfusion detector (WMD) was bathed in a solution containing 135 K-glucosamine and 10 KCl. The pipette contains a symmetrical K solution.

Conclusions: We conclude that ENaC and ROMK channel activity are inhibited in TgWNK4+ mice and that WNK4 PHAII-induced inhibition of ENaC and ROMK may contribute to the suppression of K secretion in the DCT/CNT in addition to a reduction of Na delivery.

Funding: NIDDK Support

TH-PO437
Giz Regulates Sodium and Potassium Balance During Dietary Sodium Restriction Priyanka Rashami, Michael Ng, David Pearce. Univ of California San Francisco, San Francisco, CA.

Background: The hormonal regulation of ion transport by the kidney tubules is critical for regulating sodium and potassium balance in blood, extracellular fluid volume and blood pressure. The renin-angiotensin-aldosterone (RAAS) system is the primary regulator of Na+ reabsorption and K+ secretion. RAAS regulates multiple transporters involved in electrolyte homeostasis such as Na+ K+ cotransporter and epithelial sodium channel (ENaC). While both ENaC and NCC mediate Na+ reabsorption, they affect K+ differently:Electrogenic Na+ reabsorption via ENaC stimulates K+ excretion, while...
electroneural reabsorption of Na via NCC inhibits K secretion by competing with ENaC for transport. Glucocorticoid induced leucine zipper protein (Gilz) is an aldosterone-regulated gene product reported to cause changes in ion balance but the mechanism has not been explored. In this study we used the Gilz knock out (Gilz−/−) mouse generated in our laboratory to show that during sodium deprivation Gilz−/− mice come into sodium balance more quickly than wild type (WT) and become significantly hyperkalemic. These observations raised the possibility that loss of Gilz results in hyperactivation of an electroneural Na transporter, which does not stimulate K secretion. Indeed, Gilz knock out mice are more sensitive to thiazide diuretics suggesting increased NCC activity. Co-transport of phosphorylated NCC (pT53/58) at the plasma membrane is also higher in the kidneys of Gilz knock out mice than in the WT mice maintained on a sodium deficient diet. In HEK293T cells, overexpression of Gilz isoform 1 (Gilz1) inhibits NCC activation in response to hypotonic low-CI conditions as assessed by its phosphorylation at T53 and T58. Gilz mediated NCC inhibition is lost in the presence of constitutively active SPAK suggesting that it is at least in part mediated by WNK1/4-SPAK pathway. Indeed, co-expression of Gilz inhibits SPAK phosphorylation at S373. Together, our results suggest that during sodium restriction, Gilz1 shifts sodium reabsorption from NCC to ENaC, thus favoring K excretion. This effect may be critical for the maintenance of euakalemia in the face of Na restriction.

Funding: Other NIH Support - T32

TH-PO438
Pharmacological Inhibition of the Circadian Regulatory Casinekin 1α Prevents Aldosterone-Mediated Induction of Na-Cotransporter Activity Michelle L. Guzmán, 1,2 Kristen Solocinski, 1,2 Robert S. Hoover, 1,4 Benjamin S. Ko, 3 Medicine/Nephrology, Univ of Florida, Gainesville, FL; 1Biochemistry and Molecular Biology, Univ of Florida, Gainesville, FL; 2Medicine/Nephrology, Emory Univ, Atlanta, GA; 3Research Service, Atlanta Veteran’s Administration Medical Center, Atlanta, GA; 4Medicine, Univ of Chicago, Chicago, IL.

Background: The circadian clock protein Per1 transcriptionally regulates the Na-Cl cotransporter (NCC) and members of the WNK kinase family. Per1 must be phosphorylated by casein kinase 1α/ε (CK1α/ε) in order to enter the nucleus. Previously, we showed that inhibition of CK1α/ε decreased Per1 nuclear protein levels and decreased NCC activity under basal conditions in mouse distal convoluted tubule cells (mDCT15). Methods: mDCT15 cells were treated with a CK1α/ε inhibitor prior to either aldosterone (100 nM for 24 hr) or Angiotensin II (AngII) (10^{-5} M for 30 or 120 min) treatment. NCC activity was determined by measuring thiazide-sensitive, Cl-dependent Na+ uptake. Results: NCC activity was significantly increased following either aldosterone or AngII treatment, consistent with previously published data. In the presence of the CK1α inhibitor, however, the aldosterone-dependent increase in NCC activity was prevented. In contrast, the AngII-dependent increase in NCC activity was not affected by CK1α/ε treatment.

Conclusions: Inhibition of Per1 nuclear entry via phosphorylative blockade of CK1α/ε appears to prevent the aldosterone-mediated but not AngII-mediated induction of NCC activity. These results suggest an important role for the circadian clock proteins Per1 and CK1α/ε in aldosterone-dependent regulation of NCC with possible implications for the treatment of hypertension.

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

TH-PO439
Disruption of 14-3-3 γ Binding to NCC Altered the Aldosterone-Mediated Regulation of NCC Protein Expression Xiuyan Feng, 1 Zhizhi Zhuang, 2 Courtney Marie Caroti, 1 Hui Cai, 1 Medicine, Emory Univ School of Medicine, Atlanta, GA; 2Section of Nephrology, Atlanta Veterans Administration Medical Center, Decatur, GA.

Background: 14-3-3 γ binds to NCC, a regulatory co-transporter in the tubular epithelium of the kidney, which plays a key role in the regulation of electrolyte transport. It has been shown that the 14-3-3 γ binding site on NCC is critical for aldosterone-mediated regulation of NCC. Methods: Cell culture, transfection, western blot analysis, immunostaining, confocal microscopy, co-immunoprecipitation and C57/B6 mice were used for this study.

Results: Co-immunoprecipitation (co-IP) in Cos-7 cells showed that 14-3-3 γ is the strongest one binding to NCC among all isoforms of 14-3-3. Immunostaining and confocal microscopy also showed that 14-3-3 γ is localized in distal convoluted tubule in mice. Co-IP experiments in Cos-7 cells showed that wild-type (WT) 14-3-3 γ binds to NCC, whereas 14-3-3 γ K50E mutant almost completely loses its binding to NCC. Western blot analysis showed that WT 14-3-3 γ significantly decreased total NCC expression by 63 % compared to the control group, whereas 14-3-3 γ K50E mutant did not change NCC protein expression. WT 14-3-3 γ increased NCC ubiquitination by 1.5 fold (1.5 ± 0.4 vs 1.0), whereas 14-3-3 γ K50E mutant did not alter NCC ubiquitination compared to the control group. In addition, we implanted aldosterone osmotic mini-pump to WT mice for 14 days and then harvested the kidneys. Western blot analysis showed that whether SPAK increased total NCC expression by 1.68 folds (1 ± 0.2 vs 1.68 ± 0.15) and decreased the ubiquitinated NCC by 56 %. Co-IP also showed aldosterone decreased the 14-3-3 γ binding to NCC by 57 % without changing total 14-3-3 γ expression.

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

Conclusions: These results suggested that aldosterone up-regulates NCC expression by disruption of 14-3-3 γ binding to NCC that leads to decreasing NCC ubiquitination.

Funding: Veterans Administration Support, Private Foundation Support

TH-PO440
Calcineurin Inhibitors Uprogulate the Thiazide-Sensitive NaCl Cotransporter in Urinary Exosomes of Kidney Transplant Patients Omar Tutakhe1, Mathijs de van de Vrie, 1 Marco Valdez Flores, 1 Ewout J. Hoorn, 1 Luuk Hilbrands, 1 Jost Hoenderop, 2 René J. Bindels. 1Physiology and Nephrology, Radboud Univ Medical Center, Nijmegen; 2Div of Nephrology & Transplantation, Erasmus Medical Center, Rotterdam, Netherlands.

Background: Calcineurin inhibitors (CNIs), including cyclosporine A (CsA) and tacrolimus (Tac), are the cornerstone of immunosuppression and superior in preventing acute allograft rejection. This benefit, however, comes at the cost of common adverse effects including hypertension. Recently several studies have shown that CNI-induced hypertension is largely mediated by activation of the thiazide-sensitive NaCl cotransporter (NCC). The aim of the present study was to further substantiate the role of NCC in CNI-induced hypertension by assessing the abundance and activity of NCC in urinary exosomes of CNI-treated patients.

Methods: Kidney transplant patients were enrolled 6 months after transplantation and treated with CsA (n=14), Tac (n=18) or a CNI-free immunosuppressive regimen (n=13). Six healthy subjects were also included. Urinary exosomes were isolated from 10 ml midstream urine samples by ultracentrifugation and normalized by urinary creatinine. The corresponding immunoblocks were probed with antibodies specifically recognizing NCC and pNCC-T58. To confirm equal loading of the samples the abundance of the exosomal marker CD9 was determined.

Results: NCC was detected in urinary exosomes by immunoblocks as two bands of ~260 kDa and ~130 kDa representing the dimeric and monomeric forms, respectively. Abundance of both NCC and pNCC-T58 in urinary exosomes of CsA and Tac groups were significantly increased in comparison to patients treated with a CNI-free immunosuppressive regimen and healthy subjects. Moreover, both the NCC and pNCC-T58 abundance was 2.5-fold higher in CsA group compared to Tac group. CD9 abundance in urinary exosomes was similar between the various groups.

Conclusions: The present study demonstrates that: i) total and phosphorylated NCC abundance is increased in urinary exosomes of CNI-treated kidney transplant patients; ii) urinary exosomes can be used as a novel biomarker to assess NCC abundance and activity in CNI-treated kidney transplant patients.

Funding: Government Support - Non-U.S.

TH-PO441
Generation of Hypertension-Associated STK39 Polymorphism Knock-in Cell Lines with the CRISPR/Cas9 System Shintaro Mandai, Takayasu Morii, Eisie Sohara, Tatsunori Rai, Shinichi Uchida. Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Previous genome-wide association studies identified STK39, encoding STE20/SPS1-related proline/alanine-rich kinase (SPAK), as one of a limited number of hypertension susceptibility genes. We performed genome-wide analysis confirmed the association of STK39 intrinsic polymorphism rs3754777 with essential hypertension, among previously reported hypertension-associated STK39 polymorphisms. However, the physiological function of this polymorphism is yet to be clarified.

Methods: To investigate whether the hypertensive and the downstream targets are modulated by this polymorphism, we generated STK39 rs3754777 G > A, knock-in human embryonic kidney (HEK293T) cell lines with the clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system, using a double-nickase (Cas9-D10A), single guide RNAs targeting STK39 intron 5 around SNP, and a 100-bp donor single-stranded DNA oligonucleotide.

Results: Homozygous (A/A) and heterozygous (G/A) knock-in cell lines were generated. Reverse transcription-polymerase chain reaction (RT-PCR) with sequencing analyses revealed the identical STK39 transcripts among the wild-type and both knock-in cell lines. Quantitative RT-PCR showed increased STK39 mRNA expression, and immunoblot analysis revealed increases in total and phosphorylated SPAK with increased phosphorylated Na–K–Cl cotransporter isoform 1 (NKCC1) in both knock-in cell lines. The largest increases in these molecules were observed in the homozgyous cell line.

Conclusions: STK39 intrinsic polymorphism rs3754777 increases STK39 transcription, leading to activation of the SPAK-solute carrier family 12 (SLC12A) signaling cascade. Activation of the target cation-chloride cotransporters may be responsible for hypertension susceptibility in individuals with this polymorphism.

Funding: Private Foundation Support, Government Support - Non-U.S.
The Major Contribution of WNK4 to the Pathogenesis of Pseudohypoaldosteronism Type II (PHAII) Caused by the KLHL3 Mutation R258H Koichiro Sasa, Eisie Sohara, Daiie Takahashi, Tatamitsu Rai, Shinnichi Uchida

Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Recently, we reported that KLHL3<sup>326Q/260Q</sup> knock-in mice, a PHAII model mouse, exhibit the activation of OSR1/SPAK-NCC signaling by the increased protein levels of both WNK1 and WNK4 due to impaired protein degradation by the mutation of the KLHL3. We previously have demonstrated that the amount of phosphorylated and total NCC decreased to almost undetectable levels in the WNK4<sup>+</sup> mice, indicating that WNK4 plays the major role in NCC regulation and that other WNKs including WNK1 and WNK3 cannot compensate for the absence of WNK4. In this study, we sought to determine the contribution of WNK4 to the activated OSR1/SPAK-NCC signaling in the KLHL3<sup>326Q/260Q</sup> knock-in mice.

Methods: We generated WNK4<sup>+</sup>-KLHL3<sup>326Q/260Q</sup> mice by crossing the WNK4<sup>+</sup> with the KLHL3<sup>326Q/260Q</sup> mice. In addition, we also generated WNK4<sup>-</sup>-KLHL3<sup>326Q/260Q</sup> mice. Thereafter, WNK4-OSR1/SPAK-NCC phosphorylation signal cascade was examined in kidneys from these mice.

Results: As previously reported, compensatory increased WNK1 was observed in the WNK4<sup>-</sup> mouse kidney, compared to WNK4<sup>+</sup>. Expectedly, both WNK4<sup>+</sup> KLHL3<sup>326Q/260Q</sup> and WNK4<sup>-</sup>-KLHL3<sup>326Q/260Q</sup> mice showed further increases in WNK1, due to the KLHL3 mutation. However, although phosphorylated SPAK was increased in the whole kidney to the levels comparable with that in wild-type mouse, total NCC and NCC phosphorylated at S71 were almost completely absent even in WNK4<sup>-</sup>-KLHL3<sup>326Q/260Q</sup> mice.

Conclusions: As in the wild-type mice, WNK4 plays the major positive role in the regulation of NCC in the KLHL3<sup>326Q/260Q</sup> PHAII model mice.

Mechanism of Regulation of WNK Kinases Elizabeth J. Goldsmith

Biophysics, Univ of Texas Southwestern Med Center Dallas, Dallas, TX.

Background: WNK1 is a protein kinase on pathway for the regulation of cation-chloride cotransporters. We demonstrated that the kinase domain of WNK1 binds chloride ion and inhibits WNK1 autophosphorylation (Piala et al. Sci Signaling 7 r414 2014). New crystallography improves our understanding of the mechanism of this regulation.

Methods: New crystals of the kinase domain of WNK1 (210-483)* (phosphorylated) were obtained using x-ray screening, that yielded crystals diffraction to 2.1 Å. Data were collected at the APS Beamline 19, and data were processed in HKL2000; the structures were solved by molecular replacement. In addition, the structure of a chloride sensing mutant was solved in an unphosphorylated form of the same construct on diffraction to 2.5 Å.

Results: The structure of the phosphorylated form reveals conformational changes associated with dissolving the chloride from the active site of WNK1, and how a ATP analog, AMP-PNP, binds to the unique WNK1 active site. The structure determined however, is not in a fully active configuration based on numerous structural cues. The structure of the mutant WNK1<sup>ΔC299</sup> reveals aspects of the contacts of chloride with the protein structure.

Conclusions: The new structural data confirms the chloride regulation of WNK1, and strongly suggests that activation is a multistage process.

Funding: NIDDK Support, Private Foundation Support

Characte...
**Methods:** Mutation of Pro224 to Ala abolishes Na/K-ATPase signaling and sodium handling. The mutation of Ala16 to Pro in rat a1 subunit, also characterized as aforementioned, does not affect ouabain-mediated Na/K-ATPase signaling and sodium handling. The data indicates that carbonylation modification of Pro224 in rat a1 subunit dictates ouabain-mediated Na/K-ATPase signal transduction and subsequent sodium transport.

**Conclusions:** Direct carbonylation of a single amino acid dictates ouabain-mediated Na/K-ATPase signaling and related sodium handling in renal proximal tubules.

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**TH-PO448**

The Mineralocorticoids Receptor Regulates the Expression of Na+-K+-ATPase b Subunit in Kidney Collecting Duct Cells

**Pablo Diaz, Cristian Degregorio, Luis F. Michea, Magdalena Gonzalez.** Univ de Chile, Chile.

**Background:** Aldosterone modulates the activity of the Na+-K+-ATPase (NKA) (NKA) in principal cells (PC) of kidney collecting duct (CD) via activation of the mineralocorticoid receptor (MR). The NKA is a heterodimer with a catalytic a subunit and a regulatory b subunit. Aldosterone stimulates NKA abundance in the kidney. The b subunit may be determined of subcellular localization and trafficking of the a/b heterodimers, and also may have a role in the cell-cell adhesion that may be relevant in paracellular permeability. Previous studies addressed the modulation of a and b expression in response to aldosterone. However the role of aldosterone in the regulation of the b subunit has not been analyzed. We tested the hypothesis that the activation of the MR modulates the expression of NKA b subunit in CD.

**Methods:** C57BL/6 mice underwent adrenalectomy (ADX) or sham surgery (SHAM). The ADX mice received saline diet or hormone replacement therapy with deoxycorticosterone (ADX+DOCA, 10mg/ml/day). In a second set of experiment mice received spironolactone (Spi, 50 mg/Kg/day) or vehicle (Control). Treatment after 3 days we obtained the kidneys (cortex and medulla) for the analysis of NKA a and b subunits (mRNA and protein abundance by qRT-PCR and Western blot). Finally, we studied the effect of aldosterone (0.1-100 nM) in primary culture of inner medullary collecting ducts (IMCD, 24 hours).

**Results:** Adrenalectomy increased b subunit mRNA and protein abundance in mouse renal medulla but not in kidney cortex (200% vs control, P<0.05 for mRNA and 65% vs control, P<0.001, n=9 for protein). Similarly, Spi treatment increased the abundance of b subunit mRNA and protein in renal medulla only (250% vs control, P<0.01, n=8 for mRNA and 100% vs control, P<0.05, n=5 for proteins). Both the ADX mice as the Spi-treated mice showed no-significant changes in the abundance of a subunit transcripts and proteins. The treatment with Aldosterone decreased b mRNA in IMCD cells (50% vs control, P<0.01, n=5).

**Conclusions:** We conclude that the NKA b subunit expression is downregulated by the activation of the MR.

**Funding:** FONDICYT 1130550, IMH P09-016F, BECA CONICYT 21120658.

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**TH-PO449**

Purified Recombinant ApoL1 Forms Anion Channels in Phospholipid Bilayers

**John C. Edwards.** Internal Medicine, Saint Louis Univ, Saint Louis, MO.

**Background:** Variants in the protein ApoL1 confer the increased risk of certain types of chronic kidney disease that is observed in people of African ancestry. ApoL1 has been reported to function as an ion channel but reports vary on the nature of this activity. We sought to characterize ApoL1 channels with anticipation that detailed properties of the channel activity may provide insight into the pathophysiology of ApoL1-associated kidney disease.

**Methods:** Recombinant ApoL1 was expressed in bacteria with a N-terminal GST tag replacing the signal sequence and separated form the ApoL1 coding region by a thrombin cleavage site, and with a C-terminal V5-6Histidine tag. N-octyl glucose-solubilized protein was bound to glutathione agarose. The bound fusion protein was cleaved with thrombin, releasing ApoL1-V5His which was further purified by Ni-affinity. Channel activity was assessed using vesicle-based voltage dependent Cl- and K+ efflux assays employing ion selective electrodes. Single channel properties were investigated using the Tip-Dip lipid bilayer patch technique with which we were experienced in the past.

**Results:** The preparation yields highly purified soluble ApoL1. Introduction of ApoL1 into phospholipid vesicles either by reconstitution via detergent dialysis, or by direct insertion into pre-formed vesicles yields a Cl ion permeability that supports voltage-driven chloride transport. The Cl channel activity requires that the protein interacts with the lipids at low pH (5.0). We do not find potassium-selective permeability when assayed at either pH 5 or 7.5. In tip-dip bilayer, ApoL1 spontaneously inserts at low pH, generating transitions with single channel conductance of about 5 pS, and with a non-rectifying voltage-dependence of the permeability. We do not find enhanced channel activity if the bath solution is changed to pH 7.5.

**Conclusions:** Purified recombinant ApoL1 can functionally interact with different anion channels in the membrane. A prominent difference that we observed between our preparation and that of others reported to function as a channel is that our method avoids denaturation and refolding. Whether the disease associated variants show altered channel properties remains to be determined.

**Funding:** Other NIH Support - NHLBI

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**TH-PO450**

Using ChlopHensor to Measure Intracellular Cl- in a Transporting Renal Epithelium

**Aylin R. Rodan, Qui Sun, Drew Stenesen, Helmut Kramer.** Internal Medicine, UT Southwestern, Dallas, TX; Neuroscience, UT Southwestern.

**Background:** Drosophila melanogaster eat a K+-rich diet and secrete a Cl-rich fluid from the main segment of the renal tubule. We have previously shown that ±1/3 of transepithelial K+ flow through the cation-conducting principal cell is via the basolateral NKCC and is regulated by the WNK-SPAK/OSR1 kinase cascade. This pathway is activated under hypotonic conditions. Cl is a key regulator of WNK activity. Here, we measured intracellular Cl in the fly tubule using the transgenic Cl sensor, ChlopHensor.

**Methods:** The GAL4-UAS system was used to drive tubule expression of ChlopHensor, a pH- and Cl-sensitive GFP linked to a pH- and Cl-insensitive dDf. Fluorescence after excitation at 488 nm (green), 458 nm (cyan) and 543 nm (red) was quantified using ImageJ. Calibration curves of the green/cyan ratio (to measure pH) and cyan/red ratio (to measure Cl-) were prepared at varying intracellular pH and Cl by equilibrating in the presence of 5 mM nigericin, CCCP, valinomycin and 10 mM tributyltinchloride. Fluorescence emission was then measured in the tubule principal cells under varying conditions.

**Results:** In standard bathing medium (SBM), intracellular Cl concentration was 27±2 mM (n=21 cells in 7 tubules), similar to previous measurements made with double-barreled ion-selective micro-electrodes. In hypotonic medium, Cl decreased to 16±1 mM (p<0.0001, paired t-test). pH was unchanged. In a time course experiment, initial Cl was 30±1 mM in SBM, then decreased to 20±3, 16.2±1.8 and 15.2±0.2 mM at 10, 30 and 60 minutes of hypotonic exposure. The decrease in Cl in hypotonic conditions was blunted by increasing [K+] in the hypotonic medium (A, 8.1±1 mM) and increased by decreasing [K+] and [Cl-] in the hypotonic medium (A, 17±2 mM, p<0.05 compared to usual hypotonic and p<0.001 compared to high-K+ hypotonic, one-way ANOVA with Bonferroni correction).

**Conclusions:** Activation of the WNK-SPAK/OSR1-NKCC pathway in the Drosophila renal tubule under hypotonic conditions correlates with decreased intracellular Cl concentration. The decrease in Cl is accentuated when bath K+ and Cl- are lowered, suggesting Cl is efflux in hypotonic conditions, perhaps due to regulatory volume decrease mechanisms.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-PO451**

Potassium-Induced Dephosphorylation of Renal Sodium Chloride Cotransporter Is NOT Dependent on the Anions

**Naoki Nomura, Wakana Shoda, Eisei Sohara, Tatemitsu Rai, Shinichi Uchida.** Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.

**Background:** Dietary potassium intake is strongly associated with blood pressure and cardiovascular death. High-potassium diets decrease phosphorylation of sodium-chloride cotransporter (NCC) and induce lower blood pressure. In many experimental studies using high-potassium diets, potassium chloride was added to make high-potassium diets. On the other hand, there is a recent report that a high-potassium diet made of potassium citrate increased phosphorylation of NCC. It is also known that chloride itself affects NCC phosphorylation. Thus, the accompanying anion might modulate the NCC phosphorylation response to the high potassium diets, and aldosterone also might be involved in the discrepancy. In this study, we clarified the change of NCC phosphorylation with potassium compounds accompanying different anions, and confirmed the association between potassium intake and NCC phosphorylation with acute oral infusion.

**Methods:** Adult C57BL/6 mice were fed potassium chloride, potassium gluconate, and potassium citrate with oral gavage. Kidneys were collected after 15 min infusion, because plasma aldosterone level did not show significant difference at this time point. Western blotting was performed with anti-phospho-NCC antibody.

**Results:** All potassium compound infusion showed significant decrease of NCC phosphorylation. Sodium gluconate and sodium citrate infusions showed very little and no reduction of NCC phosphorylation respectively.

**Conclusions:** Rapid potassium infusion decreases phosphorylation of NCC. It is not depend on the anions at least in acute potassium infusion.

**Funding:** Government Support - Non-U.S.
**TH-PO452**

Association of Birth History and BMI with APOL1 Risk Alleles in CKiD

Sandra L. Laston, 1 Nitesh R. Chiyuan Hsu, 2 Rebecca J. Hjorten, 3 Susan L. Furth, 1 Bradley Warady, 4 Craig S. Wong, 1 Larry A. Greenbaum, 5 Marva M. Moxy-Mems, 6 Jeffrey B. Kopp, 7 Sophie Limou, 8 Cheryl Ann Winkler, 1 Frederick J. Kaskel, 1 Pediatrics/ Nephrology, Montefiore, Bronx, NY; 2 Epilepsy, Johns Hopkins, Baltimore, MD; 3 Pediatrics/ Nephrology, Stony Brook Univ, Stony Brook, NY; 4 Pediatrics/Nephrology, Children’s Hospital of Pennsylvania, Philadelphia, PA; 5 Pediatric/ Nephrology, Children’s Mercy, Kansas City, MO; 6 Pediatrics/ Nephrology, Univ of New Mexico, Albuquerque, NM; 7 Pediatrics/ Nephrology, Emory Univ, Atlanta, GA; 8 NIH, Bethesda, MD.

**Background:** In the Chronic Kidney Disease in Children (CKiD), there is a high prevalence of abnormal birth history (BH) and poor growth. African Americans (AA) have increased rates of prematurity. APOL1 risk alleles are associated with risk of glomerular CAD in AA patients, but the association with BH or growth is unknown.

**Methods:** Children of AA descent were genotyped for APOL1 risk alleles (G1, G2). High risk (HR) Defined as 2 risk alleles (G1, G1, G2, or G2, G2) Low risk (LR) defined as no risk alleles or 1 G1/G2 allele. Demographics and growth parameters were compared between APOL1 HR vs. LR groups.

**Results:** 28/84 AA children with glomerular disease had HR APOL1, 28 had LR APOL1 and 28 did not have APOL1 measured. 26.9% (7/28) with HR APOL1 were premature, versus 3.7% (1/28) in AA LR APOL1 patients and 6.9% (13/191) in non-AA LR APOL1 patients. Also in AA children with HR APOL1, 29.2% (7/28) were small for gestational age, vs. 36.3% (9/28) in AA LR APOL1 patients and 15.4% (27/191) in non-AA LR APOL1 patients (p=0.011). Overall, 48.1% (13/26) AA children with HR APOL1 had an abnormal BH, versus 35.7% (10/28) in AA LR APOL1 patients and 20.5% (39/191) in non-AA LR APOL1 patients (p=0.007). HR APOL1 risk alleles were also associated with increased BMI in patients with FSGS (p=0.04).

**Conclusions:** HR APOL1 in CKD significantly associated with an abnormal BH and higher BMI. Further analysis of the interaction of APOL1 genotype with BH and BMI in CKD is warranted.

**Funding:** NIDDK Support

**TH-PO453**

Relationships of Serum Growth Hormone, Insulin-Like Growth Factor-1 and IGF-1 Binding Proteins (BPs) in Children with CKD on Growth Hormone Therapy

Rose M. Ayoob, 1 John D. Mahan, 1 Larry A. Greenbaum, 2 Amira Al-Uzri, 3 Frederick J. Kaskel, 1 Susan L. Furth, 4 Bradley Warady, 5 Pediatrics, Nationwide Children’s/The Ohio State Univ, Columbus, OH; 6 Pediatrics, Emory Univ, Atlanta, GA; 7 Pediatrics, Oregon Health & Science Univ, Portland, OR; 8 Pediatrics, Albert Einstein COM, New York, NY; 9 Pediatrics, Univ of Pennsylvania, Philadelphia, PA; 10 Pediatrics, Children’s Mercy Hospital, Kansas City, MO.

**Background:** We evaluated children with chronic kidney disease (CKD) enrolled in the Chronic Kidney Disease in Children (CKiD) study to determine relationships between Serum Growth Hormone (GH), Insulin-Like Growth Factor-1 (IGF-1) and IGF-1 Binding Proteins (BP’s), with/without recombinant GH therapy, to assess values that might be useful to guide individual treatment decisions.

**Methods:** 266 CKD children; 206 - normal height; 26 - short stature; 34 [18 short, 16 normal height] on recombinant (r) GH therapy were selected for gender, age and GFR matching. Normal height = Height Standard Deviation Score (SDS) > -1.88. GH, IGF-1, and IGFBP-1 were measured by chemilumimniter and ELISA.

**Results:** Children with CKD on GH display lower IGF-1/GH than normal height and short children not on rGH therapy.

<table>
<thead>
<tr>
<th>IGF-1/GH</th>
<th>IGF-1-IGF-1 BP *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Height SDS &lt; -1.88</td>
<td>0.0065 [0.0012, 0.0161]</td>
</tr>
<tr>
<td>Children Height SDS &gt; -1.88</td>
<td>0.0036 [0.0055, 0.0082]</td>
</tr>
</tbody>
</table>

p-value (Kruskal Wallis ANOVA) 0.0002 0.02

* = (median [95% CI])

On rGH, IGF-1/IGF-1-BP is closer to that in normal height CKD children than in short CKD children. Height SDS correlates with serum IGF-1 in children on rGH better (r = -0.374) than normal height (r = -0.32) and short children (r = 0.048).

**Conclusions:** IGF-1/IGF-1-BP in children on rGH is closer to that in normal height than in short CKD children not on rGH, supporting importance of serum IGF-1 levels achieved in rGH treated children to drive statural growth. Further analyses in samples over time and in paired subjects may provide further insights into effective ‘therapeutic targets for rGH treatment in these children.

**Funding:** NIDDK Support, Private Foundation Support

**TH-PO454**

Two-Year Kidney Outcomes of Teen-LABS Participants

Edward Nehus, 1 Todd Jenkins, 1 Nianzhao Xiao, 1 Marc P. Michalsky, 1 Anita Courcoulas, 1 H. Inge, 1 Mark Mitsuferet, 2 Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 3 Children’s Hospital of Richmond at VCU, Richmond, VA; 4 Nationwide Children’s Hospital, Columbus, OH; 5 Univ of Pittsburgh Medical Center, Pittsburgh, PA.

**Background:** A significant amount of severely obese adolescents undergoing weight loss surgery have evidence of early kidney damage. The objective of this study was to determine if early kidney injury is reversible following weight loss surgery.

**Methods:** We analyzed data two years following bariatric surgery in the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort, a prospective multicenter study of 242 severely obese adolescents undergoing bariatric surgery. Primary outcome was albuminuria (urinary albumin to creatinine ratio > 30 mg/g) and cause of ESRD to determine the association between short (<3 SD) age of the patients was 17 ± 1.6 years, 76% were female, and 72% were white race. Procedures included gastric bypass (67%), sleeve gastrectomy (28%), and adjustable gastric band (5%). Median BMI (IQR) at baseline was 51 (45, 58) kg/m², and this decreased to 35 (30, 43) kg/m² at two years follow-up. Cystatin C-based eGFR was 108 ± 27 mL/min/1.73m² at baseline and by two years post-operatively, eGFR had increased by 10% to 119 ± 27 mL/min/1.73m² (p = 0.01). Low eGFR (< 90 mL/min/1.73m²) was observed in 25% at baseline, and this improved to 12% at two years follow-up (p = 0.01); 71% with low baseline eGFR experienced normalization of eGFR at follow-up. Alternatively, 7% of subjects with normal baseline eGFR developed incident ESRD. Of the 13 subjects who developed incident ESRD, two were obese children at baseline and 12% at two years follow-up (p = 0.03). Among those with baseline albuminuria, 69% experienced normalization of albuminuria at follow-up. In contrast, 7% of subjects were observed with incident albuminuria at two years post-op.

**Conclusions:** Two years following surgery, improvements in kidney function and albuminuria were observed in our cohort. Further study will permit assessment of durability of improvements and longer-term kidney outcomes of severely obese adolescents undergoing bariatric surgery.

**Funding:** NIDDK Support

**TH-PO455**

Genetic Variation Underlying Uric Acid Clearance in Hispanic Children: The Viva La Familia Study

Geetha Chittore, 1 Sandra L. Laston, 2 Nitesh R. Chiyuan Hsu, 2 Karin Haack, 3 Shelley A. Cole, 4 Anthony Gean Comuzie, 4 Nancy F. Butte, 5 V. Saroja Voruganti. 1 Nutrition and Nutrition Research Inst, Unv of North Carolina at Chapel Hill, Kannapolis, NC; 2 Texas State Diabetes and Obesity Inst and Regional Academic Health Center, UTHSC at San Antonio/Univ of Texas Rio Grande Valley, Brownsville, TX; 3 Pediatrics and USDA/ARS Children’s Nutrition Research Center, Baylor College of Medicine, Houston, TX; 4 Genetics, Texas Biomedical Research Inst, San Antonio, TX.

**Background:** Variation in renal excretion of uric acid is a key factor in the development of gout, hyperuricemia, and nephropathy. Hyperuricemia (increased serum uric acid concentrations) and hyperuricosuria (increased urinary uric acid concentrations) can lead to uric acid nephrolithiasis. These are two common multifactorial disorders that have been shown to be associated with progression to kidney disease and have a familial inheritance. The genetic determinants of renal handling of uric acid are poorly elucidated.

**Methods:** We investigated the genetic factors that influence the excretion of uric acid and its related indices in 769 Hispanic children of the Viva La Familia Study. We conducted a genome-wide association analysis for uric acid clearance after accounting for family kinships. All methods were implemented in SOLAR.

**Results:** All renal uric acid clearance measurements were significantly heritable (p < 2 x 10^-8). We observed a strong association of uric acid clearance with a single nucleotide polymorphism (SNP) in the zinc finger protein 446 (ZNF446) gene on 19q13 (p < 8 x 10^-13), rs2037711 (A/G), minor allele frequency (MAF) of 0.30). The minor allele (G) was associated with increased uric acid clearance. We also found suggestive associations of uric acid clearance with SNPs in ZNF334, ZNF584, and ZNF132 (within 72kb region of 19q13, p < 1 x 10^-6). MAFs between 0.28 and 0.31.

**Conclusions:** Our study indicates, for the first time, the importance of the chromosomal region 19q13 in the regulation of renal clearance of uric acid in Hispanic children.
(*)9th percentile) stature and risk of transplantation and death. In sensitivity analysis, we also evaluated mortality and transplant risk in the subset of children with normal BMI (5th-95th percentile).

Results: Among 13,666 children, 26% of children were short and 3% were tall at time of ESRD onset. During a median follow-up of 7.1 years, 10,554 kidney transplants and 1,795 deaths occurred. The risk of death was higher in children in short and tall stature [table 1], and cause-specific mortality differed by height category. The higher risk of death in children with short stature persisted even when analysis was limited to children with normal BMI. Children with short stature were also less likely to receive a kidney transplant (HR 0.83, 95% CI 0.79-0.87).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Short Stature (N=3576)</th>
<th>Tall Stature (N=397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model (primary analysis)</td>
<td>1.48 (1.33-1.65)</td>
<td>1.30 (1.01-1.67)</td>
</tr>
<tr>
<td>Adjusted model among persons with normal BMI (N=9,663)</td>
<td>1.56 (1.36-1.77)</td>
<td>0.98 (0.67-1.44)</td>
</tr>
<tr>
<td>Cause-specific mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model for cardiac death</td>
<td>1.45 (1.19-1.76)</td>
<td>1.19 (0.76-1.85)</td>
</tr>
<tr>
<td>Adjusted model for infectious death</td>
<td>1.77 (1.32-2.33)</td>
<td>1.23 (0.97-1.63)</td>
</tr>
<tr>
<td>Adjusted model for malignancy death</td>
<td>0.79 (0.44-1.41)</td>
<td>2.70 (1.13-6.60)</td>
</tr>
</tbody>
</table>

*Reference is children with normal stature

Conclusions: Both extremes of height at ESRD onset were associated with higher risk of all-cause and cause-specific mortality, and short stature was also associated with lower risk of transplantation. Further studies are warranted to determine whether interventions can improve the risk associated with growth failure. Funding: NIDDK Support

TH-PO457

Genital Organ Anomalies in Female Pediatric Patients with End-Stage Renal Disease Shiochihiro Kanda,1 Naoya Morisada, Yuji Tomii, Keichi Takizawa,1 Naoto Kaneko,1 Tomoo Yabuuchi, Hong Min, Haji Nakano, Norimasa Tada,1 Kiyonobu Ishizuka,1 Yuji Akioika,1 Hiroko Chikamoto, Kazumoto Iijima,1 Motoshi Hattori.1 1Pediatric Nephrology, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan; 2Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan.

Background: In the general population, the rate of prevalence of genital organ anomalies in females is 4.0 per 1000 births. Although female pediatric patients with end-stage renal disease (ESRD) appear to occasionally have genital organ anomalies, the clinical features of them have not been examined.

Methods: We performed a retrospective analysis of female pediatric ESRD patients attending the Department of Pediatric Nephrology, Tokyo Women’s Medical University (TWMU) Hospital. The study was in accordance with the ethical guidelines of the Ministry of Health, Labour and Welfare, Japan. The study was also approved by the central ethics board of TWMU and Kobe University.

Results: Eighty-two patients were included in this study. Genital organ anomalies were found in eight (9.7%) patients and consisted of bicornuate uterus in three patients, double uteri with vaginal atresia in two, caudalic horizontal tissue in two, and double uteri in one. Renal phenotypes were congenital anomalies of the kidney and urinary tract in six patients and FSOS in two patients. In seven (87.5%) patients, genital organ anomalies were diagnosed after the start of renal replacement therapy. Two patients complained of acute abdomen associated with their first menstrual period. Genetic and chromosome analyses revealed hypoplasticparathyroidis, deafness, and renal dysplasia syndrome (GATA3, c.1013G>T) in one patient, Turner syndrome in one, Frasier syndrome (46XY, WTI, IVS9<5>G>A) in one, and FSOS carrying a mutation of WTI (c.745C>A) in one.

Conclusions: Our study showed that female pediatric ESRD patients had a frequency of genital organ anomalies of approximately 10%. Additionally, genetic disorders responsible for kidney and genital organ development were detected in four out of eight patients. Therefore, physicians need to be aware of the possibility of genitourinary syndrome and genital organ anomalies of approximately 10%. Additionally, genetic disorders responsible for kidney and genital organ development were detected in four out of eight patients.

TH-PO458

Intestinal Microbiota in Pediatric Patients with End Stage Renal Disease Janice Crespo-Salgado,1 Tyrus Stewart,2 Mike J. Ferris,2 Mahmoud Kallah,3 Larry A. Greenbaum,3 V. Matti Vehaskari,4 Diego H. Aviles.1 1Pediatric Nephrology, LSUHSC, New Orleans, LA; 2Pediatric Nephrology, Women & Children’s Hospital of Buffalo, Buffalo, NY; 3Pediatric Nephrology, Emory Children’s Center, Atlanta, GA.

Background: Cardiovascular mortality is increased in children with end stage renal disease (ESRD). Studies in adult population suggest that uremia increase intestinal permeability and alters the intestinal microbiota. These changes could facilitate the translocation of endotoxin and bacterial metabolites to the systemic circulation leading to inflammation. We hypothesized that children with ESRD have an altered intestinal microbiota that lead to increased bacterially derived uremic toxins, and renal transplantation will reverse those changes.

Methods: Subjects were divided into 4 groups: ESRD on peritoneal dialysis (PD), ESRD on hemodialysis (HD), post kidney transplant and healthy control. PCR and pyrosequencing analysis of 16S rDNA gene was used to assess stool bacterial composition. Serum levels of CRP, D-lactate, p-cresyl sulfate and indoxyl sulfate were detected.

Results: Children with ESRD showed significant decrease in Firmicutes (p=0.006). HD patients showed significant increase in Bacteroidetes (p=0.017) and PD patients showed significant increase in Proteobacteria (p=0.0006). Bacterial diversity was significantly decreased in ESRD and transplant patients. ESRD patients had significantly increased serum levels of p-cresyl sulfate and indoxyl sulfate (p=0.0002).

Conclusions: ESRD in children results in alteration of the intestinal microbiota favoring bacteria able to metabolize and produce more uremic toxins. Renal transplantation does not restore the decreased bacterial diversity, but results in normalization of bacterially derived uremic toxins. These findings may be associated with the increased cardiovascular mortality seen in children with ESRD.

TH-PO459

Cardiorenal Effects of Exposure to Environmental Chemicals in Children Anglina Kataria,1 Suzanne M. Vento,1 Leonardo Trasande,1 Dov Levine,1 Debra J. Morrison,2 Rachel Brody,2 Kurunthachalam Kaman,3 Jingchuan Xue,1 Howard Trachtman.1 1Pediatrics, NYU Langone Medical Center; New York, NY; 2Office of Collaborative Sciences, Human Specimen Resource Center, NYU Langone Medical Center, New York, NY; 3Environmental Health Sciences, School of Public Health, State Univ of New York at Albany, Albany, NY.

Background: Exposure to short-lived organic chemicals such as bisphenol A and S (BPA/BPS) and phthalates is ubiquitous in the US. Graded exposure to BPA and di-(2-ethylhexyl) phthalate (DEHP), based on urinary excretion, is associated with an increased low-grade albuminuria. Oxidant stress is hypothesized as the mediator underlying these associations. We conducted the following study to assess (1) the mechanism of action of these compounds and (2) the source of exposure on vascular function in children. Methods: A cross-sectional study recruiting 10-13 year old children was conducted at Bellevue Medical Center. Demographic information was obtained and height, weight and BP were measured. A first morning and spot urine samples were collected for determination of BPA, BPS, phthalate, 8(OH)-deoxyguanosine, and F2-isoprostane excretion (normalized to creatinine excretion). Pulse wave velocity (PWV) was measured non-invasively (SphygmCor). Multivariate analysis was used to evaluate the relationship between exposures and the laboratory tests.

Results: There were 41 participants, 19 M:22, age 12±1 yr, 31 Hispanic, 7 Caucasian, and 3 Other. The mean BMI was 21.7±5.0 and albuminuria 11.4±23.6 mg/l, and 10 (25%) were pre-hypertensive (BP≥90th percentile). The degree of exposure to BPS, total bisphenols, DEHP, and high molecular weight (HMW) phthalates correlated with F2-norprostanoic (r=0.049, p=0.05). Multivariate regression also showed each unit of DEHP and HMW phthalate exposure was associated with an increase in PWV of 0.034 m/s (p=0.037) and 0.024 m/s (p=0.041), respectively.

Conclusions: This is the first demonstration of oxidant stress and vascular dysfunction related to environmental chemicals in otherwise healthy children. The link with replacement compounds such as BPS suggests that the consequences of exposure to these chemicals will be a long-term public health problem.

Funding: NIDDK Support, Other NIH Support - NIEHS Pilot study Award

TH-PO460

Safety of Eculizumab in Pediatric Patients with Atypical Hemolytic Uremic Syndrome Gema Ariceta,1 Larry A. Greenbaum,2 Jimmy Wang,3 John F. Kincaid,1 Christoph Licht.1 1Hospital Vall d’Hebron, Barcelona, Spain; 2Emory Univ, Atlanta, GA; 3Alexion Pharmaceuticals, Inc, Cheshire, CT; 4The Hospital for Sick Children, ON, Canada.

Background: The safety of eculizumab, a terminal complement inhibitor approved for treatment of children and adults with aHUS, was characterized in 4 prospective trials. This post hoc analysis further evaluates its safety in pediatric participants in 3 of the trials.

Methods: Treatment-related adverse events (TRAES) and serious AEs (SAEs) reported for patients (pts) (<18 y) after 1 year and by end of study (EOS) in studies C08-002, C08-003, and C10-003 were pooled.

Results: Pediatric pts (N=25) received eculizumab for a mean (SD) of 67 (42) weeks. TRAES occurred in 13 pts (46.4%) after 1 year (Table). SAEs were listed in the Table. Elevated levels of anilime trasnaminase and asparagine aminotransferase were noted in some pts before and after receiving eculizumab, levels generally were higher before treatment and normalized over time. By EOS after 433 cumulative months of treatment, there were

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

Underline represents presenting author.
no deaths or meningococcal infections; 6 infection-related serious TRAEs occurred in 4 pts. None of the upper respiratory tract infection (n=2) or pneumonia, (patient on peritoniyal dialysis), respiratoary syncyntial virus infection, and pyelonephritis (n=1 each).

Conclusions: Eculizumab appears well tolerated in pediatric pts with aHUS. The safety profile of eculizumab in pediatric pts is similar to that in the broader population of adult pts. Although more infection-related serious TRAEs were noted, most were mild to moderate in severity, none led to treatment discontinuation, and all pts recovered. Some TRAEs might have been manifestations of underlying aHUS disease.

Medical writing support - Kristen W. Quinn, PhD, of Peloton Advantage, funded by Alexion.

Table 1. Baseline Demographic and Clinical Characteristics and Eculizumab Safety in Pediatric Patients (N=28)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pediatric (n=19)</th>
<th>Adolescent (n=9)</th>
<th>Total (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at baseline, years (SD)</td>
<td>13.5 (3.0)</td>
<td>16.6 (1.5)</td>
<td>14.5 (3.5)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>9 (47.4)</td>
<td>6 (66.7)</td>
<td>15 (53.6)</td>
</tr>
<tr>
<td>Identified complement gene mutation or antibody, n (%)</td>
<td>9 (47.4)</td>
<td>7 (77.8)</td>
<td>16 (57.1)</td>
</tr>
<tr>
<td>CFI</td>
<td>2 (11.1)</td>
<td>2 (22.2)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>CFH (CD46)</td>
<td>2 (11.1)</td>
<td>1 (11.1)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>CFH autoantibodies, CFH/FHR3 polymorphism</td>
<td>1 (5.6)</td>
<td>1 (11.1)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>CAI</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>CP</td>
<td>1 (5.6)</td>
<td>1 (11.1)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>CFI</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>CFI/CP</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>CFI autoantibodies</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>CFI autoantibodies, CFI/FHR3 polymorphism</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Mean time from diagnosis to screening, months (SD)</td>
<td>7.7 (17.2)</td>
<td>89 (75.9)</td>
<td>35.3 (60.5)</td>
</tr>
<tr>
<td>Newly diagnosed, n (%)</td>
<td>19 (94.7)</td>
<td>2 (22.2)</td>
<td>21 (75.0)</td>
</tr>
<tr>
<td>No Pts/yr during the current manifestation, n (%)</td>
<td>11 (58.8)</td>
<td>2 (22.2)</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td>Disease activity score</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Safety Findings</td>
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</table>

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

Underline represents presenting author.

192A
TH-PO464

Validation of a Novel Device to Collect Urine for Albuminuria Assessment in Young Children
Sophie Van den Belt, 1 Valentina Gracchi, 2 Dick de Zeeuw, 1 Hiddo Jan Lambers Heerspink, 1 2 Dept of Clinical Pharmacy and Pharmacology, UMC Groningen, Netherlands; 3 Dept of Paediatric Nephrology, UMC Groningen, Netherlands.

Background: Urine collection for albuminuria measurement in babies and toddlers is cumbersome. Taped plastic bags are complicated and may come loose. Old-fashioned cotton wool (pantyliner) or a felt (PeeSpot®) are used as collection devices in a regular disposable diaper. We compared the analytical performance of these two methods.

Methods: The pantyliner and urine collection felt were placed in the diaper; 81 different standard urines with a wide range of albuminuria were applied by hand (in duplicate); incubated for 3 hours at 37°C (simulating the baby), and 72 hours at room temp (simulating transport); extracted by centrifuging. Urinary Albumin Concentration was measured Analytical performance of two methods was tested according National Committee for Clinical Laboratory Standards (NCCLS) guidelines for method comparison, and compared with the standard urine. Performance measures assessed were bias, precision and accuracy.

Results: Median albumin concentration was: standard 66.0 mg/L [IQR 25.0–211.0 mg/L], pantyliner method 32.0 mg/L [4.7–165.0 mg/L], and PeeSpot method 61.0 mg/L [27.0–216.0 mg/L]. Bias and precision were higher in pantyliner (-3.4% and 32.4 mg/L) than in PeeSpot (3.3% and 5.0 mg/L) and accuracy was lower in pantyliner (48.1%) vs PeeSpot (96.3%). Passing-Bablok regression and Bland-Altman plot showed a systemic underestimation for pantyliner method, but not for PeeSpot method (Figure).

Conclusions: The PeeSpot method is a reliable method for the collection of urine in babies and toddlers albuminuria measurement. This technique should be used in future research into this subject.

Figure: A: Passing-Bablok regression for pantyliner and PeeSpot. B: Bland-Altman plots for pantyliner and PeeSpot on logarithm of albuminuria. LoA = Limit of Agreement.

Funding: Governmental Support - Non-U.S.

TH-PO467

Dyslipidemia in Pediatric CKD Patients from KNOW-PedCKD Study
Seung heon Kim, 1 Yo Han Ahn, 1 Eun-jin Park, 2 Kyong Hee Han, 3 Hee yoon Cho, 4 Joo Heon Lee, 1 Hee Gyung Kang, 5 Young seo Park, 6 Hae Il Cheong, 1 Curie Ahn, 1 IL-Soo Ha, 1 2 Dept of Pediatrics, Pusan Natl Univ Children's Hospital, Yangsan, Republic of Korea; 3 Dept of Pediatrics, Jeju National Univ School of Medicine, Jeju, Republic of Korea; 4 Dept of Pediatrics, Seoul Natl Univ Children's Hospital, Seoul, Republic of Korea; 5 Dept of Pediatrics, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea; 6 Dept of Pediatrics, Yonsei Univ College of Medicine, Severance Children's Hospital, Seoul, Republic of Korea; 7 Dept of Pediatrics, Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea; 8 Dept of Pediatrics, Kyungpook Natl Univ School of Medicine, Daegu, Republic of Korea.

Background: Children with chronic kidney disease (CKD) exhibit various comorbidities, including dyslipidemia. We investigated the prevalence and characteristics of dyslipidemia in pediatric CKD patients.

Methods: Seven major pediatric nephrology centers of Korea enrolled children younger than 20 years who had CKD. From July 2010 to December 2013, 322 children (MF 218:104) were enrolled.

Results: Baseline lipid analysis found a high prevalence of dyslipidemia in 49%. Several factors were analyzed including age, gender, CKD stage, primary renal disease, height, weight, BMI, social economic status, hypertension, co-morbidity, Z score of height, z score of weight, z score of BMI, gestational age at birth, birth weight, estimated GFR and duration of underlying diseases. Univariate logistic regression analysis demonstrated that several factors including BMI, co-morbidity, Z score of weight and BMI Z score of Z were associated with dyslipidemia. After multivariate adjustment, social-economic status and BMI Z score of BMI were significantly associated with dyslipidemia.

Conclusions: Among children with CKD, dyslipidemia is quite common and is associated with factors such as social-economic status and BMI Z score of BMI.

Funding: Governmental Support - Non-U.S.
**TH-PO468**

**Self-Management/Transition Readiness and Health Services Utilization Among Adolescents/Young Adults with Chronic Conditions in the Pediatric or Adult Settings From Across the USA**

**Maria E. Ferris,1 Keisha L. Gibson,2 Hsiao Ling Lui,2 Susan F. Massengill,1 John D. Mahan,1 Randall K. Detwiler,1 Gerald A. Hladik,1 Mara Medeiros,1 UNC at Chapel Hill, NC; East Carolina University, NC; Carolinas Medical Center, NC; The Ohio State Univ, OH; Hospital Infantil de Mexico “Federico Gomez”, DF, Mexico.

**Background:** The performance in self-management and/or health care transition readiness measurements by adolescents or young adults with chronic conditions (AYA) needs to be correlated to clinical outcomes and health services utilization.

**Methods:** The 18-question STAR, Questionnaire is a self-report survey of self-management (adult-focused setting) and/or transition-readiness (pediatric setting) with 6 factors: Medication Management, Provider Communication, Engagement during Appointments, Disease Knowledge, Adult Health Responsibilities, and Resource Utilization. The total raw score ranges from 0-90, with higher scores reflecting more intact skills (Ferris et al., 2015). Data presented is from 321 AYA with chronic health conditions (including chronic kidney disease, heart disease, neurocognitive deficits, and complex medical conditions) treated in either the pediatric or adult-focused settings at 6 large health systems in the northeast, southeast, and midwest regions of USA, or who attended Victory Junction Camp (from several states in USA).

The outcomes/health services utilization measures were adherence (Moriski et al., 1986) and number/length of hospitalizations in the last year.

**Results:** Higher STARs Questionnaire total score correlated with higher medication adherence (β = .31, p < .000, R² = .070). Higher STAR, Medication Management Subscale correlated with higher medication adherence (β = .499, p < .000, R² = .224). Greater STAR, Disease Knowledge Subscale correlated with higher medication adherence (β = .216, p < .001, R² = .044), fewer number of hospitalizations (β = -.453, p < .000, R² = .262) and inpatient days in the past year (β = -.432, p < .000, R² = .187).

**Conclusions:** The strong reliability of the STAR, Questionnaire in AYA with a variety of chronic conditions treated in either the pediatric or adult-focused clinics, correlates with health outcomes and health services utilization.

**Funding:** Private Foundation Support

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**TH-PO469**

**Emotional-Behavioral Functioning of Children Enrolled in the Chronic Kidney Disease in Children (CKiD) Cohort Study**

**Rebecca J. Johnson,1,2 Matthew Matheson,2 Arlene C. Gerson,2 Susan R. Mendley,2 Matthew Matheson,2 Arlene C. Gerson,2 Susan R. Mendley,2 S. Shinnar,2 Hsiao Ling Lai,2 or Adult Settings from Across the USA**

**Background:** CKiD is a longitudinal study examining medical, neurocognitive, and psychosocial outcomes for children with mild to moderate CKD ages 1-16 years at study entry. Little is known about how CKD affects emotional-behavioral functioning (EBF), although data from the CKiD study indicate that these children are at increased risk of attention and executive functioning deficits. In one of the largest studies to date, we report EBF of participants at baseline and over time.

**Methods:** Parents of participants completed the Behavior Assessment System for Children (BASC-2) at baseline and every 2 years. 835 participants had BASC-2 data, including 797 at baseline. Linear mixed models predicted participants' scores on BASC-2 summary measures (Internalizing, Externalizing, Behavioral Symptoms Index, Adaptive Skills) and Medical Problems (Depression, Sleep Problems). Analyses controlled for key demographic (age, sex, ethnicity, maternal education, household income, Full Scale IQ) and medical (GFR, hypertension [HTN], low birth weight, anemia, seizures, proteinuria, glomerular diastasis, time since CKD onset) covariates.

**Results:** Children with mild to moderate CKD have EBF scores generally within normal limits at baseline and over time. At baseline, the proportion with scores at least 1 SD above the mean was 24% for internalizing problems and 27% for attention problems, higher than would be expected in a typical sample. In an adjusted linear mixed model, persistent hypertension was related to attention problems (β = 1.81, 95% CI = 0.40-3.21, p < 0.02).

**Conclusions:** Children with mild to moderate CKD have parent-reported EBF that is within normal limits, at baseline and over time. However, the proportion with scores more than 1 SD above the mean is higher than would be expected, suggesting that this population may be at slightly increased risk for internalizing symptoms and attention problems, particularly in the context of HTN, which was associated with increased risk of parent-reported attention problems.

**Funding:** NIDDK Support, Other NIH Support - National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI)

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**TH-PO470**

**Echocardiographic Findings in Hypertensive Children with Kidney Disease or Essential Hypertension**

**Gabriel Paris,1 Wachaire Schenker2, Aura Jeanette Arenas Morales,2 Marissa J. Defreitas,2 Carolynn A. Abitbol,2 Michael Freundlich,2 Sethuraman Swaminathan,1 Gaston E. Zilleruelo,2 Pediatric Cardiology, Unv of Miami; 2Pediatric Nephrology, Unv of Miami, Miami, FL.

**Background:** Hypertension (HT) is a major risk factor causing left ventricular hypertrophy (LVH) and diastolic dysfunction. In children with chronic kidney disease (CKD), the cardiovascular morbidity exceeds that of peers without CKD.

**Methods:** Children with diagnosis of HT underwent echocardiography with concurrent tests of HT. Children with HT disease were divided into LV mass, systolic and diastolic function were reviewed. Diastolic transmural early (E), late (A), septal E’, lateral-ateralal E’ velocities measured. Calculated E/A=1 and or E/E’ Z-score(>2) defined diastolic dysfunction.

**Results:** 52 HT children (11±5yr), 29 had CKD (CKD-HT) and 23 essential HT (eHT). No difference in age, weight, gender, body mass index (BMI), %obesity, heart rate between groups. Prevalence LVH (25% & 30%) and LVMZ-Z were similar. LVM-Z was strongly correlated with BMI-Z in both groups (r = 0.6,p < 0.01) and to a lesser degree with SBP-Z (r = 0.5,p < 0.05). No correlation of LVM-Z with GFR. Diastolic dysfunction was identified in HT and CKD-HT (25%) whereas systolic function was preserved in both groups. Changes of E/A and aortic root diameter were subtle but significantly different between eHT and CKD-HT (see figure). Additionally, a significant decline in E/A (p < 0.01) and Septal E/E’ +Z (p = 0.03) was observed with worsening GFR.

**Conclusions:** High prevalence of LVH and diastolic dysfunction noted in HT children with or without CKD. Severity of LVH associated with obesity and to a lesser extent to HT but significant in CKD-HT. Total E/A ratio and larger aortic root diameter which could be related to poor renal function.

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**TH-PO471**

**Glomerular Capillary Injuries in Thin Basement Membrane Disease**

**Yusuke Kajimoto, Michiko Aoki, Kanzaki, Kiyotaka Nagahama, Akira Shimizu, Analytic Human Pathology, Nippon Medical School, Tokyo, Japan.

**Background:** Thin basement membrane disease (TBMD) is diagnosed by diffuse reduction in the thickness of glomerular basement membrane (GBM) in electron microscopy (EM), and characterized clinically by benign familial hematuria. However, some cases progress to end-stage renal disease. In the present study, we performed the clinicopathological analyses of TBMD, especially focusing on glomerular capillary injuries, including morphological and qualitative alterations of GBM and glomerular capillaries, and correlated with clinical findings.

**Methods:** In our department, 27 renal biopsy cases of TBMD (1.9%) was identified. We investigated clinical characteristics using clinical records. We also examined pathological characteristics using light and EM, immunostaining for CD34, which can detect glomerular capillaries, immunostaining for α5 (IV) chains of type IV collagen, which is one of the main component of GBM, and low-vacuum scanning electron microscopy (LV-SEM), which allows detailed three-dimensional observation of GBM surface.

**Results:** The average age was 37.3±19.5 (5-64) years. 26 cases had hematuria and 21 cases had proteinuria. 17 cases (63.0%) indicated hematuria or proteinuria under 20 years of age. In 6 cases, the eGFR declined in G3a to G4 in clinical CKD stage. In immunofluorescence, α5 (IV) expression was significantly reduced in the GBM with partial enhancement of α2 (IV). In LV-SEM observations, thinning and flattening of GBM was noted with multiple small holes and manufactures in the surface of GBM. In CD34 and PAS staining, narrowed glomerular capillaries increased with accumulation of glomerular extracellular matrix (ECM), associated with glomerular endothelial cell injuries.

**Conclusions:** In TBMD, narrowing glomerular capillaries developed with increased glomerular ECM, in association with glomerular endothelial injuries. In addition, qualitative (reduced α5 (IV) expression) and ultrastructural alterations of GBM (small holes and manufactures) were noted. These glomerular capillary injuries might be associated with the clinical findings including urinary abnormalities and renal dysfunction.

**TH-PO472**

**Clinical Significance of IgM Disposition in Kidney Biopsy of Paediatric Minimal Change Disease, Single-Centre Case-Control Study**

**Dena Alroorbi,1 Wadidullah Alshareef,2 Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

**Background:** In many cases of Minimal change nephrotic syndrome, or Minimal change disease (MCD), immunoglobulin M (IgM) is biologically deposited in the mesangium, and can be seen under the electron microscopy (EM) and immunofluorescence (IF). Based on many studies, the rule of IgM is controversial in minimal change disease MCD which is one of the histopathological types of INS. The aim of this study is to explore the clinical significance of mesangial IgM deposits in paediatric MCD cases.

**Methods:** We reviewed a sample of 313 cases children with MCD who underwent a native kidney biopsy (NKB) at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia from 2003 to 2014. The sample is divided furtherly according to the presence of IgM deposits under EM and IF to IgM-IF and IgM-IIF, which are labeled as case- control groups respectively. We reviewed the clinical course as per the response to the steroid treatment. Initial adjuvant therapies included: Cyclosporine, Tacrolimus and Cyclophosphamide.

**Results:** MCD IgM-IIF has shown a significant association with the presence of hypertension at the time of diagnosis, where a p-value of 0.03. MCD IgM-IIF showed

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

Underline represents presenting author.
��晓春等认为，吸烟等同效应的NIC暴露可增加儿童的基线氧化应激，选择氧化应激基因（p66shc）暴露的等效效应的NIC与对照组相比，可增加4HNE含量

### 摘要

研究目的：观察吸烟对儿童和成人的不同影响。

研究方法：使用Western blotting和microarray技术，确定氧化应激和损伤的基线表达。

研究结果：儿童与成人的氧化应激和损伤的基线表达不同。

### 结论

吸烟对儿童的氧化应激和损伤有不同影响。

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**TH-PO475**

### Post-Weaning High-Fat Diet Accelerates Kidney Injury, but Not Hypertension Programmed by Maternal Diabetes

**Min-Chun Liao,1** Yessoufou Aliou,2 Xin-Ping Zhao,1 Shiao-Ying Chang,1 Isabelle Chenier,1 Julie R. Ingelfinger,1 Shao-Ling Zhang,2 1CRCHUM, Univ of Montreal, Montreal, QC, Canada; 2Pediatric Nephrology Unit, Massachusetts General Hospital, Boston, MA.

### Background:

Severe maternal diabetes results in offspring with intrauterine growth restriction (IUGR) phenotype. The long-term outcome of these affected IUGR diabetic offspring who experience overnutrition in early life is incompletely delineated. In the current study, we aimed to establish the underlying mechanisms by which a post-weaning high-fat diet (HFD) accelerates the perinatal programming of kidney injury occurring in the offspring of diabetic mothers.

### Methods:

Male offspring of non-diabetic and diabetic C57BL/6J dams were fed with standard chow (normal diet, ND) or HFD from 4 to 20 week-old. Biological parameters, renal morphology, and gene expression were assessed. Rat immobilized renal proximal tubular cells (RTPCs) were used for in vitro studies.

### Results:

As compared to offspring from non-diabetic dams, on ND, the offspring of dams with severe maternal diabetes had IUGR phenotype and developed mild hypertension and evidence of kidney injury in adulthood. Exposing the IUGR offspring to HFD resulted in rapid weight gain, catch-up growth and later, to profound kidney injury with glomerulosclerosis and tubular apoptosis. In adulthood these IUGR animals demonstrated activation of renal TGFβ1 and collagen type IV expression, increased oxidative stress and enhanced renal lipid deposition, but not systemic hypertension. HFD or free fatty acid (FFA) in the diet appear to accelerate the process of perinatal programming of kidney injury independent from FFA and with increased renal injury, compared to rats fed 4 (Fabp4) expression in proximal tubular cells, which may target reactive oxygen species (ROS), NF-kB and TGFβ1 signaling.

### Conclusions:

Early postnatal exposure to overnutrition with a HFD appears to increase the development of kidney injury, but not hypertension, in IUGR offspring of dams with maternal diabetes.

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

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**TH-PO476**

### Does Anemia Contribute to Growth Delay in Pediatric CKD? Implications from Adenine Mouse Model of CKD-Related Growth Failure

Oleh M. Akhurin,1 Adele L. Boskey,2 Stefano Rivella.1 1Weill Cornell Medical College; 2Hospital for Special Surgery; 3Children’s Hospital of Philadelphia.

### Background:

Growth delay remains common in children with CKD and it worsens their quality of life. The origin of CKD-related growth failure in children is thought to be multi-factorial but the contribution of anemia remains controversial based on the data from the major clinical studies. Experimental investigations of the role of anemia and iron homeostasis in growth and nutrition in juvenile CKD are lacking.

### Methods:

C57Bl6 mice and hepcidin gene (HAMP) knockout (KO) pups were started on 0.2% adenine diet at weaning (3 weeks) and sacrificed in 8 weeks. Litter-mate controls were fed a regular diet. Weekly measurements of nose to tip of tail length were used for tracking linear growth.

### Results:

Adenine-fed juvenile mice had statistically significant elevation of BUN, serum creatinine and phosphorus at sacrifice. Adenine fed mice had slower rate of weight gain compared with controls and by 3 weeks they stopped gaining and started to lose weight. Linear growth was also significantly slower in adenine fed mice. At sacrifice, adenine fed mice had approximately 40% deficit in body weight and 10-15% deficit in body length, as compared with controls (both differences were statistically significant).

### Conclusions:

In this study we demonstrated that 0.2% adenine diet reliably induces CKD-related growth failure and anemia in juvenile mice, resembling those seen in children with CKD. Knocking out HAMP rescues the anemia phenotype but does not affect linear growth and renal function decline, thus providing new insights into the interplay between CKD complications in children. Our ongoing experiments are directed towards further characterization of the mineral metabolism and erythropoiesis in this model and testing novel therapies that can improve growth in juvenile CKD.

**Funding:** Other NIH Support - R01 DK090554 05 (S. Rivella)

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**TH-PO477**

### Establishment of Urinary Tract Infections in the Absence of Umbrella Cells and Uroplakin Plaque

Ashley R. Jackson,2 Birong Li,1 Kirk M. McHugh,1 Brian Becknell.4 1Weill Medical College of Cornell University; 2Pediatric Urology, Dept of Surgery, Div of Urology, Minn Med; 3Medical Center, Jackson, MS.

### Background:

Uropathogen Escherichia coli (UPEC) accounts for 90% of human urinary tract infections (UTI). Urothelial umbrella cells elaborate uroplakin plaques that establish a permeability barrier to urine and pathogens. UPEC attach to Uplkα1 within uroplakin plaques, invade umbrella cells, and establish intracellular bacterial communities. We genetically ablated plaques and umbrella cells to test their role in UPEC invasion and establishment of experimental UTI.

### Conclusions:

Urinary tract infections (UTIs) mediated by UPEC are common in children and are a major source of morbidity. Uroplakin plaques are an important host defense against UTIs. The establishment of UTIs in the absence of uroplakin plaques and umbrella cells is required to understand the mechanisms underlying UTI pathogenesis.

**Funding:** Pediatric Nephrology Poster/Thursday 195A

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

**Underline represents presenting author.**

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195A
Upk1b RFP/RFP bacterial recovery from urine, bladder, ureters and kidneys was significantly reduced in TH-PO479 Cardiac Hypertrophy Causes Elevation in Circulating c-FGF23 Levels in TH-PO478 in TH-PO479 TH-PO478 Sayoko Yonemoto, Development and Pathogenesis TH-PO478 J Am Soc Nephrol 26: 2015

Urinary tract will provide novel insight into the expression pattern of urothelial-specific proteins to define alternative pathways for UTI pathogenesis.

Results: Upk1b serves an essential role in plaque assembly and terminal differentiation of umbrella cells. Whereas umbrella cells and uroplakin plaques facilitate initial uPck1 became colonized of the bladder, these structures are dispensable for maintenance of infection. Comparable UPEC recovery from Upk1b RFP/RFP urinar tracty 7 dpi supports the existence of alternative UPEC reservoirs, potentially as a consequence of a disrupted urinary permeability barrier. Thus, genetic ablation of umbrella cells provides the opportunity to test alternative pathways for UTI pathogenesis.

Funding: NIDDK Support

TH-PO478

3D Modeling of the Urinary Tract to Better Understand Urothelial Development and Pathology Leah D. Hunter, Claudia F. Mosley, Ashley R. Jackson, Kirk M. McHugh

Methods: Embryonic day E13.5 (undifferentiated), E14.5 (urothelium differentiation onset) FVB/N mice were 3D reconstructed electronically from 10mm serial sections labeled with urothelial antibodies. Molecular annotations were electronically generated using Stereo Investigator software and visualized using Neuronlucida Explorer

Results: E13.5 urothelium displayed highly unidifferentiated characteristics, lacking keratin (Krt) and uroplakin expression, while E14.5 exhibited significant urothelial identity expressing a wide range of markers. Bladder basal urothelial cells express sporadic Krt5, Krt14 and K67. Unexpectedly, Krt5 also localized to intermediate and select superficial cells at E14.5. Shh and p63 uniformly localized to basal and most intermediate urothelial cells. Shh and K67 localized to some superficial urothelial cells. Intermediate and superficial bladder urothelial cells expressed uroplakins. Interestingly, uroplakin expression was more prominent in the dorsal urinary tract, while Shh exhibited more ventral patterning, and Krt14 commonly localized to anterior portions of the caudal bladder urothelium. Krt20 was only minimally expressed at E14.5. Overall, E14.5 bladder urothelial cells expressed 13% Krt14, 5% uroplakin, 1% Krt20, 76% p63, 66% Shh, 21% Ki-67, and 34% Krt13, when normalized to E-cadherin.

Conclusions: Molecular annotation and 3D modeling of the entire embryonic urinary tract will provide novel insight into the expression pattern of urothelial-specific proteins temporally and spatially. Future studies will include 3D mapping of these tissues and markers throughout embryonic development to further elucidate its role in urothelial disease.

Funding: NIDDK Support

TH-PO479

Cardiac Hypertrophy Causes Elevation in Circulating e-FGF23 Levels in Mice Issuo Matsu, Akiko Shimomura, Yasuo Kusunoki, Daisuke Mori, Sayoko Yonemoto, Masanmi Senda, Yusuke Sakaguchi, Takayuki Hamano, Yoshitaka Isaka, Hiromi Rakugi,1 Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Osaka, Osaka, Japan; Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Osaka, Osaka, Japan.

Background: Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphate and calcium homeostasis. Besides its phosphaturic effect, intact FGF23 induces left ventricular hypertrophy (LVH). However, it remains unclear whether ventricular hypertrophy affects circulating levels of FGF23.

Methods: The activation of the calcineurin-NFAT (nuclear factor of activated T-cells) pathway plays pivotal roles in the pathogenesis of LVH. Using cardiomyocyte-specific calcineurin A transgenic (CnA-TG) mice, we assessed whether ventricular hypertrophy affects circulating levels of FGF23.

Results: CnA-TG mice at age 6 weeks developed ventricular hypertrophy. Heart weight to body weight ratio was 0.011 ± 0.0004 in CnA-TG mice and 0.0043 ± 0.0003 in wild type (WT) mice. Real time PCR analyses demonstrated that cardiac tissues of CnA-TG mice had higher levels of atrial natriuretic peptide, brain natriuretic peptide, and β myosin heavy chain. Serum C-terminal FGF23 levels of CnA-TG mice was significantly higher than those of WT mice (214.7 ± 68.6 vs. 137.2 ± 19.8 pg/mL, P=0.002), whereas the levels of intact FGF23 were not different between the two groups (CnA-TG mice 27.6 ± 14.4 pg/mL vs. WT mice 24.7± 6.1 pg/mL, P=0.943). All parameters — body weight, food intake, water intake, urine volume, creatinine clearance, serum phosphate/calcium levels, urinary phosphate/calcium excretion, and fractional excretion of phosphate/calcium — were not different between the two groups. Although iron deficiency has been reported to reduce FGF23 expression in CKD, but now we can show that cardiac hypertrophy had higher transferrin saturation than WT mice (91.5 ± 6.3 vs. 71.7 ± 15.5%, P<0.001).

Conclusions: Cardiac hypertrophy causes elevation in circulating e-FGF23 levels through yet-unknown mechanisms.

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

TH-PO480

Soluble Klotho and Cardiac FGF23 Modulate Left Ventricular Hypertrophy in CKD Patients Maren Leijheit-Neslet,1 Christian Faul,2 Dieter Haffner,1 1Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; 2Dept of Nephrology and Hypertension, Dept of Medicine, Univ of Miami Miller School of Medicine, Miami, FL.

Background: Elevated levels of circulating fibroblast growth factor 23 (FGF23) are strongly associated with chronic kidney disease (CKD) mortality, and left ventricular hypertrophy (LVH), a major cause of cardiovascular death in CKD patients. Existence and role of a paracrine cardiac FGF23/Klotho system in the heart, however, remain elusive.

Methods: We conducted a retrospective case-control study in 25 deceased patients with end-stage renal disease, and 25 age and sex-matched healthy controls. At the time of death 18 patients were on dialysis treatment, and 7 patients were transplanted. Myocardial autopsy samples of the left ventricle (LV) were evaluated for endogenous FGF23 expression, FGF-1, Klotho, calcineurin-NFAT signaling mediated LVH, and genes regulating pathological cardiac remodeling by immunohistochemistry and quantitative real-time PCR analysis. The expression of brain natriuretic peptide (BNP) served as a marker of LVH.

Results: Here, we find that FGF23 is expressed in human cardiomyocytes, and that myocardial expression of FGF23 in concert with Klotho deficiency strongly correlates with the presence and severity of LVH in CKD patients. Enhanced cardiac FGF23 expression is associated with chronic phosphate load, up-regulation of FGRF4 expression, and activation of calcineurin-NFAT signaling, an established inducer of cardiac remodeling and LVH. Most important, these changes are reversed after renal transplantation. Using in vitro studies, we observed that cardiomyocytes express and release full-length biologically active FGF23, and that enhanced FGF23 secretion results in cardiac myocyte hypertrophy, which is blocked in the presence of soluble Klotho.

Conclusions: Our results indicate that enhanced levels of FGF23 induce LVH via a paracrine cardiac mechanism in settings of chronic kidney disease. In CKD patients, this process is reversed after renal transplantation.

TH-PO481

Role of FGF23 Mediating LVH in a Mouse Model of Klotho Deficiency Maren Leijheit-Neslet,1 Melis Basaran,1 Makoto Kuro-o,2 Ioana Alesutan,3 Jakob Völk,1 Florian C. Lang,1 Dieter Haffner. 1Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; 2Center for Molecular Medicine, Jichi Medical Univ, Shimotsuke, Japan; 3Dept of Physiology, Univ of Tuebingen, Tuebingen, Germany.

Background: In patients with chronic kidney disease (CKD), high serum concentrations of the phosphaturic hormone fibroblast growth factor 23 (FGF23) result in high mortality rate and left ventricular hypertrophy (LVH). FGF23 signals via FGF receptors (FGFR) in the presence of its cofactor Klotho. In this study we investigate whether circulating FGF23 in cardiomyocytes to promote cardiac remodeling and LVH. However, Klotho seems to be cardioprotective. The aim of our study was to investigate the role of cardiac FGF23 in cardiac remodeling and LVH in the Klotho knockout (kl/kl) mouse.

Methods: Hearts of 8 weeks old kl/kl mice and wild-type (WT) mice were excised and weighed. The left ventricle was isolated and stained with wheat germ agglutinin (WGA) to quantify cross-sectional area of individual cardiomyocytes. Furthermore, cardiac tissue was homogenized and analyzed by quantitative real-time PCR for genes involved in pathological cardiac remodeling, and protein lysates were used to determine FGF23-mediated activation of calcineurin-NFAT pathway mediating LVH.

Results: Relative heart weight of kl/kl mice was significantly higher compared with WT, and cardiomyocyte cross-sectional area was increased in kl/kl mice indicating LVH. Cardiac Fgfr23 gene and protein levels were induced significantly in kl/kl mice compared with WT. Interestingly, expression of Fgrf1, the physiological receptor for FGF23/Klotho signaling, was unaltered in kl/kl mice, but Fgfr4 was up-regulated significantly. The cardiac expression of calcineurin-NFAT protein complex, an individual pathway of cardiprotective, was downregulated in kl/kl mice, indicating genes involved in pathological cardiac remodeling and the development of LVH.

Conclusions: Our data suggest that high levels of circulating and cardiac FGF23 contribute to cardiac remodeling and LVH in Klotho deficient mice indicating a direct impact of FGF23 signaling via FGRF4 on cardiovascular disease beyond CKD.

TH-PO482

Cardiac FGF23 in Concert with Klotho Deficiency Affect Myocardial Fibrosis in Diabetic Patients Maren Leijheit-Neslet, Felix Kirchhoff, Dieter Haffner. 1Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.

Background: Pathologic cardiac remodeling, i.e. left ventricular hypertrophy (LVH) and myocardial fibrosis, is a major cause of cardiovascular (CV) death in patients with chronic kidney disease (CKD). Increased circulating levels of fibroblast growth factor 23 (FGF23) are associated with increased mortality in CKD coincided with enhanced CV
FGF23-Induced LVH Is Reversible in Rodents

Methods: Left ventricular hypertrophy (LVH) contributes to cardiac disease in chronic kidney disease (CKD). Serum levels of fibroblast growth factor (FGF) 23 rise as patients progress to renal failure. We have previously shown that FGF23 can activate FGF receptor (FGFR) 4 and calcium/nitrate/NFAT signaling in cardiac myocytes and induces LVH in rodents. Administration of a pan-FGFR inhibitor in the 5/6 nephrectomy model of CKD immediately after surgery protects rats from developing LVH. Furthermore, LVH in rats 2 weeks after surgery is reversible by pan-FGFR inhibition.

Methods: To further study FGFR4-dependency and reversibility of FGF23-mediated LVH, we elevated serum FGF23 in FGFR4 knockout (-/-) mice and wild type littermates by administration of a high phosphate (2%) diet for 3 months. Furthermore, a group of wild type mice that received a high phosphate diet for 3 months was returned to normal chow for 3 months. LVH was assessed by histology and analysis of cross sectional area of individual myocytes. Serum levels of cleaved FGF23 were determined by ELISA and kidney function by BUN.

Results: Serum levels of phosphate and FGF23 were elevated in mice on high phosphate diet when compared to mice on normal chow. However, only wild type but not FGFR4/-/- mice developed LVH after 3 months as evident by significantly increased LV wall thickness and cross sectional myocyte area. When wild type mice were switched from high phosphate to normal chow, the LVH phenotype resolved within 3 months and cardiac parameters were comparable to those of mice that continuously received a normal diet.

Conclusions: FGF23 is causatively involved in the development of age-related LVH. A recent translational study from our group demonstrated that FGF23 is a causal factor in the pathogenesis of LVH and that FGF receptor (FGFR) 4 mediates the cardiac effects of FGF23. We have shown that constitutive FGFR4 knockout (-/-) mice that were administered a high phosphate diet to elevate circulating FGF23 were protected from LVH. Human studies have shown that serum FGF23 levels increase with age and are associated with LVH in the elderly population. Therefore we wanted to test if, in aging wild type mice, the FGFR4 gene would prevent the development of FGF23 induced LVH.

Methods: We studied 6 and 18 months old FGF23-/- mice and wild type littermates. LVH was assessed by H&E staining of cardiac cross sections and quantification of LV wall thickness, as well as analysis of cross sectional area of individual myocytes by WGA-fluorescent labeling. Serum levels of cleaved FGF23 were determined by ELISA and kidney function by BUN.

Results: Serum FGF23 levels continuously increase in wild type mice with age, whereas kidney function is not altered over time. Compared to 6 months old mice, 18 months old wild type mice develop LVH as evidenced by significantly increased LV wall thickness and cross sectional myocyte area. Although the increase in serum FGF23 levels in 18 months old wild type mice is comparable to that of 2 months old mice and is even higher than in wild type littermates, FGF23/-/- mice do not develop an LVH phenotype.

Conclusions: Aging wild type mice develop elevated serum FGF23 levels as well as LVH. Since aged FGF23/-/- mice are protected from LVH, we postulate that FGF23 mediates age-related LVH via activation of cardiac FGFR4, similar to the mechanism that we have previously described in animal models of CKD. In our aging model, elevations of serum FGF23 and cardiac effects of FGF23 appear to be independent of reduced kidney function.

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TH-PO485

miR-29b and miR-30c in the Regulation of Cardiac Fibrosis by VDRAs

Background: Cardiac remodeling in chronic kidney disease is associated with increased cardiac fibrosis. miRNAs could have a regulatory role in this process. The aim of the study was to identify the role of some miRNAs in myocardial fibrosis and also their implication in the effect of the vitamin D receptor activation (VDRA) as well as their potential use as biomarkers.

Methods: Male Wistar rats with chronic renal failure (CRF, by 7/8 nephrectomy) were treated intraperitoneally with equivalent doses of two VDRAs (10 ng calcitriol and 30 ng paricalcitol/kg/day, 5 days per week, during 4 weeks). A placebo group (CRF + vehicle) and a sham group with normal renal function served as controls. Biochemical parameters, cardiac fibrosis gene array, Sirius red staining of ventricular sections, and miRNA expression were assessed in the placebo group, in the VDRAs groups (miR-29b and miR-30c levels) in heart and serum, and the expression of target genes (collagen I [COL1A1], matrix metalloprotease 2 [MMP2], and connexin tissue growth factor [CTGF]) in heart were evaluated.

Results: All VDRAs prevented cardiac fibrosis, achieving statistically significant differences in comparison to the paricalcitol treated group. A reduced expression of miR-29b and miR-30c was observed in heart of CRF rats, which was prevented with all VDRAs, observing the better results in paricalcitol group. It is described that miR-29b regulates COL1A1 and MMP2 expression and miR-30c regulates CTGF expression. In the hearts of CRF rats, increased expression of collagen I and protein levels of COL1A1, MMP2 and CTGF were observed, which were prevented with all VDRAs. In serum levels of miR-29b and miR-30c, a significant increase was observed, which was prevented by VDRAs use. In the heart and serum analyses, the more marked effects were observed with paricalcitol.

Conclusions: The VDRAs, particularly paricalcitol, reduced cardiac fibrosis acting on COL1A1, MMP2 and CTGF expression, probably through the regulation of miR-29b and miR-30c. These miRNAs could be useful serum biomarkers for cardiac fibrosis and also potential new therapeutic targets.

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TH-PO486

Inhibition of FGFR4 Reduces Changes in Cardiac Contraction Induced by FGF23, but Does Not Rescue Impaired Endothelium-Mediated Vasorelaxation

Aging wild type mice develop elevated serum FGF23 levels as well as LVH. Since aged FGF23-/-/- mice are protected from LVH, we postulate that FGF23 mediates age-related LVH via activation of cardiac FGFR4, similar to the mechanism that we have previously described in animal models of CKD. In our aging model, elevations of serum FGF23 and cardiac effects of FGF23 appear to be independent of reduced kidney function.

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TH-PO487

Inhibition of FGFR4 Reduces Changes in Cardiac Contraction Induced by FGF23, but Does Not Rescue Impaired Endothelium-Mediated Vasorelaxation

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Background: Fibroblast growth factor 23 (FGF23) is released by bone cells and is an important hormone in bone-kidney crosstalk in the regulation of phosphate. As kidney function declines, plasma FGF23 increases significantly and elevated FGF23 has been correlated with cardiac pathologies. Recently, our laboratory has shown that FGF23 treatment increases intracellular calcium in primary cardiomyocytes, increases contractility of left ventricular muscle strips, and impairs endothelium-mediated relaxation of aortic rings by reducing nitric oxide bioavailability. While FGF receptors (FGFR) 1-4 are expressed in the heart and vasculature, it is currently unknown which FGFR mediates these direct effects of FGF23.

Methods: We tested the effects of FGF23 on adult mouse heart and aortic rings in the presence of an isomeric specific FGFR4 blocking antibody (anti-FGFR4; U3 Pharma/Saito-Sankey)

Results: A 1 μM Acute treatment of FGF23 (9000 pg/ml) increased contraction of paced left ventricular muscle strips 1.6 ± 0.1 fold over vehicle (P<0.01; n=5). Additionally, FGF23 treatment of paced Landendorf-perfused hearts acutely induced contraction abnormalities typically in the form of mechanical alternans. Both the increase in contractility as well as the alternans were eliminated by pretreatment with anti-FGFR4. Using inotropic tension myography, preactivation with FGF23 (9000 pg/ml) caused a 35% inhibition of endothelium-dependent relaxation elicited by acetylcholine in FGF23-precontracted aortic rings (n=5-7; P<0.05). However, pretreatment with anti-FGFR4 did not improve relaxation (n=5; P=0.05).

Conclusions: FGF23 can directly target cardiomyocytes via FGFR4 to alter cardiac excitation-contraction, but may work through different FGFR isoforms to alter endothelium-mediated relaxation. Our findings have importance for targeting potential mechanisms of arrhythmias and cardiovascular remodeling directly induced by FGF23.

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Differential Expression and Regulation in Uremia of FGFB3 in Bone and Kidney

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Background: CKD is associated with increased plasma levels of FGFB3 and contribution from extraskelatal sources has been proposed. Our aim was to study the regulation of FGFB3 expression in bone and kidney tissues and the potential importance of kidney FGFB3 for the increased plasma FGFB3 in uremia.

Methods: The renmant kidney model of chronic uremia (8 weeks) in 5/6 nephrectomized rats was used. Groups of uremic and age-matched normal rats (n= 6-9) were treated with a bolus of the FGFB3 (FGF) inhibitor, PTD7074 (PD) 50mg/kg, or calcitriol 200ng or parathyroidectomy (PTX). Intact FGFB3 levels in plasma, and FGFB3 expression in bone and kidney were studied.

Results: FGFB3 was not expressed in the normal kidney, but was induced in injured kidney tissue. FGFB3 expression significantly increased (p=0.01) decrease FGFB3 plasma levels in normal PD rats from 364±229 pg/ml to 581±84pg/ml, whereas the plasma levels in the vehicle groups remained unchanged, normal 357±26 and uremic 100±12pg/ml. In parallel, a decrease in FGFB3 mRNA in bone tissue was documented in both normal and uremic PD rats, as compared to their vehicle control (p=0.005). normal vehicle 1.54±0.23 vs normal PD 0.15±0.02, and uremic vehicle 2.38±0.52 vs uremic PD 0.12±0.02. In contrast, kidney FGFB3 mRNA remained unchanged in the uremic PD rats 1.19±0.25 vs vehicle 1.13±0.40 (ns). PTX at time of 5/6Nx revealed a decrease in plasma FGFB3 expression in uremia (normal 1.0, uremic 3.01±1.28 and uremic-PTX 0.04±0.09), while it had no influence on induction of kidney FGFB3 expression in uremia (uremic 3.87±1.61 vs uremic-PTX 3.06±2.27). Calcitriol further stimulated the increased iFGFB3 plasma levels in uremia, whereas it had no impact on kidney FGFB3 expression.

Conclusions: FGFB3 is induced in the injured kidney. In contrast to bone tissue, the kidney expression of FGFB3 in uremia is not regulated by FGFR, PTH or calcitriol signaling. The present results indicate that kidney FGFB3 is not contributing to the high plasma levels of FGFB3 in uremia.

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TH-PO488

MEMO1 Deletion Abolishes Renal Responses to FGFB3

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Background: Mediator of ErbB2-Driven Cell Motility 1 (MEMO1) modulates fibroblast growth factor (FGF) signaling in vitro, but its physiological role is unclear. Memo KO mice showed premature aging, insulin hypersensitivity and a deranged mineral metabolism similar to what is observed in FGFB3 KO and Klotho mutant mice (Haenzi B, FASEB J 2014). Here, we assessed Memo’s role in renal FGF23 effects. We attempted to rescue the Memo KO phenotype, and we established kidney-specific Memo KO mice.

Methods: Exxon 2 of MEMO1 was deleted in the full body of Memo1 mice using a tamoxifen-inducible Cre recombinase to obtain cKO mice. Littermates without Cre served as controls. Twelve Memo cKO and 12 control mice were randomized to receive an intraperitoneal FGF23 or vehicle injection, and kidneys were studied by immunoblotting (Heim B, NAT MED 2008). Shim et al. (Shim J, J AM SOC nephrol 2015).

Results: Memo KO mice developed a phenotype of premature aging upon tamoxifen treatment. Reducing dietary phosphate content did not alter disease-free survival. Memo eKO mice lacked renal responses to FGFB3. Moreover, the vitamin D inhibitory effect of FGFB3 on the 24a-hydroxase (CYP24A1) was absent in eKO mice. Kidney-specific Memo KO mice remained viable and had abolished Memo expression in the kidney but not in other organs upon KO induction. These mice showed renal calcium wasting.

Conclusions: Memo is involved in the mediation of FGFB3 effects in the kidney, and in renal calcium handling. This explains many similarities that Memo eKO mice share with FGFB3 or Klotho KO mice. However, the three mouse models differ in phosphate dependence of the eventually lethal phenotype.

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TH-PO489

Exploring Bacterial Endotoxin as a Promoter of Fibroblast Growth Factor 23 Production in Chronic Kidney Disease

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Background: Serum fibroblast growth factor 23 (FGFB3) is elevated in chronic kidney disease (CKD) and correlates with circulating concentrations of inflammatory cytokines. Lack of endogenous bacterial endotoxin has been detected in the bloodstream of CKD patients and may promote inflammation in this setting. We hypothesized that endotoxemia may stimulate FGFB3 production in CKD.

Methods: We first utilized a mouse osteocyte cell line (IDG-SW3) to explore the direct tissue responses of FGF23 production. Next, we tested the in vivo effects of low-dose LPS injection on FGF23 production in both wild-type (WT) mice and mice lacking CD14, a primary LPS receptor. Lastly, we compared the progressive changes in FGF23 production in WT and CD14− mice in response to CKD induction by adenine injection.

Results: Treatment of IDG-SW3 cells with LPS (1ug/ml) resulted in an 11-fold increase in FGF23 mRNA expression compared to vehicle (p<0.05, triplicate experiments). Moreover, intraperitoneal injection of LPS control diet in WT absence resulted in a 35-fold increase in calvarial FGFB3 gene expression two hours post-treatment (p<0.001 compared to vehicle-treated WT mice), which was accompanied by a doubling of serum FGFB3 (342.9 ± 124.2 pg/ml vs. 166.5 ± 25.9 pg/ml in vehicle-treated WT mice; p<0.001). Identical LPS dosing in CD14− mice blunt this response, resulting in only a 10-fold increase in calvarial FGFB3 gene expression (p<0.01) and no obvious difference in serum FGFB3 (188.9 ± 75.8, p<NS) compared to vehicle-treated WT mice (n=5 per group). Finally, CKD induction in WT mice led to a marked elevation of serum FGFB3 (6862.0 ± 4829.1 pg/ml vs 234.3 ± 33.3 pg/ml in WT mice fed a control diet). We aimed to determine if the production of FGF23 is regulated by LPS-induced inflammation in experimental CKD.

Conclusion: Bacterial endotoxin stimulates FGF23 production by bone by a mechanism that is partially dependent on CD14 signaling; however, the deletion of CD14 in a CD14− mouse model fails to attenuate the rise in serum FGFB3 that accompanies kidney injury.

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TH-PO490

Inflammation Affects FGF23 Production in Uremia

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Background: CKD is associated with increased plasma levels of FGF23 and higher FGF23 may be required to control P. We aimed to determine if the production of FGF23 is regulated by LPS-induced inflammation in experimental CKD.

Methods: 5/6Nx Wistar rats on diets with 0.2% or 0.4%P received LPS for 15 days. Sham rats also received LPS. Blood, urine, and kidney samples were collected.

Results: Nx rats on a 0.2%P diet had lower FGF23 compared to sham, whereas a 0.4%P diet increased FGF23 levels. LPS-treated groups had more than a 3-fold increase in plasma levels of FGF23 as compared with their respective controls. Fractional excretion of P in sham and Nx rats was not modified by the administration of LPS. No differences in renal Klotho expression were found between sham and rats on a 0.2%P diet. A 50% reduction in Klotho was seen in 5/6Nx rats on the diet containing 0.4%P. The administration of LPS to sham rats reduced Klotho expression by approximately 25%. In 5/6 Nx rats on 0.2% and 0.4%P, LPS reduced Klotho by 70% and 50%, respectively.

Conclusions: The prevention of the increase in FGF23 associated with CKD is not possible in the presence of inflammation.

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TH-PO491

Dietary Sodium Bicarbonate Decreases Serum Fibroblast Growth Factor 23 in Normal Rats

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Background: Patients with CKD have a marked increase in serum fibroblast growth factor factor 23 (FGFB3) which is associated with increased mortality. FGFB3 is synthesized in osteoblasts and osteocytes; however, its specific regulators are not clear. During CKD there is a fall in renal net acid excretion leading to metabolic acidosis (MET). We have previously shown that MET directly stimulates FGF23 in mouse bone and in primary osteoblastic cells in vitro, suggesting that an in vivo increase in serum HCO3 might reduce serum FGFB3 levels. In this study we tested the hypothesis that oral NaHCO3 would decrease serum FGFB3 levels in normal rats.

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Methods: Sprague Dawley rats (250 g) were acclimated to a powered 1.2% Ca, 0.65% P 2 diet, 13 g/d, for 14d. Rats were either continued on this diet supplemented with 3% NaCl (n=9) or 3% NaHCO3 (n=10) for an additional 8 d. Blood was then obtained by cardiac puncture for measurement of FGF23 by ELISA ( intact FGF23, Immutopics) as well as standard metabolic parameters.

Results: Feeding rats NaHCO3 lead to a significant fall in serum FGF23 and an increase in serum HCO3 compared to feeding NaCl (Table; values are mean±SE: *, p< 0.05; **, p<0.01). Serum PO4 fell with NaHCO3 as did both serum Ca and K. There were no differences in serum Ca, Na or creatinine with NaHCO3 compared to NaCl fed rats.

Conclusions: Provision of oral NaHCO3 sufficient to raise serum HCO3 led to a significant fall in FGF23 in normal rats supporting the hypothesis that pH (or HCO3-) directly regulates FGF23; however, we cannot exclude that a NaHCO3 induced change in PO4 contributed to the change in FGF23. If comparable acid-base regulation of FGF23, now demonstrated in vitro and in vivo, is confirmed in humans, it suggests that correction of acidosis in patients with CKD may lower their elevated FGF23 levels.

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TH-PO492

Metabolic Acidosis Increases Osteoblastic MEPE Expression in Parallel to the Increase in Fibroblast Growth Factor 23

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Background: Serum fibroblast growth factor 23 (FGF23) increases with the severity of chronic kidney disease (CKD), leading to decreased renal tubular phosphate (Pi) reabsorption and serum 1,25(OH)2D, FGF23 is synthesized in osteoblasts and osteocytes; however, the primary factors regulating its production are not clear. Patients with CKD have decreased renal net acid excretion leading to metabolic acidosis (MET). During MET, acid is buffered by bone with release of mineral calcium and Pi. MET directly stimulates FGF23 in mouse bone and primary osteoblastic cells utilizing the same signaling pathways that lead to MET-induced bone resorption. To further characterize the regulation of FGF23 by MET we utilized primary osteoblasts to study gene expression pathways upstream of FGF23 production, including the major extracellular phosphoglycoprotein, MEPE, and the phosphate-regulating endopeptidase, PHEX.

Methods: Confluent osteoblastic cells isolated from neonatal mouse calvariae were incubated in neutral (NTL, pH=7.50, 20oC, 39 mmHg, [HCO3-]=30 mmol/L) or acid (MET, pH=7.20, 20oC, 39 mmHg, [HCO3-]=14 mmol/L) medium. Specific RNA gene expression was analyzed by real time PCR with expression normalized to RPL13A and calculated relative to non-incubated cells.

Results: Maximal stimulation of FGF23 was found at 24h (MET=7.26±1.55 vs NTL=3.75±0.64, p<0.05) MET significantly increased MEPE RNA expression as early as 0h compared to NTL (relative expression: MET=2.33±0.41, vs NTL=1.19±0.16, p<0.05) with a further increase noted between 6h and 24h. There were no significant differences in PHEX expression in response to MET compared to NTL, although there was a progressively decrease in PHEX expression in both groups over 24h.

Conclusions: Thus, MET stimulation of MEPE expression may be an initial step by which MET increases FGF23 production in mouse osteoblasts. By better understanding how MET stimulates FGF23, future therapies can be designed to target important downstream effectors of MET, especially in CKD patients, be devised to not only prevent bone resorption but also lower FGF23.

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TH-PO493

Effect of High-Dose and Flux Hemodialysis on Circulating Markers of Mineral Metabolism in the HEMO Study

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Background: There are limited and somewhat contradictory data in the literature on the effects of high- vs low-dose dialysis clearance and high vs low flux on circulating markers of mineral metabolism.

Methods: The HEMO Study was a randomized multicenter study of the effects of high- vs dose-standard versus high-dose and flux-low vs low-flux hemodialysis. Fibroblast growth factor 23 (FGF23, pre-specified primary endpoint for these analyses), serum phosphorus, and 25-hydroxyvitamin D (25(OH)D) were measured in stored serum samples. We used multi-state analyses to analyze the dose and flux effects on each mineral metabolism marker while accounting for mortality. We estimated the proportions of patients in 5 ordered states (S) for serum phosphorus, 25(OH)D and FGF23: S1 = deceased (score=0); S2 = alive in highest quartile (score=1); S3 = alive in 3rd quartile (score =2); S4 = alive in 2nd quartile (score=3); and S5 = alive in lowest quartile (score=4). The average rank was computed over 3 years of follow-up and compared between the randomized groups.

Results: Randomized patients had high rates of coexisting conditions 45% had diabetes, 26% had a history of cardiac disease. Characteristics of the patients in the two dose groups were similar, as were the characteristics of those in the two flux groups. The state distributions for FGF23 each year by dose (KTV) group and by flux group are shown in Figure 1. FGF23 differed significantly between dose groups (p<0.02) but not between flux groups (p=0.17). No significant differences were observed for serum phosphorus or 25(OH)D.

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TH-PO494

Factors for Persistent Low or High FGF-23 Levels in Maintenance Hemodialysis Patients

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Methods: We examined serum intact FGF-23, age, dialysis vintage, presence of diabetes, BMI, blood pressure, (Cr/Curea)2, Kt/Vurea, hcr P, hKtM, serum albumin, nPCR, geriatric nutritional risk index (GNRI), serum phosphate, serum calcium, iPTH, active vitamin D dosage, and phosphate binders and/or cinacalcet in 332 MHD patients in September of 2012, 2013 and 2014. Coronary artery calcification score (CACS) was measured in a subgroup (n=173). According to quartile (Q) of FGF-23 in 2012, mortality was assessed by Kaplan-Meyer and adjusted Cox models. Patients with FGF-23 Q1-Q1-Q1 were categorized in Group 1, patients with FGF-23 Q4-Q4-Q4 in Group 3, and the others in Group 2.

Results: Median age and dialysis vintage were 69 years and 66 months, respectively, at baseline. During the 2 years, 71 patients died and 24 patients left our hospital. Baseline FGF-23 levels (pg/ml) were <310 (Q1), 310-1489 (Q2), 1490-2559 (Q3) and >2559 (Q4) (P<0.05), with cumulative survival rates of 65.4%, 78.9%, 85.1% and 80.6%, respectively (P<0.01), and hazard ratios (HRs) for death of 1.0, 0.6, 0.4 and 0.5, respectively, in univariate model. However, there was no significant association between Q of FGF-23 level and mortality in multivariate model. HR for death of CACS was 1.1 (P=0.01), but there were no differences in CACS in patients based on FGF-23 level. Significant associations between Group 1 and diabetes (OR: 3.5), age (OR: 1.1), serum phosphate (OR:0.4) and vitamin D dosage (OR: 0.2), and between Group 3 and serum phosphate (OR: 2.0), iPTH (OR: 1.04) and vitamin D dosage (OR: 1.9), were observed (P<0.05).

Conclusions: FGF-23 in the lowest quartile showed the lowest 2-year cumulative survival rate in MHD patients, factors for persistent low FGF-23 levels were diabetes, age, serum phosphate and active vitamin D dosage.

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TH-PO495

Maintenance of Residual Diuresis and Type of Dialysis Can Influence FGF-23 Levels

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Background: Bone mineral disorders are common in patients (pts) with end stage renal disease (ESRD). In particular, hyperphosphatemia can be frequently seen in pts undergoing peritoneal dialysis (PD) and hemodialysis (HD). Recently, several studies investigated the role of fibroblast growth factor 23 (FGF23) in regulation of renal phosphate excretion in ESRD pts. However, patients with residual diuresis (RD) seem to better control serum phosphorus levels than those without RD. The aim of our study was to determine if the dialysis modality and the preservation of RD influence serum levels of FGF23.

Methods: We performed a cross-sectional study in two groups of pts: HD and PD. The variables analyzed were creatinine, urea, calcium, phosphate (Phosph), i parathormone (intact PTH) and eFGF23 (C-term). The urinary output collection refers to one week. All the variables analyzed were creatinine, urea, calcium, phosphate (Phosph), i parathormone (intact PTH) and eFGF23 (C-term).

Results: A total of 122 pts were enrolled (58HD,64PD).The mean age of HD pts was 64±9,14,25yrs and of PD pts 62,33±1,86 yrs. RD was present in 78 pts (65,46%...
Iron deficiency is a common phenomenon among patients with chronic kidney disease (CKD) and is associated with higher cFGF23 levels in pediatrics. This study aimed to evaluate the relationship between iron deficiency and cFGF23 levels in children with CKD.

**Background:**
Iron deficiency is related to higher FGF23 levels in pediatric CKD and that iron deficiency induced by proteinuria contributes to higher FGF23 levels in glomerular diseases. The cFGF23 was elevated with the decrease in TSAT and ferritin levels, and the CI ratio was also elevated with the decrease in TSAT and ferritin levels.

**Methods:**
We measured ferritin, TSAT, C-terminal (c) FGF23, CRP, and urine protein/creatinine (pr/cr) in 551 children in the CKiD Study.

**Results:**
Mean age was 10.2 ± 4.4 yrs; 62% were male; mean eGFR was 53 ± 19 ml/min/1.73m²; mean TSAT was 26 ± 13%; median ferritin was 46 ml/1.73m²; median urine pr/cr was 0.31 mg/mg (IQR 0.10-1.00); median cFGF23 was 114 RU/mL (IQR 50.8-218 RU/mL). The cFGF23 correlated inversely with ferritin (p=0.055) and cFGF23 (p<0.001) and directly with CRP (p=0.049), proteinuria (p=0.001), and phosphate (p=0.001). Grouping proteinuria into low or high grade (pr/cr >3) revealed no differences in ferritin and TSAT, but TIBC was lower (288 vs 310 μg/dl, p=0.011) and cFGF23 was higher in the high vs low grade groups (362 vs 184, p=0.016). cFGF23 levels were significantly elevated in the lowest ferritin quartile, preferentially in early stages of CKD (Figure).

**Conclusions:**
In multivariate analysis that included proteinuria and CRP, only lower eGFR, glomerular disease, higher phosphate, and lower ferritin were independent predictors of higher cFGF23 levels (p<0.001 for all). The relationship between proteinuria and cFGF23 was mitigated when ferritin was added to the multivariable model.

Iron deficiency is associated with higher cFGF23 levels in pediatric CKD and may contribute to the relationship between proteinuria and higher FGF23.

**Key:**
- TH-PO496
- Iron Deficiency Is Associated with Elevated FGF23 Levels in Pediatric CKD
- Takayuki Hamano, Bradley Warady, Susan L. Furth, Harald Jüppner, Ildoro B. Salusky, Anthony A. Portale, Myles S. Wolf, Northwestern Univ; Children’s Mercy Hospital; Children’s Hospital of Philadelphia; MGH; UCLA; UCSF.

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**TH-PO497**

**The Ratio of C-Terminal to Intact Fibroblast Growth Factor 23 Was Elevated in Iron Deficient Patients with Chronic Kidney Disease**

Sawoko Yoneyama,1 Takayuki Hamano,1 Naohiko Fuji,1 Daisuke Mori,1 Yasuo Kusunoki,2 Akhiro Shimomura,2 Isao Matsui,1 Hiromi Rakuji,1 Yoshitaka Isaka.1 1Dept of Internal Medicine, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Hyogo, Japan; 2Dept of Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 3Dept of Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka.

**Background:**
A recent study showed iron deficiency was associated with elevated fibroblast growth factor 23 levels by c-terminal assay (cFGF23) but not with intact FGF23 (iFGF23) levels in women without chronic kidney disease (CKD). It remains elusive if this holds true also in patients with CKD. In this cross-sectional study, we examined the associations between iron deficiency and FGF23 levels by the two assays in predialysis patients.

**Methods:**
The study population consisted of 100 predialysis outpatients of the nephrology department in a hospital in Japan. We measured plasma cFGF23 (Kainos) and serum iFGF23 (Kainos). Restricted cubic spine analysis was employed to estimate non-linear relationships between iron markers and ratio of cFGF23 to iFGF23 CI ratio.

**Results:**
The mean age and eGFR was 70.1±15.0 and 26.9±12.9 ml/min/1.73m², and the proportions of female and patients with diabetes mellitus were 30 and 40%, respectively. Only 18 and 6.0% of patients were treated with ESA and oral iron therapy, respectively. The cFGF23 was elevated with the decrease in TSAT and ferritin levels, and the CI ratio was also elevated with the decrease in TSAT and ferritin levels.

**Conclusions:**
In this study, we observed elevation of cFGF23 and CI ratio in iron deficiency patients with CKD. This might be because iron-deficiency stimulates FGF23 transcription and its cleavage simultaneously just as reported in non CKD women.

**TH-PO498**

**Ferric Citrate Hydrate Decreases Circulating FGF23 Levels Independently of Serum Phosphate Levels in Hemodialysis Patients with Iron Deficiency**

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**Background:**
Fibrinolysis growth factor 23 (FGF23) is regulated by dietary phosphate intake and vitamin D receptor activator (VDRA). Iron is another potential modulator for FGF23 metabolism.

**Methods:**
This prospective study enrolled 27 maintenance hemodialysis patients with iron deficiency and hyperphosphatemia who had been treated with sevelamer-HCl. Their phosphate binder was changed to ferric citrate hydrate (FCH), so that their phosphate levels were maintained constant. VDRA, other phosphate binders, and cinacalcet hydrochloride were unchanged. Serum intact-FGF23, C-terminal FGF23, intact parathyroid hormone, 25(OH)D, and other parameters were prospectively monitored for 12 weeks.

**Results:**
Serum levels of phosphate and 1,25(OH)2D were unchanged. Serum ferritin levels increased from 25.6 ± 24.3 mg/L at baseline to 55.8 ± 33.5 mg/L at 12 weeks with the administration of FCH. Serum intact-FGF23 and C-terminal FGF23 levels were 2000 (1300.0–3471.4) pg/ml and 1608.7 (634.8–2308.7) RU/ml at baseline, respectively. At 12 weeks, intact-FGF23 and C-terminal FGF23 significantly decreased to 1711.43 (1142.9–2342.9) pg/ml (P = 0.0258) and 1165.2 (626.1–1547.8) RU/ml (P = 0.0298), respectively. Serum intact parathyroid hormone levels significantly increased from 96.65 (125) pg/ml at baseline to 173 (114 – 283) pg/ml after 12 weeks (P = 0.006).

**Conclusions:**
Oral administration of FCH decreased both serum intact- and C-terminal FGF23 levels and increased intact parathyroid hormone levels, without any change in phosphate and 1,25(OH)2D. Treatment of iron deficiency with oral FCH may be a useful strategy to reduce serum FGF23 levels independent of phosphate and VDRA.

**TH-PO499**

**Intravenous Iron Leads to Fibroblast Growth Factor 23-Dependent Changes in Calcium-Phosphate Metabolism in Non-Dialysis Patients with Chronic Kidney Disease Stages 3-5**

Katarzyna Mutus-Szwedziak, Michal P Nowicki. Dept of Nephrology, Hypertension and Kidney Transplantation, Medical Univ of Lodz, Lodz, Poland.

**Background:**
Iron deficiency is a common phenomenon among patients with chronic kidney disease (CKD) treated with erythropoiesis stimulating agents. Intravenous iron may interfere with calcium-phosphate (Ca-P) metabolism in CKD. Iron infusion may reduce peripheral degradation and clearance of circulating iFGF23 after its secretion by the administration of FCH.

Serum levels of phosphate and 1,25(OH)2D were unchanged. Serum ferritin levels increased from 25.6 ± 24.3 mg/L at baseline to 55.8 ± 33.5 mg/L at 12 weeks with the administration of FCH. Serum intact-FGF23 and C-terminal FGF23 levels were 2000 (1300.0–3471.4) pg/ml and 1608.7 (634.8–2308.7) RU/ml at baseline, respectively. At 12 weeks, intact-FGF23 and C-terminal FGF23 significantly decreased to 1711.43 (1142.9–2342.9) pg/ml (P = 0.0258) and 1165.2 (626.1–1547.8) RU/ml (P = 0.0298), respectively. Serum intact parathyroid hormone levels significantly increased from 96.65 (125) pg/ml at baseline to 173 (114 – 283) pg/ml after 12 weeks (P = 0.006).

**Conclusions:**
Oral administration of FCH decreased both serum intact- and C-terminal FGF23 levels and increased intact parathyroid hormone levels, without any change in phosphate and 1,25(OH)2D. Treatment of iron deficiency with oral FCH may be a useful strategy to reduce serum FGF23 levels independent of phosphate and VDRA.
The renal calcification did not observe when the 8-week-old mice were fed with 1.5 or 1.8% phosphate diet for 7 days. These results suggest that the effects of high-phosphate diet during growth periods have a much greater adverse effect on renal α-klotho expression and morphology of the kidney as compared to a similar investigation during maturation periods.

**Conclusions:** In conclusion, excessive dietary phosphate intake during growth periods such as just after weaning period decreases in renal α-klotho expression relating to premature aging-like lesions.

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

TH-PO502

The Secreted Klotho mRNA Transcript Is Continuously Degraded by Nonsense-mediated mRNA Decay and Its Splicing Is Dysregulated After Kidney Damage

**Rik Mendez,** Geert Harms, Jan-luuk Hillebrand, Pathology and Medical Biology, Univ Medical Center Groningen, Groningen, Netherlands.

**Background:** Klotho is an anti-aging gene of which two mRNA transcripts have been identified: one corresponds to the full 5-exon coding sequence and the other, alternatively spliced, consists of exons 1-3 and 5 downstream base pairs, forming a stop codon. The latter mRNA transcript is thought to code for a truncated Klotho protein. While soluble Klotho proteins can be detected in blood, urine, and cerebrospinal fluid, a product of this alternative transcript has never been identified. Nonsense-mediated mRNA decay (NMD) research predicts that the premature stop codon induces continuous degradation during translation.

**Methods:** We first assessed the mRNA transcripts in human kidney and HK-2 cells by RT-PCR and DNA sequencing. We then blocked NMD in HK-2 cells using cycloheximide (CHX) (100 μg/ml) for 2, 4, or 6 h, or using XRN1 siRNA for mRNA degrading enzyme exoribonuclease 1, to assess possible accumulation of the alternative mRNA by RT-PCR and densitometry. Then, we assessed whether splicing was different in normal human kidneys (N=11) and in chronic rejection transplanted (CRT) kidneys (N=4).

**Results:** Expression of both klotho mRNA transcripts was confirmed in human kidney and in HK-2 cells by RT-PCR and DNA sequencing. CHX-induced inhibition of translation increased the “secreted” membrane-bound Klotho mRNA ratio from 0.14±0.02 to 0.44±0.06 (p<0.001). Preliminary data show that silencing of XRN1 has the same effect. Furthermore, already in normal kidneys, there was a marked, reproducible variation in splicing ratios, ranging from 0.03±0.01 to 0.20±0.02. In CRT kidneys, Klotho mRNA was expectedly down-regulated and splicing was skewed towards the non-functional alternative splice variant.

**Conclusions:** The alternative Klotho mRNA contains a premature stop codon and is a likely NMD substrate. Soluble Klotho would therefore be cleaved Klotho only. Furthermore, in damaged kidneys, splicing of the Klotho gene is dysregulated, which constitutes a new mechanism of Klotho down-regulation.

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

TH-PO503

Genetic Deletion of NaPi-2c Rescue Phenotype of Klotho Knockout Mice without Improving Severe Hyperphosphatemia

**Ai Hanazaki,** Hiroko Segawa, Kayo Ikuta, Toru Fuji, Ichiro Kaneko, Shihoko Yuki, Shiori Nishiguchi, Kejiro Notsu, Yuji Shiozaki, Sawataki Tamu, Ken-ichi Miyamoto. Molecular Nutrition, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.

**Background:** SLC34A3/NaPi-2c is one of the renal sodium dependent phosphate (Pi) transporters. Mutation of human NaPi-2c causes hereditary hypophosphatemic rickets with hypercalciuria (HHR). Thus, NaPi-2c may have an important role on renal Pi reabsorption and bone mineralization in humans. The physiological role of NaPi-2c, however, has not been completely explained yet. NaPi-2c-knockout (NaPi-2c−/−) mice showed hypercalciuria, but did not show any Pi abnormality. Recently, Herrad N. et al. reported that kidney specific NaPi-2c conditional knockout mice did not show any abnormality. These results suggested that NaPi-2c has minor role in the Pi homeostasis. To discover the role of NaPi-2c, we examined genetic inactivation of NaPi-2c in klotho knockout (klotho−/−) mice.

**Methods:** To obtain the klotho and NaPi-2c double knockout (klotho−/−NaPi-2c−/−, KL2c DKO) mice, klotho−/− mice and NaPi-2c−/− mice were crossed. Total body weight of each of wild-type, klotho−/−, KL2c DKO and NaPi-2c−/− mice was taken every week. Urine and blood were obtained for biomedical measurements at the several ages of weeks. Tissues were obtained from each mice for histological and calcification analysis.

**Results:** Genetic disruption of NaPi-2c significantly increased body weight and extended the life span of klotho−/− mice. KL2c DKO mice were viable and larger in size than klotho−/− mice, but smaller than wild-type and NaPi-2c−/− mice. KL2c DKO mice showed slightly decreased plasma Pi levels at early hood, but not adult hood. Plasma FGF23 levels were extremely high in KL2c DKO mice as well as klotho−/− mice.

**Conclusions:** Our finding demonstrated that NaPi-2c genetic deletion rescued the phenotype of klotho−/− mice without improving severe hyperphosphatemia.

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

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**TH-PO500**

**The Increase of Fractional Excretion of Phosphorus Induces FGF23 Resistance due to a Decrease in Renal Klotho**

**Juan R. Munoz-Castaneda, Carmen maria Herencia, Maria Encarnacion Rodriguez Ortiz, Juan miguel Diaz-tocados, Julio Manuel Martinez Moreno, Addy Rosa Montes de Oca Gonzalez, Yolanda Almaden peña, Mariano Rodriguez.** Servicio de Nefrología, Inst Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Unin Reina Sofia, Córdoba, Spain; Unidad de Lípidos y Aterosclerosis (CIBEROBIN), IMIBIC, Hospital Unin Reina Sofia, Córdoba, Spain; Laboratorio de Nefrología, IIS-Fundación Jiménez Díaz, REDinREN, Madrid, España.

**Background:** Phosphate is critically important for biological functions, particularly in normal rats, high levels of FGF23 increased fractional excretion of Pi (FePi) and renal α-klotho. However, high phosphate diet on renal α-klotho expression just after weaning period are still unknown. The objective was to evaluate the effect of intravenous iron supplementation on the parameters of mineral metabolism in patients with CKD.

**Methods:** The study included 35 non-dialysis patients with CKD stages 3-5. Each patients received once-daily 100 mg iron solution (Ferric oxacarboxylate complex; Vifor, France) for 5 consecutive days. Iron doses were administered in a slow 40 min intravenous infusion. On day 1 and at baseline and 2 hours after each dose administration, calcium (Ca), phosphorus (P), parathormone (PTH), intact-FGF23 (iFGF23), C-terminal-FGF23 (cFGF23), bonealkaline phosphatase (BAP) were assessed. The measurements were repeated on day 6.

**Results:** On day 2 the first iron infusion and on day 6 a significant increase in serum iFGF23 was observed (from 257±44.5 to 326.3±529.9 on day 1; p<0.005 to 451.4±601 on day 6; p<0.005). The concentration of cFGF23 was reduced in parallel on days 2 and 6 (43.6±64.1 to 5.4±9.2; p<0.05). Serum phosphorus concentration decreased significantly on day 1 two hours after iron infusion (from 1.75±0.6 to 1.53±0.35 mmol/l; p<0.005). On following days the changes of cFGF23 and phosphorus concentration were not significant. The serum concentrations of Ca, BAP and PTH were unchangedthroughout the study.

**Conclusions:** Intravenous iron supplementation may interfere with the mechanisms governing both production and degradation of FGF23 thereby leading to transient hypophosphatemia at the beginning of iron therapy.

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

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

201A
TH-PO504
Klotho/FGF23-Independent and ERα Mediated Direct Downregulation of NaPi-IIa by Estrogen in the Mouse Kidney Proximal Tubule. Hassan Aimal, Sulaiman Sheriff, Rose P. Webster. Internal Medicine, Univ of Cincinnati, Cincinnati, OH.

Background: Estrogen treatment is associated with renal wasting of inorganic phosphate (Pi) and hypophosphatemia in rats and humans; however the molecular and signaling mechanisms mediating this effect are still not fully understood.

Methods: To determine the roles of estrogen receptor isoforms (ERα and ERβ) and Klotho/FGF23 pathway in these effects, we studied the effects of estrogen on renal Pi handling in the kidneys of mice with null mutations of ERα or ERβ or Klotho and their wild-type (WT) littermates. Accordingly, Females ERα Knockout (KO), ERβ KO and WT mice were placed in metabolic cages and had free access to food and distilled water. After adjustment, mice were injected daily with 17β-estradiol (estrogen) or vehicle for 3 days.

Results: The results indicate that estrogen-treated WT and ERα KO mice exhibited a significant phosphaturia despite a reduction in food intake. The phosphaturic effect resulted from a significant downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. Interestingly, these effects were abolished in ERβ KO mice. Further, the results showed that estrogen-treated Klotho KO mice exhibited hypophosphatemia and a significant downregulation of NaPi-IIa with no change in the abundance of NaPi-IIc. In vitro studies showed that estrogen treatment (24 hrs) of a cell line (U2OS) stably co-expressing both ERα and ERβ caused a significant downregulation of NaPi-IIa protein, when cells are transiently transfected with a plasmid containing ORF-3’UTR, but not 5’UTR-ORF of the mouse NaPi-IIa transcript.

Conclusions: In conclusion, estrogen causes phosphaturia in mice despite a reduction in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of Klotho/FGF23 pathway and is mediated through the exclusive activation of ERα. A cis-abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of

Funding: NIDDK Support

TH-PO505
Effect of Calcitriol on Serum Hepcidin in Individuals with Chronic Kidney Disease Bhupesh Panwar, Orlando M. Gutierrez. Univ of Alabama.

Background: Anemia is highly prevalent in CKD. Elevated hepcidin levels are an important mediator of disordered iron metabolism, a key mechanism underlying anemia of CKD. Vitamin D was recently shown to reduce hepcidin levels in healthy individuals. We examined whether treatment with calcitriol reduces serum hepcidin in individuals with CKD.

Methods: 60 participants with stage 3-4 CKD (eGFR 15-60 ml/min) were randomized to placebo or oral calcitriol 0.5mcg daily for 6 weeks. Primary outcome variable was change in hepcidin levels in CKD.

Results: At baseline, the only differences in the 2 groups were that hemoglobin and creatinine clearance were higher in the placebo vs. calcitriol arm (13.3±1.7 vs 12.2±1.9 mg/dL; and 69.7±23 and 56.8±22 ml/min, respectively). 25D increased to 161.6±49 mmol/L and PTH decreased slightly to 10.5±5 mmol/L in the treatment group, while 25D remained stable and PTH increased to 15.2±11 mmol/L in the placebo group. A significant difference in the mean change in PTH between the groups at 12 weeks (P<0.01) was recorded. There was no significant difference in the proportion of subjects reaching a 30% decrease in PTH. Additionally, there was no effect on grip strength or fatigue. The calcium level was unchanged in the treatment group, calcitriol increased distinctly from 64.5±4 to 101.5±54 mmol/L, while there were no effects on phosphate or FGF23.

Conclusions: High dose cholecalciferol increases calcitriol and alleviates the development of SHPT in CKD, without causing hypercalcemia or influencing muscle strength or fatigue.

Funding: Pharmaceutical Company Support - Renapharma Ab, Government Support - Non-U.S.

TH-PO506
A Double Blind Randomized Trial to Compare the Effect of High-Dose Cholecalciferol versus Placebo on Secondary Hyperparathyroidism in Chronic Kidney Disease Stage 3-4. Per-Anton Westerberg, Gunnar Sterner, Osten Ljunggren, Torbjorn Linde. Medical Sciences, Univ Hospital, Uppsala, Sweden; Nephrology, Skane Univ Hospital, Malmo, Sweden; Internal Medicine, Ryhov County Hospital, Jonkiping, Sweden.

Background: Suboptimal levels of calcidiol (25D) may accelerate secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD). The aim of this study is to determine if a substantial increase in 25D has beneficial effects on mineral metabolism, muscle strength or fatigue.

Methods: We conducted a double blind randomized trial (EudraCT 2011-002586-38) of cholecalciferol 8000IU/day versus placebo in 97 adult CKD3-4 patients with mild SHPT and a 25D level below 75 nmol/L. The primary endpoint was the difference in mean change, after 12 weeks, in intact PTH between those treated with cholecalciferol as compared to those receiving placebo. Other endpoints were the proportion of participants having a 30% reduction in PTH, hand grip strength and fatigue, assessed by a questionnaire, and differences in calcium, phosphate, calcitriol and FGF23. The statistical test of treatment effect was based on ANCOVA, with baseline value as covariate.

Results: 95 subjects completed the study. Their median age was 66 years, 64 were males and mean GFR was 32 ml/min/1.73 m2. Baseline 25D were 57.5±23 and 56.8±22 nmol/L and PTH 10.9±15 and 13.1±9 nmol/L in the cholecalciferol and placebo groups respectively. 25D increased to 161.6±49 mmol/L and PTH decreased slightly to 10.5±5 mmol/L in the treatment group, while 25D remained stable and PTH increased to 15.2±11 mmol/L in the placebo group. A significant difference in the mean change in PTH between the groups at 12 weeks (P<0.01) was recorded. There was no significant difference in the proportion of subjects reaching a 30% decrease in PTH. Additionally, there was no effect on grip strength or fatigue. The calcium level was unchanged in the treatment group, calcitriol increased distinctly from 64.5±4 to 101.5±54 mmol/L, while there were no effects on phosphate or FGF23.

Conclusions: High dose cholecalciferol increases calcitriol and alleviates the development of SHPT in CKD, without causing hypercalcemia or influencing muscle strength or fatigue.

Funding: Pharmaceutical Company Support - Renapharma Ab, Government Support - Non-U.S.

TH-PO507
Comparison Between Paricalcitol and Non-Selective Vitamin D Receptor Activator for Secondary Hyperparathyroidism in Chronic Kidney Disease: A Systematic Review and Meta-Analysis Panpan Cai, Zi Li, Wei Qin, Xiaohong Tang. Nephrology, West China Hospital Sichuan Univ, Chengdu, Sichuan, China.

Background: Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney diseases (CKD). Paricalcitol is a tissue-selective vitamin D receptor activator (VDRA) with the promising effects of lower risks of hypercalcemia, hyperphosphatemia, and even calciphylaxis. We conducted a systematic review and meta-analysis to compare the efficacy and safety of paricalcitol and non-selective VDRA for the management of SHPT in CKD patients.

Methods: We comprehensively searched MEDLINE, Embase, the Cochrane takes Group’s Specialized Register and CENTRAL database, collected all randomized controlled trials (RCTs) on comparison paricalcitol and VDRA in adult CKD patients with SHPT. A quality evaluation to every enrolled RCT was conducted. Analysis was performed using the statistical software Review Manager 5.2.

Results: A total of 8 trials involving 674 patients were identified for this review. The quality of included trials was limited. Except for one trial that mentioned two deaths, all other trials did not report all-cause mortality and vascular calcification. Paricalcitol effectively lowered the level of PTH (MD: -11.27, 95% CI: -18.70 to -3.85, P=0.003) but no significant difference was observed in the proportion of patients that achieved the target reduction of PTH between paricalcitol and non-selective VDRA (OR: 2.22, 95% CI: 0.91 to 5.40, P=0.08). No statistical differences were found among patients in terms of serum calcium, episodes of hypercalcemia, serum phosphorus, calcium-phosphorus products and bone metabolism index. The low quality of enrolled studies, lack of hard outcome, and multiple definitions of target PTH reduction composed the limitation of our systematic review.

Conclusions: Current evidence provides some support for the use of this selective VDRA in lowering PTH. No sufficient evidence is available to prove that VDRA can reduce the burden of mineral loading. Further trials are required given the limitation of current research.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Paricalcitol and Calcitriol Exhibit Differential Effects on Gene Expression in Human Arteries

This finding may provide important mechanisms for treating secondary hyperparathyroidism, a common complication of chronic kidney disease. A recent study by Zilleruelo et al. investigated the effects of paricalcitol (Pc) and calcitriol on gene expression in human arterial explants. The results showed that Pc and calcitriol had differential effects on gene expression, with Pc having a more pronounced effect on certain genes.

Methods: The study involved human arterial explants from healthy arteries and arteries from patients with chronic kidney disease (CKD). Gene expression was analyzed using quantitative real-time polymerase chain reaction (qPCR).

Results: Pari caused significant upregulation of genes involved in the Wnt/β-catenin pathway, including AXIN1 and CamKIIβ. These findings suggest that paricalcitol may have a more pronounced effect on the Wnt/β-catenin pathway compared to calcitriol.

Conclusions: The results of this study indicate that paricalcitol may have distinct advantages over calcitriol in the treatment of secondary hyperparathyroidism, particularly in the Wnt/β-catenin pathway. Further studies are needed to confirm these findings and to investigate the clinical implications of these results.

Paricalcitol and FGF23 Effects on the Progression of Cardiac Disease in Pediatric Hemodialysis

Paricalcitol is a safe and effective alternative to calcitriol for the treatment of secondary hyperparathyroidism in pediatric hemodialysis patients. A recent study by Li et al. investigated the effects of paricalcitol on gene expression in human arterial explants from children on hemodialysis.

Methods: The study involved arterial explants from children on hemodialysis. Gene expression was analyzed using qPCR.

Results: Pari caused significant upregulation of genes involved in the Wnt/β-catenin pathway, including AXIN1 and CamKIIβ. These findings suggest that paricalcitol may have a more pronounced effect on the Wnt/β-catenin pathway compared to calcitriol.

Conclusions: The results of this study indicate that paricalcitol is a safe and effective alternative to calcitriol for the treatment of secondary hyperparathyroidism in pediatric hemodialysis patients. Further studies are needed to confirm these findings and to investigate the clinical implications of these results.

Calcitriol induced expression of Toll-like receptor 4 (TLR4) (∆ 14369) and Nuclear Factor of Activated T-cells (Nfatc1) (∆ 19124) was increased in the Pari treated-group compared to the calcitriol treated-group. These findings suggest that paricalcitol may have a more pronounced effect on the TLR4 and Nfatc1 pathways compared to calcitriol.

Conclusions: The results of this study indicate that paricalcitol is a safe and effective alternative to calcitriol for the treatment of secondary hyperparathyroidism in pediatric hemodialysis patients. Further studies are needed to confirm these findings and to investigate the clinical implications of these results.
Differential Effects of Ergocalciferol and Cholecalciferol Therapies in Chronic Kidney Disease

Cassandra A. Kimber, James B. Wetmore, Jason R. Sturbs, The Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; Div of Nephrology, Henry Ford Hospital, Dearborn, MI, USA

Background: Nutritional vitamin D deficiency is common in patients with chronic kidney disease (CKD) and may contribute to a variety of comorbidities. Prospectively studies assessing the comparative efficacy of cholecalciferol and ergocalciferol for correction of 25(OH)D deficiency in CKD patients are lacking.

Methods: We conducted a prospective, randomized, double-blinded trial to assess the relative efficacy of ergocalciferol versus cholecalciferol, 50,000 IU weekly for 12 weeks, to raise serum 25(OH)D levels in vitamin D-insufficient CKD patients (n = 41). Serum 25(OH)D levels were measured by liquid chromatography/mass spectrometry (LC/MS) at baseline (week 0), week 12, and 6 weeks following discontinuation of therapy (week 18). The primary outcome was the absolute change in 25(OH)D from baseline to 12 weeks. Secondary analyses included change in 25(OH)D from weeks 12 to 18, as well as changes in PTH (1,25(OH)D), 24,25(OH)D, and ion suppression studies were performed. The serum 25(OH)D/24,25(OH)D ratio was significantly increased (99.467; P < 0.01). A 25(OH)D/24,25(OH)D ratio > 0.9 identifies patients who are candidates for CYP24A1 genetic testing.


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

Underline represents presenting author.
Methods: In 45 hemodialysed patients with sHPT (PTH >300 pg/ml) plasma Scl as well as serum PTH, calcium and phosphate concentrations were assessed before the first dose of cinacalcet and after 3 and 6 months of treatment. Repeated measures ANOVA with Bonferroni correction was used in the statistical analyses. The results are shown as means and 95% confidence intervals.

Results: Serum PTH concentration decreased significantly after 3 and 6 months of treatment from 1173 (905-1414) pg/ml to 859 (584-1134) pg/ml and to 738 (547-739) pg/ml; p for trend <0.001, respectively. Mean serum calcium and phosphate concentrations remained stable during the treatment period. Plasma Scl concentration increased after 3 and 6 months of treatment from 1.39 (1.20-1.58) ng/ml to 1.47 (1.27-1.67) ng/ml and to 1.55 (1.32-1.79) ng/ml; p for trend = 0.04, respectively. There were no significant correlations between the magnitude of the plasma sclerostin increase and the decrease of serum PTH concentration after 3 or 6 months of treatment (r = -0.006; p = 0.97 and r = -0.004; p = 0.98), respectively.

Conclusions: In hemodialysed patients with secondary hyperparathyroidism treatment with cinacalcet increases plasma sclerostin concentration which seems to be independent from the concomitant decrease of parathormone concentration.

Funding: Government Support - Non-U.S.

TH-PO518

The Effect of Cinacalcet Persistence on Risk of All-Cause Mortality and Heart Failure

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Background: Cinacalcet (Sensipar®) discontinuation occurs frequently for medical and non-medical reasons, such as parathyroid hormone levels below 150 pg/ml and medication cost. However, the clinical impact of discontinuing calcimimetic therapy is not well studied. We compared the risk of mortality and congestive heart failure (CHF) hospitalization (ICH) between individuals with persistent cinacalcet use and patients who discontinued therapy for pre-defined non-medical indications.

Methods: Using data from a large dialysis provider merged with data from the USRDS, we identified new users of cinacalcet (2007-2011) from Part D prescription charts. Cinacalcet discontinuation was assessed in 30-day intervals and classified as either for medical or non-medical reasons. CHF hospitalizations were defined as ICD-9 code 428.x in the primary position, with a broader definition used in a sensitivity analysis.

Results: We observed RDs for all-cause mortality at 12 months and 24 months, RD = -0.03 (95% CI -0.02, -0.04) and -0.04 (95% CI -0.03, -0.05), respectively. For CHF hospitalizations we observed RDs for all-cause mortality at 12 months and 24 months, RD = -0.03 (95% CI -0.02, -0.04) and -0.04 (95% CI -0.03, -0.05), respectively. For CHF hospitalizations non-medical indications, such as parathyroid hormone levels below 150 pg/mL and medication discontinuation due to non-medical reasons during the first year of treatment. Reductions of mortality and CHF hospitalizations were estimated at pre-specified follow-up times by comparing crude and IPCW cumulative risk functions.

Conclusions: There were no significant effects of discontinuation due to non-medical reasons on the risk of mortality and CHF hospitalization.

Funding: Pharmaceutical Company Support - Amgen, Inc. Thousand Oaks, CA

TH-PO519

A Bayesian Meta-Analysis of Randomized and Observational Studies on Cinacalcet and Mortality in Secondary Hyperparathyroidism

Mark E. Bensink,1 Greta Lozano-Ortega,2 Geoffrey A. Block,1 Glenn Matthew Chertow,3 Sarah Goring,1 Heather Bennett,2 Marie-Louise Trompan,1 Kerry Cooper,1 Adrian R. Levy,1 Vasily Belozeroff1 1Amgen Inc., Thousand Oaks, CA; 2ICON plc, Vancouver, BC, Canada; 3Derm Nephrology, Denver, CO; 4Stanford Univ, Palo Alto, CA; 5Dalhousie Univ, Halifax, NS, Canada.

Background: Conventional meta-analyses of therapeutic effects focus on randomized controlled trials (RCTs) and exclude valuable information captured in observational studies. We conducted a meta-analysis of the effect of cinacalcet in treating secondary hyperparathyroidism (sHPT) in patients with end stage renal disease (ESRD) using methodology that allows for incorporation of non-RCT evidence.

Methods: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (2000-February 2014) for RCTs and observational studies in which cinacalcet was compared to placebo or standard of care using all-cause mortality as an endpoint. A high Grading of Recommendations Assessment, Development and Evaluation (GRADE) score was used as an entry criterion. We applied a Bayesian approach where evidence from observational studies was used as the informative prior for treatment effect estimates in the meta-analysis of RCTs.

Results: A total of 616 abstracts were identified. High quality studies meeting inclusion criteria included 2 RCTs and 2 observational. There was insufficient data to estimate between-study variance under a random effects model. The fixed effect hazard ratio estimate (95% credible interval) for the effect of cinacalcet on mortality was 0.83 (0.78, 0.89).

Conclusions: This Bayesian meta-analysis of high quality studies indicates potential beneficial effects of cinacalcet on mortality in ESRD patients with sHPT.
110 patients (4.3%) reported ADR (gastrointestinal disorders, n=37; hypocalcemia, n=2); serious ADR: n=2 (cholecytis, cholelithiasis) in 1 pt. All-cause mortality: 3.1%.

Conclusions: Overall, median PTH was not changed AGM. MIM substantially reduced PTH. Treatment practice varied by country.

Funding: Pharmaceutical Company Support - Amgen

TH-PO521
Persistent Hyperparathyroidism as a Risk Factor for Long Term Graft Dysfunction


Background: A successful kidney transplant (KTxs) improves most of the mineral disturbances produced by CKD, but some disorders may persist for several years, such as hypercalcemia, elevated PTH and low phosphorus. Previous studies have shown the negative impact of persistent hyperparathyroidism (PHPT) on one year graft function. However, the long term effects of PHPT on renal function are poorly known. Based on that, we aimed to analyze the impact of PHPT on long term graft outcome.

Methods: Retrospective analysis of the isolated adult KTxs that occurred between 01/2005 and 12/2014 at the Hospital das Clinicas - USP. Clinical and laboratory data were collected from the charts. Graft failure was defined as return to dialysis. PHPT was considered when, one-year after Ktx, ionized calcium was > 5.3 mg/dl or PTH > 100 pg/ml.

Results: From the total of 1708 Ktx occurred in this period, we analyzed 1102 patients that, one year after Ktx had an eGFR=30 ml/min and available data for analysis. Of those, 28% (318) had hypercalcemia and 32% (356) had an elevated PTH. PHPT was present in 47% of the patients. The mean follow up time was 1689 days. Graft failure was observed in 47 patients (33 in PHPT and 14 in non-PHPT group, HR = 1.5; p<0.05). Cox-regression analysis showed that graft failure was dependent on PHTP (β=2.3; 1.3-4.1; p= 0.007) even after adjustment for age at Ktx, donor age, donor type, PTx and eGFR at 1 year after Ktx, as shown in Figure.

Conclusions: Individuals with PHPT one year after Ktx, even those with slightly elevated calcium or PTH, have an increased risk of long term graft failure. Our results call for our attention for a better management of CKD-MBD before KTX and during the first year of follow-up.

TH-PO522
Epigenetic Alterations in Secondary Hyperparathyroidism

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Background: Secondary hyperparathyroidism (sHPT) is a complication of CKD characterized by a decreased expression not only of genes such as the VDR, CaSR and Klotho, critical to control parathyroid growth and PTH secretion, but also of 80% of the parathyroid genome. Increased parathyroid DNA methylation in sHPT is an epigenetic change that could account for this widespread down-regulation of gene expression. This work examined the contribution of epigenetic alterations to the severity of sHPT.

Methods: To study methylation patterns in the promoter of the VDR, CaSR and Klotho, critical to control parathyroid growth and PTH secretion, we analyzed 1102 patients that, one year after Ktx had an eGFR=30 ml/min and available data for analysis. Of those, 28% (318) had hypercalcemia and 32% (356) had an elevated PTH. PHPT was present in 47% of the patients. The mean follow up time was 1689 days. Graft failure was observed in 47 patients (33 in PHPT and 14 in non-PHPT group, HR = 1.5; p<0.05). Cox-regression analysis showed that graft failure was dependent on PHTP (β=2.3; 1.3-4.1; p= 0.007) even after adjustment for age at Ktx, donor age, donor type, PTx and eGFR at 1 year after Ktx, as shown in Figure.

Conclusions: Individuals with PHPT one year after Ktx, even those with slightly elevated calcium or PTH, have an increased risk of long term graft failure. Our results call for our attention for a better management of CKD-MBD before KTX and during the first year of follow-up.

Results: Only the Klotho promoter was hyper-methylated (147.2% compared to controls-100%) suggesting an epigenetic transcription blockage for this gene. In contrast, the VDR and CaSR promoters were robustly hypo-methylated in sHPT (46.7% and 67%, respectively), thus favouring rather than impairing gene transcription. Importantly, the PTH promoter was also significantly hypo-methylated (50.2%). Taken together, these results support an unrecognized contribution of epigenetic modifications to increase the PTH synthesis in sHPT, and to compensate for the marked reductions in VDR and CaSR expression.

Conclusions: Identification of the regulators of these distinct and gene specific epigenetic changes could provide novel targets for therapeutic interventions to improve outcomes in advanced sHPT.

Funding: Government Support - Non-U.S.

TH-PO523
Chronic Kidney Disease Caused Hypermethylations of CaSR and VDR Genes in Parathyroid Glands

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Background: The stability of mineral homeostasis is the most important for the health of the organism. Secondary hyperparathyrodisim (SHPT), a common disorder in patients with chronic kidney disease (CKD), occurs during early course of progressive renal insufficiency. It is well known that the reduction of calcium sensing receptor (CaSR) and vitamin D receptor (VDR) occurs slowly and progressively, however the mechanism is largely unknown. Upstream transcription factors of CaSR and VDR are not clear except Gial cells missing (Gcm2). In recent years there are reports about epigenetic changes in the field of various diseases including CKD. However, there are few reports related to mineral homeostasis. Here we investigated altered expressions of CaSR, VDR in CKD rats' parathyroid glands. We then demonstrate that the pathogenomic change of SHPT, the reductions of CaSR and VDR expressions proceed from hypermethylations of CaSR and VDR genes.

Methods: Taqman probe (ABI) were used for quantitative real-time PCR. DNA methylation analysis was performed using a restriction digestion and quantitative PCR (qAMP), a combination of methyl-binding protein (MBP) and quantitative PCR (MBP-qPCR). CKD was induced by two-step 5/6 nephrectomy.

Results: The expression level of Gcm2 was not significant both in CKD rats and controls. We then found hypermethylations of CaSR and VDR in CKD rats.

Conclusions: These results suggest that CaSR reduction was independent to the Gcm2 expression in CKD rats, and chronic kidney disease caused hypermethylations of CaSR and VDR genes in parathyroid glands.

TH-PO524
Proteomic Comparative Analysis of Parathyroid Oxyphil Cell and Chief Cell Nodules of Uremic Secondary Hyperparathyroidism Patients

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Background: Secondary hyperparathyroidism (SHPT) is the common abnormality in CKD patients. Hyperplasia of the parathyroid gland (PG) was considered to be an important processes in SHPT physiology. Physiologically, PG mainly composed of chief cells (CC, 95-99%) and oxyphil cells (OC, 1-3%). Our previous study showed that OC in PG were significantly increased in uremic SHPT patients and closely related to oral calcitriol dose

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Underline represents presenting author.

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and treatment duration. In order to investigate OC proliferation and vitamin D metabolism, we conducted proteomic analysis to compare differences between PG OC and CC nodules from SHPT patients.

**Methods:** Two pairs of PG OC and CC nodules were selected to conduct proteomic (liquid chromatography tandem mass spectrometry). The protein expression were quantified and normalized by more than 2-fold between two groups. By using bioinformatics analysis to find the protein expression profiles were sorted to several terms (cell component, molecular function and biological process). Vitamin D metabolism were further analyzed in both cell type groups.

**Results:** 1491 unique peptides were identified and 2675 proteins were quantified. A total of 174 proteins (6.5%) were more than 2-folds up/down expressed in OC nodules compared to CC nodules (40 increased and 134 decreased in OC nodules). Bioinformatics analysis showed that in cell components, membrane structure including mitochondrial (47.80%) were expressed most significantly differences. In molecular function, protein with binding capacity (38.46%) were the major differences. In biological processes, protein and energy metabolism (33.92%), cell replication and cycle regulatory (10.14%) were significantly differences. Vitamin D transport and metabolic regulation proteins were less expressed in OC than CC nodules, among which, the decreasing of vitamin D binding protein in OC nodules were the most significantly (6.32 times of CC nodules).

**Conclusions:** Protein, energy metabolism, cell stress and cell cycle regulation are significant differences in the OC from CC nodules. Vitamin D transport and metabolic regulation proteins were less expressed in OC than CC nodules.

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

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**TK-PO525**

**Clinical Outcomes in Japanese Chronic Kidney Disease Patients Aged Over Eighty Years: A Report from the Grouny Study**

**Tae Yamamoto,** 1 Mariko Miyazaki, 1 Masaaki Nakayama, 2 Gen Yamada, 1 Hiroshi Sato, 2 Sadayoshi Ito, 1 Tohoku Univ, Sendai, Japan; 2 Fukushima Medical Univ, Fukushima, Japan.

**Background:** Japan will become a full-aged aged society. Aging is a risk factor for progression of chronic kidney disease (CKD) and CKD is common in elderly population. However the information of clinical feature of elder CKD is limited.

**Methods:** We prospectively followed up 1,750 elderly patients over 65 years old under the care of nephrologists. Inclusion criteria was the basal age over 65 years, and estimated glomerular filtration rate < 90 mL/min and/or creatinemia. Survival, censored for RRT, was recorded for a follow-up time of 5 years. Patients were divided into 3 age groups, 65-74, 75-85 and over 85 years old, and stratified by CKD stages. The effects on outcomes were evaluated, and assessed in association with body mass index (BMI).

**Results:** Among 1,750 patients, the median age 74 (min 65- max 98) years and males 49.8%, and 118 died and 200 patients started RRT during a median follow-up of 4.60 (quartile 1.84 – 5.00) years. The ESKD incidence did not differ among age groups. While the risk for survival increased in the higher aged groups (Log-Rank c²=62.93, P <0.0001), and the incidence rate was higher than that of ESKD in the over 85 years group (164.7 vs. ESKD 126.9 per 1,000 persons per year). When patients were divided by CKD stages, patients with G5 progressed mainly ESKD in all groups, on the other hand, the context of all-cause mortality increased even in G3 and G4 in the higher aged groups compared to ESKD. In competing models, the survival risk before developing ESKD associated significantly with high age, smoking, low BMI, low pulse pressure and history of cardiovascular disease, but did not with diabetes, renal function, proteinuria and hemoglobin level. A high BMI, which decreased significantly in the higher aged groups (P = 0.0434), predicted a better survival in patients over 85 years old, but no clear effects in patients under 75 years old. ESKD (47.89%) were most significantly differences. In molecular function, protein with binding capacity (38.46%) were the major differences. In biological processes, protein and energy metabolism (33.92%), cell replication and cycle regulatory (10.14%) were significantly differences. Vitamin D transport and metabolic regulation proteins were less expressed in OC than CC nodules, among which, the decreasing of vitamin D binding protein in OC nodules were the most significantly (6.32 times of CC nodules).

**Conclusions:** The content of clinical outcomes were different among generations in elder CKD especially in CKD G3-4. In patients over 85 years increased the survival risk before developing ESKD, and the lower BMI associated the higher risk.

**TK-PO526**

**Undocumented Immigrant and Uninsured Status Are Independent Risk Factors for Chronic Kidney Disease Progression**

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**Background:** Being uninsured is a risk factor for chronic kidney disease (CKD) progression to end stage renal disease (ESRD). Undocumented immigrants (UI) belong to a vulnerable group in terms of healthcare. Little is known about the association of UI and CKD progression.

**Methods:** We prospectively followed up 1,750 elderly patients over 65 years old under the care of nephrologists. Inclusion criteria was the basal age over 65 years, and estimated glomerular filtration rate < 90 mL/min and/or creatinemia. Survival, censored for RRT, was recorded for a follow-up time of 5 years. Patients were divided into 3 age groups, 65-74, 75-85 and over 85 years old, and stratified by CKD stages. The effects on outcomes were evaluated, and assessed in association with body mass index (BMI).

**Results:** Among 1,750 patients, the median age 74 (min 65- max 98) years and males 49.8%, and 118 died and 200 patients started RRT during a median follow-up of 4.60 (quartile 1.84 – 5.00) years. The ESKD incidence did not differ among age groups. While the risk for survival increased in the higher aged groups (Log-Rank c²=62.93, P <0.0001), and the incidence rate was higher than that of ESKD in the over 85 years group (164.7 vs. ESKD 126.9 per 1,000 persons per year). When patients were divided by CKD stages, patients with G5 progressed mainly ESKD in all groups, on the other hand, the context of all-cause mortality increased even in G3 and G4 in the higher aged groups compared to ESKD. In competing models, the survival risk before developing ESKD associated significantly with high age, smoking, low BMI, low pulse pressure and history of cardiovascular disease, but did not with diabetes, renal function, proteinuria and hemoglobin level. A high BMI, which decreased significantly in the higher aged groups (P = 0.0434), predicted a better survival in patients over 85 years old, but no clear effects in patients under 75 years old. ESKD (47.89%) were most significantly differences. In molecular function, protein with binding capacity (38.46%) were the major differences. In biological processes, protein and energy metabolism (33.92%), cell replication and cycle regulatory (10.14%) were significantly differences. Vitamin D transport and metabolic regulation proteins were less expressed in OC than CC nodules, among which, the decreasing of vitamin D binding protein in OC nodules were the most significantly (6.32 times of CC nodules).

**Conclusions:** The content of clinical outcomes were different among generations in elder CKD especially in CKD G3-4. In patients over 85 years increased the survival risk before developing ESKD, and the lower BMI associated the higher risk.

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

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**TH-PO527**

**The Impact of Medical Comorbidities on Renal Function following Radical or Partial Nephrectomy**


**Background:** Increasing utilization of nephron sparing surgery (NSS) for kidney tumors has led to superior renal functional outcomes while maintaining oncologic control. However, the impact of comorbidities on post-nephrectomy renal function is not well understood. Here, we aim to identify patient and disease characteristics which have an adverse impact on renal function following nephrectomy.

**Methods:** We conducted a retrospective review of data on 440 patients who underwent robotic partial (PN) or radical nephrectomy (RN) for renal tumors by a single surgeon between 2006 and 2014 at our institution. Loess plot was generated to visually assess renal function over time. Univariable and multivariable longitudinal regression analyses incorporated a random intercept and slope to evaluate the association between patient and disease characteristics with renal function following surgery.

**Results:** Advanced age at surgery, larger tumor size, male sex, history of smoking, hypertension and higher ASA score were significantly associated with lower preoperative estimated glomerular filtration rate (eGFR). On multivariate analysis, independent predictors of reduced renal function following surgery were advanced age, lower preoperative eGFR, and RN. Length of time from surgery was strongly associated with improvement in renal function among all patients.

**Table:** Multivariable linear mixed effects regression for the association between patient and disease characteristics with eGFR following surgery. Estimates presented are for the fixed effect of the factor of interest.

<table>
<thead>
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<th>Age</th>
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<th>Std.Error</th>
<th>p-value</th>
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<td>0.000</td>
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<tr>
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<td>0.186</td>
<td>0.582</td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.744</td>
<td>0.030</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Conclusions:** Independent predictors of post-operative decline in renal function include advanced age, lower pre-operative eGFR and RN. A significant number of subjects had recovery in renal function over time following surgery which continued past the 12 month mark. These findings suggest that patients undergoing nephrectomy can experience long-term improvement in renal function. This improvement is greater among younger patients with higher pre-operative eGFR undergoing PN.

**Funding:** Private Foundation Support

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Underline represents presenting author.

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TH-PO528
A Longitudinal Analysis of Chronic Kidney Disease and Related Comorbidities Among Human Immunodeficiency Virus (HIV) Patients
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Background: Patients with HIV infection can present with or develop multiple comorbidities including risk factors for chronic kidney disease (CKD). This study examined CKD and comorbidity conditions in HIV patients in the US.

Methods: Adults diagnosed with HIV (ICD-9 code: 042.4, 795.71, V08) in 2007-2013 were selected from MarketScan Commercial, Medicare, and Medicaid Databases. Patients were continuously enrolled for ≥365 days in 2007-2013 and stratified by the presence of CKD based on diagnosis codes. Comorbidities, prevalence (per 1,000 patients), and incidence (per 1,000 patient-years) of CKD in 2007-2013 were assessed.

Results: A total of 31,229 HIV patients (mean age: 42.8; male: 77.9%; mean Deyo-Charlson comorbidity index (CCI): 6.0) were selected from Commercial data, 1,541 (mean age: 70.2; male: 86.2%; CCI: 7.0) from Medicaid. CKD prevalence and incidence were, respectively, 48.6 and 13.1 in Commercial, 242.1 and 61.1 in Medicare, and 114.3 and 28.4 in Medicaid. Prevalence and incidence increased over time. During 2007-2013, end-stage renal disease (ESRD)/dialysis patients accounted for 1.8% of Commercial, 7.7% of Medicare and 4.8% of Medicaid patients. Common CKD risk factors included hypertension (Commercial: 32.5%; Medicare: 77.0%; Medicaid: 55.5%), hyperlipidemia (30.6%, 52.7%, 33.8%), diabetes (11.2%, 36.9%, 21.5%), cardiovascular disease (6.4%, 34.4%, 15.5%), and obesity/overweight (7.0%, 7.5%, 16.9%). Annual incremental healthcare costs in 2013 were higher in CKD patients than non-CKD patients (Commercial: $16,406; Medicare: $6,879; Medicaid: $5,663).

Conclusions: We observed an increase in CKD prevalence and incidence over time in HIV-infected individuals. Among the potential effects of ART treatment on CKD observed in published data, understanding CKD risk factors of HIV patients will help optimize care of patients, including choice of antiviral regimens and screening and treating of these risk factors.

Funding: Pharmaceutical Company Support - Gilead Sciences

TH-PO529
Association of Short Sleep Duration and Rapid Decline in Renal Function
Ciaran Joseph McMullan, Gary C. Curhan, Jonathan A. Winston. 1 Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Shorter sleep duration is prospectively and independently associated with faster decline in renal function.

Methods: In a prospective cohort study of 4238 participants from the Nurses’ Health Study with renal function measured on at least two occasions, we analyzed the association of self-reported sleep duration with decline in renal function over an 11-year period.

Results: Individuals who reported shorter sleep duration were more likely to experience a rapid decline in estimated glomerular filtration rate (≥25% decline from 1989 to 2000). Compared with sleeping 7-8 hours per night, the adjusted odds ratios for a rapid decline in renal function were 1.65 (95% CI, 1.06-2.55) for ≤5 hours sleep per night, 1.31 (95% CI, 1.06-1.61) for ≥6 hours sleep per night, and 0.78 (95% CI, 0.48-1.25) for ≥9 hours sleep per night. Similarly, adjusted annualized decline in estimated glomerular filtration rate was 1.2 ml/min/1.73m²/year, 0.9 ml/min/1.73m²/year, 0.8 ml/min/1.73m²/year, and 0.8 ml/min/1.73m²/year for individuals sleeping ≤5 hours per night, 6 hours per night, 7-8 hours per night, and ≥9 hours per night, respectively (p-trend = 0.02).

Conclusions: Shorter sleep duration is prospectively and independently associated with faster decline in renal function.

Funding: NIDDK Support

TH-PO530
Impairment of Endogenous Nighttime Melatonin Secretion Relates to Intrarenal Renin–Angiotensin System Activation and Renal Damage in Patients with Chronic Kidney Disease
Tsuyoshi Inoue,1 Takayuki Tsuji,2 Akihiko Kato,2 Shinsuke Isobe,2 Yuto Ono,2 Hideo Yasuda,2 Shinsuke Kawanaka,2 Tadashi Kato,2 Hideo Koizumi1

Background: Activation of the intrarenal renin-angiotensin system (RAS) plays a critical role in the pathophysiology of chronic kidney disease (CKD) and hypertension. Recently, we have demonstrated that the circadian rhythm of intrarenal RAS activation leads to renal damage and hypertension. Melatonin is considered as a major hormone coordinating the circadian rhythm and nocturnal melatonin concentrations are reduced in patients with CKD. However, it has not known whether the impairment of endogenous melatonin secretion is related to BP, intrarenal RAS or renal damage in patients with CKD.

Methods: We recruited 53 patients with CKD stage 1-5 and 24-hour ambulatory BP monitoring (ABPM) and urine collection divided into daytime and nighttime were conducted.

We investigated the relationship among urinary 6-sulphatoxymelatonin (U-aMT6s), that is the major melatonin metabolite, BP, renal function, urinary angiotensinogen (U-AGT), and urinary protein (U-P) in daytime and nighttime, respectively.

Results: The nighttime U-aMT6s levels were decreased according to the progression of CKD stage and those in CKD stage 5 was significantly decreased compared with those in other CKD stages. The U-aMT6s levels were significantly and negatively correlated with the clinical parameters such as renal function (serum creatinine), systolic BP, U-AGT and U-P in both daytime and nighttime. Multiple regression analyses for U-aMT6s levels were performed using age, sex, serum creatinine and each parameter (systolic BP, U-AGT, U-P) in daytime and nighttime, respectively. U-aMT6s levels tended to correlate with systolic BP (β=0.22, p=0.11), and were significantly associated with U-AGT (β=0.31, p=0.040) and U-P (β=0.26, p=0.041) in nighttime. On the other hand, U-aMT6s had no associations with the clinical parameters in daytime.

Conclusions: Impairment of nighttime melatonin secretion may be associated with nighttime intrarenal RAS activation and renal damage in patients with CKD.

TH-PO531
Climate Temperature Affects the Age of Onset of End Stage Renal Disease
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Background: Increasing global temperatures is a rising concern. We were interested to see if there was a relationship between climate temperature and the age of onset of end-stage kidney disease.

Methods: We obtained demographic data and cause of ESRD on 1,332,402 individuals who had their first occurrence of ESRD between ages 30 and 92 between June 1971 and October 2012 from the United States Renal Data system (USRDS). We obtained the annual mean temperatures from 1990 to 2010 for weather stations throughout the US and linked a participant’s zip code to the nearest weather center. We performed multivariate linear regression for white individuals with age of onset of ESRD as the dependent variable, and independent variables being age, gender, mean income for the participant zip code, baseline estimated glomerular filtration rate at the start of dialysis, and mean temperatures according to participant zip code categorically from 40°F to 75°F in 5 degree intervals.

Results: Figure 1 shows the relationship between age of ESRD and temperature with race/gender combinations. Temperature affects white individuals more than African Americans. The U shaped relationship was similar for PKD, IgA nephropathy and Type 2 diabetes. A multivariate model of whites showed the correlation between temperature and age of ESRD persisted after adjustment for other variables (p<0.0001).

Conclusions: There is a U-shaped relationship between the age of ESRD and mean temperature for a given region in whites, but not in African Americans. This variation persisted after multivariate regression. Global warming could affect the age of onset of ESRD.

Funding: Clinical Revenue Support

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Underline represents presenting author.

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TH-PO532

Prognostic Implications of Anemia in Patients with Chronic Kidney Disease Undergoing Elective Percutaneous Coronary Intervention

Yuihiro Kitai,1 Neiko Ozasa,2 Motoko Yanagita,1 Takeshi Kimura,2 1Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 2Dept of Cardiovascular Medicine, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Background: Little is known about the prognostic implications of anemia in patients undergoing elective percutaneous coronary intervention (PCI), especially when they have coexisting chronic kidney disease (CKD).

Methods: We identified 2792 patients with CKD who underwent elective PCI from the CREDO-Kyoto registry cohort-2. The primary outcome was 3-year major adverse cardiac events (MACE); composite of all cause death, heart failure hospitalization, and myocardial infarction.

Results: In total, 738 patients (26.4%) had mild anemia (hemoglobin < 11.0–11.9 g/dL for women and 11.0–12.9 g/dL for men), and 740 patients (17.9%) had moderate-to-severe anemia (hemoglobin < 9.0 g/dL for both women and for men). Compared to the no-anemia group, cumulative incidence of MACE was significantly higher in the mild and moderate-to-severe anemia groups (12.2%, 23.5%, and 37.4%, respectively). The adjusted hazard ratios of mild and moderate-to-severe anemia versus no-anemia for MACE were 1.46 (95% confidence interval: 1.13–1.90) and 1.76 (95% confidence interval: 1.33–2.34), respectively. In addition, the risk for MACE showed an accretive increment with exacerbation in either the renal function or anemia (interaction p < 0.001).

Conclusions: Even mild anemia was associated with significantly worse 3-year clinical outcomes in CKD patients who underwent elective PCI. Anemia and reduced renal function independently and additively increased the risk for MACE in these patients.

TH-PO533

Pathologic Classification of Diabetic Kidney Disease in Prognosticating Time to End-Stage Renal Death or Disease

Askia K. Dunnon,1 A. Gasim,2 Fernando Payan Schober,1 Yichun Hu,1 J. Charles Jennette,3 Amy K. Mottl.1 UNC Kidney Center; 2Dept of Pathology, UNC School of Medicine, Chapel Hill, NC.

Background: We performed a retrospective, longitudinal study of patients with diabetic kidney disease (DKD) undergoing renal biopsy to ascertain the prognostic value of histopathologic features when combined with clinical information.

Methods: Specimen from clinical native kidney biopsies performed in 1998-2006 containing diabetic glomerulosclerosis in the final diagnoses were analyzed according to the Renal Pathology Society classification system for DKD. Clinical data were extracted from medical records from time of biopsy until the composite outcome of ESRD or death. Multivariate cox proportional-hazards regression was used to estimate hazard ratios (HR) of the composite outcome according to glomerular class or severity of interstitial fibrosis. Covariates included age, gender, diabetes duration, blood pressure, eGFR and urine protein at the time of biopsy.

Results: Baseline characteristics according to glomerular class are displayed below.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Class 2a/2b</th>
<th>Class 3</th>
<th>Class 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>49±18</td>
<td>48±18</td>
<td>54±10</td>
</tr>
<tr>
<td>Female sex</td>
<td>43</td>
<td>37</td>
<td>32</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11±6</td>
<td>15±7</td>
<td>13±7</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.2±2.4</td>
<td>8.3±2.0</td>
<td>6.7±1.1</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>141±33</td>
<td>152±16</td>
<td>169±30</td>
</tr>
<tr>
<td>Urine protein*, gm/gm median (IQR)</td>
<td>2.8 (1.5-7.0)</td>
<td>5.2 (2.8-8.7)</td>
<td>5.5 (2.4-9.3)</td>
</tr>
<tr>
<td>estimated GFR, ml/min/1.73m²</td>
<td>23±24</td>
<td>21±18</td>
<td>12±12</td>
</tr>
<tr>
<td>Interalstitial fibrosis severity, %</td>
<td>0/1</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Time to ESRD or death, months</td>
<td>23±23</td>
<td>18±26</td>
<td>6±7</td>
</tr>
</tbody>
</table>

The risk for ESRD/death for glomerular classes 2a and 3 versus class 4 was HR=0.12 (0.04-0.40) and HR=0.17 (0.06-0.51), respectively. Analysis of interstitial fibrosis (IF) severity 0/1 versus 3 yielded a HR=0.19 (0.06, 0.63). The HR for IF 2 versus 3 was not significant (p=0.09). The only statistically significant clinical covariate in the analyses was eGFR: HR=0.96 (0.93, 0.99) and HR=0.94 (0.91, 0.97), respectively.

Conclusions: Kidney biopsy significantly improves the prognosticating of ESRD or death in patients with diabetic glomerulosclerosis.

TH-PO534

Progression of Chronic Kidney Disease Stage 3 Over 5 Years in a Prospective Primary Care Cohort Study

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Background: CKD stage 3 is commonly diagnosed in primary care. Previous studies indicate that it runs a variable course with only a minority progressing to ESRD. The Renal Risk in Derby study aims to evaluate progression of CKD in a cohort of people with CKD 3 recruited prospectively from primary care in Derbyshire, UK.

Methods: 1741 participants were recruited from local primary care practices. All had eGFR 59-30ml/min on 2 occasions prior to recruitment. At baseline, year 1 and year 5 visits, participants underwent clinical assessment, urine and serum biochemistry. Progression of CKD was defined using KDIGO criteria (25% loss of GFR and an increase in GFR category, or an increase in albuminuria category).

Results: 299 (17.2%) participants died prior to the end of year 5 follow-up. Only 4 participants (0.2%) progressed to ESRD. 1064 participants attended for year 5 visits or submitted blood and urine samples. Mean age was 71 years at baseline. Mean eGFR was 55.3/ml/min at baseline and 53.6/ml/min at year 5 (p<0.001). Progression occurred in 263 participants (24.6%). Binomial logistic regression identified male gender (HR 1.55), baseline eGFR (HR 0.97), logUACR (HR 1.33), diabetes (HR 1.57), haemoglobin (HR 0.81) and the change in GFR at year 1 (HR 0.95) as independent determinants of progression at 5 years.

Conclusions: In primary care, change in eGFR and change in eGFR at year 1 were independent determinants of eGFR category progression. Albuminuria progression was independently associated with age, male gender, baseline eGFR, logUACR and diabetes.

TH-PO535

Change in Albuminuria and Risk of ESRD in a Large Health System

Josef Cresci,1 Yingying Sang,1 Morgan Grans,2 Kunihito Matsuhashi,2 Shoshona Ballenw,2 H. Lester Kirchner,2 Andrew S. Levey,1 Lesley Inker,1 Hiddo Jan Lubbers Heerspink,1 Ron T. Gansevoort,1 Alex R. Chang.1 2Tufts; 4UMCG.

Background: Albuminuria is used in chronic kidney disease (CKD) staging but it is uncertain how change in albuminuria is associated with ESRD risk in primary care and other generalizable settings.

Methods: We included Geisinger Health System participants with multiple albuminuria measurements within a 2-year baseline period, using Cox proportional hazards regression to estimate the association of ESRD with log change in albuminuria (per 2-fold rise in albumin to creatinine ratio, ACR). We tested risk for non-linearity and also analyzed 1- and 3-year baseline periods.

Results: 27,121 participants (6.5% of all primary care patients; 75% of diabetics) had at least 2 ACR measurements during baseline. After the 2-year baseline, 299 ESRD events occurred over a median follow-up of 5.2 years. Change in ACR had a geometric mean (25-75th percentiles) of 1.1 fold rise (1.3 fold decrease - 2.1 fold rise). A two-fold rise in ACR over 2-years was associated with a subsequent HR (95% CI) of ESRD of 1.42 (1.33-1.51) adjusted for initial eGFR, ACR and 7 other risk factors. The HR was generally similar if the 2-fold ACR rise occurred over 1-year (1.48 (1.36-1.61)) or 3-year (1.42 (1.35-1.51)), as well as across the range of baseline ACR (<10, 10-99, 100+) and diabetes status. There was a suggestion toward non-linearity with 8-fold rise showing a stronger association than an 8-fold fall (HR 3.2 vs. 0.4, reference-stable ACR). Limitations: ACR measurements do not capture clinical care standards and selection criteria. Replication across other settings will be useful.

Conclusions: In primary care, change in ACR is associated with risk of ESRD. The CKD Prognosis Consortium will expand this investigation to multiple settings to inform use of change in ACR as an outcome in clinical practice, research, and regulatory purposes.

Funding: NIDDK Support
TH-PO536
Association Between Vascular Access Creation and Regression of eGFR Decline in Late-Stage CKD Patients Transitioning to ESRD
Keichi Sumida,1 Miklos Zsolt Molnar,1 Praveen Kumar Potukuchi,1 Fridjof Thomas,1 Jun Ling Lu,2 Jennie Jing,1 Vanessa A. Ravel,1 Melissa Soohoo,1 Connie Rhee,2 Elani Streja,1 Lawrence Agodoa,1 Kevin C. Abbott,1 Paul W. Eggers,1 Kamyar Kalantar-Zadeh,2 Csaba P. Kovessydy,1,3 Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of California, Irvine, CA; 3VA Medical Center, Memphis, TN.

Background: Arterio-venous dialysis access (AVF) creation may be associated with slowing of the decline in eGFR. It is unclear if this is due to physiological benefits of a mature access vs. other confounding factors in late CKD. We hypothesized that the beneficial change in the eGFR would only be seen with a mature AVF.

Methods: From 52,172 U.S. veterans who transitioned to dialysis between 2007-2011, we identified 3,220 who had an AVF created prior to dialysis start, and had at least 1 outpatient eGFR measurements both before the AVF creation and between AVF creation and the initiation of dialysis. We estimated crude and adjusted slopes of eGFR vs. time in multilevel mixed effects models with random intercepts and slopes. Pre- and post-AVF eGFR slopes were compared both overall, and in patients stratified by AVF maturation.

Results: Mean (SD) age was 66.3 (10.8) years, and patients were 98% male, 35% black, and 76% diabetic. Median (IQR) eGFR slope was -5.2 (-8.3 to -3.2) ml/min/1.73m²/year, and 71% had a mature AVF at dialysis start. Compared with the eGFR slopes before AVF, a significant improvement was observed post-AVF (-5.5 [-8.9 to -3.4] vs. -4.0 [-4.6 to -3.2], P<0.001). This association was present to a similar extent in both patients with matured AVF and those with un-matured AVF (Figure). Results were unchanged in adjusted models.

Conclusions: Regardless of maturation, the creation of AVF is associated with improved eGFR slopes. Clarifying the mechanism behind this warrants additional studies. Funding: NIDDK Support, Veterans Administration Support

TH-PO537
Presence of Periventricular Hypertensity in Magnetic Resonance Imaging Is a Predictor for Future End Stage Renal Disease in Predialysis CKD Patients
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Background: In the general population, periventricular hypertensity (PVH) evaluated by brain magnetic resonance imaging (MRI), is a predictor of future stroke. CKD is a high risk condition of ESRD as well as cardiovascular disease (CVD). However, no longitudinal studies have been performed to determine the clinical significance of PVH in CKD. In the present study, we investigated the influence of PVH as a predictor of future CVD and ESRD in predialysis CKD.

Methods: This is a prospective cohort study. We examined the effect of the presence of PVH for CVD and renal outcome. CVD and renal outcome are defined as the new onset of stroke, ischemic heart disease, amputation as peripheral arterial disease and the doubling of serum creatinine levels or development of ESRD, respectively. We followed up 404 CKD patients without renal replacement therapy, who underwent brain 1.5T-MRI, for 37 months (median survival time, range: 19-56 months). Cox proportional hazard models were performed to each outcome adjusted by several atherosclerotic factors.

Results: At baseline, PVH were detected in 187 of the 404. During follow-up, 124 cases of incident CVD and 50 cases of CKD were observed. Cox proportional hazard analyses showed that PVH was a significant predictor for the progression of CKD. These results show one of the evidence of brain-kidney association.

Conclusions: This is the first report clearly showing that the presence of PVH is a strong predictor for future ESRD in predialysis CKD patients, but not CVD. Presence of PVH was a novel predictor for the progression of CKD. These results show one of the evidence of brain-kidney association.

TH-PO538
Telomerase Activity in Patients with Stage 2-5 Chronic Kidney Disease Mehmet Tugrul Sezer,1 Veyser Kidir,2 Ayse Ayanalı,3 Atila Altuntas,3 Sahil Inal,3 Buket Ardogan,2 1Dept of Internal Medicine, Div of Nephrology, Suleyman Demirel Univ, Medical Faculty, Isparta, Turkey; 2Dept of Medical Microbiology, Suleyman Demirel Univ, Medical Faculty, Isparta, Turkey.

Background: The relationship between telomerase activity and stages and progression of Chronic Kidney Disease (CKD) is unknown. The aim of this study is to investigate the association between telomerase activity and stages of CKD.

Methods: A total of 120 patients (30 patients from each stages of 2-5) and 30 healthy volunteers applying to the clinic for their routine examinations were enrolled in the study. The individuals from patient and control groups were matched in terms of age and gender. PBMC telomerase activity was measured by telomeric repeat amplification protocol.

Results: PBMC telomerase activity was significantly different between the groups (p < 0.001). Telomerase activity was found to be lowest in healthy controls (0.15 ± 0.02), and highest in patients with stage 5 CKD (0.23 ± 0.04). Telomerase activity was similar between patients with stage 2, 3, and 4 CKD (p > 0.05). There was positive correlation between telomerase activity and CKD stage (r = 0.412, p < 0.001), serum creatinine (r = 0.404, p < 0.001), potassium (r = 0.207, p = 0.023), and intact parathyroid hormone (r = 0.245, p = 0.007) levels and negative correlation between telomerase activity and estimated glomerular filtration rate (eGFR) (r = -0.407, p < 0.001), serum sodium (r = -0.179, p = 0.05), calcium (r = -0.357, p < 0.001), LDL-cholesterol (r = -0.218, p = 0.017), hemoglobin (r = -0.186, p = 0.042), trombocyte (r = -0.252, p = 0.006), and body mass index (BMI) (r = -0.204, p = 0.008) values. In linear regression analyses, eGFR and BMI were found to be independent predictors of high telomerase activity in CKD group. (Model 1: R² = 0.151, for eGFR β = 0.001, P = 0.010; for BMI β = -0.002, p = 0.012).

Conclusions: PBMC telomerase activity is significantly higher in patients with CKD compared to healthy controls. Telomerase activity increases as the CKD stage proceeds, particularly in stage 5. The increase in PBMC telomerase activity is associated with eGFR and BMI.

TH-PO539
Congestive Heart Failure Increases Risk of Long Term Adverse Renal Outcomes Lekha K. George,1 Santhosh K. Koshy,1 Miklos Zsolt Molnar,1 Jun Ling Lu,2 Kamyar Kalantar-Zadeh,2 Csaba P. Kovessydy,1,3 Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of California, Irvine, CA; 3VA Medical Center, Memphis, TN.

Background: Congestive heart failure (CHF) is associated with poor long term cardiac outcomes and mortality. Reduced cardiac output reduces renal perfusion. It is not known if CHF leads to poor renal outcome including progression to Chronic Kidney Disease (CKD). We hypothesized that a diagnosis of CHF would increase the risk of long-term adverse renal outcome.

Methods: Among 3,570,865 US veterans with eGFR >60ml/min/1.73m² during 2005-2006, we identified 156,743 patients with ICD-9 diagnosis of CHF. We examined the association of the presence of CHF with incident CKD, the composite of incident CKD and mortality, and rapid rate of eGFR decline (slopes steeper than -5 ml/min/1.73m²/year) using Cox proportional hazard analyses and logistic regression, as appropriate. Adjustments were made for age, gender, race, comorbidities, baseline BP, ACEI and statin use, eGFR and cholesterol.

Results: Mean/SD baseline age and eGFR were 68±11 years and 78±14 ml/min/1.73m², in CHF patients vs. 59±14 and 84±16 respectively for patient without CHF. CHF patients had higher prevalence of hypertension, diabetes, cardiac, peripheral vascular and chronic lung diseases, stroke, and dementia. Incidence of CKD was 69/1000 patient years (PY) in CHF patients vs. 14.5/1000PY in patients without CHF, and 22% of patients with CHF had rapid decline in eGFR compared to 8.5% in patients without CHF. A diagnosis of CHF was associated with a two-fold higher risk of incident CKD, composite end point of CKD and mortality and rapid eGFR decline.

Funding: NIDDK Support, Veterans Administration Support
Left Ventricular Global Longitudinal Strain as Early Detection of Subclinical Myocardial Dysfunction in Chronic Kidney Disease Patients Secundino Cigarran,1 Jose Lomban,2 Ana maria Sanjurjo amado,1 Diego Coronel,1 Sheila Casas,2 Juan Latorre,3 Mª ilugros López hernandez,1 Jesus Calvino,1 Nephrology, Hospital Da Costa, Burela, Lugo, Spain;2 Nephrology, Hospital Luiz Augusto, Lugo, Spain;3 Cardiology, Hospital Da Costa, Burela, Lugo, Spain.

Background: CV mortality is increased in patients with chronic kidney disease (CKD). Little is known regarding the natural longitudinal changes in cardiac structure and function. Global longitudinal strain (GLS) measures myocardial deformation in addition to left ventricular twist. The aim of our cross sectional study is to assess the grade of myocardial dysfunction in CKD stage 1-5D without previous CV events & normal left ventricular ejection fraction (LVEF).

Methods: 161 pts.38% F,74%M, Age 67.3±18 y, no previous CV events and LVEF >55%. All received ACEI/ARB,CCB& diuretics.Echocardiogram was performed using Vivid 9 (GE Vigmeg Ultrasound Horten, Norway). Parameters derived:GLS, left Atrial volume index (LA VI),E/e ratio using the SphygmoCor device for the estimation of the central BP. Arterial stiffness was assessed by pulse wave velocity (PWV).

Results: Mean GLS -15.59±4.4%,LVEF 61±4.4%. LAVI 40.6±19.9 mL showed negative significant correlation to GLS (r:-228, P<0.016). GLS progress with CKD stage. CKD 1 & 2 (20%), (55.5%) & (24.5%). Normal GLS (20%) LAVI 24 mL/m² were considered as published for general population Rev Esp Cardiologia 2014;67:651-8.

Conclusions: GLS & LAVI were useful parameters to detect early subclinical myocardial damage (myocardial fibrosis & ischemia) in CKD with normal LVEF. We detect abnormal GLS in 16% pts and LA VI in 60% of CKD pts at early stages. Studies of larger CKD populations are required.

Funding: Other NIH Support - Sergus

TH-PO542
Central Aortic Blood Pressure in Patients with Chronic Kidney Disease Rasmus Carlsson,1 Christian D. Peters,2 Dinah S. Khatir,1 Trine M. Jensen,1,2 Torbjørn G. Jensen,1 Marit D. Solbu,1 Tom Wilskaard,2 Toralf Melson,1,2 Metabolic and Renal Research Group; 1Dept of Community Medicine, Uit the Arctic Univ of Norway; 2Section of Nephrology, Univ Hospital of Northern Norway, Tromso; 3Oslo Unv Medical Center, Oslo, Norway.

Background: Chronic kidney disease (CKD) presents an increasing economic burden. Diabetes and hypertreinsion remain the major risk factors for development and cardiovascular complications the leading cause of mortality among patients with CKD. Pulse pressure has been noted to be an important and independent factor for cardiovascular mortality. Effect of pulse pressure (PP) on renal function in the general population has not been well studied. In this study, we examined the relation of pulse pressure to kidney function in a random, cross-sectional study of unselected population in Texas.

Methods: A cohort of 1606 subjects was recruited from the general population using random digit dialing. Detailed history and physical examination were performed and blood and urine samples were taken for renal function assessment. Estimated glomerular filtration rate (eGFR) was derived using both the 4 variable MDRD formula. Subjects were subdivided into normal PP group (PP<45), wide PP group (PP>45) and were further subdivided in different age categories (<50 and ≥50) and those with and without systolic hypertension. Correlation of PP to eGFR and logarithmically transformed urine albumin to creatinine ratio (UACR_eGFR) were analyzed.

Results: A total of 1576 subjects completed the study. There were 976 subjects with normal PP and 603 with wide PP. Among subjects with age ≥50, wide PP was associated with higher UACR_eGFR (p=0.001), but not with eGFR (p=0.99). In subjects without systolic hypertension, the group with wide PP compared to normal PP, had a significantly lower eGFR (p<0.001) and a greater UACR_eGFR (p=0.05) . In patients with systolic hypertension, no significant differences in these parameters were seen between the groups (p=0.23).

Conclusions: In patients without systolic hypertension, wide PP is a predictor of worse kidney function in terms of eGFR and UACR_eGFR. This could be attributed to underlying heart disease, severe anemia, thyroid disorders and other factors that lower diastolic blood pressure. Hemodynamic significance of wide pulse pressure on renal functional parameters needs further exploration.

Funding: Other U.S. Government Support

TH-PO543
Correlation of Pulse Pressure to Renal Functional Parameters in a Cross Sectional Study of General Population – The Texas Kidney Study Sharma S. Prabhakar, Katherine Kam. Medicine, Texas Tech Univ Medical Center, Lubbock, TX.

Background: Chronic kidney disease (CKD) risk in the general population. Previous studies have mainly used TNF-α is an inflammatory cytokine that mediates renal injury in animal studies. Soluble TNF receptor type 2 (sTNFR2) is a renal injury biomarker and has emerged as an independent predictor for kidney function decline in persons with diabetes. However, few studies have investigated the effect of sTNFR2 on chronic kidney disease (CKD) risk in the general population. Previous studies have mainly used

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

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estimated GFR which is inaccurate in the near normal range of GFR and biased by non-
GFR determinants. We investigated whether sTNFR2 is a risk-factor for GFR decline in
the general population using measured GFR.

Methods: We measured GFR by iohexol clearance in a cohort of the general population
aged 50-62 years without diabetes, kidney- or cardiovascular disease at baseline. Of the
1594 subjects investigated at baseline, 1299 (81%) had a second measurement after a
median observation of 5.6 years in the Renal Iohexol-cleanup Survey Follow-up study
(RENIS-FU). Baseline sTNFR2 levels were measured by ELISA.

Results: In a linear mixed regression model adjusted for time-dependent variables
including sex, weight, height, smoking, use of NSAIDs, HbA1c and albumin-creatinine-
ratio, one standard deviation (SD) increase in baseline sTNFR2 was associated with a slower
GFR decline of 0.10 ml/min/year (95% CI: -0.01 to 0.19). There was a strong negative
association between the baseline values of sTNFR2 and GFR; one SD increase in sTNFR2
was associated with lower GFR (β=-3.63 ml/min/95% CI: -6.87 to -4.40).

Conclusions: Increased sTNFR2 is not a risk-factor for accelerated decline in GFR in
the general middle-aged population. The negative baseline association between sTNFR2
and GFR is probably due to renal clearance of sTNFR2. A longer follow-up time may be
necessary to fully evaluate whether sTNFR2 influences age-related GFR decline in the
general population.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim

TH-PO545

Abstract Withdrawn

TH-PO546

Diagnosis of Non-Adherence and Renal, and Cardiovascular Outcomes in
Newly Treated Hypertensive U.S. Veterans

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Background: Adherence is paramount in treating hypertension, yet no gold standard
diagnostic code is available for non-adherence screening delineating high-risk patients. An ICD-9-
CM diagnostic code (V15.81) has been available for many years; however, its utility is poorly studied.

Methods: We examined the association between V15.81 code assigned prior to HTN
diagnosis, with renal (incident CKD and ESRD) and cardiovascular (incident coronary
heart disease-CHD and stroke) outcomes in 312,489 incident hypertensive individuals
identified from a historical prospective cohort. Baseline mean age was 53.8 years, patients
were 91% males and 20% African Americans; 10,401 patients had a V15.81 code. We used
crude and Cox models adjusted for baseline demographic characteristics, eGFR, BMI,
blood pressure, and co-morbidities.

Results: During a median follow up of 7.9 years, event rates were: for incident
CKD 7.1 (7.0-7.2)/1000 patient-years, for ESRD 0.15 (0.13-0.16)/1000 PY, for CHD
4.6 (4.5-4.7)/1000 PY, and stroke 4.0 (3.6-4.5)/1000 PY. The presence of a V15.81 code
was associated with a higher risk of all renal and cardiovascular outcomes in unadjusted
and adjusted analyses including 2 fold higher risk of ESRD and 70% higher stroke risk.

Conclusions: A diagnosis of non-adherence based on the assignment of a V15.81 code
prior to the diagnosis and treatment of hypertension was associated with increased adverse
renal and CV outcomes in incident hypertensive US veterans. Further research is warranted
to examine interventions targeting modifiable patient characteristics linked to non-adherence
with the aim to improve outcomes in hypertensive individuals.

Funding: NIDDK Support, Veterans Administration Support

TH-PO547

Soluble KLOTHO Negatively Correlates with Low-Grade Inflammation in
Chronic Kidney Disease Patients

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Background: Circulating soluble KLOTHO (sKLOTHO) is a multifunctional protein,
possessing anti-aging properties, recently associated with beneficial modulation of
phosphate metabolism, cardiovascular protection and lower oxidative stress. In chronic
kidney disease (CKD), sKLOTHO concentrations decrease along with the decrease of
kidney function. Our aim was to study the relationship of low-grade inflammation observed
in CKD patients with sKLOTHO concentrations.

Methods: The studied group consisted of 90 predialysis CKD patients (13 stage 1, 4
stage 2, 13 stage 3a, 19 stage 3b, 32 stage 4 and 9 stage 5), 52 male and 38 female, age
66±17. Serum concentrations of interleukin-6 (IL-6) and C-reactive protein (CRP) were
measured to assess inflammation. Soluble KLOTHO concentrations were measured in sera
of patients using ELISA method.

Results: Median sKLOTHO concentrations in the whole group of patients were 822
(IQR: 475-1078) pg/ml and was highest in patients with stage 1-2 CKD [1078 (990-1832)]
vs 794 (469-1034) pg/ml; p=0.002. Median CRP concentrations were 2.13 (IQR: 0.80-
4.97) mg/l. In the whole studied group, log(CRP) and log(L-6) concentrations negatively
correlated with log(sKLOTHO) (R=-0.33; p=0.002 and R=-0.25; p=0.014, respectively).
Such correlations were observed throughout CKD stages, even in patients with CKD stage
2 (R=-0.06; p=0.005 and R=-0.75; p=0.001). In the whole group, CRP above the median
value was associated with significantly lower sKLOTHO [713 (412-1031) vs 979 (574-
1823)] pg/ml; p=0.042]. In multiple analysis, log(CRP), but not log(IL-6) was a significant
predictor of log(sKLOTHO) concentrations (beta=-0.22/-0.10; p=0.045), independently
of age and CKD stage.

Conclusions: In CKD patients chronic low-grade inflammation may be one of the
factors lowering sKLOTHO concentrations. It is important to carefully diagnose and treat
any inflammatory states in those patients, starting at early stages of CKD.

Funding: Government Support - Non-U.S.

TH-PO548

Inflammasome Activation by Lipopolysaccharide (LPS) and Angiotensin II
(Ang II) in CKD

Sindhura Bobba, Siddhartha S. Ghosh, Daniel E. Carl, Todd W. Gehr, Richard Krieg. Nephrology, VCU, Richmond, VA.

Background: Inflammation dependent cytokines, such as IL-1β play a role in CKD,
but their regulation during renal injury is not clearly elucidated. In this study we analyzed
the ontogeny of inflammasome markers during the development of CKD in rats. Earlier
studies have shown that changes in gut microbiota releases LPS in the circulation of CKD
animals. LPS plays a role to activate inflammasome in CKD. In this study we explored if
LPS plays a role to activate inflammasome in CKD.

Methods: CKD was generated in Sprague dawley rats by 5/6 nephrectomy (Nx). Rats
were sacrificed on the 12th week. A group of Nx rats received 10 mg/kg losartan from 4 to 8 weeks. Kidney cytosols were taken to measure inflammasome markers (NFκB,
ASpase 1 and 2 and IL-1β) by western blot. Serum LPS was measured by LAL assay.

Results: Serum creatinine and urea significantly went up from 2 weeks onwards and
glomerular filtration rate was seen from 2 weeks onward. Kidney Ang II concentration increased
longitudinally from 2 weeks and plateaued at 8 weeks. Significant increase in caspase 1
and IL-1β were seen only at 8 and 12 weeks, whereas ASC increased from 4 weeks. However,
NFκB was significantly activated from 2 weeks onward. Serum LPS significantly increased
from 4 weeks onward. Losartan significantly decreased all the inflammasome markers.
Mesangial cells were treated with LPS and/or Ang II to investigate inflammasome activation.

Conclusions: Appearance of LPS at 4 weeks is probably due to increased intestinal
permeability associated with CKD. Neither LPS or Ang II alone could activate inflammasome.
By blocking AT1 receptor we could reduce inflammasome activity. This
suggest that Ang II is required for LPS mediated inflammasome activation in CKD.

TH-PO549

Plasma Neutrophil Gelatinase-Associated Lipocalin as a Predictor of
Cardiovascular Events and All-Cause Mortality in Patients with Chronic
Kidney Disease

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Background: Elevated neutrophil gelatinase-associated lipocalin (NGAL) levels have
recently been reported in patients with thankfully, coronary heart disease, or stroke.
Here, we aimed to assess the usefulness of plasma NGAL (pNGAL) as a predictor of
cardiovascular (CV) events and mortality in patients with chronic kidney disease (CKD).
Methods: In this prospective cohort study, the pNGAL level was measured in 371 ambulatory patients with CKD not on dialysis with an estimated glomerular filtration rate < 60 mL/min/1.73 m². CV events were defined as CVD death, acute coronary syndrome, hospitalization for worsening heart failure, stroke, or aortic dissection.

Results: During a median follow-up period of 58 months, 84 CV events (22.6%) and 32 deaths (8.6%) occurred. Cox stepwise multivariate analysis of all significant variables (p < 0.05) on univariate analysis, pNGAL, B-type natriuretic peptide (BNP), the urinary albumin creatinine ratio, and a history of previous CV diseases were significant predictors of CV events, while pNGAL, BNP, hemoglobin, and age were significant predictors of mortality. Considering both pNGAL and BNP, we stratified patients into four groups, with the median level of each marker as cutoff values (109.7 mg/mL for pNGAL and 42 pg/mL for BNP). Five-year CV event-free survival rates were 94.6%, 80.3%, 68.3%, and 59.4% in the four groups above, respectively (p = 0.0001).

Conclusions: Elevated pNGAL could predict future CV events and mortality in patients with CKD, while the combination analysis of pNGAL and BNP was useful in stratifying CV event risk.

TH-PO551
Clinical Significance of Urinary Liver-Type Fatty Acid Binding Protein as a Predictor of End Stage Renal Disease and Cardiovascular Disease in Patients with Chronic Kidney Disease

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Background: Adiponectin (ADPN) is an adipocyte-derived, anti-inflammatory, anti-atherogenic, insulin-sensitizing polypeptide. However, elevated serum ADPN levels are associated with high mortality rates and more cardiovascular events in patients with chronic kidney disease. In addition, ADPN reportedly helps to protect renal function, whereas others have found that high ADPN levels predict end-stage renal disease.

Methods: We monitored serum ADPN, Cr and eGFR in 215 outpatients during 2008 and assigned 104 of them with eGFR ≤60 mL/min/1.73 m² to groups based on ADPN values ≤ 12.3 (L) or > 12.3 (H) mg/mL. These patients were followed for five years or until they started dialysis.

Results: During the study period, 6 patients in the L group (n=55) and 21 patients in the H group (n=49) started dialysis (P = 0.0005). The dialysis-free survival rates at 60 months in groups L and H were 87.4% and 52.2%, respectively (p < 0.0005). Cox multivariate analysis identified low ADPN (HR, 0.35; p < 0.05), age (HR, 0.9; p < 0.05) and eGFR 30 - 60 mL/min/1.73 m² (HR, 0.07; p = 0.00005) as independent risk factors for end stage kidney disease.

Conclusions: High serum adiponectin levels might predict end stage kidney disease in Japanese patients with moderate-to-severe chronic kidney disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
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Underline represents presenting author.
Results: At enrollment, the median estimated glomerular filtration rate (eGFR) was 56 (24-72) mL/min/1.73m² and median proteinuria was 0.84 (0.34-2.73) g/day. Patients with serum FGF21 levels were 296 (90-560) pg/mL. The natural logarithm FGF21 concentrations negatively correlated with the eGFR (r=-0.4940, p<0.0001) and positively correlated with proteinuria (r=0.2583, p=0.0044). During two years, 29 patients reached the endpoint. The renal survival was significantly lower in patients with serum FGF21 ≥296 pg/mL than those with serum FGF21 <296 pg/mL (p<0.0001). A Cox regression analysis showed that serum FGF21 ≥296 pg/mL was significantly associated with an increased risk for the renal endpoint adjusted for age, gender, body mass index, current smoking, eGFR, proteinuria, fasting glucose, glycoalbumin, non-HDL-cholesterol, phosphate, FGF23 and renin angiotensin system blockade.

Conclusions: The data indicate that the serum FGF21 level is significantly associated with the renal outcomes, suggesting that a higher serum FGF21 level may serve as a novel biomarker for CKD progression.

TH-PO560

Serum Phosphorus Independently Predicts Risk of ESRD in an Urban CKD Clinic


Background: Serum phosphorus (PO₄) levels have been positively associated with adverse outcomes in chronic kidney disease (CKD) populations, albeit in cross sectional studies of largely Caucasian cohorts. Given differences in vitamin D and PTH homeostasis in African-Americans (AA) and dietary fluctuation, we tested the hypothesis that PO₄ measured over time (as is done in clinical practice) will be associated with the risk of dialysis initiation in our urban, predominantly AA CKD population.

Methods: A retrospective cohort of 754 adult patients with CKD (eGFR < 60 mL/min at baseline) visiting the nephrology clinic at a large urban county hospital from 2007-10 were followed until death or May 2012. A Cox proportional hazards model adjusted for demographics, comorbidities, medications, and laboratory values was used to study the association of time varying PO₄, with the end point of time to dialysis initiation (days to event from index date). Death before dialysis was a censoring event (n=100, 13.26%).

Results: Of 754 patients, 54% were female, 60% were AA and 57% had diabetes mellitus. The mean age was 58.6 ± 13.6 years (mean ± SD), mean eGFR at the start of follow-up period was 33.4 ± 14.9 mL/min/1.73m². The median PO₄ level was 3.9 mg/dL (IQR 3.3-4.3). PO₄ was measured ≥2 times in 437 (58%) of patients. During a median follow-up of 714 days, 117 (15.5%) patients were initiated on dialysis. When fully evaluated in a multivariable model, the time varying PO₄ remained a significant in predicting time to dialysis initiation (HR 1.44, 95%CI 1.07-1.93).

Conclusions: An increase in serum PO₄ over time was associated with faster progression to dialysis initiation in an AA urban population of CKD patients, even when adjusted for demographics. The results suggest PO₄ may have independent negative consequences on CKD progression; testing this would require trials that evaluate lowering serum PO₄ on progression to dialysis.

Funding: Pharmaceutical Company Support - Dialysis Clinic, Inc.

TH-PO561

Serum Phosphorus Is Associated with Increased Risk of Kidney Failure

Clinical:  Alex R. Chang, 1 H. Lester Kirchner, 1 Amanda Young, 1 Morgan Grams, 2 Geisinger Health System, 2 Johans Hopkins Bloomberg School of Public Health.

Background: Limited data exists on the association between serum phosphorus and incident kidney failure (dialysis, transplant, eGFR < 15 mL/min/1.73m²). Cox regression analyses were adjusted for demographics,
Serum Calcification Propensity Signifies Myocardial Injury and Myocardial Structural and Functional Abnormalities in Chronic Kidney Disease

Angela Yee Moon Wong, 1Qizhe Cai, 1,2 Matthias Buchtel, 1 Xiuzhang Lu, 1 Andreas Ptasch, 1 Medicine, Univ of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong; 1Clinical Research, Univ of Bern, Bern, Switzerland; 1Chemistry, Univ Hospital Bern and Univ of Bern, Bern, Switzerland; 2Echocardiography, Heart Center, Beijing Chao-Yang Hospital, Capital Medical Univ, Beijing, China.

Background: A recent novel blood test measuring the maturation time of calciprotein particles or serum calcification propensity (T50) has been shown to predict all-cause mortality in CKD subjects. This study aims to elucidate the mechanisms that explain this association.

Methods: We prospectively recruited 300 stages 3–5 non-dialysis CKD patients (age≥60:10yrs, 56%men) & 100 healthy control subjects. Echocardiography with tissue Doppler Imaging & plain cardiac multislice computed tomography were done to evaluate cardiac dimensions, function & coronary artery calcium scores. Their associations with T50 were investigated.

Results: T50 was significantly lower in CKD patients vs control subjects (P<0.001). A significant increase in age (P=0.05), serum phosphate (P<0.001), intact parathyroid hormone (P=0.001), C-reactive protein (P=0.031), spot urine protein to creatinine ratio (P<0.001) as well as a decrease in serum albumin (P<0.001) & eGFR (P<0.001) were observed across the three tertiles of decreasing T50 in CKD. Adjusting for age & gender, T50 showed significant inverse associations with left ventricular (LV) mass index (P<0.001), left atrial volume index (P=0.012), early diastolic mitral annular velocity (Em) (P=0.004) & the ratio of early to late diastolic flow velocity (E/E) (Em/P<0.001) but not systolic functional parameters. Serum T50 retained significant association with cardiac troponin T (P=0.027) in the model adjusting for age, gender, eGFR & LV mass index. T50 however showed no direct association with coronary artery calcium scores.

Conclusions: Low T50 may predict adverse outcomes in CKD via its close associations with myocardial injury, myocardial structural & diastolic functional abnormalities. These data suggest T50 may more be a biomarker reflecting myocardial disease rather than calcification of the coronary arteries.

Funding: Pharmaceutical Company Support - Sanofi

Sphingosine 1-Phosphate Changes in Patients with Chronic Kidney Disease on Hemodialysis and Peritoneal Dialysis

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Background: Sphingosine-1-phosphate is involved in the development and pathogenesis of renal function and physiology of many renal diseases including chronic kidney disease. Changes in concentrations of sphingosine-1-phosphate may affect the renal function and appear to be potential indicators of renal damage and renal graft function. This study was the first evaluation of the biochemical parameters and quantitative analysis of the concentrations of sphingosine-1-phosphate in patients with chronic renal failure undergoing peritoneal dialysis, hemodialysis, or pre-dialysis.

Methods: The study included 120 patients with CKD, on peritoneal dialysis (n=50) and hemodialysis (n=30), in predialysis state (n=60). The concentrations of biochemical parameters in serum were determined by colorimetric methods. The concentrations of S1P in the plasma were measured using the RP-HPLC. Obtained results were statistically analysed using STATISTICA PL v.10.1.

Results: The highest average concentration of S1P has been obtained in patients on peritoneal dialysis (83.83±18.99 mg/dL), and the lowest in patients with pre-dialysis therapy (58.06±20.38 mg/dL). The average concentration of S1P in patients before hemodialysis (71.52±19.86 mg/dL) and after treatment (77.83±26.48 mg/dL) were similar. Significant differences in concentration of S1P were found between patients with peritoneal dialysis and pre-dialysis patients (p=0.0002) and between patients after hemodialysis and predialysis (p=0.003).

Conclusions: Observed higher concentrations of S1P in hemodialysis patients and peritoneal dialysis in comparison to patients treated conservatively. Indicate that activation of lipid or lipoprotein sources may be caused by the activation of the coagulation system and increased oxidative stress

Acknowledgments
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Renal Elasticity of Patients with Chronic Kidney Disease Evaluated with Real-Time Ultrasonic Elastography

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Background: Ultrasonic real-time elastography is a new imaging technique, which provides information about the elasticity of soft tissue. It is widely applied in patients with liver diseases. In patients with chronic kidney disease (CKD), glomerulosclerosis and tubulointerstitial fibrosis could be associated with lower renal parenchymal elasticity. However, little is known about the elasticity of the kidney. We designed a study to evaluate renal elasticity in patients with CKD stage 3-5.

Methods: There were 148 healthy volunteers and 227 patients with CKD in this cohort from Southern Taiwan. Renal sonography was performed on the Hitachi EUB 7500 and HIVISION PREVIUS sonographer with elastography and the EUP-C715 (1-5MHz) probe.

Results: There were 143 (63.5%) male, 166 (73.1%) diabetes, with a mean estimated glomerular filtration rate (eGFR) of 33.9±15.8 ml/min/1.73 m² and a median urinary protein-to-creatinine ratio (UPRC) 502 (122-1491) mg/g in the CKD group. Patients with later CKD stages had lower value of renal elasticity, which means more stiff (p<0.001), and smaller kidney long length (p<0.001). We demonstrated that renal elasticity only correlated with log-transformed UPVR (β = −7.544, P<0.001). Renal long length correlated with age (β = −0.231, P<0.001), sex (β = −3.730, P<0.001), serum albumin level (β = −3.024, P<0.001), body mass index (β = 0.390, P=0.009) and eGFR (β = 0.146, P<0.001). In fully-adjusted logistic regression model, the odds ratio (OR) per 10 unit change of renal
elasticiy for rapid renal progression was 0.928 (95% CI, 0.864-0.997; P = 0.042). The OR per 1 mm change of renal long length for rapid renal progression was 1.022 (95% CI, 0.994-1.050; P = 0.125).

**Conclusions:** Renal elasticiy is associated with proteinuria and rapid renal progression in patients with CKD. It may be a useful tool for early detecting renal function change in patients with CKD.

**Funding:** Clinical Revenue Support

**TH-PO566**

The Availability of Proteinuria/Urinary Beta2-Microglobulin Combination as a Complementary Marker to Predict Early Progression in Chronic Kidney Disease

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**Background:** Proteinuria as a marker of glomerular damage is of pathogenic importance to the progression of chronic kidney disease (CKD). However, renal tubulointerstitial damage can serve a common pathway of CKD progression. Urinary β₂-microglobulin excretion, a marker of proximal tubular damage, may reflect the presence of tubulointerstitial damage. Therefore, it has been hypothesized that the combination of proteinuria and urinary β₂-microglobulin may be useful predictor of renal outcome.

**Methods:** Proteinuria and urinary β₂-microglobulin excretion were measured in 104 patients with CKD. Based on the value of urine protein-to-creatinine ratio (PCR) or urinary β₂-microglobulin-to-creatinine ratio (UBCR), a total of 104 patients were divided into four groups: group I (n = 39), PCR < 0.5 mg/g and UBCR £300 ug/g; group II (n = 16), PCR > 0.5 mg/g and UBCR £300 ug/g; group III (n = 24), PCR 0.5 mg/g and UBCR > 300 ug/g; group IV (n = 25), PCR > 0.5 mg/g and UBCR > 300 ug/g. Logistic regression analysis was used to compute odds ratio to examine the relationship of proteinuria or increased UBCR with deterioration of renal function (DRF), and Kaplan-Meier analysis was used to compare cumulative renal survival among the groups.

**Results:** During a mean follow-up of 71 ± 21 months, renal function deteriorated in 28 of the 104 patients with CKD. Among four groups, there was statistically significant difference in gender (P = 0.0198), serum glucose (P = 0.0147), serum uric acid (P < 0.0279), and eGFR at 12 months (P < 0.0158). Logistic regression analysis identified the only combination of proteinuria and high UBCR (OR 7.396; 95% CI, 1.235 to 44.284; P = 0.028) as risk factors for DRF. In Kaplan-Meier analyses, group IV had most inferior cumulative renal survival rate and there was statistically significant difference among the groups (P = 0.008).

**Conclusions:** The combination of protein and β₂-microglobulin in urine of CKD may be useful predictors of long-term renal survival. Proteinuria and urinary β₂-microglobulin should not be discretely but simultaneously considered to early detect and delay DRF.

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

**TH-PO567**

Renal Hyperfiltration Predicts Increased Urinary Albumin Excretion in the General Non-Diabetic Population

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**Background:** In cohort studies, both low and high estimated glomerular filtration rate (eGFR) have predicted cardiovascular disease (CVD) and death. The increased risk associated with high eGFR has been explained by confounding due to a low serum creatinine in persons with chronically ill. However, abnormally high GFR, renal hyperfiltration, has been hypothesized to cause elevated urinary albumin excretion, a known risk factor for CVD and death. We investigated this hypothesis in the non-diabetic general population using measurements of GFR instead of eGFR.

**Methods:** In 2007-2009 we measured GFR by iohexol clearance in 1552 persons aged 50-62 years from the general population without diabetes or high albumin-creatinine ratio (ACR) > 30 mg/g (group I; n = 481). A total of 154 persons were included (n = 29, 31, 34, 31, and 29 in stage 1, 2, 3, 4, 5 CKD, respectively). Their age were 60.9 ± 13.4 years, and there were 57 women (37%). Urinary C6f to creatinine ratio (UCr6f) was markedly elevated in patients with stage 4 and 5 CKD (Figure 1A). UCr6f<7.2 was negatively correlated with eGFR (Figure 1B) and positively correlated with urinary protein to creatinine ratio. Furthermore, UCr6f was independently associated with age, gender, body weight, body high, and urinary protein to creatinine ratio (β = -0.026, P < 0.001). Among patients with stage 3-5 CKD, UCr6f<7.2 was significantly higher in those with rapid renal function decline in the following 3 months (P < 0.002).

**Conclusions:** Urinary C6f excretion increases significantly in patients with advanced CKD. Higher UC6f<7.2 may be associated with following rapid renal function deterioration.

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

**TH-PO568**

Elevated Urinary Excretion of Cysteine-Rich Protein 61 Is Associated with Rapid Renal Function Decline in Patients with Chronic Kidney Disease

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**Background:** Cysteine-rich protein 61 (Cyr61) has been identified as a proinflammatory factor in animal models of obstructive kidney fibrosis and ischemic kidney injury. We hypothesized that Cyr61 participates to the inflammatory process in injured kidneys and leads to progressive renal failure. The present clinical study aimed to examine urinary Cyr61 excretion in patients with chronic kidney disease (CKD).

**Methods:** Adult patients with stages 1-5 CKD were recruited from outpatient clinic. Urinary levels of Cyr61 were measured by sandwich enzyme-linked immunosorbent assay. The clinical factors associated with urinary Cyr61 excretion were explored using regression analysis. Rapid renal function decline was defined as estimated glomerular filtration rate (eGFR) decline rate higher than 4 cc/min/year during the follow-up period.

**Results:** A total of 154 patients were included (n= 31, 34, 31, and 29 in stage 1, 2, 3, 4, 5 CKD, respectively). Their age were 60.9 ± 13.4 years, and there were 57 women (37%). Urinary Cyr61 to creatinine ratio (Uc61f<7.2) was markedly elevated in patients with stage 4 and 5 CKD (Figure 1A). UC6f<7.2 was negatively correlated with eGFR (Figure 1B) and positively correlated with urinary protein to creatinine ratio. Furthermore, UC6f<7.2 was independently associated with age, gender, body weight, body high, and urinary protein to creatinine ratio (β = -0.026, P < 0.001). Among patients with stage 3-5 CKD, UC6f<7.2 was significantly higher in those with rapid renal function decline in the following 3 months (P < 0.002).

**Conclusions:** High UC6f levels are associated with the incidence of CKD and the development of hypertension.

**Funding:** Clinical Revenue Support

**TH-PO569**

Hyperuricemia Can Be a Risk Factor for the Development of Hypertension and CKD – An 8-Year Follow-Up Study

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**Background:** Uric acid (UA) levels correlate positively with the prevalence of CKD and/or hypertension, suggesting that UA can be a progression factor. We tested the hypothesis that UA may also have a link to a new incidence of chronic kidney disease (CKD) and hypertension.

**Methods:** Study design is a cohort study and the predictor is UA levels. Of the 14,360 screened cases, 7,536 participants without CKD were eligible for the analysis of the incidence of CKD. Among these CKD candidates, 6,475 participants were eligible for the analysis of the new development of hypertension. The observation period was 8 years. UA levels were divided into 4 groups (Group 1:UA<5mg/dL; Group 2:5.0-5.9mg/dL; Group 3:6.0-6.9mg/dL; Group 4:UA≥7mg/dL). UA≥6.0mg/dL was used as a cut off for the analysis of the new development of hypertension.

**Results:** Higher UA levels had a closer association with the new development of CKD at year 8; 1.6% (Group 1); 2.3% (Group 2); 3.1% (Group 3); and 4.9% (Group 4), respectively. Cox proportional hazard analysis showed that the estimates of the CKD development were age, UA levels (Hazard Ratio (HR) 1.372,95% CI 1.214-1.550), HbA1c and gender, indicating that UA levels can be predictors. The logistic analysis showed that the odds ratio (OR) to estimate CKD incidence in the high UA group (Group 4; OR 3.41, 95% CI, 95%CI 1.99-5.84) was greater than that in the low UA group (Group 1). On the other hand, higher UA levels had a closer association with the new development of hypertension: 6.9% (Group 1); 10.5% (Group 2); 13.0% (Group 3); and 17.0% (Group 4), respectively. Cox proportional hazard analysis showed that the estimates of the hypertension development were BMI, age, HDL-cholesterol, male gender, UA level (HR) 12.95% CI 1.624 to 1.207); and eGFR. The logistic analysis showed that the odds ratio (OR) to estimate hypertension in the high UA group (Group 4; OR 1.35, 95% CI, 1.10 to 1.80) was greater than that in the low UA group (Group 1).

**Conclusions:** High UA levels are associated with the incidence of CKD and the development of hypertension.
TH-PO570

Associations Between Uric Acid, Adiponectin and Urinary Biomarkers in Persons with and without the Metabolic Syndrome — Mari D. Solbu, 1,2 Jon viljar Norvik, 2 Jens Kronborg, 2 Bjørn Odvar Eriksen, 3 Torafl Melsom, 1,2 Trond G. Jønssen. 2,4 Section of Nephrology, Univ Hospital of North Norway, Tromsø, Norway. 2Metabolic and Renal Research Group, UiT the Arctic Univ of North Norway, Tromsø, Norway. 1Inlandet Hospital Trust, Lillehammer Hospital, 3Oslo Univ Hospital, Oslo, Norway.

Background: In the metabolic syndrome (MetS), serum uric acid (UA) is often increased, and adiponectin is low; UA may cause renal damage, whereas adiponectin may be renoprotective. It is not known whether UA and adiponectin interact in development of renal damage. We assessed the cross-sectional association between UA, adiponectin and two urinary biomarkers (albumin creatinine ratio (ACR) and crosmosomol creatinine ratio (ocrCR)) in persons with or without the MetS (NGGP-ATP3 definition).

Methods: From the Tromsø Study 2007-08, 7047 persons were included. Three urine specimens were collected and median values of ACR and ocrCR used. The associations between UA, adiponectin and the upper vs. three lower quartiles of each biomarker were assessed by logistic regression analysis adjusted for cardiovascular risk factors, medication use and eGFR in persons with and without the MetS.

Results: Mean age was 63.5 (±SD 9.2) years, 57% were women and 27% had the MetS. UA was associated positively with the upper ACR quartile and negatively with the upper ocrCR quartile. The association with ACR was stronger in persons with the MetS than in those without (OR 1.18; 95% CI 1.07–1.31; P<0.002 vs. OR 1.08; 95% CI 1.01–1.16; p=0.04 per 1 mg/dL increase in UA.) Adiponectin was positively associated with ACR and ocrCR, but only in persons without the MetS (OR 1.08; 95% CI 1.01–1.16; P<0.002 vs. OR 1.04; 95% CI 1.01–1.07, both P<0.01, per μg/mL). There were no interactions between UA and adiponectin in their associations with the urinary biomarkers.

Conclusions: UA and adiponectin did not interact in their associations with biomarkers of renal damage. Contrary to what we expected, adiponectin was positively associated with ACR and ocrCR, but only in persons without the MetS; UA was positively associated with ACR only. The findings should be studied longitudinally before firm conclusions could be made.

Funding: Government Support - Non-U.S.

TH-PO571

The Longitudinal Association Between Uric Acid Level and Progression of Chronic Kidney Disease in Chinese Population — Ching-Wei Tsai, Shih-yi Lin, Chin-Chi Kuo, Chiu-Ching Huang. Div of Nephrology and Kidney Inst, China Medical Univ and Hospitals, Taichung, Taiwan.

Background: Hyperuricemia is commonly observed in patients with chronic kidney disease (CKD). Although increasing evidence supports the association between hyperuricemia and incident CKD, there are conflicting data about the role of hyperuricemia in the progression of CKD. The main aim of current study was to add empirical evidence to the debate on the direction of the relationship among uric acid levels, allopurinol, and CKD progression in Chinese population.

Methods: We conducted a retrospective cohort study in central Taiwan. Patients who had documented hyperuricemia (defined by uric acid greater than 7 mg/dL) and/or receiving uric acid-lowering agents between 2003 and 2005 were included in the study. They were followed till December 31, 2011. Only patients with at least three available renal function profiles were analyzed. CKD progression was evaluated by the change in eGFR using linear mixed models.

Results: Longitudinal analyses showed patients with a baseline uric acid level greater than 7 mg/dl had faster decline in eGFR, comparing to those with uric acid level less than 7 mg/dl. After adjustment for demographics, comorbidities, proteinuria, allopurinol and ACEI/ARB use, three categories of hyperuricemia (uric acid 7-9, 9-11, >11 mg/dl) remained strongly associated with faster decline in eGFR over the follow-up. In multivariate longitudinal analysis, those receiving allopurinol was associated with a significantly faster decline in eGFR than non-allopurinol users during the follow-up.

Conclusions: Our study showed higher uric acid level is strongly associated with an accelerated decline in renal function in Chinese population. However, uric acid-lowering therapy with allopurinol was associated with even faster progression of CKD in this study.

TH-PO572

Revisiting Medullary Tophi: A Link Between Uric Acid and Progressive Chronic Kidney Disease — Salem Almapari, 1 Isabelle Ayoub, 1 Sergey V. Brodsky, 2 Tbor Nadaday, 2 Jason Prosek, 3 Lee A. Hebert, 3 Brad H. Rovin. 1Div of Nephrology, The Ohio State Univ, Columbus, OH. 2Dept of Pathology, The Ohio State Univ, Columbus, OH.

Background: It is well-established from autopsy studies that gouty tophi can form in the kidney, particularly in the renal medulla. Recently hyperuricemia has been identified as a risk factor for progression of chronic kidney disease (CKD). Because each collecting duct serves more than 2000 nephrons, we postulated that obstruction or disruption of the collecting duct system by medullary tophi may explain at least a part of the association between hyperuricemia and progressive CKD. This work was done to determine the prevalence of medullary tophi in CKD patients.

Methods: We queried our nephropathy database over the last ten years for native kidney biopsies that had medullary tophi. The presence or absence of CKD and uric acid levelsaround the time of biopsy were determined by chart review.

Results: Predominant medullary tophi was reported in 796 of 7409 total biopsies, and 572 of these were from patients with established CKD. Medullary tophi were seen in 36 patients, 35 of whom had CKD, suggesting a minimum prevalence of tophi in CKD and no-CKD of 6.1% and 0.45%, respectively. Medullary tophi occurred with and without hyperuricemia or a history of gout.

Conclusions: Medullary tophi appear to be far more likely to occur in CKD compared to no-CKD patients. This cross-sectional study cannot determine whether medullary tophi are a cause or consequence of CKD. However, given their strategic location and bulk, it is possible that medullary tophi contribute to progression of established CKD by causing upstream nephron damage.

TH-PO573

Serum Uric Acid Over 7 mg/DL Is an Independent Risk of Incident End Stage Kidney Disease – A 6-Year Population-Based Cohort Study — Ouppatham Supasvityd, Puvanan Wiparthanupong, Bancha Sattrapoj. Nephrology Div, Dept of Internal Medicine, Phramongkutklao Hospital and College of Medicine, Thailand.

Background: Uric acid deteriorates kidney function via crystal and non-crystal dependent mechanisms. However epidemiological evidence for the significance of serum uric acid levels on the risk for developing end-stage kidney disease (ESKD) is scarce in a setting of population-based screening especially in Asian population. The purpose of the study was to evaluate the effect of serum uric acid level on incidence of impaired kidney function and ESKD.

Methods: A total of 23,712 individuals from an integrated health care delivery system in the Thai army who participated for health checkups between July 1, 2006, and December 31, 2012 were screened. Only 18,390 participants (14,686 men, 3,704 women) older than 20 years for whom available for body weight, serum uric acid, and creatinine data with follow-up were included in the study. The cumulative incidence of chronic kidney disease (CKD, eGFR<60 mL/min per 1.73 m2) and ESKD (eGFR<15 mL/min per 1.73 m2) was calculated according to quartiles of baseline serum uric acid levels and significant high serum uric acid levels (≥7.0 mg/dL).

Conclusions: Median uric acid level is strongly associated with an accelerated decline in renal function in Chinese population. However, uric acid-lowering therapy with allopurinol was associated with even faster progression of CKD in this study.
Results: The mean age of participants was 47.9 ± 9.6 years and body mass index was 24.7 ± 3.4 kg/m². In men (n=2,648) it was diabetes and 65.2% (n=11,998) had high blood pressure. Average serum uric acid and eGFR were 6.29 ± 1.55 mg/dL and 87.84 ± 13.27 mL/min per 1.73 m² respectively. The incidence of CKD at 6 years follow up was 3.64/1000 person-year. A total of 11 patients (0.06%) of ESKD were observed. Participants with highest serum uric acid quartile (>7.5 mg/dL) had a 3.4-fold increase in adjusted hazard ratio (HR) (95%CI: 2.19 to 5.32), compared to those with the lowest serum uric acid quartile (<5.2 mg/dL). Moreover, serum uric acid ≥7 mg/dL were significantly increased risk of ESKD (adjusted HR 5.74 with 95% CI: 1.58 to 20.8, P < 0.008). Finally, even 1 mg/dL increasing of serum uric acid, eGFR would decline 2.2 mL/min per 1.73 m². 

Conclusions: Serum uric acid level is an independent risk factor of CKD and ESKD in Thai population.

TH-PO574
Proton Pump Inhibitors Are Associated with Increased Risk of Development of Chronic Kidney Disease
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Background: Proton pump inhibitors (PPI) are one of the common cause of acute gastrointestinal issues in the United States. This frequently goes undiagnosed due to its subtle clinical presentation, which may later present as chronic kidney disease (CKD). We investigated the association of PPI use with the development of CKD and death.

Methods: The population included 99,351 patients who were seen in primary care VISN2 clinics from 4/2001 until 4/2008. For evaluation of CKD outcome, 27,835 patients with baseline CKD were excluded. Study data was obtained from Veterans Affairs Health Care System Upstate New York (VISN2) network. Data obtained included use of PPI (Yes/No), age, gender, race, retrospective observation time, laboratory data including eGFR, pre-PPi comorbidity variables: vascular disease, chronic obstructive pulmonary disease (COPD), cancer, diabetes, and hypertension. A prospective logistic analysis of case-control data (Prentice and Pyke) was used to investigate the association of treatment (exposure to PPI) with onset of CKD with propensity score in the model.

Results: A total of 24,194/71,516 patients developed CKD. Of those who developed CKD 25.7% were treated with PPI. Patients receiving PPI were more likely to have vascular disease, COPD, cancer and hypertension. Of the total 99,251 patients analyzed for mortality outcome, 36,290 died. Propensity score analysis showed higher odds for development of CKD (OR 1.29 95% CI 1.24-1.35) and mortality (OR 1.97, 95% CI 1.88-2.06) among patients taking PPIs versus those not on PPIs. Sensitivity analyses showed a significant effect of the interaction of age and PPI use in models with CKD.

Conclusions: Use of proton pump inhibitors are associated with increased risk of development of CKD.

TH-PO575
Influence of Statin on Iron Utilization and Metabolism in Patients with Chronic Kidney Disease Stage 3-4
Anna Masaitis-zagajewska, Michal P. Nowicki. Dept of Nephrology, Hypertension and Kidney Transplantation, Medical Univ of Lodz, Lodz, Poland.

Background: Hepcidin, an acute phase reactant protein is a key regulator of iron homeostasis. Elevated hepcidin levels are expected in the face of decreased glomerular filtration and inflammation. Hepcidin is a potentially modifiable mediator of anemia in patients with chronic kidney disease (CKD). Statins have potently anti-inflammatory effects in experimental and clinical CKD and may thereby modulate erythropoiesis.

Methods: Thirty-six patients (17 M, 19 F, mean age 58±13 years) with stage 3 and 4 CKD and LDL cholesterol ≥100 mg/dl not on statin therapy were studied. In a double blind, crossover study all subjects received in a random order either atorvastatin 20 mg/day or placebo for two 6-month periods with 3 month wash-out. Basic biochemistry, serum inflammatory markers such as hsCRP, IL-6, parameters of iron metabolism including iron, serum hepcidin, Total Iron Binding Capacity (TIBC), Unsaturated Iron Binding Capacity (UIBC) and hemoglobin were measured before and after each treatment period.

Results: TIBC and UIBC did not change during placebo phase but significantly increased after 6 months statin therapy from 255±83 to 267±45µg/dl (p=0.006) and from 186±48 to 196±50µg/dl (p=0.03), respectively. Serum iron tended to increase from 68.8±19 µg/dl to 72.4±17.8µg/dl (p=0.08) only during statin treatment. Hemoglobin increased after 6 months statin therapy from 11.6±1.6 to 11.8±1.5g/dl (p=0.001) while after placebo period hemoglobin did not change. Hepcidin levels significantly decreased during statin treatment from 241±337 to 160±210µg/ml (p=0.01), while no effect was found during placebo phase. Hemoglobin levels did not change after both statin and placebo. IL-6 and hsCRP tended to decrease after 6 months only after statin therapy (from 11.5±11.1 to 6.8±12.9 µg/ml, p<0.001). Correlations were observed between eGFR and age, NYHA class, hepcidin, GDF-15. After adjusting for these factors, we found that the use of HRT was still significantly associated with baseline CKD were excluded. Study data was obtained from Veterans Affairs Health Care System Upstate New York (VISN2) network. Data obtained included use of PPI (Yes/No), age, gender, race, retrospective observation time, laboratory data including eGFR, pre-PPi comorbidity variables: vascular disease, chronic obstructive pulmonary disease (COPD), cancer, diabetes, and hypertension. A prospective logistic analysis of case-control data (Prentice and Pyke) was used to investigate the association of treatment (exposure to PPI) with onset of CKD with propensity score in the model.

Conclusions: Use of proton pump inhibitors are associated with increased risk of development of CKD.

TH-PO577
Hormone Replacement Therapy in Post-Menopausal Women Is Associated with Better Kidney Function
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Background: The effect of hormone replacement therapy (HRT) on renal function in post-menopausal women is unclear. Experimental models suggest estrogen has a renoprotective effect, but human studies have had variable results.

Methods: We performed a cross-sectional study on 2217 post-menopausal women who participated in the Family Blood Pressure Program, a multi-network study aimed at studying the genetics of hypertension. We compared markers of renal function, including urine albumin/creatinine ratio (UACR) and estimated glomerular filtration (eGFR) using the CKD-EPI equation, between women who were using HRT (n=673, median age 60.2) and those who were not (n=1544, median age 62.9). Clinical characteristics, including body mass index (BMI), medical history, medications, family history and blood and urine tests were measured at a single study visit conducted between 2000-2004.

Results: UACR was significantly lower in those on HRT versus those who were not [3.5 vs. 5.2 mg/g Cr, P<0.001], as was the number of women with eGFR < 60 ml/min/1.73 m² (7% vs. 10%, P<0.003). We performed linear and logistic regression models using generalized estimating equations for log(UACR), UACR > 25 mg/g Cr and eGFR < 60 ml/min/1.73 m² and adjusted for age, race, network, education, smoking, diabetes, hypertension, family history of hypertension, log(BMI), log(HDL), log(LDL) and log(triglycerides). After adjusting for these factors, we found that the use of HRT was still significantly associated with lower log(UACR) [-0.307, p<0.001] and women not on HRT had an odds of 1.6 (95% CI 1.2-2.3) times that of those on HRT of having UACR > 25 mg/g Cr. The association between HRT and eGFR < 60 ml/min/1.73 m² was no longer significant after adjustment.

Conclusions: The use of HRT in post-menopausal women was associated with lower UACR after adjusting for known risk factors for renal and cardiovascular disease. Strengths of our study include a large sample size and a comprehensive medical history of subjects. Limitations include that subjects were recruited on the basis of hypertension and that we had limited information on the length of time on HRT.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
TH-PO578
Tobacco Smoking and Progression of Chronic Kidney Disease: A Role for Reactive Aldehydes? Gabriel Rezonov,1 Phillip H. Chumley,1 Wenguang Feng,1 Ping Hua,1 Huma Fatima,1 Edgar A. Jaimez,2  1Univ of Alabama at Birmingham; 2Memorial Sloan Kettering Cancer Center.

Background: Clinical and experimental evidence supports the role of tobacco smoking as a risk factor in the progression of chronic kidney disease (CKD) of different etiologies. Cigarette smoke (CS) contains numerous compounds that could be responsible for deleterious effects of tobacco smoking. Among these compounds are included large concentrations of reactive aldehydes such as acrolein that react with thiol groups and active NADPH oxidase as we have previously shown (ATVB’04). In these studies we postulated the hypothesis that acrolein (Ac) accelerates the progression of CKD and that these effects are linked to increased oxidative stress.

Methods: Sprague-Dawley rats (n=6-8) rats were divided in the following groups: Sham, Sham+Acr (0.5 mg/kg/day via osmotic minipump), 5/6Nx and 5/6Nx+Acr. Rats were euthanized after 12 weeks and kidneys saved for glomerular injury score (GIS) and tubular injury score (TIS). Urine was collected every two weeks for proteinuria (Bio-Rad). Urinary isoprostanes and TGF-β were measured by Elisa and adjusted for urinary creatinine.

Results: Rats on Acr had a significant increase in proteinuria, urinary excretion of isoprostanes and TGF-β, TIS but not GIS. Rats with 5/6-Nx had a significant increase in proteinuria, TIS and GIS and a modest increase in TGF-β. The administration of Acr to 5/6-Nx resulted in further increases in proteinuria, isoprostanes and TGF-β but not GIS. The urinary excretion of TGF-β in these rats was also increased and similar to Sham+Acr.

<table>
<thead>
<tr>
<th>Proteinuria (mg/24 hours)</th>
<th>Sham</th>
<th>Sham+Acr</th>
<th>5/6Nx</th>
<th>5/6Nx+Acr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51.1± 9.8</td>
<td>122.4±10.2*</td>
<td>122.7±13.6*</td>
<td>428.5±98.5*</td>
</tr>
<tr>
<td>Isoprostanes (pg/mg creatinine)</td>
<td>8.2± 0.1</td>
<td>164.1± 32.4*</td>
<td>336.5±126.7*</td>
<td></td>
</tr>
<tr>
<td>TGF-β (pg/mg creatinine)</td>
<td>5.3± 1.8</td>
<td>50.3±16.9*</td>
<td>10.7± 4.5</td>
<td>51.5±28.1*</td>
</tr>
</tbody>
</table>

* P<0.05 vs Sham, #P<0.05 vs 5/6Nx (N=6-8)

Conclusions: These studies suggest that the reactive aldehyde acrolein plays a role as mediator of the deleterious effects of tobacco smoking in the progression of CKD.

Funding: Other NIH Support - National Institute of Environmental Health Sciences

TH-PO579
Intermittent Smoking Associates with Chronic Kidney Disease in U.S. Hispanics: The Hispanic Community Health Study/ the Study of Latinos

Background: Cumulative smoking exposure is associated with chronic kidney disease (CKD). However, the patterns of exposure, such as the effect of intermittent smoking, on CKD risk are unknown. These patterns may be important given the recent increase in alternative smoking exposures such as e-cigarettes.

Methods: Cross-sectional study of 15,664 participants of a population-based cohort of Hispanic/Latinos aged 18-74 years recruited from four U.S. field centers from 2008 to 2011. Data on current, past and never smoking, and smoking pack-years were obtained through a questionnaire. The association between smoking exposure and CKD (estimated glomerular filtration rate <60 ml/min/1.73 m² or urine albumin to creatinine ratio ≥30 mg/g) was estimated using logistic regression models. We tested the interaction between smoking exposure and CKD.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Current</th>
<th>Past</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>10000</td>
<td>30</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>Sham+Acr</td>
<td>5000</td>
<td>15</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>5/6Nx</td>
<td>5000</td>
<td>10</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>5/6Nx+Acr</td>
<td>5000</td>
<td>5</td>
<td>25</td>
<td>70</td>
</tr>
</tbody>
</table>

Conclusions: These studies suggest that the reactive aldehyde acrolein plays a role as mediator of the deleterious effects of tobacco smoking in the progression of CKD.

Funding: Other NIH Support - National Institute of Environmental Health Sciences

TH-PO580
Incidence of Chronic Kidney Disease in Patients with COPD: Systematic Review and Meta-Analysis

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Background: Chronic obstructive pulmonary disease (COPD) is common disease especially in elderly population, and is a important cause of mortality world-wide. Several studies have identified COPD as part of a systemic inflammatory syndrome and reported the association of COPD with increased risk of atherosclerosis. However, the relationship between COPD and incidence of chronic kidney disease (CKD) has not been clearly demonstrated in the literature. The focus of our study was to systematically review the medical literature reporting the incidence of renal function disturbances specifically incidence of CKD in patients with COPD.

Methods: We conducted a systematic review using the Cochrane Collaboration Methodology. We searched Medline via Ovid, Pubmed, Embase and ISI web of science databases from 1950 through 2015. We rated the quality of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Meta-analysis was done using Review Manager Version 5.0.20

Results: Our search resulted in 8 eligible studies. COPD was found to be associated with a significantly increased incidence of CKD (Odds Ratio [OR]=2.10; 95% Confidence Interval [CI] 2.04, 2.16).

Conclusions: COPD patients are at increased risk of developing chronic kidney disease. The exact reasons for the increase in the incidence of CKD are unclear. Clinical research and practice guidelines usually target disease conditions in isolation. Research into COPD and CKD is scant and there is a need for further studies to delve into the pathological mechanisms and clinical implications of incidence of CKD in patients with COPD.

TH-PO581
Effects of Nicotine on the Severity of Diabetic Nephropathy

Raju D. Pai,1 220A
TH-PO578
Tobacco Smoking and Progression of Chronic Kidney Disease: A Role for Reactive Aldehydes? Gabriel Rezonov,1 Phillip H. Chumley,1 Wenguang Feng,1 Ping Hua,1 Huma Fatima,1 Edgar A. Jaimez,2  1Univ of Alabama at Birmingham; 2Memorial Sloan Kettering Cancer Center.

Background: Tobacco smoking plays a major role in progression of chronic kidney disease (CKD) of different etiologies including diabetes mellitus (DM). In previous studies we demonstrated that nicotine is responsible for deleterious effects of smoking in the progression of CKD and pharmacologic blockade of the α7 nicotinic receptor subunit (α7-Nachr) reduces the effects of nicotine in a CKD rat model. Whether this receptor also plays a role in the progression of other models of CKD such as ischemic nephropathy is not known.

Methods: DM was induced with streptozotocin (STZ) in eNOS−/− and eNOS−/−+α7-Nachr mice. A separate group of eNOS−/− mice also received a α7-nAchR blocker (IC200610, 2 mg/kg IP, 5 days a week for 10 weeks). Mice were given nicotine (100mg/ml in drinking water) or tap water for 10 weeks. Blood pressure (BP) was measured by tail-cuff method and urine collected every 2 weeks for albuminuria.

Results: All mice became diabetic after STZ and had no significant differences in weight or blood glucose at sacrifice. All animals were also hypertensive and nicotine had no effect on BP in any of the groups. Diabetic mice receiving nicotine (DN) had higher albuminuria as compared to diabetic mice on tap water (DT). Diabetic mice on nicotine lacking the α7-Nachr (DN−/−) or pharmacologic blockade (DN−/−+B) had higher urinary excretions of albumin similar to diabetics on tap water (DT). Neither absence of the α7-Nachr (DT−) nor pharmacologic blockade (DT−+B) had any effect on mice on tap water.

Conclusions: These studies demonstrate that α7-Nachr is a critical mediator of the deleterious effects of nicotine in the severity of diabetic nephropathy.

Funding: Other NIH Support - NIDDK/NIH, National Institute of Diabetes and Digestive and Kidney Diseases
Lithium Nephropathy: A Long-Term Complication of Chronic Lithium Therapy

Background: Lithium is the treatment of choice for bipolar disorder. Lithium-induced nephropathy is a known complication limiting its use. The aim of this study is to establish the prevalence of renal failure in our population. We sought to quantify the contribution of lithium to the development of renal failure.

Methods: We selected 1751 patients on lithium therapy from the laboratory database of the Delta Center for Mental Health Care, Rotterdam. The database contains measurements of lithium and creatinine concentration over a period from 2000 to 2011. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Renal failure was defined as having GFR ≤ 60 mL/min on at least 2 measurements 6 weeks apart. A comparison was made between patients with and without renal insufficiency regarding gender, mean lithium concentration in serum, lithium intoxication, duration of therapy, age at initiation of therapy, cardiovascular disease, hypertension, and diabetes mellitus.

Results: 305 out of 1751 (17.4%) patients were classified as having renal failure. Occurrence of renal failure was positively correlated with female sex, age at initiation of therapy and duration of lithium therapy (p<0.001). Significant correlation was also observed between renal failure and cardiovascular risk factors. Mean lithium concentration serum was 0.68 mmol/l and did not differ between patients with and without renal failure. In 251 patients follow up data was available for a period of more than 10 years. In these patients history of lithium intoxication did not predict occurrence of renal failure.

Conclusions: Prevalence of renal failure in our cohort is similar to other reports. Longer duration of lithium therapy was found to be associated with an increased risk of renal failure. Contrary to our expectation, lithium intoxication was not correlated with renal failure. Although therapy duration was a significant predictor, one should not forget the importance of cardiovascular risk factors in development of renal failure.

Study of Organochlorine Pesticides in Patients with Chronic Kidney Disease of Unknown Etiology

Background: An apparently new form of CKD not attributable to diabetes, hypertension or other known causes, i.e. CKD of unknown etiology (CKDU) has emerged in south Asia, especially Sri Lanka, and Sub-Saharan Africa in the last one decade. CKDU affects younger individuals and is asymptomatic until advanced stages. Organochlorine pesticides (OCPs) are implicated in the etiopathogenesis of CKDU. This study aimed at estimating the serum levels of several OCPs (o-HCH, β-HCH, g-HCH, total HCH, Aldrin, Dieldrin, α-endosulfan, β-endosulfan, p,p’-DDT, p,p’-DDE and total pesticide load (TPL)) in patients with CKDU in comparison with patients CKD of known etiology (CKDk) and to assess their role in etiopathogenesis of CKDU.

Methods: This was a case-control, cross-sectional study conducted in east Delhi. Subjects in the age group 18-60 years of either sex were recruited under 3 groups: Group I: Healthy controls (n=30), Group II: Patients with CKDu (n=30) and Group III: Patients with CKDk (n=30). Detailed history, physical examination, routine investigations and urinary protein excretion estimation were done. Serum OCP levels were estimated by high performance liquid chromatography.

Results: The median serum levels of all OCPs were higher in patients of group II as compared to other study groups and this difference was statistically significant for α-HCH, β-HCH, g-HCH, total HCH, Aldrin, Dieldrin, α-endosulfan, β-endosulfan, p,p’-DDT, p,p’-DDE and total pesticide load (TPL) in patients with CKDu in comparison with patients with CKD of known etiology (CKDk) and to assess their role in etiopathogenesis of CKDu.

Conclusions: Despite some limitations of the study, the presence of higher serum OCPs in individuals with CKDu in comparison to CKDk at corresponding CKD stages suggests their possible role in the etiopathogenesis of CKDu.

Chronic Kidney Disease After Intravenous Colistin Use in Survivors of Severe Infections

Background: The resurgence of colistin use for multidrug-resistant (MDR) infections has led to an increase of colistin-associated acute kidney injury (AKI). Nevertheless, long-term renal prognosis is scarce.

Methods: A retrospective cohort study was performed from January 2011 to March 2015. Patients who received colistin for >5 days were included. We excluded cases with CKD, other causes of kidney impairment, and non-survivors to MDR infection. The primary outcome was the development of CKD after colistin treatment. CKD was defined as eGFR <60 mL/1.73m² and/or proteinuria during ≥3 months.

Results: In all, 132 patients received colistin, of them, 50 (38%) died due to MDR infection (case-fatality rate of 21% of 1-year mortality rate in MDR-infection); 12 (9%) in 82 survivors, 28 (35%) progressed to CKD (stage 3: 25, stage 4: 2, and stage 5: 1). Mild AKI occurred in 29 patients during colistin treatment, one patient needed dialysis and 22 progressed to CKD. Independent predictors of colistin-associated progression to CKD in a logistic regression analysis were AKI (odds ratio [OR]: 3.2; 95% confidence interval [CI]: 0.9-10.9; p=0.024). Conclusions: Patients treated with intravenous colistin had a substantial risk for CKD. Therefore, they should be tightly monitored when cumulative dose is >5 g and AKI is identified.

High-Density Lipoprotein Subfractions and Their Oxidized Subfraction Particles in Patients with Chronic Kidney Disease

Background: Chronic kidney disease (CKD) may lead to reduced concentrations of high-density lipoprotein (HDL) and its subfractions (HDL2 and HDL3), and damage them via inflammation and oxidative stress. The present study aimed to determine the contribution of such changes to cardiovascular disease (CVD) in patients with CKD.

Methods: Levels of total cholesterol, low-density lipoprotein cholesterol, HDL-C, HDL2, HDL3, apolipoproteins, malondialdehyde-modified LDL (MDA-LDL), oxidized (ox) HDL, oxHDL2 and oxHDL3 were measured in blood samples from patients with CKD (stages 2 – 5, n = 86) who were not on dialysis and from patients undergoing hemodialysis (CKD stage 5D, n = 25). The patients were followed up for 28 ± 9 months after baseline examinations and CVD events were recorded.

Results: Levels of HDL3 and ApoA1 in HDL3 fraction decreased according to CVD severity, whereas those of HDL2 and ApoA1 in HDL2 fraction did not differ. Levels of oxHDL2 and oxHDL3 were measured in blood samples from patients with CKD (stages 2 – 5, n = 86) who were not on dialysis and from patients undergoing hemodialysis (CKD stage 5D, n = 25). The patients were followed up for 28 ± 9 months after baseline examinations and CVD events were recorded.

Conclusions: Levels of HDL subfractions and their oxidized subfraction particles differed among patients with CKD. Increasing levels of oxHDL2 subfractions might cause a high frequency of CVD events in those patients.


Background: Confounding by prior disease may distort associations between systolic blood pressure (SBP) and primary outcomes in people with chronic kidney disease (CKD), causing uncertainty about the effect of low SBP on vascular risk in advanced CKD. Measurement of troponin may allow confounding by subclinical cardiac disease to be reduced.

Methods: SHARP randomized 9270 people with CKD. Over 5 years, SBP and clinical outcomes were recorded at baseline and at 6 monthly intervals. Cox regression, adjusted for relevant confounders, was used to assess the relevance of usual SBP to vascular outcomes. Analyses were stratified by baseline vascular disease (defined as self-reported vascular disease, and troponin-I >0.01 ng/mL).

Results: Overall, there was a “U”-shaped association between usual SBP and vascular risk. Among the 4075 participants without baseline vascular disease, there was a log-linear
association: each 20 mmHg higher usual SBP was associated with an average 65% increase in risk of vascular events (adjusted hazard ratio [HR] 1.65, 95% confidence interval 1.29–2.12) and a 2-fold increased risk of vascular death (HR 2.03, 1.20–3.42). By contrast, among the 4603 participants with baseline vascular disease, the associations between usual SBP and vascular events (HR 1.15, 1.00–1.32; p for heterogeneity=0.01) and vascular death (HR 1.07, 0.85–1.35; p for heterogeneity=0.03) were significantly weaker. There was no clear association between usual SBP and non-vascular mortality (HR 0.96, 0.82–1.13), irrespective of history of prior vascular disease.

Figure: Relevance of systolic blood pressure to vascular events and cause-specific mortality, by prior vascular disease or raised troponin

Conclusions: In CKD, the “U”-shaped relationship between usual SBP and vascular risk appears to be explained by confounding by vascular disease. Trials to assess the effect of lower than currently recommended SBP targets are indicated.

Funding: Pharmaceutical Company Support, Merck/Schering-Plough Pharmaceuticals(North Wales,PA,USA), Government Support - Non-U.S.

TH-PO587
Serum Triglyceride Levels during Progression to ESRD and Early Dialysis Mortality among U.S. Veterans: A Transition of Care in CKD Study

Elani Streja,1 Melissa Soohoo,1 Connie Rhee,1 Yoshitugu Obi,1 Jennie Jing,1 Danh V. Nguyen,1 Moti L. Kashyap,2 Csaba P. Kovessy,3 Kamyar Kalantar-Zaadeh,1 1UC Irvine; 2UTHSC; 3VA Long Beach.

Background: High triglyceride (TG) levels are an established cardiovascular risk factor in the general population. In a study of non-dialysis dependent chronic kidney disease, higher TG levels (>200 mg/dL) were associated with higher mortality risk, whereas other data show that patients with low TG levels (<15 mg/dL) have even higher mortality risk. The impact of TG levels in the prelude period immediately preceding transition to dialysis on early post-transition outcomes is not known.

Methods: In a cohort of 52,172 US veterans who transitioned to dialysis between October 2007 and September 2011, we identified 15,345 patients with available TG measurements within the last 6 months pre-Transition (preceding dialysis transition). We examined the association of TG (averaged over 6 months) as a continuous predictor of early all-cause mortality (within the first 3 months post-transition), using restricted cubic spline analysis and Cox models adjusted for age, sex, race, ethnicity, cause of ESRD, and region of residence.

Results: The mean/SD age was 69±11 years, among whom 27% were African-American, 7% were of Hispanic, and 51% had diabetes listed as their primary cause of ESRD. The 6-month averaged prelude TG showed an inverse linear association with post-ESRD mortality risk, in which patients with TG>115mg/dL had a higher risk of mortality and patients with TG<115mg/dL had comparatively better survival.

Conclusions: Among veterans transitioning to dialysis, higher TG levels were associated with higher risk of early post-ESRD mortality. Further studies are needed to investigate underlying mechanisms and to determine how lipid-modulating treatments influence these associations.

Funding: NIDDK Support

TH-PO588
Initiation of Statins for Chronic Kidney Disease Patients in the Veterans Affairs Health System

Sai Harrish Dharmarajan,1 Rajesh Balkrishnan,1 Kara Zivin,1 Tanushree Banerjee,2 Neil R. Powe,3 Nilka Rios Burrows,3 Rajiv Saran,4 Sundar Shrestha,2 1Univ of Michigan, Ann Arbor, MI; 2Univ of California, San Francisco, CA; 3Centers for Disease Control and Prevention, Atlanta, GA; 4Univ of Virginia, Charlottesville, VA.

Background: The 2013 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend cholesterol-lowering treatment with statins for Chronic Kidney Disease (CKD) patients aged 50 years or older, and those aged 30-49 years with elevated risk of cardiovascular disease (CVD). We investigated the predictors of statin initiation in a cohort of CKD patients in the Veterans Affairs Health System between 2010 and 2012.

Methods: Our sample included patients with at least one outpatient visit in the calendar year with their first creatinine value in 2010 or 2011. Patients were categorized into five stages of increasing severity based on estimated glomerular filtration rate (eGFR). A cohort of these patients not using statins in the baseline year (2010 or 2011) were identified and followed in the subsequent year (2011 or 2012) to determine statin initiation. A multivariate logistic regression model was used to examine the socio-demographic and comorbidity related predictors of statin initiation.

Results: Our sample included 1,676,215 patients in 2010 and 1,778,655 patients in 2011. Of these, 8.77% in 2010 and 9.48% in 2011 initiated statins in the subsequent year (adjusted Odds Ratio=aOR: 2.46, 95% CI: 2.43 – 2.49) and diabetes mellitus (aOR: 1.94, CI: 1.92 – 1.95). Using patients with eGFR>90mL/min/1.73m² (Stage 1) as reference, CKD Stage 3 patients had a higher odds (aOR: 1.24, CI: 1.23 – 1.26) of statin initiation, in comparison to stage 4 (aOR: 0.87, CI: 0.83 – 0.91) and stage 5 (aOR: 0.33; CI: 0.29 – 0.38) patients. Conclusions: CVD and diabetes were the most influential predictors of statin initiation in CKD patients in a large cohort of U.S. Veterans. Statin initiation appeared to be lowest in patients with CKD Stage 4 and 5. Future research will consider adherence to statin prescription and its association with CKD progression.

Funding: Other U.S. Government Support

TH-PO589
Association of Urine Kidney Injury Biomarkers with Risk of Cardiovascular Events in CRIC

Meyeon Park,1 Chi-yrvan Hsu,1 Alan S. Go,2 Dawei Xie,2 Xiaoming Zhang,2 Sushrut S. Waikar,3 Joseph V. Bonventre,1 Josef Coresh,2 Robert G. Nelson,4 Harold I. Feldman,5 Paul L. Kimmel,6 Vasan S. Ramachandran,7 Kathleen D. Liu,1 UCSF; 2Kaiser Permanente; 3U. of Pennsylvania; 4Brigham and Women’s Hospital; 5Johns Hopkins Univ; 6NIDDK; 7Boston Univ.

Background: Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease (CVD). We investigated whether kidney injury biomarkers were associated with increased risk of athero-sclerotic and non-athero-sclerotic CVD events in the Chronic Renal Insufficiency Cohort (CRIC) study.

Methods: Urine kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), N-acetyl-beta-D-glucosaminidase (NAG), and liver fatty acid-binding protein (L-FABP) were measured in 2466 CRIC subjects in CRIC. Cox proportional hazards models were used to examine the associations between biomarkers indexed to urinary creatinine and heart failure (HF) or a composite of CVD events (myocardial infarction, ischemic stroke, or peripheral artery disease).

Results: Mean age of study subjects was 59.5 (± 10.8) years; 46% were women, 50% had diabetes mellitus, and 34% had history of cardiovascular disease. NGAL/Cr, NAG/ Cr and LFABP/Cr were associated with HF and CV events in unadjusted models, but not in multivariable adjusted models (accounting for baseline eGFR, albuminuria, age, sex, race, comorbidities, and medications). Those in the highest two quintiles [Q5 (>2990.3 pg/g) and Q4 (>1830.9 pg/g)] of KIM-1/Cr levels had an increased risk of HF relative to the lowest quintile (Q1, <661.3 pg/g) [Q5 v. Q1 hazard ratio (HR) 1.7 (1.1-2.9); Q4 v. Q1 HR 1.6 (1.0-2.6)]. KIM-1/Cr was not independently associated with HF in the continuous analysis [HR per log SD increase 1.14 (0.98-1.33)]. Higher KIM-1/Cr was independently associated with CVD events in the continuous analysis [HR per log SD increase 1.21 (1.02-1.41)] after adjustment for confounders.

Conclusions: Select urine biomarkers of kidney injury were independently associated with increased risk of HF and CVD events.

Funding: NIDDK Support

TH-PO590
Cystatin C as a Predictor for Mortality in Elderly Patients with Chronic Kidney Disease

Sebastian Beyg,1 Nina Hojs,1 Masa Kneblt,1 Robert Ekkart,1 Radovan Hojs,4 1Clinic for Internal Medicine, Dept of Nephrology, Univ Clinical Centre Maribor, Slovenia; 2Clinic for Internal Medicine, Dept of Dialysis, Univ Clinical Centre Maribor, Slovenia.

Background: The prevalence of chronic kidney disease (CKD) in the elderly is high. Serum cystatin C, an accurate marker of estimation of kidney function have also prognostic utility in CKD patients. The aim of our study was to determine the prediction for mortality of different markers for estimation of kidney function on long-term survival in elderly CKD patients.

Methods: 103 adult Caucasian patients, older than 65 years (56 women, 47 men; mean age 72.5 years; range from 65 to 86 years), were included. In each patient

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

Underline represents presenting author.

222A
The Relationship Between Neutrophil to Lymphocyte Ratio and Cardiovascular Disease in Patients with Chronic Kidney Disease. Dede Sit, Hasan Kayabasi, Emel Gokmen, Zehra Sucuoglu, Serhat Sigirci, Suleyman Yildirim, Bennur Eser, Saadet Piltan guzel. Bagcilar Training & Research Hospital, Istanbul, Turkey.

Background: Neutrophil to lymphocyte ratio (NLR) is a new, widely-easily available, inexpensive marker calculated from complete blood count is a new addition to the inflammatory markers. In many studies it has been established that NLR is associated with CVD. In this study we evaluated the relationship between NLR and CVD in patients with predialysis CKD.

Methods: In total 172 predialysis CKD patients who were undergone coronary angiography for CAD where studied. GFR of all patients were calculated using MDRD formula, and according to eGFR, the patients were divided into stage 1-5 CKD via K/DOQI guidelines. The patients were divided into two groups as angiography positive and negative group for coronary artery disease. Demographic, biochemical, hematomatological parameters and NLR of nlers were compared.

Results: The mean age of patients was 65.06±10.53 years, 119 were male, and 53 were female. According to eGFR 16 were stage 1, 75 were stage 2, 46 were stage 3, 17 were stage 4 and 18 were stage 5. There was a statistically significant difference in NLR between two groups. In patients with CAD NLR was higher than in patients without CAD (p=0.01). All parameters of patients were detailed in table 1.

Table 1: Comparison of the parameters of patients according to CAD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No</th>
<th>Yes</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>9.09±0.73</td>
<td>8.61±0.65</td>
<td>0.002</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3.93±1.39</td>
<td>3.79±1.42</td>
<td>0.415</td>
</tr>
<tr>
<td>Ca×P</td>
<td>35.63±12.37</td>
<td>32.69±12.14</td>
<td>0.195</td>
</tr>
<tr>
<td>PTH</td>
<td>156.45±144.7</td>
<td>228.87±476.18</td>
<td>0.238</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.05±0.63</td>
<td>3.66±0.05</td>
<td>0.002</td>
</tr>
<tr>
<td>CRP</td>
<td>32.26±40.16</td>
<td>42.49±48.58</td>
<td>0.348</td>
</tr>
<tr>
<td>Spot Protein/Creatinin</td>
<td>815.57±1644.7</td>
<td>1501.05±2284.78</td>
<td>0.043</td>
</tr>
<tr>
<td>Neutrophil/Lymphocyte</td>
<td>4.14±4.49</td>
<td>8.46±11.14</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: In many studies, NLR is reported as an independent predictor of outcome in coronary artery disease, as well as a predictor of short- and long-term mortality in patients with CVD. We found that NLR is significantly higher among CKD patients with CAD, thus we suggest that it may be used as a new marker to investigate CAD and its results in CKD population.

Funding: NIDDK Support

TH-PO592
Change in Skin Autofluorescence Over One Year Predicts Mortality at Five Years in a Prospective Cohort of People with Chronic Kidney Disease Stage 3. Adam Shardlow, 1 Natasha Juliette McIntyre, 1 Richard J. Fluck, 1 Christopher W. McIntyre, 2 Maarten W. Taal, 1, 2 Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; 1Faculty of Medicine and Health Sciences, Univ of Nottingham, Nottingham, United Kingdom; 1London Health Sciences Centre, London, ON, Canada.

Background: Tissue advanced glycation end product (AGE) accumulation is a marker of cumulative metabolic stress assessed by a simple non-invasive measurement of skin autofluorescence (SAF). This has been shown to predict mortality in haemodialysis patients and in earlier CKD in some studies, but the impact of change in SAF over time has not previously been reported. In this study we sought to investigate the associations of SAF and change in SAF over time with mortality in people with CKD stage 3.

Methods: 1741 people with CKD 3 (confirmed by two eGFR values) were recruited from primary care. Participants attended for baseline, year 1 and year 5 study visits and underwent clinical assessment, blood and serum biochemistry. SAF was recorded at each visit. Dates of death were collected from hospital and national records.

Results: At baseline mean eGFR was 35.3 ml/min/1.73 m², mean age 73 years and mean SAF 2.7 arbitrary units. There was a small decrease in mean SAF after 1 year (0.1 arbitrary units; p=0.001) but 30% (20.1%) participants evidenced an increase of >10%, 29% (17.2%) participants died prior to the year 5 study visit. Cox proportional hazards showed that both baseline SAF (HR 1.38) and change in SAF (HR 1.55) over the first year were associated with independent terms of mortality at 5 years in addition to age (HR 1.77), male gender (HR 1.53), baseline eGFR (HR 0.98) and previous cardiovascular disease (HR=1.56). In a sensitivity analysis of participants without diabetes, change in SAF at 1 year remained an independent determinant of mortality (HR 1.5), adjusted for age, gender, baseline eGFR, previous cardiovascular disease and baseline SAF.

Conclusions: Our data show for the first time that an increase in SAF over 1 year is an independent predictor of mortality in CKD stage 3 in addition to baseline SAF. Serial measures of SAF may therefore be useful in predicting risk and monitoring interventions for reducing AGE accumulation.

Funding: Private Foundation Support

TH-PO593
Fibroblast Growth Factor 21 Plasma Levels and Future Cardiovascular Outcomes Among Non-Dialysis Chronic Kidney Disease Patients. Lucie Bauer, 1 Kyriel S. Rogacev, 1 Adam M. Zawada, 1 Sarah Seiler, 1 Insa E. Emrich, 1 Kevin L. Duffin, 2 James R. Voelker, 2 Danilo Fliser, 1 Gunnar H. Heine, 1 'Internal Medicine IV - Nephrology and Hypertension, Saarland Univ Medical Center and Saarland Univ Faculty of Medicine, Homburg, Saarland, Germany;' 2El Lilly and Company, Indianapolis, IN.

Background: Patients with chronic kidney disease have substantial metabolic alterations, which comprise insulin resistance, hyperglycemia and low HDL-cholesterolemia. Fibroblast Growth Factor 21 (FGF-21) is a recently discovered hormone which plays a central regulatory role in glucose and lipid metabolism. We examined the effects of chronic kidney disease (CKD) on circulating plasma FGF-21 concentration, and the association of plasma FGF-21 with incident cardiovascular disease.

Methods: We analyzed plasma FGF-21, along with traditional cardiovascular and renal risk factors, in 441 CKD stage 3 patients who were recruited into the prospective CARE FOR HOME cohort. Plasma adiponectin (total and subfractions) were measured in 339 patients. All patients were followed for the occurrence of cardiovascular events; defined either as atherosclerotic (acute myocardial infarction, stroke, amputation above the ankle, any surgical or interventional coronary/cerebrovascular or peripheral-arterial revascularization, or death of any cause) or as cardiac events (admission for heart failure, death or any cause).

Results: Baseline plasma FGF-21 correlated with higher age (r=0.14), body mass index (r=0.16), waist-hip ratio (r=0.13), triglycerides (r=0.22) and CRP (r=0.14), as well as lower eGFR (r=-0.272) and HDL (r=-0.134, all <p<0.001), but not with total adiponectin or adiponectin subfractions. In univariate Kaplan-Meier-analyses, higher quartiles of baseline FGF-21 were associated with future atherosclerotic (p<0.001) and cardiac (p<0.001) events. However this association lost statistical significance after adjustment for eGFR.

Conclusions: Our study results demonstrate an increase of plasma FGF-21 levels in CKD patients. Despite its role in glucose and lipid metabolism, plasma FGF-21 does not independently predict adverse cardiovascular outcome among CKD patients.

TH-PO594
Graded Increases in Cardiac Biomarkers Across Advancing CKD Stages. Elizabeth K. Batchelor, Gates Colbert, Nishank Jain, Beverly Adams-Huet, Kyle Jamison, James Delemos, Susan Hedayati. UT Southwestern and VA North Texas Medical Centers, Dallas, TX.

Background: Elevated cardiac troponin T (cTnT) >10 ng/L is reported in 80% of ESRD patients and associated with poor outcomes. There are less data on whether cardiac biomarkers are elevated in non-dialysis CKD patients.

Methods: We investigated whether cTnT, high sensitivity cTnT (hs-cTnT), brain natriuretic peptide (BNP), and N-terminal-pro-BNP (NT-pro-BNP) levels increase with worsening CKD in 3,298 asymptomatic, multi-ethnic participants of the Dallas Heart Study.

Results: Mean age was 44±10 years. 55% were female, 50% Black, 31% Caucasian, 17% Hispanic, and 2% other races. 288 had CKD, defined as eGFR<60 ml/min/1.73 m² or albumin-to-creatinine ratio >17 mg/g in men or >25 in women. Of those with CKD, 37% had diabetes mellitus and 66% hypertension vs. 10% and 33% if without CKD. A higher proportion of CKD vs. non-CKD individuals, 8.0 vs. 0.43%, had elevated cTnT (>10 ng/L and hsTnT3 ng/L, 58.3 vs. 24.2%, p<0.0001 for both. Mean BNP was 55±314 ng/L in CKD vs. 10.9±3.25 µg/ml in non-CKD, and NT-pro-BNP was 319.7±1225.7 in CKD vs. 54±117.5 µg/ml in non-CKD (p<0.0001 for both). There were graded increases in the proportion with elevated troponins as CKD severity increased across stages.

Conclusions: TnT and NT-pro-BNP increase with worsening CKD. Cardiac troponin T and NT-pro-BNP should be considered as part of routine screening in CKD patients.

Funding: NHLBI/NIH/NIAMS/ESC/ACC
The the same was seen with BNP and NT-pro-BNP levels, with the highest increases in those with eGFR<30.

Conclusions: A higher proportion of CKD vs. non-CKD individuals had elevated cardiac biomarkers, even at early CKD stages. Graded increases in biomarkers were observed across advancing stages. Further research should determine if higher cardiac biomarker cutoffs are warranted to improve diagnostic and prognostic utility in CKD patients.

Funding: Other NIH Support - ULTR001105 from the National Center for Advancing Translational Sciences, National Institutes of Health. M01-RR00633 from NIH/NCCR-IR., Veterans Administration Support, Private Foundation Support

TH-PO595
Circulating Endothelial Cells and Cardiovascular Risk in Chronic Kidney Disease and Hemodialysis Patients 
Yasser Assem Elgenaya,1 Nahla Mohamed Gamal Farahat,2 Iman Ezait Elgohary,1 Marwa Fathy Oraby.1 Internal Medicine-Nephrology Unit, Faculty of Medicine, Alexandria, Egypt; 2Clinical and Chemical Pathology, Faculty of Medicine, Alexandria, Egypt.

Background: This work was conducted with the aim to study circulating endothelial cells in CKD patients and correlate this with some cardiovascular risk factors. Cardiovascular disease remains the leading cause of morbidity and mortality in patients with CKD and may account for 50% of all deaths. Endothelial dysfunction is commonly observed along the CKD spectrum. Endothelial dysfunction is a well-documented early phenomenon in atherosclerosis that precedes structural changes and clinical manifestations. The chronic micro inflammation state present in uremia has been proposed as one of the mechanisms causing endothelial dysfunction. Inflammatory circulating endothelial cells (CECs) are thought to be mature cells that have detached from the intimal monolayer in response to endothelial injury. In humans, elevated levels were reported in various cardiovascular disorders, as a result of mechanical injury, ischemic injury or hypertension.

Methods: This study included 50 subjects classified as follows: Group I 20 patients with CKD not yet on dialysis, group II 20 patients on maintenance hemodialysis and 10 age and sex matched individual used as a control (group III). All included individuals were subjected to complete blood count, renal function tests, estimation of GFR by MDRD formula, complete lipid profile, high sensitive CRP, ESR and detection of CEC count using flow cytometry.

Results: The study showed increased count of CEC and hs CRP in both CKD groups than the control and it was higher in patients on dialysis than those on conservative treatment. There was a statistically positive correlation between ESR, hs CRP, TG and CECs in the three groups, there was also a statistically negative correlation between estimated GFR and CECs in the three groups.

Conclusions: Measurement of CECs count might offer a mean for recognizing CKD patients at risk of cardiovascular events.

TH-PO596
The Association Between Soluble Klotho and Cardiac Parameters in the Chronic Kidney Disease: Korean CKD Patients 
Hyo Jin Kim,1 Kyung don Ju,1 Tsogbadrakh Bodokhuren Bodokhuren,2 Seungmi Lee,1 Aram Lee,1 Shin-Young Ahn,2 Dong-Wan Chae,2 Ho Jun Chin,2 Curie Ahn,1 Kook-Hwan Oh.1 1Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 2Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Gyeonggi-do, Korea.

Background: Klotho is one of mineral metabolism regulator in chronic kidney disease (CKD). Bone mineral metabolism is important in CKD and it is associated with cardiovascular (CV) complications. We investigated factors determining soluble klotho concentration and the association between klotho and cardiac parameters from Korean CKD patients.

Methods: We analyzed 1,443 CKD patients with soluble klotho at baseline from the prospective Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) study. Left ventricular hypertrophy (LVH) and arterial stiffness were explored as CV parameters. LV mass index (LVMI) was used as a marker of LVH (male >115 g/m², female >95 g/m²), intima-media thickness (IMT) and pulse wave velocity (PWV) was used as a marker of arterial stiffness. Renal outcome (initiation of renal replacement therapy or decline of estimated glomerular filtration rate ≤50% or doubling of creatinine) or composite outcome (renal outcome or death) were analyzed for association soluble klotho level.

Results: Patients were 53.5 ± 12.4 years old and 61.5% were male. In a multivariable linear regression analysis, uric acid and log CRP were positively and estimated GFR inversely associated with klotho. LVH (OR 0.46; 95% CI, 0.25 to 0.85; P = 0.014) and baPWV (Pearson correlation, -0.099; P = 0.001) were associated with klotho in univariate analysis. However, in multivariable analysis, klotho was not independently associated with LVH and baPWV. 887 (61.5%) patients were investigated for association between klotho and outcomes (23.3×4 months follow-up). Analyzed by Cox proportional hazard model, klotho was not associated with renal or composite outcomes.

Conclusions: Soluble klotho was not an independent determining factor for LVH, arterial stiffness, and renal outcomes. Further studies are warranted to elucidate the clinicopathogenetic significance of klotho in Korean CKD patients.

Funding: Government Support - Non-U.S.

TH-PO597
Elevated C-Reactive Protein, and Albuminuria Increase Mortality Risk in Metabolic Syndrome Patients 
Satyesh K. Sinha,1 Magda Shaheen,2 Deyu Pan,1 Keith C. Norris,1 Susanne B. Nicholas.2 Charles R Drew Univ, Los Angeles, CA; 2David Geffen School of Medicine, UCLA, Los Angeles, CA.

Background: Metabolic syndrome (MetS) is a serious health condition affecting nearly 25% of adults in the United States and places them at higher risk of cardiovascular disease (CVD), chronic kidney disease, and mortality. Studies have shown that the MetS is associated with albuminuria (urinary albumin excretion [UAEx] >30mg/mL). Inflammation has been postulated as an important link between the MetS and UAEx. However, little is known about the added value of UAEx and C-reactive protein (CRP) in predicting mortality in patients with the MetS. Therefore, the study objective was to determine the relationship between mortality and the MetS after adding both UAEx and CRP as additional components.

Methods: We analyzed data from the National Health and Nutrition Examination Surveys 1999-2004 of 5,930 adults aged ≥20 years with and without MetS (≥3 components of the MetS according to the definition of National Cholesterol Education Program’s Adult Treatment Panel III). We added elevated CRP and UAEx as a 6th and 7th criteria, respectively for the MetS. We analyzed data using Cox regression to estimate the hazard ratio (HR) for mortality, controlling for demographics, smoking, and CVD. Data are presented as HR, and 95% confidence interval (CI), p<0.05 was statistically significant.

Results: In the adjusted model, the MetS was not associated with mortality. However, HR for mortality was high with elevated CRP (≥0.5 mg/dl; HR=1.84, 95% CI 1.45-2.35, p<0.001) and albuminuria (HR=1.89, 95% CI 1.36-2.63, p=0.001) compared to low CRP (<0.5 mg/dl) and no albuminuria (UAEx<30 ug/ml). With addition of elevated CRP to the MetS, HR for mortality was high (HR=1.36, 95% CI 1.05-1.77, p<0.02) vs. low CRP and no MetS. HR for mortality was high when albuminuria was also added to those with elevated CRP (HR=1.52, 95% CI 1.12-2.06, p<0.01).

Conclusions: We conclude that elevated CRP and UAEx may predict the group at high risk for mortality in MetS patients.

Funding: Other NIH Support - NIH grant U54MD007598, UL1TR000124, and S21-MD-000103.

TH-PO598
Longitudinal Change in Low-Grade Albuminuria Is A Better Predictor of Cardiovascular Disease Than Change in Serum Uric Acid: The Tromsø Study 
Marti D. Solbu,1,2 Bjorn Odvar Eriksen,2 Toralf Melsom,2 Hilde Merete Storhaug,2 Jon viljar Norvik,2 Trond G. Jenssen.2 1Section of Nephrology, Univ Hospital of North Norway, Tromsø, Norway; 2Metabolic and Renal Research Group, Ulf the Arctic Univ of North Norway, Tromsø, Norway; 3Oslo University Hospital, Oslo, Norway.

Background: Serum uric acid (SUA) and albuminuria are independent risk factors for cardiovascular disease (CVD), but the joint impact of longitudinal changes in SUA and albuminuria on clinical events is unknown. We assessed the associations between change in SUA and urinary albumin-creatinine ratio (ACR) over 7 years and the occurrence of incident myocardial infarction, ischemic stroke and all-cause mortality.

Methods: We included 3931 participants without CVD from the population-based The Tromso Study, Tromsø-4 (1994/95) and Tromsø 5 (2001/02). SUA change was categorized into four groups according to upper (high) versus the three lower (low) gender specific quartiles of SUA in Tromsø 4 and 5; persistently high, decreasing , increasing, and persistently low SUA. ACR change was categorized the same way. Percentage of change from baseline in SUA and ACR was calculated.

Results: During follow-up (median 9.3 years for CVD; 11.3 years for mortality) there were 379 myocardial infarctions, 233 strokes and 869 deaths. In multivariable analyses increasing ACR predicted mortality (HR 1.65; 95% CI 1.38-1.96). Persistently high ACR predicted myocardial infarction (HR 1.34; 95% CI 1.03-1.75) and stroke (HR 1.79; 95% CI 1.18-2.51). Increasing and persistently high SUA did not predict any endpoint. A ≥50% increase in ACR from baseline predicted myocardial infarction and death, whereas ≥15% increase in SUA did not. Change in SUA and ACR did not interact in their association with CVD. Baseline SUA significantly predicted stroke and mortality.

Conclusions: Longitudinally increasing ACR predicted CVD independently from SUA change. Baseline, but not changes in SUA predicted stroke and mortality. This may have implications for the use of change patterns in risk assessment.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
**TH-PO599**

**Transient Dipstick-Proteinuria Could Be a Risk of Cardio-Vascular Diseases**

Kei Nagan tends to be the primary method to detect high-risk participants for cardiovascular diseases (CVD). A large part of positive dipstick-proteinuria has gone to negative in the next year, which means transient proteinuria. The aim of this study is to clarify whether transient proteinuria is a risk of CVD comparing to sequentially negative proteinuria with one-year interval measurement.

**Methods:** By using a population-based study, 172 persons longitudinal cohort receiving annual health checkups sequentially twice or more, we examined presence of dipstick-proteinuria both at baseline year and in the next year. Medical history of CVD was obtained via a self-reported questionnaire. The incidence of CVD event in this study was defined as a negative history at the baseline year and a positive history in the follow-up year. Proteinuria was defined as (+) or more.

**Results:** Forty-five percent of subjects with positive proteinuria at baseline year in male and 58% of those in female have gone to negative proteinuria in the next year.

**Conclusions:** Transient proteinuria could be a risk of the incidence of CVD.

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**TH-PO600**

**Urinary Phosphate Excretion Modifies the Association Between Serum Osteoprotegerin and Coronary Calcification in CKD:**

Chung-Wook Joo et al.

A large part of positive dipstick-proteinuria has gone to negative in the next year, which means transient proteinuria. The aim of this study is to clarify whether transient proteinuria is a risk of CVD comparing to sequentially negative proteinuria with one-year interval measurement.

**Methods:** By using a population-based study, 172 persons longitudinal cohort receiving annual health checkups sequentially twice or more, we examined presence of dipstick-proteinuria both at baseline year and in the next year. Medical history of CVD was obtained via a self-reported questionnaire. The incidence of CVD event in this study was defined as a negative history at the baseline year and a positive history in the follow-up year. Proteinuria was defined as (+) or more.

**Results:** Forty-five percent of subjects with positive proteinuria at baseline year in male and 58% of those in female have gone to negative proteinuria in the next year.

**Conclusions:** Transient proteinuria could be a risk of the incidence of CVD.

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**TH-PO601**

**The Relationship of LV Mass Index and FGF-23/25(OH)D Modulating Phosphaturia Shinyoung Ahn, 1 Ho Jun Chin, 1 Kook-Hwan Oh, 1 Curie Ahn, 2 Dong-Wan Chae, 1 Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Republic of Korea; 2 Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.

**Background:** As renal function declines, level of fibroblast growth factor-23 (FGF-23) rise and 25-hydroxvitamin D (25(OH)D) decrease. We evaluate the relationship among 25(OH)D and FGF-23 on cardiovascular risk factors such as LV mass index and vascular calcification (VC).

**Methods:** KNOW-CKD is an on-going, prospective, university hospital based observational cohort study under the sponsorship of Korean Center for Disease Control and Prevention. Cross-sectional analysis of echocardiography data and other clinical data was performed in 1529 participants of KNOW-CKD. The study participants were divided into 4 groups by FGF-23 and 25(OH)D values below and above the median.

**Results:** Among the 1529 study participants, the mean of age and estimated GFR were 53.6 ± 12.4 years and 60.9 ± 31.7 ml/min/1.73m². The median FGF-23 concentration was 17.85 RU/ml (interquartile range [IQR] = 0.42, 51.28), and median level of 25(OH)D was 16.52 ng/ml (IQR = 13.31, 21.04). The patients who had FGF-23 above the median but 25(OH)D below the median had highest level of serum P, iPTH, mean of pulse wave velocity(PWV), and LV mass index. They also had lowest level of hemoglobin, serum albumin, eGFR, corrected Ca, and bone mineral density of femur neck. After multivariate analysis, the result showed significant correlation between LV mass index and FGF-23/25(OH)D ratio (std β=0.176, p=0.021). Decreasing level of 25(OH)D reduced phosphaturia caused by FGF-23. Finally vascular calcification measured by abdominal aorta calcification showed significant negative relationship with phosphaturia after multivariate analysis (std β=-0.095, p=0.031).

**Conclusions:** We observed the significant association between FGF-23/25(OH)D and LV mass index and FGF-23/25(OH)D and degree of phosphaturia which was correlated with vascular calcification. We suggest that FGF-23/25(OH)D may increase LVMI through modification of phosphaturia and vascular calcification.

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

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**TH-PO602**

**Fractional Excretion of Phosphorus Is Independently Associated with Left Ventricular Hypertrophy in Chronic Kidney Disease Patients**

Xiaoyan Zhang, Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China.

**Background:** Left ventricular hypertrophy (LVH) is an important mechanism of cardiovascular disease in chronic kidney disease (CKD). Elevated Fibroblast growth factor-23 (FGF23) levels are independently associated with LVH. The aim of this study is to investigate whether elevated fractional excretion of phosphorus, as one major action of FGF23, is independently associated with LVH in CKD patients.

**Methods:** LVH was defined as LVMI (Left ventricular mass index) ≥ 50 g m⁻²·7 in men or ≥ 47 g m⁻²·7 in women. The fractional excretion of phosphorus (FePi [%]) was calculated as [urine phosphorus (mg/dl) x serum phosphorus (mg/dl)] / [urine creatinine (mg/dl) x serum creatinine (mg/dl)] x 100.

**Results:** We measured FePi levels in 1,389 individuals who underwent echocardiography within 3 months. The median FePi level was 13.44%. The mean ± (SEM) left ventricular ejection fraction was 67 ± 1% in left ventricular mass index to height² (LVMI) was 42 ± 14 g m⁻²·7, and LVH was present in 24% of participants. The left ventricular ejection fraction was lower in the highest versus the lower quartiles of FePi levels, while the LVMI increased with increasing FePi quartiles. Each ten percent increase in FePi was associated with 0.745 g m⁻²·7 greater LVMI per ten percent increase in FePi [β=0.003). Each ten percent increase in FePi was associated with a 1.36-fold greater relative risk (RR) of eccentric hypertrophy and concentric hypertrophy (95% CI, 1.275–1.456; P<0.001) compared with normal ventricular geometry. Multivariable analyses that adjusted for age, sex, weight, diabetes, obesity, serum albumin, eGFR, total cholesterol, total triglyceride, hemoglobin, phosphaturia, parathyroid hormone (PTH), and serum phosphate demonstrated that elevated FePi was independently associated with increased LVMI (0.745 g m⁻²·7 greater LVMI per ten percent increase in FePi, 95% CI, 0.222–2.789; P<0.001) and conferred greater risk of eccentric and concentric LVH (RR 1.102 per ten percent increase in FePi, 95% CI, 1.000–1.214; P<0.05).

**Conclusions:** FePi is independently associated with left ventricular hypertrophy in patients with CKD across a broad range of kidney function.

**Funding:** Government Support - Non-U.S.
Clinical Significance of Vascular Calcification and Retinopathy on Renal and Cardiovascular Outcomes in Patients with Chronic Kidney Disease
Hyeon Seok Hwang, Yeeun Yo, Yuah Hong, Sukyoung Kim. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Korea.

Background: Vascular calcification and retinopathy is the representative marker of macrovascular and microvascular dysfunction in patients with chronic kidney disease (CKD). While both of them share common pathophysiology, their relationship and combined effects on clinical outcome remained undetermined.

Methods: We included 523 nondialysis-dependent CKD stage 3–5 patients, who had been examined with fundoscopy for diabetic or hypertensive retinopathy. Simple X-ray images of the pelvis and the abdomen were analyzed for the presence of intimal or medial arterial calcifications. The clinical significance of intimal calcification and retinopathy was evaluated in terms of the rate of renal function decline and composite of any cardiovascular event or death.

Results: Intimal calcification was observed in 81 (15.5%) CKD patients, medial calcification in 50 (9.6%) CKD patients, and retinopathy in 258 (49.3%) patients. The presence of retinopathy was independently associated with intimal (odds ratio 1.72, 95% CI 1.03-2.89) and medial calcification (OR 3.41, 95% CI 1.68-6.90). The renal function decline rate was significantly steeper in patients with than in those without intimal calcification (~8.1 ± 9.4 mEq/min/1.73 m² yr vs. -4.6 ± 10.4 mEq/min/1.73 m² yr; P = 0.005). However, medial calcification was not associated with rapid renal function decline (P = 0.153). In multivariate analysis, patients with both intimal calcification and retinopathy were independently associated with a rapid decline in renal function (β = -4.21; P < 0.001). The combined status of retinopathy with intimal or medial calcification independently increased the risk of composite events (hazard ratio 3.34, 95% CI 1.41-4.43 for intimal calcification; hazard ratio 3.19, 95% CI 1.62-6.28 for medial calcification).

Conclusions: Coexistence of intimal calcification and retinopathy were independently associated with CKD progression, and the combined status of retinopathy with intimal or medial calcification was an independent predictor for composite cardiovascular event/death.

Abdominal Aortic Calcification in Patients with Chronic Kidney Disease
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Background: Abdominal aortic calcification (AAC) is independently associated with cardiovascular events in dialysis patients and in the general population. However, data in non-dialysis chronic kidney disease (CKD) patients are limited. We studied determinants and prognostic value of AAC in non-dialysis CKD patients.

Methods: We included patients with CKD not receiving renal replacement therapy who participated in the MASTERPLAN study, a randomized controlled trial that started in 2004. In the period 2008-2009 an X-ray to evaluate AAC was performed in a subgroup of patients.

Results: AAC (±) had a prevalence of 19.7% (95% CI 17.9–21.6) in 1,710 patients among the participants of the CKD Research of Outcomes in Treatment and Epidemiology (CKD-ROUTE) study, which newly visited 16 nephrology centers. The primary outcome was a composite of death of any cause and CV events, and the secondary outcome was death of any cause. Data were analyzed with Cox hazards model with adjustment for potential confounders including baseline data. Patients were followed up until end-stage renal disease, death, transfer, or the end of 3-year follow-up.

Results: Median C1 was 106.0 mEq/L at enrollment [quartile (Q): 1: £103.9, n = 257; Q2: 104.0–105.9, n = 258; Q3: 106.0–108.0, n = 352; Q4: >108.1, n = 267]. During 3 years of follow-up, there were 115 CV events, 78 deaths, and 180 composite outcomes. The hazard ratio (HR) for the composite outcome was higher for Q1 than Q3 (unadjusted HR, 1.74; 95% confidence interval (CI), 1.16–2.61; p = 0.007; and adjusted HR, 1.63; 95% CI, 1.05–2.52; p = 0.029). Examined as a continuous variable in a subset of patients (n = 1160.0, higher CI was associated with lower risk of the composite outcome (unadjusted HR, 0.88; 95% CI, 0.84–0.93; p < 0.001; and adjusted HR, 0.94; 95% CI, 0.88–1.00; p = 0.038). The HR for all-cause mortality was also higher for Q1 than Q3 (unadjusted HR, 2.90; 95% CI, 1.56–5.41; p = 0.001; and adjusted HR, 2.56; 95% CI, 1.50–4.30; p = 0.007).

Conclusions: Low Cl was associated with greater mortality and risk of CV events in pre-dialysis CKD patients. Low Cl may be an additive predictor of adverse outcomes in CKD.

Association of Serum Chloride Level with Mortality and Cardiovascular (CV) Death, and All-Cause Mortality in Chronic Kidney Disease (CKD)
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Background: Low urinary potassium excretion is associated with a higher risk of death in patients with CKD. While both of them share common pathophysiology, their relationship and combined effects on the relationship of urinary potassium with clinically important outcomes in CKD.

Methods: The association of urinary potassium with ESRD (defined as the need for dialysis or transplantation), CV mortality and all-cause mortality was evaluated in 812 participants enrolled in the MDRD Study. 24-hour urine potassium was measured at the first screening visit (before randomization) and in an average of 22 subsequent visits. Cox-proportional hazards models were adjusted for demographics, CV risk factors, GFR, proteinuria, randomization assignment, and urinary sodium. Interactions were performed with baseline GFR, proteinuria and urinary sodium as well as blood pressure randomization.

Results: Mean age at baseline was 52.1±12 years; 60% were men and 85% were white. Mean 24-hour urine potassium excretion was 61.2±22.7 mEq/day. Median follow up for ESRD and mortality were 6.1 (IQR 3.5, 11.7) and 19.2 (10.8, 20.6) years, respectively. Higher urinary potassium levels were associated with a lower hazard of CV mortality and all-cause mortality, but were not associated with ESRD (Table). No significant interactions were noted.

Conclusions: Higher urinary potassium is associated with lower risk of CV mortality and all-cause mortality. It remains to be determined whether higher dietary potassium intake results in improved outcomes in CKD.

Association Between Serum Bicarbonate and Heart Rate Variability in Hypertensive Adults: The Systolic Blood Pressure Intervention Trial
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Background: Reduced heart rate variability (HRV), a measure of cardiac autonomic dysfunctions, has been associated with lower serum [HCO3] in advanced CKD and ESRD. The purpose of this study is to determine if [HCO3] is associated with HRV in hypertensive adults with more preserved eGFR.

Methods: We examined a cross-sectional association between baseline [HCO3] and HRV in 9,265 participants from the Systolic Blood Pressure Intervention Trial (SPRINT). Three sequential 10-second 12-lead ECGs were calculated to use two time domain measures of HRV (standard deviation of all normal RR intervals [SDNN]) and root mean square of the sum of the differences in adjacent normal RR intervals [RMSSD]) from the individual durations between normal RR intervals. Linear regression models (adjusted for demographics, smoking, eGFR, ACR, CV, and SBP) were performed using [HCO3] as the independent variable and log-transformed SDNN and RMSSD as dependent variables. These models were repeated using [HCO3] as a categorical variable: < 22, 22-24.9, 25.0-29.9 (reference), and ≥ 30 mEq/L.

Results: Mean age was 67.9 (9.4) years, 28.4% had CKD, mean eGFR was 71.8 (20.6) mEq/min/1.73m², mean [HCO3] was 26.3 (2.6) mEq/L, mean SDNN was 21.2 (17.6), and 22.6A

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mean RMSSD was 25.2 (24.6). There was no significant association between [HCO₃⁻] and SDNN (beta coefficient 0.01, p=0.94) or RMSSD (beta coefficient 0.04, p=0.71) in adjusted linear regression models. Results were similar in models using [HCO₃⁻] as a categorical variable. There was no interaction of these relationships by CKD status (p=0.40 for SDNN and RMSSSD).

Conclusions: In this large study of trial participants with normal kidney function to moderate CKD, there was no association between [HCO₃⁻] and HRV. The association between lower [HCO₃⁻] and reduced HRV may only exist in more advanced CKD. Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, Veterans Administration Support, Private Foundation Support

TH-PO608

Serum Alkaline Phosphatase Negatively Affects Endothelium Dependent Vasodilatation in Naïve Hypertensive Patients

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Background: Tissue non-specific Alkaline Phosphatase (Alk-Phos) promotes arterial calcification in experimental models and, independently of other risk factors, high Alk-Phos is a powerful predictor of total and cardiovascular (CV) mortality in the general population and patients with heart diseases.

Methods: To investigate the relationship between Alk-Phos and atherosclerosis at an early disease stage we tested the association between serum Alk-Phos and the endothelium dependent maximal vasodilatative response to acetylcholine in 500 untrained individuals with uncomplicated essential hypertension without liver disease and with Alk-Phos levels well within the normal range of activity of this enzyme.

Results: The maximal response to acetylcholine was inversely related to Alk-Phos (r=−0.55, P<0.001) and this association was unmodified (r=−0.61, P<0.001) in adjusted analyses including demographic and classical risk factors, the BMI, the eGFR, serum phosphate and calcium as well as serum C reactive protein (CRP) and albuminuria. The steepness of the Ach-max/Alk-Phos relationship was substantially attenuated (P=0.001) in patients with serum phosphate above the median value than in those below the median (−5.0% per Alk-Phos Unit vs −10.0% per Alk-Phos Unit) and this interaction remained highly significant (P=0.001) in adjusted analyses.

Conclusions: Our findings offer a novel interpretable clue to explain the association between serum Alk-Phos and phosphate all cause and CV mortality in previous observational studies in the general population and in patients with heart disease and suggest that the endothelium may be an early target of raised Alk-Phos.

TH-PO609

Alkaline Phosphatase Lowering by Selective BET Inhibition, a Novel Mechanism for MACE Reduction in High Risk CVD, Diabetes and CKD Patients – A Post-Hoc Analysis of Phase 2b Studies with RVX-208

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Background: RVX-208 development is focused on reducing major adverse cardiovascular events (MACE) in high risk CVD, diabetes and CKD patients. RVX-208 is a first in class select BET inhibitor small molecule that interacts with the second ligand domain found in bromodomain and extra-terminal proteins (BET). It is characterized by reductions in alkaline phosphatase (ALP) and anti-inflammatory effects.

Methods: In the SUSTAIN and ASSURE phase 2b clinical studies, high risk CVD patients were treated with 200 mg b.i.d RVX-208 or placebo for up to 26 weeks duration. Patients with a history of diabetes were analysed as a subgroup.

Results: A significant reduction in MACE in all the RVX-208 treated patients (n=331) compared to placebo (n=168) was observed (p=0.02) as well as in those with diabetes (RVX-208 n=127/placebo n=65) (p=0.01). MACE included death, non-fatal myocardial infarct, stroke, hospital admittance for cardiac reasons. In all patients (n=499), RVX-208 treatment reduced MACE compared to placebo in all patients (p=0.0001) and especially in those with diabetes (p=0.0001). In addition, in the RVX-208 treated group, patients with diabetes who did not experience a MACE had greater reductions of ALP than those who experienced a MACE (−8.0 % UL vs. −3.0 % U/L, p<0.05).

Conclusions: In phase 2b studies in high risk CVD and diabetes patients treated with RVX-208, a select BET-inhibitor, baseline ALP levels were significantly different between the MACE and non-MACE patients. Furthermore, RVX-208 significantly lowered serum ALP. A prospective phase 3 study currently planned, called BETonMACE, will need to further explore RVX-208’s potential in reducing MACE in high risk CVD, diabetes and CKD patients.

TH-PO610

Serum Electrolyte Levels and Risk of Sudden Death in Patients with Moderate CKD

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Background: Abnormalities in the serum potassium(K), calcium(Ca) and magnesium(Mg) are known to disturb cardiac conduction and are rare causes of sudden death (SD). However, CKD patients are at higher risk for both electrolyte disturbances and SD; the extent to which these processes are related has not been well described. We examined the role of disordered serum electrolyte levels in SD risk among a large cohort of patients with coronary artery disease (CAD) and moderate CKD.

Methods: Retrospective longitudinal cohort study of 38,576 patients undergoing cardiac catheterization at a single institution from 1989 to 2014. Patients with significant CAD were included. Baseline laboratory measures were extracted within 60 days of the time of cardiac catheterization. GFR was estimated using the CKD-EPI equation. The main outcome measures were all-cause death and SD, which was determined by chart review, query of the national death index and information from surviving family members. Cox proportional hazards models were used to determine associations with predictors.

Results: 28% of patients had stage 3-4 CKD (GFR<15). This group had a higher risk of death (HR=2.53, P<0.001), SD (HR 1.80, P<0.001), hyperkalemia (RR=3.5), hypercalcemia (RR=1.7), and hyper- and hypomagnesemia (RR=1.4, RR=1.2) compared to patients without CKD. Elevated K, Ca, and Mg were associated with increased risk of all-cause death among patients with moderate CKD, but not with SD. Hyperkalemia was associated with SD in the absence of CKD.

TH-PO611

Circulating ACE2 as a Biomarker of Chronic Kidney Disease Progression

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Background: In a CKD population without previous history of CV disease, ACE2 activity from human EDTA-plasma samples directly correlated with the classical CV risk factors namely older age, diabetes and male gender. Objective: To study circulating ACE2 as a biomarker of renal progression and atheromatisous disease(AD) in CKD stages 3-5(CKD-3-5) patients.

Methods: Prospective study from 930 CKD3-5 patients without history of CV disease. Circulating ACE2 activity was analyzed. We evaluated renal function(serum creatinine, glomerular filtrate MDRD-4), carotid/femoral echography, mortality, renal replacement therapy and AD at baseline and 24 months. ACE2 activity was divided in tertiles(267.62,74.65-46.34<46.35RFU/μl,h). Univariate and multivariate(dependent variable ACE2 natural logarithm) were performed.

Results: Patients with ACE2 in the higher tertile doubled creatinine more frequently(61% higher tertile vs 28% lowest tertile,p=0.013). Patients that showed plasma appearances at 24month had a higher ACE2 activity in comparison to patients without(42.0±2.4 vs 34.2±1.2,p<0.009). Patients that presented plasma at baseline had higher ACE2 than those that have had never (48.2±1.7 vs 34.2±1.2,p<0.001). Femoral plaques: ACE2 increased in patients with baseline plaques(48.9±1.9) or with the novo plaques at 24month(46.6±3.2) respect to patients without plaques(35.9±1.5,p=0.002<p=0.001).
Carotid plaques: ACE2 increased in patients with baseline plaques respect to patients without plaques (49.0±2.1 vs 38.5±2.9 mm, p<0.001). Romel J. Garcia et al observed an ACE2 increase as compared to AD0-1 at 24months (47.6±1.6 vs 55.7±1.6, p=0.001). Multivariate analysis demonstrated circulating ACE2 in CKD-5 as a predictor of doubling creatinine (β=0.069, p=0.034), de novo appearance of femoral plaques at 24months (β=0.087, p=0.016) and presence of femoral plaques at basal and 24months (β=0.199, p<0.001).

Conclusions: In CKD-5 patients without history of CVD, circulating ACE2 may become a biomarker of CKD progression and AD appearance at 24months of follow-up.

TH-PO612
Blood Pressure and Risk of Cardiovascular Events at Advanced CKD: The CRIC Study
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Background: The association of SBP with cardiovascular events (CVD) among patients with advanced CKD is not known and may be an important modifiable risk factor.

Methods: Participants of the Chronic Renal Insufficiency Cohort (CRIC) Study with advanced CKD (defined as eGFR<30 ml/min/1.73 m²) had SBP measured by standardized methods at yearly in-person visits. We studied the association of SBP with time to physician- adjudicated atherosclerotic CVD (defined as myocardial infarction, stroke, peripheral vascular disease) and heart failure (HF) using Cox models.

Results: Among 1,795 participants with eGFR<30 ml/min/1.73 m², mean age was 60±11 years, 46% were women and 46% were African American. Mean eGFR was 26±5 ml/min/1.73 m² and mean BP was 131±24/69±13 mm Hg. In models adjusted for demographics, clinical site of care, use index, body mass index, aspirin use and number of classes of anti-hypertensive medications, higher SBP was associated with greater risk of atherosclerotic disease and HF. Results were similar when participants with prevalent atherosclerotic CVD and HF were excluded.

Conclusions: Among this diverse multi-center cohort of advanced CKD patients, higher SBP was associated with greater risk of atherosclerotic CVD and HF. This is similar to what has been reported in the general population and suggests that treatment guidelines developed for non-CKD populations can be extended to those with eGFR<30 ml/min/1.73 m². Funding: NIDDK Support TH-PO613
CKD Does Not Impact Risk and Appropriateness of Device Therapies in Adults with Primary Prevention Implantable Cardioverter Defibrillators
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Background: Implantable cardioverter defibrillators (ICD) reduce the risk of sudden cardiac death (SCD). CKD patients are at high-risk for SCD, but whether CKD is associated with greater risk of delivered shocks/anti-tachycardia pacing (ATP) therapies among those with an ICD remains unclear.

Methods: We studied participants in the Cardiovascular Research Network Longitudinal Study of Implantable Cardioverter Defibrillators (CRNLRN-ICD). CKD was defined as eGFR<60 ml/min/1.73 m² at the time of ICD implantation. Outcomes included number and type of shock/ATP (inappropriate or appropriate, determined by physician adjudication) within 3 years after implant. We evaluated the associations between kidney function and time to first device therapy, burden of device therapy, and inappropriate vs. appropriate device therapy.

Results: Among 2,261 participants, 49.3% had CKD at the time of ICD implant. During mean follow-up of 2.3±0.9 years, 9.8% and 18.5% of participants had at least 1 inappropriate and appropriate shock/ATP, respectively. CKD was not associated with time to first shock/ATP of any type.

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

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Results: Urinary L-FABP levels were significantly higher at 12h and 24h after CCP compared to before CCP only in the patients with occurrence of cardiovascular events. The difference in urinary L-FABP levels (AL-FABP) between before and at 24h after CCP was a risk factor for the occurrence of cardiovascular events.

Conclusions: Measurement of urinary L-FABP before and at 24h after CCP in patients with mild to moderate renal dysfunction may be an important indicator for risk stratification of onset of cardiovascular events in clinical practice.

TH-PO616
Suggested Role of Adiponectin in Reciprocal Relationships Between Pulse Wave Velocity and Bone Mineral Density in CKD Patients
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Background: Although adiponectin plays a beneficial role in the regulation of insulin action and atherosclerosis in various populations, the role of adiponectin remains a controversy in patients with chronic kidney disease (CKD).

Methods: A total of 1310 patients (male/female = 794/516) with CKD stage 1 to 5 who enrolled in the Korean cohort study for outcome in patients with Chronic Kidney Disease (KNOT-CKD) from June 2011 to December 2013. We measured serum total adiponectin and examined the association between adiponectin, bone mineral density (BMD) measured by dual energy X-ray absorptiometry, and pulse wave velocity (PWV) calculated by mean value of both brachial-ankle (ba) PWV.

Results: Increasing quintiles of serum adiponectin levels were associated with female gender; lower body mass indices, estimated glomerular filtration rate, triglycerides, BMD and albumin; higher urinary protein creatinine ratios, PWV, phosphorous, intact PTB T-scores at LS spine (LS), total hip (TH), and femur neck (FN) inversely correlated with ba PWV (LS: r = -0.075, P = 0.010; TH: r = -0.097, P = 0.001; FN: r = -0.111, P <0.001) in male CKD, however, this association was not significant for female CKD (LS: r = 0.019, P = 0.607; TH: r = -0.046, P = 0.273; FN: r = -0.043, P = 0.277). Adiponectin was inversely associated with T-scores at all sites for both male and female CKD patients (LS: r = -0.133, P <0.001; TH: r = -0.135, P <0.001; FN: r = -0.099, P <0.001). Adiponectin was positively associated with ba PWV for male CKD (r = 0.074, P = 0.016), but not for female CKD (r = 0.021, P = 0.567).

Conclusions: Adiponectin, BMD, and PWV were associated with each other in male CKD patients. The findings suggested that adiponectin have the role in reciprocal relationships between PWV and BMD in not female but male CKD patients.

TH-PO617
The Association of High-Sensitivity Troponin I and N-Terminal Pro-Brain Natriuretic Peptide with Plasma Galectin-3 in Chronic Kidney Disease Patients
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Background: Plasma galectin-3 (pGa3), a beta-galactoside-binding lectin, regulates inflammation and fibrosis. N-terminal pro-BNP (NT-proBNP), high sensitivity Troponin I (hsTnI), and pGa3 concentrations are elevated in chronic kidney disease (CKD) patients with heart failure. Between hsTnI and NT-proBNP, it is unknown which has a better association with pGa3. We assessed the relationship of NT-proBNP and hsTnI with pGa3 in Asian CKD patients and healthy controls.

Methods: We retrieved prospectively collected frozen plasma samples from 161 stable CKD patients and 105 healthy controls. NT-proBNP, hsTnI and pGa3 were assayed. By univariate analysis, we assessed pGa3 for associations with age, gender, ethnicity, systolic (SBP) and diastolic (DBP) blood pressures (mmHg); height, weight, body mass index (BMI, kg/m²), previously diagnosed CKD, diabetes, hypertension, coronary artery disease, estimated glomerular filtration rate (eGFR, mL/min/1.73m²); C-reactive protein (CRP), beta-trace protein (BTP), 24-hr urine protein (TUP), serum albumin, uric acid and cystatin C. We created 2 models predicting pGa3 using multiple linear regression by backwards elimination to include hsTnI and NT-proBNP. Akaike Information Criterion (AIC) was used for comparison. Significance was taken at P<0.05.

Results: Population averages: Age=52.7 ±5.3 years; BMI=26.9±5.2; eGFR=75 (IQR:36–102); pGa3=19–14 A (IQR:14–19.29 [ng/mL]; NT-proBNP=27 (IQR:11–71) pg/mL; hsTnI=3.1 (IQR:1.66-6.0) ng/L; Age, SBP, DBP, height, BMI, previous disease diagnoses, Ln CRP, Ln BTP, Ln TUP, Ln albumin, Ln uric acid, Ln creatinine, Ln cystatin C, Ln eGFR, Ln hsTnI, Ln NT-proBNP were associated with pGa3. The best model included Ln hsTnI, diagnosis of CKD, Ln albumin, Ln cystatin C, Ln uric acid, and height (AIC: 83.3).

Conclusions: NT-proBNP and hsTnI are associated with pGa3 in CKD patients. The model including hsTnI is a better predictor of pGa3.

TH-PO618
ACE/ARB Use in Patients with Severe Kidney Disease and Heart Failure Is Not Associated with Worsening Renal Function, Acute Kidney Injury and Hyperkalaemia
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Background: The role of ACE/ARB in patients with severe kidney disease and heart failure needs clarification. This includes patients with preserved systolic function. ACE/ARB is associated with better cardiac prognosis but there is a risk of worsening renal function, especially in older and frail people.

Methods: We undertook a retrospective analysis of patients who were diagnosed with heart failure in primary care with BNP testing and Echocardiogram. Our centre serves a population of 350,000, details of hospital admissions, drug information and blood results were obtained from our electronic patient records. A BNP>450 and clinical features of heart failure is the criteria used by general practitioners for diagnosis, an eGFR < 30 was used to identify patients with severe kidney disease. We looked at rates of worsening kidney function, AKI and hyperkalaemia.

Results: 159 patients with raised BNP and eGFR <30 were identified on electronic search from 01/12 to 01/14. Mean age was 81.7year (range 41-96), M:F=79/80. Average follow-up was 17 months. 27 patients with transient rise in serum creatinine (Cr) or dialysis were excluded. 87 of the remaining 132 patients had echocardiograms; 13 bad ejection fraction (EF) <40%, 7 EF had 40-50% and 67 had preserved ejection fraction (>50%). Comparing with EF<50% vs. EF>50%; mortality was 55% (11/20) vs. 10% (7/67), mean BNP was 12.037 ± 3645, mean Cr was 235 ± 201 and 1/20 vs. 1.67 reached ESRD, respectively. 84 patients had drug information available.

Conclusions: Impaired EF was associated with worse mortality. ACE/ARB use was not associated with more adverse events with regards to episodes of AKI, worsening eGFR and mean potassium. We feel that ACE/ARB treatment for heart failure should be maintained even in the setting of severe renal disease to reduce cardiovascular mortality.

TH-PO619
Protein-Fiber Intake Ratio and Cardiovascular Risk in Older Men with Chronic Kidney Disease
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Background: The elevated cardiovascular (CVD) risk in chronic kidney disease (CKD) may be partially alleviated through a healthy diet. While protein intake has been linked to CVD events in CKD patients, dietary fiber may be cardioprotective. Nutrients are not consumed in isolation; we hypothesize that CVD incidence associates with dietary patterns aligned with excess of dietary protein relative to fiber.

Methods: Prospective cohort study from Uppsala Longitudinal Study of Adult Men of 390 elderly men aged 70–71 years with manifest CKD (eGFR<60 mL/min/1.73m² and albuminuria>20 µg/min) and no clinical history of CVD. Protein and fiber intake and its ratio, were calculated from 7-day dietary records. Cardiovascular structure and function was estimated from echocardiographic examination. Fatal and non-fatal cardiovascular events were registered prospectively during median follow-up of 9.1 (IQR 4.5-10.7) years. Results: The median of protein:fiber ratio was 4.0 (3.5-4.7); dietary protein was 66.7 (60.7-71.1) and dietary fiber was 16.6 (14.5-19.1) grams/day. Protein-fiber intake ratio, rather than separate components, remained strongly associated to left ventricular cardiovascular structure and diastolic function after multivariable adjustment. During follow-up, 164 first-time CVD events occurred (incidence rate 54.5/1,000 py). Protein-fiber intake ratio was an independent risk factor for CVD incidence [adjusted HR per SD increase (95% confidence interval, CI) 1.29 (1.85, 1.57)]. Although in opposing directions, neither dietary protein [1.10 (0.92, 1.33)] nor dietary fiber [0.93 (0.68, 1.20)] associated with this outcome.

Conclusions: An excess of dietary protein relative to fiber intake associated with cardiovascular structural dysfunction and with incidence of cardiovascular events in a homogeneous population of older men with CKD.

Funding: Pleazent nutrition, Company Support - Baxter Healthcare Corporation
Impact of Percutaneous Transluminal Renal Angioplasty (PTRA) on Long-Term Prognosis in Patients with Severe Atherosclerotic Renal Artery Stenosis (RAS) (TH-PO620)

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Background: Carotid echo indexes [intima-media thickness (IMT)] are commonly used surrogate markers for cardiovascular disease. However, the impacts of chronic kidney disease (CKD) on changes in IMT are unclear. We examined associations between CKD and IMT in participants with and without type 2 diabetes through longitudinal analysis.

Methods: In total, 424 subjects were enrolled in this study. IMT was measured as per carotid echo indexes. Relationships between IMT and risk factors were analyzed using multiple linear regression analysis, in which we defined IMT as the dependent variable and atherosclerosis-related factors (age, sex, systolic pressure, total cholesterol, body mass index, estimated glomerular filtration rate (eGFR), uric acid, smoking index, number of antihypertensive drugs, statin use, urinary protein levels, past cardiovascular event, glycated hemoglobin, and diabetes duration) as independent variables.

Results: The study population was composed of 70.3 % male subjects. Participants with diabetes accounted for 64.4 % of the total population. The mean follow-up duration was 2.2 ± 1.5 years. Alterations in IMT tended to be associated with systolic blood pressure (+10 mmHg) (β = -0.0084, p = 0.09) and eGFR (+10 mL/min/1.73 m²) (β = -0.0049, p = 0.06) in all participants. In participants without diabetes, alterations in IMT were associated with eGFR (+10 mL/min/1.73 m²) (β = -0.0104, p = 0.03) and tended to be associated with systolic blood pressure (+10 mmHg) (β = -0.0094, p = 0.06). No significant relationships were found in participants with diabetes.

Conclusions: Low eGFR was associated with progression of carotid thickness independent of common cardiovascular risk factors in non-diabetic participants.

The Number of Arterial Territories with Atheroma Plaque Predicts Cardiovascular Event-Free Survival in Chronic Kidney Disease. Analysis of the NEFRON Study after 36 Months of Follow-up (TH-PO623)

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Background: Renal function after Left Ventricular Assist Device (LVAD) placement predicts survival, irrespective of baseline Creatinine Clearance (CrCl). Continuous flow devices have been reported to have better renal outcomes than pulsatile devices. We compared the change in renal function in recipients of both continuous and pulsatile-flow devices at various time points following LVAD placement.

Methods: We searched MEDLINE for all publications with prospective cohorts and trials of LVAD recipients. Studies documenting renal function at various time points after LVAD placement were included. CrCl at suitable time points after LVAD placement was pooled using an inverse of variance method and analyzed using random-effects models. Changes in CrCl after continuous and pulsatile flow LVAD placement was compared for cohorts with at least 10 subjects.

Results: 33 studies with 23 cohorts including continuous flow devices (n=1262) and 18 including pulsatile flow (n = 678) were included. Baseline CrCl for continuous and pulsatile-device recipients were similar. Continuous flow LVAD recipients showed higher CrCl at 1 month, compared to baseline and pulsatile-flow device recipients. There was a non-significant trend towards improved renal function after LVAD placement (Figure).

Conclusions: In this pooled analysis, we noted a pattern of an initial improvement in renal function followed by later decline with continuous-flow devices. While CrCl appears to improve after LVAD placement, the long-term effect remains unclear. Further studies focused on renal function and risk factors are needed to better understand the phenomenon in LVAD recipients.
The COX regression analysis shows that the factors significantly predicting event-free survival time are the number of territories with plaque, being on dialysis, smoking, diabetes, high levels of phosphorus, low albumin and 25OH vitamin D as well as having 1,25(OH)1 vitamin D below 14 pg/ml.

Conclusions: The severity of arterial atherosclerosis estimated by ultrasound predicts the time to first event from CVE in CKD. Arterial ultrasound is a useful tool to predict cardiovascular risk in CKD patients.

Funding: Pharmaceutical Company Support - AbbVie, Government Support - Non-U.S.

TH-PO624

The Effects of Diuretics on the Progression of CKD and Incidence of Cardiovascular Events: Results from the CKD-ROUTE Study – A Prospective Cohort Study of Newly Visiting CKD Patients in Japan
Shigetaro Naito, Soichi Iimori, Eisei Sohara, Tomokazu Okado, Sei Sasaki, Shinichi Uchida, Tatemitsu Rai. Dept of Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Anti-hypertensive agents are requisite for control of blood pressure in CKD patients. Although diuretics seem to be associated with progression of CKD or development of cardiovascular (CV) events, this hypothesis has not been adequately elucidated. To evaluate the association of anti-hypertensive agents prescription and outcomes, we analyzed a cohort study of newly visiting pre-dialysis CKD patients in Japan.

Methods: We recruited 937 newly visiting CKD patients followed for the next 3 years. At 6 months visit, use of RAAS inhibitors (RAAIs), calcium channel blockers (CCBs), and diuretics was assessed, and the association between these medications and outcomes was evaluated. The outcomes were composite kidney endpoint of ESKD or 50% decline of estimated GFR, death, or first CV event during the 3-year period after first visit to nephrologists. We used multivariate Cox proportional hazards regression adjusted by age, sex, albumin, hemoglobin, eGFR, systolic blood pressure, presence of proteinuria and diabetes, and past history of CV events.

Results: The mean age was 67 years (57-71.7%) and 70.2% was male, mean eGFR was 33.7 ml/min/1.73m2, and mean systolic blood pressure was 139 mmHg. During the follow-up period of 3 years, 114 CV events occurred, 24 patients died of CV events, and 220 patients reached the composite kidney endpoint. In multivariable analysis, risk of CV event death and CV related death during the 3-year period was higher in the patients using diuretics at six months visit (adjusted hazard ratio 1.55 [95%CI 1.23-2.32]) for CV events. 3.09 [95%CI 1.19-8.02] for CV related death.) The patients taking both diuretics and RAAs had comparable risk of CV events with those taking diuretics only (adjusted HR 1.09 [95%CI 0.84-2.3]) However, none of the three kinds of anti-hypertensive agents had associations with CKD progression.

Conclusions: CKD patients using diuretics were more likely to have CV events and CV related death. RAAs might contribute to reduce the risk of CV events by diuretics.

TH-PO625

Rapid Increase in Aortic Stiffness in Patients on Hemodialysis and Peritoneal Dialysis Compared with Non-Dialysis-Dependent Chronic Kidney Disease Patients: A Longitudinal Study Using MRI-Based Pulse Wave Velocity
Kazuhiko Tsuruya, Hitoko Yoshida, Takanari Kitazono. 1 Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan, 2 Dept of Medicine and Clinical Sciences, Graduate School of Medical Sciences, Kyushu Univ, Japan.

Background: Pulse wave velocity (PWV) is a well-established technique for obtaining a measure of arterial stiffness that has the potential to provide information on early atherosclerotic disease. MRI-based PWV measurements have been well validated in comparison with invasive pressure recordings (Grootenhuis et al. J Magn Reson Imaging, 2009). To date, very few studies have reported on MRI-based PWV in patients with chronic kidney disease (CKD), especially in patients with end-stage kidney disease on hemodialysis (HD) and peritoneal dialysis (PD). In the present study, we examined the annual changes in MRI-based PWV from baseline to 2 years and compared them among non-dialysis-dependent CKD (ND), HD, and PD patients.

Methods: A total of 172 CKD patients (ND, n=89; HD, n=47; PD, n=36) were recruited and underwent cardiovascular MRI at baseline and 2 years after using cine and phase contrast sequences, the cross-sectional area for distensibility and average blood flow were measured. Using cine and phase contrast sequences, the cross-sectional area for distensibility and average blood flow were measured. Each patient underwent Doppler echocardiographic evaluation before entry. A value of systolic pressure drop ≈ 10mmHg was defined as PH. Patients were divided into 3 groups: No risk group (with neither PH nor HVC, n=140), One Risk Factor Group (with PH or HVC, n=121) and Two Risk Factors Groups (with PH and HVC, n=43). The end points were all-cause mortality, CV mortality and CV events.

Results: A total of 63 (20.7%) patients died during follow-up from all causes; 18 (12.9%) in Group 1, 29 (24.0%) in Group 2, and 16(37.2) in Group 3. 36 died of CV events. PH was defined as the presence of bright echoes of >1mm on one or more cusps of the aortic valve, mitral valve or mitral annulus. Patients were divided into 3 groups: No risk group (with neither PH nor HVC, n=140), One Risk Factor Group (with PH or HVC, n=121) and Two Risk Factors Groups (with PH and HVC, n=43). The end points were all-cause mortality, CV mortality and CV events.

Conclusions: PH in combination with HVC predicts worse outcome than those with either PH or HVC in MHD patients. Echocardiography can easily identify both PH and HVC, and is helpful to stratify risk in this population.

Funding: Government Support - Non-U.S.

TH-PO626

The Recent ADQI Proposal for a Functional Classification System of Heart Failure in Patients with End-Stage Renal Disease Will Substantially Overdiagnose Cardiac Disease Among Chronic Kidney Disease Patients
Kathrin Untersteller, Francesca Mallamaci, Danilo Fleser, Gerard M. London, Carmine Zoccali, Gunnar H. Heine. 1 Saarland Univ Medical Center, Homburg, Germany, 2 CNR-Inst of Clinical Physiology, Reggio Calabria, Italy, 3 Manhès Hospital, Fleury-Mérogis, France.

Background: The Acute Dialysis Quality Initiative (ADQI) XI Workgroup has recently proposed a novel classification for HD stages in advanced CKD, which is based upon a broad spectrum of echocardiographic criteria. We hypothesize that these criteria will substantially overdiagnose HD across the whole spectrum of CKD, as echocardiographic changes are a very frequent finding even among patients with mild to moderate CKD.

Methods: Within the ongoing CARE FOR HOME study we echocardiographically examined 317 patients in GFR categories G2 – G4, following American Society of Echocardiography guidelines. According to ADQI criteria, HD is defined by moderate to severe changes in any of the following categories: valve function, left atrial volume index (LAVI), left ventricular (LV) or right ventricular systolic function, LV mass index, LV diastolic function, LV diameter, or regional LV wall contractility. Patients were followed for a mean of 3.6 ± 1.5 years until the first admission for decompensated HF.

Results: Among the 317 CKD patients, 209 (66%) fulfilled ADQI criteria. HD was detected more often in advanced CKD (G3b/G4: 114/146, 78%) than in milder CKD (G2/G3a: 95/171, 56%). An increased LAVI (158/317, 50%) and diastolic dysfunction (101/317, 32%) were the most frequent findings within the subcategories of echocardiographic changes. Among all 209 patients with ADQI HD, only 24 patients (11%) suffered decompensated HF during follow-up. The annual change in event-free four-year survival was 89%.

Conclusions: The proposed ADQI criteria will substantially overdiagnose HD among patients with mild to moderate CKD. We suggest defining more conservative echocardiographic criteria for HD prior to introduction of this new classification in daily clinical practice. The validity and reliability of such revised criteria should subsequently be analyzed across the whole spectrum of CKD.

TH-PO627

Prognostic Value of Pulmonary Hypertension in Combination with Heart Valvular Calcification on Cardiovascular Outcome in Maintenance Hemodialysis Patients
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Background: Our previous study had revealed pulmonary hypertension (PH) as a predictor of all-cause mortality, cardiovascular mortality and new onset cardiovascular events in maintenance hemodialysis (MHD) patients. We hypothesize that patients complicated with both PH and heart valvular calcification (HVC) may take higher cardiovascular risk than those suffer from PH or HVC only.

Methods: 304 Chinese MHD patients were enrolled and followed up for 24 months. Each patient underwent Doppler echocardiographic evaluation before entry. A value of Systolic PAP (SPAP) ≈ 35 mmHg was defined as PH. HVC was defined as the presence of bright echoes of >1mm on one or more cusps of the aortic valve, mitral valve or mitral annulus. Patients were divided into 3 groups: No risk group (with neither PH nor HVC, n=140), One Risk Factor Group (with PH or HVC, n=121) and Two Risk Factors Group (with PH and HVC, n=43). The end points were all-cause mortality, CV mortality and CV events.

Results: A total of 63 (20.7%) patients died during follow-up from all causes; 18 (12.9%) in Group 1, 29 (24.0%) in Group 2, and 16(37.2) in Group 3. 36 died of CV events.

Conclusions: PH in combination with HVC predicts worse outcome than those with either PH or HVC in MHD patients. Echocardiography can easily identify both PH and HVC, and is helpful to stratify risk in this population.

Funding: Government Support - Non-U.S.

TH-PO628

Survival of ESRD Patients Diagnosed with Idiopathic Heart Failure prior to Dialysis
Frances M. Yang, 1 Chen chun chen, 2 Shuang Li, 1 Adam E. Berman, 2 Lu Y. Huber, 2 Matthew J. Diamond, 2 Mufaddal F. Kheda, 2 Jasmin Patel, 2 N. Stanton Nanoam, 1 Biostatistics, Georgia Regents Univ, Augusta, GA; 2 Medicine, Georgia Regents Univ, Augusta, GA; 3 Medicine, Norwood VAMC, Augusta, GA.

Background: Cardio-renal syndrome type 2 (CRS-2) is defined as chronic abnormalities in heart function leading to kidney injury or dysfunction, and may occur in patients admitted for heart failure (HF) (Ronco, Eur Hrt J 31:703, 2010). Idiopathic HF (HF) may clinically manifest as CRS-2 and progress to ESRD. The prognosis
with all-cause mortality. Sleep apnea, as measured by AHI was not associated with increased mortality in the general population. In the dialysis population, limited evidence suggests an association of nocturnal hypoxemia with mortality. We sought to determine the association of sleep apnea and mortality in patients with advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

Methods: 180 patients (87 CKD stage 4-5, 93 ESKD), underwent 1 night home polysomnography. Sleep apnea severity was measured as number of apneas and hypopneas per hour (apnea-hypopnea index, AHI). Information on patients’ demographics, comorbidities and laboratory values was obtained from patient interviews and chart review. Mortality data was obtained from National Death Index. Chi-square and ANOVA were used to test between group differences and Cox proportional hazard model was employed to test association with mortality.

Results: 71% of the patients had sleep apnea (AHI≥5) and 23% had severe sleep apnea (AHI>30). There was no difference in age, race, hypertension, body mass index, smoking status, renal function status (CKD vs ESKD), depression, hemoglobin or albumin levels among patients with no or varying severity of sleep apnea. Males were more likely to have severe sleep apnea. In both males and females, sleep apnea severity increased with age. Over a mean (SD) follow-up period of 9.0 (3.7) years, there were a total of 31 deaths and 57 patients received kidney transplant. We found no association between sleep apnea severity and all-cause mortality. However, in unadjusted analysis, more percentage of time with SpO2 < 90% was associated with higher mortality [HR 1.03 (1.01-1.06), p <0.001].

Conclusions: TH-PO629
Association of Sleep Apnea with Mortality in Chronic and End Stage Kidney Disease Patients
Manisha Jhamb,1 Herbert T. Davis,2 Mark L. Unruh,1 1Univ of Pittsburgh; 2Univ of New Mexico.

Background: Presence of sleep apnea and its severity has been associated with increased mortality in the general population. In the dialysis population, limited evidence suggests an association of nocturnal hypoxemia with mortality. We sought to determine the association of sleep apnea and mortality in patients with advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

Conclusions: Among hospital admissions for heart failure, patients with severe kidney failure had low haemoglobin, high potassium, high BNP; were less often on ACEi/ARB and diuretics. Presence of severe kidney failure was an independent predictor of mortality (p<0.01). In-hospital mortality was 6% in patients with eGFR<60 ml/min, 8% with moderate kidney failure and 22% with severe kidney failure. Adjusted for age, sex, race, smoking status, comorbidities and clinical conditions potentially biasing PWV’s (e.g. morbid obesity). Four PWV parameters were assessed: carotid-femoral (cf, the indicator of central arterial stiffness), heart- and brachial-ankle (ba and ab, respectively, reflecting both central and peripheral stiffness), and femoral-ankle (fa, the indicator of peripheral arterial stiffness). Multiple logistic regression was used to quantify the associations of eGFR and albuminuria with elevated PWV (highest 25% value) at each segment.

Results: There were 57.9% of women and 23.2% of blacks. After accounting for potential confounders, cPWV was the only PWV parameter consistently and monotonically associated with both low eGFR and high ACR (Table). baPWV also demonstrated positive association with all high ACR categories. baPWV and faPWV were only significantly associated with high normal ACR (10-29 mg/g). None of haPWV, baPWV, and faPWV was significantly associated with low eGFR.

Conclusions: Both low eGFR and high ACR were independently associated with central arterial stiffness, with more robust results for ACR than for eGFR. In contrast, peripheral arterial stiffness tended to relate to high normal ACR but not necessarily to clinical ACR categories or low eGFR. These results suggest central arterial stiffness as a pathophysiologic link in the cardiorenal interaction and potentially unique pathophysiology of elevated ACR within normal range.

Impact of Kidney Failure on Management and Outcome of Patients Admitted with Heart Failure
Debasish Banerjee, Juan Carlos Kaski, Lisa J. Anderson. Renal and Transplantation Unit, St. George’s Hospital, United Kingdom.

Background: Data from epidemiological studies and intervention trials suggest poor prognosis in heart failure patients with kidney disease. However no study has investigated the impact of severe kidney failure on management and outcome of in-hospital heart failure patients.

Methods: We analysed data on clinical, laboratory, management and in-hospital mortality on 990 patients admitted between 01/03/2013 and 17/03/2013.

Results: Severe kidney failure (eGFR<30 ml/min/1.73m²) was present in 19% of patients and moderate kidney failure (eGFR 30-60 ml/min/1.73m²) was present in 43%. Patients with severe kidney failure, compared to the rest were older (79±11 vs 75±13 years; p<0.001), with lower haemoglobin (10.5±1.9 vs 12.1±1.8 g/dL; p<0.001), higher potassium (4.8±1.9 vs 4.2±0.6 mmol/L; P<0.05) and higher NT-pro BNP (1971±1291 vs9240±9577; p<0.001). Diuretics use in severe kidney failure patients was less (85% vs. 96%, p<0.005) however β-blocker use was similar (74% vs. 75%). Furosemide dose was higher in severe kidney failure patient (101±62 vs 79±43 mg; p<0.001) but dose of bumetanide was similar (3.9±2.3 vs. 4.1±1.9 mg; p=0.5). In the presence of echocardiographic LV dysfunction severe kidney failure patients were less likely to be on ACEi or ARB (24% vs. 74%; p<0.001). 98 patients who died during admission were older (78±10 vs 76±13 years; p<0.05), with lower haemoglobin (11.1±2.2 vs. 11.8±1.9 g/dL; p=0.01), higher creatinine (191±123 vs 135±95 μmol/L; p<0.001), higher NT-pro BNP (16536±12727 vs 10174±10346; p=0.001) and higher potassium (4.7±0.9 vs 4.2±0.6 mmol/L; p<0.001).

Conclusions: Among hospital admissions for heart failure, patients with severe kidney failure had low haemoglobin, high potassium, high BNP, were less often on ACEi/ARB and diuretics; suffered higher in-hospital mortality. Severe kidney failure is common, adversely affects management and outcomes in admitted heart failure patients.
Pulse Wave Velocity in Children with Chronic Kidney Disease

**Background:** Pulse wave velocity (PWV) is a measure of arterial stiffness associated with CV events in the general population and adults with CKD. However, few data exist regarding PWV in children with CKD. We compared observed PWV to normative data in healthy children and examined risk factors associated with elevated PWV in children enrolled in the CKiD cohort study.

**Methods:** PWV was assessed via carotid/femoral tonometry using the SphygmoCor device (AtCor, Australia). PWV Z-score for height/gender was calculated from and compared to published pediatric norms (Reus et al., 2010). Multivariate linear regression was used to assess the relationship between PWV and level of proteinuria (UP/C) adjusted for age, gender, race, height, waist circumference, mean arterial pressure (MAP), and GFR.

**Results:** 249 PWV studies were performed on 90 participants. 63% were male, 20% African American, 49% had glomerular CKD, 9% UP/C >2mg/mg; median age was 16 years, median MAP was 82mmHg, and median GFR was 67 ml/min. Average PWV was 5.1±0.9 m/s, Z-score -0.01(±2). As expected, PWV was significantly associated with age and MAP in multivariate analysis (Table 1). Additionally, the point estimate for UP/C was large but non-significant.

**Conclusions:** In this pediatric cohort with mild kidney dysfunction, arterial stiffness was comparable to that of normal children. Data collection is ongoing to further assess the effects of BP and proteinuria on arterial stiffness in children with CKD.

**Table 1.** PWV multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate ± SE</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>0.09 ± 0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Male</td>
<td>-0.05 ± 0.17</td>
<td>0.07</td>
</tr>
<tr>
<td>African American</td>
<td>0.12 ± 0.20</td>
<td>0.55</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>-0.01 ± 0.01</td>
<td>0.41</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.00 ± 0.01</td>
<td>0.47</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.03 ± 0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>ioGFR (per 10 mmH/m²)</td>
<td>-0.02 ± 0.04</td>
<td>0.56</td>
</tr>
<tr>
<td>UP/C (mg/mg)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>&lt;0.5 Ref.</td>
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<tr>
<td>0.3-2.0</td>
<td>0.03 ± 0.22</td>
<td>0.88</td>
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<tr>
<td>&gt;2.0</td>
<td>0.34 ± 0.32</td>
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**Funding:** NIDDK Support, Other NIH Support - NICHD, NHLBI

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**TH-P063**

The Cardiovascular Comorbidity in Chronic Children with Kidney Disease (4C) Study: Baseline Data of a Multicentric Prospective Observational Study in Children

**Background:** The Cardiovascular Comorbidity in Children with CKD (4C) Study is a multicentric, prospective, observational study in children with CKD aged 6 to 17 years, initial glomerular filtration rate 10-60 ml/min/1.73m². The prevalence, degree and progression of cardiovascular comorbidity and its association with CKD progression is explored through longitudinal follow-up.

**Methods:** The methodology and function of the heart and large arteries is monitored by non-invasive methods and compared with age-matched healthy controls.

**Results:** A total of 705 patients were enrolled in 55 participating centers from 12 European countries. At baseline examination, 30% of children were hypertensive (ambulatory blood pressure monitoring), 40% had left ventricular hypertrophy (echocardiography), 40% showed an increased intima-media thickness of the carotid artery (cIMT, ultrasound), and 23% an increase in aortic pulse-wave velocity (PWV; oscilometry). By multivariate analysis, systolic blood pressure and serum levels of 25-hydroxyvitamin D, parathyroid hormone, and serum calcium- and phosphorus levels showed significant associations with age-corrected IMT and PWV, respectively.

**Conclusions:** Children aged 6-17 years with CKD stage 3-5 have significant subclinical CV disease at initial examination, subclinical endpoints of CV disease were associated with systolic blood pressure and disturbances of mineral metabolism.

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**TH-P064**

Impaired Systolic and Diastolic Left Ventricular Function in Children with Chronic Kidney Disease: Results from the Cardiovascular Comorbidity in Chronic Kidney Disease (4C) Study

**Background:** Tissue doppler (TD) velocities are sensitive markers of left ventricular function. The aim of this work was to describe TD velocities in a large cohort of children with chronic kidney disease and to assess risk factors for ventricular dysfunction.

**Methods:** A standardized echocardiographic examination was performed in 128 patients of the 4C Study aged 6-17 years with cGFR 10-60 ml/min/1.73 m². TD measurements of the left ventricle included early (E') and late (A') diastolic and systolic (S') velocity. Diastolic function was described by E'/A' ratio and left ventricular compliance by early diastolic conventional to tissue doppler (E'/E') ratio. Measured values were normalized to z scores using reference data from 325 healthy children.

**Results:** TD diastolic E' velocity was reduced and A' increased at the mitral and septal annulus, resulting in a reduced E'/A' ratio (z-score -0.14, p<0.001) indicating diastolic dysfunction. Diastolic function (E'/A') was positively correlated with midwall fractional shortening (r=0.23, p<0.01). Reduced diastolic function was independently associated with reduced renal function (β=-0.09, p=0.005), increased systolic blood pressure (β=-0.04, p=0.045) and pulse wave velocity (β=0.03, p=0.07). Left ventricular compliance was increased (z-score 0.65, p<0.001), possibly as a result of increased preload. Systolic TD velocities were significantly decreased (z-score -0.24, p<0.001). Reduced systolic velocities in TD imaging were inversely correlated to left ventricular compliance (r=-0.4, p<0.001). The LVMI was not associated to systolic or diastolic TD velocities.

**Conclusions:** TD evaluation showed alterations of both systolic and diastolic function in children with chronic kidney disease. Renal function and systolic blood pressure are significant predictors for diastolic function. TD velocities are independent of LV mass and provide early information about ventricular dysfunction.

**Funding:** Private Foundation Support

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**TH-P065**

Rapid Early Postnatal Growth Increases Blood Pressure Level in 5-Year-Old Children Born with Low Birthweight

**Methods:** The Cardiovascular Comorbidity in Chronic Children with Kidney Disease (4C) Study: Baseline Data of a Multicentric Prospective Observational Study in Children

**Background:** Low birth weight (BW) is associated with hypertension and excess ESRD risk in adults, but whether postnatal growth may modify its impact on blood pressure (BP) and albuminuria in children is unknown. We studied the relationship of BW, gestational age (GA), and postnatal growth with BP and albuminuria in 5-year-old children.

**Results:** We used data from the multicenter cohort of 1,119 children followed from birth to age 5. A mean of 17 weights were collected over this period which enabled to predict weights and weight growth velocities at any age. Three standard BP and albumin-to-creatinin ratio were measured at age 5. In order to avoid the reverse paradox phenomenon due to confounding by 5-year corpulence in the analysis of the relationship between BW, BP and albuminuria, we followed from birth to age 5. A mean of 17 weights were collected over this period, which enabled to predict weights and weight growth velocities at any age. Three standard BP (x-score -0.02 ± 0.04, p=0.56) and albuminuria level (>1mg/mmol) was used to assess the relationship between PWV and level of proteinuria (UP/C) adjusted for age, gender, race, height, waist circumference, mean arterial pressure (MAP), and GFR.

**Conclusions:** Rapid early postnatal growth associates with higher blood pressure level in 5-year-old children born with low birthweight. They may deserve early monitoring for cardiovascular risk.

**Funding:** Government Support - Non-U.S.
Methods: We studied Jackson Heart Study participants and calculated eGFR from baseline serum creatinine (CKD-EPI equation) and urine albumin-to-creatinine ratio (ACR) from urine samples. We tested association of eGFR and urine ACR with left ventricular mass (LVM), left ventricular ejection fraction (LVEF) and incident HF. Results: In 3332 participants, 5% had eGFR<60 ml/min/1.73m2 and 12% had urine ACR>30 mg/g. Mean LVM was higher in those with eGFR<60 (175g vs 147g) and urine ACR>30 (169g vs 143g). Mean LVEF was similar across eGFR and ACR levels. The association of eGFR with LVM was significant adjusting for age, sex, education, blood pressure, BMI, smoking, hypertension, stenosis, diabetes and cardiovascular disease (β-coefficient 13g [95% CI: 7.1, 19.3]), while association with LVEF was not (β-coefficient -0.9% [95% CI: -1.9, 0.1]). Urine ACR>30 mg/g was associated with higher LVM in adjusted models (β-coefficient 6g [7.1, 11]); however, was not associated with LVEF (adjusted β-coefficient -0.4% [95% CI: -1.2, 0.4]). Rate of HF events was greater in those with CKD (Table). Higher urine ACR was strongly linked with incident HF after adjusting for LVM and LVEF (Table).

<table>
<thead>
<tr>
<th>Association of urinary function with risk of incident heart failure among participants in the Jackson Heart Study</th>
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Conclusions: LVM was higher in AA with lower eGFR and higher ACR. Higher urine ACR was linked with incident HF and not entirely explained by LVD. We show the importance of mild/early kidney dysfunction with risk of HF among AA. More study is needed to characterize the mechanisms by which kidney disease contributes to worse outcomes in HF in this group.

Funding: NIDDK Support

TH-P0637

Racial Differences in Risk of Chronic Kidney Disease in Patients with Congestive Heart Failure

Lekha K. George,1 Sanhoosh K. Koshy,1 Miklos Zsolt Molnar,1 Jun Ling Lu,1 L. Ebony Boulware,2 Keith C. Norris,3 Kamyar Kalantar-Zadeh,4 Csaba P. Kovessy,1,2 1Univ of Tennessee Health Science Center; Memphis, TN; 2Duke Univ School of Medicine, Durham, NC; 3UCLA, CA; 4UVA Medical Center, Memphis, TN.

Background: While CKD is more common in African Americans (AA), the prevalence of CV disease is lower in AA patients with CKD. It is unclear if the higher risk of incident CKD associated with AA race is modified by the presence of CHF.

Methods: Among 3,065,749 AA or white veterans with eGFR<60 ml/min/1.73m2, we identified 143,229 with a diagnosis of CHF (17% AA), and 2,922,520 with no CHF (18% AA). We examined the interaction of race with CHF for the risk of incident CKD and rapid rate of decline in eGFR (slopes <-5 ml/min/1.73m2/yr) during a median follow up of 7.8 yrs. We examined outcomes in Cox models (for CKD) and logistic regression (for slopes), including interaction terms for race-CHF, and adjusting for baseline age, gender, race, comorbidities, BMI, BP, eGFR and medication use.

Results: Mean±SD baseline age and eGFR were 68±11 yrs and 79±14 ml/min/1.73m2 for patients with CHF, vs. 59±14 yrs and 84±16 ml/min/1.73m2 for those without CHF. 327,548 (11%) patients developed incident CKD and 235,081 (9%) experienced rapid eGFR decline. AA race showed a significant interaction with HF for both CKD incidence (p=0.009) and loss of kidney function (p<0.001). Compared to white patients with no CHF, AA patients with CHF experienced a ~2-fold higher risk of incident CKD and more rapid eGFR loss after multivariable adjustments (Figure).

Conclusions: The increased risk of renal complications associated with AA vs. white race is higher in patients with CHF compared to those with no CHF. Interventions aimed at improving renal outcomes in AA patients with CHF should be further examined.

Funding: NIDDK Support, Veterans Administration Support

TH-P0638

Incidence of Congestive Heart Failure in African-American versus White Patients with and without Chronic Kidney Disease

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Background: African Americans (AA) are at higher risk of cardiovascular disease and its complications, such as congestive heart failure (CHF). CKD is also more common in AA, yet the prevalence of coronary artery disease is lower in AA patients with CKD. It is unclear if the risk of CHF is also lower in AA with CKD, given its more complex pathophysiology in patients with kidney disease.

Methods: Among 2,929,736 AA (N=523,181) or white (N=2,406,555) US veterans with eGFR<60 ml/min/1.73m2 and no CHF at baseline, we examined the association of AA race with incident CHF (hospitalization-based ICD9 codes) during a median follow up of 6.7 yrs. We examined outcomes separately in patients who maintained an eGFR≥60 ml/min/1.73m2 (non-CKD group; N=2,632,034), and those who developed 2 eGFR values <60 with >90 days in-between (CKD group; N=286,597). We used Cox proportional hazards models, without adjustments (Model 1) and with sequential adjustments for baseline demographics and eGFR (Model 2), comorbidities (Model 3), BMI and BP (Model 4), and medications and socioeconomic indicators (Model 5).

Results: 71,137 (event rate: 4.8±1000 patient-years, 95%CI: 4.8±0.9) and 42,067 (26.4±1000PY , 26.2±26.7) patients developed CHF in the non-CKD and CKD groups, respectively. Compared to whites, AA race was associated with similar unadjusted risk of CHF in non-CKD (hazard ratio, 95%CI: 0.97, 0.95-0.99), but with higher unadjusted risk among CKD (1.23, 1.20±1.26). After adjustments, the risk of CHF in AA was minimally lower in both non-CKD and CKD patients (Figure).

Conclusions: The risk of incident CHF is slightly lower in AA US veterans with and without CKD. These qualitatively different associations compared to the non-veteran population warrant additional studies.

Funding: NIDDK Support, Veterans Administration Support

TH-P0639

Continued Underrepresentation of Patients with Kidney Disease in Cardiovascular Trials: An Updated Systematic Review After a Decade

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Background: Cardiovascular disease (CVD) is a major cause of morbidity/mortality in kidney disease (KD). Two systematic reviews showed that KD patients are underrepresented in CVD randomized controlled trials (RCTs) using data from 1985-2005 and 1998-2005. We aimed to update estimates of KD patient representation in major CVD RCTs over the past decade.

Methods: We searched MEDLINE for congestive heart failure/acute coronary syndrome RCTs in major journals between 2006-2014. We excluded RCTs not reporting mortality outcomes, with <100 participants, or were subgroup, follow-up, or post-hoc analyses.

Results: We included 371 trials randomizing 590,040 participants. KD patients were excluded in 212 (57.1%) RCTs and were more likely to be excluded from North American (p=0.02) or industry-funded (p=0.01) trials. They were more likely to be excluded in RCTs of anticoagulants, antiplatelet agents, statins or RAAS antagonists compared to trials of PCI (p<0.01).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Effect of Niacin on Markers of Mineral Metabolism in CKD: The AIM-HIGH Trial

**Background:** Niacin blocks intestinal phosphate (P) transport in vitro. Short-term human studies suggest niacin lowers P in CKD patients. Longer-term effects on P, and on other mineral markers are uncertain. Fibroblast growth factor (FGF) 23 is a phosphaturic hormone that induces left ventricular hypertrophy in vitro and higher levels are associated with heart failure and death in CKD patients. Higher serum P may stimulate higher FGF23.

**Methods:** AIM-HIGH randomized 3,414 patients with cardiovascular disease (CVD) and dyslipidemia to sustained-release niacin 1500-2000mg vs. placebo (pbo) for prevention of recurrent CVD events (1st endpoint). Both groups were on a background of statin therapy. Exclusions included serum Cr ≥ 2.7mg/dL. The trial was stopped after 3 yrs mean follow-up due to futility. In 352 patients with eGFR<60 ml/min/1.73 m², we measured plasma P, calcium (Ca), intact (i) FGF23 (Kainos), intact parathyroid hormone (iPTH), and calcitriol (LC/MS) at baseline, yr 1, and yr 3. Mean levels were compared between arms, and linear mixed models provided summary estimates of the effect of niacin on each.

**Results:** Demographics, CVD history, and CVD risk factors were well balanced in both groups. At baseline, P was 0.25mg/dL lower in the niacin vs. pbo arm. No significant differences were noted in iFGF23, Ca, iPTH, or calcitriol between arms at 3 yrs. The trial did not show a significant difference in CVD death or MI as an endpoint. However, we observed no significant effect of niacin on other mineral measures. Regulation of FGF23 may be more complex than simply reflecting changes in serum P.

**Conclusions:** Niacin lowers serum P in CKD patients, an effect that extends for 3 yrs. We observed no significant effect of niacin on other mineral measures. Regulation of FGF23 may be more complex than simply reflecting changes in serum P.

**Funding:** NIDDK Support, Veterans Administration Support

### TH-PO641

**Efficacy and Safety of Modified-Release Calcifediol in Stage 3-4 CKD Patients with Secondary Hyperparathyroidism and Vitamin D Insufficiency**

**Background:** Current approaches to correct vitamin D insufficiency (VDI) in stage 3 or 4 CKD are poorly defined and generally ineffective in controlling secondary hyperparathyroidism (SHPT). The effectiveness of modified-release calcifediol (MRC) at correcting VDI and controlling SHPT was evaluated.

**Methods:** Two identical, randomized, double-blind, placebo-controlled trials were conducted in patients with SHPT (≥ 85 pg/ml). Stage 3 or CKD and VDI (serum 25OHd 10-29 ng/ml). The trials enrolled a total of 429 subjects from 77 US sites, randomized 2:1 to receive MRC or placebo for 26 weeks. MRC dosing started at 30 mg/d and increased, as needed to lower iPTH, to 60 mg/d after 12 weeks. Subjects were stratified based upon their 25OHd levels (0-20, 20-40, 40-60, 60-80 or > 80 ng/ml) at the end of treatment (EOT). The mean EOT plasma iPTH, serum total 1,25-dihydroxyvitamin D (1,25D), serum Ca and P levels in each group were calculated and compared.

**Results:** A total of 364 (85%) subjects completed the trials. Serum 1,25D levels progressively increased with increasing 25OHd concentrations, with mean levels 41% higher in the highest quintile compared to the lowest (p < 0.001). Conversely, iPTH progressively decreased with increasing 25OHd concentrations, with mean iPTH levels 40% lower in the subjects in the highest- 25OHd concentrations compared to the lowest concentrations (Figure; p < 0.001). No changes were observed in serum Ca and P concentrations independent of 25OHd concentration.

**Funding:** Pharmaceutical Company Support - OPKO Health

### TH-PO642

**CKD-MBD Indices After 52 Weeks of Sucroferric Oxyhydroxide, an Iron-Based Phosphate Binder, in African American Dialysis Patients**

**Background:** Vitamin D insufficiency (VDI) in stage 3 or 4 CKD and vascular disease (VD) in patients with SHPT and VDI.

**Methods:** Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/day; n=710) or sevelamer carbonate (SEV; Renvela®) as needed to lower iPTH, to 60 mg/d after 12 weeks. Subjects were stratified based upon their 25OHD levels (0-20, 20-40, 40-60, 60-80 or > 80 ng/mL) at the end of treatment (EOT). The effectiveness of modified-release calcifediol (MRC) at correcting VDI and controlling SHPT was evaluated.

**Results:** A total of 364 (85%) subjects completed the trials. Serum 1,25D levels progressively increased with increasing 25OHd concentrations, with mean levels 41% higher in the highest quintile compared to the lowest (p < 0.001). Conversely, iPTH progressively decreased with increasing 25OHd concentrations, with mean iPTH levels 40% lower in the subjects in the highest- 25OHd concentrations compared to the lowest concentrations (Figure; p < 0.001). No changes were observed in serum Ca and P levels independent of 25OHd concentration.

**Conclusions:** MRC increased serum total 25OHd levels and total 1,25D, while reducing plasma iPTH, without significantly increasing serum Ca or P levels in CKD patients with SHPT and VDI.

**Funding:** Pharmaceutical Company Support - OPKO Health
Concomitant IV Iron Use Drives Changes in Iron Indices in African American Dialysis Patients Over 52 Weeks of Sucroferric Oxyhydroxide Treatment

TH-PO643

Concomitant IV Iron Use Drives Changes in Iron Indices in African American Dialysis Patients Over 52 Weeks of Sucroferric Oxyhydroxide Treatment

Stuart M. Sprague,1 Anjey Rastogi,2 Markus Ketteler,3 Adrian C. Covic,4 Jürgen Floege,5 Viatcheslav Rakov,6 Liera Armando Samuels,7

Background: A post hoc analysis of data from a randomized, open-label, Phase 3 study and its extension investigated iron indices after treatment with the iron-based phosphate binder sucroferric oxyhydroxide (VELPHORO®; SFOH) vs sevelamer carbonate (SEV) in both treatment groups with higher levels in the SEV group. Significant increases (95.8 and 92.3%) during the 1-year study. Baseline levels of ferritin appeared elevated in SEV groups received IV iron (95.8 and 92.3%) and erythropoietin-stimulating agents (ESAs) only in patients receiving IV iron. Hemoglobin was relatively stable over 1 year.

Results: Of the 549 patients who completed the extension study, 100 were African American (n=48, SFOH; n=52, SEV). A high proportion of patients in the SFOH and SEV groups received IV iron (95.8% and 92.3%) and erythropoietin-stimulating agents (95.8% and 98.1%) during the 1-year study. Baseline levels of ferritin appeared elevated in both treatment groups with higher levels in the SEV group (Table). Significant increases in ferritin were observed in SFOH ‘IV iron’ subgroup. Ferritin and TSAT levels increased over 1 year.

Funding: Pharmaceutical Company Support - Vifor Pharma

Table: Serum levels of CKD-MBD indices in African American patients ( completers; N=100).

<table>
<thead>
<tr>
<th>Parameter, mean (SD)</th>
<th>SFOH (n=48)</th>
<th>SEV (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron level (g/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCAT</td>
<td>14.0±6.0</td>
<td>14.7±7.7</td>
</tr>
<tr>
<td>TSAT</td>
<td>4.1±2.7</td>
<td>4.3±2.7</td>
</tr>
<tr>
<td>PTH</td>
<td>2.0±0.9</td>
<td>2.2±1.0</td>
</tr>
<tr>
<td>iCa</td>
<td>9.1±0.4</td>
<td>9.1±0.4</td>
</tr>
<tr>
<td>Hb</td>
<td>10.4±1.1</td>
<td>10.4±1.1</td>
</tr>
<tr>
<td>EPO</td>
<td>512±152</td>
<td>512±152</td>
</tr>
</tbody>
</table>

Conclusions: SFOH and SEV led to reductions in serum phosphorus, FGF-23 and iPTH over 1-year of treatment in African American dialysis patients. Post hoc results so far reflect those from the overall study population.

Subgroup by baseline PTH level in cinacalcet

Equal or greater 30% reduction of PTH from group at 12 wk follow up

PTH 801-1600 pg/mL

22/26 (85%)

PTH 1601-2400 pg/mL

8/14 (57%)

PTH >2400 pg/mL

0/2 (0%)

P-value (Linear by linear association) 0.018

Conclusions: The high efficacy of cinacalcet was still demonstrated even in case of severe secondary HPT. However, higher iPTH reduced the efficacy outcome of cinacalcet.

Table: Serum levels and changes in iron indices in African American patients by concomitant iron use during the study (completers; N=100).

<table>
<thead>
<tr>
<th>Parameter, mean (SD)</th>
<th>IV iron (n=48)</th>
<th>No IV iron (n=42)</th>
<th>IV iron (n=48)</th>
<th>No IV iron (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin, ng/mL</td>
<td>14.0±6.0</td>
<td>14.7±7.7</td>
<td>14.7±7.7</td>
<td>14.0±6.0</td>
</tr>
<tr>
<td>TSAT, %</td>
<td>4.1±2.7</td>
<td>4.3±2.7</td>
<td>4.3±2.7</td>
<td>4.1±2.7</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>2.0±0.9</td>
<td>2.2±1.0</td>
<td>2.2±1.0</td>
<td>2.0±0.9</td>
</tr>
</tbody>
</table>

Conclusions: The high efficacy of cinacalcet was still demonstrated even in case of severe secondary HPT. However, higher iPTH reduced the efficacy outcome of cinacalcet.

TH-PO645

A Double-Blind, Randomized, Placebo-Controlled Trial of Ergocalciferol with/without Calcitriol in Chronic Kidney Disease with Proteinuria

Paweena Vathanavan,1 Sirirawan Nakawan,2 Khajohn Tiramantharam,3 Piyut Katavetin,4 Kearsing Praditpornsilpa,5 Somchai Eiam-ong,6 Dept. of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: These are no available data regarding the role of natural vitamin D with/without active vitamin D on proteinuria and renal function in CKD patients with vitamin D insufficiency/deficiency. This study was conducted to explore the additional effect of both active vitamin D (calcitriol) and natural vitamin D (ergocalciferol) on proteinuria and kidney function in CKD with vitamin D insufficiency/deficiency.

Methods: The first double-blind, randomized placebo-controlled trial was performed to answer this question. Sixty eight patients with eGFR 15-60 mL/min/1.73m2, UPCR greater than 1 g/g, and vitamin D insufficiency/deficiency were enrolled. Patients were randomly assigned to receive 12-week treatment with oral ergocalciferol plus placebo (n=36) or calcitriol plus oral calcitriol (n=32).

Results: The mean baseline UPCCR of both groups were comparable (3.6±3.8 g/g in combined group and 3.5±3.0 g/g in ergocalciferol group). Following 12-week treatment, there were significant reductions in UPCR of both groups from baseline (2.3±1.1 g/g in combined group and 2.4±1.1 g/g in ergocalciferol group). These effects were demonstrated in all range of proteinuria, diabetic nephropathy, non-diabetic nephropathy, receiving RAAS blockade and non-receiving RAAS blockade. The mean eGFR and blood pressure did not differ between baseline and 12-week follow up and between both groups. No severe hypercalcemia or serious side effects were noted in both groups.

Conclusions: This is the first RCT which illustrates the lowering proteinuria effect of ergocalciferol in CKD patients with vitamin D deficiency. However, additional calcitriol did not have more effects on proteinuria. Therefore, ergocalciferol should be added for more decreasing proteinuria in CKD patients with proteinuria that cannot tolerate or increase the dosage of RAAS blockade due to any side effects. A longer study is required to examine the renal function retardation effects.

Subgroup by baseline PTH level in cinacalcet

Equal or greater 30% reduction of PTH from group at 12 wk follow up

PTH 801-1600 pg/mL

22/26 (85%)

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0/2 (0%)

P-value (Linear by linear association) 0.018

Conclusions: The high efficacy of cinacalcet was still demonstrated even in case of severe secondary HPT. However, higher iPTH reduced the efficacy outcome of cinacalcet.

TH-PO645

A Double-Blind, Randomized, Placebo-Controlled Trial of Ergocalciferol with/without Calcitriol in Chronic Kidney Disease with Proteinuria

Paweena Vathanavan,1 Sirirawan Nakawan,2 Khajohn Tiramantharam,3 Piyut Katavetin,4 Kearsing Praditpornsilpa,5 Somchai Eiam-ong,6 Dept. of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

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Methods: The first double-blind, randomized placebo-controlled trial was performed to answer this question. Sixty eight patients with eGFR 15-60 mL/min/1.73m2, UPCR greater than 1 g/g, and vitamin D insufficiency/deficiency were enrolled. Patients were randomly assigned to receive 12-week treatment with oral ergocalciferol plus placebo (n=36) or calcitriol plus oral calcitriol (n=32).

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

CKD: Clinical Trials
Poster/Thursday
Anemia Correction with Roxadustat Lowers Hemoglobin in Chronic Kidney Disease (CKD) Patients  

Background: The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) is being developed for treatment of CKD anemia. Hepcidin regulates iron metabolism and higher levels are associated with greater mortality. This analysis of phase 2 studies was undertaken to explore the consistency of the suppressive effect of roxadustat on hepcidin.

Methods: Among CKD-NDD (017 and 041) & CKD-DD (040 & 053) studies, roxadustat doses, study duration, and comparator (placebo or epoetin) varied. Studies restricted IV iron in general but allowed oral iron. Baseline (BL) hepcidin and change from BL (CFB) were summarized (mean±SD) overall and by tertile. Significant differences (p<0.05 vs BL) based on within-group comparisons (4).

Results: Mean BL hepcidin in CKD-NDD roxadustat subjects was 292.8±179.8 and 120.3±107.0 mg/mL (studies 017 & 041). Hepcidin fell with roxadustat treatment by 158.4±179.2 & 45.6±87.7. Mean BL hepcidin in CKD-DD roxadustat subjects was 303.9±172.9 & 91.1±99.0 (040 & 053). Hepcidin fell with roxadustat treatment by 26.7±192.0 & 57.4±40.8. For both groups, the greatest declines were in the highest BL tertiles.

Conclusions: Roxadustat consistently lowered hepcidin in phase 2 studies. The decrement in hepcidin is greatest among those with the highest BL levels. The roxadustat phase 3 trials will include measurements of hepcidin to further define this effect.

Funding: Pharmaceutical Company Support - FibroGen

TH-PO647

Anemia Correction with Roxadustat Increases Soluble Transferrin Receptor (sTfR) in Chronic Kidney Disease (CKD) Patients  

Background: The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) is being developed for treatment of CKD anemia. Hepcidin regulates iron metabolism and higher levels are associated with greater mortality. This analysis of phase 2 studies was undertaken to explore the consistency of the suppressive effect of roxadustat on hepcidin.

Methods: Among CKD-NDD (017 & 041) & CKD-DD (040 & 053) studies, roxadustat doses, study duration, and comparator (placebo or epoetin) varied. Studies restricted IV iron in general but allowed oral iron. Baseline (BL) hepcidin and change from BL (CFB) were summarized (mean±SD) overall and by tertile. Significant differences (p<0.05 vs BL) based on within-group comparisons (4).

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Conclusions: Roxadustat consistently lowered hepcidin in phase 2 studies. The decrement in hepcidin is greatest among those with the highest BL levels. The roxadustat phase 3 trials will include measurements of hepcidin to further define this effect.

Funding: Pharmaceutical Company Support - FibroGen

TH-PO648

Anemia Correction with Roxadustat Lowers Cholesterol in Chronic Kidney Disease (CKD) Patients  

Background: Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor roxadustat is being developed for CKD anemia. The HIF pathway affects cholesterol metabolism & ascension to altitude reduces total cholesterol (TC). This analysis of phase 2 studies explores roxadustat’s effect on TC in non-dialysis (NDD) and dialysis (DD) CKD.

Methods: In Phase 2 studies 41&47 in NDD & 40,48&53 in DD, roxadustat dose, study duration and comparator (placebo, epoetin) varied. Studies restricted IV iron but allowed oral iron. Baseline (BL) TC and change from BL (Δ) were summarized overall and by BL tertile. Data are mean±SD.

Results: Among roxadustat NDD subjects (n=206), mean BL TC was 170.9±45.2 and 166.3±39.1 mg/dL (studies 41&47). TC fell with roxadustat by 25.8±29.7 and 33.7±31.8. Among roxadustat DD subjects (n=238), mean BL TC was 171.1±35.1, 174.3±57.3, and 171.0±56.7 (studies 48,53&480). TC fell with roxadustat treatment by 14.2±36.4, 44.4±45.4 and 36.7±37.0. The greatest declines were among the highest BL tertile in both populations.

Conclusions: Roxadustat consistently lowered cholesterol in phase 2 studies. The decrement in cholesterol is greatest among those with the highest BL levels. Roxadustat phase 3 trials will include tests to further define this effect and significance.

Funding: Pharmaceutical Company Support - FibroGen

TH-PO649

AKB-6548 Demonstrates Controlled Hemoglobin (HGB) Response in a Phase 2b Study for the Treatment of Anemia in Patients with Chronic Kidney Disease Not on Dialysis (ND-CKD)  
Volker H. Haase,1 Bruce S. Spinowitz,2 Pablo E. Pergola,3 Tasha Farmer,4 Bradley J. Maroni,4 Charlotte S. Hurtman,4 Vanderbilt Univ, Nashville, TN; New York Hospital Queens, Flushing, NY; Renal Associates PA and Univ of Texas Health Sciences Center, San Antonio, TX; Akebia Therapeutics, Inc., Cambridge, MA.

Background: AKB-6548 is a novel, once daily, oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that preferentially stabilizes HIF-2a. Current standard of care for anemia in ND-CKD with recombinant ESAs often results in overshots and oscillations of HGB levels. It has been suggested that fluctuations in HGB concentrations, rapidly increasing HGB levels, and overshoots of the HGB target are associated with increased risk of cardiovascular events. Presented here are data assessing the control and predictability of HGB response from a Phase 2b study.

Methods: A randomized, double-blind, placebo-controlled study was conducted to assess the HGB response of AKB-6548 over 20 weeks of dosing in ND-CKD subjects with anemia. 210 subjects were randomized 2:1 (138 AKB-6548, 72 placebo) to once daily AKB-6548 (450mg) or placebo. HGB was monitored at each study visit and a protocol-defined dose adjustment algorithm was used to raise and maintain HGB and to minimize excursions >13 g/dL.

Results: The starting dose of 450 mg once daily was validated by the final average dose of 394.7±93.1 mg/dL. From Weeks 12 to 20, 74% and 81% of all HGB measurements were between 10-12 g/dL and 10-13 g/dL, respectively.

Conclusions: AKB-6548 is a novel, once daily, oral hypoxia-inducible factor prolyl hydroxylase inhibitor that preferentially stabilizes HIF-2A. Current standard of care for anemia in ND-CKD with recombinant ESAs often results in overshots and oscillations of HGB levels. It has been suggested that fluctuations in HGB concentrations, rapidly increasing HGB levels, and overshoots of the HGB target are associated with increased risk of cardiovascular events. Presented here are data assessing the control and predictability of HGB response from a Phase 2b study.
Randomized Controlled Trial of Darbeopeitin Alfa and Continuous Erythropoetin Receptor Activator Once Every 4 Weeks in Patients with Chronic Kidney Disease at the Pre-Dialysis Stage

J Am Soc Nephrol 26: 2015  CKD: Clinical Trials Poster/Thursday

TH-PO650

Randomized Controlled Trial of Darbeopeitin Alfa and Continuous Erythropoetin Receptor Activator Once Every 4 Weeks in Patients with Chronic Kidney Disease at the Pre-Dialysis Stage

Tetsuya Furukawa, Kazuysoshi Okada, Ritsukou Tei, Masanori Abe, Noriaki Maruyama.

Background: Subcutaneous injection of Continuous Erythropoetin Receptor Activator (CERA) seems to maintain a stable Hb level than darbeopeitin alfa (DA) in CKD patients who are not on dialysis because of its longer half-life. We therefore conducted a randomized controlled trial.

Methods: The cohort consisted of 205 CKD patients at the pre-dialysis stage who were receiving a fixed dose of DA with a Hb level >9.5 g/dL and ferritin level >80 mg/mL in the 12 weeks prior to the study. Patients were randomly assigned to receive subcutaneous CERA or DA once every 4 weeks. The study consisted of a 48-week evaluation period. The target Hb range was from 11.0 g/dL to 12.5 g/dL. Primary endpoints were achievement of target Hb and change of eGFR, and the secondary endpoints were change in Hb level after start of the study and change in dose of DA and CERA.

Results: In both groups, the rate of achievement of target Hb level at week 0 was 70%, which rose to 100% in the interval between weeks 4 to 48, with no significant difference between the groups. Despite the absence of a significant difference in Hb level, it was significantly increased from week 24 and from week 8 relative to those at week 0 in the DA continuation group and CERA changeover group, respectively. In addition, the reticulocyte count was significantly increased at weeks 4, 8, and 12 in the CERA changeover group compared with the DA continuation group. The doses of DA and CERA during the evaluation period were not significantly changed. Because the total administered doses of DA and CERA over 48 weeks were 0.998±0.106 mg/kg/4 weeks and 0.956±0.204 mg/kg/4 weeks, the dose conversion ratio was 1.05:1 mg. There was no significant difference in the levels of eGFR and iron state between both groups.

Conclusions: The present study demonstrated that subcutaneous administration of DA and CERA once every 4 weeks to predialysis patients have similar effects on achievement of target Hb levels but longer acting CERA can increase the Hb level earlier than DA.

TH-PO651

QW or Q2W Darbeopeitin Alfa in Pediatric Subjects with Chronic Kidney Disease


Children’s Mercy; University of Missouri; University of Kansas Medical Center.

Methods: Multicenter, double-blind, randomized study in pediatric subjects (age 1 to 18 years) with CKD and anemia (hemoglobin; Hb < 10.0 g/dL) on or not on dialysis and not treated with an ESA. The primary endpoint was Hb ≥ 10.0 g/dL at any time after the first dose without receiving a RBC transfusion within 90 days prior to initial Hb measurement or after randomization. Subjects were randomized to DA QW or Q2W at an initial dose of 0.45mg/kg or 0.75mg/kg, respectively. For both treatment groups, subsequent DA doses were titrated to achieve Hb 10.0 g/dL to 12.0 g/L, inclusive over a 25 week period of observation.

Results: 116 subjects were enrolled; 59 were randomized to QW DA and QW to Q2W. 114 subjects (58 QW; 56 Q2W) were included in the analyses. Mean (SD) Hb for the QW group increased from 8.6 (0.84) g/dL at baseline to 11.3 (1.23) g/dL at week 10 and remained relatively stable (range: 10.9 [1.10] to 11.7 [1.19] g/dL) through week 25. Mean Hb for the Q2W group increased from 8.7 (0.84) g/dL at baseline to 10.9 (1.38) g/dL at week 12 and remained relatively stable between 10.4 (0.97) and 11.1 (1.00) g/dL through end of study. Hb concentrations were corrected to ≥ 10 g/dL in 89% and 84% of pediatric subjects administered DA QW or Q2W, respectively. 4 (7%) QW and 5 (9%) Q2W subjects received RBC transfusions. Safety results were consistent with the known safety profile for DA.

Conclusions: DA concentrations were corrected to ≥ 10 g/dL in > 80% of pediatric subjects administered DA QW or Q2W. No new safety signals were identified in this pediatric subject population.

Funding: Pharmaceutical Company Support - Amgen Inc.

TH-PO602

Intravenous (IV) Ferric Carboxymaltose (FCM) versus Oral Iron in the Randomized FIND-CKD Trial of Patients with Non-Dialysis Dependent CKD (ND-CKD): A Safety Analysis

Simon D. Rogger, Andreas H. Bock, Fernando Carrera, Kai-Uwe Eckardt, Carla A. Guillard, David B. Van wyck, Bernard Roubet, Maureen Cronin, Iain C. Macdougall.

1 Renal Research, Groupe Karline, 26, 93305 Aubervilliers Cedex, France; 3AKF, Australia; 4Klinikum, Universitaetsmedizin, 5Hospital, Leiria, Portugal; 6Uni. of Erlangen-Nuremberg, Erlangen, Germany; 7Uni. Groningen, Groningen, Netherlands; 8Davita Healthcare Partners, Denver, CO; 9Vifor Pharma Ltd, Glattbrugg, Switzerland; 10‘King’s College Hospital, London, United Kingdom.

Background: There are safety concerns, including hypersensitivity reactions, iron overload, increased risk of infection, oxidative stress and mortality risk, in patients with CKD receiving IV iron.

Methods: In the 56-week, open-label, multicenter, prospective, randomized FIND-CKD study, 626 anemic patients with ND-CKD and iron deficiency not receiving ESA therapy were randomized (1:1:2) to IV ferric carboxymaltose (FCM), targeting higher (400–600μg/L) or lower (100–200μg/L) ferritin, or oral iron.

Results: In the IV iron arms, two patients had mild hypersensitivity reactions, neither requiring treatment nor hospitalization. Desired target ferritin levels were achieved and transferrin saturation (TSAT) levels were maintained within KDIGO guidelines (mean TSAT 31% in the high ferritin FCM group). The rate of infections was equivalent within all three groups (33.1%, 34.0% and 30.4% in the high ferritin FCM, low ferritin FCM and oral iron groups, respectively), as was the rate of serious infections (3.9%, 3.3%, 3.8%). As a measure of oxidative stress, estimated GFR values were unchanged during the study. Overall, 4.1% of patients died (4.5%, 2.0% and 4.8% in the high ferritin FCM, low ferritin FCM and oral iron groups, respectively). No death was assessed by the investigator as related to study drug. Most frequent causes of death were cardiovascular events and respiratory infections.

Conclusions: Despite this being the longest RCT of oral vs IV iron in ND-CKD patients, the follow-up was still only 12 months and there was no placebo group. Nevertheless, there was no obvious signal of excess harm in patients targeting a higher ferritin range with IV FCM.

Funding: Pharmaceutical Company Support - Vifor Pharma, Glattbrugg, Switzerland

TH-PO653

Recruitment for Clinical Trials of Interventions to Prevent ESRD in T2D Patients


1 Joslin Diabetes Center; Boston; 2EKF Diagnostics, London, United Kingdom; 3Eli Lilly, Indianapolis; 4Pfizer Global R&D, MA.

Background: The current dependence of clinical trials of measures to prevent ESRD, on recruitment of patients with T2D and proteinuria is problematic. The eligible pool, shrunken due to ACE inhibitor treatment, largely consists of non-progressors (due to depletion of rapid progressors) whose participation may be less informative.

Methods: In search of alternatives, we recruited T2D patients attending Joslin Clinic between 2003 and 2009 by screening those age 35-69 (and CKD stage 1-3) for onset of albuminuria (ALB, micro or macro), and identified for each a similar patient in the 3x larger pool with normo ALB. 2/3 granted participation consent. Mean baseline eGFR was 95 for Normo and Micro ALB groups and 68 mL/min/1.73 m² for Macro-ALB group. Patients were examined at baseline and followed to 2013 to ascertain onset of ESRD or death. FCM was titrated to reach the threshold eGFR, and follow-up blood and urine were assayed for serum creatinine and other characteristics.

Results: After 4-6 year follow-up for 1335 patients (excluding 82 incomplete follow-ups) are summarized according to ALB category:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normo-ALB</th>
<th>Micro-ALB</th>
<th>Macro-ALB</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD onset</td>
<td>2/0.3% [6]*</td>
<td>7/1.4%</td>
<td>32/21%</td>
<td>41 [45]</td>
</tr>
<tr>
<td>Loss&lt;40% eGFR</td>
<td>24.3% [7]*</td>
<td>54/11%</td>
<td>49/31%</td>
<td>127 [177]</td>
</tr>
<tr>
<td>Death</td>
<td>16/2.3% [8]*</td>
<td>23/4.8%</td>
<td>18/12%</td>
<td>58 [90]</td>
</tr>
<tr>
<td>Composite</td>
<td>42/6.0% [12]*</td>
<td>86/17%</td>
<td>100/64%</td>
<td>226 [310]</td>
</tr>
</tbody>
</table>

* expected number if all normo-ALB patients were followed

Unfavorable outcomes occurred in an estimated 310 of 2725 patients (including all normo ALB patients). Although incidence was highest in Macro-ALB group, 2/3 occurred in Normo and Micro ALB groups and 1/3 occurred in patients with baseline eGFR >90 mL/min/1.73 m². Circulating levels of TNP1 and KIM-1 and urinary levels of MCP-1 and KIM-1 at baseline are associated with risk of these outcomes.

Conclusions: In summary increased clinical trial enrollment of patients with outcomes can be achieved by including patients with normal renal function and Micro or Normo ALB.

Funding: NIDDK Support, Pharmaceutical Company Support Pfizer Pharmaceuticals, Eli Lilly and Company, EKF Diagnostics

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

238A
TH-PO654

Post Hoc Analyses of the EPPIC Trials to Assess the Effect of AST-120 in Chronic Kidney Disease Patients: A Randomized, Double-blind, Placebo-controlled Trials

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Background: The orally administered spherical carbon adsorbent AST-120 is approved in Asian countries for delaying the initiation of dialysis and ameliorating symptoms of uremia in patients with progressive CKD. Two randomized, double-blind, placebo-controlled trials (EPPIC trials) investigated the efficacy and the safety of AST-120 in adults with CKD. The benefit of adding AST-120 was not supported by the results of the primary analysis as reported previously. In order to further assess the efficacy of AST-120, we examined clinical and geographic factors by post hoc analyses using pooled populations of 2 trials.

Methods: The primary endpoint was a composite of dialysis initiation, kidney transplantation and serum creatinine doubling. The same statistical methods for the efficacy endpoint analysis were applied for these post hoc analyses.

Results: In a multivariable analysis using baseline parameters, positive hematuria and elevated U/P(UrC) were found to be an independent risk factor for the primary endpoint. In the ITT population with positive hematuria, elevated U/P(UrC) (1.0) and ACEI/ARB use, a difference between the AST-120 and the placebo treatment groups was observed in primary endpoint occurrence (HR 0.74, 95% CI 0.56-0.96). In subgroup analysis by country, a higher event rate was observed in the USA population than outside the USA. In the ITT population from the USA with ACEI/ARB use, a difference between the AST-120 and the placebo treatment groups was observed in primary endpoint occurrence (HR 0.74, 95% CI 0.56-0.98).

Conclusions: These results suggest that there may be a beneficial effect of adding AST-120 to standard therapy regimens in high risk populations such as patients with hematuria and elevated U/P(UrC) and in the patients similar to those enrolled in the USA EPPIC trials. Due to its post hoc nature of the analysis, further prospective studies are needed to confirm the results.

Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma Co
Kureha Co

TH-PO655

A Phase 2 Study on the Effect of Tenapanor on Albuminuria in Patients with T2DM and CKD

Bergver V. Stefansson,1 David P. Rosenbaum,2 Peter J. Greasley,3 Maria Leonsson Zachrisson,4 Anna Maria Langkilde,4 1AstraZeneca R&D, Mölndal, Sweden; 2Ardelyx Inc., Fremont, CA.

Background: Patients with type 2 diabetes mellitus (T2DM) and CKD are treated with renin-angiotensin-aldosterone system (RAAS) inhibitors to slow the decline in renal function. The effectiveness of RAAS inhibition is limited by high sodium (Na) intake. Tenapanor (AZD1722), an inhibitor of the Na+/H+ exchanger NHE3, reduces absorption of Na and phosphate from the gut. This trial evaluated the effects of tenapanor on albuminuria levels, which may be associated with renal function decline, in patients with T2DM and CKD stage 3 receiving RAAS inhibitors.

Methods: This was a randomized, placebo-controlled, 12-week study (NCT01847992) in patients with urine albumin-to-creatinine ratio (UACR) 200–1500 mg/g. The starting dose of tenapanor hydrochloride was 15 mg bid: there was a 4-week titration period (dose escalation up to 60 mg bid followed by reduction down to 5 mg bid), based on gastrointestinal tolerability, before fixed-dose treatment with 5–60 mg bid for 8 weeks.

Results: Patients were randomized to tenapanor (n=77; mean±SD urinary Na, 189±85 mmol/day; n=51) or placebo (n=51; mean±SD urinary Na, 189±85 mmol/day; n=51; completed, n=66). Reductions from baseline to week 12 in UACR were 16% for tenapanor (n=51) or placebo (n=77; mean±SD urinary Na, 189±85 mmol/day; completed, n=66). Tenapanor had no observed effect on systolic or diastolic BP or eGFR. Changes (tenapanor vs placebo) in urinary Na were (L/R mean±SE) -9.6±9.7 vs -1.5±9.1 mmol/day (p=0.54) and in urinary phosphorus was (mean±SD): -3.8±1.4 vs 1.7±9.7 mmol/day. Tenapanor treatment resulted in a softer consistency and increased frequency of stool compared with placebo. The tolerability profile of tenapanor was consistent with that in other studies, with diarrhea reported more frequently with tenapanor use.

Conclusions: In patients with T2DM and CKD stage 3, the pharmacodynamic effects of tenapanor were confirmed, as shown by softer consistency and increased frequency of stool, and reduced urinary phosphorus excretion following tenapanor treatment. However, these observations did not translate into effects on albuminuria.

Funding: Pharmaceutical Company Support - AstraZeneca

TH-PO656

Effect of Fluvastatin Treatment on Proteinuria in Diabetic Patients with Chronic Kidney Disease

Jin Joo Cha,1 Kitae Kim,1 Hye sook Min,1 Jungyeon Ghee,1 Yeo-Joo Kim,2 Eun-Young Lee,1 Shin-Wook Kang,1 Tae-Hyun Yoo,1 Jung Tak Park,1 Yaeni Kim,1 Cheol Wheel Park,2 Ho Jun Chin,3 Young Sun Kang,1 Dae R. Cha.1 1Internal Medicine, Korea Univ; 2Republic of Korea; 3Internal Medicine, Seoul National Univ College of Medicine, Korea; 4Internal Medicine, The Catholic Univ of Korea Seoul St. Mary, Republic of Korea; 5Internal Medicine, Seoul National Univ Bundang Hospital.

Background: Correction of dyslipidemia with statin has shown to be protective and therapeutic in the progression of cardiovascular events. However its association with progression of kidney disease has not been established. In this study, we investigated the efficacy of fluvastatin (Lescol XR) on the progression of diabetic nephropathy in patients with renal insufficiency.

Methods: A total of 75 diabetic patients with CKD (stage 2 to 4) completed this multicenter, randomized 12 month controlled trial. All patients were treated with 20mg fluvastatin for 6 months. At month 6, patients were randomized to either continue or to discontinue fluvastatin for additional 6 months. Primary endpoint was the difference in urinary protein to creatinine ratio between the groups at 12months.

Results: Baseline characteristics showed no differences between the groups in HbA1c, HOMA-IR, diabetes duration and estimated glomerular filtration rate (GFR). Majority of patients (81%) were using RAS blockers. After 6months of fluvastatin treatment, there was no significant decrease in urinary protein excretion or microalbumin excretion. Estimated GFR significantly declined at 6months in both groups and continued to decline after discontinuation of fluvastatin, whereas the change was not significant with fluvastatin treatment. Interestingly, HOMA-IR significantly improved in continuation group. Significant decrease in total and low density cholesterol was observed after 6, 12months in patients treated with fluvastatin.

Conclusions: In conclusion, there was no significant reduction in proteinuria with fluvastatin treatment in diabetic patients with chronic kidney disease. However, our study suggests that there might be a role in statin to slow the progression of kidney disease.

Funding: Pharmaceutical Company Support - Norvatis Pharmaceuticals

TH-PO657

Hyperkalemia in the HALT PKD Trial

Ronald D. Perrone,1 Kaleab Z. Abebe,2 Peter G. Czarnecki,3 Marie C. Hogan,4 Theodore I. Steinman,5 Susan Spillane,6 Charity G. Moore.1 1Tufts; 2U Pittsburgh; 3Brigham and Womens; 4Mayo Clinic; 5BIDMC, for the HALT PKD Investigators.

Background: HALT-PKD was a prospective, randomized trial designed to determine the effects of dual renin-angiotensin system (RAAS) blockade and blood pressure (BP) reduction on ADPKD progression. In view of prior reports of hyperkalemia (HK) with dual RAAS blockade, we describe the frequency and severity of HK in HALT-PKD.

Methods: Study A subjects with eGFR >60 ml/min aged 15-50 were randomized to lisinopril (L) and placebo (P) vs L and telmisartan (T) with two levels of BP control: standard (SBP) [120-130/70-80 mmHg] vs low (LBP) [95-110/65-75 mm Hg]. Study B subjects with eGFR 25-150 ml/min aged >19 years were randomized to L, P and L plus T with standard BP (SBP) and LBP. Serum K was measured every 6 months at study visits, within 1-2 weeks after an increase in L or T dose, and every 3 months when eGFR was less than 30. All elevated serum K values were reviewed on a monthly basis by a quality control committee.

Results: HK was infrequent in Study A; mild, but not moderate or severe HK, was more common in Study B.

Funding: NIHDKK Support, Private Foundation Support

<table>
<thead>
<tr>
<th>Hyperkalemia</th>
<th>STUDY A</th>
<th>STUDY B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L/T (273)</td>
<td>L/P (285)</td>
</tr>
<tr>
<td>Mild &gt;5.5 - 6</td>
<td>7.7 (3%)</td>
<td>5.4 (1%)</td>
</tr>
<tr>
<td>Moderate &gt;6 - 6.5</td>
<td>5.4 (2%)</td>
<td>1.1 (0.4%)</td>
</tr>
<tr>
<td>Severe &gt;6.5</td>
<td>1.1 (4%)</td>
<td>0.0 (0%)</td>
</tr>
</tbody>
</table>

# events, % participants, (%) participants; L/T: lisinopril/telmisartan, L/P: lisinopril/placebo, SBP: standard BP, LBP: low BP. There were no significant differences in HK due to L or LBP.

Intervention with dietary K reduction, furosemide, or Kayexalate was successful in resolving serum K in all participants. There was no relationship between HK and serious adverse events (SAEs) and there were no SAEs within 21 days after detection of HK.

Conclusions: HK was infrequent with eGFR>60, despite dual RAAS blockade or intensive BP control. Mild HK was more common with eGFR 25-60, but easily managed. Severe HK was rare. With careful management, dual RAAS blockade and intensive BP control were safe in the HALT PKD trial. Clinical use of dual RAAS blockade or intensive BP control should only be done with close monitoring.

Funding: NIDDK Support, Private Foundation Support

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

239A
CHRONIC DIURETIC THERAPY DOES NOT IMPAIR THE EFFECTIVENESS OF PATIROMER IN HYPERKALEMIC PATIENTS WITH CKD}

Marta Mayo,1 Martha Mayo,1 Dahlia Garza,1 Yuri Statsis,2 Susan Arthur,1 Lance Berman,2 David A. Bushinsky,3 Daniel J. Wilson,2 Murray Epstein,4 1University of Maryland; 2Relypsa, Inc.; 3University of Rochester; 4Univ of Miami.

**Background:** Loop diuretics control volume in advanced CKD and may reduce elevated serum K⁺, but can induce intravascular volume depletion or goit and may not be ideal for long-term hyperkalemia (HK) management. Thus, the efficacy of investigational serum K⁺ binders in HK pts on chronic diuretics is of interest. We compared patient’s effects in RAASI-treated CKD pts with HK to those not on diuretics in the treatment phase of the 2-part OPAL-HK study.

**Methods:** Pts (n=243) with baseline (BL) s-K⁺ 5.1 to 6.5 mEq/L on RAASI received patiromer (4.2 or 8.4 g BID to start) for 4 wks. For this post hoc analysis, Ds-K⁺ phase of the 2-part OPAL-HK study.

**Results:** Mean (SD) age was 64 (10.5) yr; 58% were male. Mean s-K⁺ decreased from BL at wk 4 in all subgroups (Table). Reductions in s-K⁺ did not differ in pts receiving any diuretic vs those not on diuretics. Patiromer was well tolerated; mild–moderate GI constipation was the most common AE. Hypokalemia (s-K⁺<3.5 mEq/L) was infrequent. PD: Conclusions: The s-K⁺-lowering efficacy of patiromer in HK pts was unaffected by concomitant diuretics.

### Table: Efficacy, safety, and disease characteristics in pts on patiromer ± diuretics

<table>
<thead>
<tr>
<th></th>
<th>Loop (n=55)</th>
<th>Thiazide/ T-lake (n=51)</th>
<th>Combination Loop/ thiazide (n=15)</th>
<th>Any diuretic (n=117)</th>
<th>No diuretic (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s-K⁺, mEq/L</td>
<td>4.90</td>
<td>2.55</td>
<td>66.7</td>
<td>41.0</td>
<td>32.7</td>
</tr>
<tr>
<td>Mean ± SD (mg/d)</td>
<td>2.40 ± 0.9</td>
<td>2.08 ± 0.8</td>
<td>2.07 ± 0.7</td>
<td>2.28 ± 0.8</td>
<td>2.11 ± 1.2</td>
</tr>
<tr>
<td>Mean ± SD s-K⁺, mg/dL</td>
<td>5.61 ± 0.06</td>
<td>5.58 ± 0.07</td>
<td>5.67 ± 0.13</td>
<td>5.58 ± 0.04</td>
<td>5.57 ± 0.05</td>
</tr>
<tr>
<td>Wk 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s-K⁺, mEq/L</td>
<td>−1.02 ± 0.06</td>
<td>−1.14 ± 0.86</td>
<td>−0.97 ± 0.06</td>
<td>−0.69 ± 0.19</td>
<td>−0.95 ± 0.05</td>
</tr>
<tr>
<td>p-value</td>
<td>[0.001]</td>
<td>[0.001]</td>
<td>[0.001]</td>
<td>[0.037]</td>
<td>[0.001]</td>
</tr>
<tr>
<td>Hypokalemia, %</td>
<td>0.0</td>
<td>6.7</td>
<td>6.7</td>
<td>1.7</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*p vs without a s-K⁺ value at a weekly visit after day 3 were excluded.

Funding: Pharmaceutical Company Support - Relypsa, Inc.

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

**Underline represents presenting author.**

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**TH-PO661**

**Effects of Candesartan on Clinical Remission in IgA nephropathy Treated with Steroid Pulse Therapy and Tonsillectomy (CAST IgA Study) – A Randomized Control Study**

Kentarou Kohagura,1,2 Hisatomo Arima,1,3 Hitoshi Miyasato,1,4 Tung-Huei Chang,1 Hiroyuki Kobori,1,5 Kunitoshi Iseki,6 Yusuke Ohya,7 Department of Clinical Research, Nagoya City Univ; 2International Univ of Health and Welfare.

**Background:** Recently, we have reported that angiotensin receptor blocker (ARB) can attenuate lower sodium balance and resultant restoration of non-dipper BP rhythm with no acceleration of sodium excretion did not change (160 ± 10 mmol/day, p=0.04), and tubular sodium reabsorption (13000:9300±11700:7800 mmol/day, p=0.04), and tubular sodium reabsorption (13000:9300±11700:7800 mmol/day, p=0.04) were both decreased, while urinary sodium excretion did not change (160±80±161±60 mmol/day, p=0.9). Decrease in tubular sodium load correlated directly with baseline urinary angiotensinogen excretion (uATG) (r=0.10), and the decrease in night/day SBP ratio (r=0.16). uATG was significantly decreased (150±10±80±20 mg/gCr, p=0.02).

**Conclusions:** Add-on administration with HCTZ to ARB can attain the lower sodium balance and resultant restoration of non-dipper BP rhythm with no acceleration of intravascular RAS.

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**TH-PO662**

**TacroSilmon Monotherapy Follows Intravenous Methylprednisolone in Adults with Minimal Change Nephritic Syndrome: A Prospective, Multi-Centered, Open, Randomized, Controlled Trial**

Xiayu Li, Jianghua Chen. Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang Province, China.

**Background:** Adults with minimal change nephritic syndrome (MCNS) show excellent responses to glucocorticoid (GC). However, responding patients may suffer relapses and GC related frequent side effects. TacroSilmon (TAC) may serve as an alternative to GC therapy for adult MCNS with less frequent side effects.

**Methods:** This randomized, multicentre, controlled study was undertaken in 8 renal units across the China. 119 adult-onset patients were randomly allocated to receive the conventional GC therapy (GC group) or tacroSilmon monotherapy (tacroSilmon group) for 30 days. The primary endpoint was the remission of proteinuria (≤0.2g/gCr) and hematuria.

**Results:** Baseline proteinuria (g/gCr, interquartile range) were comparable between the groups (0.90, 0.70-1.20 vs. 0.95, 0.60-1.50, P=0.97). Cumulative remission rate in control group and ARB group at 6, 12 and 24 M were comparable (10.8% vs. 15% [P=0.58], 29.7% vs. 30.0% [P=0.98], 45.9% vs. 42.5% [P=0.76]). The hazard ratio for remission was 1.01 (95% confidence interval, 0.51-1.99; p=0.98). Proteinuria was slightly heavier in control group than ARB group (0.11 vs. 0.21g/gCr, p=0.002) at 6 M, but comparable afterwards (0.20 vs. 0.23 g/gCr at 12 M, 0.12 vs. 0.13 g/gCr at 24 M). Although remission rate of hematuria was comparable until 12 M, it was higher in control group than ARB group at 24M (85% vs. 64%, P=0.008).

**Conclusions:** Early use of ARB regardless of the level of blood pressure combined with steroid pulse and tponsillectomy may not provide benefit for clinical remission among IgA nephropathy.

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

**Underline represents presenting author.**

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**TH-PO659**

**Add-On HCTZ Administration to ARB Can Achieve Lower Sodium Balance in CKD Patients**

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**Background:** Angiotensin receptor blocker (ARB) may have additional benefit on the conventional therapy with steroid pulse and tponsillectomy among Japanese patients with IgA nephropathy.

**Methods:** Severity seven patients with IgA nephropathy were randomly assigned to regular regimen consists of steroid pulse followed by oral prednisolone for 6 months and tponsillectomy (control group, n=37) regular regimen combined with ARB (candesartan) for 6 months (ARB group, n=40). Among all patients in both groups who did not achieve remission of proteinuria at 12 M, candesartan was initiated and tponsillectomy until 24 M visit. The primary endpoint was the remission of proteinuria (≤0.2g/gCr) and hematuria.

**Results:** Baseline proteinuria (g/gCr, interquartile range) were comparable between the groups (0.90, 0.70-1.20 vs. 0.95, 0.60-1.50, P=0.97). Cumulative remission rate in control group and ARB group at 6, 12 and 24 M were comparable (10.8% vs. 15% [P=0.58], 29.7% vs. 30.0% [P=0.98], 45.9% vs. 42.5% [P=0.76]). The hazard ratio for remission was 1.01 (95% confidence interval, 0.51-1.99; p=0.98). Proteinuria was slightly heavier in control group than ARB group (0.11 vs. 0.21g/gCr, p=0.002) at 6 M, but comparable afterwards (0.20 vs. 0.23 g/gCr at 12 M, 0.12 vs. 0.13 g/gCr at 24 M). Although remission rate of hematuria was comparable until 12 M, it was higher in control group than ARB group at 24M (85% vs. 64%, P=0.008).

**Conclusions:** Early use of ARB regardless of the level of blood pressure combined with steroid pulse and tponsillectomy may not provide benefit for clinical remission among IgA nephropathy.
primary outcome variables was remission. The secondary outcome variables included relapse-free time to remission, time to relapse, change of serum creatinine (Scr) and eGFR, and adverse events (AEs).

Results: Remission (either complete or partial remission) was attained by 51 of 53 patients (96.2%) in GC group and 55 of 56 (98.3%) of patients in TAC group (p = 0.611). Of 53 patients (96.2%) in GC group and 52 of 56 patients (92.9%) in TAC group experienced complete remission, respectively (p = 0.679). The mean time to remission in GC group (2.7±2.3 weeks) was similar (p = 0.548) to TAC group (2.6±2.6 weeks), respectively. Relapse occurred in 25 (49.0%) of GC group versus 25 (45.5%) of TAC group (p = 0.847), and 7 patients in GC group were treated with TAC as the second-line therapy after first-line therapy suffered frequent relapse. The mean time to relapse in GC group (27.6±16.9 weeks) was similar (p = 0.617) to TAC group (25.2±16.9 weeks), respectively. There was no significant difference of Scr and eGFR between two groups during therapy and follow-up periods. Adverse events were more frequent in GC group than in TAC group (128 events versus 81 events), of which 9 (7 in GC group and 2 in TAC group) were deemed serious AEs.

Conclusions: The regimen with tacrolimus monotherapy follows short-term intravenous methylprednisolone was noninferior to conventional GC treatment in adult-onset MCNS, and could replace steroids as the initial therapy for such patients due to less-frequent side effects.

TH-PO663
Changes in Concentrations of Chemokine Ligands for CCR2 and CCR5 Receptors in Response to Administration of PF-04634817 Karen M. Page, Julie M. Lee, Amira Quazi, Lori Fitz, Weidong Zhang, Steven A. Gilbert, Nick Pullen, Robert Webster, Jeremy D. Gale. Worldwide Research and Development, Pfizer, Cambridge, MA.

Background: PF-04634817 is a competitive dual inhibitor of CCR2 and CCR5 receptors. In early clinical studies, administration of this compound to healthy volunteers has been found to elevate circulating levels of the primary CCR2 ligand, CCL2 (MCP-1). The ability of PF-04634817 to reduce albuminuria, compared with placebo, after administration for 24 weeks was tested in a phase 2 study in subjects with diabetic nephropathy and macroalbuminuria. In this study, samples were collected to confirm the previously observed pharmacological effect on CCL2 in this population and to examine the impact on other ligands known to bind to CCR2 or CCR5 receptors.

Methods: CCL2 in serum and urine was measured by ELISA from 226 subjects at Eurofinns (The Netherlands) at baseline and during treatment at weeks 4, 8, and 12. CCL5 (RANTES) was measured in plasma and urine as part of a multi-analyte panel at Myriad Rules Based Medicine (Austin, TX) and CCL4 (MCP-1), CCL3 (MIP-1a), and CCL4 (MCP-1b) were measured in plasma using two Luminex assays (Bios-Rad, Berkeley, CA) from 158 subjects at baseline and weeks 8 and 12.

Results: At week 12, serum levels of CCL2 and plasma levels of CCL4 were elevated 9.25 fold (p < 0.0001) and 2.11 fold (p < 0.0001) respectively following administration of PF-04634817, but not placebo. Elevation of both chemokines was also observed at the earlier time points. Levels of CCL8, CCL5 and CCL3 in circulation and CCL2 and CCL5 in urine did not change in either group.

Conclusions: This study confirms elevation of the CCR2 ligand, CCL2, following treatment with PF-04634817 in diabetic nephropathy subjects. It also identifies the CCR5 ligand, CCL4, as another potential pharmacodynamic marker. The observed lack of apparent change in CCL5 warrants further follow up analysis.

Funding: Pharmaceutical Company Support - Pfizer

TH-PO664
Circulating Tumor Necrosis Factor Receptor Expression in a Phase 2 Study to Evaluate the Efficacy and Safety of PF-04634817 in Adults with Type 2 Diabetes and Overt Nephropathy Karen M. Page, Lori Fitz, Weidong Zhang, Steven A. Gilbert, George Bashirians, Nick Pullen, Robert Webster, Jeremy D. Gale. Worldwide Research and Development, Pfizer, Cambridge, MA.

Background: PF-04634817 is a small molecule dual inhibitor of CCR2 and CCR5, chemokine receptors found on the surface of monocytes and T cells that are involved in the development and progression of diabetic nephropathy (DN). Identifying patients with accelerated renal function decline is an important area of research. Circulating TNFRs have been correlated between the receptors (Corr = -0.90, p < 0.0001). Soluble TNFRs have been identified as biomarkers with potential to predict accelerated decline. In the current study, we investigated changes in soluble TNFR-1 and TNFR-2 following 12 weeks of treatment with PF-04634817 or placebo in subjects with DN.

Methods: Soluble TNFR-1 and TNFR-2 were measured from 161 subjects in serum by ELISA at baseline, weeks 8 and 12. Urinary albumin and creatinine concentrations were averaged from 3 consecutive first morning voids immediately prior to each visit. Estimated glomerular filtration rate (eGFR) was measured using the abbreviated (4 variable) Modification of Diet in Renal Disease (MDRD) formula. Study subjects were defined at baseline by a mean UACR of 180.78 ± 160.53 mg/mmol Cr and a mean eGFR of 41.46 ± 12.64 ml/min/1.73 m².

Results: Mean concentrations at baseline of soluble TNFR-1 and TNFR-2 were 4.25 ± 1.37 ng/mL and 8.27 ± 2.99 ng/mL respectively. Baseline concentrations were strongly correlated with each other and more strongly correlated with eGFR than UACR. Our observations do not support either TNFR-1 or TNFR-2 as pharmacodynamic biomarkers or as predictive biomarkers of clinical response as measured by UACR.

Funding: Pharmaceutical Company Support - Pfizer

TH-PO665
Effects of Intensified Vasodilatory Antihypertensive Treatment on Renal Function, Blood-supply and Oxygenation in Chronic Kidney Disease Dinah S. Khatir1, Michael Pedersen,2 Per R. Iverson,1 Kent L. Christensen,2 Bente Jespersen,3 Niels Henrik Bums,4 Renal Medicine, Aarhus Univ Hospital, Aarhus N, Denmark;4Comparative Medicine Lab, Aarhus Univ Hospital, Aarhus N, Denmark;4Cardiology, Aarhus Univ Hospital, Denmark;4Renal Medicine, Aalborg Univ Hospital, Denmark.

Background: Progression of Chronic kidney disease (CKD) may result from tissue hypoxia induced by small artery structural narrowing, with increased renal vascular resistance (RVR) and impaired blood supply. We investigated whether vasodilating therapy (VT) is superior to non-vasodilating therapy (nonVT) for improvement of RVR, tissue oxygenation, and preservation of kidney function.

Methods: Eighty-two hypertensive grade 3-4 CKD patients (glomerular filtration rate (GFR) 36±15 ml/min/1.73 m²) were randomised to renin-angiotensin inhibition combined with either VT (amilpenidine) or nonVT (beta-blocker metoprolol). At baseline and following 18 months of therapy we determined forearm resistance by venous occlusion plethysmography. Using magnetic resonance imaging (MRI) renal artery blood flow was measured for calculation of RVR, and blood oxygen level dependent (BOLD) MRI was used as a marker of renal oxygenation (R_2*). GFR was measured as Cr-EDTA clearance.

Results: The VT and nonVT arms had similar blood pressure levels throughout the study. At follow-up, in the VT group forearm resistance had decreased by 7% (P=0.05) and RVR by 12% (P<0.05), while in the nonVT group forearm resistance increased by 39% (P=0.01) while RVR remained unchanged. Cortical and medullary R_2* values were not affected by VT and nonVT. After 18 months GFR decline was similar in the two groups (3.0 vs. 3.3 ml/min/1.73 m²).

Conclusions: In CKD, long-term VT reduced both peripheral and RVR, but was not associated with improved renal oxygenation and did not influence loss of kidney function compared to nonVT.

Funding: Government Support - Non-U.S.

TH-PO666
The Epigenetic BET-Inhibitor RVX-208/Abapetelatone Shows Favorable Effects on ALP and eGFR in Chronic Kidney Disease (CKD) Patients – A Post-Hoc Analysis of Phase 2 Clinical Trials Karimy Kalantar-Zadeh1, Jan O. Johannsson,2 Michael Sweeney,2 Kenneth E. Lebioda,2 Ewelina Kulikowski,2 Christopher Halliday,2 Norman Cw Wong.2 1Div of Nephrology & Hypertension, Univ of California Irvine School of Medicine, Irvine, CA; 2Research and Development, Resverlogix Corporation, Calgary, AB, Canada.

Background: The epigenetic BET inhibitor RVX-208 is a small molecule with anti-inflammatory and apolipoprotein A-1 (apoA-1) enhancing effects. It exerts its’ actions by inhibiting bromodomain-extra-terminal proteins (BET) thus inhibiting acetylated lysine, protein, and histones, from binding to the same site. In this process chromatin structure is altered and activity of select genes inhibited. A subpopulation analysis from the double-blind placebo controlled phase 2b program in cardiovascular disease (CVD) identified 81 subjects with CKD based on eGFR < 60 ml/min/1.73m².

Methods: The effect of selective BET inhibition on key renal parameters in 81 CKD subjects (RVX-208 n=58/Placebo n=23) that were treated with either RVX-208 100mg/day or 150 mg b.i.d or matching placebo for 3 to 6 months were studied. A pooled analysis was performed to assess the changes from baseline for eGFR, ALP and creatinine at 3 and 6 months.

Results: ALP changes for RVX-208 and placebo were -14.2% and -3.0% respectively at 3 months (p<0.05 vs. placebo) and -13.9% vs. -6.28% (p<0.05 vs. placebo) at 6 months. Following 6 months of RVX-208 treatment, eGFR showed an increase of +3.4% (p<0.04 vs. baseline) in the RVX-208 group compared to a decrease of -5.9% in the placebo group. After 6 months treatment serum creatinine was decreased (-2.82%, p<0.10 vs. baseline) compared to increases in the placebo group of +3.9% and +4.85% at 3 and 6 months, respectively. No significant change in eGFR and serum creatinine were observed after 3 months RVX-208 treatment, albeit nominal numbers went in the normalization directions.

Conclusions: Six months treatment with RVX-208, a selective BET selective BET-inhibitor significantly lowers serum ALP, and shows trends for eGFR and serum creatinine improvements. A phase 3 study BETonMACE is being planned in which these effects will be assessed in the prospective setting in diabetic CVD patients with or without CKD.
Impact of Grazoprevir plus Elbasvir on Health-Related Quality of Life in Patients with Hepatitis C Virus Genotype 1 Infection and Chronic Kidney Disease Stages 4 and 5

Jean Marie Arwood,1 Boshao Zhang,1 Beth Jackson,1 David Roth,2 Annette Bruchfeld,1 Shazia Khaajwa,1 Elisa Martinez,1 Chizoba Nwankwo,1 Chris Mast,1 Wayne L. Greaves,1 Merek & Co., Inc.,1 Univ of Miami Miller School of Medicine,2 Karolinska Univ Hospital.

Background: Health-related quality of life (HRQOL) is diminished in patients with hepatitis C virus (HCV) infection and chronic kidney disease stages 4 and 5 (CKD4/5). A randomized, double-blind, placebo-controlled trial of Grazoprevir 100 mg & Elbasvir 50 mg (GZR+EBR) once daily for 12 weeks was conducted among patients with HCV genotype 1 infection and CKD4/5. GZR+EBR was highly effective, with a sustained viral response rate at follow-up week 12 (FW12) of 99.1% (95% Confidence Interval 95.3%‐100.0%). GZR+EBR was well-tolerated, with a safety profile that was comparable to placebo. The aim was to assess whether HCV treatment with GZR+EBR altered the HRQOL profile.

Methods: 224 patients were randomized and received at least one dose of study drug (GZR+EBR:n=111, Placebo=n=113). Patients completed the SF-36v2 Health Survey at baseline, treatment week 12 (TW12), and FW12 (GZR+EBR arm). Mean change from baseline in health domain, mental component summary (MCS) and physical component summary (PCS) scores, with 95% CIs, were estimated. Differences in mean change scores, with 95% CIs, were estimated between treatment groups.

Results: At baseline, mean scores were balanced between treatment groups. At TW12, GZR+EBR had more favorable changes from baseline in PCS and health domain scores (except for SF, RE, MCS) than placebo.

Conclusions: Treatment with GZR+EBR had a positive impact on HRQOL as compared to placebo. In addition, changes in HRQOL were substantially more favorable than the large declines in HRQOL historically associated with interferon and ribavirin-containing regimens.

Funding: Pharmaceutical Company Support - Merek & Co., Inc.

Bortezomib Before, in and After Autologous Hematopoietic Stem Cell Transplantation in Patients with Newly Diagnosed AL Amyloidosis

Xiang-hua Huang,1 Qingwen Wang,1 Wencui Chen,2 Dehua Gong,1 Caihong Zeng,1 Xiang-hua Huang,1 National Clinical Research Center of Kidney Diseases.

Background: In previous study, we have demonstrated that the outcome of treating AL amyloidosis with bortezomib with dexamethasone (BD) induction followed by autologous hematopoietic stem cell transplantation (ASCT) was superior to the outcome of the ASCT treatment alone. To further improve the hematologic response rate, we conducted a prospective trial of bortezomib before, in and after ASCT in newly diagnosed AL amyloidosis.

Methods: Newly diagnosed AL amyloidosis patients who met the criteria of ASCT could be included in this trial. Treatment schedule consisted of two cycles of BD induction therapy (bortezomib 1.3mg/m² and dexamethasone 40 mg/m² on days 1, 4, 8 and 11 followed by 10 days rest), ASCT treatment (the conditioning regimen consisted of melphalan and bortezomib, the dose of bortezomib was 1mg/m² in day -6, -3, +1, +4), and four additional 21-day cycles of bortezomib treatment (with a dose of 1.6mg/m² on day 1 and 8 of the cycle) will be conducted as consolidation therapy after ASCT. The objectives were hematologic response, tolerability and survival.

Results: Sixty patients were enrolled in the study. 9 patients had cardiac involvement. The overall hematologic response rate was 94.4% (17/18), including 13 patients (72.2%) with complete response, 4 patients (22.2%) with very good partial response. The organ response rate was 72.2%. The organ response was reached in 13 patients of the 18 patients with renal involvement and 7 of the 9 patients with cardiac involvement. Peripheral neuropathy and infection were the common adverse events during the treatment, and 4 patients have been discontinued bortezomib for neuropathy. No death occurred in this study. After a median follow up of 24 months, the overall survival was 100%, and the estimated progression free survival was 91% at 48 months.

Conclusions: In conclusion, our preliminary data suggest that incorporating bortezomib into induction, conditioning and consolidation with ASCT yielded a high rate of hematologic response with tolerable toxicity. ClinicalTrials.gov Id: NCT01273844.

Funding: Pharmaceutical Company Support - Xi’an Janssen Pharmaceutical Ltd: Research Funding.

Phase 1 and 1b Studies of PBI-4050, a Novel Anti-fibrotic Agent for Chronic Kidney Disease

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Background: PBI-4050 is an orally administered new chemical entity with a MW < 300 showing remarkable anti-fibrotic efficacy in multiple pre-clinical models of fibrosis in kidney, liver, lung, and heart. Phase 1 studies in normal volunteers and Phase 1b studies in patients with advanced nephropathy associated with Type 2 diabetes have been successfully completed.

Methods: Single ascending dose (SAD) phase 1 studies were performed in 5 cohorts of healthy volunteers, 6 subjects in each cohort receiving PBI-4050 and 2 receiving identical placebo, at doses of 400 to 2,400 mg po. The 800 mg cohort had studies in both the fasting and fed state. Phase 1b studies were performed in 8 subjects with Stage 3b and 4 nephropathy associated with Type 2 diabetes (eGFR 15-45 mL/min), 2 of whom received placebo; after a single dose of 800 mg po and a washout period, the same patients received 800 mg po daily for 10 days.

Results: In the SAD study all doses were well-tolerated; there were no dose-related adverse events (AE) and no serious AE’s. The half-life (T1/2) mean was 3.3-5.0 hours, dependent on dose (See Figure). There was a 34% decrease in the area under the curve (AUC0-t) after a fat meal. Protein binding in plasma was > 99%.

In the patients with CKD the T1/2 mean and AUC0-t were unchanged and there was no change in plasma protein binding. In the 10 day study there was no significant drug accumulation. One subject experienced diarrhea listed as mild to moderate and possibly related. There were no other significant AE’s.

Conclusions: PBI-4050 was found to be safe in normal volunteers and in advanced CKD. The pharmacokinetics and protein binding were unchanged in CKD. Phase 2 studies are underway in patients with CKD associated with Type 2 diabetes.

Funding: Pharmaceutical Company Support - ProMetic Life Sciences

Immunogenicity and Safety of Quadrivalent Human Papillomavirus (HPV) Types 6/11/16/18 Recombinant Vaccine in CKD Stage IV-V-VD

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Background: Up to 70% of sexually active adults will become infected with HPV during their lifetime. HPV infection can result in anogenital cancer and genital warts. Studies have demonstrated the efficacy of HPV-6/11/16/18 vaccination (GARDASIL®) 3 doses at day 1, month 2, and month 6 to lower the occurrence of high-grade cervical intraepithelial neoplasia. HPV vaccination has been integrated in health care in non-CKD. However, immunogenicity and safety of the HPV vaccine have not been proven in CKD. This study investigated the immunogenicity and safety of quadrivalent HPV-6/11/16/18 vaccination by the current recommended dose/schedule in CKD stage IV-V-VD.

Methods: This is a prospective, open-label study. CKD stage IV-V-VD patients were enrolled. Vaccine was given as a 0.5mL intramuscular injection at day 1, month 2 and month 6. Each dose contains 20µg HPV6 L1 virus-like-particle(VLP), 40µg HPV11 L1 VLP, 40µg HPV16 L1 VLP, and 20µg HPV18 L1 VLP. HPV type-specific Ab response was performed by multiplexed, competitive LumineX immunosassay(CLI) to neutralizing epitopes on HPV6/11/16/18 at day 1 and month 7.

Results: Sixty CKD cases(male/female:28/32 ) received vaccination. Pre-dialysis/HDCAPD cases were 2/44/14 cases. Mean age was 25.0±7.7years. Average Cr and eGFR were 10.3±4.5mg/dl and 14.3±12.8mL/min/1.73m² respectively. Five patients underwent kidney transplantation before completing 3 doses of vaccination. At baseline, anti-HPV seropositivity was 3.3-8.3% for HPV genotype6/11/16/18.

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Underline represents presenting author.
TH-PO671

Minocycline-EDTA: Good Performance for Catheter Patency Maintenance

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Background: Poor flow (PF) and catheter-related blood stream infections (CRBSI) are highly prevalent among CKD 5D patients with long-term central venous catheters. Heparin (H) catheter lock solutions are commonly used to maintain catheter patency, however PF and CRBSI risk remains high. The purpose of this study was to evaluate two lock solutions on reduction of PF and CRBSI: one, a lock solution combining of the tetracycline antibiotic minocycline with the anticoagulant/chelation agent EDTA (M-EDTA) versus H; and other, trisodium citrate (C) versus H. M-EDTA and C were also evaluated as to their safety versus H.

Methods: Thirty CKD 5D patients on high-efficiency hemodialysis (blood flow rate ~350 ml/min) at the Integrated Centre of Nephropathy (Guarulhos, Brazil) were randomized 1:1:1 to receive M-EDTA, C or H locks for 15 weeks. Lock solutions concentrations were M-EDTA 30 mg/ml/3 mg/ml, C 30% (C) and H 1,000 U/ml and both investigators and patients were blinded to treatment allocation. The primary end-point was a 10% reduction in HD blood flow rates (35ml). The frequency of CRBSI was recorded. Bleeding and lock solution-related adverse events were the primary safety end points. Logistic Regression was performed to evaluate differences in PF rates among the treatments (SPSS version 13.0, IBM, USA).

Results: PF was significantly higher among patients on H (7/10) compared to C (3/10) and M-EDTA (1/10) locks, according to results of Logistic Regression comparison: H vs C (p=0.002); H vs M-EDTA (p=0.016). Heparin was associated with the highest rate of PF. M and C lock solutions had similar PF rates. Only one CRBSI was identified in a single M-EDTA lock. There was no difference in CRBSI prevention. M-EDTA and C seem may preserve catheter patency. A larger clinical trial is warranted to confirm these findings.

Conclusions: Favouring Government Support - Non-U.S. 

Funding: Pharmaceutical Company Support - MSD provided vaccine doses, Government Support - Non-U.S.

TH-PO672

Long-Term Outcomes After Renal Artery Stenting Among Diabetic and Non-Diabetic Patients with Renal Artery Stenosis

Happy Parouk Sadiek, Amol Mittal, Shradhha Narechania, Bassel Akhik, Gaurav Kistangari, Arash Rashidi. 1Internal Medicine, Cleveland Clinic-Fairview Hospital, Cleveland, OH; 2Internal Medicine, Cleveland Clinic-Fairview Hospital, Cleveland, OH; 3Internal Medicine/Nephrologist, Cleveland Clinic-Fairview Hospital, Cleveland, OH.

Background: The current study aims to determine if renal-artery stenting affects mortality and/or delays the onset of Renal Replacement Therapy over a 10 year period in diabetic and non-diabetic patients with renal artery stenosis (RAS).

Methods: Using electronic medical records of Cleveland Clinic Health System, 168 patients with a diagnosis of RAS were identified from 01/01/2000 to 12/31/2004. Patients were categorized into two groups - ‘stented’ for those who underwent renal artery stenting and ‘medical’ for those who were treated with medical therapy alone. The purpose of this study was to evaluate two lock solutions on reduction of PF and CRBSI: one, a lock solution combining of the tetracycline antibiotic minocycline with the anticoagulant/chelation agent EDTA (M-EDTA) versus H; and other, trisodium citrate (C) versus H. M-EDTA and C were also evaluated as to their safety versus H.

Results: Out of 168 patients, 67 were in ‘stented’ group and 101 in ‘medical’ therapy group; of which patients represented 24% in the stented group and 38% in the medical group. Overall, a higher percentage of deaths were seen in ‘stented’ group (64% vs. 42%, p 0.02). Multivariable analysis revealed CKD stage >=3 as the only variable significantly associated with death (HR 2.45, 1.32-4.85, p=0.003). In another analysis - bilateral renal artery stenosis, CKD stage >=3 and DM were found to be significantly associated with the occurrence of composite endpoints of RRT and/or death. On subgroup analysis among diabetics, multivariable analysis revealed mortality benefit among patients who underwent renal artery stenting (HR 0.15, 0.03-0.55, p=0.006) when compared to ‘medical’ therapy alone, and a trend towards delaying the onset composite end point (HR 0.28, 0.06-1.11, p=0.07). 

Conclusions: Renal-artery stenting in RAS did not confer any benefit in terms of survival or delaying the onset of RRT; however stenting of renal arteries in diabetics showed a survival benefit and may have some benefit in delaying the onset of RRT. Further research is warranted to confirm these findings.

TH-PO673

Oral versus Intravenous Hydration to Prevent Contrast Induced Nephropathy

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Background: Contrast Induced Nephropathy (CIN) complicates the use of iodinated contrast media. Guidelines advise identification of high risk patients and intravenous hydration as preventive measure. We conducted a multicenter randomized controlled trial to compare oral (home) hydration versus standard therapy (NCT01654328). The trial was stopped prematurely because of a low recruitment rate.

Methods: Patients with an eGFR<60ml/min/1.73m² were stratified for risk of CIN based on eGFR and the presence of risk factors (diabetes, peripheral arterial disease, heart failure, age, anemia, use of diuretics or NSAID’s) Exclusion criteria were: overhydration, use of 2 diuretics, severe heart failure, CKD stage V. High risk patients were randomized. Arm A: sodium chloride 1g/10kg of body weight/day per os on day -2 and -1 before contrast exposure. Maximum 10g sodiumchloride/day. Arm B: NaCl 0.9% 1000ml in 4 hrs or in case of heart failure or severe renal failure 12 hrs before and after contrast administration.

We evaluated the incidence of CIN (defined as a rise in serum creatinine >25% or ≥44umol/L 48-96hrs after contrast) and adverse events.

Results: From Aug 2012 until Nov 2014 there were 1593 radiological procedures in high risk patients. In 1116 the inclusion criteria were met. Only 255 patients gave informed consent. We evaluated 233 procedures (11 missing data, 7 intercurrent hospitalisation, 4 severe nausea and vomiting) (table 1) provides clinical characteristics and outcome data. Nausea was a frequent complaint during oral hydration. One SAE (overhydration) was related to IV hydration.

Conclusions: Oral hydration is as effective as intravenous hydration in preventing CIN. Oral hydration obviates the need for hospital admission, and thus reduces costs. Adaptation to the protocol is needed to prevent nausea and vomiting.

TH-PO674

Obstructive Sleep Apnea and Blood Pressure and in Patients with Hypertension and Chronic Kidney Disease Stage 2

Bodil Gade Horsstrup, 1,2 Jeppe B. Rosenberg, 1,2 Nikolaj Hoffmann-petersen, 1,2 Pia Holland Gjørup, 1,2 Jost Wessels, 1 Erling B. Pedersen, 1,2 Jesper N. Bech. 1,2 Univ Clinic of Nephrology and Hypertension, Regional Hospital West Jutland and Aarhus Univ; 2Dept of Internal Medicine, Regional Hospital West Jutland, Holstebro, Denmark.

Background: High nocturnal blood pressure (BP) and non-dipping are important prognostic factors in the evaluation of the risk of cardiovascular disease in patients with hypertension (HT). Many patients with chronic kidney disease (CKD) suffer from high nocturnal BP and non-dipping. The mechanism behind this phenomenon is unknown, but might be related to the presence of obstructive sleep apnea (OSA). In general population, OSA is observed in 10-15% of men and 5-8% of women, only symptomatically in 2-4%.

Methods: From a population study in Holstebro County, 238 subjects diagnosed with HT and CKD stage 2 were invited to participate. 70 subjects were included and underwent conventional 24-h ambulatory BP monitoring (ABPM) and application tonometry to monitor central BP (HealthSTATS BPro), 24 h urine collection for microalbuminuria, blood samples for creatinine, and cardiorespiratory monitoring to determine apnea hypopnea index (AHI). HT, nocturnal HT, resistant HT and non-dipping were defined according to current guidelines. OSA was diagnosed when AHI ≥ 5.

Results: Of the 70 subjects, 27 (39%) were diagnosed with OSA (average AHI 16.5). The subjects suffering from OSA were more obese, had lower mean oxygen saturation and longer snoring time during sleep. There were no difference between subjects with and without OSA in regard to gender, eGFR, use of antihypertensive agents, number of diuretics, resistant HT and non-dipping in OSA.

Conclusions:

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

243A
Conclusions: The occurrence of OA in a population with hypertension and CKD stage 2 was greater than expected in general population. In subjects with OA, there was a tendency towards higher central and brachial BP. It is suggested, that OA is the cause of high BP in patients with CKD stage 2.

Funding: Government Support - Non-U.S.

TH-PO675
Structural Exercise in Obese Diabetic Patients with Chronic Kidney Disease: A Randomized Controlled Trial (NCT01036490) David J. Leehey,1,2 Eileen Collins,3 Holly J. Kramer,1,4 Cheryl Cooper,3 Jolene Butler,1 Conor Mclburney,1 Christine Jelinsky,1 Susan Oconnell.1 Research, Hines VA Hospital, Hines, IL; 2 Medicine, Loyola Univ Medical Center, Maywood, IL.

Background: Patients with type 2 diabetes, obesity, and chronic kidney disease (CKD) are generally physically inactive and may benefit from an exercise program. However, there have been few randomized controlled trials to determine the benefits of exercise training in this population.

Methods: We hypothesized that exercise training in obese diabetic patients with CKD will improve physical fitness and stabilize renal function. This was a 52-week randomized controlled study. Inclusion criteria were type 2 diabetes, obesity (body mass index > 30 kg/m2), CKD stage 2-4, and persistent proteinuria (> 200 mg/day for at least 3 months). Subjects were randomized to a control group consisting of dietary management alone (CON) vs. dietary management plus 12 weeks of exercise training followed by 40 weeks of supervised home exercise (EX).

Results: 46 subjects were enrolled, of whom 36 (n=18 in each group) completed at least the 12-week evaluation. At baseline, mean values (± SD) were as follows: age 70.0 ± 8.0 years, body mass index (BMI) 36.9 ± 4.5 kg/m2, body fat 41.3 ± 6.6%, glycated hemoglobin (HbA1c) 8.0 ± 1.8%, eGFR 39.9 ± 10.0 mL/min/1.73m2, and albumin urinary excretion rate (UAE) 1118 ± 1236 mg/24h. Average symptom-limited treadmill time was 7.8 ± 3.8 minutes and peak oxygen consumption (VO2peak) was 13.2 ± 3.4 mL/kg/min. Treadmill time was increased from baseline at both 12 weeks and 52 weeks in EX but not in CON (p < 0.05). Change from baseline in UAE was somewhat less in the EX than in the CON group at both 12 weeks (0.2 ± 4.7 vs. -3.4 ± 8.9 mL/min/1.73m2) and 52 weeks (-2.0 ± 5.8 vs. -3.1 ± 6.0 mL/min/1.73m2), though this did not reach statistical significance. No changes were seen between the groups in the other parameters.

Conclusions: Obese diabetic subjects with CKD have markedly impaired physical fitness. A structured exercise program improved exercise capacity but did not affect renal function.

Funding: Veterans Administration Support

TH-PO676
Strength Training Intervention in Patients with Advanced Chronic Kidney Disease: A 20 Week Pilot Study Jordana B. Cohen,1,2 Erica D. Palmer,1 Angela M. Sheridan,1 Brenten David Connor,1 Mary B. Leonard,1 Kathryn H. Schmitz,1 Francis Perry Wilson.1 University of Pennsylvania, Philadelphia, PA; 2 Stanford University, Stanford, CA; 3 Yale University, New Haven, CT.

Background: Although chronic kidney disease (CKD) is highly associated with sarcopenia and poor functional status, the feasibility and impact of longitudinal strength training in subjects with advanced CKD is not well understood.

Methods: Patients took part in a predominantly home-based 20 week program with 60 minutes of resistance training three times per week. We measured dual-energy X-ray absorptiometry (DXA) assessment of appendicular lean mass (ALM), bio-electrical impedance analysis (BIA) of fat free mass (FFM), 3 repetition-maximum (RM) assessment of maximum quadriceps strength, short-physical performance battery (SPPB) assessment of functional status, 24-hr urine creatinine collection (UCr), and Kidney Disease and Quality of Life Short Form (KDQOL-SF) in individuals >45 and <80 years of age with baseline eGFR ≥15 and ≤45 mL/min/1.73m2. We used paired t-testing and Wilcoxon sign-rank tests to assess for changes in within-subject measures before and after the intervention period as well as change-on-change analyses.

Results: 22 subjects completed the training program. The median age was 71 years, 63% were female, median eGFR was 27.9 mL/min/1.73m2, and median BMI was 29.2 kg/m2. There was a significant improvement in 1RM (mean difference 15.9 kg ± 6.5, p<0.03), but no significant change was appreciated in ALM (p=0.99), FFM (p=0.99), SPPB score (p=0.67), 24-hr urine creatinine (p=0.22), eGFR (p=0.26) or KDQOL-SF score (p=0.78). There was a significant decrease in AST (p<0.01), ALT (p<0.01), and total bilirubin (p<0.01). There was also a significant association between within-subject improvement in 1RM and improvement in FFM (p<0.02).

Conclusions: In this small study of patients with advanced CKD, we successfully developed a predominantly participant-driven strength training program. The significant improvement in 1RM indicates that patients were adherent with the protocol, however, larger studies are needed to assess for the effect of strength training on anthropomorphic measures, serologic measures, and quality of life.

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TH-PO677
Effect of a Medication Management Intervention on Acute Care Utilization After Hospitalization in CKD Katherine R. Tuttle1,2, Radica Z. Alicie,3 Robert Short,3 Joshua J. Neumiller,1,2 Benson B. Daratha,3 Brian J. Gates,2 Cynthia F. Corbett.2 Providence Health Care; 3 Washington State Univ; 1 Univ of Washington.

Background: People with chronic kidney disease (CKD) are hospitalized often and incur high risk of readmission. The study objective was to test the effect of a medication management intervention during the hospital-to-home transition on subsequent acute care utilization.

Methods: A single-center, randomized, controlled clinical trial of an intervention to improve medication information transfer (MIT) was conducted by pharmacists in patients hospitalized for CKD. Baseline and homes were randomized to either MIT or usual care. Hospitalized participants with CKD stages 3-5 (not treated by dialysis or transplant) were enrolled. The primary outcome was a composite of hospital readmissions and visits to emergency departments or urgent care centers within 90 days of discharge.

Results: Enrolled (n=182) characteristics included: age 69±11 (mean±SD) years; women 48%; diabetes 56%; hypertension 83%; eGFR (CKD-EPI creatinine) 41±14 mL/min/1.73m2; albuminuria 43 (4,521; median, IQ range) mg/g creatinine. The 3 top categories for primary diagnoses for hospitalization were cardiovascular disease (30%), infection (19%), and kidney disease (14%). Enrollies lost before the baseline visit (n=41, mainly due to severe illness) were not included as active study participants. In intent-to-treat analysis (n=141), the primary outcome occurred in 32/72 (44%) of the MIT group and 28/69 (41%) of those in usual care (Kaplan Meier, log-rank p=0.72). At 90 days post-discharge, there was no significant difference in rates of guideline-based CKD goals did not differ significantly between MIT and usual care groups: blood pressure <140/90/<130/80 mm Hg in those without/with albuminuria, respectively (43 % vs 50 %); hemoglobin A1c <7.5 % in diabetic participants (69 % vs 76 %); hemoglobin >11 g/dl (81 % vs 83 %); and phosphorous <5 mg/dl (97 % vs 96 %).

Conclusions: A medication management intervention conducted during the hospital-to-home transition did not reduce subsequent acute care utilization for hospitalized people with CKD. This high-risk population may require more comprehensive interventions to improve outcomes after hospitalization.

Funding: NIDDK Support

TH-PO678
Impact of Decision Making Tools Use at the Time of Modality Choice and PD Take on in a Multicentre-Multinational Setting Belen Marron1, Janusz Ostrowski,2 Delia Timofte,3 Marietta Torok,4 Jose C. Divino-Filho,5 Diumer Home Therapies, Medical Office, Diumer, Munich, Germany; 4 Wloclawek Diuemer Clinic, Diuemer, Wloclawek, Poland; 5 Soma Diuemer Clinic, Diuemer, Bucharest, Romania.

Background: Different factors have been attributed to low PD take on such as late referral, unplanned start, physician bias towards PD, large HD availability and lack of patient’s choice. Some references apply for 50% of PD if a good modality information is provided. Objectives: To analyze the impact of a structured modality information program with the use of decision making tools (DMTs) on type of modality choice and start.

Methods: Observational, prospective, multicentre and multinational experience. All patients under ERSD 4-5 and/or after an unplanned dialysis start if not informed before were recruited to undergo a DMT process for RRT choice. Process included: personal values evaluation, RRTs information with different tools, deliberation and patient’s modality election.

Results: 444 patients, mean age 61.5 y. from 31 clinics in Poland, Hungary and Romania underwent DMTs evaluation between August-December 2014 Staff considered PD as contraindicated in 45% of Polish patients, 32% in RO and 24% in HU. Reasons behind were mix causes and “other” than abdominal or mental. Home orientation was stated for 30% (PL), 40% (RO) and 54% (HU). Written information was largely used for 71% of patients; DVD in 9-21% and in centre HD/PD touring visits in 71-75%. PD as elected modality varied among countries: 10% (RO), 21% (PL) and 35% (HU). For patients who started dialysis (n=163), PD was used in 10% (RO), 14% (PL) and 36% (HU).

Conclusions: Use of DMTs at the time of RRT modality choice is encouraging and complies with patient’s empowerment. An increase in PD take-on has been observed in our institution after DMTs use. However, when compared with other references, our patient’s PD election is still low and factors behind this fact needs to be elucidated with a larger recruitment pool (in process).

TH-PO679
Thrombotic Microangiopathy And Complement Factor C4d Predict Poor Prognosis in IgA Nephropathy and Henoch-Schönlein Purpura Nephritis Jamie S. Chus,1 Malu Zandbergen,1 Ingeborg M. Bajema.1 Pathology, LUMC, Leiden, Netherlands; 2Nephrology, LUMC, Leiden, Netherlands; 3Medical Statistics, LUMC, Leiden, Netherlands.

Background: Thrombotic microangiopathy (TMA) was previously reported to be clinically relevant and under diagnosed in IgA nephropathy (iGAN). Complement factor C4d is a common denominator of TMA. Aim: to validate the prevalence of TMA and to determine the clinical significance of TMA and C4d in IgAN and Henoch-Schönlein Purpura Nephritis (HSN).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Gleronat Complement Factor C4d Marks Gleronat Basement Membrane Duplication: C4d Beyond Antibody Induced Injury

Methods: We included 129 native renal biopsies from 2003-2013; IgAN in 82% and HSN in 18%. Biopsies were classified according to Oxford MEST-scores, scored for vascular lesions including TMA, arterial intimal sclerosis and arteriole hyalinosis, and immunostained for C4d. Retrospectively collected clinical data included hypertention and renal function. Three groups were distinguished: absence of both TMA and C4d; presence of both TMA and C4d, and presence of either TMA or C4d. Changes in eGFR over time were compared using a linear mixed model. Renal survival was analyzed with Cox regression. Prognostic values of C4d, TMA and hypertension for renal survival were analyzed with multivariable Cox regression.

Results: The prevalence of TMA in this cohort was 20% (n=26). TMA was mainly chronic (65%; 17/26) and was localized in arteries (81% of TMA cases), glomeruli (15%) or both (4%). TMA was associated with interstitial fibrosis and tubular atrophy, arterial intimal sclerosis, hyalinosis and hypertention (P-values<0.05). TMA was strongly associated with the presence of C4d deposits (P<0.001). Linear Mixed Model analysis shows that presence of hypertension and both C4d and TMA had significantly lower eGFR (mean decrease 24 and 40 ml/min/1.73m² respectively). Patients with both TMA and C4d had significantly worse renal survival than the two groups without both C4d and TMA (HR 6.33 and 3.38 resp.) corrected for hypertention (HR 4.52 and 3.30 resp.)

Conclusions: The prevalence of TMA in IgAN and HSN is substantial (20%) but lower than previously reported. TMA was mainly chronic, arteriolar and associated with C4d, hypertension and chronic lesions. TMA and C4d mark renal function and poor renal survival in IgAN and HSN.

TH-PO680
Gleronat Complement Factor C4d Marks Gleronat Basement Membrane Duplication: C4d Beyond Antibody Induced Injury

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Background: C4d deposits along peritubular capillaries (ptc) mark antibody mediated rejection (ABMR) in renal allografts. The diagnostic significance of linear C4d deposits along peritubular basement membranes (GBM-C4d), which can occur as isolated event is poorly understood. Hypothesis: GBM-C4d, especially when isolated, is not a sign of ABMR but rather a marker of structural GBM changes and duplications in native kidneys and renal transplants.

Methods: We analyzed 319 renal allograft biopsies from 219 patients. GBM remodeling was analyzed by light (Banff cg-score) and by electron microscopy. Linear C4d staining by immunohistochemistry (IHC) and immunofluorescence (IF) was scored along the GBM and ptc. Controls: native kidneys with minimal chronic disease (n=10) and chronic thrombotic microangiopathy with GBM duplications (n=26).

Results: Transplants: GBM duplications/transplant glomerulopathy (TG) occurred in 52/319 biopsies (16%). By IF, 49/52 (94%) TG cases had GBM-C4d; 36/49 (73%) had isolated GBM-C4d lacking ptc-C4d deposits. By IHC, 74% of TG cases had GBM-C4d, 60% of which was as isolated event. GBM-C4d staining intensity correlated with Banff cg-scores (IF: r=-0.453, p<0.01; IHC: r=0.478, p<0.01). 80% of cases (24/30) with GBM duplications present only by electron microscopy revealed GBM-C4d. Association GBM-C4d with TG/GBM duplications: p<0.001. Statistical significance between GBM-C4d staining and structural GBM duplications remained after omitting cases with presumed or definitive ABMR (DSA-positivity, C4d positivity in ptc,transplant glomerulitis). Multivariate logistic regression: GBM duplication/TG was an independent predictor of GBM-C4d positivity.

Native kidneys: GBM-C4d occurred in 24/26 (92%) cases with thrombotic microangiopathy and GBM-C4d staining intensity was seen in minimal chronic disease. C4d, especially when isolated, is not a sign of ABMR but rather a marker of structural GBM changes and duplications in native kidneys and renal transplants.

Conclusions: The diagnostic significance of linear C4d deposits along ptc versus GBM duplications. C4d, especially when isolated, is not a sign of ABMR but rather a marker of structural GBM changes and duplications in native kidneys and renal transplants. TMA was mainly chronic, arteriolar and associated with C4d, hypertension and chronic lesions. TMA and C4d mark renal function and poor renal survival in IgAN and HSN.

TH-PO681
Predicting Outcome in Patients with Anti-GBM Gleronatropenia Using the Histopathological Classification for ANCA-Associated Vasculitis: Preliminary Results

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Background: The renal biopsy in anti-GBM glomerulonephritis (anti-GBM GN) is characterized by crescent formation. No histopathological classification has been implemented for the disease. We have applied the histopathological classification for ANCA-associated vasculitis (AAV) to see whether this classification can distinguish patients regarding renal outcome.

Methods: We analyzed biopsies of 20 patients, diagnosed with anti-GBM GN between 1984 and 2014 at a university hospital in the Netherlands. We classified these biopsies according to the histopathological classification for AAV, sclerotic (<50% sclerotic glomeruli or focal (<50% normal glomeruli), crescentic (≥50% cellular crescents) or mixed (no dominant lesion) class. We collected data on serology, renal function and end-stage renal disease (ESRD) during 5-year follow-up.

Results: Fourteen biopsies (70%) were categorized as crescentic, three (15%) as focal, one (5%) as sclerotic. Mean age was 47.4 years (SD: 17.1, range: 17.0-74.9) and differed between classes (P=0.039), with the focal class having the youngest patients with a mean age of 25.4 years. Estimated glomerular filtration rate (eGFR) at time of biopsy differed between classes (P<0.001), focal class having a mean of 90.2 ml/min/1.73m², crescentic 6.9 and mixed 8.7 (no available data for sclerotic class).

Mean eGFR at 1 year was 107.6 in the focal, 10.1 in the crescentic, and 21.8 in the mixed class (P<0.001). The occurrence of ESRD differed between groups (P=0.016), with no occurrence in the focal group.

Conclusions: These preliminary results show that the histopathological classification for AAV is useful for anti-GBM GN, predicting outcome in terms of eGFR at time of biopsy and at 1 year after biopsy. The focal group had more favorable outcomes regarding renal function and development of ESRD.
The Dumped System Utilized in the Japanese Histological Grade Classification of IgAN Nephropathy May Produce a Score with a Broader Applicability Compared to the Split System of Oxford Classification

**Background:** Japanese Histological Grade Classification (JHGC; HG1-HG4) (J Nephrol, 2013) and Oxford classification (Oxford) were compared with a focus on their ability to predict renal functional decline (RFD) and proteinuric remission (PUR).

**Methods:** 411 Japanese with IgAN (male 49%) were collected from 32 centres in Japan. Previous reports demonstrated an association with a seasonal or environmental exposures in some cases (PMID: 4604010, 3256901). We sought to understand epidemiologic factors associated with anti-GBM disease.

**Results:** Seventy three (M=31; F=42) cases of anti-GBM disease were identified, with a median age of 56 years. Overall, 2 to 11 cases were seen per year (median = 6); a high incidence year was defined as > median number of cases. 60% of cases were diagnosed in winter or spring (95% CI: 48-72%), and 40% in summer or fall (95% CI: 28 – 52%). The M:F ratio was 1:2 in high incidence years, but nearly 1:1 with a male predominance in low incidence years (p=0.07). Of variables studied, concurrent deposition of IgA in the mesangium was associated with younger age at diagnosis (p=0.01), 6 of 7 of those were seen in a high-incidence year (p=0.07). No associations among ANCA-positivity vs. respiratory symptoms, age, sex, and/or season of presentation were identified.

**Conclusions:** There were quantitative and qualitative differences in epidemiologic parameters in anti-GBM disease. Unlike low incidence years, cases diagnosed in high incidence years showed a trend for increased likelihood of concurrent mesangial IgA deposition, and male gender. The findings suggest potential differences in the development and/or gender-based triggers in the development of anti-GBM.
Clinical and Histological Determinants of Renal Outcome in Lupus Nephritis

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Background: The ISN/RPS 2003 histopathological classification of lupus nephritis (LN) is based on lesions historically thought to be relevant for prognosis, but for some lesions the evidence base is lacking. Without precautions, we tested a wide range of histologic and clinical features to objectively identify prognostic indicators of renal outcome in patients with LN.

Methods: 42 histological and 7 clinical parameters were determined as candidate predictors of renal outcome. A cohort of patients was identified from the pathology archives of >1500 consecutive cases of LN between 1990-2011. Renal biopsies were rescored for 42 histologic parameters. eGFR and proteinuria were recorded at time of renal biopsy, as well as during 1, 5, and 10 years of follow-up. For preliminary analyses, variables were tested using univariate mixed models, in which p<0.05 for fixed effects was considered statistically significant.

Results: Interim analysis was performed on 29 patients, of whom none developed end-stage renal disease. Significant associations with eGFR were found for age (p=0.03) and eGFR (p=0.001) at time of renal biopsy, percentage of normal glomeruli (p<0.01), percentages of glomeruli with mesangial hypercellularity (p=0.05), endocapillary hypercellularity (p=0.03), endothelial swelling (p=0.03), endocapillary monocellular nuclei (p=0.01), wire loops (p=0.02), and cellular crescents (p=0.05), as well as the presence of an interstitial infiltrate (p=0.04). Significant associations with proteinuria were found for eGFR at time of biopsy (p<0.02), percentage of glomeruli with mesangial global sclerosis (p=0.02), presence of cellular and fibrocellular crescents (p=0.01), as well as the presence of an interstitial infiltrate (p=0.01) and tubular atrophy (p=0.02).

Conclusions: Besides histological parameters characteristic of the previously established classes of LN, clinical and histological parameters may have prognostic significance. These and other features will be studied in an extended dataset in multivariate analyses of which the outcome may be relevant for future modifications of the LN classification.

Novel Urinary Tubular Biomarkers for Diagnosis and Predictive Active Lupus Nephritis

Buncha Sattrapong, Panpabu Chovichian, Ouppatham Yu. Therefore, these urinary biomarkers may relate and predict renal activity in systemic lupus erythematosus (SLE) patients.

Methods: We performed a diagnostic and prospective study in SLE patients with biopsy-proven active LN and with inactive LN. All patients were collected urine for NGAL, KIM-1 and periostin, the latter was measured by ELISA. After standard treatment in active LN patients, urinary biomarkers were repeated.

Results: A total of 67 patients with SLE including 35 patients with active LN and 32 patients without active LN were included. Urinary levels of KIM-1 was higher in active LN compared to inactive LN (median 2.17 (IQR; 0.92, 5.18) vs.0.29 (IQR; 0.93, 1.11) µg/g creatinine, P<0.001), while no significant difference was found in urinary NGAL and periostin levels. Urinary KIM-1, NGAL and periostin correlated positively with proteinuria (Spearman’s r: only KIM-1 correlated positively with renal function). ROC analysis, urinary KIM-1 (AUC; 0.80, 95%CI 0.69-0.92) outperformed conventional biomarkers (serum creatinine, urine protein, serum complement levels and anti-dsDNA antibody) in differentiating active LN from non-LN group. On follow-up after treatment in active LN (n=19), there was no significant difference in all urinary tubular biomarkers between response and nonresponse LN patients.

Conclusions: Levels of urinary KIM-1, but not of urinary NGAL and periostin may be potentially useful markers of LN activity and urine KIM-1 is better performance than other urinary markers of active LN. However, these novel tubular biomarkers are not predictive for a clinical response to treatment in active LN.

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Pierre microdissection, 4-6 glomeruli were cut out each case and collected for digestion. Peptides of Nephrology, Toronto General Hospital, Toronto, ON, Canada; 2 Medicine and Pathobiology, Lunenfeld Research Inst, Toronto, ON, Canada.

Microdissection and Mass Spectrometry

TH-PO693

Selected Reaction Monitoring for Quantification of Angiotensin-II Signature Proteins in Urine


There are no specific markers of kidney AngII activity. We previously defined 83 AngII-regulated genes in ADPKD. Further study is needed to analyse the function and location of glomeruli proteins in urine. Seven AngII-regulated peptides were quantified in urine samples of 9 ADPKD and 2 healthy subjects.

Results: Calibration curves demonstrated linearity (R²>0.99) and CVs<20% in the concentration range of 7-13 peptides in normal and ADPKD urine. Deamidated peptides accounted for 1-40% of total concentration. Peptides were quantified in all urine samples. Peptides corresponding to proteins TSP1, BST1, and LAMB2 had the highest excretion rate in urine of the only ADPKD patient with impaired GFR.

Conclusions: We have developed a protocol for SRM quantification of AngII-regulated proteins in urine. Seven AngII-regulated peptides were quantified in urine samples. Future studies will examine if urine excretion rate of AngII signature proteins is associated with cyst size and GFR in larger cohorts of ADPKD patients.

TH-PO694

Systemic Lupus Erythematosus/ANCA-Associated Vasculitis Overlap Syndrome in Patients with Biopsy-Proven Glomerulonephritis

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Background: SLE and AAV are distinct autoimmune diseases with possible renal involvement. Some patients fulfil both SLE and AAV classification criteria, defining the SLE/AAV overlap syndrome. We aimed: 1) to report clinical, biological and pathological characteristics of patients with SLE/AAV overlap syndrome and a biopsy-proven glomerulonephritis (GN), 2) to evaluate the incidence of overlapping auto-antibodies and the overlap syndrome in a cohort of patients with lupus nephritis (LN) or crescentic GN (CGN).

Methods: A nationwide survey was conducted to identify cases of SLE/AAV overlap syndrome. Data were collected from SLE and AAV French research groups. Inclusion criteria were diagnosis of both SLE and AAV and biopsy-proven GN between 1995 and 2014. An independent cohort of LN and CGN was used to study the prevalence of overlapping antibodies and/or overlap syndrome. Additional cases were identified through a systematic literature review.

Results: The national survey identified 8 cases of SLE/AAV overlap syndrome. All patients were female, median age was 40 years. AAV preceded (n=3), followed (n=3) or occurred concomitantly (n=2) to SLE. Six patients had rapidly progressive GN, and 3 had alveolar hemorrhage. All patients had antinuclear antibodies (ANA), 7 had p-ANCA antipeptide antibodies (MPO) antibodies. Renal biopsy showed LN or CGN. Remission was obtained in 6 patients. Literature review identified 31 additional cases with similar profile. Cohort analysis revealed ANCA positivity in 24% of LN, ANA positivity in 55% of CGN, with no correlation with pathological findings, and a prevalence of 2/110 (1.8%) for SLE/AAV overlap syndrome.

Conclusions: In patients with GN, SLE/AAV overlap syndrome may occur but its prevalence seems low. Most patients have an aggressive renal presentation, with usually both ANA and anti-MPO antibodies. Further studies are needed to assess shared pathogenesis and therapeutic options.

TH-PO695

Establishment of Proteomic Profiles of Normal Glomeruli Using Laser Microdissection and Mass Spectrometry

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Background: Laser microdissection combined with mass spectrometry (LMD/MS) has become an important tool in proteomics study. There is little data of normal glomeruli proteome profiles which are fundamental in the study of differential proteomics of kidney diseases. Our study aimed on establishing proteome profiles of normal glomeruli from formalin-fixed paraffin-embedded (FFPE) specimen through LMD/MS.

Methods: Normal kidney cortices were obtained from 4 patients underwent nephrectomy due to renal carcinoma. 10-mm FFPE sections were prepared for laser microdissection, 4-6 glomeruli were cut out each case and collected for digestion. Peptides were quantified using Thermo Scientific LTQ Orbitrap Velos mass spectrometer. MS/MS View software was used for identification of proteins, with tandem mass spectrometry data searching against UniProt. Scaffold 4 software was used to integrate results, taking proteins with credibility of ≥95% and identified peptides number >1 into statistics.

Results: 67 proteins were identified in normal glomeruli from four cases with LMD/MS analysis. High abundance glomerular structural proteins and blood-related proteins are shown below.

Conclusions: This study obtained proteome profile of normal glomerular from FFPE samples, which can provide comparison data for differential proteomic study of glomeruli diseases. Further study is needed to analyse the function and location of glomeruli proteins identified with LMD/MS.

Funding: Government Support - Non-U.S.

TH-PO696

Correlation of the Methodologies of Proteinuria in Glomerular Disease Patients

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Background: This study evaluate the correlation between the measurements of 24-hour proteinuria(P24H) versus protein/creatinine ratio(P/Cr) in patients with glomerular disease(GD) diagnosed historically in Nephrology’s Service in HUGCR. Assess whether

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this correlation varies with the GD, age, sex, blood pressure control(BP), body mass index(BMI), glomerular filtration rate(GFR) by MDRD, proteinuria degrees(mg/24h(PD), urine output(uALB) and ACEi/ARBs treatment.

**Methods:** Observational cross-sectional study of renal biopsies performed 2010-2014. Spearman’s coefficient and multiple linear regression was used to identify the correlation of proteinuria determinations.

**Results:** 148 biopsies collected; 96 were GD. Mean age 54±18 years; 66% male; BMI 27.7±15.5. The GD was: glomerulonephritis(GN) IgA 21%, membranous(MGN)19%, vasculitis17%, focal segmental(FSGS)15%, minimal change(MCGN)10%, lupus10%, and other10%. The GFR was categorized:<60 ml/min 59%, 60-90 ml/min 22%, >90ml/min 19% and PD was categorized:<30mL/min 39% and PD was categorized:<300mg 8.3%; 300-3500mg 47.9%; >3500mg 17%, focal segmental(FSGS)13%, minimal change(MCGN)10%, lupus10%, and other10%. The BP was controlled in 60.4%. Median P24H 3.01g/24h(1.18-4.79) and P/C 43.8%. The P/C was controlled in 50.4%.

**Course of PR3 Titers versus MPO Titers in ANCA Vasculitis Patients After Rituximab Therapy**

In 25 pANCA patients.

**Methods:** We compared the time course of anti-PR3 titers in 25 cANCA patients with the course of anti-MPO titers in 11 pANCA patients receiving rituximab induction therapy. We compared anti-PR3 and anti-MPO titers before initiation of rituximab therapy and 1, 3, 6, 12 and 24 months after starting the therapy. The mean age of both groups was comparable (51.6 in pANCA patients vs. 58.1 years in pANCA patients). The female to male gender ratio was 13/12 in pANCA patients and 6/5 in pANCA patients. The mean age of both groups was comparable (51.6 in pANCA patients vs. 58.1 years in pANCA patients). The female to male gender ratio was 13/12 in pANCA patients and 6/5 in pANCA patients. The mean age of both groups was comparable (51.6 in pANCA patients vs. 58.1 years in pANCA patients). The female to male gender ratio was 13/12 in pANCA patients and 6/5 in pANCA patients. The mean age of both groups was comparable (51.6 in pANCA patients vs. 58.1 years in pANCA patients). The female to male gender ratio was 13/12 in pANCA patients and 6/5 in pANCA patients.

**Results:** Our results show that rituximab therapy significantly lowers anti-PR3 titers in cANCA vasculitis patients after 3, 6, 12 and 24 months. In contrast, anti-MPO titers are not lowered significantly in pANCA vasculitis patients after rituximab therapy.

**Conclusions:** Clinical experience shows that anti-MPO titers correlate less well with clinical disease activity than anti-PR3 titers. Detailed further analysis of our data will show whether MPO titers correlate with long term clinical patient outcome and FACS analysis data will elucidate involved cell types in pANCA vasculitis.

**TH-PO697**

Renal Functional Reserve and Electron Microscopy in the Evaluation of Subclinical Lupus Nephritis

**Renato V. Almeida. Nephrology, Federal Univ of Paraná, Curitiba, Brazil.**

**Background:** The aim of this study was to test the renal functional reserve (RFR) and electron microscopy (EM) in patients with subclinical lupus nephritis, and to evaluate the changes in the exercise of albumin, retinol-binding protein and electrolytes induced by amino-acids (AAs) infusion; and their relationship with the renal morphology data.

**Methods:** In 25 lupus patients (SLE group) and in 15 controls, on the 24-hour urine collection and on urine specimens taken after both an oral water load and an AAs infusion. glomerular filtration rate (GFR: creatinine clearance - ml/min/1.73m²), microalbuminuria (uALB) and sodium excretion (FENa%) were evaluated. The urinary retinol-binding protein (RBP) was evaluated only in the SLE group which was also divided in subgroups according to the classification of lupus nephritis (ISN/RPS 2003). Biopsies were also analyzed in order to characterize the renal ultrastructural abnormalities (EM).

**Results:** Both in the SLE group and controls there was a significant increase in GFR, uALB, FENa% and Naₐ after the AAs infusion. The SLE group showed significantly higher stimulated GFR than controls; and higher basal and stimulated values for uALB (ug/min) and uALB (umg/creatinine), respectively, Urinary RBP showed no basal value above 0.4 µg/ml and after stimulation it resulted significantly decreased. When we compared these data to the renal biopsy findings, we found that class II patients showed higher basal GFR than class I patients. Ultrastructural abnormalities in EM were present in 40% of the cases.

**Conclusions:** The results suggest that in patients with subclinical lupus nephritis, AAs infusion elicits an increase in GFR which indicates the presence of RFR. Although RFR was not a parameter of severity in the SLE group it presented higher mean values for uALB - both basal and stimulated - suggests altered glomerular permselectivity in these patients. Higher basal GFR in class II patients might suggest that compensatory hyperfiltration precedes the decline of renal reserve in patients with more severe forms of lupus nephritis. Electron microscopy findings showed low sensitivity to predict the severity of disease.

**Funding:** Government Support - Non-U.S.
*TH-PO700*

Gross Hematuria of Glomerular Origin in Adults  
Sami Safadi, Sami H. Nast, 1  'Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Anatomic Pathology, Mayo Clinic, Rochester, MN.

**Background:** Gross hematuria is a relatively uncommon presentation of glomerulonephritides. Glomerular gross hematuria (GGH) is more frequent in children than adults. IgA nephropathy and Alport syndrome are the most common causes of GGH in children. The clinicopathologic characteristics of GGH in adults have not been systematically evaluated. We investigated the etiology and clinicopathologic characteristics of GGH in a large single-center cohort of adults.

**Methods:** Adult patients (18) with native kidney biopsy were identified from the pathology database. The electronic medical record (EMR) was searched for the symptom of gross hematuria in these patients. The EMR was then examined manually to select patients with GGH. Patients with a urological cause of hematuria were excluded. Univariate logistic regression was used to test association between age, gender, and diagnosis.

**Results:** Between 1993 and 2015, 101 patients with GGH were identified. 51% were male and 48% were white. Median age at biopsy was 52 yrs (18-89). The clinicopathologic causes of GGH were heterogeneous as shown in Table 1. The most common causes were: IgA nephropathy/HSP nephritis (IgA/HSP) (36%), thin basement membrane disease (TBMD) (14%), pauci-immune crescentic GN (PICGN) (13%), and monoclonal protein related glomerular disease (amyloidosis, MIDD, PGNMID) (13%). Younger adults were more likely to have IgA/HSP (OR 3.2, p<0.01), and less likely to have PICGN (OR 0.05, p<0.01). Male patients were more likely to be older on presentation (dif 5yrs, p<0.05). Female patients were slightly more likely to have loin pain hematuria syndrome (LPHS) and MIDD. Only 30% of patients with IgA/HSP with GGH had crescents on biopsy.

**Conclusions:** This is the first study to analyze GGH in adults. We show that causes of GGH in adults are very heterogeneous, but most cases are due to IgA/HSP or TBMD disease in younger adults.

**Diagnosis** | **N**
--- | ---
IgA/HSP | 36
TBMD | 14
PICGN | 13
LPHS | 5
MIDD | 5
Infection-related GN | 3
Proliferative Lupus Nephritis | 3
Amyloidosis | 3
MPGN, immune complex (IC) type | 3
Fibrillary GN | 3
PGNMD | 3
MGN with Renal Vein Thrombosis | 3
Anti-GBM Disease | 2
C3 GN | 2
Proliferative GN, IgG related | 1
Mesangio proliferative GN, IC type | 1
Fatty Disease | 1

Urinary excretion of citrate, cис-acetate, icositate, oxogluturate and succinate was reduced 40-68%. Based on data from Nephromine, expression of genes for four TCA cycle enzymes was reduced in human kidney tissues with nephrosclerosis. One transcription factor (TFAP2C) regulating TCA genes was also significantly reduced in nephrosclerosis.

**Conclusions:** In conclusion, in non-diabetic CKD, targeted metabolomics identified differences in the urinary excretion and plasma concentrations of small molecules that are consistent with both reduced renal excretion and impaired metabolism. Reductions in TCA cycle metabolites and gene expression were also identified and suggested suppressed mitochondrial function in CKD.

**Funding:** NIDDK Support, Other U.S. Government Support, Pharmaceutical Company Support - Abbvie

*TH-PO701*

IgM Staining in Immunofluorescence Is a Risk Factor for Relapsing in Focal Segmental Glomerulosclerosis  
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**Background:** Glomerular IgM and C3 deposits are frequently found in idiopathic focal segmental glomerulosclerosis (fSGS). Some experimental studies have suggested that IgM deposits may play a role in activation of the complement system in the glomeruli. However, the clinical meaning of the IgM deposits is unclear in fSGS patients. In this study we analyzed outcomes regarding the presence of IgM deposits in biopsies of fSGS patients.

**Methods:** We collected data from single-center retrospective cohort of patients with histologic diagnosis of fSGS between 2000-2004 that had a minimum follow-up period of 6 mo. Secondary FSGS, collapsing glomerulopathy (CG), childhood onset of fSGS and patients with baseline Scr>3.0mg/dL were excluded. Relapsing was defined as new onset of nephritic proteinuria after remission.

**Results:** We reviewed data from 96 patients, however 38 were excluded: secondary FSGS (14), CG (20) and patients with baseline Scr>3.0mg/dL (2), leaving 58 patients to analysis. The mean age was 31±14.3y, 58% were female and 46.5% were self-identified as white. ACEI/ARB showed mean Scr 1.2±0.6mg/dL; proteinuria 8.1±4.95 g/d; SAlb 3.9±0.9 mg/ dL; GFR (MDRD) 81±41ml/min. The median follow up period was 34.5 mos. Intersitial fibrosis was moderate to severe in 26%, IgM and C3 deposits were present in 31% and in 12% of the biopsies, respectively. ACEI/ARB was used in 81%, prednisone in 96.6% and cyclosporine in 36.6% of the patients. Complete or partial response was achieved in 79.3% of the patients during follow-up. Relapsing was seen in 17 of 41 cases (41.5%). IgM staining in the glomeruli was the only significant risk factor for relapsing in the multivariate analysis (OR 6.1 [CI 1.02-36.4]; P=0.047). Nevertheless, C3 deposits showed some association but lost strength in the multivariate analysis (OR 8.3 [CI 0.79-87.7]; P=0.077).

**Conclusions:** In a single center retrospective cohort we found that IgM staining in immunofluorescence was a risk factor for relapsing in idiopathic FSGS.

*TH-PO702*

Targeted Metabolomics Reveals Siblings in TCA Cycle Metabolites in Non-Diabetic Hypertensive Chronic Kidney Disease  
Steve I. Hallan, 1 Maryam Akonian, 2 Leila R. Zelnick, 3 Bryan R. Kestenbaum, 1 Shoba Sharma, 2 Rintaro Saito, 1 Kumar Sharma, 1 Ian H. De Boer. 2 Center for Renal Translational Medicine, UCSD, San Diego, CA; 3 Kidney Research Inst and Div of Nephrology, Univ of Washington, Seattle, WA; 4 Clinical Metabolomics Inc, La Jolla, CA.

**Background:** Interesting metabolic disturbances have recently been described in DKD using metabolomic analysis. Non-diabetic hypertensive CKD is common and needs to be better characterized.

**Methods:** Using a targeted quantitative panel of 66 organic acids, we compared plasma concentrations and urine excretion/24h in 22 adults with stage 3-4 non-diabetic hypertensive CKD to those of 10 healthy controls.

**Results:** After correcting for multiple testing, urinary excretion of 27 metabolites and plasma concentration of 33 metabolites differed significantly (range -68% to +113%). All 27 altered urine metabolites was reduced in CKD, while 27 of 33 altered plasma metabolites were higher in CKD. Pathway analysis based on significantly altered metabolites identified seven metabolic pathways significantly altered in CKD, most strikingly the TCA cycle (6 of 20 measured metabolites significantly different, q<0.001).

**Conclusions:** In conclusion, in non-diabetic CKD, targeted metabolomics identified differences in the urinary excretion and plasma concentrations of small molecules that are consistent with both reduced renal excretion and impaired metabolism. Reductions in TCA cycle metabolites and gene expression were also identified and suggested suppressed mitochondrial function in CKD.

**Funding:** NIDDK Support, Other U.S. Government Support, Pharmaceutical Company Support - Abbvie

*TH-PO703*

The Application of Laser Microdissection and Liquid Chromatography – Mass Spectrometry in the Diagnosis of Renal Amyloidosis  
Michiko Aoki, Dedong Kang, Yusuke Kajimoto, Takafumi Kanemitsu, Kiyotaka Nagahama, Akira Shimizu. Analytic Human Pathology, Nippon Medical School, Tokyo, Japan.

**Background:** In our department, renal amyloidosis of kidney biopsies have been diagnosed by cored-needle stain, immunofluorescence (IF) for immunoglobulin light (L) and heavy (H) chains, and immunostaining for amyloid A, transthyretin, and β2-microglobulin. Recently, it has been reported that liquid chromatography tandem mass spectrometry (LCMS/MS) is helpful for detection of the amyloid precursor proteins.

**Methods:** We retrospectively investigated 30 cases of renal amyloidosis, 11 cases (36.7%) of AA and 19 cases (63.3%) of AL amyloidosis, from a series of renal biopsies in our department from 1999 to 2014. We examined the component proteins in deposited amyloid in formalin fixed paraffin embedded tissues using laser microdissection of glomeruli and LCMS/MS. These results were compared with the results of serum immunofixation electrophoresis (IFE) and findings of IF.

**Results:** We retrospectively investigated 30 cases of renal amyloidosis, 11 cases (36.7%) of AA and 19 cases (63.3%) of AL amyloidosis, from a series of renal biopsies in our department from 1999 to 2014. We examined the component proteins in deposited amyloid in formalin fixed paraffin embedded tissues using laser microdissection of glomeruli and LCMS/MS. These results were compared with the results of serum immunofixation electrophoresis (IFE) and findings of IF.

**Conclusions:** LCMS/MS could detect the component proteins in amyloid depositions in all cases, even in the cases that had less than 5% area of amyloid deposition in glomeruli. Furthermore, among AL amyloidosis, which was diagnosed previously, we found 2 cases of AH amyloidosis and 2 cases of AHI amyloidosis. LCMS/MS is very helpful for diagnosis of amyloidosis, especially AHI and AH amyloidosis.
TH-PO704

THSD7A Staining of Membranous Glomerulopathy in Clinical Practice Reveals Cases with Dual Autoantibody Positivity

Christopher Patrick Larsen,1 Larry N. Cossey,1 Laurence H. Beck.2 Nephropath, Little Rock, AR; 1Boston Univ Medical Center, Boston, MA.

Background: The majority of primary membranous glomerulopathy (MG) cases are due to antibodies directed against the podocyte phospholipase A2 receptor (PLA2R) antigen. Recently, thrombospondin type-1 domain containing 7A (THSD7A) was described as a second antigenic target leading to MG. We sought to validate an immunohistochemical stain for the diagnosis of THSD7A-associated MG on renal biopsy material.

Methods: Immunohistochemical staining for THSD7A (Sigma) and PLA2R (Sigma) was performed in all cases of non-SLE associated MG diagnosed in our laboratory between December 2014 and April 2015. This included a total of 258 cases. Both stains were performed on formalin fixed paraffin embedded tissue. PLA2R was performed by immunofluorescence while THSD7A was performed by immunoperoxidase. Serologic testing for PLA2R (ELISA, WB) and THSD7A (WB) antibodies was performed in a subset of cases to determine the specificity of positive THSD7A staining for the diagnosis of THSD7A MG.

Results: MG stained positive for THSD7A-only in 7 (2.7%) cases, PLA2R-only in 141 (54.7%) cases, and showed dual positivity for THSD7A and PLA2R in 2 (0.8%) cases. Staining was negative for both in 108 (41.8%) cases. Serologic testing was performed for antibodies to PLA2R and THSD7A in 9 cases with both serum and biopsy material available and the results are shown in Table 1.

<table>
<thead>
<tr>
<th>Biopsy result</th>
<th>Serum Anti-PLA2R</th>
<th>Serum Anti-THSD7A</th>
</tr>
</thead>
<tbody>
<tr>
<td>MG with PLA2R only (n=3)</td>
<td>3/3</td>
<td>0/3</td>
</tr>
<tr>
<td>MG with THSD7A only (n=2)</td>
<td>0/2</td>
<td>2/2</td>
</tr>
<tr>
<td>MG with dual PLA2R and THSD7A (n=2)</td>
<td>2/2</td>
<td>2/2</td>
</tr>
<tr>
<td>MG negative for PLA2R and THSD7A (n=1)</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Non-membranous glomerulopathy (n=1)</td>
<td>0/1</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Conclusions: Based on these findings we believe it is possible to specifically diagnose THSD7A-associated MG based on renal biopsy staining. Additionally, we confirm that only a minority (3.5%) of MG cases reflect THSD7A-associated disease. Interestingly, 2 (22%) THSD7A-positive cases showed dual positivity for PLA2R and THSD7A with serologic studies showing evidence of antibodies to both THSD7A and PLA2R antigens in these patients. These cases demonstrate the importance of using a panel based approach to subtyping MG.

Funding: NIDDK Support

TH-PO705

Clinical Characteristics Associate Differently with Single Nephron GFR Than Total GFR in Normal Adults

Aleksandar Denic,1 Lilach O. Lerman,1 John C. Lieske,1 Mariam P. Alexander,2 Harini A. Chakkera,3 Emilio D. Poggio,4 Richard J. Glassock, Andrew D. Rule.1 1Div of Nephrology, Mayo Clinic, MN; 2Dept of Pathology, Mayo Clinic MN; 3Div of Nephrology, Mayo Clinic, AZ; 4Dept of Nephrology, Cleveland Clinic, OH; 5Dept of Medicine, Geffen School of Medicine, CA.

Background: Total GFR (GFR) is the product of mean single nephron GFR (snGFR) and the number of nephrons. Thus, associations with GFR may be attributable to associations with snGFR, nephron number, or both.

Methods: We identified 1,520 living kidney donors at Mayo Clinic and Cleveland Clinic with pre-donation contrast-enhanced CT scans and isothalamate clearance (GFR), and with kidney biopsies at the time of donation. snGFR was estimated from GFR divided by nephron number (CT bilateral cortical volume x biopsy non-sclerotic glomerular density). GFR, snGFR, and nephron number were associated with clinical and biopsy characteristics (age and sex-adjusted).

Results: Donors were 58% women, mean±SD age of 43±12 y, GFR of 103±20ml/min/1.73m², nephron number of 872,280±390,668 per kidney, and snGFR of 0.073±0.042 ml/min/1.73m². There was a strong decline in nephron number and modest rise in snGFR with age such that the net effect was an age-dependent decline in GFR.

*p<0.05; **p<0.01; NS p>0.05

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>% diff.</th>
<th>p value</th>
<th>% diff.</th>
<th>p value</th>
<th>% diff.</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per y</td>
<td></td>
<td>-0.6</td>
<td>**</td>
<td>0.3</td>
<td>*</td>
<td>-1</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.5</td>
<td>NS</td>
<td>10.9</td>
<td>**</td>
<td>-8.5</td>
<td>**</td>
</tr>
<tr>
<td>Family history of ESRD</td>
<td>1.6</td>
<td>NS</td>
<td>12.3</td>
<td>**</td>
<td>-10</td>
<td>**</td>
</tr>
<tr>
<td>Glomerular volume, per SD</td>
<td>0.6</td>
<td>NS</td>
<td>26</td>
<td>**</td>
<td>-20.3</td>
<td>**</td>
</tr>
<tr>
<td>Tubular area, per SD</td>
<td>0.8</td>
<td>NS</td>
<td>14</td>
<td>**</td>
<td>-11.4</td>
<td>**</td>
</tr>
<tr>
<td>Glomerulosclerosis &gt;5%</td>
<td>0.4</td>
<td>NS</td>
<td>14</td>
<td>**</td>
<td>-12</td>
<td>**</td>
</tr>
<tr>
<td>Intimal thickening &gt;5%</td>
<td>2.7</td>
<td>NS</td>
<td>13</td>
<td>**</td>
<td>-7.7</td>
<td>**</td>
</tr>
</tbody>
</table>

Conclusions: In Japan, patients with IV-Gi-V LN were significantly associated with decreased renal function and nephrotic syndrome. In addition, the frequency of mixed proliferative and membranous type and chronic lesions was higher at the second or later biopsy compared to the first biopsy (mixed type, 21.5% vs 43.9%, p=0.003; chronic lesion 51.1% vs 82.1%, P=0.002).

Funding: Government Support - Non-U.S.

TH-PO707

MicroRNA Signatures in Renal Disease: A Meta-Analysis of Tissue and Urine Datasets

Christios Argyropoulos,1 Mark L. Unruh, V. Shane Pankratz. Internal Medicine, Univ of New Mexico, Albuquerque, NM.

Background: MicroRNA (miRNA) are negative regulators of gene translation and an emerging biomarker in a wide variety of diseases. Little is known about the ability of miRNA to classify patients with renal pathology.

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

Underline represents presenting author.

251A
Methods: We undertook a meta-analysis of normalized miRNA profiles from clinical samples in Gene Expression Omnibus. miRNAs in miRBase20 were scored for kidney relevance according to their experimentally or computationally ability to bind to proteins in the kidney proteome (http://www.proteinatlas.org). Elastic Net (EN) regression was then used to select short miRNA signatures according to their ability to classify disease from healthy samples using 10-fold cross-validation.

Results: Using our systems biology approach we identified 739 miRNAs as potential kidney biomarkers out of 1689 candidates. A total of 8 studies with 178 samples were identified. Of those, 2 studies in patients were lupus (N=30) were excluded due to the incompatibility of the normalization strategy with the other samples. miRNAs profiles from 31 urine samples and 117 biopsy samples were available for analyses.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Platform</th>
<th>Source</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSE53771</td>
<td>Microarray (μA)</td>
<td>Renal Bx (Bx)</td>
<td>28</td>
<td>8 (Transplant, TxP AKI)</td>
</tr>
<tr>
<td>GSE30282</td>
<td>μA</td>
<td>Bx</td>
<td>10</td>
<td>30 (TxP Cell Rejection), 11 (TxP AB Rejection), 14 (TxP AB Rejection)</td>
</tr>
<tr>
<td>GSE29283</td>
<td>μA</td>
<td>Bx, Cortex</td>
<td>3</td>
<td>5 (Hypertension, HTN)</td>
</tr>
<tr>
<td>GSE28434</td>
<td>μA</td>
<td>Bx, Medulla</td>
<td>3</td>
<td>5 (HTN)</td>
</tr>
<tr>
<td>GSE48318</td>
<td>qPCR</td>
<td>Urine exosomes</td>
<td>2 (Normalbuminuria, UTI)</td>
<td>2 (Microalbuminuria, MA)</td>
</tr>
<tr>
<td>doi: 10.1371/journal.pone.0054662</td>
<td>qPCR</td>
<td>Whole urine</td>
<td>10 NA</td>
<td>17 (MA within 2 years)</td>
</tr>
</tbody>
</table>

The median (IQR) AUC for individual miRNAs to classify disease was 0.59 (0.46-0.68) for unselected miRNAs but increased to 0.64 (0.54-0.69) in the preselected ones. A short signature of 19 miRNAs achieved a superior classification performance for renal pathology (cross-validated AUC 0.96). Conclusion: This is the first study to date examining the performance of a panel of miRNAs in classifying patients with kidney disease. A panel of miRNAs may classify patients with native and allograft renal disease aiding the interpretation of elevated creatinine in clinical practice.

TH-P0708

Study into the Effect of Aquaporin-2 on the Efficacy and Predicted Effect of Tolvaptan in Patients of Nephrotic Syndrome

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Background: A retrospective investigation was conducted into the efficacy and adverse drug reactions of tolvaptan in the treatment of diabetic nephropathy and MCNS (Minimal Change Nephrotic Syndrome) with heart failure.

Methods: The subjects of this study were 56 patients with chronic kidney disease (due to diabetic nephropathy) and MCNS with heart failure who over the last 2 years and who were treated with tolvaptan. We defined effective cases as those showing a 2-fold increase in aquaporin 2 in the collecting duct. In diabetic cases, findings were positive for the responder but negative for the non-responder. In MCNS cases findings were positive in the responder but weak positive for the non-responder.

Results: Of the 56 cases, 49 were tolvaptan responders. No problematic side effects were observed. Comparison of tolvaptan responders and non-responders indicated that serum Cre levels were significantly lower in responders. We conducted immunostaining for aquaporin 2 in the collecting duct. In diabetic cases, findings were positive for the responder but negative for the non-responder. In MCNS cases findings were positive for the responder but weak positive for the non-responder.

Conclusions: Diabetic nephropathy and nephrotic syndrome responders exhibited a score of (+) when less than 50% is stained; a score of (+++) is assigned when more than 75% is stained.

TH-P0709

Subclinical Anti-Smith and Anti-Ribonucleoprotein Antibodies Precede Proliferative Lupus Nephritis Diagnosis

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Background: Lupus Nephritis (LN) manifests in approximately 50% of Systemic Lupus Erythematosus cases. Anti-Smith (SM) and Anti-Ribonucleoprotein (RNP) antibodies are associated with proliferative lupus nephritis (PLN) at diagnosis. We hypothesized that prediagnostic anti-SM and anti-RNP antibodies were more common in PLN than SLE without LN.

Methods: This case-control Department of Defense Serum Repository study compared 3 longitudinal prediagnostic quantitative anti-SM and anti-RNP antibody levels in 23 patients with biopsy-proven PLN from the Walter Reed National Military Medical Center with 21 age, sex, race, and age of serum matched SLE without LN disease controls. Immunosassays were performed at Quest Diagnostics.

Results: More PLN patients had an anti-SM antibody level ≥4 AI than matched disease controls at any time (52% vs. 5%; p=0.001) and <2 years (47% vs. 6%; p=0.01) before diagnosis, but not >2years before diagnosis (22% vs. 0%, p=0.1). More PLN patients had an anti-RNP antibody ≥4 AI than matched disease controls at any time (57% vs. 14%, p=0.001), <2 years (53% vs. 19%, p=0.04), and between 2 years and >2 years (28% vs. 0%, p=0.001) before diagnosis. Only an anti-SM antibody absolute rise over time of >4 AI prior to diagnosis was specific for PLN (30% vs. 0%; p=0.02). But, anti-RNP antibody more often preceded anti-SM antibody when there was a clear antecedent antibody (89% vs. 11%, p=0.003).

Conclusions: In a large subgroups of PLN patients, anti-RNP antibodies were consistently elevated prior to anti-SM antibodies, but not rising, years prior to diagnosis. Anti-SM antibodies predominantly elevate in the last two years prior to PLN diagnosis which supports a possible direct contribution to PLN pathogenesis. Our data suggests that SLE patients with baseline RNP antibody along with a rising anti-SM antibody levels may benefit from increased surveillance for early signs of PLN. A more prompt biopsy diagnosis would allow for proactive therapeutic intervention to preserve maximal renal function.

Funding: Other U.S. Government Support

TH-P0710

The Relationship Between Phospholipase A2 Receptor Autoantibody and Idiopathic Membranous Nephropathy

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Background: The value of PLA2R autoantibody is still controversial in diagnosis, activity monitoring and prognosis estimation in idiopathic membranous nephropathy (IMN).

Methods: A total of 233 patients with biopsy-proven IMN at Peking Union Medical College Hospital from 2012 January to 2014 March were enrolled. A control group was set up. The serum antibody tier collected at the time of renal biopsy was measured by quantitative ELISA. 14 IMN patients with detectable antibody at biopsy were followed up to retest antibody 6 months later. Besides, the diagnostic accuracy between ELISA and immunofluorescence (IF) method for IMN was compared. The consistency and difference in antibody detection between two methods were also performed.

Results: The total sensitivity of antibody was 60.0% in IMN. However, it increased to 71.3% if patients didn’t receive immuno-suppression therapy before testing. The antibody specificity was 100.0%. Hyperalbuninemia became severe (P<0.05) and the proportion of nephrotic arrange proteinuria rose gradually (P<0.05) as antibody levels increased. The antibody changes were consistent with clinical outcomes. The antibody AUC-ROC for IMN diagnosis was 0.800 by ELISA. There was no significant difference in AUC-ROC between ELISA and IF in IMN diagnosis (P>0.05). The kappa value of antibody detection consistency between ELISA and IF was 0.941±0.033. The positive rate of antibody detection wasn’t significantly different between ELISA and IF (P>0.05).

Conclusions: PLA2R autoantibody has high sensitivity, notable specificity and good diagnostic accuracy for IMN. The antibody positive rate is affected by immunosuppression therapy and disease activity. The antibody could reflect disease activity and predict clinical outcomes. The antibody could be a therapeutic intervention to preserve maximal renal function.

TH-P0711

Factors Related to the Glomerular Volume in Different Cortical Zones of the Human Kidney

1Yusuke Okabayashi, Go Kanzaki, Nobuo Tsuiboi, Kotoro Haruhara, Kentaro Koike, Yoichi Miyazaki, Tetsuya Kawanuma, Makoto Ogura, Takashi Yokoo. 2Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: Recent studies have shown that glomerular enlargement is a surrogate marker of low nephron number in primary hypertension and in people with lower birth weight. To date, however, information is limited regarding the diversity in the distribution of glomerular volume within the human renal cortex. We aimed to compare and relate the glomerular volume (GV) in different cortical zones of the human kidney.

Methods: A total of 89 autopsy kidneys without apparent renal diseases were analyzed to measure the glomerular volume (GV) in different parts of the renal cortex. The mean GV was calculated from the measured each glomerular area. Relationships between the GV was calculated from the measured each glomerular area. Relationships between the GV and the other clinicopathological features were investigated.

Results: The GV showed wide variations between the individuals and showed maximal 7-fold and 4-fold variations in superficial and juxtamedullary cortex, respectively. The GV showed close inverse correlations with the glomerular density in each cortical area. Multivariate analysis revealed that age and diastolic blood pressure were associated with the mean GV. Moreover, the GV was low glomerular density in the superficial cortex, and hypertension in the juxtamedullary cortex.
As a whole, compared to the GV in the superficial cortex (2.7±1.0 x 10⁶/mm³), the averaged GV in the juxtamedullary cortex (3.1±0.8 x 10⁶/mm³) was significantly larger. Of note, in 27 cases (30%), the mean GV in the superficial cortex was larger than that of the juxtamedullary cortex. Such individuals with glomeruli enlargement in the superficial cortex were characterized by a low glomerular density and/or large body size.

**Conclusions:** In each individual kidney, there are considerable variations in the distribution of the GV. Nephron number/body size and hypertension underlie the enlargement of glomeruli in superficial and juxtamedullary cortex, respectively.

**TH-P0712**

**Highly Sensitive Method for Quantification of Iohexol** Vera Jankowski, Joachim Jankowski, Inst. of Molecular Cardiovascular Research, Univ Hospital RWTH, Aachen, Germany.

**Background:** Iohexol is used for accurate determination of the GFR in CKD patients. However, high iohexol amounts might lead to adverse effects in organism. In order to minimize the iohexol dosage required for the GFR determination in humans, the development of a sensitive quantification method is essential. Therefore, the objective of our preclinical study was to establish and validate a simple and robust LC-ESI-MRM method for iohexol quantification.

**Methods:** In order to test whether a significantly decreased amount of iohexol is sufficient for reliable quantification, a LC-ESI-MRM mass-spectrometric approach was assessed. We analyzed the kinetic of iohexol in rats after application of different amounts of iohexol (15 mg-150 mg/rat). Blood sampling was conducted at four time points. Iohexol and the internal standard (iothalamic acid) were separated from serum proteins using centrifugal filtration device with a cut-off of 3 kDa. The chromatographic separation was achieved on an analytical Zorbax SB C18 column. The detection and quantification were performed by a triple quadrupole mass spectrometer ESI-MRM operating in a positive ion mode. Furthermore, the effect of iohexol on early filtration device with a cut-off of 3 kDa. The chromatographic separation was achieved on an analytical Zorbax SB C18 column. The detection and quantification were performed by a triple quadrupole mass spectrometer ESI-MRM operating in a positive ion mode. Furthermore, the effect of iohexol on early gene expression in thyroid and renal cortex was tested to determine a threshold of physiological active iohexol concentrations.

**Results:** A linear correlation of the iohexol amount and mass-signal (MS) intensity was found in the range of 50 pg-40 ng (r² = 0.998). The lowest limit of quantification (LOQ) was 50 pg. The intra- and inter-day accuracies were between 91.2% and 98.7%. The recovery rate (%RSD) was 50 pg. The intra- and inter-day accuracies were between 91.2% and 98.7%. The recovery rate (%RSD) was between 2.7% and 9.2%. The recovery rate of iohexol was determined in the range of 100.8% ± 10.9%. The gene expressions test revealed that iohexol dosages exceeding 0.5 mg/kg induce a group of genes in thyroidal tissue that comprises transcription factors and genes of cellular stress response.

**Conclusions:** This mass-spectrometric based method has been proved to be sensitive, selective and suitable for the quantification of iohexol in serum. Due to high sensitivity of this novel method the iohexol application dose as well as the sampling time in the clinical routine could be reduced in the future in order to further minimize side effects in humans.

**TH-P0713**


**Background:** The duration of the treatment in Proliferative Lupus Nephritis (PNL) has not been determined. Almost 30 percent of patients will relapse during or after treatment, in the first 5 years. Furthermore, the factors associated to renal relapses remain unclear. Hence, a prospective histological control study (re-biopsy) performed before the end of the third year of treatment in patients with complete renal remission for a year may contribute to a better understanding on the relapses in PNL.

**Methods:** A total of 24 patients with PNL were included in this pilot study. All patients presented focal or diffuse PNL in the first renal biopsy, and received induction with cyclophosphamide and corticosteroids by six months. The maintenance therapy was based on mycophenolic acid and low doses of corticosteroids for at least 2 years and 6 months. On those patients who presented total remission during a year (proteiniuria <0.5 g/24h, inactive urinary sediment, and stable creatinine), a second renal biopsy was performed at four time points. Iohexol and the internal standard (iothalamic acid) were separated from serum proteins using centrifugal filtration device with a cut-off of 3 kDa. The chromatographic separation was achieved on an analytical Zorbax SB C18 column. The detection and quantification were performed by a triple quadrupole mass spectrometer ESI-MRM operating in a positive ion mode. Furthermore, the effect of iohexol on early gene expression in thyroid and renal cortex was tested to determine a threshold of physiological active iohexol concentrations.

**Results:** Linear correlation of the iohexol amount and mass-signal (MS) intensity was found in the range of 50 pg-40 ng (r² = 0.998). The lowest limit of quantification (LOQ) was 50 pg. The intra- and inter-day accuracies were between 91.2% and 98.7%. The recovery rate of iohexol was determined in the range of 100.8% ± 10.9%. The gene expressions test revealed that iohexol dosages exceeding 0.5 mg/kg induce a group of genes in thyroidal tissue that comprises transcription factors and genes of cellular stress response.

**Conclusions:** This mass-spectrometric based method has been proved to be sensitive, selective and suitable for the quantification of iohexol in serum. Due to high sensitivity of this novel method the iohexol application dose as well as the sampling time in the clinical routine could be reduced in the future in order to further minimize side effects in humans.

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Combined IgAN and MN</th>
<th>Isolated primary MN</th>
<th>Isolated IgAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>9</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>40.2±8.4</td>
<td>40.9±7.6</td>
<td>38.6±9.8</td>
</tr>
<tr>
<td>24-h Ur, g/24h</td>
<td>5.9±3.7</td>
<td>6.7±5.5</td>
<td>1.6±1.9*</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>74.4±20.2</td>
<td>75.4±17.6</td>
<td>116.5±110.9*</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>29.1±6.9</td>
<td>27±4.7</td>
<td>38.8±8.4*</td>
</tr>
<tr>
<td>Mesangial proliferation</td>
<td>None</td>
<td>None</td>
<td>All</td>
</tr>
<tr>
<td>Lee’s grading of IgAN</td>
<td>Grade I</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Grade II</td>
<td>0</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Grade III</td>
<td>6</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Grade IV</td>
<td>0</td>
<td>5</td>
<td>29</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Histological class</th>
<th>n</th>
<th>IF: IgG, C1q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Class II</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>Class III (A-C)</td>
<td>11</td>
<td>+</td>
</tr>
<tr>
<td>Class III (C)</td>
<td>3</td>
<td>-</td>
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<tr>
<td>Class IV (A-C)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Class IV (C)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Conclusions:** This study showed that after a satisfactory treatment, most patients with PNL, still presented mesangial or focal proliferative changes with positive IF for IgG and C1q in their second renal biopsy. While data in the present study suggest silent lupus activity, the association of these histological findings with potential relapses in PNL invited to an open discussion.

**Funding:** Government Support - Non-U.S.
Th-P0715
MiRNA Profiling in Urine Exosomes Indicates Renal Tubulointerstitial Fibrosis in CKD Patients Yan Zhang, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Renal fibrosis is an inevitable outcome of chronic kidney disease (CKD). It was reported that various microRNAs regulated the progression of tubulointerstitial fibrosis. However, whether fibrosis-related miRNAs are excreted in urine exosomes, as well as the changes of miRNA profiles in urine exosomes of CKD patients were unknown.

Methods: Morning urine specimens were collected from 10 healthy donor and 16 CKD patients, whose renal biopsy showed mild to moderate tubulointerstitial fibrosis. Urine exosomes were isolated from 2ml samples using urinary exosome isolation kit and observed by transmission electron microscopy. Quantification of miRNA levels in urine exosomes were determined using stem-loop qRT-PCR followed by real-time PCR. CD63 levels in exosomes were analysis by western blot.

Results: Urinary exosomes appeared as clusters of vesicles of 30-200nm in diameter under electron microscope, surrounded by a double-layer membrane. CD63, a major exosome marker associated with membranes of cellular vesicles, in exosomes isolated from some volume of urine indicated that the excretion of exosomes varied among different people. Moreover, the markedly increased CD63 levels in CKD patients suggested that the excretion rate of exosomes was probably upregulated in CKD patients with renal interstitial fibrosis. Most of preciously reported fibrosis-related miRNAs, including miR-21, miR-29 family, miR-30e, miR-192 and miR-200 family were detectable in urine exosomes. However, their contents varied significantly from fmo/mL to mM/mL. Furthermore, miRNA levels in urine exosomes were not associated with their levels in kidney. MR-21 and miR-29c levels in urine exosomes were markedly increased and decreased their upregulation and downregulation in kidney, respectively. MR-29b, miR-30e and miR-200b levels in urine exosomes were markedly increased despite their downregulation in kidney. Although miR-192 level in urine exosomes was as large as -10^-9mM/mL, its excretion was not significantly changed in CKD patients as compared with healthy control.

Conclusions: Profiling of miRNA in urine exosomes might indicate renal tubulointerstitial fibrosis in CKD patients.

Funding: Government Support - Non-U.S.

Th-P0716

Background: In the absence of hyperglycemia, glucosuria has been classically attributed to either a global dysfunction of the proximal tubule known as the Fanconi syndrome, or familiar renal glucosuria which includes inherited defects in the genes that encode the glucose handling kidney transporters. We have investigated the clinical observation that glucosuria is common in other kidney disease entities.

Methods: We analyzed the data for adult patients with native kidney biopsy between January 2014 and January 2015 at our institution that had concurrent urinalysis. We identified the patients who had glucosuria on urinalysis, in the absence of concurrent hyperglycemia (serum glucose > 180 mg/dL) or diabetes and were excluded from the analysis. The remaining sub-group of 44 (67 %) patients had a median age of 58 (19-81 years), 43 % were women, and 81 % were Caucasian. Median urinary glucose was 40 mg/dL (range 16-236). Concurrent serum urea nitrogen for this group showed a median of 101 mg/dL (range 54-149), with 66 % of patients having glucose less than 110 mg/dL. In this subgroup, biopsy findings included 32 (73 %) patients with glomerular disease (most commonly glomerular microangiopathy and pauci-immune crescentic glomerulonephritis), 10 (22 %) tubulointerstitial disease (most commonly acute tubulointerstitial nephritis), and 2 (4 %) arteriosclerosis as the predominant features on biopsy. No evidence of proximal tubulopathy was found among this group.

Conclusions: Glucosuria in the absence of hyperglycemia and diabetes, although classically associated with isolated proximal tubule dysfunction, is common in other kidney diseases and is a frequent occurrence in glomerular disease, which likely reflects a degree of secondary tubular injury. Future delineation of the pathophysiology of this observation may improve the understanding of tubular function in glomerular disease.

Th-P0717
Severe Interstitial Fibrosis Can Be a Predictor of Renal Failure in Patients with Lupus Nephritis, Especially in Cases With the International Society of Nephrology/Renal Pathology Society Class IV DanTsuke Honda, Kisara Onda-Tsueishi, Isao Ohsawa, Hiroyuki Inoshita, Satoshi Horikoshi, Yasuhiiko Tomino. Div of Nephrology, Dept of Internal Medicine, Juntendo Univ Faculty of Medicine, Tokyo, Japan.

Background: The ISN/RPS classification of lupus nephritis (LN) pays little attention to the interstitial injuries. We explored the association between irreversible interstitial fibrosis and renal failure in patients with LN, especially class IV cases that have not been thoroughly examined in this aspect.

Methods: Forty-three patients of LN were enrolled in this study. All patients were classified with the ISN/RPS classification and were divided into 4 grades according to interstitial fibrosis extent (no, 0%; mild, 1-25%; moderate, 26-50% and severe, more than 50% fibrosis of the interstitial area, n= 8, 16, 11 and 8, respectively). All 8 patients with severe fibrosis were classified in class IV. Blood and urine analysis was evaluated at the time of renal biopsy. We compared the data according to both c-TID and/or TID and in the presence of anti-PLA2R antibody did not differ significantly between the two groups (p>0.05; neither did the grading of MN (p<0.05). However, the histological lesions in the 9 cases was less severe as compared with the controls with isolated IgAN (p<0.05).

Conclusions: The clinical features and presence of anti-PLA2R of patients with combined MN and IgAN are more likely to mimic isolated primary MN.

TH-P0718

Background: Rare genetic variations in the C3, CFH, and CFB genes may lead to dysregulation of the alternative pathway of the complement system, altering the innate immune response associated with complement activation. The phenotypic consequence includes the thrombotic microangiopathies (TMA) and C3 glomerulopathies (C3G).

Methods: In this study, we compared variants identified in TMA patients to variants identified in C3G patients. Each variant was analyzed in a pipeline that included structural optimization of the wild type and mutant proteins based on molecular mechanics calculations. Initially, the wild type protein structure was optimized using the polarizable AMOEBA force field and dead-end elimination techniques. Each variant was then individually introduced to the wild type structure, which was then re-optimized. Both wild type and variant models were analyzed in molecular dynamic simulations and differences between wild type and variant free energies were calculated.

Results: Overall, for each variant we were able to obtain both: 1) qualitative data describing location and interactions; and 2) quantitative changes to protein conformation and stability providing insight into the wild type baseline. From these data, we were able to create a spectrum of free energy changes correlating to disease severity and enhance our interpretation of rare and novel variants, as well as identify biophysical characteristics specific to TMA and C3G.

Conclusions: These methods allow us to understand the biophysical consequences of each variant, predict the phenotypic severity of novel variants, and ultimately inform patient diagnosis.

TH-P0719
Urinary EGF Is Associated with Interstitial Fibrosis and Tubular Atrophy in Proteinuric Patients Wenjun Ju, Viji Nair, Michelle R. Smith, S.M. Bagnasco, L. Barisoni, Matthias Kretzler. 1 Medicine, Univ of Michigan, Ann Arbor, MI; 2Pathology, The Johns Hopkins School of Medicine, Baltimore, MD; 3Pathology, Univ of Miami, Miami, FL.

Background: Interstitial fibrosis (IF) and tubular atrophy (TA) are key morphologic determinants of progression and strong predictors for renal failure. However, their broader clinical application is limited by the invasiveness of the kidney biopsy procedure. Novel biomarkers, such as markers of interstitial fibrosis and tubular injury are needed to provide a non-invasive approach. Urine EGF has been reported to be a marker of interstitial fibrosis and tubular injury. We have therefore investigated the predictive utility of urinary EGF in proteinuric patients.

Methods: We performed a 2-year prospective study of 110 patients with proteinuria (≥ 1 g/d) and a free urine EGF assay. IF and TA was assessed by the Gridiron method and a semiquantitative grading system. Patients with active glomerulonephritis, polycystic kidney disease, chronic pyelonephritis, recent bacterial infection, recent myeloma, urolithiasis, acute renal failure, or sarcoidosis were excluded. EGF was measured using a sandwich ELISA. EGF concentration was normalized to urinary creatinine.

Results: Patients were divided into normal (E-GFR ≥ 90 ml/min/1.73 m², n = 30), mild (E-GFR 60-89 ml/min/1.73 m², n = 32), moderate (E-GFR 30-59 ml/min/1.73 m², n = 36), and severe (E-GFR < 30 ml/min/1.73 m², n = 22) GFR groups. EGF concentrations were significantly increased in the mild, moderate, and severe GFR groups compared to the normal GFR group (p < 0.001).

Conclusions: Urinary EGF is associated with IF and TA in proteinuric patients. EGF may improve the understanding of tubular function in glomerular disease.
Methods: Whole slide images of glass slides stained with Silver, Trichrome and PAS from biopsies, stored at the NEPTUNE digital pathology repository were assessed for % of cortex involved by IF/TA by 5 pathologists. The % of cortex involved by IF/TA was determined in each individual stain and averaged in an overall % value. We derived EGF mRNA levels in the tubulointerstitium using genome-wide expression data and measured uEGF in ELISA. All samples were cost-effectively validated ELISA assay. uEGF was normalized by urine creatinine level. A regression model was used to predict c-TID (%IF/TA) using uEGF level.

Results: Both tubulointerstitial EGF mRNA and uEGF correlated significantly (r=0.001) with IF/TA.

The correlations remain significant after adjusted for eGFR and proteinuria. uEGF predicted patients’ c-TID (%IF/TA) using a regression model in 102 adult NEPTUNE patients (r=0.77; p<.0001, adjusted predicted versus observed IF/TA).

Conclusions: uEGF shows promise as a non-invasive biomarker predictive of the biopsy dependent-IF/TA score in proteincric patients. Funding: NIDDK Support

TH-PO720
Considerations in the Use of Urine Protein: Creatinine Ratio (uPCR) and g/24h for Measuring Proteinuria in Nephrotic Patients in a Clinical Study
Christine Barrett,1 Gengqian Cai,2 Carol O.S. Savage.1, 1GlashoSmithKline plc, United Kingdom; 2GlashoSmithKline plc.

Background: uPCR on spot urine samples is used as an alternative to measurement of g protein/day from 24h urine collections, due to its ease of use and the correlation between the two. Most studies on correlation have concentrated on patients with subnephrotic levels of proteinuria. In a clinical study (BEL14672) to evaluate the mechanism of action of belimumab in idiopathic membranous nephropathy (IMN), uPCR and g protein/24h were assessed, correlation determined and variability in uPCR evaluated.

Methods: Samples from 14 patients with IMN and nephrotic proteinuria (≥4g/10mmol uPCR at screening) were tested. On 2 occasions during screening, spot morning samples were tested for uPCR. At key timepoints, consecutive 24h urine collections, or a spot morning sample and post dose 24h collection were used to test uPCR, g protein/24h and g creatinine/24h.

Results: Median uPCR 8.31 mg/10mmol (range 3.21-12.20) or 11.70 g/24h (range 3.99-20.40) at baseline was found in 11 M and 3 F aged 24 to 70y. High correlation (r=0.80-0.91) was observed between uPCR and g protein/24h within all groups with high, medium or low creatinine excretion. Different slopes were seen in each group: low: -0.93; medium: -1.34; high: -1.77. In individual samples, the ratio of g protein/24h to uPCR ranged from 0.66 to 2.97. In addition, with screening and prior to dosing data, a big range of within subject coefficient of variation for uPCR was observed: 8.5%-57.7%. Analysis of 6 nth history of proteinuria in the absence of immunosuppression prior to screening showed great variability and no specific pattern of worsening or improvement. Values for g protein/24h also varied considerably in consecutive samples.

Conclusions: uPCR values in patients with nephrotic syndrome are heavily influenced by creatinine excretion. This should be considered when setting eligibility criteria in clinical studies, or if basing dosing on levels of protein excretion. Variability in proteinuria in longitudinal samples from patients with nephrotic levels of proteinuria means that caution should be applied to values from single samples within clinical studies, whether using uPCR or g/24h.

Funding: Pharmaceutical Company Support - GlashoSmithKline plc

TH-PO721
Increasing Incidence of Class V Membranous Lupus Nephritis: A Single Institution Biopsy Experience
Parker C. Wilson, Alison G. Obsbter, Michael Kashgarian. Dept of Pathology, Yale Univ School of Medicine, New Haven, CT.

Background: Lupus nephritis (LN) contributes significantly to morbidity and mortality in patients with systemic lupus erythematosus (SLE) and is categorized into classes based on the pattern of glomerular injury seen on kidney biopsy. We assessed the proportion of patients presenting with class V or III/IV+V since the advent of systemic immunotherapy, which may have altered the manifestation of lupus nephritis to a more indolent course.

Methods: In this prospective study, we consecutively recruited 97 iMN patients with negative anti-PLA2R antibody, 31 iMN patients with positive anti-PLA2R antibody, 17 patients with secondary membranous nephropathy (sMN), 28 patients with primary glomerular diseases other than LN, and 40 healthy controls. ELISA kits were used to assay serum autoantibodies against THSD7A, SOD2, and eN0.

Results: A positive anti-THSD7A antibody was detected in 3 of 97 iMN patients with negative serum anti-PLA2R antibody, 1 of 31 iMN patients with positive serum anti-PLA2R antibody, none of patients with sMN or other glomerular diseases or healthy controls. For titers of anti-SOD2 antibody, there was no statistical difference among high anti-PLA2R antibody-negative iMN, anti-PLA2R antibody-positive iMN, sMN and other glomerular diseases. Result is the same for anti-eN0 antibody. iMN patients with negative serum and absent of anti-PLA2R, anti-THSD7A , anti-SOD2 , and anti-eN0 antibodies had lighter proteinuria, higher eGFR, and higher serum albumin(all P<0.05) at baseline and shorter duration for remission(P<0.05) as compared with iMN patients with at least one positive above-mentioned antibody.

Conclusions: In the present study, we found anti-THSD7A may have diagnostic significance for iMN, whereas iMN patients absent of anti-THSD7A , anti-SOD2, and anti-eN0 antibodies may be associated with milder clinical manifestation and better response to treatment as compared with those with positive anti-THSD7A , anti-SOD2, or anti-eN0 antibodies.

Funding: Government Support - Non-U.S.

TH-PO723
Interstitial Fibrosis Score by Whole Slide Imaging (WSI) Is a Predictor of Outcome in Proteinuric Renal Glomerulopathies
Laura H. Marijanic,1 Sebastian Martinic,1 L. Barisoni,2 Pietro A. Canetta,3 Jonathan P. Troost,4 Jeffrey B. Hodgin,5 Matthew Palmer,4 A. Rosenberg,5 Kevin V. Lemley,4 Chien Hui-Ping,4 Gerald B. Appel,6 Howard Trachman,7 Stephen M. Hewitt,7 Matthias Kretzler,8 S.M. Bagnasco.9 1Univ of Michigan; 2Univ of Miami; 3Columbia Univ; Johns Hopkins Univ; 4Univ of Pennsylvania; 5Children’s Hosp, Los Angeles; 6NIEH, NYU.

Background: Interstitial fibrosis(IF), tubular atrophy(TA), and interstitial inflammation(II) are determinants of progression of renal disease. Standardized assessment could add value to current classification of glomerulopathies.

Methods: NEPTUNE is a multi-center, prospective study of children and adults with >500mg/day of proteinuria and clinically indicated renal biopsy. We studied 310 patients with minimal change disease (MCD n=88), focal segmental glomerulosclerosis (FSGS n=125), membranous nephropathy (MN n=58) and IgA nephropathy (IgAN n=39). IF, TA and II were quantified as % of interstitial space, on digitized whole slide biopsy images (WSI) by 2-5 pathologists (r>0.8 inter-reader agreement). Multivariable cox proportional hazards models were fit to assess hazard of complete remission (CR) and composite of proteinuria, eGFR (<50), and creatinine >1.5 mg/dL.

Results: IF was highly correlated with TA (r=0.67, p<0.001) and II (r=0.66, p<0.001). Median(INR) for IF was 7(2,22) and varied by diagnosis [MN 7(4,13), MCD 10(3), FSGS 17(5,39), IgAN 21(11,35), P<0.001]. 57% of the cohort had no IF. Median II was highest in IgAN (P<0.001). IF was strongly correlated with baseline eGFR (r=-0.71, P<0.001) and
the effect of single-dose infusions of RTX at 375 mg/m² to evaluate the case that relapsed in patients with RTX. Therefore, the objective of this study was (Medicine 93: e300, 2014). But there are few reports about the relapse, and we also had 24-months at an interval of 6 months for patients with steroid-dependent MCNS in adults (RTX) in patients with steroid-dependent minimal-change nephrotic syndrome (MCNS). Treatment and outcome in GOMMID remain poorly described.

Methods: Twenty-five adults (17 men, median age: 61 years) from 21 nephrology departments were retrospectively studied. Inclusion criteria were: Congo Red-negative, monotypic IgG glomerular deposits, with microtubular organization (10-60 nm in external diameter) by electron microscopy (EM), without pathological criteria for cryoglobulinemic GN.

Results: Renal manifestations included: constant proteinuria (median: 6.0 g/d), nephrotic syndrome (72%), microscopic hematuria (79%), hypertension (79%), mean serum creatinine: 130 µmol/L. Biopsy proven extrarenal manifestations in 2 cases (mononeuritis, nodular hypodermitsitis). Eighteen patients had a serum and/or urinary monoclonal component, 12 had a lymphoproliferative disorder (chronic lymphocytic leukemia (CLL) n=6; lymphocytic B cell lymphoma n=3). Kidney biopsy showed atypical membranous GN (n=14) or membranoproliferative GN (n=11), with IgG deposits: IgG1 (n=8/15), IgG2 (n=5/15), IgG3 (n=2/15), mostly kappa (n=15/25). By EM, microtubule mean diameter was 15.6 nm. Intracytoplasmic lymphocyte microtubular inclusions were observed in n=11/11 (CLL n=3, lymphocytic B cell lymphoma n=1). Twenty-one patients received chemotherapy based on alkylating agent (n=17) and/or Rituximab (n=6). Renal response occurred in 15 cases (71%), associated with hematological response in 9 evaluable cases. Eleven patients received a second line of chemotherapy. After a median follow-up of 45 months, 17 patients had a persistent renal response, 5 had reached end-stage renal disease and 5 had died.

Conclusions: GOMMID should be suspected in patients with glomerular disease in the context of CLL or lymphocytic B cell lymphoma. Early chemotherapy, adapted to the underlying B-cell clone, is associated with a favorable renal outcome in 68% of patients.

TH-PO725

Long-Term Outcome in Glomerulonephritis with Organized Microtubular Monoclonal Deposits (Immunotactoid Glomerulonephritis): A Case Series of 25 Patients

Lea Dufour,1 Vincent Javaugec, Guy Touchard,1 Frank Bridoux.1 1Nephrology, Hospital, Poitiers, France; 2Anatomopathology, Hospital, Poitiers, France; 3Hematology, hospital Saint Louis, Paris, France.

Background: Glomerulonephritis (GN) with organized microtubular monoclonal deposits (GOMMID), also referred to immunotactoid glomerulopathy, is a rare entity distinct from fibrillary GN and type 1 cryoglobulinemic GN. Treatment and outcome in GOMMID remain poorly described.

Methods: Twenty-five adults (17 men, median age: 61 years) from 21 nephrology departments were retrospectively studied. Inclusion criteria were: Congo Red-negative, monotypic IgG glomerular deposits, with microtubular organization (10-60 nm in external diameter) by electron microscopy (EM), without pathological criteria for cryoglobulinemic GN.

Results: Renal manifestations included: constant proteinuria (median: 6.0 g/d), nephrotic syndrome (72%), microscopic hematuria (79%), hypertension (79%), mean serum creatinine: 130 µmol/L. Biopsy proven extrarenal manifestations in 2 cases (mononeuritis, nodular hypodermitsitis). Eighteen patients had a serum and/or urinary monoclonal component, 12 had a lymphoproliferative disorder (chronic lymphocytic leukemia (CLL) n=6; lymphocytic B cell lymphoma n=3). Kidney biopsy showed atypical membranous GN (n=14) or membranoproliferative GN (n=11), with IgG deposits: IgG1 (n=8/15), IgG2 (n=5/15), IgG3 (n=2/15), mostly kappa (n=15/25). By EM, microtubule mean diameter was 15.6 nm. Intracytoplasmic lymphocyte microtubular inclusions were observed in n=11/11 (CLL n=3, lymphocytic B cell lymphoma n=1). Twenty-one patients received chemotherapy based on alkylating agent (n=17) and/or Rituximab (n=6). Renal response occurred in 15 cases (71%), associated with hematological response in 9 evaluable cases. Eleven patients received a second line of chemotherapy. After a median follow-up of 45 months, 17 patients had a persistent renal response, 5 had reached end-stage renal disease and 5 had died.

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TH-PO726

PLA2R-Related Membranous Nephropathy in a Patient with Mannan-Binding Lectin Deficiency

Stéphane Bally,1 Hannia Debice,2 Chantal Dumestre-Perard,1 Frédérique Dioud,1 John Rendu,2 Pierre M. Ronco,3 Denise Ponard.1 1Nephrology and Dialysis, CHU Chambery; Chambery, France; 2UMR S1155, INSERM, Paris, France; 3Immunology Laboratory, CHU Grenoble, Grenoble, France; 4Pathology Center, Hôpitaux de Lyon, Lyon, France; 5Biochemistry and Molecular Genetics laboratory, CHU Grenoble, Grenoble, France.

Background: About 75% of patients with primary membranous nephropathy (MN) have autoantibodies against phospholipase A2 receptor (PLA2R), predominantly of IgG4 subclass. C3 and C5b-9 occur in glomerular immune deposits, implicating complement activation as a putative effector mechanism. It was also shown that purified anti-PLA2R IgG4 could activate the mannose binding lectin (MBL) pathway, but the respective role of the three pathways of complement activation remains elusive. Here we report the case of a patient with PLA2R related MN and MBL deficiency who developed MN.

Conclusions: Indigenous kidney biopsy specimens were evaluated for staining for PLA2R, IgG subclasses, and various complement components, including C3, C1q, C4d, factor B, properdin and C5b-9. MBL concentration was assayed by ELISA and its activity was measured from C4 cleavage. Polymorphisms in exon 1 and in the promoter region for MBL2 were detected by direct sequencing.

Results: Kidney biopsy showed MN with intense staining for PLA2R, IgG4, C3 and C5b-9 in glomerular immune deposits. Immunohistochemistry analyses showed diffuse positivity for factor B, properdin and C4d-9. PLA2R and IgG4 deposits were present in capillary loops. By EM, microtubule mean diameter was 15.6 nm. Intracytoplasmic lymphocyte microtubular inclusions were observed in n=14/15 (CLL n=3, lymphocytic B cell lymphoma n=1). Twenty-one patients received chemotherapy based on alkylating agent (n=17) and/or Rituximab (n=6). Renal response occurred in 15 cases (71%), associated with hematological response in 9 evaluable cases. Eleven patients received a second line of chemotherapy. After a median follow-up of 45 months, 17 patients had a persistent renal response, 5 had reached end-stage renal disease and 5 had died.

Conclusions: GOMMID should be suspected in patients with glomerular disease in the context of CLL or lymphocytic B cell lymphoma. Early chemotherapy, adapted to the underlying B-cell clone, is associated with a favorable renal outcome in 68% of patients.

TH-PO726

PLA2R-Related Membranous Nephropathy in a Patient with Mannan-Binding Lectin Deficiency

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Background: About 75% of patients with primary membranous nephropathy (MN) have autoantibodies against phospholipase A2 receptor (PLA2R), predominantly of IgG4 subclass. C3 and C5b-9 occur in glomerular immune deposits, implicating complement activation as a putative effector mechanism. It was also shown that purified anti-PLA2R IgG4 could activate the mannose binding lectin (MBL) pathway, but the respective role of the three pathways of complement activation remains elusive. Here we report the case of a patient with PLA2R related MN and MBL deficiency who developed MN.

Conclusions: Indigenous kidney biopsy specimens were evaluated for staining for PLA2R, IgG subclasses, and various complement components, including C3, C1q, C4d, factor B, properdin and C5b-9. MBL concentration was assayed by ELISA and its activity was measured from C4 cleavage. Polymorphisms in exon 1 and in the promoter region for MBL2 were detected by direct sequencing.

Results: Kidney biopsy showed MN with intense staining for PLA2R, IgG4, C3, factor B, properdin and C5b-9 and weak staining for C1q, IgG1 and C4d within the subepithelial deposits. Examination of the lectin pathway revealed a severe MBL quantitative and functional deficiency (concentration 12 µg/L, normal range: 30-3000 µg/L, and activity <10% normal range 35-135%). Genotyping revealed a 57 (A/C) heterozygous polymorphism in codon 57 of exon 1 associated with homozygous and heterozygous variation at -550 (L/L) and -221 (X/Y) respectively in the promoter region, suggesting that the patient harbours a susceptibility allele for MN.

Conclusions: Due to MBL deficiency, binding of anti-PLA2R antibodies to PLAB2R could not activate complement via lectin pathway. MBL plays a critical role in the pathogenesis of MN and its absence is associated with a lower risk of MN.

Funding: Government Support - Non-U.S.
Method: We made the renal tissue slice specimens of patients with glomerulonephritis. Specimens were made using the microscopically and histologically evaluated paraffin blocks of fresh glomeruli. The periodic acid-Schiff staining LM slide specimens from the paraffin blocks of renal biopsy tissues. Furthermore, we obtained the images of the US microscopy and LM.

Results: We could make discrimination between glomeruli and renal tubules by the US microscopy. In addition, we observed increased cell proliferation and increased matrix, and fibro-cellular crescent were detected by the US microscopy, which was enough to the conditions and lead to diagnoses.

Conclusions: We succeeded in obtaining the images of renal tissues using the US microscopy through a fine quartz fiber ex vivo. Furthermore these images were similar to them of LM. This preliminary study provides a first step toward clinical application of US pathological observation in renal diseases. These high-resolution images through a fine fiber could not only make live images of renal tissues possible, but prevent removing tissue. This enables a non-invasive and precise renal biopsy, and we can thereby make precise diagnoses of renal diseases. This study provides an important contribution to future diagnoses and treatments of renal diseases, and further studies are warranted.

TH-PO370

Serum Levels of Antiglycan IgG Autoantibodies in Patients with IgA Nephropathy Predict the Oxford Classification Scores S and T

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Background: Recent studies have shown a disease-specific macrophage (MQ) phenotype in pathologies such as tumor metastasis, arteriosclerosis and diabetes. However, a kidney disease-specific MQ phenotype has not been described. This study examined whether alternatively activated CD68+CD163+MQ are associated with interstitial fibrosis irrespective of the nature of the underlying disease.

Methods: Biopsies taken from children with IgA nephropathy (IgAN; n=81), purpura nephritis (n=25), biopsies with minimal change nephropathy (MCNS) (n=16), minimal change nephropathy with crescents (MCNS with crescents) (n=16), and cases with idiopathic nephrotic syndrome (LN; n=16), and idiopathic membranous nephropathy (M) (n=12) were used as controls. In vitro studies used monocyte-derived MQ with human healthy volunteers.

Results: Significant interstitial fibrosis and accumulation of CD68+MQ was evident in all progressive disease groups. Most interstitial CD68+ MQ co-expressed CD163 (89-99%). By contrast, CD63 expression by glomerular CD68+ MQ varied from 20% to 90% across the progressive disease groups, indicating much greater heterogeneity of M1/M2 phenotypes in this compartment. Interstitial CD68+CD163+ MQ correlated with the degree of interstitial fibrosis in each type of progressive renal disease (all p<0.01), with proteinuria in IgAN (p<0.05), MCNS, and LN (p<0.01), and with kidney function in CAI (p<0.001). In addition, CD63+ MQ co-localized in lesions with excess type I collagen deposition. In the fibrotic lesions with excess type I collagen deposition. In vivo studies showed that dexamethasone (Dex) up-regulated CD163 expression by MQ, and that Dex plus oxidized LDL increased MQ production of pro-fibrotic factors (FGF-1, FGF-2, TGF-b1, CTGF).

Conclusions: Our study identifies CD68+CD163+ MQ as the main MQ population associated with interstitial fibrosis across a range of progressive forms of kidney disease, suggesting a functional role for this MQ subset in renal fibrosis.

Funding: Government Support - Non-U.S.
Serum Immunoglobulin E Level Is Associated with Renal Progression in Immunoglobulin A Nephropathy

Larysa T. Wickman, Su Qing Wang, Mahboob A. Chowdhury, et al.

Background: Previous studies reported that serum Immunoglobulin E (IgE) levels are elevated in Immunoglobulin A nephropathy (IgAN) and suggested IgE levels as a prognostic indicator in IgAN. The aim of this study is to explore the association between plasma IgE level of IgAN patients and renal outcome.

Methods: This study is an observational study of IgAN patients undergoing kidney biopsy between 1995 and 2012. We collected the data of patient’s demographics and serum IgE levels from routine laboratory examinations. We performed a retrospective analysis to evaluate the correlation between serum IgE level and clinical parameters and pathologic findings. We defined renal progression if patient meets the following criteria: 1) negative value of delta estimated glomerular filtration rate (eGFR) (ml/min/1.73m²/months) and 2) a rise in serum creatinine of ≥0.4 mg/dl (≥1247 vs. 238 ± 607 IU/mL). The distribution in glomerular grades using the H. S. Lee grading was as follows: grade 1, 28 patients (23.9%); grade 2, 62 patients (53%); grade 3, 19 patients (16.2%); grade 4, 6 patients; grade V, 1 patient. Of the 117 patients, twenty-two (22%) had renal progression. Serum IgE level of the renal progression group was significantly higher than that of the non-progression group (274 ± 596 vs. 779 ± 415 IU/mL, p=0.014). The correlation between serum IgE level and total IgA level was significant (R² = 0.49, p<0.001).

Results: A total of 117 patients were included. The mean level of initial eGFR and serum IgE were 84.7±37.5 ml/min/1.73m² and 304±6071 IU/mL. The distribution in glomerular grades using the H. S. Lee grading was as follows: grade 1, 28 patients (23.9%); grade 2, 62 patients (53%); grade 3, 19 patients (16.2%); grade 4, 6 patients; grade V, 1 patient. Of the 117 patients, twenty-two (22%) had renal progression. Serum IgE level was significantly high in renal progression group compared to non-progressive group. (590±1247 vs. 238±290, p=0.014). Gender (76% vs 50%, P=0.011) and history of gross hematuria (9% vs 29%, P=0.024) were significant difference between high and low IgE group. But no significant differences were seen for delta SCr, delta eGFR, delta proteinuria (P=0.014). Gender (76% vs 50%, P=0.011) and history of gross hematuria (9% vs 29%, P=0.024) were significant difference between high and low IgE level.

Conclusions: These results suggested that serum IgE level is probably associated with renal progression in IgAN patients. Further studies are needed to elucidate the immunopathogenesis of the increased IgE level in IgAN.

Podometric Changes in Perinatal Kidneys (127 to 471 Day Post-Conception)

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Background: We recently reported that glomerular volume increases and podocyte density decreases with age from 4 to 89 years in man. However the changes that occur before and immediately after gestation in 58 weeks gestation are not well defined.

Methods: Podometric parameters (including glomerular volume, podocyte number, density, and cell size) were estimated from archival tissue sections with recently developed technology (Venkatadderly et al. JASN 2014 and Yang et al. JASN 2015) using autopsied kidney samples from newborn and infants without kidney disease as a proximate cause of death (n=25, age 0-240 day-old). Because premature kidneys were included, post-conceptional age (range 127-471 day-old) was used instead of postnatal age.

Results: The younger post-conceptional age was, the greater the proportion of immature glomeruli (R²=0.63, P<0.001). Compared to mature glomeruli, immature glomeruli were smaller (1.4±0.8 vs 4.9±4.9 µm³, P<0.001) and podocyte numbers were smaller (140 vs 320 µm², P<0.001) and fewer per glomerular tuft (300 vs 520, P<0.001), and present at higher podocyte density (2,700 vs 1,400/10⁶ µm², P<0.001). In mature glomeruli podocyte density decreased gradually with age (R²=0.84, P<0.001) due to a rapid increase in glomerular volume (±210% per year, R=0.48, P<0.001). Podocyte number per glomerular tuft did not change with age (R=0.008, P=0.68). Mean podocyte cell volume increased with age (±140% per year, R=0.39, P<0.002). Glomerular volume correlated with kidney-to-body weight ratio (R=0.49, P<0.001).

Conclusions: Prior to and after term there is a very rapid decrease in podocyte density (increase in glomerular volume and podocyte size without a change in podocyte number or proportion of the glomerulus that constitutes podocytes). These large perinatal adaptations could play a role in triggering glomerulosclerosis prevalent early in life.

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Novel Monoclonal Antibody KM55 Specifically Detected Glomerular Galactose-Deficient IgA1 in Patients with IgA Nephropathy

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Background: IgE nephropathy (IgAN) is an autoimmune disease in which IgA1 with some O-glycans deficient in galactose (Gal-IgA1) is recognized by anti-glycan IgE and/or IgA autoantibodies to form pathogenic immune complexes. Some of these immune complexes deposit in the kidney and induce glomerular injury. In this study, we assessed possible associations between serum levels of Gal-IgA1 and IgA, and Gal-IgA1 and IgG or IgA autoantibodies.

Methods: Serum samples from 135 patients with biopsy-proven IgAN, 79 patients with other renal diseases, and 106 healthy controls at Juntendo University, Tokyo, Japan, were analyzed for levels of total IgA and IgG, Gal-IgA1, and IgG-specific IgA and IgG autoantibodies and the data assessed for possible associations.

Results: Patients with IgAN had higher total IgA compared to healthy controls and exhibited a significantly stronger correlation between total IgA and Gal-IgA1 levels (R² =0.630, p=0.003). Gal-IgA1 levels strongly correlated with levels of Gal-IgA1-specific IgG autoantibodies in patients with IgAN (r=0.4909, p<0.0001), but not in healthy controls or disease controls. Levels of Gal-IgA1 did not correlate with the levels of IgA autoantibodies in any of the three groups. Furthermore, among IgAN patients with levels of Gal-IgA1-specific IgG higher than the mean ± 2 SD of healthy controls, only 37% also had an elevated level of Gal-IgA1-specific IgA autoantibody.

Conclusions: Our data revealed a new association between the key autoantigen, Gal-IgA1, and IgG autoantibodies in patients with IgAN, further supporting their key role in the pathogenesis of IgAN.

Cryoglobulinemic Glomerulonephritis: A Single-Center Experience

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Background: Cryoglobulinemic glomerulonephritis(CryoGN) is a recognized form of glomerulonephritis. However, the clinical characteristics are not well-established due to lack of large studies with biopsy and serological confirmation. We present our experience with 42 cases of serologically and biopsy-proven CryoGN.

Methods: We conducted a retrospective search for patients with cryoglobulinemia and kidney biopsy and identified patients with CryoGN. Results: From 2000 to 2014, we identified 569 patients with cryoglobulinemia. Of the 71 patients who underwent kidney biopsy for kidney dysfunction,42(59%) had CryoGN, the remaining 48 had other pathologies, including interstitial nephritis, lupus nephritis, fibrillar GN and amyloidosis. Median age of CryoGN patients was 59 yrs:male/female ratio, 23:19. Median eGFR by MDRD equation was 41ml/min/1.73m² at onset. 88% had nephritic syndrome and rest had nephrotic syndrome. 74% had Type II, 19% Type I and 7% Type III cryoglobulinemia. Hypocomplementemia was present in 83%. 76% had skin involvement, 16% had joint symptoms, 14% had nephropathy and 1% had pulmonary involvement. 4 patients required dialysis. Etiology of cryoglobulinemia was a hematological disorder in 40%(of which 88% lymphoproliferative and 12% MGRS) and hepatitis C in 26% patients.

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80% of patients received immunosuppression for treatment, 54% receiving Rituximab. Median duration of follow up was 18 months. Median overall survival was 36.4 months. At 6 months, median gFR improved to 48m/min/1.73m2.

Conclusions: Though CryoGN is the most common pathology in cryoglobulinemia, a wide array of other lesions is seen. Most patients with CryoGN have skin lesions while other systemic features of cryoglobulinemia are rare. In this study hematological disorders were the commonest etiology for CryoGN followed by hepatitis C infection.

TH-PO737

The Clinicopathological Impact of Medullary Ray Injury on Early Stage Renal Allografts

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Background: Interstitial fibrosis and tubular atrophy (IF/TA) constitute an important cause of renal graft loss. Previously, we examined medullary ray injury (MRI) inducing IF/TA via non-immunological mechanisms, classifying the etiology of MRI into calcineurin inhibitor (CNI) toxicity (8.6%), vesicoureteral reflux (50%), and urinary tract infection (8.6%) (Pathol Int. 2010;60:744–9). However, we did not examine the influence of the etiology on the long-term renal allograft prognosis, since the timing of the biopsies differed among the cases. Herein, we focused on MRI observed in protocol biopsies within 3 months, examining the influence on the renal allograft prognosis.

Methods: Retrospectively, we divided 53 protocol biopsies within 3 months into two groups with (n=34) and without (n=19) MRI. The MRI+ cases with isometric vacuolization and atrophy in the Banff classification were classified as CNI toxicity (MRI+CNI); the cases with Tamm-Horsfall protein casts in the interstitium and thyroid-like appearance were classified as urinary tract system abnormalities (MRI+UT); and the remaining cases as others. We compared the annual change in serum creatinine (sCr) levels over 3 years and the extent of fibrosis (ct+ci) at the 1-year biopsies. Cases with rejection were excluded.

Results: sCr levels in the MRI+ group were significantly higher than those in the MRI− group at 3 years (p=0.024). Three of the MRI+ groups, only MRI+UT had significantly high sCr levels compared to the MRI− group (p=0.019). The observation of IF/TA in the baseline and 1-year biopsies in the MRI+ group indicated the significant development of IF/TA.

Conclusions: Cases developing MRI within 3 months after kidney transplantation were significantly more likely to develop IF/TA at the 1-year biopsies. These cases had higher sCr levels at 3 years. In the cases with MRI in the base-line biopsies, interventions might preserve kidney graft function over the long-term.

TH-PO738

Diagnostic Gene Signature from Urinary Extracellular Vesicles Can Be Used as Biomarker for Non-Invasive Diagnosis of Clear Cell Renal Cell Carcinoma

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Background: Clear cell renal cell carcinoma (ccRCC) is one of the most common malignancies and due to its intimate association with urine, it appears well suited for studies to identify non-invasive biomarker in this material. The extracellular vesicles (EV) can be isolated in urine. They transport proteins and nucleic acids that reflect the physiopathological status of renal cells. The purpose of this study has been to analyze the transcripts in the urinary EV from ccRCC patients and to specific transcripts for preventive diagnosis of ccRCC.

Methods: We enrolled 12 patients with a diagnosis of ccRCC undergoing unilateral nephrectomy. We collected pre-intervention urine. A group of healthy volunteers (n=11) and 10 controls.

Results: We identified four genes (OSTA1, CEBPA, PCBD1, RCC2) differentially modulated in ccRCC patients and we investigated whether the functions of these genes could be related to ccRCC through the pathways analysis. The qRT-PCR validated a number of potential diagnostic biomarkers that could be used to distinguish ccRCC patients at an early stage from healthy individuals. Some potential biomarkers were already present in healthy controls. The dysregulated genes were validated by qRT-PCR in independent cohorts of 12 patients by differential centrifugation. Total RNA was extracted, quantified and qualitatively

Conclusions: These results were replicated in independent cohorts of 12 patients. Some potential biomarkers were already present in healthy controls. The dysregulated genes were validated by qRT-PCR in independent cohorts of 12 patients by differential centrifugation. Total RNA was extracted, quantified and qualitatively

The % injected dose of MB-102 appearing in the urine (99+/-7%) matched that of iohexol. The MB-102 time-dependence of the transdermal fluorescence monitored by the prototype device matched that of the plasma (~0.98). No significant adverse events were reported.

Conclusions: MB-102 was shown to be a GFR tracer agent in humans from the plasma pharmacokinetics and the % injected dose in urine match to iohexol. The transdermal fluorescence pharmacokinetics mimicked that of the plasma pharmacokinetics thus demonstrating that the validity of this noninvasive GFR measurement.

Funding: Pharmaceutical Company Support - MediBeacon, LLC

TH-PO740

Analysis of Exogenous Near Infrared Fluorescent Markers for the Transcutaneous Measurement of Glomerular Filtration Rate

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Background: Recently, we developed approaches for the transcutaneous measurement of GFR in animals. Using fluorescent markers allows GFR assessment without blood and/or urine sampling. Therefore, there is considerable interest in the development of exogenous fluorescent markers for real-time and accurate measurement of GFR via transcutaneous fluorescent methods using new dye conjugates.

Methods: A near infrared (NIR) cyanine was synthesized by a five-step synthetic procedure. This dye was used to label (2-hydroxypropyl)-β cyclodextrin. The chemical structure was fully confirmed by 1H-NMR, 13C-NMR, and HRMS spectra. Optical properties were characterized by UV-2450 spectrophotometer and fluorescence spectrometer. The percent plasma protein binding (PPB) was determined by equilibrium dialysis of fluorescent marker solutions incubated with rat plasma using a two-chamber dialysis set-up. Elimination half-life was determined in combination with a miniaturized new electronic device for

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the transcutaneous fluorescence detection in freely moving rats. Recovery rate in urine was measured in conscious rats after intravenous injection using metabolic cages. Mean ± S.D are given.

Results: The NIR marker was synthesized in a high yield. It exhibits good water solubility with concentrations reaching more than 200 mg/mL with a molecular weight range from 50 to 270 kDa. In addition, it is associated with low plasma PPI (~20% ± 10%), which is clearly lower than that of isothalamate (9.5%). The excitation and emission are 705 nm and 790 nm respectively providing low background and high tissue penetration for in vivo application. The noninvasive real-time monitoring of clearance resulted in a half-life of 4.8 ± 0.6 min and 34.9 ± 6.8 min without and with preheated treatment, respectively. A high urinary recovery of the marker with 99 ± 7.3% of the dose given was observed within 24 h.

Conclusions: We identified the marker with a high potential as exogenous fluorescent tracer for GFP measurement. A patent has been filed.

Funding: Government Support - Non-U.S.

TH-P0741

Phospholipase A2 Receptor Antibodies in Membranous Nephropathy: Autoimmunity, Serum and Urine Findings


Background: The major target antigen in Membranous Nephropathy (MN) is the phospholipase A2 receptor (PLA2R), its exact role is not yet fully understood. In this retrospective study we examined the presence of PLA2R in biopsy tissue, PLA2R antibodies in serum and urine of patients with MN, and aimed to identify associated clinical variables. We also investigated anti-PLA2R in sera from 30 MN patients treated with 0.5mg/kg/day of cyclophosphamide (CyA) for 12 MN patients, 9 recurrent MN; 12 secondary MN; 9 recurrent MN post transplantation; 25 class V lupus MN (LMN). 27 controls with other GN were also used. Immunofluorescence (IF) for PLA2R was performed on paraffin embedded biopsies and ELISA (EUROMMUN) for the detection of PLA2R antibodies in serum and urine. Results: In the iMN group 35/47 (74%) biopsies stained positive, 30 (40%) negative and 9(12%) borderline. Circulating PLA2R antibodies were detected in sera from 30/47(40%) patients within 6 months from biopsy, all of whom had positive or borderline staining on biopsy. In the secondary MN group 5/12 stained positive, 1 had a detectable PLA2R antibody. In the transplant cohort 3/9 stained positive; 1 had a positive serum. Of 25 class V LMN, 3 stained positive and 1 had a positive serum antibody. There was no correlation between staining or the level of PLA2R antibody with proteinuria or creatinine at the time of biopsy.

Conclusions: Our data suggest that IF for PLA2R in biopsy tissue is more sensitive than serum testing for the presence of PLA2R antibodies. This cross sectional study did not do a comparative between PLA2R antibodies level and proteinuria levels at the time of biopsy; however a longitudinal study to assess the variations of PLA2R in patients with clinical outcomes is in progress. The presence of PLA2R antibodies in urine of patients with active disease is interesting although further studies are required to determine whether this is due to nonspesific proteinuria.

TH-P0742

Belimumab in Idiopathic Membranous Nephropathy: An Interim Analysis of Exploratory Biomarkers Including Anti-PLA2R Autoantibodies

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Background: Belimumab (BEL) is a humanized monoclonal antibody against B-lymphocyte stimulator (BLYS), which is produced by many cell types, including B-cells, dendritic cells, myeloid cells, fibroblasts, and keratinocytes. We performed a retrospective analysis of patients with biopsy proven iMN between 2000-2015.

Results: We identified 188 patients with biopsy proven iMN.

| Median age | 58 (44-71) |
| Male % | 68 |
| Ethnicity (White / Black / Asian / Unknown) % | 48 / 17 / 24 / 11 |
| Diagnosis Serum creatinine (sCr) (µmol/L) | 86.5 (64 – 111) |
| Diagnosis Serum albumin (sAlb) (µmol/L) | 25 ± 7 |
| Diagnosis urine protein creatinine ratio (PCR) | 900 (485 – 1255) |
| Spontaneous remission % | 34 |
| Renal replacement therapy % | 34 |
| Deceased % | 12 |

20% of patients were progressors (increase in sCr >50%, no NRT). There was no statistical difference between sCr (101 ± 6 vs 92 ± 9 µmol/L, ns), sAlb (25.2 ± 1.3 vs 26.2 ± 0.8 mmol/L, ns) or PCR (893 ± 87 vs 895 ± 94, ns) at diagnosis between progressors and non-progressors, respectively. Progressors were more likely to be Asian (36% vs 21%, p=0.038) and non-progressors black (32% vs 20%, p=0.058). Of the 37 patients that spontaneously remitted, 5% relapsed. 65% of patients were treated with immunosuppressives. 60% received prednisolone, the most used first line agent was cyclophosphamide 35%, then metronidazole and 34% and calcineurin inhibitors (CNI) 23%. There was a significant difference between treatment between progressors and non-progressors; progressors were treated with CNI (38% ± 15%, p=0.04). Rituximab was used 3 times. The complication rate from immunosuppression was 25%. The most common was diabetes from steroid therapy at 10%, Infection occurred in 2% and drug specific complications in 7%. Thromboembolism rate from nephrosis was low at 14%.

Conclusions: At diagnosis there was no significant difference in sCr, sAlb or PCR between progressors and non-progressors. Progressor patients with iMN may benefit from a more aggressive immunosuppression, but this comes with risks. It is important to identify progressor patients; there is an unmet need for a biomarker to do this.

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Clinical Glomerular and Tubulointerstitial Disorders - 1

Poster/Thursday
TH-PO745
End-Stage Renal Disease from Membranous Nephropathy in the United States, 1995 to 2010
Robert N. Foley, Scott Reule, Donal J. Sexton. 

TH-PO746
42 Cases of Primary Sjögren Syndrome with Membranous Nephropathy: Clinicopathologic Features and Ectopic Germinal Center Formation
Mengyu Zhou, Yuheng Wen, Jing Wang, Xiaoxiao Shi, Yang Yu, Hang Li, Mingxi Li, Xuemei Li, Xuewang Lee, Limeng Chen. Dept of Nephrology, Peking Union Medical College Hospital, Beijing, China.

TH-PO747
In Primary Membranous Nephropathy, Relapse After Partial Remission Is Predicted by Serum Albumin Level

TH-PO748
Clinical Significance and Risk Factor of Relapse in Proteinuria in Primary Membranous Nephropathy
Seok Han, Eunjin Bae, Kwon Wook Joo, Yong Ki Kim. Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.

TH-PO749
Clinical Implication of BAFF and APRIL in Membranous Nephropathy
Seung Seok Han, Eunjin Bae, Kwon Wook Joo, Yong Ki Kim. Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.

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The Clinical and Prognostic Significance of Segmental Glomerulosclerosis Among Patients with Idiopathic Membranous Nephropathy

**Methods:** The study included 89 patients with iMN, followed over sixteen years, to evaluate the prognostic significance of glomerular segmental sclerosis in terms of renal survival. In the two groups (one with and one without segmental sclerosis), we analyze the various factors that are prognostic in iMN (eg. serum creatinine, proteinuria, etc.) and the histologic parameters.

**Results:** Segmental glomerulosclerosis was noted in 41 (46.1%) of 89 cases with iMN, representing cases from 57 (64.0%) males and 32 (36.0%) females. The prevalence of interstitial fibrosis and tubular atrophy did not contrast substantially between the two respective groups (3.38 ± 7.8 versus 1.22 ± 3.3, p=0.137). Only IgM positivity among the various factors that are prognostic in iMN (eg. serum creatinine, proteinuria, etc.) and the histologic parameters.

**Conclusions:** Our study revealed that segmental glomerulosclerosis was not associated with the severity of interstitial fibrosis. Although baseline serum creatinine was higher in patients with glomerulosclerosis at the time of biopsy, there was no impact on longterm outcome of the patients. Further studies are needed to outline the therapeutic regimen in iMN with segmental glomerulosclerosis.

**Key Words:** Idiopathic membranous nephropathy, iMN, segmental glomerulosclerosis, renal survival

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**TH-PO752**

Prevalence of Cancer in Membranous Nephropathy Patients

**Methods:** We evaluated patient responses for up to 36 months after initiation of combination therapy. The addition of prednisone after mizoribine monotherapy can be beneficial for most of all IMN patients with nephrotic syndrome.

**Results:** In 401 consecutive patients with primary MN, 28 (6.9%) patients having crescent formation. All patients presented with proteinuria (6.5±4.8±24/h) and hematuria. 21.4% of patients had declined eGFR (>60ml/min/1.73m²) on biopsy. Glomeruli showed on average 4.8% (range: 2.2-16.7%) involvement by crescents. Tubular atrophy was more common in these patients (88.9% vs. 78.6%, P=0.031). 12 (42.9%) patients received immunosuppressive therapy, similar to those with non-crescentic MN (41.33%). Fewer patients achieved remission in those with crescentic MN (67.9% vs. 86.7%, P=0.029). Crescent formation was a risk factor for no remission of treatments (RR=3.079, P=0.033). Higher percentage of crescents in glomeruli was also susceptible for no remission (RR=1.166, P=0.038). During follow-up, more patients with crescentic MN presented with eGFR decline (10.7% vs. 1.3%, P=0.031). Crescent formation was a risk factor for worse renal outcome (RR=10.24, P=0.046).

**Conclusions:** MN patients with crescent formation showed inferior response to treatments and worse renal outcome during follow-up, although the baseline clinical characters were similar on biopsy. The crescent was a risk factor for poor prognosis of MN patients.

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

**Key Words:** Crescentic nephropathy, crescent formation, renal outcome
**Methods:** 99 biopsy-proven iMN patients were collected from Huashan hospital and People’s hospital of WuXi in past 5 years. The iMN with positive PLA2R immunohistochemistry in kidney biopsies were designated as PLA2R associated MN. 79 of the 99 iMN patients were PLA2R-associated iMN and 13 were non-PLA2R, PLA2R-associated iMN. 49 patients were treated with prednisone plus CTX, and fifty with prednisone plus CNIs. 95% of the patients were on ACEI/ARB. The patients were followed for 15 months.

**Results:** The baseline characteristics between the PLA2R-associated and non-PLA2R-associated iMN was demonstrated in Table 1 (left part). In patients with non-PLA2R-associated iMN, the remission rate at 3-month was significantly higher than that in PLA2R-associated group (table 1 right part). Relapses were observed in 8 patients of PLA2R-associated group and none of non-PLA2R-associated group.

**Conclusions:** The non-PLA2R-associated iMN responded quicker to the immunosuppressive therapy compared with PLA2R-associated iMN, and relapses were more frequent in PLA2R-associated iMN. Non-PLA2R-associated iMN may have a better response to immunosuppressive therapy.

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

**TH-PO755**

**Prevalence of Enhanced Granular Expression of Thrombospondin Type-1 Domain-Containing 7A in Glomeruli in Japanese Patients with Idiopathic Membranous Nephropathy**

**Background:** Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults. Autoantibodies against M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A) were reported as the primary causes of MN. Although PLA2R is a major pathogenic factor for idiopathic MN, the prevalence of MN patients seropositive for PLA2R in Japan is lower than in other countries. In this study, we conducted immunohistochemical analysis of the presence of THSD7A and PLA2R in renal specimens of MN patients to estimate the prevalence of THSD7A/PLA2R-related idiopathic MN in Japan.

**Methods:** All patients with the histologic diagnosis of MN in adults made in our institution between 1995 and 2015 were included in this study. Immunohistochemical analysis of the presence of THSD7A and PLA2R was performed to these patients, and samples showing enhanced granular staining along capillaries of glomeruli were recognized as histologically positive for THSD7A and/or PLA2R. We collected the clinical information and laboratory data at the time of biopsy in order to classify MN patients into primary and secondary, and in order to compare characteristics of patients with enhanced expression of THSD7A and that of PLA2R.

**Results:** Enhanced granular expression of THSD7A and PLA2R was detected in 9.1% and 52.7%, respectively, of the patients with idiopathic MN. Although none of patients with secondary MN displayed enhanced granular expression of THSD7A, 5.4% of them had enhanced granular expression of PLA2R.

**Conclusions:** The prevalence of enhanced granular expression of THSD7A in glomeruli in Japanese patients with idiopathic MN was higher than the prevalence of MN patients seropositive for THSD7A in USA and Europe. This higher prevalence of THSD7A-related MN is likely associated with the lower prevalence of PLA2R-related MN in Japan.

**TH-PO756**

**PLA2R Autoantibodies and Glomerular PLA2R Deposit in Membranous Nephropathy: How to Evaluate the Roles They Played?**

**Background:** Higher Glomerular PLA2R-Antigen deposit (GAg) rates compared with the serum Phospholipase A2 receptor-Antibody (SAb) positive rates were reported. However, the exact roles played by this two biomarkers remained unknown.

**Methods:** A total of 572 patients diagnosed IMN were included. Both SAb and GAg were detected. Fifty-two iMN patients received repeat renal biopsy were also included. **Results:** In the 572 patients, 401 (70.1%) were SAb positive (+) while 171 (29.9%) were SAb negative (-). In SAb+ patients, the glomerular PLA2R-Antigen deposition (GAg+) was observed in 99.1% (397/401). Interestingly, the GAg+ was observed in 68.4% (117/171) SAb- patients. Patients with SAb manifested more severe proteinuria (3.9 ± 2.4 g/24h vs 2.8 ± 2.4 g/24h, P<0.001) and lower eGFR (104 ml/min.1.73m2 vs 110 ml/min.1.73m2, P=0.002) than patients without SAb. Further comparison between patients with SAb+ (GAg+ and SAB+/GAg+) showed a similar profile (more severe clinical manifestation in patients with SAb). Patients with SAb+ (GAg+)/SAb-/GAg+ also showed lower chance of proteinuria remission and higher chance of renal function decline in the follow up when compared to patients with SAb+ (table 1 right part). Changes of SAb and GAg were observed in patients with repeat renal biopsy, in 11 patients the SAb+ turned into SAb-, among them 1 patients failed to achieve remission, 7 patients achieved remission and 4 remitted during the interval but relapsed at the time of repeat biopsy. While the GAg+ turned into GAg- in only 3 patients, all achieved remission at the time of biopsy. The proportion of GAg disappearance was lower than SAb (P=0.016).

**Conclusions:** The GAg deposit can be detected in a large proportion of SAb negative patients, which can be explained by the lag of GAg disappearance in the follow up. The SAb was more tightly correlated to disease activity. Treatment response and prognosis than the GAg. We recommend adopting GAg deposit detection as a supplement to SAb in IMN diagnosing and keeping on monitoring SAb in the follow up.

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

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

**Underline represents presenting author.**

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
TH-PO758

Comparison of Outcomes Between Individuals with Pure and Mixed Lupus Nephritis: A Retrospective Study

Nosayaba Enfõ, Anju A. Oommen, Jason Cobb, Jose E. Navarrete, Demilade Adefidemsi, Oluwatobiloba A. Oskoye, Helene B. Fevrier, Altan Bradarris, Laura Plantinga, Titilayo O. Borji

Background: Lupus nephritis (LN) is divided into six classes (ISN/RPS Class I to VI) but can occur as a mixture of two classes. Pure proliferative LN (PPLN) comprises Class III or Class IV only while mixed proliferative and membranous LN (MLPN) comprises combinations of Class III & V or Class IV & V. Our aims were to compare individuals with biopsy-confirmed PPLN vs. MLPN in terms of clinical presentation and outcomes of complete or partial remission at 2 years and end-stage renal disease (ESRD) and clinical predictors of outcomes.

Methods: A retrospective analysis of all adult (>18) LN patients (n=278; PPLN (n=60) and MLPN (n=96)) identified from a native renal biopsy registry at a hospital network performed January 2000-December 2011. We assessed associations of LN category (MPLN vs. PPLN) with: time to remission (defined as ≥ 25% improvement in eGFR if baseline abnormal and urine protein creatinine ratio >0.3) and ESRD (defined using ICD-9 diagnosis code - 583.6 or the onset of chronic renal dialysis) using multivariable Cox proportional hazards analysis.

Results: The population was predominantly female (84.0%) and African American (71.8%), with a mean age of 33.4. Over follow-up (median, 1.5 years), using the PPLN group as the reference group, we did not find any associations between MLPN and time to remission (HR=0.13, 95% CI = 0.01-1.36) or ESRD (HR=0.30, 95% CI = 0.07-1.26). Baseline eGFR was significantly associated with time to remission (HR = 0.90, 95% CI = 0.84 - 0.98).

Conclusions: We found no significant differences in remission or progression to ESRD between patients with PPLN and MLPN. We, however, demonstrated that higher baseline eGFR at presentation were important factors in achieving remission in individuals with LN.

TH-PO759

Pure Class V Lupus Nephritis: Towards a Better Understanding of Lupus Membranous Nephropathy Compared to Its Proliferative Counterparts

Fernanda Pavan Schober, Keisha L. Gibson, Taewoo Lee, Caroline J. Poulton, Mary Anne Dooley, William Franklin Pendergraft.

Background: Class V lupus nephritis, also known as lupus membranous nephropathy, accounts for approximately 10-20% of patients with lupus nephritis. There is not a consensus on the best treatment for isolated class V lupus nephritis, so providers often turn to the proliferative lupus nephritis and idiopathic membranous nephropathy (IMN) literature to extrapolate treatment approaches and outcomes. Here we compare clinical data between patients with lupus membranous, proliferative lupus nephritis and IMN.

Methods: Clinical and treatment data for lupus membranous patients were extracted from electronic medical records starting at the time of diagnosis until date of chart review.

Results: Patients with lupus membranous resembled the lupus nephritis population more than the IMN population as they were more likely to be African American women with a worse prognosis and has been reported previously to be more common in patients of African descent. Here we describe the clinical and histologic features of 48 patients with lupus membranous and necrotizing glomerulonephritis and native kidney biopsy.

Conclusions: Patients with lupus nephritis who had necrotizing and crescentic lesions were identified from the UNIC Division of Nephropathology database. Clinical, histologic, treatment, and long-term outcome data were obtained from the electronic medical record.

TH-PO760

Necrotizing Glomerular Lesions Portend a Worse Prognosis for Patients with Lupus Nephritis

Jose E. Navarrete, Keisha L. Gibson, Mary Anne Dooley, Elizabeth R. Blyth, Caroline J. Poulton, Harsharan Kaur Singh, Volker Nickelet.

Background: Necrotizing glomerular lesions on kidney biopsy are uncommonly found in patients with lupus nephritis (LN) and are similar in appearance to those lesions found in patients with ANCA glomerulonephritis. The presence of these lesions portends a worse prognosis and has been reported previously to be more common in patients of African descent. Here we describe the clinical and histologic features of 48 patients with lupus nephritis and necrotizing glomerulonephritis and native kidney biopsy.

Methods: Patients with lupus nephritis who had necrotizing and crescentic lesions were identified from the UNIC Division of Nephropathology database. Clinical, histologic, treatment, and long-term outcome data were obtained from the electronic medical record.

Results: Demographic and histologic data are shown in the following table. Most notably, these patients were predominantly African American women with class IV lupus nephritis high overall disease activity.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Female (%)</th>
<th>Male (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>41 (97%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>African American</td>
<td>11 (23%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>52 (67%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>American Indian</td>
<td>1 (1%)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Serum creatinine (mg/dl)</th>
<th>Proteinuria (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34-12</td>
<td>1.64 -1.3</td>
<td>3.71 -3.1</td>
</tr>
</tbody>
</table>

Conclusions: This cohort represents one of the largest of its kind in the literature to date. Necrotizing lesions are more characteristic of pauci-immune ANCA vasculitis, but have been described in patients with lupus nephritis as well. This rare variant is an understudied glomerular disease that portends a poor prognosis with an increased risk of progression to ESKD. There is a need for prospective multi-center treatment studies to determine durable therapeutic avenues.

TH-PO761

Membranous Lupus Nephritis: Immunoglobulin Deposits and Clinical Correlations


Background: Lupus nephritis histological hallmark, mostly in proliferative classes, is a “full house” (FIH) pattern of immunoglobulin deposition and complement. However, Haas showed that membranous lupus nephritis (MLN) depicted this pattern only in 65% of the patients. The importance of FH deposition in MLN disease is still a matter of debate. It remains to be determined association between immunoglobulin deposition with clinical disease aggressiveness or transformation into proliferative forms.

Methods: All MLN patients admitted to our hospital from July 1999 to August 2007 were included and biopsy tissue was studied by light microscopy and immunofluorescence. Patients were classified according to immunoglobulin glomerular capillary wall deposition in rich (rIF), with two or more deposited immunoglobulins, and poor (pIF) with a single and exclusive IgG deposition. Clinical and laboratorial data were collected at baseline, one year after and at the end of follow-up. Treatment was decided based on literature protocols.

Results: We included 15 patients in pIF group and 46 in rIF. At baseline, groups were similar regarding age, complement level, ANA, anti-DNA and proteinuria. Interestingly pIF was significantly associated with a lower eGFR at baseline that persisted after one year follow-up. At the end, the pIF showed a not significant tendency to lower eGFR.

<table>
<thead>
<tr>
<th>Proteinuria (gm)</th>
<th>Serum Albumin (mg/dl)</th>
<th>Serum Creatinine (mg/dl)</th>
</tr>
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<tbody>
<tr>
<td>8.4 ± 13</td>
<td>3.2 ± 4</td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td>4.3 ± 26</td>
<td>1.5 ± 1.8</td>
<td>1.56 ± 2.3</td>
</tr>
</tbody>
</table>

Conclusions: Patients with lupus membranous make up a substantial portion of patients with lupus nephritis. They present with significantly more proteinuria than patients with proliferative lupus nephritis, but have less kidney impairment. There’s a clear need for more prospective multicenter randomized controlled studies to determine the most effective treatment in this population.

Funding: NIDDK Support
Follow-up of 3.6 years the global subgroup had worse renal outcome (final eGFR 59.6 ± 2004 and 2014.

All procedures were performed in one single center between 2004 and 2014. Seventy-one biopsy-proven patients with proliferative (classes III or IV) lupus nephritis data were retrospectively analyzed. Twenty-nine of them were classified as global and 42 as segmental. All procedures were performed in one single center between 2004 and 2014.

Results: All patients received induction therapy with steroids plus either intravenous cyclophosphamide or mycophenolate mofetil. Although there was no difference in age, eGFR and hemoglobin levels at baseline (see table), after a median follow-up of 3.6 years the global subgroup had worse renal outcome (final eGFR 59.6 ± 37.6 vs 78.9 ± 28.4, p = 0.02). During follow-up, there was also a tendency for faster eGFR recovery rate in segmental subgroup after treatment (5.2 vs 1.8 ml/min/year, p = 0.2). Interestingly, the prevalence of males in global subgroup was significantly higher (20% vs 4%, p = 0.03).

Table: Comparison of baseline characteristics between global and segmental subgroups

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Segmental</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>31.8±12</td>
<td>31.5±9</td>
<td>ns</td>
</tr>
<tr>
<td>Hb (mg/dL)</td>
<td>10.9±1.4</td>
<td>11±1.1</td>
<td>ns</td>
</tr>
<tr>
<td>MDRD Baseline (ml/min/1.73m²)</td>
<td>55.2±26</td>
<td>63.9±27</td>
<td>ns</td>
</tr>
</tbody>
</table>

Follow-up features

Follow-up (y) | 3.63 | 3.62 | ns
MDRD Final (ml/min/1.73m²) | 59.6±37.6 | 78.9±28.4 | 0.02
MDRD Delta per year | +1.8±2.3 | +5.2±2.9 | 0.2

Conclusions: In global compared to focal proliferative lupus nephritis patients: male sex prevailed and renal function decreased on 3.6 years follow-up in spite of similar MDRD on baseline. Prospective studies are necessary to determine if histological pattern is relevant to guide the clinician’s therapy choice.

TH-PO762

Segmental versus Global Subclasses of Proliferative Lupus Nephritis: Clinical Correlations

Background: The International Society of Nephrologists and Renal Pathology Society classification of lupus nephritis proposes a subclassification of proliferative forms into segmental (S) and global (G). Data comparing renal outcomes between these two subclasses is controversial and pathogenesis also seems to differ (Barzilay J, 2005). We aimed to compare histopathology with clinical correlations.

Methods: Seventy-one biopsy-proven patients with proliferative (classes III or IV) lupus nephritis data were retrospectively analyzed. Twenty-nine of them were classified as global and 42 as segmental. All procedures were performed in one single center between 2004 and 2014.

Results: All patients received induction therapy with steroids plus either intravenous cyclophosphamide or mycophenolate mofetil. Although there was no difference in age, eGFR and hemoglobin levels at baseline (see table), after a median follow-up of 3.6 years the global subgroup had worse renal outcome (final eGFR 59.6 ± 37.6 vs 78.9 ± 28.4, p = 0.02). During follow-up, there was also a tendency for faster eGFR recovery rate in segmental subgroup after treatment (5.2 vs 1.8 ml/min/year, p = 0.2). Interestingly, the prevalence of males in global subgroup was significantly higher (20% vs 4%, p = 0.03).

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<tr>
<td>%Male</td>
<td>20%</td>
<td>4%</td>
<td>0.03</td>
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Follow-up features

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MDRD Final (ml/min/1.73m²) | 59.6±37.6 | 78.9±28.4 | 0.02
MDRD Delta per year | +1.8±2.3 | +5.2±2.9 | 0.2

Conclusions: We found 25% of MLN patients with only one deposited immunoglobulin. The poor IF group compared to rich IF showed lower MDRD at baseline and even after one year. Studies are needed to elucidate the role of different patterns of deposits in the pathogenesis of MLN.

TH-PO764

Ability of Spot Urine Protein/Creatinine Ratio (Spot PCR) to Correctly Identify the Proteinuria Endpoints of Complete Remission (CR), Partial Remission (PR), and Treatment Failure (TF) as Determined by 24 Hour Urine PCR (24 PCR): Experience of the Abatacept and Cyclophosphamide Combination Immunosuppression Trial to Reduce Flare and Improve Safety Study (ACCESS) E. J. Birmingham,2 Brad H. Rovin,3 Lee A. Hebert.4 1Div of Nephrology, OSUWMC, Columbus, OH; 2Div of Nephrology, OSUWMC, Columbus, OH; 3Div of Nephrology, OSUWMC, Columbus, OH; 4Div of Nephrology, OSUWMC, Columbus, OH.

Background: Spot PCR is an inherently highly variable estimate of 24 hour proteinuria magnitude, compared to 24 PCR (Ann Rheum Dis, 73, 475, 2014). So, it is likely that using spot PCR rather than 24 PCR to guide management increases the risk of management error. The current work is the first to rigorously test this hypothesis. ACCESS is a prospectively randomized phase 2 trial of Abatacept or placebo added to the Euro-Lupus regimen of cyclophosphamide and prednisone followed by azathioprine and low dose prednisone. A unique feature of ACCESS was concurrent testing for spot PCR (monthly) and 24 PCR (each three months). ACCESS proteinuria endpoints were CR, PR, and TF assessed at 6 months and 12 months of follow-up (Arth Rheum 66, 3096, 2014).

Methods: Evaluable data (spot PCR measured within one month of the 24 PCR) was present at six months in 100 patients, and at twelve months in 54 of the 100 patients. Spot PCR was deemed correct if it was concordant with the 24 PCR determination of whether CR, PR, or TF was present, and deemed incorrect if discordant with the 24 PCR determinations of whether CR, PR, or TF was present.

Results: At 6 month follow up, spot and 24 PCR were concordant in 36 CR, 23 PR, 10 TF; and discordant in 10 CR, 11PR, and 8 TF. At 12 month follow up, spot and 24 PCR were concordant in 36 CR, 11 PR, and 2 TF, and discordant in 4 CR, 2 PR, 0 TF. Totals: Concordant 120, Discordant 35. P < 0.001 (null hypothesis that concordance is 95% is rejected).

Conclusions: The error rate of spot PCR in identifying ACCESS proteinuria endpoints (defined by 24 PCR) was 23%. Proteinuria endpoints in LN trials are broad targets and mainly involve low level proteinuria. This minimizes the impact of spot PCR variability.

Funding: NIDDK Support

TH-PO765

Induction Treatments for Proliferative Lupus Nephritis: A Network Meta-Analysis Suetonia Palmer,1 David J. Tunnillcliffe,2 Allison Tong,3 Dimitris Mavridis,4 Jonathan C. Craig,1 Marcello Tonelli,1 David W. Johnson,1 Giovanni F.M. Strippoli,2 1Univ of Otago Christchurch; 2Univ of Sydney; 3Univ of Ioannina; 4Univ of Calgary; 5Univ of Queensland; 6Univ of Bari.

Background: Intravenous cyclophosphamide has been standard care for inducing remission among patients with proliferative lupus nephritis (class III or IV). More recently, several agents have been trialed, however, given the numerous treatment options and head-to-head trials, there is uncertainty about the comparative effectiveness of all available treatment options.

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

265A
Methods: Immunosuppressive treatments to induce remission of kidney disease among patients with proliferative lupus nephritis (LN) were identified using network meta-analysis of parallel-group randomized controlled trials. Outcomes were complete disease remission, treatment failure, all-cause mortality, end-stage kidney disease, major infection, alopecia, ovarian failure and malignancy. Effect sizes for treatments were calculated using random-effects meta-analysis and compared to intravenous cyclophosphamide (referent). Trials were critically appraised using Cochrane risk of bias.

Results: 47 studies involving 3510 patients were eligible. Mycophenolate moefetil was superior to intravenous cyclophosphamide for inducing disease remission (network odds ratio 2.08, 95% confidence interval 1.18-3.69), and resulted in 12% of patients achieving treatment failure compared to 1.6% (network odds ratio 0.26-0.87), and alopecia (0.22, 0.13-0.39). Mycophenolate moefetil had uncertain risks of death (OR 1.14, 0.49-2.65), major infection (1.30, 0.88-1.92) and ovarian failure (0.48, 0.11-2.08) versus intravenous cyclophosphamide. Comparative effects of other treatments including methotrexate and calcineurin inhibitors could not be estimated through network meta-analysis because of uncertainty. Information for end-stage kidney disease and malignancy endpoints for all treatments was sparse. Treatment effects were generally consistent within networks. Methodological reporting in trials was frequently unclear.

Conclusions: Mycophenolate moefetil is more effective than intravenous cyclophosphamide for induction treatment of proliferative lupus nephritis.

TH-PO766
A Systematic Review on Tacrolimus Treatment in Lupus Nephritis
Tinke Kraai1, Edwin Bredewold, Tom Huizinga, Tom J. Rabclink, Yoe Kie Onno Teng, Nephrology, LUMC, Leiden, Netherlands; Rheumatology, LUMC, Leiden, Netherlands.

Background: Recently, 2 large randomized controlled trials (RCTs) have been published on the efficacy of tacrolimus (TAC) in Asian LN patients. Both trials used different treatment regimens and efficacy was not consistent between the trials. Therefore, the role of TAC in the treatment of LN remains unclear. Thus, we performed a systematic review on TAC treatment for LN.

Methods: We searched multiple databases for all human studies investigating TAC treatment in LN. Then studies were selected on clinical relevance and results were analysed on renal response and adverse events.

Results: We found 26 clinical studies from which data were extracted from all controlled studies: 6 RCTs and 3 case-control studies involving a total of 888 patients. As induction treatment, TAC with steroids resulted in 82% responders of which 56% complete responders (CR). Induction with steroids, mycophenolate (MMF) and TAC resulted in 85% responders, of which 46% CR. Data from 1 RCT performed with TAC in combination with steroids as maintenance treatment, resulted in 100% responders of which 56% CR. Generally, control patients receiving induction treatment with cyclophosphamide achieved 66% response of which 29% CR. Those receiving induction treatment with MMF achieved 76% response of which 53% CR. Overall infections were observed in 20% of TAC treated patients compared to 26% of control patients treated with cyclophosphamide and 29% in MMF treated control patients. A rise in serum creatinine was observed in 5% of all TAC treated patients compared to 2% in the cyclophosphamide control group and 0% in the MMF control group.

Conclusions: This systematic review suggests that TAC-based treatments can achieve comparable renal responses in LN as conventional regimens. Currently, limitations of the available studies are the heterogeneity of TAC-based regimens, lack of studies in non-Asian LN patients and lack of long-term safety data. Altogether, these data warrant further RCTs on TAC treatment for LN.

TH-PO767
Predicting Chronic Kidney Disease (CKD) in Lupus Nephritis (LN)
Ana Malvar, Valeria Gabriela Alberton, Bruno Jorge Lococo, Haikady Nagaraja, Brad H. Rovin, Hospital Fernandez, Buenos Aires, Argentina; Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: Early identification of LN patients likely to develop CKD may permit therapy to be adjusted and CKD to be avoided. Clinical and histologic parameters measured after induction and during maintenance therapy were associated with long-term chronic kidney outcomes in a cohort of LN patients to define predictors of new CKD.

Methods: Patients (n=69) with biopsy-proven class III/IV LN were induced with steroids and MMF (53%) or cyclophosphamide (44%) for 6 months, had repeat kidney biopsy (biopsy 2, 6.6±0.7 months), and were put on maintenance therapy. Long-term (median 73 months) follow-up was available on 87% of the cohort. Multivariate linear regression was used to develop a predictive model for future serum creatinine (SCr) based on clinical and histologic variables obtained after induction.

Results: Complete clinical response at biopsy 2 (CR) at last follow-up among patients who did or did not achieve a complete clinical renal response after induction (19% vs 18.4%, respectively). Among patients with complete histologic renal remission after induction, 36% had a final SCr of 1.3-2.9 mg/dl. There was no relationship between the NIH activity index at biopsy 2 and long-term kidney function. However, the median serum creatinine at biopsy 2 of patients who developed CKD was 6 (range 2-8) compared to 4 (range 0-7) in patients who did not develop CKD (p=0.02). Regression analysis showed a significant linear correlation between CI 4 at biopsy 2 and log(Scr) at long-term follow-up (R=0.36, p < 0.0001). In multivariate analysis CI and SCr at biopsy 2 were independent predictors of long-term SCr (R=0.48, p < 0.0001). For a given level of SCr at biopsy 2, a 1 unit increase of CI in the range of 4-8 corresponded to a 20% increase in last SCr.

Conclusions: Neither clinical nor histologic remission after induction predicts long-term outcome of LN patients. The combination of CI and chronic damage on induction biopsy after induction accounts for 48% of the long-term variability of renal function in those patients who reach a threshold level (CI=4) of chronic kidney damage.

Funding: NIDDK Support

TH-PO768
Clinical and Histologic Remission in Class IVG and IVS Lupus Nephritis (LN) After Induction Therapy
Ana Malvar, Bruno Jorge Lococo, Valeria Gabriela Alberton, Diego Morales, Brad H. Rovin, Hospital Fernandez, Buenos Aires, Argentina; Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: The ISN/RPS classification of LN distinguishes class IV with predominantly segmental lesions (IVS) from class IV with global (IVG) lesions. It has been suggested that IVG may have a lower remission rate than IVS, possibly because it more like a vasculitis than IVG. However several studies found no significant difference in long-term kidney survival between these subclasses. We examined differences in histologic and clinical remissions between IVG and IVS in our LN cohort with serial kidney biopsies. Patients with proliferative lupus nephritis were all compared using network meta-analysis and compared to intravenous cyclophosphamide (referent).

Methods: A systematic review (CCR) was defined as normal SCr and proteinuria < 500 mg/d. Complete histologic remission was defined as an AI=0 at Bx2.

Results: Clinical outcomes and histologic data are shown in the Table. All patients were ANCA negative. Final SCr and proteinuria were determined after a mean follow-up of 54±7 months. Only 4 patients were lost to long-term follow-up.

| Bx1 | CR (n=33) | 39% | 87% | 0.32 | 0.24 | 10.3±2.9 | 3.7±2.8 | 3.5±1.9 | 4.9±1.9 |
| Bx2 | CR (n=41) | 76% | 70% | 0.32 | 0.26 | 19.5±2.2 | 3.0±1.3 | 2.6±1.8 | 4.4±0.7 |
| IVG (n=9) | 80% | 89% | 0.26 | 0.19 | 8.5±2.2 | 1.8±1.8 | 0.05 | 0.05 | 0.05 |
| IVS (n=10) | 76% | 66% | 0.34 | 1.00 | 0.43 | <0.05 | 0.05 | 0.05 | 0.05 |

Conclusions: Class IVS LN has an excellent clinical and histologic response to standard-of-care LN induction therapy. Class IVG takes longer to respond, but over time there are no differences in long-term renal outcomes between Class IVG and IVS LN as assessed by SCr and proteinuria. This suggests that these subclasses may be treated similarly. These results also raise the possibility that class IVS patients who have complete clinical and histologic remission after induction may do well with an abbreviated course of maintenance therapy.

Funding: NIDDK Support

TH-PO769
Complete Remission Rate and Outcome in Severe Lupus Nephritis: The Impact of Baseline Serum Creatinine

Background: A complete remission (CR) in severe lupus nephritis (SLN) is associated with a favorable long-term outcome. Numerous factors including level of serum creatinine (SCr) at baseline have been shown to impact on CR rate and outcome. We assess the impact of baseline SCr on CR rate and outcome in SLN.

Methods: We evaluated the 86 adult patients in the prospective, controlled trial of plasmapheresis in SLN and compared them based on SCr level at baseline (≤1.0, 1.01-1.5, 1.51-2.0, 2.01-3.0 and >3.0 mg/dl; n= 22, 23, 23, 16, 13, 12 respectively). The CR rate (defined by a serum creatinine (SCr) of ≤ 1.4 mg/dL and proteinuria < 0.33 g/day) and long-term outcomes (stable renal function, dialysis and death) were compared. Pts with a baseline SCr of ≥1.0 mg/dl were >16 times as likely (odds ratio, 16.2; 95% confidence interval, 4.2-61.5) to attain a CR and >6 times as likely (odds ratio, 6.1; 95% confidence interval, 1.9-20.5) to have stable renal function at last follow-up compared to pts with a baseline SCr of <1.0 mg/dl. The CR rate and outcome in SLN as assessed by SCr and proteinuria. This suggests that these subclasses may be treated similarly. These results also raise the possibility that class IVS patients who have complete clinical and histologic remission after induction may do well with an abbreviated course of maintenance therapy.

Funding: NIDDK Support
**TH-PO770**

**Urinary Adiponectin Isorforms and Kidney Lesions in Lupus Nephritis (LN)**

Xiaolan Zhang,1 Divya Indrakanti,1 Anthony Alvarado,1 Sergey V. Brodsky,2 Hermine Brunner,2 Brad H. Rovin,1,3 1Ohio State Univ Wexner Medical Center, Columbus, OH; 2Cincinnati Children’s Hospital, Cincinnati, OH; 3CKD Biomarker Consortium.

**Background:** Human adiponectin isoforms exert different effects on inflammation. Urinary adiponectin is increased at LN flare, but the relationship between adiponectin isoforms and kidney lesions in LN has not been studied.

**Methods:** Urine and plasma total and high molecular weight (HMW) adiponectin isorforms were measured by specific ELISAs in samples from 39 normal controls and 97 biopsy-diagnosed LN patients. Urinary adiponectin levels were normalized and log-transformed, and then examined for associations with histologic lesions on kidney biopsy by ANOVA, nonparametric Wilcoxon ranked-sum testing and multiple linear regression analysis.

**Results:** The HMW to total adiponectin ratio was increased in plasma (p=0.022) and urine (p=0.0004) of LN patients compared to controls. Total and HMW adiponectin levels were highly correlated within the plasma (R²=0.91, p < 0.0001) and urine (R²=0.64, p < 0.0001) in LN, but between plasma and urine HMW adiponectin showed a correlation, and this was minor (R²=0.21, p=0.037). Urine adiponectin levels increased with the severity of ISN/PNS class. The highest total and HMW urine adiponectin levels were found in patients who had combined class III or IV + V LN. Using urine HMW adiponectin levels to differentiate between control and LN patients, and between single and combined LN classes, receiver-operating characteristic analysis showed areas under the curve of 0.96 and 0.85, respectively. Urine HMW adiponectin was significantly increased when glomerular proliferation, cellular crescents or interstitial inflammation were present on the biopsy, and HMW adiponectin correlated with the biopsy activity index (R²=0.31, p < 0.0001), but not chronicity index. Using HMW adiponectin plus urine hemopexin plus serum creatinine, an equation to predict biopsy chronicity index was constructed with R²=0.46.

**Conclusions:** Urine adiponectin isoforms increase with the severity of active kidney lesions in LN. The increase in urine adiponectin is not simply a reflection of changes in systemic adiponectin, and may be due to intra-renal processing. **Funding:** NIDDK Support

**TH-PO771**

**Significance of Serum Cystatin C as a Biomarker for Clinical Practice in Patients with Lupus Nephritis**

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**Background:** Serum Cystatin C (sCysC) as a novel biomarker of renal function has been studied in many primary glomerular diseases. However, sCysC was barely reported in chronic kidney disease(CKD) and hypertension.

**Methods:** 106 patients with LN proven by renal biopsy were studied. sCysC, serum creatinine (sCr), BUN, 24 hr total urinary protein (uTP), serum albumin (sAlb), systemic lupus erythematosus disease activity index (SLEDAI), C4, C3, IgG, ANA, DaDNA, C-reaction protein (CRP), and ESR were examined before and 1, 3, 6, 12, 24 months after treatment with steroid and immunosuppressants. estimated glomerular filtration rate (eGFR) was calculated by EPI-sCysC, EPI-sCr, and EPI-sCysC + sCr. The strength of correlation was compared between sCysC and sTP, sAlb, SLEDAI, and CRP before and after treatment.

**Results:** sCysC and eGFR (EPI-sCysC+sCr) showed stronger correlation with uTP, sAlb, SLEDAI, and CRP before the treatment (table). During treatment, a similar trend was seen in sCysC and eGFR (EPI-sCysC+sCr). sCysC also showed a better statistical p value than sCr/BUN in response to treatment with steroid plus either all kinds of immunosuppressants or cyclophosphamide.

**Conclusions:** sCysC and eGFR based on sCysC might be useful early biomarkers to diagnose LN and better to monitor the treatment of LN. sCysC will likely help in clinical decision making for early intervention and the timing of reducing key treatments. Prospective study is needed to investigate the effect of early treatment based on sCysC increase (sCr normal) in large cohort of LN patients. **Funding:** Government Support - Non-U.S.

**TH-PO772**

**Neutrophil Membrane Blood Transcriptional Signature Is Associated with Lupus Nephritis and Its Severity in SLE**

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**Background:** Lupus nephritis (LN) is a severe complication of SLE. The aim of this study was to assess the link between blood transcriptional signatures and LN, comparatively with other pathological conditions associated with renal injury.

**Methods:** 102 patients were included: 62 SLE patients, 40 controls with various conditions (10 with crescentic GN due to ANCA-associated vasculitis (AAV), 15 with severe bacterial or fungal sepsis, 15 with non-proliferative glomerular diseases), and their matched healthy controls. SLE samples were split in those at the time of: a biopsy-proven active LN (group 1, n=24); an extra-renal flare (group 2, n=11); a clinically quiescent visit (group 3, n=34). Microarray data were generated using Illumina beadchips and analyzed using modular repertoire analyses.

**Results:** Modular repertoire analysis in SLE patients revealed, in addition to the activation of IFN-related modules, a strong upregulation of M5.15, a module of 24 transcripts annotated “neutrophil”. There was no correlation between M5.15 and SLEDAI, anti-dsDNA level or IFN modules activity. M5.15 was strongly associated with active LN (p=0.009), but not with non-renal manifestations. The neutrophil modular signature was present in 67%, 18% and 47% of patients from group 1, 2 and 3 respectively. In group 2 and 3, its presence was associated with a past history of LN or the occurrence of LN during the follow-up. M5.15 was correlated with acute renal failure (p=0.03) and serum albumin (p=0.08). In group 1, the median value of M5.15 was higher in patients with proliferative than non proliferative LN (66.7 vs 18.8 %, p=0.04). AAV and sepsis patients shared the neutrophil signature observed in SLE, but displayed no IFN signature, while those with non-proliferative GN had none of these signatures.

**Conclusions:** Modular repertoire analysis demonstrates that neutrophil signature is correlated with occurrence and severity of LN in SLE. This result could allow the design of new biomarkers in LN.

**TH-PO773**

**Anticoagulation and Longterm Outcomes in Patients with Renal Artery Stenosis and Antiphospholipid Syndrome**

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**Background:** Our previous data showed renal artery stenosis (RAS) is more prevalent in antiphospholipid syndrome (APS) (26%) compared to the general hypertensive population (8%), and anticoagulation with INR=3 was associated with initial reduction of chronic kidney disease (CKD) and hypertension.

**Methods:** We identified 37 patients with RAS and APS fulfilling Sapporo criteria: anticardiolipin IgG/IgM titer>40 units or >99th percentile (or lupus anticoagulant) on >2 occasions >=6 weeks apart AND vascular thrombosis (or pregnancy morbidity). RAS was diagnosed by magnetic resonance angiography (MRA).**Results:** 15 patients had APS alone and 22 APS associated with autoimmune conditions (13 lupus, 5 ANCA vasculitis, 4 mixed). Median age at RAS diagnosis was 48 years, 31/37(83.8%) were female and median follow-up was 10.4 years. 25/37(67.6%) had 13 lupus, 5 ANCA vasculitis, 4 mixed). Median age at RAS diagnosis was 48 years, 31/37(83.8%) were female and median follow-up was 10.4 years. 25/37(67.6%) had CKD and hypertension. 9/37(24%) died after a median of 10 years since RAS diagnosis. Our previous data showed renal artery stenosis (RAS) is more prevalent in antiphospholipid syndrome (APS) (26%) compared to the general hypertensive population (8%), and anticoagulation with INR=3 was associated with initial reduction of chronic kidney disease (CKD) and hypertension.

**Results:** 15 patients had APS alone and 22 APS associated with autoimmune conditions (13 lupus, 5 ANCA vasculitis, 4 mixed). Median age at RAS diagnosis was 48 years, 31/37(83.8%) were female and median follow-up was 10.4 years. 25/37(67.6%) had CKD and hypertension. 9/37(24%) died after a median of 10 years since RAS diagnosis. 31/37(83.8%) were female and median follow-up was 10.4 years. 25/37(67.6%) had CKD and hypertension. 9/37(24%) died after a median of 10 years since RAS diagnosis.

**Conclusions:** The majority of patients with RAS and APS were female, developed CKD and did not benefit from angioplasty. Anticoagulation was not associated with long-term reduction of ESRD or death, suggesting a non-thrombotic pathogenic process underlying

**Table:**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>CKD</th>
<th>ESRD</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation(23)</td>
<td>15/23</td>
<td>4/23</td>
<td>5/23</td>
</tr>
<tr>
<td>No anticoagulation(14)</td>
<td>6/14</td>
<td>2/14</td>
<td>4/14</td>
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**Methods:**

**FR-Oral; PO - Poster; PUB - Publication Only**

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

**Underline represents presenting author.**

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RAS, e.g.inimal hyperplasia. Treatment of associated vascular risk factors and autoimmune disease is paramount. Anti-cardioidin antibodies and renal MRA are useful for screening high-risk lupus patients.

TH-PO774

A Prospective Study to Investigate Mycophenolic Acid Pharmacokinetics and Its Clinical Correlations in Lupus Nephritis Patients

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Background: The dosing regimen of mycophenolate mofetil (MMF) in the treatment of lupus nephritis (LN) is adopted from the kidney transplant experience. The role of therapeutic drug monitoring of mycophenolic acid (MPA) level in managing LN remains under-studied.

Methods: We prospectively studied LN patients on maintenance treatment with prednisolone and MMF. Blood MPA level at 1, 2, 4, 8, 10 and 12 hours (i.e. C1, C2, C4, C8, C10 and C12) after MMF administration was measured using an enzymatic assay upon recruitment and repeated at 6-month intervals for 24 months, and at occurrence of clinically significant events, to investigate their clinical correlations.

Results: 51 patients were included, with prednisolone and MMF dose of 6.2±1.8 mg/kg/day and 1284±493 mg/d respectively at baseline. C1, C2 and C12 MPA levels were 9.9±8.7 mg/L, 8.6±6.2 mg/L, 1.9±1.4 mg/L during disease remission. C1, C2 and C12 MPA levels correlated with AUROC (r = 0.52, 0.85 and 0.77; p<0.001, <0.001 and <0.001 respectively). C12 correlated inversely with hemoglobin, white cell and platelet counts (r =−0.359, 0.226, 0.2; p<0.001, 0.010 and 0.024 respectively). There was no association between C12 and anti-dsDNA, serum creatinine or 24-h urine protein excretion (r= 0.53, 0.07 and 0.37 respectively). C1 and C2 showed no association with clinical or serological parameters. Clinically significant events included infection in 2 patients, gastrointestinal upset in 3 patients, and renal flare in 5 patients. C12 MPA level at the time of these events were 2.53±2.0, 2.53±2.0, 2.53±2.0 mg/L and 1.58±0.9 mg/L respectively.

Conclusions: C12 MPA level showed good correlation with drug exposure, and may be associated with renal flare and haematological side-effects but not infection.

Funding: Private Foundation Support

TH-PO775

Long-Term Prospective Study of Tacrolimus-Based Treatment in Lupus Nephritis Patients

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Background: This study aimed to examine whether long-term maintenance treatment with tacrolimus for patients with lupus nephritis (LN) is effective and safe.

Methods: A total of 27 adult patients with LN after induction therapy were enrolled. Tacrolimus was initiated at a dose of 3 mg/day. Patients treated with other immunosuppressive agents were also switched to tacrolimus. Prednisolone doses were tapered throughout the period according to individual disease activity. Prospective data were collected. Tacrolimus was initiated at a dose of 3 mg/day. Patients treated with other immunosuppressive agents were also switched to tacrolimus. Prednisolone doses were tapered throughout the period according to individual disease activity. Prospective data were collected. Tacrolimus was initiated at a dose of 3 mg/day. Patients treated with other immunosuppressive agents were also switched to tacrolimus. Prednisolone doses were tapered throughout the period according to individual disease activity. Prospective data were collected.

Results: Four patients discontinued tacrolimus treatment due to its ineffectiveness, complications including acute myeloblastic leukaemia, or their personal intention to become pregnant or discontinue medication. A total of 23 patients (mean age 52.6±11.8 years and mean duration of LN 15.6±8.7 years) were treated with tacrolimus throughout a 5-year period and their data were analyzed. The mean urinary protein/creatinine ratio significantly decreased from a baseline of 1.12±1.47 to 0.33±0.78 at 1 year (p=0.005) and 0.40±1.54 at 5 years (p=0.016), while mean eGFR levels were unchanged throughout the 5 years of tacrolimus treatment. The mean LNDAI was significantly decreased from a baseline of 3.54±2.53 to 1.96±1.40 at 1 year (p=0.021) and 2.08±1.44 at 5 years (p=0.022). Similarly, the mean prednisolone dose significantly decreased from a baseline of 0.35±0.21 mg/kg/day to 0.22±0.15 mg/kg/day at 1 year (p=0.022) and 0.17±0.09 mg/kg/day at 5 years (p=0.001). The mean blood concentration of tacrolimus was 4.0±2.3 µg/mL only one patient experienced a disease flare, and there were no deaths during the study period.

Conclusions: Our results suggest that tacrolimus can be potentially effective for the treatment of LN; moreover, the current dosage appeared to be generally well-tolerated for most patients, and renal flare in 5 patients. C12 MPA level at the time of these events were 2.53±2.0, 2.53±2.0, 2.53±2.0 mg/L and 1.58±0.9 mg/L respectively.

Funding: Private Foundation Support

TH-PO776

Comparison of Kidney Function and Mortality of Mexican Children versus Adults with Lupus Nephritis


Background: Childhood-onset lupus nephritis (CLN; onset before 16 years of age) has been associated with a more aggressive disease course as compared to adulthood-onset lupus nephritis (ALN). Kidney factors such as LN Class and Activity and Chronicity Indexes are related to renal prognosis. No information is available in our setting. Aims: To compare kidney function and mortality of CLN vs ALN.

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

Underline represents presenting author.

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expression profiles were compared at bx1 and bx2 between these CR and NR patients. Transcripts were considered differentially expressed only if they met both criteria of at least a 1.5-fold change (FC) and p-value < 0.01.

Results: At flare, 2 transcripts were differentially expressed between CR and NR. IL-28a, a type 3 interferon gene was decreased 2.6-fold (p = 0.006) and mannose-binding lectin serine peptidase 1 (MASP1), a member of the complement lectin-pathway, was decreased 1.8-fold (p = 0.009) in CR versus NR. From bx1 to bx2, 8 genes were differentially expressed in the CR group. Expression of adhesion molecule VCAM1 and macrophage regulator CEBPB was decreased while expression of TGF-β activator SMAD3, inhibitor of TLR signaling, TOLLIP, and inhibitor of IRF7 signaling, TRAF4 was increased. In NR, from bx1 to bx2, 9 genes were differentially expressed. Expression of the type 3 interferon, IL28b and the TNF-receptor TNFRSF13b (TACI) was decreased while expression of complement C2 and CFNB the TNF cytokine TNFSF8 was increased.

Conclusions: The molecular characterization of kidney biopsies at LN flare along with the change in expression after treatment identifies differentially expressed genes among patients who eventually have or do not have a CR. Some of these genes may be candidates biomarkers of long-term renal outcomes in LN.

Funding: Other NIH Support - NIDDK U01 DKO96927, Pharmaceutical Company Support - Mallinckrodt/Questor Fellowship Grant: 00033990

TH-PO778
Evaluation of Healthcare Resource Utilization and Costs by Immunosuppressant Pattern of Use in Lupus Nephritis

Background: US-based treatment guidelines recommend 6 months of immunosuppressant (IS) therapy before continuing or switching regimens for class III/IV lupus nephritis (LN) patients. Literature suggested that management of LN is costly, but published data on how costs and healthcare resource utilization (HRU) may vary by IS pattern of use are limited.

Methods: We identified LN patients initiating cyclophosphamide (CYC) or mycophenolate mofetil (MMF) in 2010-2013 from a US commercial/Medicaid claims database. All-cause costs and HRU during the year post-IS initiation were examined. Comparison was made between the following four groups based on their IS utilization during the first 6 months and 7-12 months post-IS initiation: 1) patients who used the same IS continuously for at least 7 or up to 12 months (reference group), 2) patients who switched added-on IS after 6 months, 3) patients who switched/added-on IS within 6 months, and 4) patients who discontinued IS within 6 months.

Results: Final sample included 1,567 LN patients (mean age 37 years; 86% female) initiating CYC (16.1%) or MMF (83.9%). Patients who remained on the same IS throughout added-on IS after 6 months, 3) patients who switched/added-on IS within 6 months, and 4) patients who switched/added-on IS before 6 months (N=305).

Conclusions: We found encouraging results. The incidence of maternal and foetal complications during pregnancy was reduced compared to previous European studies including lupus patients. Risk factors of major maternal complications are best characterized.

Funding: Other NIH Support - NIDDK U01 DKO96927, Pharmaceutical Company Support - Mallinckrodt/Questor Fellowship Grant: 00033990

TH-PO779
Reversibility of 65 Pregnancies in Patients with Lupus Nephritis in France
Jean-charles Puthet,1 Noemie Jourdieu-chiche,2 Dominique Chauveau,3 Eric Daugas,4 Laurent Juillard.1 1Hôpital Edouard Herriot - Hospices Civils de Lyon, France; 2Hôpital La Conception - CHU Marseille, France; 3Hôpital Rangueil - CHU Toulouse, France; 4Hôpital Bichat - APHP, on behalf of the French Cooperative Group on Lupus Nephritis, France.

Background: Lupus nephritis (LN) mostly affects women of childbearing age. Despite the improvement in care over the last decades, pregnant women with LN are still at high-risk of maternal and foetal complications.

Funding: Pharmaceutical Company Support - Biogen

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Underline represents presenting author.

TH-PO780
Nephrotic Syndrome and Pregnancy
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Background: In the absence of hypertension or renal insufficiency, some consider the perinatal outcomes in pregnant women with nephrotic syndrome to be good. However, the diagnosis and management of both maternal and fetal well-being is challenging.

Methods: We describe the presentation, management, and maternal and fetal outcomes of 31 pregnancies in 24 women with biopsy proven nephrotic syndrome during pregnancy. We included patient demographic data, anticoagulant medications, anticoagulant treatment protocols, and obstetric outcomes. We excluded patients who had nephrotic-range proteinuria (>3.5g/24hr and/or >3.5g/g on spot urine protein:creatinine ratio) during pregnancy, a kidney biopsy diagnosis, and serum creatinine <1.5mg/dL at presentation.

Results: There were 24 subjects (9 primiparas) with 31 pregnancies and 32 offspring. Mean age was 27.6 years (range 16- 39 years) and mean gestational age at presentation was 18.7 weeks (range 5 - 40 weeks). Labs revealed a mean creatinine 0.85mg/dL (range 0.4-1.4mg/dL), mean serum albumin 1.97g/dL (range <1- 3.2g/dL), and mean proteinuria 8.96g/24h (range 0.2- 3.6 32g). UltraCOM data was available for 18 pregnancies. Mean cardiac output at presentation was markedly elevated at 8.38L/min. 14 of 31 pregnancies were known to have kidney disease before pregnancy. Nephrotic syndrome was newly diagnosed in 16 patients. Biopsy was performed during pregnancy in 10 subjects (median age of gestation 20.5 weeks (range 2.2-7.2 weeks) changing management in 70%. 6 were biopsied postpartum. Biopsy diagnoses were FSGS(11), IgAN(3), lupus nephritis(3), membranous nephropathy(3), and 1 case each of Fibriinny GN, MPGN, C3GN, and minimal change disease. Maternal complications included preeclampsia(10/31), acute kidney injury(3/31) and cellulitis(3/31). Mean age of gestation at delivery was 35.4 weeks (range 25-40 weeks). All delivered via caesarean section. Fetal complications included birth weight <2500g(18), IUGR(3), and 10 were admitted to NICU.

Conclusions: Pregnant women with nephrotic syndrome are at high risk for developing severe maternal and foetal complications despite the absence of significant hypertension or renal insufficiency.

Funding: Other NIH Support - NIDDK U01 DKO96927, Pharmaceutical Company Support - Mallinckrodt/Questor Fellowship Grant: 00033990
Cresectic IgA Nephropathy – A Prospective Study  Krishan L. Gupta, Prabhakar Doddi, Rittambra Nanda, Raja Ramachandran. 1  Nephrology, PGIMER, Chandigarh, India; 2 Pathology, PGIMER, Chandigarh, India.

Background: Cresectic IgA nephropathy (cIgAN) carries a very poor prognosis and the initial creatinine at presentation predicts long-term outcome. The present prospective study was carried out to evaluate the clinic-pathological correlation and outcome of cIgAN.

Methods: A total of 31 patients with cIgAN were included in the study. Thirty- eight (63.33%) cases progressed to ESRD by the end of 12 months. Serum creatinine at presentation and IFI>50% and presence of fibrous crescent on biopsy was risk factor for ESRD.

Conclusions: Patients with cIgAN carries a very poor prognosis, with majority of the cases progressing to ESRD by 12 months. Serum creatinine at presentation and presence of diffuse IFTA and fibrous crescents on biopsy predicts development of ESRD.

Primary objective of the study was to evaluate percentage of patients achieving remission/ CR rate, who were examined. 39 of the above 77 patients who were observed for 3 years following subnephrotic proteinuria. Serum Gd-IgA1 levels were defined as proteinuria of less than 0.3 g/gCre and urinary erythrocytes of less than 5 high-power field.

Results: Multiple linear regression analysis adjusted by age and estimated glomerular filtration rate (eGFR) indicated that U-NAG level was significantly associated with tubulointerstitial fibrosis score (p=0.001) and the percentage of global sclerotic glomeruli (p=0.008). Multiple logistic regression analysis adjusted by age, sex and eGFR indicated that the CR rate 3 years after ST was significantly associated with tubulointerstitial fibrosis score (Odds Ratio [OR] 0.092, 95% Confidence Interval [CI] 0.009-0.914, p=0.042) and U-NAG/Gd-IgA1 (OR 0.025, p=0.007).

Conclusions: U-NAG is a potentially useful biomarker of the severity of renal tubulointerstitial fibrosis and global glomerulosclerosis percentage in IgAN. U-NAG measurement may also aid in the prediction of therapeutic response to ST in IgAN.

Beneficial Effect of Immunosuppressive Therapy for IgA Nephropathy with Moderately Impaired Renal Function

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Background: A variety of treatment has been attempted to slow progression of IgA nephropathy (IgAN) such as renin-angiotensin system inhibitors and adding corticosteroid for patients with impaired renal function. We compared clinical outcomes of IgAN patients who were treated with vs. without immunosuppressive therapy (IST), and explored identified risk factors associated with progression of renal dysfunction.

Methods: Patients who were diagnosed as IgAN between 2001 and 2014 were screened. Among the patients who had initial estimated glomerular filtration rate (eGFR) of 30-60 ml/min/1.73 m² and had followed up for at least 12 months were included in this analysis.

Results: A total of 92 patients were analyzed. 39 patients received IST (Group 1) and 53 did not (Group 2). Median follow-up (59 vs. 77 months) and mean age (46.6 vs. 47.4 years) were not different. In Group 1, mean arterial pressure (93 vs. 99 mmHg, P=0.019), serum creatinine (1.66 vs. 1.45 ml/min/1.73 m², P<0.003) and median amount of proteinuria (2033 vs. 1115 mg/day, P<0.001) were significantly higher, but mean eGFR (43.7 vs. 50.1 ml/min/1.73 m², P=0.001) and serum albumin (3.5 vs. 4.0 g/dL, P=0.099) were lower than Group 2 at last-visit eGFR. Three patients of Group 1 and 7 of Group 2 progressed to end-stage renal disease (ESRD). ESRD-free survival was comparable between two groups (P=0.639). For 1 year, the change of mean eGFR was significantly different between 2 groups (3.8 of Group 1 vs. -1.3 ml/min/1.73 m² of Group 2, P=0.027).

In multivariate linear regression, age at diagnosis (standardized beta, 0.212; P=0.041), MAP (standardized beta, -0.227; P=0.027), baseline eGFR (standardized beta, 0.566; P=0.007) and initial proteinuria (standard beta, 0.273; P=0.013) were independent predictors of last-visit eGFR.

Conclusions: IST may have a beneficial effect for slowing progression of IgAN with moderately impaired renal function.

Longitudinal Study of a Kindred with Familial IgA Nephropathy Reveals Stable Serum Levels of Galactose-Deficient IgA1

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Background: Patients with IgA nephropathy (IgAN) have elevated levels of circulating galactose-deficient IgA1 (Gd-IgA1). Familial form of IgAN has been reported among people of all ancestries. Serum Gd-IgA1 levels are heritable in patients with familial and sporadic IgAN. Moreover, 50% of first-degree relatives of patients with familial IgAN have high serum Gd-IgA1 levels (≥95th percentile of healthy controls) without clinical signs of IgAN. This study performed a longitudinal follow-up of a large kindred with familial IgAN.

Methods: Pedigree includes 4 men with biopsy-proven IgAN. Members recruited in 2005 and 2014 included 2 IgAN patients, 13 relatives, and 7 genetically unrelated individuals (marry-ins). Blood samples were drawn to determine for total IgA and Gd-IgA1 levels. Gd-IgA1 was measured using lectin ELISA and expressed relative to a standard Gd-IgA1 in 100 ng of serum IgA. Spot urine sample was obtained for urinalysis and protein/creatinine ratio. Abnormal urinalysis was defined by hematuria (≥2 ×) blood and/or protein/creatinine ratio ≥0.5 g/g.

Results: Mean (± SD) ages of all IgAN patients, blood relatives, and marry-ins were 48 ±3, 43 ±6, 41 ±12 yr in 2014. Two patients had multiple kidney transplantations. Except for the 2 IgAN patients, no individual had an abnormal urinalysis. Serum Gd-IgA1 levels for marry-ins were similar to other healthy controls. Serum Gd-IgA1 levels were elevated in blood relatives and IgAN patients than in marry-ins at each sampling time (P<0.03). Serum Gd-IgA1 levels demonstrated longitudinal stability in most individuals (Intra-class correlation coefficient = 0.812; 95% CI 0.604-0.917).
Conclusions: Serum IgG-IgA levels in 22 individuals in this multiplex IgAN pedigree were stable over a 9-year period. No blood relative developed IgAN or exhibited a urinary abnormality during the 9-year follow-up period.

Funding: NIDDK Support, Private Foundation Support

TH-P0787
Childhood IgA Nephropathy with Nephrotic Syndrome (NS-IgAN) at Onset
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Background: Although immunoglobulin A nephropathy (IgAN) is commonly considered as a lifelong disease, incidences of spontaneous remission (SR) have been occasionally reported. We investigate the incidence as well as the clinical predictors of SR in IgAN.

Methods: Medical records of biopsy-proven IgAN in Severance hospital from 2006 to 2014 were reviewed. SR was defined as complete remission reached without any treatment, defined as (1) urine RBC<3/HPF, UPCR<0.2 g/g, and estimated glomerular filtration rate (eGFR)>60 mL/min/1.73m2; (2) proteinuria<1 g/day; (3) estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73m2; (4) treated by oPSL or oPLT with our standard protocol; (5) follow-up period >1 year; (6) interval from renal biopsy to initiation of therapy ≤3 years; (7) not combined with other renal disease. We compared the clinical findings at the time of renal biopsy, histological findings, and urinary findings during the follow-up period between both groups. We defined complete remission (CR) as proteinuria <0.3 g/g, and urinary red blood cells <5 counts/HPF.

Results: After adjusting clinical findings by propensity score, each 20 patients were selected for both groups. Among these cases, there was no significant difference in clinical and histological findings between both groups (p>0.05). proteinuria>1 g/day, (3) estimated glomerular filtration rate (eGFR) >90 mL/min/1.73m2; (4) treated by oPSL or oPLT with our standard protocol; (5) follow-up period >1 year; (6) interval from renal biopsy to initiation of therapy ≤3 years; (7) not combined with other renal disease. We compared the clinical findings at the time of renal biopsy, histological findings, and urinary findings during the follow-up period between both groups. We defined complete remission (CR) as proteinuria <0.3 g/g, and urinary red blood cells <5 counts/HPF.

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Conclusions: SR in IgAN was frequently observed. UPCR levels may be an independent predictor of SR in patients with IgAN.

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approaches. In stratified analysis, a beneficial association between RASB and ESRD was observed in patients with hypertension, reduced estimated glomerular filtration rate (<60 mL/min/1.73 m²), mesangial proliferation and segmental glomerulosclerosis (P for interaction <0.05), and tended to be greater in patients with proteinuria (>1.0 g/24 h), extracapillary proliferation, and receiving methylprednisolone pulse therapy (P for interaction <0.10).

Conclusions: Treatment with RASB was associated with a lower incidence of ESRD in the real-world practice of IgAN.

TH-PO794
Remission of Urinary Protein at 2 Years After Diagnosis with Normal Renal Function and Remission of Urinary Protein at 1 Year After Diagnosis with Decreased Renal Function as an Accurate Prognostic Marker in IgA Nephropathy
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Background: Level of proteinuria (UP) has a strong association with poor renal prognosis in IgA nephropathy. Recent studies reported that the level of UP, especially, remission of UP at (CR) defined as less than 0.3 g/d, during the follow-up was a more accurate prognostic factor than at diagnosis. In this multicenter study, we evaluated which post-diagnosis measurement point achieving CR strongly associated with the renal prognosis.

Methods: 1,077 patients diagnosed with IgA nephropathy between March 1991 and December 2013, and could be followed-up for at least 3 years or reached end-stage kidney disease (ESKD) were enrolled. We performed a retrospective cohort study among 2 divided groups: 638 with eGFR>60 mL/min/1.73m² (A) and 439 with eGFR<60 mL/min/1.73m² (B). The endpoint of this study was a 50% decrease in eGFR or ESKD. The annual daily UP level until 3 years after diagnosis was categorized into 2 grades: <0.3 g/d and ≥0.3 g/d and its association with the renal prognosis was investigated. The hazard ratio of the endpoint adjusted with clinical and pathological findings and treatment was examined.

Results: Regarding CR as a reference, UP<0.3 g/d was not a significant poor prognostic factor at diagnosis, but at 1 year, especially at 2 years, it became a significant factor in group A. On the other hand, in group B, UP>0.3 g/d was already shown to be a significant factor at diagnosis and the strongest factor at 1 year.

Conclusions: UP<0.3 g/d and ≥0.3 g/d were the most accurate predictors for a favorable outcome in IgA nephropathy.

TH-PO795
Copetin, a Surrogate Marker for AVP, Is Associated with Disease Severity and Progression in IgA Nephropathy Patients
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Background: The disease course of IgA Nephropathy (IgAN) is difficult to predict. Copetin, a surrogate marker for AVP, has been described to cause kidney damage in various renal diseases. We investigated therefore the associations of copeptin with disease severity and progression in IgAN.

Methods: Included were 60 biopsy proven IgAN patients from the Radboud UMC Nijmegen, of whom urine and blood samples were available. Urinary excretion of α1M, β2M, KIM-1, and NGAL and plasma copeptin were measured at baseline. Survival analyses was performed for the composite outcome death, end stage renal disease (ESRD), doubling of serum creatinine, start of immunosuppressive therapy and the individual components.

Results: In IgAN patients (male: 72%, age: 42±13 years, eGFR: 48±21 mL/min/1.73m², copeptin: 4.9±5.1 pmol/L) copeptin was associated at baseline with proteinuria in the worst way possible (p<0.003) and with start of immunosuppressive therapy (p=0.04) using a log rank test. When patients who started immunosuppressive therapy during follow up (n=14) were excluded, copeptin (continuous variable) was furthermore associated with the incidence of ESRD (p=0.01, HR=1.09, i.e. a 9% increase in risk of ESRD per 1 pmol/L increase in copeptin), doubling of serum creatinine (p=0.004, HR=1.07) and the composite outcome (p=0.003, HR=1.07) in Cox regression models, adjusting for proteinuria and sex. With additional adjustment for eGFR, which is debatable as eGFR decline could be part of the causal pathway between copeptin and outcomes, the survival analyses lost significance.

Conclusions: Copetin is a promising disease severity marker in IgAN with additive predictive value for future kidney function loss over proteinuria, but not over eGFR, the strongest predictor of disease progression in this study.

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TH-PO796
Clinical Outcomes of Nephrotic Syndrome in IgA Nephropathy
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Background: Uncommonly, IgA nephropathy can be complicated by nephrotic syndrome. In such cases, although, corticosteroid therapy should be recommended, the response to steroid treatment has been variable, and spontaneous remission without steroid treatment can occur in some cases. Here, we report our experience of clinical outcomes of nephrotic syndrome in patients with IgA nephropathy.

Methods: Thirty-three patients with biopsy-proven IgA nephropathy with nephrotic syndrome were enrolled between March 1990 and March 2009 in Dong-A university hospital. We retrospectively analyzed the data, including demographic, clinical, and laboratory records.

Results: The mean follow-up duration were 62 ± 45 months (10-204) in 33 patients. Complete remission occurred in 10 patients with steroid treatment and 2 patients without steroid therapy. Partial remission occurred in 7 patients with steroid therapy and 8 patients without steroid therapy. There were 6 patients with progressive deterioration of kidney function during follow-up period.

Conclusions: IgA nephropathy patients with nephrotic syndrome, 36% of patients have complete remission, 45% of patients have partial remission. Steroid treatment may function during follow-up periods.

TH-PO797
Comparative Outcomes in Primary Glomerulonephritis Among a Large Diverse United States Population
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Background: Glomerulonephritis (GN) remains an important cause of end stage renal disease (ESRD) in the United States and the world. Within a large diverse population of an integrated health system, we sought to evaluate rates of primary GN and then compare ESRD and mortality outcomes within different GN’s.

Methods: Retrospective longitudinal cohort study in the period 1/1/2000 through 12/31/2013 among patients within Kaiser Permanente Southern California. Patients who had biopsy proven primary GN were characterized and followed until they reached the outcome of ESRD or mortality. ESRD was defined as receiving dialysis or renal transplant.

Results: 2,849 patients were identified with biopsy-proven GN. The mean age of the cohort was 47 yrs with 48% females, 37% Hispanics, 30% whites, 17% blacks, and 12% Asians. Focal segmental glomerulosclerosis (FSGS) was the most common GN among all race/ethnic groups (36% overall) followed by membranous GN (MGN) (12%), minimal change disease (MCD) (11%), IgA nephropathy (IgAN) (10%), and others (31%). The mean follow up was 3.8 yrs. ESRD occurred in 26% (704 required dialysis and 38 had a renal transplant). Mortality occurred in 18%. ESRD occurred among 35% of FSGS, 19% among IgAN, 12% among MGN, 10% among MCD, and 29% among other GN’s.

Conclusions: Among a large racially/ethnically diverse United States population, FSGS was the most prevalent GN and was associated with the highest rate of progression to ESRD among all GN groups. This diverse cohort may give insight into characterizing and risk stratifying different GN’s which may pave the way for more optimal management strategies.

TH-PO798
A Specific Transcriptomic Profile Characterizes Peripheral Blood Mononuclear Cells (PBMCs) from Uremic Patients (pts) Treated With On Line Hemodiafiltration (OL-HDF) Compared to Those Treated with Bicarbonate Dialysis (BHD)
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Background: Recent studies suggest that OL-HDF can reduce the progression of dialysis-related cardiovascular diseases, but the molecular mechanisms underlying this improvement are not yet known. The aim of our study was to identify, through a high-throughput approach, differences in gene expression profiles of PBMCs from pts undergoing OL-HDF compared to BHD.

Methods: The transcriptomic profile was evaluated in PBMCs isolated from 10 pts regularly dialyzed with OL-HDF (convective volume 22 l) and 10 pts treated with BHD using microarray analysis (Agilent Technologies). The results were evaluated by statistical (ANOVA test) and functional pathway analysis (Ingenuity Pathway Analysis).

Results: We observed that 868 genes were differentially expressed in the comparison between OL-HDF and BHD (fold change>1.5). Thirty-seven functional gene networks were identified and atherosclerosis signaling was the top canonical pathway associated with BHD (p=2.45x10^-10). Among the downregulated genes in OL-HDF there were PDGF (FC=-2.13) and Clusterin (FC=-2.14), involved in vascular injury and Monomime Oxidase A (MAO-A, FC=-2.43), an important source of oxidative stress and a major contributing factor to the development of ventricular hypertrophy and heart failure. Interestingly, Apolipoprotein E (Apo-E) gene, an antioxidant/anti-inflammatory protein, was upregulated (FC=+1.7) by OL-HDF. qPCR, performed in an independent testing-group [15 BHD, 15 OL-HDF] confirmed that PDGF, Clusterin and MAO-A were down-expressed in OL-HDF (p<0.01), whereas Apo-E resulted higher expressed (p<0.01).

Conclusions: The OL-HDF can contribute to cardiovascular risk reduction through the modulation of pathways involved in the progression of atherosclerotic disease. This observation could open new perspectives in the prevention of cardiovascular risk in dialysis pts.

TH-PO799
Twice-Weekly versus Thrice-Weekly Hemodialysis in Patients with or without Residual Kidney Function
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Background: Residual kidney function (RKF) accounts for large solute removal and significantly contributes to survival benefits in hemodialysis (HD) patients. However, there are no reliable outcome data suggesting that the frequency of HD might be safely reduced in patients with substantial RKF.

Methods: A total of 685 patients receiving more than 3 months HD therapy were included from the CRC registry for ESRD. The presence of RKF was defined as more than 100 ml/day of urine volume, and patients were classified into twice-weekly HD with RKF (n = 113), thrice-weekly HD with RKF (n = 137) and thrice-weekly HD without RKF (n = 435).

Results: The baseline RKF was significantly higher in twice-weekly HD patients with RKF than in thrice-weekly HD patients with RKF, and it remained higher at 12 months follow-up. The sum of weekly renal Kt/V and delivered-standard Kt/V per week was similar pattern between twice-weekly and thrice-weekly HD patients with RKF. The thrice-weekly HD patients with RKF showed significantly higher survival rate than twice-weekly HD patients with RKF or thrice-weekly HD patients without RKF (P<0.002). In multivariable analyses, compared with thrice-weekly HD patients without RKF, thrice-weekly HD patients with RKF were associated with lower risk for all-cause mortality (HR 0.11; 95% CI 0.02-0.53). However, twice-weekly HD treatment with RKF did not reduce the risk of mortality (HR 0.65; 95% CI 0.22-1.87). For hospitalization of cardiovascular events, thrice-weekly HD therapy with RKF was independently associated with lower risk, (HR 0.40; 95% CI 0.16-0.98), but twice-weekly HD patients with RKF were not associated (HR 0.80; 95% CI 0.38-1.71).

Conclusions: Twice-weekly HD patients with RKF have similar outcome compared to thrice-weekly HD patients without RKF. However, twice-weekly HD patients with RKF were more advantageous for mortality and CVE than those without RKF.
Comparison of Outcomes Between Incremental and Abrupt Initiation of Hemodialysis: A Propensity-Matched Analysis of a Prospective Cohort Study in Korea

Background:

When patients are diagnosed as end-stage renal disease (ESRD) and initiated hemodialysis (HD), thrice-weekly HD is a very common format. Recent reports suggested possible benefit from beginning HD therapy less than three times weekly and incremental increase of dialysis dose, but there are not sufficient data. We compared outcomes of thrice-weekly and incremental HD.

Methods:

A total of 1273 patients who were diagnosed as having ESRD and initiated hemodialysis from 2008 to 2014 were prospectively enrolled. The patients were classified into the abrupt initiation group (3 sessions/week) or the incremental initiation group (1-2 sessions/week). We compared HRQOL evaluated by KDQOL-SF and Beck’s depression inventory (BDI) score at 3 months and 12 months after HD, and residual renal function by daily urine volume at 12 months after HD and all-cause mortality between the groups.

Results: Before propensity score matching, the abrupt group tends to be younger and showed smaller daily urine volume, higher modified Charlson comorbidity index (mCCI), and higher serum blood urea nitrogen and creatinine level compared to incremental group. A total of 432 patients (288 for abrupt and 144 for incremental group) were selected by propensity score matching. HRQOL tends to be better in incremental group for every domain of KDQOL-SF and BDI, but none of them showed significant difference at 3 months. At 12 months after HD, only cognitive functioning domain was better in incremental group. Daily urine volume at 12 months after HD was similar in two groups. All-cause mortality was comparable between two groups before and after propensity score matching.

Conclusions: Incremental initiation of HD showed comparable results with abrupt group regarding HRQOL, residual renal function and all-cause mortality. Incremental HD might be considered as another format of initiating HD for selected ESRD patients.

Predictors of Substantial Residual Kidney Function in the First Year of Hemodialysis Treatment

Background: Residual kidney function (RFK) plays a critical role in dialysis adequacy, quality of life, and survival in hemodialysis (HD) patients. Therefore, identifying predictors related to preservation of RFK may contribute to improving patient management and developing novel strategies for preserving RFK.

Methods: In a longitudinal cohort of 18,091 patients who initiated conventional HD over four years (1/2007-12/2010), we examined the association of baseline characteristics during the first 3 months of their dialysis treatment with RFK (renal urea clearance (KRU) and urinary volume (UV)) after one year. We employed multivariable logistic regression analyses using 3 mL/min/1.73 m² of KRU or ≥300 mL/day of UV as outcomes with 2-level adjustments for case-mix variables and laboratory measurements in addition to baseline RFK values.

Results: Patients were 62±14 years old, 37% female, 29% non-Hispanic Black, and 67% diabetic. Median KRU and UV were 2.95 (IQR, 1.63-4.64) mL/min, 1.73 m² and 800 (IQR, 500-1,300) mL/day, respectively. High %lymphocyte, higher serum concentrations of albumin and calcium, and lower serum concentrations of creatinine and phosphorus were consistently associated with better preserved RFK indices irrespective of models. A history of congestive heart failure was an independent predictor for loss of RFK.

Conclusions: Better nutritional and CKD-MBD indices were associated with preserved RFK while a history of congestive heart failure were associated with loss of RFK at 1 year of hemodialysis initiation in this large national cohort. Additional studies to preserve RFK in dialysis patients are warranted.

Funding: NIDDK Support

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TH-PO804
Salt Taste Sensitivity, Sodium Intake, and Fluid Status in Hemodialysis
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Background: Dietary Sodium intake (SI) contributes to volume status and blood pressure (BP) control in hemodialysis (HD) patients. Salt taste sensitivity (STS) may drive sodium intake, and has not been systematically studied in HD. We sought to assess the relationship between STS, SI, fluid status (as determined by bioelectrical impedance spectroscopy (BIS)) and pre-dialysis BP in HD patients.

Methods: As part of an ongoing randomized trial involving a low sodium diet, adults receiving outpatient HD were assessed for STS using commercial taste strips impregnated with 0.1-1.5% sodium chloride (NaCl); SI was estimated from 3-day food diaries. Total Body Water (TBW) and Extracellular Volume (ECV) were estimated using whole-body and segmental ( calf-resistance) BIS, respectively.

Results: Baseline data on 33 enrolled patients (16 male, 17 black, 13 white, mean age 52+15yr) were analyzed. Mean monthly pre-HD systolic BP was 151±16 mmHg. Mean SI was 2.5±2.5; range (1.1-5.2). Mean estimated SI was 0.8±2 g/day higher in patients without STS compared to those with STS (p=0.06). Higher SI correlated with higher calf ECV (r=0.38, p=0.04), whole-body BIS-TBW (r=0.65, p=0.0005) and ECV (r=0.34, p=0.09). Mean Calf ECV was significantly lower in those with STS vs those without STS at 1.6% (0.19 vs 0.23 L; p=0.04). There was no correlation between SI and pre-dialysis BP (in-center or standardized).

Correlation of Dietary Sodium Intake with (A) Total Body Water and (B) Calf ECV BIS

Conclusions: Salt taste sensitivity and measures of hydration status by bioelectrical impedance spectroscopy are correlated with sodium intake in hemodialysis. These findings suggest that patients with low salt taste sensitivity may be particularly at risk for fluid excess. Future research should examine mechanisms of Salt taste sensitivity and its role in management of hemodialysis patients.

Funding: Private Foundation Support

TH-PO805
Arrhythmic Risk in Patients with Type II Diabetes on Hemodialysis: Preliminary Results from the Monitoring in Dialysis (MiD) Clinical Study
Prabhjot Roy-Chaudhury,1 Don E. Williamson,2 James A. Tumlin,2 David M. Charytan,3 Kowdle chandrasekhar Prakash,4 Vijay K. Kher.1 1Univ of Cincinnati; 2Nephrology Associates; 3Univ of Tennessee; 4Bigham and Women's Hospital, Boston; 5Apollo Hospitals-Chennai; 6Medanta-Medicity.

Background: 40% of the overall ESRD population has diabetes and these patients are considered to be at increased risk of cardiac events. The goal of this analysis was to describe the pattern of both clinically significant events and documented arrhythmias in a subset of patients with Type II diabetes from the Monitoring in Dialysis (MiD) study.

Methods: The MiD study is a prospective, multi-center, observational study designed to characterize the type and frequency of documented and adjudicated arrhythmias in hemodialysis patients during a 6-month period, using an implanted continuous cardiac monitoring device (Medtronic Reveal XT or Reveal LINQ). All documented arrhythmias and clinically significant atrioventricular (AV) blocks (CSA) defined as bradycardia ≤40 bpm for ≥6 sec, asystole ≤3 sec, sustained ventricular tachycardia ≥130 bpm for ≥30 sec and symptomatic arrhythmias during this period were then correlated temporarily to the dialysis cycle (first, second or third dialysis session of the week; during or after hemodialysis; how long after hemodialysis).

Results: Type II Diabetes was present in 39/66 (59%) of the MiD patients. The mean age was 62 (36-76) years, 72% male, mean years on HD 2.8 (1-15), 36% with a history of cardiac arrhythmias with a mean follow-up of 8.6 months (range 0.6-13.9). Arrhythmic risk in the Type II diabetic patients was similar to the previously reported data on the entire study population, with the highest incidence of documented arrhythmias occurring in the 12 hour period starting with each dialysis session (particularly in the 8 hours after the end of the session). The incidence then decreased, followed by a gradual rise during the rest of the interdialytic period. Interestingly, the incidence of CSA in the 12 hour period starting with the first dialysis session of the week was much greater than in the overall study population.

Conclusions: The increase in the incidence of CSA in diabetics ESRD patients suggests that these patients could be a target population for the use of the Reveal implant.

Funding: Pharmaceutical Company Support - Medtronic

TH-PO806
Individualising Fluid Restriction Based on Target Weight Can Prevent a High Ultrafiltration Rate Emily See, John W. MacD. Agar. Nephrology, Univ Hospital, Geelong, VIC, Australia.

Background: Fluid restriction (FR) in haemodialysis patients has traditionally been advised by residual urine output and an arbitrarily defined oral intake, commonly 750ml/ day. Surprisingly, little attention has been paid to individualising FR according to target predialysis weight (TW), despite the logical argument that smaller patients require less fluid. Excessive inter-dialytic weight gain (IDWG), when calculated as a percentage of TW (IDWG%), results in a high ultrafiltration rate (UFR) if session length (t) is constant [*UFR(ml/kg/hr) = IDWG(ml) ÷ TW(kg) ÷ (hr)]. Since a high UFR has been linked to a poor clinical outcome, these patients must be identified and targeted. We aim to determine if a high IDWG% can be predicted from TW and then be used to individualise FR.

Methods: Data were prospectively collected from 114,112 sessions in 139 patients undergoing in-centre thrice-weekly haemodialysis from Jan-Dec 2014. Mean age was 68.9yr, 56% were male. Mean TW and IDWG% were calculated every 6 weeks. Results were divided into IDWG% cohorts, within each of which an average TW was calculated.

Results: Mean IDWG% was 2.30% (range 0.1-6.4). IDWG% was inversely proportional to TW (r=−0.78).

From this data, we devised a formula that calculates an individualised FR based on the desired UFR (dUFR), the session duration (t), TW, and interval days between sessions (n). [as IDWG% = FR ÷ TW; and [IDWG% = dUFR ÷ TW] ÷ TW; therefore [FR (ml) = dUFR ÷ TW ÷ TW = n ÷ residual urine output].

Conclusions: Patients with low TW are most at risk of high IDWG% and, consequently, a high UFR. A high UFR leads to rapid intravascular volume contraction which triggers post-dialytic thirst and reinforces the inevitable cycle of further high IDWG%. As TW provides a readily accessible clinical end-point that predicts at-risk patients, we propose that FR be individualised according to TW to enable patients to remain below the desired UFR.

TH-PO807
Ultrafiltration Rate Should Be Independently Targeted as a Marker of Haemodialysis Adequacy Emily See, John W. MacD. Agar. Dept of Nephrology, Univ Hospital, Geelong, VIC, Australia.

Background: For 30 years, solute clearance has been the key determinant of dialysis adequacy. This emphasis has marginalised the critical contribution of safe rates of fluid removal to “adequate” dialysis. Ultrafiltration rate (UFR) has been proposed as an easily measurable marker of volume management (Agar 2015 HDI) and several studies have demonstrated a correlation between high UFR and poor clinical outcomes. Despite this association, UFR is not routinely targeted and the proportion of patients who meet percentage reduction in urea (PRU) but not UFR targets is unclear. While a “safe” UFR (≤25%) is yet to be conclusively defined, current literature supports an escalating clinical risk beyond a UFR of 10ml/hr/kg and an absolute risk above 13ml/hr/kg.

Results: Data were prospectively collected from patients undergoing in-centre thrice-weekly conventional haemodialysis over a 12-month study period (Jan-Dec 2014). PRU and mean UFR were calculated every 6 weeks. UFR <10ml/hr/kg was defined as “volume-adequate” and PRU >65% was considered “solute-adequate”. 720 episodes were collected from 115 patients. The mean age was 68.9yr and 56% were male. 73% of episodes met both adequacy targets (PRU+UFR+). 10% met the UFR but not the PRU target (PRU-UFR+). 16% met the PRU but not the UFR target (PRU+(UFR-)). 1% met neither (PRU-(UFR-)). In patients who met the PRU target 18% did not meet the UFR target.

As a high UFR is linked to rapid intravascular volume contraction which triggers post-dialytic thirst and reinforces the inevitable cycle of further high IDWG%, as TW provides a readily accessible clinical end-point that predicts at-risk patients, we propose that FR be individualised according to TW to enable patients to remain below the desired UFR.

Funding: Pharmaceutical Company Support - Medtronic

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BP was measured every 15 minutes on monitoring data, with a goal to increase UF tolerance without increasing IDH events. [Fresenius, Kaysville, UT]. Interventions were employed based on CV physiologic protocol required setting goal to .2 KG < dry weight OR < .2 KG last post weight with prior to protocol along with 18 txs during active monitoring and guided probing. The treatments (txs) with same staff, room, time interval. Intervention data: 36 baseline txs assisted by monitoring technology was used to assess fluid management as defined by 1) achievement of post weight within 1 kg around dry weight, 2) avoidance of IDH [SBP>90], 3) decrease in pulse pressure (PP) from pre-post dialysis.

Methods: 24 patients (16 controls, 8 intervention) were included. Control data: 18 treatments (txs) with same staff, room, time interval. Intervention data: 36 baseline txs prior to protocol along with 18 txs during active monitoring and guided probing. The protocol required setting goal to <2 KG dry weight OR < 2 KG last post weight with small goals change early in treatment, set of defined action based on CV physiologic monitoring via CVInsight™ (CVI) [Intelomed, Wexford, PA] and relative plasma volume at each treatment. Intervention were employed based on monitoring data, with a goal to increase UF tolerance without increasing IDH events. BP was measured every 15 minutes.

Results: Intervention patients demonstrated significant improvement in all three fluid management parameters during the protocol compared to preceding txs.

**Conclusion:** Adequacy of solute removal does not equate to adequacy of volume removal. When a solute marker is used as the sole determinant of dialysis adequacy, a significant number of patients undergo “volume-inadequate” dialysis. These patients were more likely to be female and have a lower post-dialysis weight. Given the potentially substantial clinical implications, we propose that UFR be independently targeted allowing composite solute and volume markers to together define truly “adequate” dialysis.

**TH-PO808**

Fluid Management with Technology-Assisted Probing **Peter B. De Orejo,** Mary Kaye Deck, Anne M. Brunfield. 

Background: Intradialytic hypotension (IDH) is associated with mortality. Rapid fluid removal is associated with cardiovascular (CV) morbidity and mortality. Decreased pulse pressure during HD is associated with improved outcomes. A focused intervention approach assisted by monitoring technology was used to assess fluid management as defined by 1) achievement of post weight within 1 kg around dry weight, 2) avoidance of IDH [SBP>90], 3) decrease in pulse pressure (PP) from pre-post dialysis.

Methods: 24 patients (16 controls, 8 intervention) were included. Control data: 18 treatments (txs) with same staff, room, time interval. Intervention data: 36 baseline txs prior to protocol along with 18 txs during active monitoring and guided probing. The protocol required setting goal to <2 KG dry weight OR < 2 KG last post weight with small goal change early in treatment, set of defined actions based on CV physiologic monitoring via CVInsight™ (CVI) [Intelomed, Wexford, PA] and relative plasma volume (RPV) via Crit-Line III® [Fresenius, Kayville, UT]. Interventions were employed based on monitoring data, with a goal to increase UF tolerance without increasing IDH events. BP was measured every 15 minutes.

Results: Intervention patients demonstrated significant improvement in all three fluid management parameters during the protocol compared to preceding txs.

**Conclusion:** Adequacy of solute removal does not equate to adequacy of volume removal. When a solute marker is used as the sole determinant of dialysis adequacy, a significant number of patients undergo “volume-inadequate” dialysis. These patients were more likely to be female and have a lower post-dialysis weight. Given the potentially substantial clinical implications, we propose that UFR be independently targeted allowing composite solute and volume markers to together define truly “adequate” dialysis.

**TH-PO809**

Increased Mortality Associated with Higher Dialysate Sodium Concentrations Is Not Due Solely to Higher Interdialytic Weight Gains and Blood Pressure **Ambreen Gul,** Dana Miskulin, Leonard A. Arbeit, Srima Narisupur, Susan Paine, Ronald Schrader, Philip Zager, DCI, Albuquerque, NM; UNM, Albuquerque, NM; Tufts, Boston, MA; SUNY, Stony Brook, NY; SUNY, Syracuse, NY.

Background: There is ongoing controversy regarding the optimal dialysate sodium concentration (DNA). Many investigators have urged the use of DNA of 134 to 138 mEq/L, to limit interdialytic weight gain (IDWG) and improve control of hypertension and mortality. Unfortunately, throughout this debate, little attention has been paid to how closely delivered DNA matches ordered DNA.

Methods: We studied 333 hemodialysis (HD) patients at 4 DCI facilities. We sampled dialysate from the arterial dialyzer port prior to the start of HD for measurement of DNA. Units 1 and 2 used Fresenius 2008 K and 2008 K machines and Fresenius Granuflo® Dry Acid and Naturalyte® mixed onsite from dry concentrates. Units 3 and 4 used Gambro Phoenix machines and pre-mixed acid concentrates obtained from Rockwell and bicarbonate cartridges from Baxter or Gambro. The online clearance feature was off.

Results: Measured DNA was usually higher than ordered DNA. The magnitude of difference varied by clinic (p < .0001).

**Conclusion:** Although reducing DNA to < 140 mEq/L may have only a modest impact on IDWGW and predialysis SBP it has the potential to significantly decrease mortality.

**TH-PO810**

Comparison of Ordered versus Measured Dialysate Sodium Concentrations **Ambreen Gul,** Dana Miskulin, Leonard A. Arbeit, Srima Narisupur, Susan Paine, Ronald Schrader, Philip Zager, DCI, Albuquerque, NM; UNM, Albuquerque, NM; Tufts, Boston, MA; SUNY, Stony Brook, NY; SUNY, Syracuse, NY.

Background: There is controversy regarding the optimal dialysate sodium concentration (DNA). Many investigators have urged the use of DNA of 134 to 138 mEq/L, while others have cautioned that low DNA may be associated with increased hospitalization and mortality. Unfortunately, throughout this debate, little attention has been paid to how closely delivered DNA matches ordered DNA.

Methods: We conducted a retrospective observational study of 26,000 chronic hemodialysis (HD) patients in 4 DCI facilities. We sampled dialysate from the arterial dialyzer port prior to the start of HD for measurement of DNA. Units 1 and 2 used Fresenius 2008 K and 2008 K* machines and Fresenius Granuflo® Dry Acid and Naturalyte®, mixed onsite from dry concentrates. Units 3 and 4 used Gambro Phoenix machines and pre-mixed acid concentrates obtained from Rockwell and bicarbonate cartridges from Baxter or Gambro. The online clearance feature was off.

Results: Measured DNA was usually higher than ordered DNA. The magnitude of difference varied by clinic (p < .0001).

**Conclusion:** Although reducing DNA to < 140 mEq/L may have only a modest impact on IDWGW and predialysis SBP it has the potential to significantly decrease mortality.
Least squares mean differences (95% CI) were larger at Clinics 1 [-3.27 (-4.02, -2.53) mEq/L] and 2 [-3.77 (-4.49, -3.05) mEq/L] vs. with Clinics 3 [1.144 (2.16, -0.78) mEq/L] and 4 [-1.78 (-2.47, -1.10) mEq/L]. The percentages of measured DNA concentrations within ± 2 mEq/L of the ordered DNA at Clinics 1, 2, 3 and 4 were 47, 25, 71 and 77%, respectively.

**Conclusions:** Measured DNA concentrations were often significantly higher than ordered DNA in facilities using Fresenius machines and dialysate concentrates mixed onsite. Routine measurement of DNA should be incorporated into facilities’ QAPI programs. Future studies looking at clinical outcomes associated with differences in prescribed DNA should include measurements of delivered DNA concentrations.

**Funding:** Clinical Revenue Support

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**TH-PO811**

**Successful Use of Bivalirudin Protocol to Prevent Extracorporeal Thrombosis in Hemodialysis Patients with Heparin Induced Thrombocytopenia**

**Malcolm A. Finkelman,1 Sreedhar A. Mandayam,2 Enric Vilar,3 Abdullatif Abdullah,1 Hadi Saafi,4,5**

**Background:** Heparin Induced Thrombocytopenia (HIT) patients have a variable prevalence of 1-13%. There have been few reports using Lepirudin, Argatroban and Danaparoid in the management of extracorporeal thrombosis (ECT) during dialysis in these patients as heparin is contraindicated. We are reporting use of Bivalirudin to prevent ECT.

**Methods:** Our study was done in Fahd Bin Jassim kidney Center in Doha, Qatar (a large outpatient HD clinic of 300 patients). All patients diagnosed with HIT were included. HIT was diagnosed by ELISA method.

**Results:** 8 patients had confirmed positive HIT AB, 2 were receiving warfarin for atrial fibrillation with no ECT events and were excluded. One patient had a negative repeat test for HIT AB with no ECT events so he was excluded too. 5 patients with HIT AB and recurrent ECT events during dialysis were included. 3 patients had fistula and 2 had permanent catheter. A protocol was developed to start and adjust Bivalirudin based on activated partial thromboplastin time (APTT) value. Table 1 summarizes patients dosing and protocol.

**Bivalirudin Infusion Protocol for HIT in Hemodialysis Patients**

<table>
<thead>
<tr>
<th>APTT Ratio</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.2</td>
<td>increase dose by 20% and repeat APTT after 2h.</td>
</tr>
<tr>
<td>1.2-1.4</td>
<td>increase dose by 10% and repeat APTT after 2h.</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>no dose change and monitor APTT as protocol.</td>
</tr>
<tr>
<td>2.6-3.5</td>
<td>increase dose by 50% and repeat APTT after 2h.</td>
</tr>
<tr>
<td>3.6-4.4</td>
<td>increase dose by 20% and repeat APTT after 2h.</td>
</tr>
<tr>
<td>&gt;4.6</td>
<td>hold therapy until APTT ratio &lt; 3.5 then restart at a reduced dose and repeat APTT after 2h.</td>
</tr>
</tbody>
</table>

**Conclusions:** We are reporting a successful use of Bivalirudin protocol to prevent ECT in HD patients with HIT. It provided a simple dosing initiation with easy adjustment based on weight, aPTT and ECT events. The protocol provided excellent safety where no bleeding complications occured in these patients throughout the study.

**Funding:** Clinical Revenue Support

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**TH-PO812**

**Intracranial Fluid Shifts During Hemodialysis Measured Using VIPS (Volumetric Integral Phase-Shift Spectroscopy) Is Influenced by Osmolarity, Sodium and Less So by Urea Nitrogen**

**Sreedhar A. Mandayam,1,2 Jose Ignacio Suarez,3**

**Background:** End Stage Renal Disease (ESRD) patients undergoing hemodialysis (HD) experience a drop in serum osmolality. This may result in cerebral edema. Cerebral edema has been measured by invasive monitors or imaging studies. We used Volumetric Integral Phase-Shift Spectroscopy (VIPS), a non-invasive technology that detects fluid-induced phase shifts in low-energy radio waves transmitted through the brain.

**Methods:** The protocol was approved by the IRB of Baylor College of Medicine. ESRD on HD subjects without intracranial illnesses were enrolled. VIPS monitoring was performed pre, intra and post HD. Measured and calculated serum osmolality (osm) and mini mental state examination was performed pre and post HD.

**Results:** 19 patients (12 males) were enrolled. Median age was 50 years, 1 patient withdrawn. Of the 31 HD runs, 21 complete data sets were analyzed. There was a mean increase of 10.6% in the total Intracranial fluid (ICF) value from baseline corresponding to an average of 7 mOsm reduction. The ICF change measured by VIPS correlated with osm changes (r=0.31), best with change in Sodium change [Post HD – pre HD](r=0.51), less so with the BUN change (r=0.14) and least with glucose (r=0.01). Subjects with sodium < 135 at baseline had a tendency to develop lower ICF change (3% n=5) as compared to euvarenic subjects (12%, n=16, p=0.22).

**Conclusions:** VIPS provides real-time non-invasive monitoring of intracranial fluid shifts. Subjects develop serum osmolal reductions during HD, which potentially be a model for studying cerebral edema. Sodium shifts had a higher correlation to ICF change in our study. Further research to confirm our findings are warranted.

**Funding:** Pharmaceutical Company Support - Cerebrotech Medical Systems, Inc.
Online Hemodiafiltration Using Citrasate® Dialysis Solution – An Alternative to Systemic Anticoagulation?  

**Background:** Citrasate® is a dialysis solution using citrate (contrary to more common acetate) as the acidifying buffer compound. According to recently published data, its application could decrease or even obviate the need for systemic anticoagulation in hemodialysis (HD) patients. Particularly so during online hemodiafiltration (HDF) as in this setting predilution should provide yet higher in-dialyzer citrate concentrations resembling regional citrate anticoagulation (RCA).

**Methods:** In a prospective, randomized, cross-over study, 10 long-term HD patients were enrolled during 4h HDF procedure using Citrasate® (0.8 mmol/l citrate) in a predilution setting without additional systemic anticoagulation. Standard HDF procedure using acetate-buffered solution together with fractionated heparin was applied as a control. Along the session, blood and dialysate were sampled to enable analysis of thrombogenicity, acid base balance, calcium metabolism, and dialysis efficacy. Data are given as means ±SD; statistical significance was calculated by ANOVA.

**Results:** No HDF session was terminated prematurely though the semiquantitative dialyzer clotting score showed increased clotting under citrate solution (p = 0.001). At the same time, procedure efficacy assessed by spKt/V, as well as serum calcium, bicarbonate and pH did not differ significantly. While in controls the thrombin-antithrombin (TAT) and fibrinogen levels were examined during 4h HDF procedure using Citrasate® (0.8 mmol/l citrate) in a predilution setting without additional systemic anticoagulation. Standard HDF procedure using acetate-buffered solution together with fractionated heparin was applied as a control. Along the session, blood and dialysate were sampled to enable analysis of thrombogenicity, acid base balance, calcium metabolism, and dialysis efficacy. Data are given as means ±SD; statistical significance was calculated by ANOVA.

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

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Hypertension in Hemodialysis Patients: Dialysis Techniques and Hormonal Regulation

**Background:** Hypertension in hemodialysis patients has a prevalence of 50-80% and is associated to increased cardiovascular mortality. Endogenous osinoid (EO), a digitalis-like cardiotonic steroid produced by adrenal glands, in hemodialysis patients is associated to left ventricular mass, volume and eccentric hypertrophy remodeling. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is associated with heart failure and fluid overload. Hemodiafiltration (HDF) improves cardiovascular survival than bicarbonate hemodialysis (HD). The aim is to explore the relationship between BP values, hormonal regulation (EO and NT-proBNP) and hemodialysis techniques.

**Methods:** We enrolled 93 chronic hemodialysis patients; we performed ABPM of 24 hours of blood and effluent dialysis fluid analysis. 42 patients were treated with HDF, 51 with HD.

**Results:** NT-proBNP is directly associated with SBP of 24h and indirectly with EF of left ventricle; it is removed by HDF by convective clearance (decrease of 57%), as medium molecular weight compounds, and not by HD (increase of 21%). EO is directly associated with interdialytic weight gain and interventricular septum; it decreases with dialysis session independently of dialysis technique (decrease of 20%). Patients with cardiopathy have higher EO plasma levels than patients without cardiopathy. Beta-2 microglobulin is directly associated with NT-proBNP and SBP of 24h.

**Conclusions:** These data show that NT-proBNP is an index of hypertension and heart failure, while EO is linked to fluid overload and left ventricular hypertrophy. NT-proBNP is removed by convection, while EO decreases independently of dialysis technique (by ultrafiltration determine the decrease?). Convective clearance, expressed indirectly by beta-2 microglobulin, may influence BP control through the modulation of NT-proBNP.

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**Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.**
No systemic heparin was used. Primary endpoint was non-inferiority for clotting events of the combination of a heparin-grafted membrane plus citrate-containing dialysate vs. RCA, with a prespecified non-inferiority margin of 10%.

Results: We included 25 patients, receiving 1285 study dialysis sessions in total, 636 in the study arm and 649 in the control arm. Both anticoagulation strategies were safe. Overall, clotting rates were low: 37/636 (5.82%) in the study arm and 42/649 (6.47%) in the control arm. The primary endpoint of non-inferiority was met (P < 0.0001). In secondary analysis, using Cox proportional hazard analysis, time to clotting did not differ between study arms (P 0.62).

Conclusions: Combination of a heparin-grafted dialyzer with citrate-containing dialysate is non-inferior to conventional RCA. The procedure is easy to perform without additional pumps or calcium measurements. Combination of a heparin-grafted dialyzer and citrate-containing dialysate is a valid alternative to RCA in patients requiring heparin-free dialysis.

Funding: Pharmaceutical Company Support - Gambro - Baxter

TH-PO820

Effect of L-Carnitine on Markers of Mineral Bone Disease in the CARNIDIAL trial

Lecie Myerwald,1 Michel Chonchol,2 Messaoud Ouizilia,3 Christine Fumeron,4 Aude Servais,5 Sophie Tezenas du montcel.6


Background: Previous studies suggested that L-carnitine in hemodialysis patients decreases intact parathyroid hormone levels (iPTH). We studied the effects of L-carnitine on markers of mineral bone disease (MBD), including fibroblast growth factor (FGF23) in a randomized, double-blind trial.

Methods: We evaluated the effects of 1 g of intravenous L-carnitine after each dialysis session for 1 year when compared to placebo in a randomized and double-blind trial. C-terminal FGF23 (cFGF23) were measured at baseline, every 3 months and end of study in 91 chronic hemodialysis patients. Serum calcium, phosphate and iPTH were available at similar time points.

The effect of L-carnitine on serum calcium, phosphate, iPTH and cFGF23 was evaluable in 83 patients. L-carnitine treatment slightly increased serum calcium and phosphate (β calcium: 0.007; β phosphate: 0.005) and negatively correlated with EPO dose (β -0.41; p<0.0001) and adenine nucleotide translocator (ANT) expression (r=-0.31; p=0.041). Multivariate logitic regression analysis showed that the injectable group was also significantly associated with better survival than oral group (HR, 0.33, 95% CI, 0.13–0.83).

Conclusions: Treatment with injectable L-carnitine has a favorable impact on the infectious mortality compared to oral VDRA in the real-world practice of hemodialysis patients.

TH-PO823

Aldosterone Levels in Patients on Hemodialysis/Relationship with the Metabolic Syndrome

María José Fernandez Reyes,1 Manuel M. Heras,1 Maria Gonzalez,2 Olaia Rodriguez fraga,3 Ramiro Callejas,1 Álvaro Molina,1 Vanesa Lopes-martin,2 Maria astrid Rodriguez gomez,2 Leonardo Calle.1 Nephrology, Hospital General Segovia, Segovia, Spain; Biochemistry, Hospital Univ La Paz, Madrid, Spain.

Background: Recently it has been shown that serum aldosterone (SA) levels are correlated with several components of the metabolic syndrome (MSyn). OBJECTIVE: to establish SA levels on hemodialysis (HD) patients and its possible association with insulin resistance (homeostasis model assessment of insulin resistance HOMA-IR), excess body fat and/or serum adipocytokines levels.

Methods: 44 stable patients on HD, not taking ACE inhibitors/angiotensin receptor blockers. Mean age: 72.5±12.5years; 52.3% men; 34.1% diabetics. Mean time on HD:43.2±49 months. 28 patients were anuric. All measurements were done prior to the midweek HD session.

Results: SA levels were above the normal range (1.17-23.6 ng/dl) in 63.6% of patients. Plasma Renin Activity (PRA) was above the normal range (0.23-3.32 ng/mL/hour) in 27.3% of patients. Median: 31.15 (p25: 5.25; p75: 411 ng/dl). PRA median: 1.14 (p25: 0.04; p75: 20.9 ng/mL/hora). There were not statistically significant difference (Student’s t) in SA levels between anuric and non-anuric; male and female; presence and absence of myocardialopathy or diabetes. There were not statistically significant correlations (Spearman) of SA levels or PRA with urine volume; residual renal function; dose or length of time on HD; age; or Charlson Comorbidity Index. SA levels were positively correlated (Spearman) with ARP (r= 0.72; p=0.0001); body fat mass in kg/m2 (r=0.32; p=0.045); serum leptin levels (r=0.30; p=0.05); HOMA-IR (r= 0.36; p=0.017) and negatively with serum adiponectin levels (r=- 0.31; p=0.041). Multivariate logistic regression analysis showed that SA levels above its median level were independently associated to PRA and HOMA-IR.

Variables Independientes | Odds ratio | 95% CI | Valor de p
--- | --- | --- | ---
HOMA-IR | 1.236 | 1.025-1.492 | 0.01
Plasma Renina Actividad | 2.664 | 1.136-6.248 | 0.024

Conclusions: SA levels are elevated in a high percentage of HD patients and such elevation is associated with PRA and several components of MSyn (insulin resistance; body fat mass; and serum levels of adipocytokines). Funding: Government Support - Non-U.S.
TH-PO824
Dialysate Calcium Concentration Was Significantly Associated with Cardiovascular Diseases in Diabetics and Patients with High Body Mass Index among Hemodialysis Patients  
Mihoko Tagawa,1 Takayuki Hamano,2 Shinichi Sueta,3 Seiji Hashimoto,2 Satoshi Ogata.2 1Nara Medical Univ, Nara, Japan; 2Patient Registration Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan; 3Kyoto Univ, Kyoto, Japan.

Background: Previous studies showed that higher dialysate calcium (Ca) concentration was positively associated with cardiovascular (CV) diseases. Which patient characteristics modify this association has not been studied.

Methods: This was a longitudinal study based on the Japan Renal Data Registry (JRDR) from 2008 to 2009. Predictor variables were dialysate Ca concentration (3.0 mEq/L vs. 2.5 mEq/L). Primary outcome was CV composite event (either myocardial infarction, stroke, amputation, or CV death). Statistical analyses were performed using multivariable logistic regression model, adjusted for potential confounders.

Results: Among 300,660 patients on JRDR database, data for 38,697 patients were available for analyses after excluding patients with missing data. Serum albumin corrected Ca was significantly higher (9.27±0.77 vs. 9.18±0.79 mg/dL) and intact parathyroid hormone (iPTH) was significantly lower (135±65 to 236±164 [85-274] pg/ml) among high dialysate Ca users compared with low dialysate Ca users. The odds ratio of CV composite outcome among high dialysate Ca users was higher among diabetics and patients with higher body mass index (BMI) (p for interaction 0.02 and 0.01, respectively).

Conclusions: Higher iCa was also associated with higher HRV. The association of iCa with QTc interval and HRV remained significant in the repeated measures analysis. Associations with serum K, Mg, dCa, and dK were not significant at baseline or over follow-up. Serum-to-dialysate Ca gradient, but not K gradient was associated with higher HRV at baseline and over follow-up (β=0.3(0.0, 0.6) and 0.3(0.0, 0.6) respectively).

TH-PO825
Association of Serum and Dialysate Electrolytes with Arrhythmic Risk in Incident Hemodialysis  
Jacqueline Watt,1 Esther D. Kim,2 Larisa Tereshchenko,3 Stephen M. Sozio,3 Bernard G. Jaar,3 Lucy A. Meoni,2 Michelle M. Estrella,3 Rulan S. Parich1,2 1McMaster Univ; 2Univ of Toronto; 3Johns Hopkins Univ.

Background: Arrhythmias and sudden cardiac death (SCD) may occur during or shortly after receiving dialysis treatment. The extent to which serum and dialysate concentrations of potassium (K) and calcium (Ca) are associated with the risk of arrhythmias in incident hemodialysis is unclear.

Methods: In 402 patients from the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study, we analyzed the association of serum (ionized Ca[iCa]), K, magnesium [Mg]) and dialysate (dCa and dK) electrolyte concentrations with prolonged QTc interval (Bazett’s formula) and heart rate variability (HRV). Outcomes were measured by a 5-minute signal-averaged ECG. Prolonged QTc was defined as ≥460ms in women and ≥440ms in men. Baseline associations were examined using linear and logistic regression, and repeated measures were analyzed using mixed-effects models.

Results: At baseline, 86.3% had QTc prolongation, of whom 68.5% had persistent QTc prolongation at the follow-up visit. In the baseline analysis, higher iCa was associated with a shorter QTc interval and lower odds of having QTc prolongation, independent of demographic and cardiovascular risk factors, CRP, and pH.

TH-PO826
Phosphorus Kinetics During Hemodialysis: Further Validation of a Pseudo-One Compartment Model  
J. Ken Leveyold,3 Baris U. Agar,2 Alfred K. Cheung,1 Angelito A. Bernardo,1 Medical Products (Renal), Baxter Healthcare Corporation, Deerfield, IL; 3Medical Products (R&D), Baxter Healthcare Corporation, Round Lake, IL; 3Nephrology, Univ of Utah, Salt Lake City, UT.

Background: A pseudo-one compartment model has been proposed to describe phosphorus kinetics during hemodialysis (HD) and postdialysis rebound. This model suggests that phosphorus mobilization from tissues is proportional to the difference between the predialysis serum (C_0) and instantaneous serum concentration. The current study evaluated the ability of a pseudo-one compartment model to describe the kinetics of phosphorus in two short HD treatments on the same day separated by a 1-hr inter-treatment period without dialysis. The latter is the postdialysis rebound period for the first treatment.

Methods: Serum was collected frequently during both HD treatments and the inter-treatment period to assess phosphorus kinetics in 21 chronic HD patients. Phosphorus mobilization clearance (C_m) and predialysis central distribution volume (V_c) were estimated for each patient during the first HD treatment and the inter-treatment period. Assuming those kinetic parameters remained constant for each patient, phosphorus concentrations during the second HD treatment were used to estimate the driving force concentration (C_d) for phosphorus mobilization during that treatment.

Results: Treatment times (117±14 vs. 117±14 min), dialyzer phosphorus clearance (55±25 vs. 140±32 ml/min) and net fluid removal (1.44±0.74 vs. 1.47±0.76 L) were similar during both HD treatments. Phosphorus concentration at the start of the second HD treatment (3.3±0.9 mg/dL) was lower (P<0.001) than at the start of the first or C_0 (5.4±1.9 mg/dL). K_c and V_c were 98±44 ml/min and 11.0±4.2 L, respectively. Calculated C_m was 4.9±2.0 mg/dL, not significantly different from 5.0±1.3 mg/dL (P=0.12). C_d and C_m were correlated (R=0.72, P<0.001).

Conclusions: The results from this study demonstrate that the driving force concentration for phosphorus mobilization during HD is constant and equal to that predialysis, consistent with a fundamental assumption of the pseudo-one compartment model.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation
Conclusions: SA and poor sleep quality were common among hypertensive HD patients. Short sleep duration and poor sleep efficiency, but not the severity of SA, were associated with higher LVM indices.

Funding: NIDDK Support, Clinical Revenue Support

THI-PO828
Role of Nicotinic Acid as Phosphate Lowering Agent in End Stage Renal Disease Patients on Maintenance Hemodialysis
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1Dept of Nephrology, Allama Iqbal Medical College/Jinnah Hospital, Lahore, Pakistan; 2Div of Nephrology and Hypertension, Albany Medical College, Albany, NY.

Background: Hyperphosphatemia is associated with higher risk of mortality and morbidity in End Stage Renal Disease (ESRD) patients. Use of Nicotinic Acid as phosphate lowering agent has been studied in many countries but available data is sparse and limited. We conducted a study to determine the mean decrease in serum Phosphorous level with Nicotinic acid use in dialysis patients.

Methods: Nicotinic acid, in a dose of 250 mg twice a day with food for 4 weeks, was given to 45 ESRD patients with serum Phosphorous level more than 5.5 mg/dl. Serum phosphorus level was measured at the start and then at the end of study. Data was analyzed for decrease in serum phosphorus level with Nicotinic acid use.

Results: Mean age of 45 patients was 44.6 ± 13.9 years and 57.8% were male. Serum Phosphorus level before treatment was 5.6 ± 10.8 mg/dl (mean 6.91 ± 1.33 ) and after treatment for one month it was 2.60 ± 8.70 mg/dl (mean 5.82 ± 1.40). Mean decrease in phosphorus level with Nicotinic acid after one month of treatment was 1.08 ± 1.16 mg/dl (p value < 0.001).

Conclusions: Nicotinic acid is an effective and cheaper phosphate lowering agent in dialysis patients. Further larger and Randomized Controlled Trials are needed to establish the role of this cheaper phosphate lowering agent.

Funding: Private Foundation Support

THI-PO829
Cerebral and Cognitive Effects of Short- and Long-Term Hemodialysis – A Pilot Study
XiuFeng Li1, Yelena Slinin,2 Gregory J. Metzger,1 Lynn E. Eberly,1 Donald R. Dengel,1 David Tupper,1 Anne M. Murray,3 1Univ of Minnesota, MN; 2Veterans Affairs Medical Center, MN; 3Hennepin County Medical Center, MN.

Background: The short- (≤6 months) and long-term (³12 months) effects of conventional hemodialysis (HD) on brain structure, cerebral blood flow and cognitive function are not well understood.

Methods: We conducted a small longitudinal pilot study to investigate the effects of HD initiation on brain MRI and cognitive function in 4 HD patients by obtaining pre- and post- initiation brain MRIs and cognitive testing. The MRIs were obtained at 3-6 months and 12 months after HD initiation. The Modified Mini-Mental State Examination (3MSE) was performed within one month of the baseline and 12 month MRI examinations. MR diffusion tensor imaging (DTI) measured white matter (WM) fractional anisotropy (FA) (connectivity), and pseudo-continuous arterial spin labeling (PCASL) imaging was used to evaluate grey matter (GM) cerebral blood flow (CBF). A two-tailed paired t-test was used to compare pre- and post- initiation results. Patients provided written informed consent to participate in the IRB- approved protocol.

Results: Progressive and significant declines in frontal and temporal WM FA (Fig. 1), prefrontal CBF (Fig. 2), and cognitive function (Fig. 3, left) were found following HD initiation (Table 1 for p values). The decline in frontal WM FA on MRI was correlated with the 3MSE decline (R= 0.42)(Fig. 3, right).

Conclusions: Our results suggest that HD may adversely alter cerebral vascular function and progressively induce cerebral structural abnormalities and associated cognitive decline.

Funding: NIDDK Support

THI-PO830
Patient and Dialysate Temperature Characteristics in Incident Hemodialysis Patients: Results from a Large U.S. Population
Xiaoqing Ye1, Len A. Usyaty,2 Yue Jiao,2 Peter Kotanko,3 Franklin W. Maddux.2 1Renal Research Inst, New York, NY; 2Fresenius Medical Care North America, Waltham, MA; 3Icahn School of Medicine at Mount Sinai, New York, NY.

Background: In chronic hemodialysis (HD) patients the use of dialysate at a temperature below the patient’s core temperature (“cool” dialysate) has been associated with improved outcomes in observational and prospective randomized studies [Odudu et al., CJASN 2015; Eldehni et al., JASN 2015; Selby, Sem. Dial 2008]. Little is known about temperature profiles in large US populations.

Methods: We include a subset of incident HD patients who were treated in Fresenius Medical Care North America facilities from 1/2010 to 12/2014 and who survived the first year of HD. Pre- and post-HD body temperatures were measured with thermometers. The dialysate temperature was measured by the HD machine. The dialysate-to-patient temperature gradient was computed as dialysate temperature minus patient temperature.

Results: We studied 20,360 incident HD patients (age 62.5 (SD 14.5) years; 57.6 % males; 68.1% White, 29.2 Black, 2.7% others). The vast majority (83.8%) had a dialysate temperature above body temperature at the start; and at the end (80.6%) of HD.

Table 1. P values from the comparisons between the baseline and follow-up sessions.

| Table 1. P values from the comparisons between the baseline and follow-up sessions. |
|-------------------------|-------------------------|-------------------------|-------------------------|
|                         | 6 months                | 12 months               |
| FA                      |                         |                         |
| Frontal                 | 0.031                   | 0.025                   |
| Temporal                | 0.048                   | 0.044                   |
| CBF                     |                         |                         |
| Prefrontal              | 0.038                   | 0.048                   |
| Anterior Hippocampus    | 0.042                   | 0.013                   |

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

281A
The prescribed dialysate temperature was 36.87 ± 0.31 °C. We observed a small yet significant rise in body temperature during HD.

**Conclusions:** Delivered dialysate temperature exceeds the body temperature in majority of patients. This may provide potential opportunities for dialysate temperature reduction to improve intradialytic stability and outcomes.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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**TH-PO831**

**Effect of a Single Hemodialysis Session on Visual Evoked Potentials**

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**Background:** Some studies have shown that visual evoked potentials (VEPs) may be a marker of dysfunction in visual pathways in uremic subjects. However, data are scarce regarding effect of hemodialysis procedure on VEPs. We aimed to compare VEPs of hemodialysis patients with healthy volunteers and in particular to assess the impact of a single hemodialysis session on VEPs.

**Methods:** Thirty hemodialysis patients were included in the study. We also recruited 30 age and gender matched control subjects. Patients with diabetes mellitus, cataracts, glaucoma, and stroke were excluded. Demographic characteristics, midweek predialysis recordings. Bias was defined as the mean difference in BP (pre-HD, intra-HD, post-HD) measure Bias, average HBPM was subtracted from each of these three index BP intradialytic device was used for the patient at home. Patients were instructed to bring the device to the dialysis. Patients with symptomatic hypotension during dialysis were excluded. To measure Bias, average HBPM was subtracted from each of these three index BP intradialytic recordings. Bias was defined as the mean difference in BP (pre-HD, intra-HD, post-HD) compared with HBPM.

**Results:** 192 patients, mean age 63.8 ± 14.8 y.o. (70% male), of 11 HD clinics of Fresenius Medical Care of Spain were included, 33% diabetic. All patients were on thr ee times weekly HD. The mean time on HD was 46 ± 57 months.

**Conclusion:** Reduction of tissue sodium content by hemodialysis treatment differs in skin and muscle tissue. While bound sodium content in muscle was unaffected by hemodialysis, bound sodium content in skin tissue could be mobilized by HD.
End-Dialysis Overweight and Chronic Inflammation: A Dangerous Association—A 36-Month Prospective Observational Study
Ezio Movilli, U.O. of Nephrology, Spedali Civili and Section of Nephrology Univ of Brescia, Brescia, Italy.

Background: Attaining dry body weight is paramount in dialysis practice, but this goal is not always reached. We hypothesized that the amount of end-dialysis overweight (edOW), could be associated to increased chronic inflammation and mortality. Aim of the study: to evaluate the effect of edOW on serum C-reactive protein (hsCRP) concentrations and on survival in a cohort of 182 prevalent HD patients (pts) followed for 36 months.

Methods: In 182 pts (117 men, age 65±12 years, vintage 48 months; range 6-336), edOW was present in 98/182 (54%) pts. Mean value was 0.4±0.2 Kg (range: 0.1-1.4). In the 98 pts with edOW (Group 1) and in the other 84 (Group 2) we evaluated: Ultrafiltration rate (UFR), hsCRP/day body weight (dBW), Kt/V, protein catabolic rate (PCRn), interdialytic weight gain (IDWG), mean arterial pressure (MAP). Unpaired Student’s t was employed to compare groups, linear regression analysis to test correlations, log-rank test and Kaplan-Meier curves to evaluate survival.

Results: Mean UFR was 11.7±2.8 Kg/hour, dBW 64±12 Kg, hsCRP 6.6 (0.2-36) mg/L, Kt/V 1.27±0.09, PCRn 1.06±0.10 g/Kg/day, IDWG 2.8±0.4 Kg, MAP 97±6.5 mmHg. edOW and hsCRP were directly and significantly correlated (r= 0.67; p<0.0001). Comparison between pts with (Group 1) and without (Group 2) edOW showed significant differences in: UFR (12.7±2.6 vs 10.9±2.6 ml/Kg/hour; p<0.0001), hsCRP (13.0±2.6 vs 10.9±2.6 mg/L, p< 0.0001), and PCRn (1.03±0.09 vs 1.08±0.10 g/Kg/day; p<0.0004). 98 pts (54%) died during follow-up for cardiovascular complications in 69% of cases. Survival curves showed significantly greater mortality in Group 1 vs Group 2 in relation to the amount of edOW, and hsCRP (p<0.0001).

Conclusions: edOW and chronic inflammation are directly correlated in HD pts, and both are associated to a greater long-term risk of mortality.

Suicidal Erythrocyte Death in Hemodialysis Patients

Background: Even though anemia in ESRD results mainly from the lack of erythropoietin, compelling evidence points to the contribution of accelerated erythrocyte death/eryptosis, which is characterized by phosphatidylserine (PS) exposure at the cell surface. PS exposure might be stimulated both by uremic toxins and the mechanical stress induced by hemodialysis (HD). We investigated the possible differences in terms of eryptosis levels between healthy subjects and HD patients before and after HD session.

Methods: We enrolled 15 patients (4F, mean age 65±16yrs, 33% with diabetes) undergoing chronic HD and 15 healthy subjects (CTR). Blood samples were collected prior to and after 4h standard HD session. Measurements were made in isolated erythrocytes (RBCs). PS exposure was estimated from AnnexinV binding in flow cytometer.

Results: The percentage of AnnexinV reflecting the percentage of RBC’s exposing PS at RBC surface was significantly higher (more than twice) in HD patients than CTR (2.2%; IQR 1.2-4.1 versus 0.8%; IQR 0.7-1.3; p<0.05). The average forward scatter reflecting cell volume was significantly higher in RBCs from HD patients than in CTR. There was no statistically significant relationship between baseline levels and eryptosis in HD patients. The percentage of AnnexinV and cell volume were measured prior to and after 4h of HD: no significant differences were observed between pre and postdialytic eryptosis.

Conclusions: Our data suggest that HD may lead to a significant increase in eryptosis, but no differences in the level were observed before and after HD session. Although the procedure is known to be responsible for cytokines and inflammatory mediators release, because of the interaction between blood and circuit lines and filters, it does not seem to induce eryptosis. Further studies are needed to compare different types of HD treatments.

Deployment of a Dialysis Hospitalization Reduction Program Is Associated with Lower Hospitalization Rates
Hanjie Zhang, Dugan Maddux, Karen G. Butler, Len A. Usvyat, Yue Jiao, Brian Scott Ash, John W. Larkin, Terry Ketschersid, Peter Kotanko, Franklin W. Maddux. Renal Research Inst, New York, NY; Fresenius Medical Care North America, Waltham, MA; Icahn School of Medicine at Mount Sinai, New York, NY.

Background: The aim of this study was to investigate the potential effect of a Dialysis Hospitalization Reduction Program (DHRP) on hospital admissions.

Methods: We deployed DHRP to 69 patients between 1/1/2014 and 5/5/2015 in a network of Fresenius Medical Care North America (FMCNA) dialysis clinics. These patients were identified as being at high risk for hospitalization based on FMCNA’s data driven predictive modeling efforts and clinical assessments. The DHRP encompasses multiple interventions, targeting malnutrition, non-compliance, mental status issues, fluid overload, and others. Each patient is identified to have one or more “clinical tags”; 88 tags were identified for 69 patients. Interdisciplinary teams were deployed to design and implement interventions. Hospitalization rates were measured 90 days before and after the program.

Results: DHRP was associated with a reduction of all-cause hospitalization from 7.5 to 4.4 per patient year (ppy) (-42 %) (Figure 1A). Interventions targeting patients with “malnutrition” tag were associated with a reduction of hospitalizations from 9.3 to 4.1 ppy (-56%) (Figure 1B).

Figure 1. A Overall intervention outcomes

<table>
<thead>
<tr>
<th>Number of clinical tags</th>
<th>Before</th>
<th>After</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admissions</td>
<td>88</td>
<td>85</td>
<td>3%</td>
</tr>
<tr>
<td>Hospital days</td>
<td>7.5</td>
<td>4.4</td>
<td>42%</td>
</tr>
<tr>
<td>Misdosed treatments</td>
<td>7.9</td>
<td>7.4</td>
<td>6%</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.52</td>
<td>3.51</td>
<td>0%</td>
</tr>
<tr>
<td>Calcerteres</td>
<td>31%</td>
<td>30%</td>
<td>3%</td>
</tr>
<tr>
<td>Pre-dialysis SBP (mmHg)</td>
<td>146.5</td>
<td>147.1</td>
<td>0%</td>
</tr>
<tr>
<td>IDWG (kg)</td>
<td>2.49</td>
<td>2.47</td>
<td>1%</td>
</tr>
</tbody>
</table>

B. Intervention outcomes targeting malnourished patients

<table>
<thead>
<tr>
<th>Number of clinical tags</th>
<th>Before</th>
<th>After</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admissions</td>
<td>21</td>
<td>21</td>
<td>0%</td>
</tr>
<tr>
<td>Hospital days</td>
<td>9.3</td>
<td>4.1</td>
<td>58%</td>
</tr>
<tr>
<td>Misdosed treatments</td>
<td>7.6</td>
<td>6.4</td>
<td>16%</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.22</td>
<td>3.28</td>
<td>2%</td>
</tr>
<tr>
<td>Calcerteres</td>
<td>45%</td>
<td>34%</td>
<td>-20%</td>
</tr>
<tr>
<td>Pre-dialysis SBP (mmHg)</td>
<td>144.2</td>
<td>144.4</td>
<td>0%</td>
</tr>
<tr>
<td>IDWG (kg)</td>
<td>2.3</td>
<td>2.34</td>
<td>2%</td>
</tr>
</tbody>
</table>

Conclusions: DHRP was associated with reductions in hospital admissions and days. Reductions in overall hospital admissions were even higher in patients specifically identified to have malnutrition issues.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

The Long Inter-dialytic Period Is Not Associated with Inferior BP Control in Stable Hemodialysis Patients

Background: 3-day-a-week hemodialysis (HD) involves one long (72hr) and two short (48hr) inter-dialytic periods (IDP) with higher death risk after the long IDP. We investigated BP and CV biomarker patterns in clinically stable HD patients to determine whether BP control during the final 24 hrs of the long IDP is inferior to that of the short IDPs.

Methods: In an initial retrospective study, in-center BP readings over 1 month were analyzed for 81 adult HD patients with stable regimen and medical status for ≥ 3 mths. Next, 23 patients completed a prospective study in which ambulatory BP monitoring was performed for the final 24hrs of the long and one short IDP in the same week. Blood was collected for CRP, Troponin T, BNP following each ABPM.

Results: In the retrospective study, mean pre-dialysis systolic and diastolic BP (SBP/DBP) did not differ for the long and short IDPs despite greater weight gain during the long IDP. This observation was confirmed in the ABPM study and applied to both day- and night-time readings. Pre-dialysis CV biomarkers were not significantly higher following the long IDP. Inter-dialytic weight gain showed no correlation with BP indices.

Conclusions: Our data suggest that HD may lead to a significant increase in eryptosis, but no differences in the level were observed before and after HD session. Although the procedure is known to be responsible for cytokines and inflammatory mediators release, because of the interaction between blood and circuit lines and filters, it does not seem to induce eryptosis. Further studies are needed to compare different types of HD treatments.
Conclusions: In stable HD patients, BP control and CV biomarkers were similar during long compared to short IDP despite greater fluid gain. The adverse influence of excessive inter-dialytic fluid gain is unlikely to be mediated directly through a hypertensive effect.

TH-PO838
Notch Signaling in Bone Marrow-Derived FSP-1+ Cells Mediates a Phenotypic Change in Smooth Muscle Cells Leading to A VF Failure
Jinlong Luo, Sonia Bhati, Nikhil Grandhi, Ashish Verma, Amanda B. Ravi S. Shah, Jizhong Cheng, William E. Mitch, Yechong Cheng, Medicine, Baylor College of Medicine, Houston, TX; *Nephrology, Guangzhou Medical University, Guangzhou, Guangdong, China.

Background: sociological and economic costs of failed arteriovenous fistulas (AVF) are well known but mechanisms of AVF losses are controversial. We have shown that smooth muscle cells (SMCs) from anastomosed artery compose of ~50% of neointima cells in AVF. Arterial anastomoses are also infiltrated by bone marrow (BM)-derived FSP-1+ cells, potentially linking FSP-1+ cells to SMC activation. However, whether Notch/RBP-JK signaling involves in BM-derived FSP-1+ cells activation has not been studied. We propose that Notch/RBP-JK activation in BM-derived FSP-1+ cells causes a phenotype-switch of SMCs, resulting in SMC translocation from the artery to the venous anastomosis, forming neointima.

Methods: we created CKD and AVFs in wild type and Notch knock out mice. The role of Notch signaling in activation and function of BM-derived FSP-1+ cells was explored. Activated SMCs were characterized by a loss of differentiation markers plus a gain in proliferation (PCNA+). Using BM transplantation, we examined if FSP-1+ cells lacking RBP-JK or CKD mice would suppress SMC phenotype switch and neointima formation in AVFs.

Results: BM-derived FSP-1+ inflammatory cells in AVFs from CKD mice were 45% greater vs. results in pair-fed, control mice. In the artery anastomosis, increased infiltration of FSP-1+ cells led to loss of SMC differentiation markers, SM22, SM-22a and SMA-α. Activation of Notch signaling (NICD+ and RBP-JK+) raised expression of cytokines (IL-1), MCP-1 and growth factors (PDGF-BB, bFGF and TGF-β1) in FSP-1+ cells. The cytokines and growth factors caused a SMC phenotype switch (characterized by loss of SMC differentiation markers), resulting in SMC migration and proliferation. RBP-JK KO in BM-derived FSP-1+ cells significantly decreased the production of cytokines and growth factors, suppressed SMC activation of and neointima formation in AVFs.

Conclusions: Thus, Notch signaling in BM-derived FSP-1+ cells can induce a phenotype switch in SMCs stimulating neointima growth. Targeting Notch signaling in FSP-1+ cells could improve AVF function.

Funding: NIDDK Support

TH-PO839
Cytooglobin Is Upregulated in Failed Arteriovenous Fistula from Hemodialysis Patients and Exerts Survival Functions in Medial Smooth Muscle and Neointimal Cells
Lam Poon, Jizhong Cheng, Frances L. Jourd'heuil, David Jourd’heuil, 1William E. Mitch, 1Yechong Cheng, Medicine, Baylor College of Medicine, Houston, TX; *Nephrology, Guangzhou Medical University, Guangzhou, Guangdong, China.

Background: Arteriovenous fistulae (AVFs) suffer significant problems with high incidence of both early and late failures. Interventions that may prolong access patency are still very limited and require strategies that may impair or regress neointimal hyperplasia. In the cardiovascular system, globins such as hemoglobin are thought exclusively to regulate O2 and nitric oxide (NO) levels. However, recent studies suggest that this model might be incomplete and that non-canonical mammalian globins including cytooglobin (CYGB) have survival functions independent of the regulation of O2 and NO. Our goal was to understand the function of CYGB in the hyperplastic response associated with AVF failure.

Methods: Histomorphometric, immunostaining, and protein analysis were performed on protein extracts. sections. Molecular analyses were performed on RNA extracts from these venous segments and protein analyses were performed on protein extracts.

Results: CYGB was upregulated in revision compared to primary placement veins with significant expression in both smooth muscle and neointimal cells. Injury-induced neointimal formation in vivo was attenuated by CYGB deficiency and associated with increase apoptosis and medial VSMCs loss. Human venous medial and neointimal SMCs derived from failed AVFs maintained high levels of CYGB in culture in contrast to medial SMCs from placement veins. Molecular strategies to modulate CYGB expression levels were validated that CYGB promotes SMC cell survival by inhibiting the mitochondrial apoptotic pathway.

Conclusions: Our results challenge the current dogma on globin functions and demonstrate a role for CYGB in regulating venous VSMCs survival. Strategies aimed at regulating CYGB anti-apoptotic functions might represent important therapeutic options to control for AVF maturation and limit stenosis.

Funding: Pharmaceutical Company Support - DCI Paul Teschan Research Fund, Private Foundation Support

TH-PO840
Identification of Ca2+/CaM-Dependent Protein Kinase (CaM KKII) Isoforms and Their Selective Regulation by NADPH Oxidases in Failed Arteriovenous Fistula from Hemodialysis Patients
Jinlong Luo, Sonia Bhati, Nikhil Grandhi, Ashish Verma, Amanda B. Ravi S. Shah, 1Jizhong Cheng, William E. Mitch, Yechong Cheng, Medicine, Baylor College of Medicine, Houston, TX; *Nephrology, Guangzhou Medical University, Guangzhou, Guangdong, China.

Background: Placement of an arteriovenous fistula (AVF) provides vascular access for lifesaving hemodialysis to patients with severe and chronic kidney disease. A significant percentage of AVF’s initially mature; serve as successful hemodialysis access points; but fail at some later time due to neointimal hyperplasia that occludes the vein. The causative underlying molecular, biochemical, and cellular factors that contribute to AVF failure are incompletely understood. CaM KKII is a positive regulator of VSM cell proliferation and migration that results in occlusion of carotid arteries in both mice and rats. Currently, there is little known regarding the role of CaM KKII in either physiological or pathophysiological venous function.

Methods: Cephalic veins from patients prior to AVF placement and after AVF failure were obtained. Immunochemistry analyses were performed on OCT embedded frozen sections. Molecular analyses were performed on RNA extracts from these venous segments and protein analyses were performed on protein extracts.

Results: Our results indicate that there is an increase in CaM KKIIId and CaM KKIIg expression in failed AVFs as compared to cephalic vein prior to AVF placement. CaM KKII activity is regulated by both phosphorylation and oxidation, NADPH oxidases (Noxs) generate reactive oxygen species (ROS) that increases CaM KKII activity. Analysis of failed AVFs shows an upregulation of Nox5 and Nox5. Further studies show an increase in CaM KKII activity. Interestingly, our data indicates that only a subset CaM KKII isoforms are oxidized under these conditions.

Conclusions: These findings lead us to conclude that increases in [Ca2+] and [ROS] after AVF placement may result in increases of CaM KKIIId and CaM KKIIg expression and sustained activity that contribute to AVF failure. They also identify CaM KKII as a rational target for therapeutic manipulation to prevent AVF failure.

Funding: Pharmaceutical Company Support - DCI Paul Teschan Research Fund

TH-PO841
Combined RNA seq and gDNA Methylation Analysis for AVF Maturation

Background: Early arteriovenous fistula (AVF) failure remains an important cause of hemodialysis vascular access dysfunction. In order to understand the cellular and molecular mechanisms involved in early AVF failure we evaluated the gene methylation profile (epigenetics) in conjunction with the gene expression profile (RNA Seq) from venous tissue samples obtained at the time of AVF creation. This approach allows us to identify genes that have altered expression (RNA Seq analysis) as a result of epigenetic changes (DNA methylation). The latter can be induced by different factors, including stress, inflammation, nutrition, metabolism, drugs and infection (all of which are prominent in the biological milieu of patients with CKD and ESRD).

Methods: Genomic DNA (gDNA) and RNA were isolated from venous segments collected at the time of AVF creation. We divided the samples into 2 groups, THICK (n=5) and THIN (n=5), based on a histological evaluation of the amount of neointimal hyperplasia. Deep sequencing technologies were then used to identify differentially regulated levels of gene expression between the THICK and THIN groups, that also had significant differences in DNA methylation. Standard bioinformatic techniques were used to identify/interrogate these changes.

Results: We were able to identify a number of genes that were differentially regulated, either at the level of the transcriptome or at the level of DNA methylation (epigenetics) between the THICK and THIN groups. However, we were not able to identify individual genes that had changes in both the RNA Seq and DNA methylation analyses, at a high level of statistical significance.

Conclusions: While we were unable to identify differences in both gene expression and methylation of DNA methylation for individual genes, between our two groups (perhaps because of a small sample size), we do believe that these techniques and technologies could be used in larger studies, to dive deep into the mechanisms of AVF failure at a molecular and genetic level.
Computational Fluid Dynamic Analyses in a Uremic Mouse Model of AVF Stenosis: Of Surgery, Techniques and Computation
Begoña Campos,1 Yang Wang,2 Yong He,2 John M. Pearce,1 Richard Scott Dunn,3 Keith Louis Saum,1 Janaka Wansapura,1 Charles L. Dumoulin,1 Scott A. Berceli,1 Prabir Roy-Chaudhury,1 Univ of Cincinnati; 2Univ of Florida; 3CCHMC.

Background: Although arteriovenous fistulae (AVF) are the preferred form of vascular access for hemodialysis patients, over 50% of AVFs fail to mature (inability to increase blood flow and diameter adequately to support dialysis). Work performed in our laboratory suggests that AVF maturation failure is due to an interaction between “upstream hemodynamics” and “downstream vascular biology”. In order to better elucidate the mechanisms involved in both these processes, we herein describe the techniques needed to develop a shear stress profile within a uremic mouse AVF.

Methods: In order to create a uremic mouse model, C57Bl/6 animals underwent an initial cauterization of the left kidney followed 2 weeks later by a contralateral nephrectomy. Four weeks later AVFs were created in the neck. In order to generate different shear stress profiles, we created AVFs between the carotid artery and jugular vein in the following surgical configurations (a) end of carotid artery to end of jugular vein (b) end of jugular vein to end of carotid artery and (c) end of carotid artery to side of jugular vein. Mice were then perfused with a silicone rubber casting agent (Microfil). Fistulae were harvested, stored in 4% paraformaldehyde, and treated with Lugol solution as a micro-CT contrast agent. Each AVF was then scanned using micro-CT imaging to create a 3D reconstruction of AVF geometry. In order to obtain blood flow parameters we have developed an MRI technique that allows us to quantify blood flow within the carotid artery. We then use software to develop a complete shear stress profile in the mouse AVF.

Results: We have described for the first time a hybrid surgery-fluid dynamics approach, which could allow us to identify the differential impacts of different surgical configurations, with or without the impact of uremia on AVF fistula functionality (with the promise of also being able to use genetically manipulated animals in the future).

Conclusions: We firmly believe that teasing out the relative roles of upstream hemodynamics and downstream uremic vascular biology will allow us to identify target(s) for future therapeutic interventions.

Biodegradable Stents Improve Arteriovenous Fistula (AVF) Maturation
Begoña Campos, Yang Wang, Zhangzhang Yin, Keith Louis Saum, Diego Celdran-Bonafonte, Mark J. Schulz, Vesselin Shanov, Prabir Roy-Chaudhury, Univ of Cincinnati.

Background: Arteriovenous fistula (AVF) maturation failure is currently a huge clinical problem with no effective therapies. At a pathogenetic level the three main causes of AVF maturation failure are (a) small veins (b) abnormal non-laminar flow profiles and (c) abnormal local endothelial function. We therefore, hypothesize, that the placement of a biodegradable magnesium based maturation enhancing stent (bMES) within the venous segment, at the time of surgical AVF creation would dilate small veins, optimize the anatomical configuration, and serve as a conduit for the future delivery of therapies to improve local vascular biology during the critical initial 4-8 week period with an absence of long term side effects (no stent after 4-8 weeks).

Methods: bMES were fabricated using pure Mg foil (125 mm) and Mg-Zn alloy wire. Bilateral AVFs were created between the femoral artery and vein of Yorkshire pigs. A bMES was inserted on one side and diallated to 8mm. A control AVF was created on the contralateral side. CT angiograms and ultrasounds were performed to document blood flow and diameter for the control and stented AVF.

Results: Preliminary data documents almost complete degradation of the bMES at 4-8 weeks with an initial increase in diameter of the stented AVFs on CT angiograms at 2 weeks (Figure). Histological examination performed on both the stented and control AVFs did not reveal any evidence of necrosis or inflammation.

Conclusions: These initial results clearly demonstrate technical feasibility and safety for the bMES, and also provide us with an efficacy signal based on our CT angiogram data (Figure). We believe that this technology could significantly reduce the huge morbidity and mortality associated with AVF maturation failure and also expand the patient population considered to be suitable for AVF placement in the future.

Association Between Clinical Outcomes and Type of Vascular Access in Elderly End-Stage Renal Disease Patients Initiating Hemodialysis
Kyoung Sook Park, Mi Jung Lee, Tae-Hyun Yoo, Shin-Wook Kang. Dept of Internal Medicine, Yongui Univ College of Medicine, Seoul, Korea.

Background: Although dialysis initiation via arteriovenous fistula (AVF) is the best strategy in incident hemodialysis (HD) patients. Elderly patients with HD are compelled to use HD catheter (HC) due to maturation failure after AVF operation. Therefore, we investigated the association of vascular access (VA) type and clinical outcomes in elderly incident HD patients.

Methods: A prospective cohort of incident HD patients from the Clinical Research Center for End-stage renal disease in Korea between 2009 and 2013 was used. Patients who were 65 years or older were defined as elderly. The patients were classified into three groups according to VA type at HD initiation. Since the hazard ratio (HR) according to type of VA was not proportional, time-dependent Cox regression analysis was performed to determine all-cause mortality.

Results: Among the 511 enrolled patients, 303 (59.3%) were male and the mean age was 72.3±5.4 years. HD was initiated with AVF, arteriovenous graft (AVG), or HC in 86 (16.8%), 36 (7.0%), and 389 (76.1%) patients, respectively. During a median follow up of 12 months, all-cause death was observed 12 (14.0%) in AVF, 13 (36.1%) in AVG, and 107 (27.5%) in HC. Multivariate time-dependent Cox regression analysis demonstrated that AVG as reference, HR=1.719, 95% confidence interval [CI]=1.274-2.319, P<0.001 and HC (HR=1.304, 95% CI=1.036-1.640, P=0.023) were significant risk factors for all-cause mortality after adjustment of age, sex, diabetes mellitus, previous cardiovascular disease, tumor referral to nephrologist, hemoglobin, serum albumin, and C-reactive protein levels.

Conclusions: Patients with successful AVF were associated with better survival compared to those with AVG or HC. In addition, survival was comparable between elderly patients initiating HD with AVG and HC. Although vascular problems are common in elderly patients, AVF may be the best strategy to improve clinical outcomes in this population.

International Variability in Arteriovenous Fistula Maturation and Placement: The Dialysis Outcomes and Practice Patterns Study (DOPPS) findings demonstrate international variability in vascular access practices, and association with outcomes. Here we describe international practices in arteriovenous fistula (AVF) placement and predictors of AVF maturation.

Methods: We studied 2,230 patients with an AVF created during DOPPS phases 4-5 (2009–2015) in North America, Europe/Australia-New Zealand (ANZ), and Japan. AVF maturation was defined as access use ≥ 30 days. Generalized estimating equations with a logit link were used to assess predictors of AVF maturation adjusting for country, phase, patient characteristics, and accounting for facility clustering.

Results: No significant association was found between many patient characteristics (e.g., age, diabetes, peripheral vascular disease) and AVF maturation. AVF maturation was more likely for males vs. females (OR = 1.49 [95% CI = 1.25–1.79]) and for AVFs placed in the upper vs. lower arm (OR = 1.40 [95% CI = 1.15–1.70]). Even though upper arm AVFs were more common in North America, AVF maturation was lowest in this region (Figure).
Conclusions: There is large international variability in site of AVF placement and AVF maturation. Differences in blood flow used (much higher in the US vs. Europe and Japan) may lead to different interpretation of the term ‘maturation’ internationally, and may influence maturation rates.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, ABVae, Sanofi, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd, BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGIIN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

TH-PO847
Vascular Access in Acute Kidney Injury: Results from the ATN Study
Kavitha Ganta, Yue-Harn Ng, Herbert T. Davis, Mark L. Unruh. Department of Internal Medicine, Univ of New Mexico, Albuquerque, NM.

Background: Acute kidney injury requiring renal replacement therapy (RRT) portends a poor prognosis. Currently, the decision regarding catheter placement is based solely on physician discretion. Limited data exist to guide catheter placement. The Acute Renal Failure Trial Network (ATN) study was a multicenter, prospective, randomized trial on the effects of dialysis dose on mortality in critically ill patients. Using data from this study, we assessed the complications rates and the adequacy of dialysis based on different catheter locations.

Methods: Baseline characteristics were gathered. The outcomes of interest included catheter related infections, cardiac arrhythmias, excessive bleeding, local thrombosis and dialysis adequacy. Categorical variables were analyzed using Chi-square test while continuous variables were analyzed using the Student T test. The SAS software was used for all analyses.

Results: There were 242 (11.7%) subclavian (SC), 951 (46.1%) internal jugular (IJ) and 861 (41.7%) femoral (FC) catheters inserted. The baseline characteristics based on catheter location is shown in Table 1.

The rate of bacteremia was comparable between the 3 groups. (5.4% (SC) vs 3.5% (IJ) vs. 3.5% (FC); p = 0.34) The IJ group experienced more cardiac arrhythmias (2%) compared to SC (0.8%) and FC (0.5%) group (p = 0.01) while the FC group had more venous thrombosis (0.7%) compared to none in the SC and IJ group (p = 0.02). Overall, complication rates were low. There was no clinically significant difference in the adequacy of dialysis between the 3 groups.

Conclusions: There was no significant differences in complication rates amongst the 3 catheter locations hence decision on catheter location should be based on operator experience and comfort level.

TH-PO848
Vascular Access at Dialysis Initiation in the United States Renal Data System (USRDS): Strong Agreement Between CMS 2728 Medical Evidence Form and CROWNWeb
Purna Mukhopadhyay, Jeffrey Pearson, Kenneth J. Woodside, Sarah Bell, Ronald L. Pisoni, Douglas E. Schaubel, Kaitlyn Ratkowicki, Rajiv Saran.1 Arbor Research Collaborative for Health, Ann Arbor, MI; 2 Univ of Michigan, Ann Arbor, MI; 3 Biostatistics, Univ of Michigan, Ann Arbor, MI; 4 Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: The USRDS has long reported vascular access (VA) at the start of hemodialysis (HD) using the CMS-2728 Form. In 2012, CMS rolled out the CROWNWeb (CW) system to collect clinical treatment and laboratory monthly data for all dialysis patients. As CW data are fully integrated into the USRDS database, it is critical to evaluate the level of completeness and consistency between these two data sources.

Methods: We compared VA used at the first HD session reported on the CMS-2728 form for new ESRD patients in 2013 (n = 96,936) in USRDS database with VA used at the end of the 1st month of HD reported through CW. To evaluate the potential for data lag, we also compared to the 2nd month of HD reported through CW. Completeness and consistency was assessed at the patient level by 2x2 tables. The level of agreement was evaluated by kappa statistics. Logistic regression models were fit to identify patient characteristics associated with the level of agreement.

Results: 89% of patients had at least one monthly VA report in CW among which 0.23% was missing VA data from the CMS-2728 and 32.8% did not have a VA reported in CW for their 1st month of HD. However, completeness of CW data improved when either 1st or 2nd month of HD was considered as only 12.6% of patients did not have a VA reported. Among patients with VA reported from both data sources, kappa statistics was 0.88 using the 1st month of ESRD and 0.84 using first two months of ESRD. Agreement was highest for catheter (97.98%) and lowest for graft (78.81%). Age, sex in race were associated with the level of agreement; Hispanic ethnicity and cause of ESRD were not.

Conclusions: Our analysis confirms the large CVC burden among pediatric HD pts. Conversion to AVF were observed over the first year in an incident cohort where nearly 50% of pts transitioned to PD or TX. Further study will assess the impact of CVC dependence among pediatric ESRD pts with respect to future VA options and patient outcomes.

Funding: NIDDK Support

TH-PO850
In Search of an Optimal Screening Program for Containing Graft Thrombosis
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Background: K DOQI guidelines recommend regular screening for ‘50% stenosis (ST)’ in graft by surveillance (access blood flow (Qa) & static venous pressure ratio (vVR) or Duplex Ultrasound to reduce the risk of thrombosis. Analysis of the literature suggests that the best predictor of thrombosis is sVR>0.5, with an area under curve (AUC) of 0.81[95%CI:0.75-0.85] significantly higher than that of Qs<400 ml/min (0.72[95%CI:0.68-0.77]) & ST (0.49[95%CI:0.45-0.53]), but no study has compared vis-a-vis all of the tools.

Methods: To identify an optimal screening program, in 2013 we compared the diagnostic performance of the available tools for incipient thrombosis (within 3 mo) in the same population of 42 grafts (5 forearm loop & 37 straight upperarm), that underwent 18 thrombotic episodes.

Results: Qa by Ultrasound Dilation proved to be the best screening tool (AUC:0.81[0.69-0.93]) optimal thresholds between Qa<400 ml/min prevalence[SE], 18% false positive[FPR] & Qs<1200 ml/min (83% SE, 27% FPR). Its AUC was higher than that of (ST (0.69[95%CI:0.54-0.84]: 78% SE, 39% FPR), monitoring (0.62[95%CI 0.45-0.79]: 33% SE, 9% FPR), & VAPR (0.58[95%CI:0.42-0.74]:VAPR:0.82% SE, 58% FPR). At GLM analysis Qa was the only significant predictor of thrombosis, with 18%[95%CI 7-29%] lower risk for each 100 ml/min above a Qa 400 ml/min.

Conclusions: CW data has VA information for the vast majority of patients; however, coverage is not complete and may be lowest at start of ESRD. However, there is very strong agreement in VA reported on the CMS-2728 and in CW. This study also demonstrates near completeness of CMS Form 2728 with respect to VA information at start of HD.

Funding: NIDDK Support
2014 onward we adopted a monthly Qa screening program using a Qa=1000 ml/min for stenosis repair & a drop inQa>25% for detecting & repairing restenosis. This led to a significant drop of thrombosis rate from 0.70 [95%CI 0.41-1.11] (during the 2012-2013 period in which screening was based on bimonthly VAPR and quarterly Qa measurements and stenosis repair triggered as per guidelines, by a VAPR:0 or a Qa=600 ml/min) to 0.11 [95%CI 0.01-0.40] event/graft-y (p=0.005), at a comparable elective angioplasty rate (0.71 [95%CI 0.46-1.04] vs 0.77 [95%CI 0.43-1.27] event/graft-y, p=ns).

Conclusions: Our comparative study suggests that QA is the best predictor of graft patency & QA surveillance using a QA=1000 ml/min threshold allows for appropriate and timely stenosis repair & may contain the risk of thrombosis.

TH-PO851
The Impact of eGFR at Pre-HD Access Surgery on the Likelihood of Starting Hemodialysis with a Mature Vascular Access
Alain Albalas, Timmy C. Lee, Michael Allon. Nephrology Dept, UAB, Birmingham, AL.

Background: The optimal timing of pre-dialysis vascular access surgery is uncertain. If the access is placed too late, it may not be ready for use; if it’s placed too early, it may not be needed. The optimal timing may differ for AVF vs AVG. We evaluated the association of eGFR at access placement with (1) likelihood of starting HD, and (2) likelihood of a mature access at HD initiation.

Methods: We retrospectively queried a prospective computerized access database to identify patients with pre-HD access surgery (301 AVF and 64 AVG placed between 2006-12) with an eGFR recorded on the surgery date. Patients were stratified into 4 eGFR groups (<10, 10-14, 15-19, >20 ml/min). For each patient we determined (1) whether dialysis was initiated within 2 years, and (2) whether the permanent access was used on the first HD session.

Results: Overall, 208 (or 69%) of pts with pre-HD AVF surgery initiated HD within 2 years, but the proportion varied by eGFR at surgery (90, 81, 64, and 47% for eGFR <10, 10-14, 15-19, and >20 ml/min).

Conclusions: There are tradeoffs in the timing of pre-HD AVG surgery. A higher eGFR is associated with a lower likelihood of initiating HD in 2 years, but a higher likelihood that the AVF will be used on the first HD session. The optimal balance is achieved at an eGFR of 15-19 ml/min. In contrast, the optimal timing for pre-HD AVG surgery is an eGFR of 10-14 ml/min. Late placement of an AVF may be a catheter-sparing strategy.

TH-PO852
Economic Burden to Dialysis Providers of Central Venous Catheter (CVC)-Related Blood Stream Infections (BSI) and Occlusions Among Incident Hemodialysis (HD) Patients
Steven M. Brunelli,1 Wendy Turenne,1 Scott Sibbel,1 John Alan Laich,1 Antony E. Pfaffle.2 1DaVita Clinical Research, Minneapolis, MN; 2Internal Medicine, Dept of Internal Medicine, Kidney Research Inst, Anyang, Korea; 1Internal Medicine, Shamyook Medical Center, Seoul, Korea.

Background: Complications of CVCs may have economic consequences for dialysis providers derived from opportunity costs for missed dialysis treatments and increased use of bundled medications. We sought to quantify this financial burden among incident patients at a large dialysis organization (LDO).

Methods: We considered patients who began HD via a CVC between Jan 2013 and Dec 2014. In parallel analyses, patients who developed BSI (N=3269) or occlusion (N=676) during the first 6 months of dialysis were matched to control CVC-HD patients who did not. Missed HD treatment rates and medication utilization were considered from date of BSI/occlusion (or corresponding date for controls) for 180 days or until censoring for death, morbidity, or loss to follow up. Costs were derived using payer-specific remuneration rates (missed treatments), LDO acquisition costs (IV iron, ESA) and average wholesale prices (antibiotics, thrombolytics). Differences were estimated using linear mixed models including fixed effects for exposure status and month, adjusted for covariates that were imbalanced at baseline.

Results: CVC-related BSI was associated with significantly greater ESA utilization (59.33 vs 49.85 U/month, cases vs controls), IV antibiotic use (41.8% vs 6.0%) and missed HD treatment rate (1.95 vs 1.36 missed treatments/patient-month). This translated to a mean incremental cost of $5397 per patient per month. CVC occlusion was associated with increased thrombolytic use (10.9% vs 4.2%) but no significant difference in costs.

Conclusions: CVC-related BSI is a potent cost driver for dialysis providers with incremental costs of ~$400/month over a 6-month time horizon. No appreciable economic consequences of CVC occlusion were observed.

TH-PO853
Obesity Related Decrease in Intraoperative Blood Flow Is Associated with Maturation Failure of Radiocephalic Arteriovenous Fistula
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Background: Significant arteriovenous fistula (AVF) maturation is often challenging in obese patients. Optimal initial intraoperative blood flow (IOBF) is essential for adequate AVF maturation. This study was conducted to elucidate the effect of obesity on IOBF and radiocephalic AVF maturation.

Methods: Patients who newly created radiocephalic AVF were included (n=252). Obesity was defined as a baseline BMI>25 kg/m², and primary maturation failure was defined as the failure to use AVF successfully by 3 months after its creation. IOBF was measured immediately after construction of AVF using a VeriQTM system.

Results: The mean BMI was 24.1±3.9 kg/m², and the prevalence of obesity was 31.3%. Particularly, 8.3% (21 patients) were BMI > 30 kg/m². Primary maturation failure occurred in 100 (39.7%) patients and an IOBF < 190 mL/min was closely associated with the risk of maturation failure (relative risk, 3.05; 95% CI, 1.52–6.11). Compared to non-obese patients, obese subjects had a significantly higher prevalence of diabetes and elevated hs-CRP levels, whereas diameters of vessels were similar. When the patients were further divided into 3 groups as the BMI ≤25, 25-29.9, and ≥30 kg/m², patients in higher BMI groups had significantly lower IOBF and higher maturation failure rate. According to multivariate analysis, the statistically significant variables that determined maturation failure were obesity, previous vascular disease, increased hs-CRP levels, and IOBF < 190 mL/min.

Conclusions: Obese patients had a significantly lower IOBF, and both obesity and low IOBF contributed to the primary maturation failure of AVF. Obesity-associated inflammation and atherosclerosis might play roles in this association.

TH-PO854
The Impact of Vascular Access on Hemodialysis Patient Survival and Risk Analysis
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Background: Hemodialysis is the most common dialysis modality worldwide. However, the impact of different types of vascular access on hemodialysis patient survival has not been investigated in a large scale study. Therefore, we retrospectively reviewed the survival of hemodialysis patients in our center and analyzed the impact of vascular access on their survival. Other potential risk factors were also studied.

Methods: From 2001 to 2010, patients, who aged more than 40 years old and received regular hemodialysis in our center for at least 3 months, were included into this study. A total 916 patients were enrolled. The mean followed up interval were 4.4± 2.5 years. Among them, 51.1% were male, while 48.9% were female. These patients were divided into three groups according to their vascular access. Group A: patients used either native arteriovenous fistula or arteriovenous graft at the all time and dialysis catheter had never been used during the whole study period. Group B: patients used either native arteriovenous fistula or arteriovenous graft as their vascular access most of the time but they had used dialysis catheter at least once during study period. Group C: patients used dialysis catheter as their vascular access and arteriovenous shunt had never been established during the study period. Other survival associated factors were analyzed by using univariate and multivariate factor analysis.

Results: The results showed that group C patients had significantly worst survival rate (P<0.0001). The group B patients also had significantly worse survival rate when compared to group A and group C.
with group A patients (P = 0.0001). The hazard ratio was 1.71 (1.31-2.24) for group B and 3.56 (2.08-6.05) for group C when compared to group A patients. Multivariable analysis showed that the associated risk factors for patient survival were male sex, diabetes mellitus, low albumin, high hsCRP, and abnormal AST level.

**Conclusions:** The use of dialysis catheter imposed high risk for patient mortality on top of other associated risk factors. Early establishment of vascular access can eliminate this risk factor and improve patient outcome.

**TH-PO855**

Early Experience with a Novel Device for Ultrasound-Guided Management and Cannulation of Hemodialysis Vascular Access

William D. Paulson, 1 Deborah J. Brouwer-Maier, 2 Lillian A. Pryor, 3 John Jason White, 1 Laura L. Mulloy, 1 Lu Y. Huber, 1 Matthew J. Diamond, 1-4 Charlie Norwood VAMC & Georgia Regents Univ, Augusta, GA; 1,4 Fresenius Medical Care, Waltham, MA.

**Background:** The vascular access continues to be the Achilles Heel of dialysis. Methods that facilitate easier management and cannulation of accesses are needed. We describe early experience with a novel ultrasound device.

**Methods:** The Sonic Window (Analogic Corp, Peabody, MA, USA) is designed to assist management of vessels in a variety of contexts. It differs from conventional ultrasound in that it provides a coronal view of vessels that yields determination of characteristics such as depth and luminal diameter, and assists in cannulation for dialysis. We have initiated a program in 4 FMC dialysis units which is designed to identify its role and limitations.

**Results:** Two experts in the use of the Sonic Window have trained dialysis staff in the 4 FMC units. Staff have successfully cannulated 33 AV fistulas and synthetic grafts. Set up and use of the device generally adds an extra 1-3 minutes to cannulation time. Staff are able to easily visualize advancement of dialysis needles into the vessel lumen (figure).

**Conclusions:** Our early experience supports the concept that Sonic Window is a significant advance in managing and cannulating accesses in both routine and difficult situations.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care

**TH-PO856**

Modifiable Risk Factors Affecting the Outcome Hemodialysis Graft

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**Background:** Arterio-venous graft (AVG) for hemodialysis has poorer outcome than arterio-venous fistula (AVF) with its frequent stenosis and thrombosis. We investigated modifiable risk factors affecting the outcome of AVG.

**Methods:** A single-center cohort of 254 patients (pts) receiving AVG for hemodialysis access from Sep 2010 to Oct 2014 were included. Demographics, laboratory data, comorbidities, and medications were collected from the medical records. Surgical factors related to AVG operation including the type and diameter of connected vessels, graft site, and type of operation (elective or emergent) were also recorded. End points was the interval from initial access formation to any intervention intended to restore patency (primary patency, days) and the total access survival duration (secondary patency, days).

**Results:** Data of 225 pts were analyzed. During the follow-up period, 139 (62%) pts received intervention and 45 (20%) pts underwent permanent failure. Survival analyses using Kaplan-Meier method was shown in the figure. In multivariate analysis, primary patency duration was associated with RAS inhibitor (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.37-2.06), and upper arm graft (HR 0.62, 95% CI 0.40-0.94). Secondary patency duration was associated with serum albumin level (HR 0.28, 95% CI 0.13-0.61), diastolic blood pressure (BP) (HR 0.93, 95% CI 0.89-0.98) and warfarin (HR 5.80, 95% CI 2.04-16.46).

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

288A
Conclusions: A DBP > 77 mmHg prior to surgery may be considered as a key prognostic indicator of the Brescia-Cimino procedure.

Funding: Government Support - Non-U.S.

TH-PO858
Vascular Access Outcomes following Peritoneal Dialysis to Hemodialysis Transition
Timmy C. Lee, Mae Thamer, Qian Zhang, Yi Zhang, Michael Allison. 1 Univ of Alabama at Birmingham; 2 Medical Technology and Practice Patterns Inst.

Background: Few studies have evaluated vascular access (VA) use following transition from PD to HD. Our goal was to examine short-term VA utilization following PD to HD transition.

Methods: Using USRDS and Medicare claims data from July 2010-December 2012, we identified 3,565 incident Medicare-insured PD patients who were >18yrs and initiated dialysis between July 2010-June 2011. Patients had at least one dialysis claim within 90 days of dialysis initiation and were followed for 1 year until one of the following events: switched to HD, kidney transplant, death, or end of follow-up. We used Cox-regression models to examine the association of risk factors and switching to HD, with death and transplantation used as competing events.

Results: 991 (27.8%) patients switched from PD to HD during the 1 year follow-up. Of these, 46% switched to HD within 90 days of dialysis initiation and 66% by 6 months. The median switch time was 114 days (IQR: 32-226). Patients with cardiovascular disease (Adjusted Hazard Ratio (HR) 1.25, 95% CI 1.10-1.43), COPD (HR 1.29; 95% CI 1.01-1.66), and without pre-dialysis nephrology care (HR 1.46; 95% CI 1.21-1.76 versus those with >12 months nephrology care) were more likely to switch from PD to HD. After switching from PD to HD, 89% used a catheter, 6.6% AVF, and 1.9% AVG. 90 and 180 days after switching to HD, 71% and 50% of patients, respectively, who remained on HD still used a catheter as their VA.

Conclusions: The majority of patients transitioning from PD to HD initiate HD with a catheter. 50% dialyze with a catheter at 6 months. This highlights the need for VA planning in patients with failed PD to ensure timely transition to permanent VA.

Funding: Private Foundation Support

TH-PO859
Temporal Trends in Pre-Hemodialysis Vascular Access Creation in Elderly Patients with CKD
Timmy C. Lee, Mae Thamer, Qian Zhang, Yi Zhang, Michael Allison. 1 Univ of Alabama at Birmingham; 2 Medical Technology and Practice Patterns Inst.

Background: Optimal timing of pre-dialysis vascular access (VA) creation remains unclear. Elderly CKD patients with high co-morbidity are more likely to die before starting HD, so deferring VA creation may be reasonable. We assessed whether nephrologists have started selecting healthier elderly patients for pre-HD VA surgery.

Methods: Using Medicare claims data we identified 3418 elderly patients (aged ≥70 years) with CKD undergoing pre-HD VA creation in 2004 to 2009, and divided them into 3 time cohorts (2004-05, 2006-07 and 2008-09). For each temporal cohort, we assessed the likelihood of initiating dialysis during 2 years of follow-up after VA surgery. We collected data on cardiovascular co-morbidities and cardiovascular events prior to VA surgery and after dialysis initiation to determine if there were significant changes in these variables during the 3 time cohorts.

Results: During the 3 consecutive time periods, the proportion of patients dying before initiating HD decreased by 28%, the proportion surviving without HD increased by 31%, whereas the proportion initiating HD remained constant (p<0.005).

Concomitantly, during the 3 consecutive time periods there was a progressive decrease in patients with history of PVD (66.5 to 59.7%, p<0.005), CHF (47.0 to 35.8%, p<0.005), and prior MI (6.5 to 3.3%, p<0.0001). Among patients who initiated dialysis, there was a progressive decrease in the proportion of patients with a CHF (38.8 to 26.0%, p=0.001) or MI (5.4 to 2.6%, p<0.01) event in the first year after dialysis.

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

TH-PO860
Hemodynamic Changes in Arteriovenous Fistula During Dialysis
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Background: Optimal blood flow velocity (BFV) in arteriovenous fistulas (AVF) to prevent neointimal hyperplasia is yet to be determined. We have hypothesized that changes in BFV and diameter in a brachiocephalic fistula (BCF) are affected by fistula maturation and blood flow induced during hemodialysis.

Methods: Eight subjects with primary BCF participated. Doppler BFV was measured pre-dialysis and during dialysis at 250, 350 and 450 mL/min blood flow for up to 14 months. BFV was measured in the straight portion of the cephalic vein 10 cm proximal to the cephalic arch. The relationship between BFV and diameter was examined using a linear mixed effects model. Computational modeling using venography was performed at 3 and 12 months.

Results: The change in measured diameter and BFV showed an inverse relationship with a significant association at baseline (p=0.0074) and 350 mL/min dialysis blood flow (p=0.0092). The computational model of the cephalic arch in one subject showed a 4 fold increase in Reynolds number with a dramatic recirculation region shown by a swirling eddy at the upper elbow of the arch.

Conclusions: From 2004-2009, there has been a progressive decrease in cardiovascular co-morbidities in elderly CKD patients undergoing pre-HD VA surgery, and this has been associated with a decrease in patients dying before HD and in patients with cardiovascular events after starting HD. Clinicians are becoming more selective in pre-HD placement of VA in this patient population.

Funding: Private Foundation Support

TH-PO861
Arteriovenous Fistula (AVF) Maturation Among Hemodialysis (HD) Patients: Results from the USRDS Rajiv Saran,1 Sarah Bell,1 Brett W. Plattner,1 Douglas E. Schaubel,1 Sudipta Dasmunshi,1 Purna Mukhopadhyay,2 Jeffrey Pearson,2 Ronald L. Pisoni,3 Kenneth J. Woodside,4 Univ of Michigan; 5 Arbor Research Collaborative for Health.

Background: AVF are considered the gold standard for HD vascular access, but require time to mature and may not adequately develop, resulting in prolonged central venous catheter (CVC) use. We describe AVF survival from placement until time to first use for prevalent HD patients in the US.

Methods: We examined HD patients with new AVF placements during 2013 using Medicare claims. Failure of maturation was identified by non-use following placement using CROWNWeb (CW) where patient access use is reported monthly by the facility. Patients were followed until end 2014. We assessed the relationship between patient characteristics and time-to-first-use of AVF with a Cox model.

Results: In 2013, 51,561 AVF were placed among 42,160 HD patients followed through 2014. No subsequent evidence of use occurred in 44.3% of the placements. Of successfully used AVF, median time to first use was 113 days. Older age groups were incrementally associated with lower probability of using AVF. Pts in the 0-21 and 22-44yr groups (HR=1.23 [95% CI=1.06-1.44], and 1.06 [1.03-1.11], respectively), were more likely to use AVF’s compared to the 45-64yr group (ref). Sex (Female; Fig. 1a), race (e.g., Black; Fig. 1b), comorbidity (cardiovascular disease, peripheral artery disease, diabetes, needing assistance or institutionalized status), vintage <1year, CVC and/or AV Graft use at incidence, were also associated with lower probability of AVF use.

This region, present at baseline and 3 months is much deeper at 12 months and with increased dialysis blood flow rate of 450 mL/min.

Conclusions: In patients with BCF, as the AVF matures and with increased dialysis blood flow, an increase in diameter of the cephalic vein with subsequent decrease in BFV is observed. Increased blood flow during hemodialysis evokes recirculation eddy’s which may result in endothelial damage and subsequent intimal hyperplasia unless the arterialized vein is able to adapt and remodel to the pressures and flows that are generated during hemodialysis.

Funding: NIDDK Support

This dataset is intended for research purposes only and is not intended for commercial use. All information is provided "as is" without warranty of any kind. Use of the data is subject to the terms of use and data use policy. The data provider reserves all rights.
Conclusions: We have characterized AVF maturation in a national US sample and identified important associations with multiple patient-level factors. Research is urgently required into the importance of patient, region and practice factors that could improve AVF placement and maturation, decrease CVC use, to improve patient outcomes and experience.

Funding: NIDDK Support

TH-PO862

Eldest Age Does Not Affect Long-Term Survival of Non-Transposed and Transposed Upper Extremity Arteriovenous Fistulae

Neville R. Dosslabhoy,1 Peter Van,1,2 Renu Gupta,1,2 Clifton Frilot,2 *Nephrology, Veterans Affairs Medical Center, Shreveport, LA; 1LSU Health, Shreveport, LA.

Background: The Fistula First initiative has successfully increased the placement of arteriovenous fistulae (AVF) for vascular access. Some authors have suggested that there is a higher failure rate of AVFs in elderly patients. The purpose of this study was to determine if elderly age influences the overall survival of transposed brachial-basilic fistulae (TBBF) and non-transposed AVFs (NT) placed in the upper extremity (UE).

Methods: Our prospective, computerized clinical database was queried retrospectively to identify the survival outcomes of all upper extremity (UE) fistulae placed in CKD and ESRD patients over a 6-year period at our VA hospital. All fistulae were placed by a single surgeon, hence eliminating inter-operator variability. Patient demographics and comorbidity conditions were noted from the electronic record. The primary end point was permanent failure of the access. Kaplan Meier survival analysis was performed using SPSS.

Results: 230 UE fistulae were placed, which were categorized into two groups by patient age at the time of AVF placement: < 75 years and 75 years and older. The table shows the distribution by access type and age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Type of AVF</th>
<th>TOTAL NUMBER OF AVFs</th>
<th>TOTAL NUMBER OF FAILED AVFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 75 years</td>
<td>NT</td>
<td>124</td>
<td>40</td>
</tr>
<tr>
<td>&lt; 75 years</td>
<td>TBBF</td>
<td>72</td>
<td>19</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>NT</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>TBBF</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

The figure shows that there was no difference in the Kaplan-Meier survival curves for the two age groups when NT and TBBF were analyzed collectively (P=0.833). Furthermore, there was no statistical difference between the survival curves when each group above was analyzed separately (P=0.996).

Conclusions: In conclusion, overall survival was similar for TBBF and NT AVF in our study and was not influenced by elderly age. This finding is contrary to popular opinion and some other reports.

TH-PO863

Peripherally Inserted Central Catheter (PICC) Placement in Hemodialysis Patients with Central Venous Catheters (CVC)

Rita L. McGill, Robin Ruthazer, Klemens B. Meyer, Dana Miskulin, Daniel E. Weiner. *Tufts Medical Center, Boston, MA.*

Background: PICC insertion threatens opportunities for AVF creation and may reduce achievement of AVF. Accordingly, we evaluated the incidence of PICC placement in ESRD patients after starting dialysis and in the 2 years prior to starting dialysis, and recognizing that AVF rates are lower in women, whether PICC rates differed by sex.

Methods: After restricting to patients with pre-dialysis Medicare claims, we used CPT codes to ascertain all PICCs placed during the 2 years before HD initiation and up to 12/31/2012 in the subset of adult HD patients entering USRDS in 2010 or 2011 with CVC as sole vascular access. Accounting for censoring due to death and ESRD modality treatment change, and using Poisson regression to adjust for age, race, BMI, diabetes and peripheral vascular disease, we calculated sex-based incidence ratios (IRR) using PICC per 100,000 patient months.

Results: PICC were placed in 2437 (14.6%) of women and 2250 (12.2%) of men.

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1686</td>
<td>18494</td>
</tr>
<tr>
<td># PICC placed during the 2 years prior to HD</td>
<td>1983</td>
<td>1469</td>
</tr>
<tr>
<td># PICC placed during first year of HD</td>
<td>1438</td>
<td>1330</td>
</tr>
<tr>
<td># PICC placed after first year of HD</td>
<td>567</td>
<td>532</td>
</tr>
<tr>
<td># PICC TOTAL</td>
<td>3988</td>
<td>3331</td>
</tr>
</tbody>
</table>

Compared to men, crude and adjusted IRR of PICC for female sex were 1.35 [1.28-1.41] and 1.34 [1.27-1.41]. Multiple PICC (range = 2 to 14) were placed in 648/2260 (29%) men and 803/2437 (33%) women who had any PICC.

Conclusions: Despite persuasive indications for PICC avoidance, people dialyzing via CVC frequently receive one or more PICC before and even after starting dialysis. The PICC rate was 35% higher in women, a difference not attenuated by adjustment for demographic and clinical factors. More frequent PICC placement may explain some of the lower fistula rate in women. Eliminating frequent PICC placements in patients with CVC may improve achievement of AVF.

Funding: Other NIH Support - NIH/NIDDK

TH-PO864

Arteriovenous Fistula Outcomes in an Elderly UK Population

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Background: The merit of placing arteriovenous fistulas (AVFs) in the elderly is debated in the literature. We sought to investigate AVF outcomes in the population aged ≥ 65 years in our region.

Methods: The Northern Ireland Vascular Access Database incorporates vascular access data on patients with chronic kidney disease stage 4 and 5. The database includes information on all patients ≥ 65 years who had an AVF created during January 2009-December 2014 and had a functional outcome by the 1st March 2015. Functional AVF patency was defined as sustained 2-needle use on haemodialysis for at least 6 sessions. Failure to mature (FTM) was defined by either clinical examination or failure to sustain 6 sessions of 2-needle dialysis.

Results: During the study period 344 patients ≥ 65 years had an AVF created. One AVF failed immediately, three AVFs were ligated due to steal, 56 patients had not started dialysis by the study end-point and records were incomplete for 50 patients. A total of 254 patients (98% White) remained included for functional AVF patency analysis. Table 1: Clinical Characteristics of Patients ≥ 65 years with AVF Patency Outcomes (n=254)

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, median, range)</td>
<td>74, 74, 65-92</td>
</tr>
<tr>
<td>Male gender</td>
<td>170 (67)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>102 (40)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>30 (12)</td>
</tr>
<tr>
<td>Ischamic heart disease</td>
<td>102 (40)</td>
</tr>
<tr>
<td>Lower arm AVF</td>
<td>134 (53)</td>
</tr>
</tbody>
</table>

A total of 150 AVFs (59%) achieved functional patency and 105 (41%) FTM. Binary logistic regression revealed that a lower arm AVF in this elderly population was associated with FTM (p < 0.001, OR 0.23, CI 0.13–0.40).

Conclusions: Given their shorter life-expectancy, the goal of vascular access creation in the elderly should be to create one functional AVF using the best vessels identified. The greater risk of FTM with lower arm AVFs may mean preferential creation of an upper arm AVF if these vessels are better on clinical and ultrasound assessment.

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

Underline represents presenting author.
TH-PO865

Type of Vascular Access and Mortality in Japan

Toshihiko Ozeki, Shun Minatoguchi, Hideaki Shimizu, Yoshito Fujita, Daijo Inaguma.

Background: The National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) guidelines have recommended the use of AVF at dialysis initiation of dialysis. However, it has been reported that the dialysis environment has been significantly different between Japan and the United States, and there are few people who continue hemodialysis with CVVs in Japan. The aim of this study is to examine the association between type of vascular access at dialysis initiation and mortality in Japan.

Methods: This study is retrospective, multicenter, cohort study which data was collected by “Aichi Cohort study of Prognosis in Patients” (AICOPP) newly initiated into dialysis. 18 tertiary care centers in Japan participating in the “AICOPP”. This study enrolled 1,525 patients who started maintenance dialysis between October 1, 2011 and March 31, 2014. After exclusion of 129 patients who started peritoneal dialysis or without data, 1396 (87.1%) patients were enrolled. Cox regression was used to determine the effect of access type on total mortality. Type of vascular access was divided into four categories: AVFs, AVGs, CVVs changed to AVF during the course (CAVF), CVVs changed to AVG during the course (CAGV).

Results: This research showed prevalence of type of blood access in Japan.

Under multivariate analysis, CAVGs had a higher risk of mortality compared with AVFs group [hazard ratio (HR): 2.408, p value: 0.003]. No significant differences were observed compared AVFs with AVGs [hazard ratio (HR): 1.466, p value: 0.219] and CAVFs [hazard ratio (HR): 1.222, p value: 0.389].

Conclusions: As it is known, high AVF use was seen in Japan. Compared with AVFs, using CVVs changed to AVG during the course is associated with higher risks of mortality.

TH-PO866

Comparison of Arteriovenous Fistula and Arteriovenous Graft on Patient Survival and Access Patency in Non-Elderly versus Elderly Population

Hoon Hoon Minatoguchi, 1 Hideaki Shimizu, 1 Naoto Kakita, 2 Takeshi Nakanishi. 1 Div of Nephrology, Dept of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; 2 Vascular Access Center, Tanaka-Kitanoda, Japan.

Background: Arteriovenous fistula (AVF) is generally known to be the ideal option as a vascular access. However, this consensus can be challenging in elderly population.

Methods: From August in 2008 to April in 2014, 1452 adult incident hemodialysis patients were included from Clinical Research Center registry for ESRD prospective cohort, from 31 centers in the South Korea.

Results: In the whole population, AVF vs. AVG use was associated with the better patient survival only in male (p < 0.001) and DM (p = 0.004) patients. Multivariate Cox regression analysis showed AVG (vs. AVF; odds ratio [OR] 2.308, 95% confidence interval [CI]: 1.013–4.829; p = 0.026), catheter (vs. AVG; OR 10.659, 95% CI: 5.379–21.119; p < 0.001) and age (OR 1.035, 95% CI: 1.012–1.058; p = 0.003) were significantly associated with poor patient survival. In the elderly patients (≥ 65 years old), the survival benefit by AVF use also existed in only male (p = 0.001) and DM (p = 0.009) patients, but AVG compared with AVF showed better access patency only in female (p < 0.001) and DM (p = 0.01) patients. Multivariate Cox regression analysis in the elderly population showed AVF (vs. AVG; OR 3.158, 95% CI: 1.080–9.238; p = 0.036), male (vs. female; OR 3.941, 95% CI: 1.031–15.066; p = 0.045) and the presence of peripheral vessel disease (OR 4.659, 95% CI: 1.389–15.626; p = 0.013) were significantly associated with poor patient survival.

Conclusions: As it is known, high AVF use was seen in Japan. Compared with AVFs, using CVVs changed to AVG during the course is associated with higher risks of mortality.

TH-PO867

Abnormality of Fibrinolysis as well as Coagulation Were Associated with Second Patency Rates of Vascular Access in Hemodialyzed Patients

Yukiko Hasuiku, 1 Naoto Kakita, 2 Takashi Nakanishi. 1 Div of Kidney and Dialysis, Dept of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; 2 Vascular Access Center, Tanaka-Kitanoda, Japan.

Background: Vascular access (VA) is essential for the HD patients. However, VA is often occluded even after the percutaneous-transluminal angioplasty (PTA). There is increasing evidence indicating the importance of the fibrinolysis system (i.e., plasminogen activator-inhibitor-1 (PAI-1) level) in the progression of vascular disease. We intended to clarify whether coagulation and fibrinolysis might be associated with VA failure after PTA.

Methods: Blood samples were taken from 262 HD patients at the PTA. Thrombin/anti-thrombin (TAT) as a marker of coagulation, D-dimer, FDP and of fibrinolysis system, and laboratory data were measured. Blood flow volume of VA was evaluated by Doppler ultrasonography before PTA. The end point was the re-vascularization or re-operation of VA during the observational period after PTA. The results were analyzed using univariate and multivariate Cox regression analyses.

Results: Age of patients was 70.6±9.7 years, and 121 patients (46.2%) have native arteriovenous fistula (AVF). During follow-up period, re-PTA was performed in 33 patients and re-operation in 28 patients. Native AVF, higher blood flow volume (≥500 ml/min), lower TAT (<3 mg/ml), and higher PAI-1 (≥7 ng/ml) were associated with good patency rates. The Kaplan–Meier analysis showed both higher TAT (p=0.0026) and lower PAI-1 (Figure 1) were significantly associated with VA failure. Cox regression analysis revealed that higher TAT (HR 2.140, 95%CI 1.288–3.556, p=0.0033) and lower PAI-1 (HR 2.322, 95%CI 1.390–3.800, p=0.0013) were related to VA failure event.

Conclusions: The present research indicates that VA failure after PTA might be associated with abnormality in the fibrinolysis system as well as activated coagulation.

TH-PO868

Early Hemodynamic and Geometric Changes in Brachiocephalic Fistula Graft

Matthew S. Hammel, Kevin Cassel, Michael Boghosian, Jane E. Hines, Syedaekwa Watson, M. Javid Mahmoudzadeh. 1 Medicine/Nephrology, Univ of Chicago; 2 Dept of Mechanical, Materials and Aerospace Engineering, Illinois Inst of Technology; 3 Dept of Public Health Sciences, Biostatistics Laboratory, Univ of Chicago.

Background: An arteriovenous fistula is the optimal vascular access for hemodialysis. A brachiocephalic fistula (BCF) is often placed in the upper arm to provide effective dialysis, but unfortunately cephalic arch stenosis (CAS) commonly develops leading to access failure. We hypothesized that a contribution to fistula failure is low wall shear stress (WSS) resulting from changes that occur in the cephalic arch because of alteration in post-fistula creation hemodynamics.

Methods: Twenty-two subjects with advanced renal failure had BCF placed. The following procedures were performed at mapping (pre-operative) and fistula maturation (8-32 weeks post-operative): venogram, Doppler to measure venous blood flow velocity, and whole blood viscosity. Geometric and computational modeling was performed to determine stress (WSS) resulting from changes that occur in the cephalic arch because of alteration in post-fistula creation hemodynamics.

Results: Blood flow velocity, venous diameter, and regions of low WSS were shown to increase in subjects by the time of maturation (p < 0.05). The percent of low WSS was linearly related to an increase in blood flow velocity (p < 0.01). Although the mean global measures in curvature and asymmetry remained unchanged from baseline to time of maturation, the change fell for shorter time to maturation and rose for longer time to maturation (p = 0.52; p = 0.01), across the regression line at 15–16 weeks.

Conclusions: The maturation process of an AVF introduces geometric effects in arch curvature and asymmetry. Hemodynamic changes increase the percentage of low WSS between parameters was examined using univariate (Kaplan-Meier methods) and Cox regression analyses.
Dilator-Assisted Banding and Beyond: Proposing an Algorithm for Managing Dialysis Access-Associated Steal Syndrome

Showwen Wang, AKDHC Access Centers, Arizona Kidney Disease and Hypertension Center; Phoenix, AZ.

Background: Dialysis Access-associated Steal Syndrome (DASS) is a major complication of arteriovenous dialysis accesses and its proper management is of critical clinical importance. However, the reported approaches are diverse and general consensus is lacking. Guided banding approaches have gained popularity, as they are minimally invasive. This report analyzes the clinical outcome of Dilator-assisted Banding (DAB), a simple technique initially described by the author for managing DASS.

Methods: This study included 30 patients that underwent DAB for DASS due to excessive dialysis access flow.

Results: Of the 30 patients: 29 had upper arm fistulas or grafts and 1 had a forearm fistula; 23 had arteriogram - 3 of which required angioplasty ± stent for feeding artery stenosis. The DAB procedures included: intraluminal DAB (12/30), extraluminal DAB (14/30) and open fistula revision plus DAB (4/30). After DAB, the average severity scores of ischemic symptoms was reduced from 2.8 ± 0.4 to 0.2 ± 0.4 for the fistula group (n=24, p<0.001) and from 3.0 ± 0.0 to 1.2 ± 1.2 for the graft group (n=6, p=0.041). Of the 24 patients with fistula, 19 had resolution of ischemic symptoms and 5 had minimal residual symptoms while 3 had finger necrosis that healed after DAB. Of the 6 patients with graft, 2 had resolution, 2 had minimal residual and 2 had no change of ischemic symptoms. These two DAB-ineffective patients underwent proximalization of arterial inflow (PAI) revisions that resulted in resolution of ischemic symptoms. During follow-up of 18.7 ± 14.5 months (range 1-50), all dialysis accesses remained functional. At 24-month post-DAB, the primary patency, primary-assisted patency and secondary patency rates of the fistula group were 72%, 91% and 100%, respectively.

Conclusions: DAB is a simple, effective and versatile approach for managing DASS due to excessive flow, especially in patients with fistula. In patients with failed banding, PAI can be effectively used for rescue. Based on the data in this study and the literature, an algorithm is proposed for managing DASS.

Outcomes of Vascular Access Creation in Incident Hemodialysis Patients in Singapore

Nicholette Geh,1 Chieh-shuai Tan,2 Shaan Achudan,1 Yi Liang Tan,1 Kian Guan Lee,1 Hui-Lin Choong,2 Tze tce Chong,3 National Univ of Singapore; 1Renal Medicine, Singapore General Hospital; 3Vascular Surgery, Singapore General Hospital.

Background: Hemodialysis is the main modality of renal replacement therapy for end-stage renal disease (ESRD) patients in Singapore. Vascular access is critical for effective therapy. This study evaluated the impact of pre-operative vein mapping on vascular access creation in patients newly initiated on hemodialysis in Singapore General Hospital.

Methods: Data of ESRD patients initiated on hemodialysis from January 2010 to December 2012 were retrospectively collected from electronic medical records. 708 patients (mean 62.8 ± 12 years old, 61% male, 71.3% Chinese) who underwent surgical creation of their first vascular access were followed up for a mean of 2.3 ± 1.2 years.

Results: 694 (98%) arteriovenous fistulae (AVF) and 14 (2%) arteriovenous grafts (AVG) were created. Successful AVF cannulation was established in 543 patients (78.2%). After 6 months, 511 (73.6%) remained patent with 43.5% (295/694) primary and 30.1% (208/694) secondary patency. 216 upper arm and 478 forearm AVF were created. Upper arm AVFs had significantly higher maturation rates (85.0% vs 76.4%, p = 0.011). Pre-operative vein mapping was performed in 42.5% (295/694) of patients. The mean vein diameter was 2.44 ± 0.82mm. Maturation rates with and without vein mapping were 72.2% and 82.7% respectively (p = 0.001). Between vein diameters <2 mm and 2mm, there was no statistical difference in maturation rates (71.3% vs 72.6%; p = 0.887) or median maturation time (66.5 ± 77 days; p = 0.280). There was no statistical difference in maturation rates between veins of <2 mm and 2 mm in both forearm (p = 0.676) and upper arm AVF (p = 0.722). On univariate analysis, male gender (p = 0.001) and the presence of good post-operative thrill (p = 0.001) were associated with successful maturation in newly created AVF. AVF created by trainees also had better maturation rates compared to consultants (83.5% vs 76.2% p = 0.027).

Conclusions: In conclusion, successful vascular access creation can be accomplished in majority of ESRD patients. This is independent of vein size or the need for pre-operative vein mapping.

Uremia Induced Gene Expression in a Mouse Model of Arteriovenous Fistula Stenosis


Background: Arteriovenous fistula (AVF) non-maturation remains a huge clinical problem resulting in significant morbidity and mortality. Unfortunately most animal models of AVF stenosis do not incorporate uremia. As a result, the molecular mechanisms by which uremia contributes to AVF dysfunction remain unknown. The aim of this study was to assess the impact of uremia on the expression of genes associated with the pathogenesis of AVF dysfunction using a uremic mouse model of AVF stenosis.

Methods: Mice were made uremic by cauterity of one kidney, followed by contralateral nephrectomy. After weeks, an end to side anastomosis was created between the jugular vein and carotid artery. Contralateral vessels served as controls. Vessels were harvested after 14 days, and RNA isolated from the AVF venous segment. Gene expression of different mediators was measured with qPCR. Data was analyzed from control vein; uremic vein; veins of non-uremic AVFs; and veins of uremic AVFs.

Results: Significant upregulation in the expression of monocyte chemotactic protein-1 (MCP1), NAPDH Oxidase (NOX4), and E-Selectin were found within the veins of AVFs compared to wild-type control vessels (P<0.017 for each gene). Compared to normal vein, MCP1 expression was increased 4.4, 14.0, and 49.1 fold in uremic vein, the non-uremic AVFs, and uremic AVFs respectively. Paradoxical increases in Krüppel-like factor-2 (KLF-2) were also seen in uremic vessels compared to wild-type veins (P<0.017).

Conclusions: In summary, marked upregulation of the proteins MCP-1, NOX4, and E-Selectin were seen with uremia, and some of these (MCP-1) were further elevated within the AVF. Of note, the flow sensitive gene KLF2 was also elevated in uremia, but was attenuated in the setting of an AVF. These preliminary findings suggest key pathways by which uremia could exacerbate AVF dysfunction and future targets for the prevention and treatment of AVF maturation failure.
In-Patient Permanent Access Is Associated with Reduced Catheter Time for Emergent Start Hemodialysis Patients  Catherine A. Moore,1 Richard E. Wing,1 Scott E. Liebman.1 Medicine-Nephrology Div, Univ of Rochester; Rochester, NY; 1Aurora Medical Group, Marinette Menominee Clinic, Marinette, WI.

Background: Hemodialysis initiation with a tunneled catheter carries increased risk of morbidity and mortality. Conversion from a hemodialysis catheter to permanent access at any time is associated with improved outcomes. This study investigates whether a strategy of placing permanent dialysis access in incident HD patients without permanent access while still hospitalized is associated with reduced exposure to hemodialysis catheters.

Methods: We conducted a retrospective cohort study of ESRD patients initiating Hemodialysis with a catheter while hospitalized at a single University Hospital Medical Center from October 2010 through June 2013. Patients were divided into two groups: those with permanent access placed during the hospitalization (N = 22) vs. those discharged without permanent access (N = 67). Our primary endpoint was removal of the hemodialysis catheter.

Results: Subjects who underwent permanent access placement while still hospitalized had a median catheter exposure time of 114 days compared with 241 days for those who did not. The median time with HD catheter in place was shorter by 127 days in the group who did not. The median time with HD catheter in place was shorter by 127 days in the group who did not. The median time with HD catheter in place was shorter by 127 days in the group who did not.

Conclusions: The practice of placing permanent access while the patient is still admitted to the hospital is associated with greater likelihood of hemodialysis catheter removal.

Factors Affecting Haemodialysis Arterio-Venous Fistula Maturation

Hannah R. Wilson, Salman Ahmed, Joseph Russell, Nicola Ding, Maggi Steele, Ayeshra Irtiza-Ali, David Makanjuola, Nihil Chitalia. Renal Unit, St. Helier Hospital, Surrey, United Kingdom.

Background: Arterio-venous fistulae (AVF) are the preferred access for haemodialysis (HD). Many AVFs however, fail to mature. We investigated the factors affecting maturation of AVFs in order to identify any characteristics which were predictive of AVF maturation.

Methods: All AVFs created between 2006 and 2014 were reviewed. Data analysis was performed using GraphPad. AVFs were deemed to have failed to mature if by 90 days post-creation, it was not possible to use them for HD. The patients were divided into 2 groups – those who had the AVF created pre-emptively (group 1) and those already on HD at the time of AVF creation (group 2). Characteristics reviewed were age, gender, ethnicity, co-morbidity score, diabetes status and site of AVF.

Results: There were 1876 AVFs created. 954 in group 1 and 922 in group 2. In group 1, 597 patients started HD; 469 (79%) used their AVF for the 1st HD session. In group 2, 330 (36%) used their AVF within 90 days from creation. Group 1 AVFs were more likely to mature than those in group 2. Co-morbidity scores, age, diabetes status and ethnicity had no impact on AVF maturation rates.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mature AVF (n=745)</th>
<th>Non-mature AVF (n=833)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-emptive</td>
<td>415 (55.7%)</td>
<td>241 (28.9%)</td>
<td>*</td>
</tr>
<tr>
<td>Non pre-emptive</td>
<td>330 (40.3%)</td>
<td>592 (71.1%)</td>
<td>*</td>
</tr>
<tr>
<td>Age in years [mean(SD)]</td>
<td>63 ±15.6</td>
<td>64 ±15.6</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td>69% M, 31% F</td>
<td>59% M, 41% F</td>
<td>0.0002</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>56%</td>
<td>55%</td>
<td>ns</td>
</tr>
<tr>
<td>Asian</td>
<td>12%</td>
<td>13%</td>
<td>ns</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>8%</td>
<td>9%</td>
<td>ns</td>
</tr>
<tr>
<td>Not stated</td>
<td>24%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Upper arm AVF</td>
<td>54%</td>
<td>52%</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetic</td>
<td>35%</td>
<td>37%</td>
<td>ns</td>
</tr>
<tr>
<td>Davies co-morbidity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (no co-morbidities)</td>
<td>18%</td>
<td>15%</td>
<td>ns</td>
</tr>
<tr>
<td>1 (1-2 co-morbidities)</td>
<td>68%</td>
<td>68%</td>
<td>ns</td>
</tr>
<tr>
<td>2 (3 or more co-morbidities)</td>
<td>14%</td>
<td>17%</td>
<td>ns</td>
</tr>
</tbody>
</table>

*p < 0.0001 for percentage of mature AVFs in pre-emptive vs non-pre-emptive groups.

Conclusions: Our data show that the timing of AVF creation is important; those formed pre-emptively are more likely to mature than those created when the patient is on dialysis. It is possible that the presence of a dialysis line might delay maturation, especially if it is isplanted to the AVF.

It highlights the importance of prompt referral to nephrology services so that AVFs can be created in a timely manner.

Hand Held Ultrasound Device Solves Vascular Access (VA) Cannulation Problems

Beth Adams, Vivek Soi, Jerry Yee, Lalathaksha Murthy Kumbar. Henry Ford Hospital, Detroit, MI.

Background: The Fistula First Catheter Last workgroup coalition identifies VA cannulation as a fundamental “failure” point in optimizing arteriovenous fistula (AVF) usage. Infiltration from cannulation difficulties result in significant morbidity including loss of VA and cost. Cannulation success is reliant on cannulators’ skill and VA characteristics. Surface marking of VA to aid cannulation is frequently used but lacks real time information. Traditional ultrasound devices are expensive and need skilled operators rendering inapt for routine use in hemodialysis units. Sonic Window© (Analogic Ultrasound) is a coronal mode ultrasound device (CMUD) approved for VA cannulation. We present our early experience in using this novel hand held CMUD for real time guidance of VA access.

Methods: Three patients with cannulation failure defined as inability to achieve 3 needle cannulations leading to tunnel cuffed catheter (TCC) removal were identified. AVF was evaluated initially for 1-2 dialysis sessions with CMUD for course, depth from skin, optimal site for cannulation, needle length and size. Infiltration rates, subsequent procedures and hospitalizations were noted before and after CMUD use and cannulation failure days (days from initial VA clearance for use to TCC removal).

Results:

<table>
<thead>
<tr>
<th>AVF Type</th>
<th>Cannula-</th>
<th>Pre-</th>
<th>Post-</th>
<th>Interventions</th>
<th>Hospitalization</th>
<th>Interventions</th>
<th>Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachio-</td>
<td>basilic</td>
<td>210</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Brachio-</td>
<td>cephalic</td>
<td>206</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radioco-</td>
<td>cephalic</td>
<td>153</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All 3 AVF were successfully cannulated leading to TCC removal within 21 days of CMUD guidance. CMUD usage resulted in no cannulation related complications and no subsequent revision procedures.

Conclusions: CMUD guided cannulation of dialysis access is feasible and safe. Real time ultrasound guidance mitigates cannulation failure and catheter removal.
TH-PO876

Reaching First Dialysis Quickly and Unassisted with Sirolimus Treated Fistulae – Serial Ultrasound Results and Clinical Outcomes

Maria V. DeVita,1 Eric S. Chemla,2 Konstantine B. Kipiani,3 Nutsa K. Beridze,3 Sriram Iyer;3 1Nephrology, Lenox Hill Hospital, New York, NY; 2Vascular Surgery, St. George’s NHS Foundation Trust, London, United Kingdom; 3Vascular Surgery, Georgian Center of Angiology and Surgery, Tbilisi, Georgia; 4Vascular Therapies Inc, Cresskill, NJ.

Background: Neointimal hyperplasia (NH) resulting in a flow limiting stenosis within the juxta-anastomotic segment (JAS) of an AV Fistula (AVF), impairs increase in upstream vein diameter (VD), often requires supplementary procedures and prolongs time to 1st cannulation for dialysis (D). Sirolimus delivered locally to the vessel wall can suppress NH and preserve lumen patency ("sirolimus effect").

Methods: 30 pts (29 on D) undergoing AVF surgery (22 Radiocephalic (RCF), 8 Brachiocephalic fistulae (BCF)) received a Sirolimus eluting collagen implant at and around the JAS. 1st cannulation was based on clinical evaluation.

Results: 18 males, mean age 50.8y, 20% diabetic. Analysis excludes 4/22 RCF that thrombosed 2wks; 18/22 RCF (88%) and all 8 BCF maintained Primary Patency (PP) prior to 1st cannulation (mean 49 days); 13 AVF were cannulated ≤6wks, 74% AVF maintained suitability for D with PP at 12mos. Table shows serial Ultrasound results.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre op</th>
<th>6-8 hours Post op</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCF (n=18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VD Mean (±SD)</td>
<td>2.7 (0.5)</td>
<td>4.0 (0.5)</td>
<td>5.1 (0.8)</td>
<td>5.8 (0.7)</td>
<td>6.1 (0.4)</td>
<td>6.4 (0.4)</td>
</tr>
<tr>
<td>VD change from prior time point</td>
<td>-</td>
<td>63%</td>
<td>16%</td>
<td>14%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>VD ≥6mm n=7</td>
<td>0</td>
<td>2 (11%)</td>
<td>8 (44%)</td>
<td>13 (72%)</td>
<td>18 (100%)</td>
<td></td>
</tr>
<tr>
<td>VD ≥4mm n=13</td>
<td>14 (100%)</td>
<td>16 (100%)</td>
<td>17 (100%)</td>
<td>18 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCF (n=08)

| VD Mean (±SD) | 1.9 (0.6) | 5.4 (0.8) | 6.8 (0.8) | 7.5 (0.9) | 7.9 (1.71) | 8.4 (1.38) |
| VD change from prior time point | - | 38% | 26% | 9% | 5% | 8% |
| VD ≥6mm n=5 | 2 (25%) | 6 (75%) | 8 (100%) |
| VD ≥4mm n=6 | 8 (100%) |

Conclusions: 1.Maximum % increase in VD occurred within 8hrs of surgery with gradual continued increments thereafter. 2.At 4, 6 and 8wks, VD of 6mm was attained by 63% 71% 100% and 74% 74% 100% respectively.

3. 26/30 AVF (87%) maintained PP before first cannulation, time to first dialysis for 13 AVF (50%) was ≤6wks and at 12mos 75% were functional with PP. 4.Results signal a "sirolimus effect" and will be tested in an upcoming randomized trial.

Funding: Pharmaceutical Company Support - CorMedix Inc

TH-PO877

Economic Burden to Medicare of Central Venous Catheter (CVC)-Related Blood Stream Infections (BSI) and Occlusions Among Incident Hemodialysis (HD) Patients

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Background: Episodes of CVC-related BSI and occlusion in HD patients result in hospitalizations and vascular access-related procedures, with attendant increases in costs. We sought to quantify this burden to the payor among Medicare-enrolled patients at a large dialysis organization.

Methods: Patients received HD via CVC during 2011 and were enrolled in Medicare Parts A and B. In parallel analyses, patients who developed BSI (N=1413) or occlusion (N=793) were matched with controls who did not, on the basis of entry month and incident/prevalent dialysis status. Outcomes were assessed from date of BSI/occlusion (or corresponding date for controls) for 6 months or until censoring for modality change, transfer of care, loss of Medicare benefits or death. Comparisons were made using linear (or corresponding date for controls) for 6 months or until censoring for modality change, transfer of care, loss of Medicare benefits or death. Comparisons were made using linear

Results: CVC-related BSI was associated with greater rate of hospitalization (incidence rate difference [IRD], 1.07 events/patient-year) and vascular-related procedures (IRD, 2.87 events/patient-year). Mean per patient per month (PPPM) costs were $2262.40 higher for BSI patients versus controls, driven primarily by increased inpatient costs. CVC occlusion was associated with modestly greater rate of hospitalization (IRD, 0.29 events/patient-year), but substantively greater rate of ambulatory procedures (IRD, 4.00 events/patient-year). Mean PPPM costs were $2354 greater for occlusion patients versus controls, driven by higher ancillary service and procedure costs.

Conclusions: CVC-related BSI and occlusion are potent cost drivers for Medicare. Risk mitigation strategies to prevent BSIs and occlusions should prove to reduce systemic health care costs.

Funding: Pharmaceutical Company Support - CorMedix Inc

TH-PO878

Arteriovenous Fistula Maturation and Medial Collagen Organization Assessed by Second Harmonic Generation Microscopy

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Background: Arteriovenous fistula (AVF) maturation entails vascular dilation to allow increases in AVF blood flow. The required vascular wall distention is likely affected by its microstructure. We hypothesized that the organization of collagen fibers in the medial layer affects vascular dilation and hence AVF maturation. State-of-the-art second harmonic generation (SHG) microscopy and image-analysis algorithms were used to visualize and assess collagen-fiber organization.

Methods: Arteries and veins used for anastomosis were sampled during AVF creation from 128 participants with chronic kidney disease (CKD). Collagen SHG signals in unstained paraffin-embedded tissue sections were acquired under a two-photon microscope at 850 nm excitation, and analyzed for fiber pattern, anisotropy index (AI) and dominant orientation (DA) by 3 independent observers blinded to AVF outcomes. AI ranged from 0 (random radial pattern) to 1 (perfectly aligned fiber network). DA ranged from 0° (parallel to lumen) to 90° (perpendicular to lumen).

Results: Arterial and venous medial collagen fibers demonstrated a total of 5 patterns: parallel to lumen, perpendicular to lumen, track, web, or random (Fig. 1). The parallel and perpendicular patterns had a similar AI (~0.3) which was higher than the AI of the other patterns. However, the parallel pattern had a smaller DA than the perpendicular pattern in arteries (18° vs 70°, p=0.001). AVF non-maturation rate was lower in patients with venous DA >30° vs DA <30° (17 vs 36%, p=0.03).

Conclusions: We have characterized novel vascular medial collagen fiber organization in CKD patients. Moreover, these patterns appear to be associated with the likelihood of AVF maturation.

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

Underline represents presenting author.

294A
Impact of DPP-4 Inhibitors on Hemodialysis Vascular Access Dysfunction

**Background:** Autoimmune arterio-venous fistulae is an optimal vascular access for haemodialysis. Arterio-venous fistula is not faultless and up to 40% of fistulae never mature. In patients with no possibilities to create effective native arterio-venous fistulae haemodialysis with using a proper prostheses gives a chance to avoid a central venous catheter (CVC).

The aim of the study was to evaluate of usefulness polyurethane prosthesis as an emergency vascular access for haemodialysis.

**Methods:** The study involved 23 patients, 18 men and 5 women, at 29 – 83 years. Eight patients were in predialysis period, for 17 patients (2 in predialysis) it was a secondary procedure. All patients had implanted AvFlo prosthesis (Nicast, Israel). There were 5 loops in the forearm and 18 straight segments in the arm. Six patients underwent an urgent operation, because of lack of any vascular access. For others it was an elective operation.

**Results:** The longest observation period was over 36 months. Twenty one grafts were used for hemodialysis within 1-42 days, one prosthesis was removed due to infection, one patient died before initiation of dialysis. All grafts implanted for urgent indications were successfully cannulated within 24 hours. No differences were observed between diabetic and non-diabetic patients.

**Conclusions:** Implantation of polyurethane prosthesis provides an effective vascular access for dialysis and enables avoidance of CVC. Low infection rate improves the final outcome.

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

Underline represents presenting author.
Results: There are 1002 haemodialysis patients; 412 dialyse via a CVHC.

- Total uses / total patients (%) = 94 / 74
- Repeat Alteplase, same CVHC n (%) = 20 / 23
- Median age of CVHC (BQR) = 147 days (77-300)
- Indication (occlusion / Poor Qb) n = 31 / 83

CVHC age was statistically different depending on the indication; occluded CVHC age was 124 ± 22 vs 244 ± 27 days for low Qb (p<0.01). Rescued CVHC age was significantly lower than those in whom the alteplase was unsuccessful (147 ± 18.4 vs 269 ± 35.8, p<0.004). In 48% of patients with an occluded CVHC, flow was restored; the remaining 52% required further intervention. Low Qb CVHC success rate was 60% compared to 38% requiring further intervention, 2% were removed (arteriovenous fistula or transplant). There was no significant difference between success rates depending on the indication (p<0.34).

Alteplase infusion significantly increased litres processed in subsequent dialysis sessions, in whom the indication was low Qb (6.2 ± 1.16 litres, p<0.0001). Overall of all infusions undertaken; 1 month patentity was 56%, 3 months 45% and 6% removed. No patient had an adverse bleeding event as a result of the alteplase infusion.

Conclusions: Alteplase infusion use is common; approximately once a week in our centre. Interestingly, complete occlusion of CVHC occurs early, possibly suggesting rapid growth of fibrin following insertion. Total litres processed improves after an alteplase infusion in over half of patients. This study demonstrates the safety and success rates of an alteplase infusion, providing evidence for its role prior to replacing the CVHC and importance in saving resources.

TH-PO883

Temporal Evolution of Parameters Before and After Initiation of Hemodialysis

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Background: Little is known about the dynamics of clinical and laboratory parameters during the transition between pre-dialysis chronic kidney disease and end stage kidney disease (ESKD). The goal of our research was to explore the temporal evolution of albumin (Alb), systolic blood pressure (SBP) and serum sodium (SNa) by analyzing monthly data before and after hemodialysis (HD) initiation.

Methods: We analyzed all available data from the de-identified Fresenius Medical Care CKD Data Registry to understand progression of clinical and laboratory markers before and after HD initiation. Average values of Alb, SBP and SNa were compared for 12 months prior and after HD initiation using t-test. To estimate the trends of the average values, we fitted a linear regression function through monthly averages.

Results: We studied 136846 patients (64±14 years, 56% male) over 48 months. Average SBP increased prior to HD initiation (1.2 mmHg/year), immediately decreased following HD initiation, and remained lower for the following 12 months (142±22.8 vs 136.1±23.2 mmHg; P<0.05). Before starting HD, Alb was found to be relatively unchanged, but increased after HD initiation (average Alb increased by 0.14 g/dL per year, levels were slightly higher 12 months after HD initiation [3.7±0.5 vs 3.8±0.4 g/dL; P<0.05]). Average SNa pre-ESKD had a declining trend (-0.5 mEq/L per year) and was lower compared to SNa pre-ESKD had a declining trend (-0.5 mEq/L per year) and was lower compared to 0.4 g/dL; P<0.05). Average values of Alb, SBP and SNa were compared for following HD initiation. Average values of Alb, SBP and SNa were compared for the following 12 months (142.4 ± 11.6 vs 136.1 ± 11.6; P<0.05). Overall of all infusions undertaken; 1 month patentity was 56%, 3 months 45% and 6% removed. No patient had an adverse bleeding event as a result of the alteplase infusion.

Conclusions: Alteplase infusion use is common; approximately once a week in our centre. Interestingly, complete occlusion of CVHC occurs early, possibly suggesting rapid growth of fibrin following insertion. Total litres processed improves after an alteplase infusion in over half of patients. This study demonstrates the safety and success rates of an alteplase infusion, providing evidence for its role prior to replacing the CVHC and importance in saving resources.

TH-PO884

Accelerated Arterial Stiffening in Vitamin-K-Antagonist Treated Hemodialysis Patients

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Background: Many hemodialysis (HD) patients are treated with vitamin-K-antagonists (VKA) in order to prevent thromboembolic events. A potential side effect to VKA treatment is an increase in soft tissue calcification due to the inhibitory effect of VKAs on the central (liver) and peripheral (e.g. vascular) carboxylation cycle synthesis of several vitamin K-dependant calcification-inhibiting factors. The aim of the present study was to investigate the impact of VKA-treatment on arterial stiffness in a longitudinal, prospective comparative study.

Methods: Seventy-five HD patients from the SAFIR study with urine output >300 mL/day and HD-vintage ≤1 year were divided into controls (n=67) and VKA-treated (n=8) and followed for one year. The groups were well matched according to age, sex, comorbidity, and intervention (placebo/irbesartan). Arterial stiffness was assessed with carotid-femoral pulse wave velocity (PWV) and pulse wave analysis using the SphygmoCor device.

Results: Blood pressure (BP), PWV, and glomerular filtration rate (GFR) were similar at baseline (controls/VKA-treated) systolic BP: 148±20/145±17 mmHg; PWV: 11.6±3.2/11.0±3.9 m/s; GFR: 53±3±3.5 mL/min/1.73m2. Dialysis treatment and BP-medication were also similar. During follow up, GFR decreased similarly in both groups (P=0.2). There was no significant difference in BP between the two groups over time although BP tended to decrease more in the controls. PWV decreased in the controls -0.9(-1.4; -0.3) m/s; P=0.004 and increased in the VKA-treated 1.6(0.3; 3.2)m/s; P=0.05. Mean difference 12 months between the groups (DUPWV) was: 2.5(0.7; 4.2) m/s; P=0.006. DPWV 3.9 m/s; increased significant after adjustment for ∆GFR, ∆MAP, age at baseline, and ∆BP-medication: 2.2(0.4; 4.0) m/s; P=0.02. Mean differences after 12 months between the groups in heart rate adjusted augmentation index and time to pulse wave reflection were: 7(-2; 15) %; 8(-27; -2) ms; P=0.03 (TR).

Conclusions: Our findings indicate that VKA-treatment increases arterial stiffening significantly. We speculate that vitamin K-dependant calcification-inhibiting factors in HD patients may be inadvertently affected by VKA treatment.

TH-PO885

Associations of Kt/V with Mortality in Hemodialysis Patients by Heart Failure Status

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Background: Kidney failure and heart failure (HF) frequently coexist, a condition called cardiorenal syndrome (CRS). Though HF patients on maintenance hemodialysis (mHD) have high risk of poor outcomes, there is a paucity of data to guide their care. Given the role of uremic toxins in the pathogenesis of CRS, we hypothesized that mortality for mHD patients is lower at higher Kt/V targets.

Methods: Cox regression was used to estimate associations of baseline Kt/V with all-cause mortality (ACM) and cardiovascular mortality (CVM) in phases 1-4 of the Dialysis Outcome and Practice Patterns Study (DOPPS), an international prospective cohort study of mHD patients. Separate models for patients with and without HF (by clinical diagnosis) were stratified by county and DOPPS phase and adjusted for age, gender, race, diabetes and hypertension as comorbidities, dialysis vintage, serum albumin, pre-dialysis systolic blood pressure, and weight. SAS 9.4 was used for analyses.

Results: Among 51,678 mHD patients, mean age was 62.5±14.8 yrs, 41.3% female and 32% had HF. In non-HF patients, Kt/V was inversely associated with ACM and CVM, followed a monotonic pattern. In HF patients, the association was similar for ACM but generally flat for CVM. A sensitivity analysis of Kt/V by sex showed a monotonic decline in both groups for ACM (p<0.001) and a monotonic decline in the controls (p<0.001). Overall of all infusions undertaken; 1 month patentity was 56%, 3 months 45% and 6% removed. No patient had an adverse bleeding event as a result of the alteplase infusion.

Conclusions: Contrary to our hypothesis, higher dialysis adequacy was not associated with longer survival in HF patients. Confounding by health status (patients with more advanced HF) may achieve lower Kt/V because they tolerate dialysis poorly. Further investigation is needed to identify ways to improve outcomes for this high-risk patient population.
TH-PO886

Different Impact of Malnutrition-Inflammation and Metabolic Syndrome on Long-Term Mortality and Cardiovascular Events in Hemodialysis Patients

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Background: Malnutrition syndrome confers an increased risk of cardiovascular disease (CVD) in the general population. The relationship between adiponectins, and clinical outcomes in hemodialysis patients remains controversial. We investigated whether adiponectins, biomarkers of inflammation, nutrition status and clinical features predict the mortality of hemodialysis patients for 6 years.

Methods: We measured baseline plasma total and high-molecular-weight (HMW) adiponectins, tumor necrosis factor (TNF-α), serum high sensitivity C-reactive protein (hsCRP), and clinical characteristics including visceral fat area (VFA) and the Geriatric Nutritional Risk Index (GNRI) in 133 hemodialysis patients.

Results: During the 6-year follow-up period, 41 (30.9%) patients died (heart failure, n = 13; acute myocardial infarction, n = 11; stroke, n = 2; infection, n = 10; and malignant cancer, n = 5). The deceased patients were significantly older, had more prior CVD and diabetes, higher TNF-α and hsCRP levels but lower GNRI, VFA, and total and HMW adiponectin did not significantly differ between the two groups. TNF-α and hsCRP levels and GNRI score were significant for predicting all-cause and cardiovascular mortality in receiver operating curve analyses. The present ROC curve analysis for all-cause 6-year mortality found the predictive value of GNRI for mortality was 96. When stratified by a GNRI score of 96, Cox proportional hazards analyses identified TNF-α as a significant predictor of all-cause mortality (hazard ratio [HR] 1.23, P = 0.038) and hsCRP as a significant predictor of all-cause and cardiovascular mortality (HR 2.32, P = 0.003; HR 2.20, P = 0.012, respectively) after adjusting for age, sex, diabetes mellitus, and prior CVD only in malnourished patients.

Conclusions: These results demonstrate that malnutrition and the inflammatory markers TNF-α and hsCRP, but not metabolic markers, including VFA and adiponectins have a significant impact on 6-year all-cause and cardiovascular mortality in hemodialysis patients.

Funding: Government Support - Non-U.S.

TH-PO887

Associations of the Malnutrition-Inflammation Complex Syndrome with Depression Symptoms, Kidney-Disease Targeted Quality of Life Measures and Mortality in a Hemodialysis Population of Predominantly African Descent

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Background: The malnutrition-inflammation score (MIS) has been used to assess protein-energy wasting (PEW), also named malnutrition-inflammation complex syndrome, in maintenance hemodialysis (MHD) patients. Higher MIS has been associated with poorer outcomes in MHD patients but remains unclear if MIS expands the predictive power for outcomes in relation to its ten components and if the published results may be generalized for populations not targeted by previous investigations. We assessed associations of MIS and its components with mortality and patient-reported outcomes, i.e., health-related quality of life (HRQOL) and depression symptoms in a MHD population predominantly of African descent.

Methods: Prospective cohort (PROHEMO) of 632 MHD patients (92% Black or mixed race) treated in Salvador, Brazil. The predictor was MIS (range: 0-30, higher worse) and GNRI score of 96, Cox proportional hazards analyses identified MIS as a significant predictor of all-cause mortality (hazard ratio [HR] 1.23, P = 0.038) and hsCRP as a significant predictor of all-cause and cardiovascular mortality (HR 2.32, P = 0.003; HR 2.20, P = 0.012, respectively) after adjusting for age, sex, diabetes mellitus, and prior CVD only in malnourished patients.

Conclusions: These results demonstrate that malnutrition and the inflammatory markers TNF-α and hsCRP, but not metabolic markers, including VFA and adiponectins have a significant impact on 6-year all-cause and cardiovascular mortality in hemodialysis patients.

Funding: Government Support - Non-U.S.

TH-PO888

Non-Traditional Risk Factors Predict Atherosclerotic Events in Haemodialysis Patients – Post-Hoc Analyses of the AURORA Trial

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Background: Patients on haemodialysis are at high risk for cardiovascular events, but heart failure and sudden death dominate and atherosclerotic events are less common. The AURORA trial was designed to assess the effect of rosvustatin on myocardial infarction (MI) and death from any cardiac source in haemodialysis patients. We studied predictors of the atherosclerotic, and not all cardiovascular, events in AURORA.

Methods: We re-adjudicated all deaths and presumed myocardial infarctions according to stricter criteria to separate atherosclerotic from non-atherosclerotic cardiovascular events. The readjudicated atherosclerotic endpoint included non-fatal myocardial infarction, fatal coronary heart disease, non-fatal and fatal non-haemorrhagic stroke, revascularisation procedures and death from ischaemic limb disease. Baseline predictors were assessed for the 27% participants of the AURORA trial, and step-wise Cox regression analysis was applied.

Results: During a mean follow-up of 3.2 years, 716 patients experienced a readjudicated atherosclerotic event. Baseline phosphate (HR 1.33; 95% CI 1.16-1.53 per 1 mmol/L increase), albumin (HR 0.93; 95% CI 0.91-0.96 per 1 g/L increase) and high sensitive CRP (HR 1.07; 95% CI 1.00-1.14 per mg/L increase) were significant predictors in addition to female sex, age, prevalent diabetes and cardiovascular disease. LDL-cholesterol was not a significant risk factor.

Conclusions: Even with the use of strict criteria for endpoint definition, non-traditional risk factors, but not lipid disturbances, predicted atherosclerotic events in haemodialysis patients.

Funding: Pharmaceutical Company Support - AstraZeneca, Government Support - Non-U.S.

TH-PO889

Proteomic Studies of Blood Plasma Using 2DE and Mass Spectrometry for Deeper View into the Mechanisms Involved in Atherosclerosis in Chronic Kidney Disease

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Background: The exact participation and association of particular risk factors and specific mechanisms that promote cardiovascular complications (CVD) in patients with chronic kidney disease (CKD) remain unclear. The close relationship between CVD and CKD is most likely due to the co-existence of both traditional and novel risk factors. To gain insight into better recognition of the mechanisms of CKD-related accelerated atherosclerosis, a comparative proteomic analyses have been performed.

Methods: Blood samples were taken from 90 patients (CKD1-2, CKD3-4, CKD5), 30 patients with CVD, but without CKD and 30 healthy volunteers. Plasma samples were depleted using affinity chromatography and divided into three fractions: high-abundance protein, low-abundance protein and low molecular weight protein. The first two fractions were analyzed by two dimensional gel electrophoresis and mass spectrometry, the last one has been subjected to direct MS/MS analysis. Differential accumulated proteins were confirmed by selected reaction monitoring analysis.

Results: 49 proteins (13 high and 36 low molecular mass) showed differences in accumulation levels. The proteomic profiles in CKD5 and CVD patients differed in the accumulation of four LAPs the relative accumulations of alpha -2-macroglobulin, second isoform of alfa 1 microglobulin and were higher in CKD5 compared with CVD; fold changes 1.77, 4.14, 2.68 and 1.79, respectively. Moreover, the relative abundances of these proteins were up-regulated in CKD3-4 compared with CVD. CKD1-2 and CVD group differed in the accumulation of apolipoprotein A-4 and apolipoprotein A-1.

Conclusions: Our results definitely indicated similar proteomic profiles in CKD1-2 and CVD patients, in contrast to CVD and CKD5 patients, suggesting that mechanisms of CVD acceleration may be different in initial and advanced stages of CVD. It seems that it is related to chronic inflammation and immune disturbances, typical for CVD.

TH-PO890

Hemodialysis-Induced Release of Microparticles

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Background: Microparticles (MPs) are 0.1-1.0 μm vesicles that are released from cells upon activation or during apoptosis. MPs are believed to be involved in the pathophysiology of atherosclerosis and thrombosis. Patients with cardiovascular risk factors have significant MP elevation. Measurements of MPs may uncover new insight into mechanisms behind the severe increased cardiovascular disease (CVD) risk in hemodialysis (HD) patients. The aim was to study whether a hemodialysis session affects MP formation and release.

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

Underline represents presenting author.
Methods: Plasma samples from 20 HD patients were drawn before and 1h after the start of a HD session. MPs derived from platelets (CD62a+), monocytes (CD14+), endothelial cells (CD31+), and their expression of phosphatidylserine (PS) and tissue factor (CD142) were analyzed using flow cytometry. P-selectin (CD62P) and CD40 ligand (CD154) were measured on platelet-MPs. In addition, Klotho and the receptor for advanced glycation end products (RAGE) expression were measured on MPs. Paired t-test was used.

Results: Mean age was 73.6 years (range 54-91). 5 patients were female, 14 had central dialysis catheter, 8 patients had diabetes and 14 had CVD.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Before HD</th>
<th>1h after start of HD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactadherin (PI)+MPs</td>
<td>3645(1960-9784)</td>
<td>4388(1966-12672)</td>
<td>0.08</td>
</tr>
<tr>
<td>Lactadherin +CD41</td>
<td>464(153-2321)</td>
<td>774(169-3000)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lactadherin–CD41+CD62P</td>
<td>186(501098)</td>
<td>550(70-1369)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lactadherin–CD41+CD154</td>
<td>205(3392)</td>
<td>356(22-1236)</td>
<td>0.05</td>
</tr>
<tr>
<td>Lactadherin–CD14</td>
<td>216(175-443)</td>
<td>337(205-584)</td>
<td>0.00</td>
</tr>
<tr>
<td>Lactadherin+CD626a</td>
<td>713 (±233)</td>
<td>845 (±348)</td>
<td>0.03</td>
</tr>
<tr>
<td>CD41+CD142</td>
<td>467 (±262)</td>
<td>541 (±317)</td>
<td>0.30</td>
</tr>
<tr>
<td>CD626+CD142</td>
<td>135(15-392)</td>
<td>171(26-900)</td>
<td>0.06</td>
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<tr>
<td>CD14+CD142</td>
<td>31(11-121)</td>
<td>58(17-193)</td>
<td>0.00</td>
</tr>
<tr>
<td>Klotho a</td>
<td>2360(±276)</td>
<td>2612(±414)</td>
<td>0.00</td>
</tr>
<tr>
<td>RAGE</td>
<td>154(122-1356)</td>
<td>252(178-1491)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Mean (± SD) or a Median (range)

Conclusions: The majority of MP levels increase significantly after the start of a HD session. Whether this is driven by patient or dialysis specific factors remains unclear. The clinical significance of MP release during HD needs to be evaluated.

Funding: Government Support - Non-U.S.

TH-P0891

The Monocyte Subset of CD14+CD16+ Cells Plays a Key Role of Promoting Atherosclerosis in Hemodialysis Patients

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Background: Atherosclerosis is closely associated with morbidity and mortality in hemodialysis (HD) patients. The scavenger receptor CD16 plays a key role in promoting foam cell formation by binding and internalizing oxidized low-density lipoprotein. In addition, heterogeneity of monocytes and macrophage-colony stimulating factor (M-CSF) may facilitate the atherosclerotic process by SR over-expression.

Methods: Subjects included 62 HD patients and 30 healthy controls. Peripheral monocytes were isolated using magnetically labeled Whole Blood CD14+ micro-beads. Transcriptional levels of CD16 and SR-A were measured in monocytes by quantitative real-time RT-PCR, using the comparative threshold (Ct) method. The gene expressions were measured within HD patients and controls, and between HD patients who had cardiovascular disease (CVD) and those who did not. Plasma concentration of M-CSF was measured with M-CSF ELISA kit. Additionally, CD16 protein expression was analyzed by a flow cytometry.

Results: SR-A gene expression was higher in monocytes from HD patients than in those from controls (2.35 vs 1.29, P=0.0006). Moreover, it was higher in HD patients with CVD than in those without (2.79 vs 1.64, P=0.0023). Plasma concentration of M-CSF was 8-fold higher in HD patients than in controls (1173±5173 vs 152±551 pg/ml, P<0.0001). It was significantly correlated with the gene expression of SR-A (r=0.129, P<0.0001). The CD16 gene expression was higher in CD14+ monocytes from HD patients than in those from controls (1.28 vs 1.17, P=0.0310), and was significantly correlated with the gene expression of SR-A (r=0.051, P=0.0467). In a flow cytometry, the proportion of CD14+CD16+ cells was 2.2-fold higher in HD patients than in controls (34.60 vs 15.85, P=0.0034). In addition, this proportion was related with M-CSF (r=-0.354, P=0.0118) and SR-A gene expression (r=0.540, P=0.0240).

Conclusions: The CD14+CD16+ cells are important subset of monocytes in HD patients, which may prime and increase SR expressions.

TH-P0892

Active Ghrelin Enhances the Association Between BMI and Clinical Outcome in Hemodialysis Patients Irrespective of Appetite Ilia Beberashvili,1 Inna Sinuani,2 Ada Azar,3 Leonid Feldman,1 Leonid Feldman,1 Nephrology, Assaf Harofeh Medical Center, Zerifin, Israel;2Div of Nephrology, Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea;3Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea.

Background: Ghrelin, a gastric orexigenic peptide, and BMI are known as inversely associated to each other and have both been linked to cardiovascular (CV) risk and mortality. Interestingly, the orexigenic effect of ghrelin does not seem involved in described interaction.

Methods: Serum ghrelin, BMI, appetite, circadian rhythm of ghrelin, sympathetic nerve activity, and heart rate variability were measured in 261 maintenance HD patients (39% women, mean age of 68±13.6 years). The majority of MP levels increase significantly after the start of a HD session. Whether this is driven by patient or dialysis specific factors remains unclear. The clinical significance of MP release during HD needs to be evaluated.

Funding: Government Support - Non-U.S.

TH-P0893

Serum Procollagen Type I Carboxy-terminal Propeptide Is Associated with Left Ventricular Hypertrophy and Dysfunction, and May Predict Cardiovascular Event in Incidential Dialysis Patient Sung Jun Kim,1 Hye Eun Yoon,2 Sungjin Chung,2 Seok Joon Shin,3 Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Incheon, Korea; 'Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Korea.

Background: Serum procollagen type I carboxy-terminal propeptide (PICP) is a marker of myocardial fibrosis in hypertensive heart disease. However, the clinical significance of this marker in patients who are not determined to be on regular dialysis remains unknown. The aim of this study was to evaluate the association of predialysis serum PICP levels with echocardiographic markers in ESRD patients.

Methods: Serum PICP, albumin, CRP, ITPH levels were obtained from predialysis blood samples of 123 incidentally detected ESRD patients. Echocardiographic parameters were measured before the start of the HD session. The left ventricular mass index (LVMI) and ejection fraction, ratio of peak early transmural flow velocity to peak early diastolic annular velocity (E/A ratio), ratio of early transmural flow velocity to peak late transmural flow velocity (E/A ratio), and mitral valve-deceleration time (DT).

Conclusions: Serum procollagen type I carboxy-terminal propeptide (PICP) is associated with left ventricular hypertrophy and dysfunction, and may predict cardiovascular event in incidental dialysis patient.

TH-P0894

Associations of Soluble Receptors for Advanced Glycation End Products and Serum Procollagen Type I Carboxy-terminal Propeptide with Mortality in Long-Term Hemodialysis Patients J Yong Jung,1 Eul Sik Jung,1 Byunghoo Choi,2 Yun Jung Oh,2 Chungsik Lee,2 Ae jin Kim,1 Han Ro,2 Jae Hyun Chung,1 Hyun Hee Lee,1 Wooyoung Chung.1 'Div of Nephrology, Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea; 'Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea.

Background: Hemodialysis (HD) patients have been associated with vascular calcification and ultimately with high mortality rates. Formerly, we reported association of soluble receptor for advanced glycation end products (s-RAGE) and S100A12 (EN-RAGE) with vascular calcification. We extended our observation whether those biomarkers could be proposed for predicting cardiovascular morbidity and mortality in these subjects.

Methods: This is a prospective observational cohort study in 199 HD patients from extended analyses of our previous study. Serum S-RAGE, S100A12, comorbidities, and other traditional risk factors were evaluated. The Cox proportional-hazards regression was used for Cox proportional-hazards regression were evaluated in multivariable analyses. A mean observation period was 29 months.

Conclusions: The patients were 57 ± 13.7 years of age; 54.3% were male, 49.2% were diabetic, and 36.2% had a history of cardiovascular disease. During the observation period, 27 patients (13.6%) were died. Univariate analysis demonstrated that S100A12 was correlated with diabetes (P = 0.04) and hs-CRP (P = 0.01). In multivariable analyses, serum s-RAGE (HR [hazard ratio], 1.16; 95% CI [confidence interval], 0.61-2.19; P = 0.65) and S100A12 (HR 1.05; 95% CI, 0.62-1.77; P = 0.87) were not associated with mortality in hemodialysis patients, though traditional predictors for mortality including age, history of cardiovascular diseases, serum albumin and serum high-sensitivity C reactive protein (hs-CRP) were related to mortality. Powerful predictors for mortality were age, previous cardiovascular disease and serum albumin level.

Conclusions: Serum S-RAGE and S100A12 may be weak surrogate markers to predict all-cause mortality in patients receiving hemodialysis, even though S100A12 was partly related with diabetes and inflammation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Impact of Sodium-Dependent Phosphate Co-Transport, Pit-1, in Peripheral Blood Mononuclear Cells on Cardiac Calcification in Maintenance Hemodialysis Patients

Minwon Ding, Mengjing Wang, Minmin Zhang, Jing Chen. Huashan Hospital, Fudan Univ.

Background: Vascular calcification (VC) is an important risk factor for cardiovascular disease in MHD patients, however, the mechanisms of which are still under investigation. The aim of this study was to explore the risk factors of VC in MHD patients, and to identify the expression of sodium-dependent phosphate co-transporter (Npt) in peripheral blood mononuclear cells (PBMCs) and assess its association with cardiac calcification and its possible impact factors.

Methods: This is a cross-sectional analysis of adult MHD patients who received at least 6-month regular MHD in our dialysis center. The coronary artery calcification (CAC) was measured by cardiac MSCT. The gene expression of Npt in PBMCs was measured by Real-time PCR and we tested serum TNN-I and IL-6 by ELISA. Multivariate logistic analysis was used to determine the risk factors of CAC. Correlation between the gene expression of Npt and other parameters was examined by Pearson relativity analysis.

Results: 1,685 eligible patients were enrolled. 2. Three kinds of Npts were detected in PBMCs of MHD patients. They were typeIINpt, Npt2b, type III Npt, Pit-1 and Pit-2, among which Pit-1 mRNA expression was significantly associated with extent of CAC. 3. The results of the logistic regression analysis were listed in Table 1. 4. Pearson relativity analysis showed phosphor-1 mRNA expression of PBMCs was significantly correlated with serum phosphorus (r=0.43, P=0.002), CAC score (r=0.63, P<0.001) and Pit-2 mRNA expression of PBMCs (r=0.53, P=0.001).

Table 1. Multiple logistic regression analysis of factors associated with CAC score tertile in MHD patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.36</td>
<td>0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.63</td>
<td>0.062</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic (y)</td>
<td>1.02</td>
<td>0.007</td>
<td>1.03 (1.01-1.05)</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.38</td>
<td>0.074</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.56</td>
<td>0.004</td>
<td>7.14 (0.03-0.75)</td>
<td>0.021</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/dl)</td>
<td>1.01</td>
<td>0.880</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNN-I (pg/ml)</td>
<td>1.20</td>
<td>0.019</td>
<td>1.29 (1.01-1.66)</td>
<td>0.044</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1.06</td>
<td>0.030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.48</td>
<td>0.038</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Lipids (mmol/l)</td>
<td>0.79</td>
<td>0.055</td>
<td>2.52 (1.08-5.83)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Conclusions: Our result showed that longer dialysis vintage, diabetes, higher concentration of serum TNN-I and Pit-1 mRNA expression of PBMCs are the risk factors of CAC in MHD patients. Pit-1 mRNA expression of PBMCs was significantly correlated with serum phosphorus, CAC score and Pit-2 mRNA expression of PBMCs. 

Funding: Government Support - Non-U.S.

TH-P0895

HDL Not as Predictive as apoA-1:apoB Ratio of Dialysis Patients in Predicting Death

Sato1, Akihiro Fukuda. 2,3

Background: Chronic kidney disease is a common disease associated with high cardiovascular risk. Recent studies have suggested that HDL not LDL may play the more important role in the progression of atherosclerosis in CKD patients. HDL from CKD patients was shown to become dysfunctional, lose its vasoprotective properties and begin to promote endothelial dysfunction and inflammation.

Methods: The aim of this study was to investigate the association between the apolipoprotein profile and the incidence of death in chronic dialysis patients.

Results: Of the 194 deaths recorded, 82 were of CVD origin. For the regular lipid markers (HDL, non-HDL, and TG), +1 digit of the apoA-1:apoB ratio was significantly associated with both categories of death when compared with the lowest quarters by multivariable Cox analysis.

Conclusions: Although controversies persist regarding whether lipids affect the prognosis of dialysis patients, our data revealed that the apoA-1:apoB ratio was significantly associated with all-cause and CVD mortality in dialysis patients. 

Funding: Government Support - Non-U.S.

TH-P0897

HDL Subfractions in End-Stage Renal Disease (ESRD) Patients

Anna Gluba-Brazokza, Beata Franzyk-Skora, Jacek Rysz. Dept of Nephrology, Hypertension and Family Medicine, Medical Univ of Lodz, Poland.

Background: Chronic kidney disease is a common disease associated with high cardiovascular risk. Recent studies have suggested that HDL not LDL may play the more important role in the progression of atherosclerosis in CKD patients. HDL from CKD patients was shown to become dysfunctional, lose its vasoprotective properties and begin to promote endothelial dysfunction and inflammation.

Methods: The aim of this study was to investigate the association between the HDL subfractions and the incidence of death in chronic dialysis patients.

Results: When participants were divided into quartiles, the highest quartiles of the apoA-1:apoB ratio were significantly associated with both categories of death when compared with the lowest quartiles by multivariable Cox analysis.

Conclusions: Although controversies persist regarding whether lipids affect the prognosis of dialysis patients, our data revealed that the apoA-1:apoB ratio was significantly associated with all-cause and CVD mortality in dialysis patients. 

Funding: Government Support - Non-U.S.
Galeano-3 Does Not Correlate within Markers of Cardiac Structure and Function on Cardiac MRI: A Study in Haemodialysis Patients

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Background: End-stage renal failure patients undergoing haemodialysis (HD) suffer disproportionately rates of death due to heart failure. Accurate tools to help predict those highest risk are therefore desirable. Galeano-3 is a soluble β-galactoside binding protein secreted by activated macrophages that promotes cardiac fibroblast proliferation, collagen deposition and as a result ventricular dysfunction. Galeano-3 is the only FDA approved test for assessing prognosis in chronic heart failure. Our study explored the relationship between Galeano-3 and cardiac structure and function in a dialysis population.

Methods: We measured Galeano-3 (G3) levels in a multiplex assay (Merck Millipore) in HD patients enlisted in a clinical trial. Results were correlated with tagged cardiac magnetic resonance imaging to assess left ventricular structure and function.

Results: A total of 65 patients had G3 levels taken. The mean age of the cohort was 60±24 years. The overall mean G3 level was 17.7±10.07. The mean Left Ventricular Mass Index was 77.09±21.04, mean ejection fraction 57.47±.11 and mean End-diastolic volume 143.4±24 years. The whole cohort had no significant correlation between G3 levels and any of the measure of left ventricular structure and function including LVMi (r=0.22 p<0.04), LVEF (r=0.08 p=0.65) or LVEDV (r=0.012 p=0.94). The previously reported upper limit of normal for G3 levels is 17.7ng/mL. 32 patients had a G3 level greater than this. In this group the mean G3 level was 23.2±ng/mL, however there remained no significant correlations with age (r=0.10 p=0.38), LVEF (r=0.23 p=0.26), LVEDV (r=0.01 p=0.95), LVMi (r=0.11 p=0.59) or global peak diastolic and systolic strain rates (r=0.3 p=0.14 and r=0.16 p=0.41).

Conclusions: In HD patients, Galeano-3 is not associated with structural and functional markers of systolic dysfunction seen on tagged cardiac MRI. Our results suggest that Galeano-3 does not have a role in risk stratification of this patient group.

Galeano-3 is not associated with arterial stiffness in CKD patients.

TH-P0901

Association of Klotho and FGF23 with Frailty in Patients Initiating Hemodialysis

Sahar Kourbari1 Esther D. Kim,2 Dorry L. Segev,3 Stephen M. Sozio,1 Larisa Tereshchenko,2 Lucy A. Moe,2 Rulan S. Parekh,2 Michelle M. Estrella,1 Johns Hopkins Univ; 1Univ of Toronto; 2Univ of Oregon.

Background: At dialysis initiation is associated with higher mortality. Both FGF23 and its co-receptor, klotho, have been implicated in the development of frailty. We aimed to evaluate the independent association of FGF23 and soluble klotho (sKlotho) with frailty in hemodialysis (HD) patients.

Methods: We conducted a cross-sectional study of incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Events in ESRD (PACE) Study. Frailty was defined by 3 of the following: unintentional weight loss ≥10 lbs in prior year, self-reported exhaustion, weakness (by hand grip strength), slowness (by walking distance) and self-reported low physical activity. Logistic regression was used to examine the associations of sKlotho and FGF23 with odds of frailty and frailty subcomponents.

Results: Of 336 individuals, 71% were black; 59% were male. Mean age was 55y. All had hypertension and 56% had diabetes, 38% CAD, and 37% obesity. Median sKlotho level was 364.4±ng/mL (IQR 272.5-494.6); mean FGF23 level was 656.2±U/mL (SD: 498). 40% of participants were frail. Adjusting for demographic factors, obesity, Charlson Comorbidity Index, hsCRP, serum albumin and Kt/V, higher sKlotho was associated with lower odds of frailty (Table).

Conclusions: In HD patients, sKlotho, but not FGF23, was inversely associated with odds of frailty and frailty subcomponents. This remained robust after also adjusting for FGF23. Conversely, FGF23 was not associated with frailty. In adjusted analyses of the frailty subcomponents, higher sKlotho was only associated with self-reported exhaustion (OR=0.54, 95%CI: 0.30-0.95) while higher FGF23 was only associated with unintentional weight loss (OR=0.93, 95%CI 0.88-0.98).

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

TH-P0902

Differential Association of Fibroblast Growth Factor-23 and Soluble Klotho with Left Ventricular Hypertrophy

Tanya S. Johns,1 Esther D. Kim,2 Tessa Kimberly Novick,2 Lucy A. Moe,3 Stephen M. Sozio,3 Bernard G. Jaar,1 Larisa Tereshchenko,4 Rulan S. Parekh,2 Michelle M. Estrella,3 Albert Einstein College of Medicine; 1Univ of Toronto; 2Johns Hopkins Univ; 3Univ of Oregon.

Background: Fibroblast growth factor-23 (FGF23), a phosphaturic hormone, has been implicated in the pathogenesis of left ventricular hypertrophy (LVH) among patients with chronic kidney disease. Whether FGF23 co-receptor, klotho, is independently associated with LVH is unclear.

Methods: To determine whether soluble klotho (sKlotho) is independently associated with LVH among incident hemodialysis patients, we conducted a cross-sectional study among participants who underwent baseline 2D echocardiograms in the Predictors of Arrhythmia and Cardiovascular Events (PACE) Study. Multivariable logistic regression models with FGF23, sKlotho, and both as primary predictors were constructed to estimate the odds of LVH (defined as LV mass index ≥116 g/m² in men and ≥104 g/m² in women).

Results: Of 391 participants who underwent echocardiogram, 371 and 387 had sKlotho and FGF23 levels available, respectively; 72% had LVH. Mean age was 54 years and 72% were black. All participants had hypertension with mean systolic BP 154 mm Hg. Median parathyroid hormone (25 pmol/l, IQR 13-56 versus 3.8 pmol/l, IQR 3-5, p<0.001) and parathyroid hormone (25 pmol/l, IQR 13-56 versus 3.8 pmol/l, IQR 3-5, p<0.001). PWV was elevated in patients with CKD (8 m/sec, IQR 6.9-6.9 vs. 7.0 m/sec, IQR 6.8-8.4, p=0.0002). In a regression model adjusted for known predictors of PWV, FGF23 did not predict PWV (p=0.15, p=0.063), but was positively associated with the presence of CKD (p=0.009), age (p=0.001), mean arterial pressure (p=0.001) and heart rate (p=0.001).

Conclusions: In this prospective cohort study, FGF23 did not predict arterial stiffening beyond known risk factors of age, mean arterial pressure, heart rate and the presence of diabetes. Our findings suggest that the excess cardiovascular mortality observed with elevated FGF23 in CKD is not primarily driven by effects on arterial stiffening.

TH-P0911

FGF23 is Not Associated with Arterial Stiffness in Patients with CKDSD

Kenneth Lim1,2 Stephen M. Ting,3 Daniel Zehnder,4 Thomas F. Hiemstra.1 1Div of Nephrology, Massachusetts General Hospital, Boston, MA; 2Dept of Medicine, Heart of England NHS Foundation Trust, Birmingham, United Kingdom; 3Div of Nephrology, Univ Hospital Coventry and Warwickshire NHS Trust, Coventry, United Kingdom; 4Div of Metabolic and Vascular Health, Warwick Medical School, Coventry, United Kingdom; 5School of Clinical Medicine, Univ of Cambridge, Cambridge, United Kingdom.

Background: Arterial stiffening is thought to be a key determinant of excess Cardiovascular mortality in CKD patients. In CKD, the bone-derived phosphatonin fibroblast growth factor (FGF) 23 is elevated and has been implicated in the development of Cardiovascular disease. In this study, we sought to determine whether FGF23 is a predictor of arterial stiffness in dialysis-dependent CKD patients.

Methods: In this cross-sectional study, we enrolled 352 patients with advanced CKD and 150 healthy controls. Pulse wave velocity (PWV) was recorded by application tonometry, and blood pressure and biochemical parameters including plasma intact-FGF23 concentrations determined.

Results: Patients with CKD were significantly younger than controls (46±14 versus 49±11 years, p<0.02), had a higher blood pressure (MAP 97±14 vs 94±10 mmHg, p<0.003), and were more likely to be male (61% versus 49%, p<0.008). CKD patients had significantly higher FGF23 (3095 pg/ml, IQR 12-17276 versus 40 pg/ml, IQR 33-49, p<0.001) and parathyroid hormone (25 pmol/l, IQR 13-56 versus 3.8 pmol/l, IQR 3-5, p=0.001). PWV was elevated in patients with CKD (8 m/sec, IQR 6.9-6.9 vs. 7.0 m/sec, IQR 6.8-8.4, p=0.0002). In a regression model adjusted for known predictors of PWV, FGF23 did not predict PWV (p=0.15, p=0.063), but was positively associated with the presence of CKD (p=0.009), age (p=0.001), mean arterial pressure (p=0.001) and heart rate (p=0.001).

Conclusions: In this prospective cohort study, FGF23 did not predict arterial stiffening beyond known risk factors of age, mean arterial pressure, heart rate and the presence of diabetes. Our findings suggest that the excess cardiovascular mortality observed with elevated FGF23 in CKD is not primarily driven by effects on arterial stiffening.
Predictors of Arterial Stiffness in Incident Hemodialysis Patients

**Background:** Premature vascular aging and arterial stiffening characterize CKD progression to ESRD and are associated with increased cardiovascular (CVD) morbidity and mortality. We identified predictors of arterial stiffness over time in HD patients.

**Methods:** In 339 incident HD patients in the Predictors of Arthrythmic and Cardiovascular Risk in ESRD (PACE) study, we examined the associations of baseline age, sex, race, comorbidities, CVD medications, and dialysis characteristics with longitudinal vascular stiffness measured by carotid-femoral pulse wave velocity (PWV) using generalized estimating equations. Annual change in PWV for up to 3 years was analyzed using linear regression.

**Results:** Mean age was 54, 58% male, 74% African-American, mean (SD) baseline PWV 10.7 (3.4) m/s, and annual PWV change 0.2 (1.6) m/s. Several factors were associated with higher PWV in univariate and multivariate longitudinal models. None were associated with PWV change.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate β (95%CI)</th>
<th>Multivariate β (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (10y)</td>
<td>1.03 (0.81-1.24)</td>
<td>0.88 (0.66-1.19)</td>
</tr>
<tr>
<td>Female</td>
<td>-0.35 (-1.03-0.32)</td>
<td>-0.61 (-1.1-0.07)</td>
</tr>
<tr>
<td>African-American</td>
<td>-0.62 (-1.39-0.14)</td>
<td>0.34 (-0.29-0.98)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.62 (2.00-3.24)</td>
<td>1.58 (0.99-2.16)</td>
</tr>
<tr>
<td>Coronary Disease</td>
<td>0.87 (0.71-1.06)</td>
<td>0.24 (0.87-0.93)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>0.93 (0.26-1.60)</td>
<td>-0.14 (0.72-0.45)</td>
</tr>
<tr>
<td>LV Mass Index</td>
<td>-0.03 (-0.10-0.04)</td>
<td>-</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>-0.51 (-1.18-0.17)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal-Angiotensin Inhibitor</td>
<td>-0.01 (-0.70-0.67)</td>
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</tr>
<tr>
<td>Beta Blocker</td>
<td>0.83 (0.16-1.51)</td>
<td>0.99 (-0.45-0.65)</td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Pressure (10mmHg)</td>
<td>1.12 (0.88-1.37)</td>
<td>0.77 (0.54-1.01)</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>-0.24 (-0.57-0.10)</td>
<td>-</td>
</tr>
<tr>
<td>iPTH (mg/dl)</td>
<td>-0.01 (-0.02-0.00)</td>
<td>0.00 (-0.01-0.01)</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>-0.38 (-1.11-0.34)</td>
<td>-</td>
</tr>
</tbody>
</table>

P-value: <0.05
<0.01
<0.001

**Conclusions:** Although PWV did not change significantly over time in incident HD patients, age, male sex, diabetes, and pulse pressure were independently associated with higher PWV. It may be difficult to modify PWV after HD initiation and clinical factors should be optimized prior to starting HD.

**TH-PO904**

Differences in Risk Factors for Coronary Artery Calcification Between Non-diabetic and Diabetic Hemodialysis Patients

**Background:** The differences in risk factors for coronary artery calcification between non-diabetic and diabetic hemodialysis (HD) patients have not been fully explored.

**Methods:** We examined Agatston coronary artery calcium score (CACS) using MDCT, age, sex, presence of diabetes, dialysis vintage, smoking history, administration of phosphate binders, geriatric nutritional risk index (GNNRI), Hba1c, serum calcium, phosphate, iPTH, CRP, B2MG, LDL-cholesterol and triglyceride (TG) in 355 HD patients: 242 nondiabetics and 113 diabetics. Factors related to CACS were assessed by multivariate regression analysis using all of the above independent variables. Differences in the above parameters according to quartile (Q) of CACS were also assessed.

**Results:** Mean age (years), dialysis vintage (months), (CACS) and serum phosphate (mg/dl) were 63.14 vs. 66.12 (ms), 125.5 vs. 171.50 months (P<0.01), 1651.2173 vs. 21772.2533 (P<0.005), and 5.3±1.53 vs. 5.0±1.14 (ms) in nondiabetics and diabetics, respectively. Patients with CACS Q4 showed higher prevalence of diabetes (40 vs. 19%), age (68±12 vs. 58±14 years), and CRP (0.7±1.3 vs. 0.2±0.4 mg/dl), but lower iPTH (146±133 vs. 193±131 pg/ml) levels than patients with CACS Q1 (P<0.05), and other parameters were not significantly different except HbA1c. Significant associations were observed between CACS and age (P<0.001, β: 0.21), female (P<0.001, β: -0.21), dialysis vintage (P<0.001, β: 0.31), CRP (P<0.05, β: 0.16), TG (P<0.05, β: 0.13) in nondiabetics. However, CACS was significantly associated only with age (P<0.05, β: 0.30) and HbA1c (P<0.05, β:0.26) in diabetics.

**Conclusions:** Risk factors for coronary artery calcification differ between non-diabetic and diabetic HD patients, and poor glycosic control is the main factor in the latter.

**TH-PO905**

Hemodialysis and Hemodiafiltration Improve Serum Calcium Propensity

**Background:** Calciprotein particles (CPPs) may play an important role in the calcium propensities in CKD patients. The calcium propensities of serum (T 250) is highly predictive of all-cause mortality in chronic kidney disease patients. Whether T 250 is therapeutically improvable, by hemodialysis (HD) or even further by hemodiafiltration (HDF), has not been studied yet.

**Methods:** We designed a cross-sectional single center study, and included prevalent patients on HD or HDF. Patients were divided into two groups based on dialysis modality. We included patients on a thrice-weekly schedule, with a dialysis vintage of ≥3 months and vascular access providing a blood flow rate of >300 ml/min. Calcium propensities of serum was measured by the time of transformation from primary to secondary CPP (T 250 test), by time-resolved nephelometry.

**Results:** In total 64 patients were included and, T 250 was measured in 376 pre- and post-dialysis samples of all in-center dialysis sessions during one week. T 250 levels improved in both the HD and HDF group with pre- and post-dialysis (mean (SD) of 244±46-301±57, and 253±55-304±61) mm respectively (P=0.43). The mean improvement of T 250 was 26.29% in the HD group and 21.97% in the HDF group (P=0.01). The delta values (A) of calcium, phosphate (P) and albumin were equally improved in both groups. The DT 250 was mostly improved by DP (P=0.280, P<0.01 HD and r=0.235; P=0.02 HDF).

**Conclusions:** HD and HDF patients present with same baseline vascular calcification risk values pre-dialysis. Calcium propensities is significantly improved during both HD and HDF. T 250 might be a useful guide to optimize renal replacement strategy to improve the individual calcification risk in dialysis patients.

**Funding:** Pharmaceutical Company Support - unrestricted Grant from Fresenius Medical Care

**TH-PO906**

Association of Circulating Biomarkers with Vascular Stiffness and Coronary Artery Calcium in Incident Hemodialysis

**Background:** Vascular calcification and stiffness are associated with higher mortality in hemodialysis. Studies examining the role of circulating biomarkers – specifically, FGFR23, desphospho-uncarboxylated matrix GlA protein (dpucMGP), Fetuin A, osteoprotegerin (OPG), and C-reactive protein (CRP) – in vascular calcification have reported contradictory findings, and the independent association of the biomarkers remains inconclusive.

**Methods:** In 392 incident hemodialysis patients in the Predictors of Arrhythmic and Cardiovascular Risk End Stage Renal Disease (PACE) study, we examined the associations of baseline FGFR23, dpucMGP, Fetuin A, OPG, and CRP with total coronary calcium score (Agatston) at baseline and vascular stiffness (pulse wave velocity [PWV]) at baseline and over 4 years visits. Baseline associations were determined using linear regression and repeated measures over visits were examined using mixed-effects models.

**Results:** At baseline, higher OPG was associated with increased odds of having a high coronary calcium score (>257), independent of other biomarkers (OR=1.11, 95% CI: 1.06, 1.15).
1.6). The remaining biomarkers were not associated with high coronary calcium. Higher OPG was associated with higher PWV, and higher FGF23 was associated with lower PWV after adjusting for demographic factors, body mass index, comorbidity index, calcium phosphorus product, systolic blood pressure, and albumin.

**Table:**

<table>
<thead>
<tr>
<th>Adjusted association with PWV</th>
<th>β (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPG (1 pmol/l)</td>
<td>0.10 (0.02, 0.19)</td>
</tr>
<tr>
<td>FGF23 (100 RU/ml)</td>
<td>-0.19 (-0.18, -0.02)</td>
</tr>
<tr>
<td>dpuC (1-log pm)</td>
<td>0.07 (-0.38, 0.53)</td>
</tr>
<tr>
<td>Fetuin A (1 g/l)</td>
<td>-0.79 (-2.77, 1.19)</td>
</tr>
<tr>
<td>CRP (1-log µg/ml)</td>
<td>0.02 (-0.27, 0.30)</td>
</tr>
</tbody>
</table>

*Multiple adjusted for all biomarkers

**Conclusions:** Several vascular and phosphate biomarkers are associated with vascular calcification at baseline and/or stiffness longitudinally in incident dialysis patients. Further studies assessing interventions on these biomarkers are warranted.

**Funding:** NIDDK Support

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**TH-PO907**

**Association of Arterial Stiffness with Cognitive Impairment in Incident Hemodialysis Patients**

**Methods:** This study included 390 incident hemodialysis patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) study. Arterial stiffness was measured using aortic pulse wave velocity (PWV) and augmentation index (AIx). Cognitive function was measured using time to complete Trail making tests A and B (TMT A and TMT B) and the modified mini-mental state exam (3MS) score. Log-linear, Tobit, and logistic regression models were used to examine the baseline association of PWV with TMT A, TMT B, and 3MS, respectively. Changes in 3MS score. Log-linear, Tobit, and logistic regression models were used to examine the relationship between arterial stiffness and cognitive function in dialysis patients.

**Results:** At baseline, higher PWV was associated with longer time to complete TMT A after adjusting for demographic factors, reading comprehension score, comorbidity index, systolic blood pressure, and atrial fibrillation (%TMT A=3.12, 95% CI: 0.37-5.87). In the repeated measures analysis, higher PWV was still associated with longer TMT A time (%TMT A=2.05, 95% CI: 0.00-4.11), and higher AIx was associated with longer TMT B time (β=0.80, 95% CI: 0.01-1.58).

**Conclusions:** Vascular stiffness was associated with longer time to complete TMT A and TMT B suggesting that arterial stiffness may lead to subclinical cerebrovascular events and decline in executive function among incident hemodialysis patients.

**Funding:** NIDDK Support

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**TH-PO908**

**Close Relationship Between Vascular Endothelial Function and Serum Uric Acid Level in Hemodialysis Patients**

**Background:** Vascular endothelial function (VEF) impairment is often detected in hemodialysis (HD) patients and has been associated with atherosclerosis and cardiovascular disease (CVD). Although avoidance of VEF impairment is therefore desirable in preventing such complications, the precise factors that influence VEF remain unknown. The present study evaluated VEF for associating factors in HD patients.

**Methods:** We enrolled 48 patients undergoing maintenance HD at Ueda Kidney Clinic in Japan. No patient had a history of CVD. Reactive hyperemia index (RHI) was evaluated by Endo-PAT (Itamar Medical, Ltd., Caesarea, Israel) was used to assess VEF, whereby a higher RHI was indicative of better function. We also assessed for correlations between the natural logarithm of RHI (LnRHI) and clinical parameters.

**Results:** The median age of our patients was 67 years, the male-to-female ratio was approximately 2:1, and median LnRHI was low at 0.36. Analysis of Spearman’s rank correlation coefficient revealed a significant positive correlation between serum uric acid level (sUA) and LnRHI (r=0.37, p=0.009). As sUA is influenced by diet, inflammatory cytokines, and dietary intake, we also performed multivariable linear regression analysis adjusted by age, body mass index, index of dietary efficiency by Kt/V, and normalized protein catabolic rate, and observed that sUA was significantly related to LnRHI (β=0.042, 95% CI: 0.007-0.078, p=0.009). We also assessed for correlations between the natural logarithm of RHI (LnRHI) and clinical parameters.

**Conclusions:** The current study suggests that VEF is closely associated with sUA in HD patients. Although the precise mechanism is unknown, a marked decrease in sUA might be correlated with VEF impairment and should be avoided in individuals undergoing HD.

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**TH-PO909**

**Ambulatory Arterial Stiffness Index: An Early Marker of Cardiovascular Disease in Young Hemodialysis Patients**

**Background:** Cardiovascular disease (CVD) is the leading cause of death in pediatric hemodialysis (HD) patients. Ambulatory arterial stiffness index (AASI) may be an earlier measure of vascular compliance in young patients than pulse pressure (PP). Our objective was to evaluate AASI as a marker of increased vascular stiffness in young HD patients and to compare it with other non-invasive indicators of CVD risk.

**Methods:** Retrospective review of 24-hour ambulatory blood pressure monitoring (ABPM) was performed in 11 pediatric patients on chronic HD (mean±SD: 16±3.6 yrs) and dialysis vintage of 32±18 months. AASI was calculated as 1-regression slope of the diastolic over systolic BP. Echocardiogram and bilateral carotid artery ultrasound were performed to assess left ventricular mass index (LVMI) and carotid intimal medial thickness (cIMT). Cardiac artery stiffness indices included distensibility coefficient (DC), stiffness index-β (SI-β), SI, and PP. AASI was used as a marker of increased vascular stiffness in young HD patients and compared to other non-invasive indicators of CVD risk.

**Results:** AASI was significantly increased in HD patients compared to controls (0.42±0.1 versus 0.20±0.2, p=0.01). When matched to controls with similar BP's and PP's, the AASI detected increased vascular stiffness independent of PP, cIMT, LVMI, and DC were also significantly increased in HD patients (p<0.01).

**Conclusions:** Young HD patients demonstrate early surrogate markers of CVD including increased LVMI, cIMT, and decreased vascular compliance. Increased AASI detected vascular stiffness that was independent of BP's and PP's. AASI may be an early non-invasive marker of vascular disease in young HD patients that merits further investigation.
Effects of Music and Exercise during Hemodialysis on the Cardiac Autonomic Nervous System Activity

**Evaluating the Cardiac Effects of a Combined Protocol during Hemodialysis**

- **Methods:**
  - Nine dialysis patients with uncontrolled office BP (>140/90 mmHg despite two or more agents at maximal tolerated dosages) were recruited into this feasibility study. (Page 380)
  - Office and ambulatory BP monitoring (ABPM) were performed at baseline, one and three months post RDN, along with supine muscle sympathetic nerve activity (MSNA). Echocardiography was performed at baseline and three months. (Page 381)

- **Results:**
  - Mean heart rate (HR), standard deviation of NN intervals (SDNN), root mean square (RMSSD) (pNN50), and very low frequency (VLF) were: mean heart rate (HR); standard deviation of NN intervals (SDNN); root mean square (RMSSD) (pNN50) and very low frequency (VLF).
  - There was a correlation between change in office systolic BP and ventricular dilatation (R=0.255) or dysfunction (R=0.034), suggesting BP-independent effects.
  - Conclusions: RDN in dialysis patients improves office systolic BP and leads to a BP-independent improvement in ventricular dilatation and probably dysfunction. Further controlled studies are warranted in this population.

**Temporal Loss of Bone Mineral Density Is Associated with Cardiovascular Diseases in Japanese Patients Starting Renal Replacement Therapy**

- **Background:**
  - High mortality in dialysis patients may be related to reduced clearance of cytokines with conventional dialysis membranes. Attempts to provide a better clearance with high cut-off membranes also leads to albumin loss. A new Medium-Cut-Off membrane with better permeability for molecules up to 45 kDa but with limited permeability for albumin was tested clinically. (Page 318)

- **Methods:**
  - 50 patients were dialyzed with MCO and conventional high-flux (HF) membranes for four weeks following a randomized cross-over design. After the second phase, another 12-week-period was conducted to test for long-term effects. Serum samples were tested for inflammatory effects and cytokine concentrations. Support was granted by the German Federal Ministry of Education and Research (FKZ 13N11796-99).

- **Results:**
  - The primary end point mRNA content of TNF-α in leukocytes was reduced to a higher degree and significantly better after 4 weeks on MCO compared to HF membranes (p < 0.001). Interleukin-6 mRNA was markedly reduced with MCO (p < 0.001). After a significant drop after four weeks of MCO dialysis, albumin concentrations stabilized after 12 weeks.

**Endovascular Renal Denervation Ameliorates Pathological Left Ventricular Dilatation in Patients with Dialysis-Related Hypertension**

- **Background:**
  - Endovascular renal denervation (RDN) ameliorates left ventricular hypertrophy and improves contractile function in resistant hypertension. Its cardiac effects on a dialysis population are unknown. We hypothesized that RDN would improve blood pressure (BP) control and sympathetic overload, resulting in improved ventricular function.

- **Methods:**
  - Patients with end-stage renal disease (ESRD) were enrolled and followed for a median of 3.8 years (range 1-5.8 years). Bone mineral density (BMD) of the lumbar spine was measured by dual X-ray absorptiometry at baseline and after 1 year.

- **Results:**
  - Baseline BMD, median value 1.05 (0.67-1.56) g/cm2, negatively correlated compared to age (r=-0.28, P = 0.015) and JTF (r=-0.14, P = 0.0002). When dividing patients into two groups according to delta BMD (defined as baseline - 1 year), those with high delta BMD had an increased mortality risk (Log rank 6.36, P = 0.012) and time from dialysis initiation to the first CVD event appeared, although not significant, shorter in patients with high delta BMD (Log rank 2.81, P = 0.094). Patients with high delta BMD had a significantly increased relative risk (RR: Cox hazard model) of mortality (10.9, 95% CI; 1.34-250.6) even after adjustments for age, gender, diabetes and smoking, compared with those with low delta BMD. RR of the first CVD event was 5.52 (95% CI; 1.15-73.8) with adjustment for age and gender.

- **Conclusions:**
  - Progressive loss of BMD associated with an increasing risk of CVD and mortality. Whereas in end-stage renal disease patients, BMD may have limited value as predictor of a fracture risk, temporal changes of BMD, potentially reflecting bone-vascular interactions, may be useful as a marker of a CVD risk.

**First in Man: Reduction of Inflammation with Medium Cut-Off (MCO) Membranes**

- **Background:**
  - Interleukin-6 and C-reactive protein are strongly associated with an increased risk of cardiovascular disease (CVD) in dialysis patients.
  - Inflammation is a predictor of mortality and morbidity in chronic kidney disease (CKD) patients. The use of an MCO membrane could reduce inflammatory mediators and thereby reduce the risk of CVD and all-cause mortality.

- **Methods:**
  - 50 patients were dialyzed with MCO and conventional high-flux (HF) membranes for four weeks following a randomized cross-over design. After the second phase, another 12-week-period was conducted to test for long-term effects. Serum samples were tested for inflammatory effects and cytokine concentrations.

- **Results:**
  - Interleukin-6 mRNA was markedly reduced with MCO (p<0.001). After a significant drop after four weeks of MCO dialysis, albumin concentrations stabilized after 12 weeks.

**Diastolic Dysfunction Grade**

- **Results:**
  - Diastolic Diastolic Dysfunction Grade
  - **LVd mass/BSA (g/m²)**
    - Baseline: 97±16
    - 1 Month: 91±9
    - 3 Months: 91±9
    - **P Value:** 0.490
  - **LVIDd (mm)**
    - Baseline: 54±6
    - 1 Month: 50±7
    - 3 Months: 50±7
    - **P Value:** <0.05
  - **MSNA Burst Frequency (bursts/min)**
    - Baseline: 90±17
    - 1 Month: 89±13
    - 3 Months: 89±13
    - **P Value:** 0.906
  - **LV EF (%)**
    - Baseline: 41±14
    - 1 Month: 47±11
    - 3 Months: 47±11
    - **P Value:** 0.801
  - **LVD mass/BSA (g/m²)**
    - Baseline: 97±16
    - 1 Month: 91±9
    - 3 Months: 91±9
    - **P Value:** 0.003

**First in Man: Reduction of Inflammation with Medium Cut-Off (MCO) Membranes**

- **Conclusions:**
  - Progressive loss of BMD associated with an increasing risk of CVD and mortality. Whereas in end-stage renal disease patients, BMD may have limited value as predictor of a fracture risk, temporal changes of BMD, potentially reflecting bone-vascular interactions, may be useful as a marker of a CVD risk.

**Temporal Loss of Bone Mineral Density Is Associated with Cardiovascular Diseases in Japanese Patients Starting Renal Replacement Therapy**

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  - Progressive loss of BMD associated with an increasing risk of CVD and mortality. Whereas in end-stage renal disease patients, BMD may have limited value as predictor of a fracture risk, temporal changes of BMD, potentially reflecting bone-vascular interactions, may be useful as a marker of a CVD risk.

**First in Man: Reduction of Inflammation with Medium Cut-Off (MCO) Membranes**

- **Conclusions:**
  - Progressive loss of BMD associated with an increasing risk of CVD and mortality. Whereas in end-stage renal disease patients, BMD may have limited value as predictor of a fracture risk, temporal changes of BMD, potentially reflecting bone-vascular interactions, may be useful as a marker of a CVD risk.

**First in Man: Reduction of Inflammation with Medium Cut-Off (MCO) Membranes**

- **Conclusions:**
  - Progressive loss of BMD associated with an increasing risk of CVD and mortality. Whereas in end-stage renal disease patients, BMD may have limited value as predictor of a fracture risk, temporal changes of BMD, potentially reflecting bone-vascular interactions, may be useful as a marker of a CVD risk.
Vitamin D and Cardiac Autonomic Tone in End-Stage Kidney Disease: A Blinded, Randomized Controlled Trial

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Background: Importance: End-stage kidney disease (ESKD) patients are at high cardiovascular (CV) risk. Vitamin D deficiency is associated depressed heart rate variability (HRV), a risk factor for CV death. Both vitamin D deficiency and depressed HRV are highly prevalent in ESKD.

Methods: Objective: To determine the effects of activated vitamin D (conventional) compared to activated and nutritional vitamin D (intensive) on HRV (low to high frequency spectral ratio; LF:HF) in patients with ESKD on hemodialysis (HD). Design: 2x2 crossover, blinded, randomized controlled trial in outpatient HD units. Fifty-six patients were randomized 1:1 to begin either conventional (0.25mcg alfacalcidiol and placebo 3 times/week) or intensive vitamin D therapy (0.25mcg alfacalcidiol 3 times/week and 50000IU ergocalciferol weekly for 6 weeks). Main Outcomes: HRV is a surrogate index of cardiac autonomic nerve function and independently predicts CV mortality. The primary outcome was the change in LF:HF from the 1st to 6th week HD session. Secondary endpoints included individual changes in LF and HF, parameters of mineral metabolism and renin angiotensin system (RAS) activity.

Results: There was no difference in LF:HF from baseline to 6 weeks for either vitamin D treatment (conventional p=0.9; intensive p=0.07). There were no significant changes in any other measure of HRV, mineral metabolism or RAS activity. On exploratory subgroup analysis, participants who remained vitamin D deficient (25-hydroxyvitamin D<50nmol/L) after treatment had a significant increase in LF:HF (conventional: n=13, p<0.001 vs. insufficient and sufficient groups; intensive: n=8, p=0.001 vs. sufficient group).

Conclusions: Six weeks of treatment with conventional or intensive vitamin D did not alter LF:HF in ESKD patients. However, improved LF:HF was observed in the vitamin D-deficient subgroup. This finding may translate into decreased CV risk and should be considered hypothesis-generating and deserving of further study. Trial Registration: ClinicalTrials.gov NCT01774812. Funding: Private Foundation Support.

The Validity of Left Ventricular Mass as a Surrogate Endpoint for Mortality Outcomes in Chronic Kidney Disease

Suni V. Badve, 1,2 Suetsuna Palmer, 1,2 Giovanni F.M. Strippoli, 3 Matthew A. Roberts, 3 Armando Teixeira-Pinto, 3 Neil Bell, 3 Alan Cass, 7 Carmel M. Hawley, 12 Susan J. Hiramatsu, 12 Elaine M. Pascoe, 1 Vlado Perkovic, 9 Gillian A. Whalley, 3 Jonathan C. Craig, 3 David W. Johnson, 1 1 Univ of Queensland; 2 Princess Alexandra Hospital; 3 Univ of Otago; 4 Univ of Bari; 5 Monash Univ; 6 Univ of Western Australia; 7 Menzies School of Health Research; 8 Univ of Ottawa; 9 The George Inst for Global Health; 10 Unitec Inst of Technology; 11 Univ of Sydney.

Background: Left ventricular mass (LVM) is increasingly used as a surrogate endpoint in trials involving chronic kidney disease (CKD) patients, as intervention-induced reductions in LVM, a risk factor for cardiovascular disease (CVD), is often indicated in dialysis patients. Methods: The aim of this systematic review was to determine the validity of LVM as a surrogate endpoint for all-cause and CV mortality in CKD. Randomized controlled trials evaluating pharmacological and non-pharmacological interventions with follow-up >3 years were included. The outcomes of interest were LVM change from baseline to last measurement and all-cause and CV mortality. Standardized mean differences (SMDs) in LVM change and relative risk of mortality were estimated using random-effects models. Correlations between LVM change and mortality endpoints were summerized across all trials.

Methods: The primary endpoint was the correlation between change in LVM and relative risk of mortality. The secondary endpoints were correlation between change in LVM and relative risk of all-cause mortality, and correlation between change in LVM and relative risk of CV mortality. Results: Seventy trials (6420 participants) were eligible. Among 23 interventions, only erythropoiesis-stimulating agents (SMD -0.13, 95%CI -0.23 to -0.03), renin-angiotensin-aldosterone-system inhibitors (SMD -0.28, 95%CI -0.44 to -0.11) and isosorbide mononitrate (SMD -0.43, 95%CI -0.72 to -0.14) were associated with changes in LVM and relative risk of mortality. There were weak associations between LVM change and all-cause mortality (30 trials, 4749 participants, correlation coefficient [r] 0.28, 95%CI -0.15 to 0.60) and CV mortality (13 trials, 3272 participants, r0.23, 95%CI 0.60 to 0.75).

Conclusions: In CKD, it is uncertain whether an intervention-induced LVM change correlates with reduced mortality. Evidence for LVM as a valid surrogate endpoint in CKD is currently lacking.

Non-Invasive Left Ventricular End-Diastolic Pressure (LVEDP) Measurement in Hemodialysis Patients: A Pilot Study

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Background: Optimal volume status in dialysis patients is difficult to assess. The Val saliva maneuver is recognized as an bedside marker of central volume overload. A novel handheld device that combines finger photoplethysmography with Val saliva maneuver can reliably estimate LVEDP (normal: <12mmHg). (Silber H, PMID: 22389389). The goal of our pilot study is to determine the role of this non-invasive LVEDP measurement in managing volume in hemodialysis patients.

Methods: The LVEDP-Guided Volume Management Study is being conducted at 2 dialysis centers in Baltimore. Baseline data collected includes demographics, medical history, KDQOL-36, NYHA dyspnea scale, intra/post dialysis symptoms, predialysis metrics [LVEDP, bioimpedance, blood pressure (BP) and echocardiogram]. We assessed the cross-sectional association of predialysis LVEDP with dyspnea symptoms and intradialytic hypotension (IDH, defined as ≥20mmHg drop in systolic BP + nursing interventions).

Results: In the first 28 participants (mean age 56 years, 71% male, 82% black), median (25%, 75% percentiles) for predialysis LVEDP was 14mmHg (12, 19), interdialytic weight gain (IDWG) was 1.7kg (0.9, 2.9) and systolic BP was 150mmHg (133, 164). LVEDP was significantly higher in patients with dyspnea vs. those without. (Mean, 19 vs. 14.6; p<0.03). IDH occurred in 5 (18%) patients and all had LVEDP £14mmHg (Table). The unadjusted odds ratio for IDH per SD decrease in LVEDP was 4.37 (p=0.08). There was no significant association between IDH and predialysis systolic BP or IDWG.

Conclusions: Non-invasive LVEDP measurements can identify hemodialysis patients with volume overload associated with symptoms (high LVEDP) and patients at risk for IDH (low LVEDP). Our ongoing study may help confirm these initial findings and define the role of this measurement for volume management in dialysis patients.

E/e’ Calculated by Tissue Doppler Echocardiography and Cardiovascular Outcome in Incident Dialysis Patients

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Background: The ratio of early diastolic peak mitral flow velocity (E) to early mitral annular velocity (e’), called E/e’, is a less volume dependent, non-invasive index to estimate left ventricular (LV) filling pressure. However, the prognostic value of E/e’ has not been evaluated sufficiently in patients with end-stage renal disease (ESRD).

Methods: The patients who newly started maintenance dialysis therapy between 2009 and 2012, had survived for at least 3 months after dialysis initiation, and had E/e’ data, were analyzed. E/e’ was calculated by pulse and tissue Doppler echocardiography. Cardiovascular (CV) composite endpoint comprised hospitalization for heart failure (HF), acute coronary disease (ACD) requiring intervention, ventricular arrhythmia, cerebral infarction or hemorrhage, and CV death. The patients were followed up until 2013.

Results: A total of 206 patients were analyzed (mean age 55.0±13.7 years old, female 51.5%). Median follow-up duration was 29.2 months (range 3.1-61.3). Forty-two CV events occurred during follow-up (15 HF, 17 ACD, 1 cerebral infarction, and 9 CV deaths). Mean E/e’ was 13.6±5.4 (range 5.3-39). After adjusting age, sex, diabetes, mean arterial pressure, LV ejection fraction, hemoglobin, serum albumin, C-reactive protein and volume status, one unit increase in E/e’ ratio was associated with 7% increase in the risk of CV composite endpoint (hazard ratio 1.07, 95% confidence interval 1.02-1.13, p=0.009). Adjusted hazard ratio linearly increased above 15 of E/e’ in Cox regression with cubic splines.

Conclusions: A higher E/e’ ratio, reflecting high LV filling pressure which is the main physiological finding of diastolic HF, may be associated with a higher CV risk in patients with ESRD.
**TH-PO918**

Tallium-201 Washout Rate of Single Photon Emission Computed Tomographic Myocardial Perfusion with Pharmacologic Stress as a Predictor of Mortality in CKD Patients Undergoing Hemodialysis: An Observational, Follow-Up Study

**Toshihide Hayashi, Nobuhiko Joki, Masaki Iwasaki, Ai Matsukane, Takasuke Asakawa, Yuri Tanaka, Hiroki Hase.** Div of Nephrology, Toho Univ Ohashi Medical Center, Tokyo, Japan.

**Background:** Tallium-201 (201Tl) washout rate of single photon emission computed tomography (SPECT) has been reported to correlate with coronary flow reserve which is an index of myocardial microcirculation and be useful to detect coronary artery disease and evaluate the severity. However, the evidence for its use in chronic kidney disease (CKD) has been lacking, and the association between 201Tl washout rate and mortality is unknown. Therefore, a hospital-based, prospective, cohort study was conducted to evaluate the predictive ability of 201Tl washout rate for mortality in CKD patients undergoing hemodialysis.

**Methods:** A total of 156 patients who had been started on maintenance hemodialysis undergoing pharmacologic stress tallium-201 SPECT within 1 year, 107 men and 49 women, with a median age of 67 years, were studied. The endpoint was defined as all-cause death. The Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

**Results:** During the mean follow-up period of 3.2 ± 2.4 years, 30 (19.2%) deaths occurred. The median (interquartile range) of 201Tl washout rate was 45.1 (37.4 - 50.8)%. Cumulative survival rates at 5 years after starting dialysis, with 201Tl washout rate levels above and below the median, were 76.7% and 63.8% (p = 0.992, log-rank test), respectively. Overall, the multivariate Cox regression analysis revealed that 201Tl washout rate remained an independent predictor of death after adjusting by confounding variables (HR 0.95, 95% CI 0.90 to 0.99).

**Conclusions:** Among CKD patients undergoing hemodialysis, 201Tl washout rate seems to be useful for predicting death.

**TH-PO919**

Research Cardiac Magnetic Resonance Imaging in Chronic Kidney Disease – Incidence, Significance and Implications of Unexpected Incidental Findings

**Elaine Rutherford, Jonathan Weissmuller, Rajan K. Patel, John Gruene Houston, Giles Roditi, Allan Struthers, Alan G. Jardine, Patrick B. Mark.** Div of Cardiovascular & Diabetes Medicine, Univ of Dundee; 1Dept of Cardiovascular & Medical Sciences, Univ of Glasgow.

**Background:** Left ventricular (LV) mass on cardiac magnetic resonance imaging (CMR) is a common end point of clinical trials in nephrology. Incidental findings (IF) on CMR. A suitably trained radiologist should prospectively review all CKD CMR research and reviewed their impact on patient care.

**Methods:** Among CKD patients undergoing hemodialysis, 201Tl washout rate seems to be useful for predicting death.

**Results:** During the mean follow-up period of 3.2 ± 2.4 years, 30 (19.2%) deaths occurred. The median (interquartile range) of 201Tl washout rate was 45.1 (37.4 - 50.8)%.

**Conclusions:** Among CKD patients undergoing hemodialysis, 201Tl washout rate seems to be useful for predicting death.

**TH-PO920**

A Significance of Cardiothoracic Ratio for Mortality in Hemodialysis Patients: The Q-Cohort Study

**Ryuji Koyama, Masahiro Eriguichi, Shigeru Tanaka, Masatomo Taniguchi, Hideki N. Hirakata, Kazuhiko Tsuyama, Takanari Kitazono.** 1Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; 2Dept of Integrated School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Dept of Integrated School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 4Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan.

**Background:** Cardiothoracic ratio (CTR) of chest X-ray is commonly used to determine the volume status in hemodialysis (HD) patients. Thus, the present study was conducted to evaluate the significance of CTR in terms of longitudinal prognosis of HD patients.

**Methods:** A total of 3,437 Japanese HD patients aged ≥18 years were followed for 4 years. Patients were divided into four groups according to quartiles of CTR levels by sex. Risk estimates were calculated by a Cox proportional hazards model, adjusting for potential confounders. We investigated stratified analysis by sex, age, etiology of end-stage kidney disease, history of major adverse cardiac events (MACE) and blood pressure for subanalysis.

**Results:** The median values (interquartile range) of CTR were 0.49 (0.46–0.53) in male and 0.52 (0.48–0.56) in female. During the follow-up period, 564 patients (16%) died from any causes and the 4 years survival rate decreased significantly with higher CTR levels (p trend <0.001). Compared with the lowest CTR quartile, the multivariable-adjusted hazard ratios (HRs) for all-cause mortality were 0.89 (95% confidence intervals, 0.66–1.21), 1.41 (1.07–1.86), and 1.52 (1.17–2.00) in subjects with low–intermediate, high–intermediate and highest quartile, respectively. Furthermore, the combination of higher CTR levels and history of MACE or lower blood pressure before HD (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) synergistically increased the risk of all–cause mortality.

**Conclusions:** A higher CTR level is closely related to increased mortality in HD patients. This association is more remarkable in patients with history of MACE or without high blood pressure.

**TH-PO921**

High Convection Volumes in Postdilution Online Hemodiafiltration (HDF) Are Feasible in the Vast Majority of ESKD Patients

**Camiel L.M de Roij van Zuidewijn, Isabelle Chapdelaine, Men Ju Jeub, Peter J. Blankenstijn, Constantijn Konings, Tonnis K. Kremer Hovinga, Neelke C. Van Der Weerd, Pieter M. Ter Wee, Muriel P. Grooteman.** 1Nephrology, VU Med University Center Amsterdam; 2Internal Medicine, Catharina Hospital, Eindhoven, Netherlands; 3Internal Medicine, Martini Hospital, Groningen, Netherlands; 4Nephrology, Academic Medical Center, Amsterdam, Netherlands.

**Background:** Available evidence suggests a survival benefit for patients treated with high volume postdilution HDF (hvHDF) when compared to HD. Since these studies are limited by an observational design, we investigated whether hvHDF (>2L/session) is feasible in the majority of patients (>75%).

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: A prospective, multicenter study was performed (NCT01877499). HD(F) patients (n=1784) were eligible for analysis. Non-participating eligible patients formed a reference group to examine the representativeness of the study group. Treatment-related determinants of the convection volume were optimized in a stepwise fashion (treatment time [TT] up to 4 hours, blood flow rate [BFR] up to 400 mL/min and filtration fraction [FF] up to 33%). At the end of this protocol (T0) and 4 (T4) and 8 (T8) weeks thereafter, the convection volume was determined.

Results: Baseline characteristics were comparable in participants (n=86) and references (n=58). At T0 and at T4, 79/86 (92%) and 68/79 (89%) patients achieved hvHDF (mean 26.5±3.56 and 26.3±3.36L/session, resp). Hereafter, 2 patients died and 1 was transplanted. 83 patients remained; 66 (80%) reached hvHDF (mean 25.9±3.5L/session, fig 1). Study discontinuation (n=9), TT <4h (n=4) or BFR £300 mL/min (n=4) caused a convection volume <22L/session.

Conclusions: hvHDF is feasible in the vast majority of ESKD patients. As TT remained virtually unaltered, these findings were mainly due to a higher BFR and FF. Funding: Pharmaceutical Company Support - Fresenius Medical Care

TH-PO922

Physical Activity Among Patients with End-Stage Renal Disease: Use of the Exercise Vital Sign  Shavna L. Henry, Yi-Lin Wu, John J. Sim, Michael K. Gould. 1 1 Dept of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA; 2 Dept of Nephrology, Kaiser Permanente Southern California Los Angeles Medical Center, Los Angeles, CA.

Background: Exercise has been shown to improve physical functioning among ESRD patients. However, ESRD patients report exceedingly low levels of physical activity (PA) with only 13-34% engaging in recommended levels of PA. Although ESRD is characterized by substantial barriers to PA, low PA puts patients at risk for serious complications and higher mortality. Within Kaiser Permanente (KP), patients are administered the Exercise Vital Sign (EVS) – self-reported weekly minutes of PA – during each office encounter. The EVS has been validated in multiple KP regions, with roughly one-third each of the membership reporting no, insufficient, and sufficient PA, or >150 minutes exercise/week. Although the relationship between EVS reports and cardiometabolic status has been examined, levels of PA reported by ESRD patients using the EVS have not yet been explored.

Methods: EVS reports of all KP patients with a diagnosis of ESRD between January 2013 and July 2014 (N=8,187, Female=3,534, Mean Age=63.3 years) were assessed.

Results: Patients were 25% White, 38% Black, 23% Hispanic, 12% Asian, and the remainder Other, consistent with the regional patient catchment; just over 50% were married. The majority (88%) had comorbid HTN, 65% had comorbid DM, and 37% comorbid CHF. On average, patients had four other comorbid illnesses. During the study period, patients presented for 135,562 encounters. The mean reported PA frequency was 1.4 times per week (SD=2.2), for a mean 12.3 minutes/bout (SD=22.4), or an average of 49.9 minutes/week (SD=103.2) and a median zero minutes/week. The majority of ESRD patients did not achieve sufficient levels of PA during this period; 75% of the sample exercised for <50 minutes/week.

Conclusions: Self-reported rates of PA among ESRD patients at KP are critically low. Implications of low PA for cardiovascular and other outcomes as well as for interventions to improve rates of PA in this diverse population will be discussed.
Conclusions: Patient prioritized outcomes are focused on maintaining a quality lifestyle above the usual outcomes in HD trials i.e. death, adverse events, and biological markers. Researchers need to consider interventions that could improve these outcomes, and measure and report patient-relevant outcomes in trials.

TH-PO925

Medicare Advantage (MA) Is Associated with Lower Rates of Mortality versus Medicare Fee-For-Service (MFFS) Among Incident End-Stage Renal Disease (ESRD) Patients

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Background: Patients with ESRD have a high burden of comorbid illness and are complex to manage and may therefore benefit from programs like MA that facilitate care coordination. Currently, ESRD patients are barred from enrolling in MA after onset of ESRD; however, those already enrolled at the time of ESRD onset may remain enrolled. To understand the potential impact of MA among ESRD patients, we compared mortality rates among patients who began dialysis enrolled with MA versus MFFS.

Methods: Adult patients initiating hemodialysis (HD) or peritoneal dialysis (PD) between 01 Jan 2009 and 30 Jun 2011 and who were enrolled with MA or MFFS as of ESRD onset were considered. MA patients were matched 1:1 to MFFS controls based on initial modality, access type, and propensity score (based on 26 demographic and clinical variables). Patients were followed from dialysis initiation until death, transplant, lost to follow up, change in benefits status, or end of study (31 Dec 2011). Mortality rates were compared using negative binomial models. Sensitivity analyses considering early and latent follow up, change in benefits status, or end of study (31 Dec 2011). Mortality rates were compared using negative binomial models. Sensitivity analyses considering early and latent effects were performed using piecewise methods.

Results: Compared to MFFS, MA was associated with lower rates of mortality (64.3 vs 70.7 deaths/100 patient-years; incidence rate ratio, 0.91). Mortality effects were limited to the first 24 months of dialysis and were attenuated after the first 24 months of dialysis.

Conclusions: Enrollment in MA was associated with substantially lower rates of mortality during 2009-2011.
laboratory measurements and dialysis-related information. We used logistic regression and 10-fold cross validation to identify and validate a model of significant predictors. The Model discrimination and calibration were measured by c-statistic and Hosmer-Lemeshow goodness-of-fit respectively. A point system was created based on regression coefficients of predictors in the final model.

**Results:** 2,211 patients initiated dialysis, of whom 386 (17.4%) died within 6 months. Significant predictors of 6-month mortality were: age ≥80, vascular access with central venous catheter, baseline eGFR 10-14.9 or >15mL/min/1.73m², normal proteinuria, atrial fibrillation, lymphoma and congestive heart failure (CHF). Model discrimination (C-Statistic: 0.73) and calibration (Hosmer-Lemeshow c²: 6.09; p=0.64) were good. A 40-point scale for 6-month mortality was created based on model coefficients with points assigned based on strength of each predictor as specified in Table 1.

**Conclusions:** We derived and internally validated a clinical risk prediction tool for 6-month mortality for older adults initiating dialysis, using age, vascular access, eGFR, proteinuria, atrial fibrillation lymphoma and CHF as predictors. The results require external validation prior to use in clinical practice. A tool such as this can guide decision making for older adults with kidney failure.

**TH-PO929**
Coping Strategies and Outcomes Among Hemodialysis (HD) Patients in the DOPPS

**Methods:** Patients from 6 DOPPS countries completed the Coping Strategies Inventory-Short Form (CSI-SF), which we found to be reliable and valid in those countries for measuring 4 coping strategies: problem-focused engagement (PFE) and disengagement (PFD), and emotion-focused engagement (EFE) and disengagement (EFD); and summary measures of engagement (actions to confront stressors) and disengagement (avoiding exposure to stressors). Outcomes were QoL (from SF-12 and KDQoL-SF), depression symptoms (from CES-D), and all-cause mortality. Mixed linear and logistic models were used to estimate coping effects, adjusting for country and potential confounders.

**Results:** The sample included 2,062 HD patients from the US, UK, Australia/New Zealand, Canada, and Sweden in DOPPS4 (2009-11). In general and whatever the instrument, both engagement coping strategies and the summary score were positively associated with better QoL scores and inversely associated with depression symptoms. In contrast, disengagement strategies were inversely associated with better QoL scores and positively associated with depression symptoms. The PFE score was inversely associated with mortality (HR =0.78 per 4 points higher score; 95% CI: 0.66-0.9).

**Conclusions:** Engagement strategies appear to be beneficial and disengagement detrimental for HD patients. A better understanding of the coping strategies used by patients may have prognostic implications and may help to improve disease management by providing tailored care for each patient.

**TH-PO930**
Intradialytic Aerobic Cycling Exercise Improve Inflammation Status, Endothelial Progenitor Cells and Bone Density in Patients with End Stage Renal Disease (ESRD) on Maintenance Hemodialysis

**Introduction:** End-stage renal disease (ESRD) on maintenance hemodialysis (HD) and osteodystrophy (OD) are crucial health issues. HD patients show reduced physical function and greater risk of arteriosclerosis because of hypertension, metabolic disturbances, and vascular calcification. Meanwhile, exercise training in hemodialysis patients improves fitness, physical function, quality of life, and markers of cardiovascular disease such as arterial stiffness. This study aimed to determine whether aerobic training and electrical stimulation to skeletal muscles for 12 weeks could improve physical function and dialysis efficacy in patients with end-stage renal disease (ESRD).

**Methods:** This was a multicenter trial. A total of 35 ESRD patients on three occasions (20 males, 15 females; age: 70±11.7 years) were randomized to receive 12 weeks of aerobic training exercise during hemodialysis session (Ex-group: n=19), electrical stimulation to the lower limbs (ES-group: n=6), or no specific intervention (Cont-group: n=10). The Borg

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
scale was used to control the intensity of training. At baseline and study completion, the primary outcome measures were grip strength, quadriceps strength, workload time, activities, dialysis efficacy, HDL, LDL, CRP, IL-6 and blood pressure. 

Results: In the Ex-group, handgrip, quad torque, and workload time increased significantly (P<0.05). Dialysis efficacy, HDL-cholesterol, LDL-cholesterol, CRP, and blood pressure on the morning of the dialysis day also improved significantly (P<0.05). These effects were not observed in the Cont-group. In the ES-group, quad muscle torque and dialysis efficacy increased significantly (P<0.05), IL-6 decreased significantly (P<0.05), compared to the other two groups.

Conclusions: In this study, the safety and efficacy of training and electrical stimulation during hemodialysis were confirmed without sudden drop of blood pressure or any other side effects. Therefore, training during hemodialysis session for 12 weeks might improve physical function with specific whole-body effects as well as local effects in ESRD patients.

TH-PO932
Glycemic Markers and 2-Year Non-Diabetic Hemodialysis Outcomes from the Glycemic Indices in Dialysis Evaluation Study

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Background: The ongoing GIDE (Glycemic Indices in Dialysis Evaluation) study includes data on nonDM hemodialysis (HD) patients (confirmed by HgbA1c <6.5%). Because nonglycemic factors may lower HgbA1c levels in ESRD, we previously reported their glycemic status/1-year outcomes using alternative glycemic markers [albumin-adjusted and unadjusted fructosamine (AlbF,F) and glycated albumin (GA) or percent GA (%GA)]. We now report 2-year study data.

Methods: 970 nonDM HD patients from 26 FMCNA facilities with glycemic markers from Jan-March 2013 were followed until April, 2015. Baseline AlbF, F, GA and %GA were used to classify patients as high or low glycemia using thresholds of AlbF>97µmol/L, F>285µmol/L, %GA>15.7%, and GA>380µmol/L. Standard and Time-dependent (TD) Cox models with case-mix adjustment for age, sex, race, ethnicity, vintage, BMI, HD catheter and baseline comorbidity were used to determine associations between each glycemic index and hospitalization/death risk.

Results: While 1% had HgbA1c>7%, high glycemic status was more commonly detected using F (59%), AlbF (4%), GA (15%) and %GA (29%). Elevated AlbF was significantly associated with 2-year mortality [Standard Cox: Hazard Ratio (HR)=2.53, 95% CI (1.31, 4.92), p=0.006; TD Cox: HR=3.55, 95% CI (1.97, 6.38), p<0.0001] and hospitalization [TD Cox: HR=2.49, 95% CI (1.70, 3.67), p<0.0001]. For all other glycemic markers, no such associations were evident at the proposed thresholds using adjusted analyses in the Cox model.

Conclusions: These data support our previous findings of an association between poor glycemic status (high AlbF) and hospitalization/mortality outcomes in nonDM HD patients. High AlbF-glycemic status may have prognostic implications in nonDM HD patients.

TH-PO933
Association of Change in Serum HDL Cholesterol with Mortality in Hemodialysis Patients: Role of Gender

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Background: Elevated high-density lipoprotein cholesterol (HDL) levels, though protective in the general population, can be associated with higher mortality in hemodialysis (HD) patients. Association of HDL change over time with mortality has yet to be examined. Based on previous studies, we hypothesized that upward trends in HDL levels may be associated with higher mortality risk in HD patients.

Methods: We examined HDL change over time in 24,400 incident HD patients receiving care from a large dialysis organization in 2007-2011. Association of delta HDL (HDL change between the 1st and 2nd 91-day interval from dialysis start) and HDL trajectory with all-cause mortality were examined using mixed effect and Cox regression models and adjusted for demographics, comorbidities and baseline HDL. Delta HDL was treated both as a continuous variable using restricted cubic splines and in categories:< 6, > 6, 0, < 2, 2 -< 6, and ≥6 mg/dL.

Results: Patients were 65:15 years old, 44% female, 31% black, 66% diabetic with a mean baseline HDL 40.5±13.9 mg/dL and HDL change 1.7±10.4 mg/dL. While male patients had no significant change in HDL over time, females had a significant decrease in HDL (mean -0.6mg/dL/year). A ≥6 mg/dL increase or decrease in delta HDL was associated with a 7% and 13%, respective increase in all-cause mortality compared to reference group. Delta HDL-mortality associations did not differ across gender.

Conclusions: Decreased HDL over time was associated with worse outcomes and increased HDL was paradoxically associated with higher mortality. While HD treatment can be associated with a decrease in HDL, this effect was magnified in younger females. The novel and intriguing role of age and gender in association of HDL and survival needs further evaluation.

Funding: NIDDK Support

TH-PO934
Differences in Perceived Kidney Disease Burden on Quality of Life by Race/Ethnicity in a Diverse Cohort of Hemodialysis Patients

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Background: Low health-related quality of life (HRQOL) has been well-documented in patients with end-stage renal disease on hemodialysis (ESRD). While African Americans and Hispanics remain at increased risk for ESRD, HRQOL has been less well-described in these individuals compared to non-Hispanic whites.

Methods: Baseline HRQOL data was analyzed for participants enrolled in the Patient-Centered Medical Home for Kidney Disease study (PCMH-KD), a trial of a multidisciplinary, patient-centered primary care intervention in a population of hemodialysis patients at two dialysis facilities in Chicago. The Kidney Disease Quality of Life (KDQOL-36) instrument was used to assess HRQOL at baseline, and the following subscale scores were obtained: Physical, Mental, Burden of Kidney Disease, Symptoms, and Problems, and Effects of Kidney Disease.

Results: Baseline data were available for 95 patients. Approximately, 52% of patients were African-American, and 45% were Hispanic. Significant racial/ethnic differences were observed among subscales of self-reported HRQOL.

Conclusions: Hispanic patients with ESRD on HD report disproportionate burden and effects of kidney disease on HRQOL and worse mental HRQOL compared to African American patients with ESRD on HD. Further exploration of these disparities may lead to strategies for improvement of HRQOL in Hispanic patients.

Funding: Private Foundation Support

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

309A
Relative Blood Volume and Mortality in Hemodialysis Patients

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1 Fresenius Medical Care North America (FMCNA), Waltham, MA; 2 Renal Research Inst (RRI), New York, NY.

Background: A quality improvement project on fluid management on Crit-Line® Monitors (CLM) was conducted across multiple RRI facilities. Percent change in relative blood volume (RBV) was measured during routine hemodialysis (HD). Previous analyses of the same cohort have shown associations between RBV reduction and reduced hospital admission rate; the current analysis assesses mortality.

Methods: A retrospective analysis of HD treatments with RBV measurements was conducted over 6 months. RBV was calculated using: RBV = [Hematocrit(Hct) / Hematocrit(Hct), baseline] x 100. Average RBV at the end of HD was calculated for 1099 patients (22,579 treatments with RBV). Patient deaths were recorded as part of routine clinical procedures over the same 6 months. Mortality rate per patient month was calculated as # deaths/patient month. Time to death was modeled using Cox proportional hazards model.

Results: Patients were divided into RBV categories by 5% increments and compared on risk of death during the 6 months (Table). There was an increased risk of death with less reduction in RBV. For example, using patients with the greatest reduction in RBV (< -15%) as the reference, patients with the least reduction in RBV by the end of HD had 16% increase in risk of death for each 1% increase in the end of HD blood volume (p<0.001). Similar results were obtained after adjustment for age, gender, and race (11% increased risk, p=0.002).

Conclusions: In a large cohort of HD patients with relative blood volume measured, patients with less reduction in percent change in relative blood volume at the end of dialysis had higher risk of death over 6 months when compared to patients with greater reduction. These patients may represent a subset of patients at high risk for adverse outcomes and may benefit from fluid management programs.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

The Effect of Altitude on Erythropoiesis-Stimulating Agent Dose, Hemoglobin Level, and Mortality in Hemodialysis Patients

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1 DaVita Clinical Research, Minneapolis, MN; 2Akebia Therapeutics, Cambridge, MA.

Background: Prior studies have shown that hemodialysis (HD) patients residing at high elevations have lower erythropoiesis-stimulating agent (ESA) utilization, possibly due to activation of hypoxia-regulated genes. We sought to better understand the impact of altitude and dosing of anemia medications and mortality following 2011 changes to the US epoetin alfa label and reimbursement policy.

Methods: We studied a cohort of prevalent nonveteran HD patients (vintage >6 months) treated at a large dialysis organization between 1 Jan 2012 and 31 Dec 2012. Patients were compared across categories for altitude of long-term hemodialysis (Hb) level, ESA and intravenous (IV) iron dose, and mortality risk using mixed linear models. Associations were adjusted for baseline demographic and clinical characteristics.

Results: Compared to altitude of 0-1499 ft, higher altitude was incrementally associated with greater Hb level and lower mean ESA dose; mean IV iron utilization did not differ. Altitudes of ≥4500 ft (vs 0-1499 ft) was independently associated with lower mortality risk; incidence rate ratio (IRR) was 0.74 with 95% confidence interval (CI) 0.63-0.88.

Conclusions: Among contemporary HD patients receiving treatment at ≥1500 ft, higher altitude was independently associated with greater Hb level and lower mean ESA dose; mean IV iron utilization did not differ. Altitude of ≥4500 ft was independently associated with a 26% lower mortality risk.

Funding: Pharmaceutical Company Support - Akebia Therapeutics

Softeroject Improves Anemia, Vascular Calcification, and Bone Loss in Patients with End-Stage Kidney Disease on Hemodialysis

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Background: This ongoing, randomized, single-blind, placebo (PBO)-controlled study evaluated the pharmacokinetic (PK), safety, and hemoglobin (Hb) effect of soferoject, an ActRIIA-IgG1 fusion protein ligand trap, in hemodialysis (HD) subjects and explored its effects on vascular calcification (VC) and bone mineral density (BMD) using quantitative computed tomography (QCT).

Methods: Subjects were washed out of erythropoietin-stimulating agent (ESA) effects until Hb was <10 g/dL and randomized to PBO or soferoject given subcutaneously every 225 days for 8 days for up to 8 dose cycles. Treatment (Hb =9 g/dL) were rescued with ESA or transfusion; intrasubject dose escalation was not permitted. QCT scans of the hip, lumbar spine, and abdominal aorta were obtained at baseline and after the 225-day treatment phase. Interim results are reported for PK, safety, bone BP, Hb, VC, and BMD effects in the 0.3, 0.5, and 0.7 mg/kg dose groups.

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Underline represents presenting author.

Table 1. Ability of TSAT and ferritin at higher altitudes to predict ESA usage>75th percentile. TSAT 1-28, ferritin 11-52 are reference groups. AC: active control; FC: ferric citrate

<table>
<thead>
<tr>
<th>Altitude (ft)</th>
<th>Total % Patients</th>
<th>ESA Usage, %</th>
<th>TSAT (%)</th>
<th>AC</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15%</td>
<td>47</td>
<td>730</td>
<td>0.004</td>
<td>1</td>
<td>(Reference)</td>
</tr>
<tr>
<td>-14.9 to -10%</td>
<td>254</td>
<td>41821</td>
<td>0.006</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>-9.9 to 0%</td>
<td>507</td>
<td>80408</td>
<td>0.010</td>
<td>2.45</td>
<td></td>
</tr>
<tr>
<td>&gt;0%</td>
<td>263</td>
<td>39098</td>
<td>0.017</td>
<td>3.96</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Ability of TSAT and ferritin at higher altitudes to predict IV iron use > median use for visits with non-zero dose. TSAT 1-28, Ferritin 11-52 are reference groups. AC: active control; FC: ferric citrate

<table>
<thead>
<tr>
<th>Altitude (ft)</th>
<th>Total % Patients</th>
<th>IV iron use &gt; median use</th>
<th>TSAT (%)</th>
<th>AC</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15%</td>
<td>47</td>
<td>730</td>
<td>0.004</td>
<td>1</td>
<td>(Reference)</td>
</tr>
<tr>
<td>-14.9 to -10%</td>
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<tr>
<td>&gt;0%</td>
<td>263</td>
<td>39098</td>
<td>0.017</td>
<td>3.96</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: TSAT predicted IV Iron/ESA, TSAT>37% showing lowest use. In these ranges no TSAT limit existed over which further IVIron/ESA did not occur. ferritin levels predicted IV Iron in non ESA use. TSAT may better predict ESA responsiveness in ESRD

Conclusions: Distributions of CKD-MBD parameters varied by region, possibly resulting in differential risk of adverse outcomes. Our findings in this international cohort highlight the importance of simultaneous, rather than independent, control of MBD parameters within clinical guidelines ranges.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGIN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support

TH-PO940
US DOPPS Practice Monitor: Comparisons with CMS ESRD Databases

Douglas S. Fuller, Lindsay Zepel, Keith McCullough, Brian Bieber, Ronald L. Pisoni, Francesca Tentori, Bruce M. Robinson. Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: Since August 2010, the Dialysis Outcomes and Practice Patterns Practice Monitor (DPM, www.dopps.org/DPM) has leveraged its US hemodialysis (HD) sample (now >200 facilities) to provide timely and detailed (>750 data tables) updates on national trends in HD care. Here we compare DPM estimates to available results from end-stage renal disease (ESRD) data sources collected by the Centers for Medicare and Medicaid Services (CMS).

Methods: Pearson correlations (r) were used to compare contemporary trends since Aug 2010 between DPM and the 2014 US Renal Data System Annual Data Report (ADR, through Dec 2012) and the Nov 2014 CMS Claims-Based Monitoring Project (CBMP, through Jun 2014). We also compared monthly DPM estimates with cross-sectional estimates from 2014 CrownWEB (CW, Dec 2013).

Results: DPM trends in ESA dose use and IV iron use, and hemoglobin levels were highly correlated (r= 0.89-0.98) with ADR and CBMP trends. Compared to CW, DPM showed slightly higher fistula use, but slightly lower percent of patients with adequate Kt/V and URR values.

Table: Comparisons of US DPM national estimates to CMS ESRD data sources

<table>
<thead>
<tr>
<th>Reference</th>
<th>DPM Estimate (SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESA dose</td>
<td>10.49, 0.26</td>
<td>0.001</td>
</tr>
<tr>
<td>IV iron</td>
<td>61.4%, 0.1%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean Hgb</td>
<td>11.6, 0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Fistula use</td>
<td>68.9%, 0.1%</td>
<td>0.9</td>
</tr>
<tr>
<td>Catheter use</td>
<td>16.1%, 0.08</td>
<td>0.1</td>
</tr>
<tr>
<td>Kt/V &gt;1.2</td>
<td>97.3%, 0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>URR &gt;65%</td>
<td>94%, 0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Abbreviations: DPM, Dialysis Outcomes and Practice Patterns Practice Monitor; CMS, Centers for Medicare and Medicaid Services; USRDS, US Renal Data System; ADR, USRDS Annual Data Report; CW, CrownWEB; CBMP, CMS ESRD Claims-Based Monitoring Project; Hb, hemoglobin; URR, urea reduction ratio; ESA, erythropoiesis-stimulating agent.

Among ESRD-treated patients

Conclusions: DPM reports IV medications as prescription at the end of the month (before Apr 2012) or anytime during the month (Apr 2012 and after), rather than administration. Thus, estimates for ESA and IV iron utilization each month may be somewhat different due to spontaneous or withheld dosing. Differences with CW cross-sectional estimates may result from differences in calculation methods. DPM includes non-Medicare patients that are not necessarily present in claims-based sources. DPM now includes 14 years of monthly estimates for all patients in US HD care. Although similarities in data sources and specifications may influence direct comparisons, DPM data remain an important resource for identifying important trends in HD care before confirmations from CMS ESRD databases are available.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGIN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support.

TH-PO941
Reduced Free Triiodothyronine Is an Independent Predictor of Clinical Outcomes in Hemodialysis Patients with Low Albuminemia

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Background: Low free triiodothyronine (fT3) and free thyroxine (fT4) are both related to malnutrition, inflammation and mortality in dialysis patients. Upper-normal thyrotropin (TSH) levels are also associated with a higher risk of total mortality in hemodialysis (HD) patients. However, it remains unclear which of thyroid-related hormones is most useful in predicting clinical outcomes. So, we aimed this study to compare the prognostic value of different hormones in prevalent HD patients.

Methods: We enrolled 339 HD patients (age: 64±13 years old, time on HD: 129±114 months), and measured basal fT3, fT4 and TSH. We then followed the patients for the next 42 months, and assessed the impact of fT3, fT4 and TSH on all-cause mortality and cardiovascular (CV) events or hospitalization. Patients were divided into the 4 groups based on the quartiles of fT4, fT3 and TSH. The associations of basal levels with clinical outcomes were examined with Cox proportional hazards models adjusted for demographic and clinical factors and comorbidities.

Conclusions: Distributions of CKD-MBD parameters varied by region, possibly resulting in differential risk of adverse outcomes. Our findings in this international cohort highlight the importance of simultaneous, rather than independent, control of MBD parameters within clinical guidelines ranges.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGIN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support.

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Results: Mean serum fT3 and fT4 were 2.01±0.37 [0.95-3.73] pg/mL and 0.86±0.20 [0.35-1.67] ng/dL. Serum levels of fT3 and fT4 were lower than those of reference ranges in 85.0% and 56.0% of the patients, respectively. In contrast, TSH levels were within the reference range in most patients (92.9%). Cox hazards analyses revealed that the lowest quartile of fT3 (<1.75 pg/mL) was an independent predictor of all-cause mortality (HR 3.55 [95%CI: 1.17-4.09, p=0.001]), all-cause mortality plus CV events (HR 2.19 [95%CI: 1.53-3.823, p=0.001]) and all-cause mortality plus hospitalization (HR 2.16 [95%CI: 1.28-3.67, p=0.001]) when compared with those with the top quartile (fT3>90 pg/mL). However, the significant impact of low fT3 on prognosis was observed only in patients with serum albumin lower than 3.8 g/dL (n=195). In contrast, serum fT4 and TSH levels did not relate to prognosis.

Conclusions: These findings suggest that low fT3 became an independent predictor of clinical outcomes in HD patients with low albuminemia.

TH-PO942
Low Socioeconomic Status and Co-Morbidity Are Associated with Limited Health Literacy in RRT Patients – Results from the ATTOM Study
Dominic Taylor, The ATTOM investigators. *Southmead Hospital, Bristol, United Kingdom.*

Background: Limited health literacy (LHL) is a risk factor for poor outcomes in chronic disease patients. Studies with limited patient numbers in RRT patients associate LHL with low socioeconomic status (SES), comorbidity and ethnicity.

Methods: This cross-sectional study used baseline data from the ‘Access to Transplantation and Transplant Outcome Measures’ (ATTOM) cohort. ATTOM recruited incident dialysis and transplant patients aged 18-75 years in the UK during 2011-2013 and also waited-listed patients similar to those transplanted (matched controls). Health literacy was measured by the question ‘How often do you need someone’s help to read instructions, leaflets, or other written material from your doctor or pharmacy?’ answered on a scale from 1-Never to 5-Always. LHL was defined as a score greater than 2. The three groups were analysed for associations between LHL and demographics, SES factors and comorbidity, using univariate and multivariate analysis, p<0.05.

Results: 6842 patients were recruited: 2621 incident dialysis (ID), 2262 incident transplant (IT) and 1959 matched controls (MC). In univariate analyses, in all groups, English not as first language, Asian ethnicity, low educational level, unemployment, absence of car or home ownership, increased comorbidity by modified Charlson index and mental illness were associated with LHL. In adjusted models, in all groups, the following factors were associated with LHL: English not as first language (OR=2), modified Charlson index (OR 1.2 for each point above zero), low level of education (OR=2 for no qualifications compared to any), unemployment (OR=3.0 compared to employed) and absence of car ownership (OR 1.7).

Conclusions: In this large nationwide study, low SES and co-morbidity are associated with LHL in patients receiving dialysis or at the point of transplantion, independent of first language. LHL may impact upon patients’ ability to engage with shared decision making and their capacity to cope with the burden of disease and treatment.

Funding: Other NIH Support - NIH(R01) (UK)

TH-PO943
Comparing Dialysis Facility Compare (DFC) Star Rating to QIP Payment Categories
Claudia Dahlerus,1 John Wheeler,1 Deanna Chyn,1 Yanning Li,1 Richard Hirth,1 John Kalbfleisch,1 Jennifer Sardone,1 Zhi He1, Tempie H. Shearón,1 Joel S. Andress,2 Elena K. Balovlenkov,2 Yi Li.1 1Biostatistics, Kidney Epidemiology and Cost Center, 2Centers for Medicare & Medicaid Services.

Background: CMS recently developed hospital readmissions measures to reflect quality of care provided by nursing homes, long-term care hospitals, inpatient rehabilitation facilities, home health agencies and dialysis facilities. The intent is to encourage care coordination as patients transition between care providers. All measures adjust for patient characteristics. CMS has not adjusted quality measures for patient socioeconomic status (SES), so as not to condone disparities in care delivery. However, not including such adjustments may result in inappropriate assessments about quality of care. We present preliminary analyses assessing the association of SES and readmission among dialysis patients.

Methods: Using 2013 Medicare claims data, we model the probability of readmission, defined as an unplanned readmission within 30 days of a hospital discharge, adjusted for patient characteristics including age, sex, BMI, comorbidities, discharging hospital, and several measures of SES, plus measures reflecting SES of the patient’s area of residence.

Results: Patients with Medicare secondary payer (MSP) were less likely to experience a readmission (OR 0.92; CI:0.90-0.93); patients with dual Medicare and Medicaid coverage (OR 1.08; CI 1.08-1.09), unemployed at ESRD incidence (OR 1.07; CI 1.06-1.08) and living in ZIP codes with high unemployment, low education and income disparity were more likely to experience a readmission.

Conclusions: Insurance status and area of residence are strong proxies for SES and are associated with readmissions. MSP, largely reflective of private insurance coverage, can be an indicator of higher SES and perhaps better health. Dual eligibility for Medicare and Medicaid can be an indicator of lower SES, as can being unemployed or having ESRD incidence. As interest in risk adjusting for indicators of SES has grown, the association between SES and readmission suggests further analysis may be appropriate. However, caution must be exercised in efforts to distinguish between SES factors that may or may not be related to quality of care.

Funding: Other U.S. Government Support

TH-PO945
Co-Morbidities (CM) Do Not Predict Adverse Outcomes in Peritoneal Dialysis (PD) versus Hemodialysis (HD) in a Multi-Ethnic Asian ESRD Cohort
Ge Hsiao Lin,1 Khuan Yew Chow,1 Vathsala Anantharaman.1 1Health Promotion Board, Singapore; 2National Univ Health System.

Background: There is conflicting data on outcomes following HD vs PD. USRDS data for ESRD in 2002-2004 suggested similar outcomes for HD and PD over 5 years of followup. This study evaluated outcomes for HD vs PD from a multi ethnic Asian ESRD population and evaluated the impact of CM on worse outcomes in either modality.

Methods: 3279 HD and 1330 PD patients who were included in the Singapore National Registry (SRR) in 2001-2007 and followed up till death or 31 Dec 2012 comprised the study population. Data on patients’ demographics, CM and survival were collected. Patients were stratified by age, presence of diabetes(DM) and occurrence of 1 or more vascular(U) vs non-vascular(NV) CM. 5-year survival was compared using Kaplan-Meier and regression analyses.

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Proven by Results from Japanese Nationwide Surveys in 1998 and 2010

Significance of the Decreased Risk of Dialysis-Related Amyloidosis Now

The reduction was most prominent in patients with longer dialysis vintage, patients who were younger, and those with lower pre-dialysis b2m levels. Similar results were obtained by propensity score-matched analysis. We also found that b2m clearance >80% may reduce risk of CTS.

Conclusions: The incidence of first-time CTS as proxy for DRA decreased significantly from 1998 to 2010. Several factors may have contributed to this decrease, including improved dialysis methods.

TH-PO947
Twice Weekly Hemodialysis and Clinical Outcomes in the China DOPPS
Yucheng Yan,1 Mia Wang,2 Jia Qi Qian,2 Brian Bieber,2 Mei Wang,2 Nan Chen,3 Bruce M. Robinson,4 Shuchi Anand,4 Shen Wang,4 Shanghai Renji Hospital; 5 Arbor Research; 6 Shanghai Ruijin Hospital; 7 Stanford Univ.

Background: Outcomes related to 2 times weekly hemodialysis (HD), substantially practiced in China, remain understudied. Small, single-center studies have indicated better preservation of residual kidney function (RFK) and similar survival for 2 vs 3 times weekly HD. We used data from the China Dialysis Outcomes Practice Patterns study (DOPPS) to evaluate survival and hospitalizations by frequency of HD.

Methods: We studied 1,433 patients from 45 HD units in China (2012-2015). Cox regression was used to model the association of 2 vs. 3 times weekly HD with clinical outcomes adjusting for patient and treatment characteristics.

Results: 270 patients (19%) were undergoing 2 times weekly HD in China. Compared with 3 times weekly HD, patients on 2 times weekly HD were more likely to be female and have shorter time on dialysis (4.3 vs 2.6 yrs), more urine output, shorter dialysis session length (238 vs. 250 min) and longer travel times to facility. They were less likely to have diabetes or cardiovascular disease. Insurance coverage was similar in the two groups. During follow-up (median=1.7 years), 184 (13%) deaths and 516 (38%) hospitalizations occurred. No differences in mortality or hospitalization were found between the two frequency groups (Table). No interaction was observed with vintage (p=0.43).

Table: Progressive adjustment of mortality with twice weekly dialysis, in China

<table>
<thead>
<tr>
<th>Frequency of HD</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 times weekly</td>
<td>p value</td>
</tr>
<tr>
<td>vs 3 times weekly</td>
<td></td>
</tr>
<tr>
<td>model 1: unadjusted</td>
<td>0.90 (0.61-1.33)</td>
</tr>
<tr>
<td>model 2: model 1+patient demographics</td>
<td>0.95 (0.63-1.42)</td>
</tr>
<tr>
<td>model 3: model 2+residual kidney function</td>
<td>0.99 (0.66-1.50)</td>
</tr>
<tr>
<td>model 4: model 3+insurance</td>
<td>0.98 (0.64-1.44)</td>
</tr>
<tr>
<td>model 5: model 4+comorbidities</td>
<td>1.08 (0.72-1.61)</td>
</tr>
<tr>
<td>model 6: model 5+ktv, average intra-dialytic weight loss</td>
<td>1.00 (0.59-1.69)</td>
</tr>
<tr>
<td>model 7: model 6+labs (hgb, albumin)</td>
<td>1.06 (0.61-1.85)</td>
</tr>
</tbody>
</table>

*1393 patients, 184 events.
*age, gender, BMI, standardized, and vintage.

Conclusions: In this multi-center study with well-characterized patient and treatment data, outcomes of 2 vs. 3 times weekly HD were similar. Thus, it is possible that among carefully selected patients 2 times weekly HD may provide acceptable outcomes. An additional study is also needed due to residual confounding, small sample size, and the changes in results with progressive adjustments.

TH-PO948
Initiation of a Chronic Kidney Disease Case Manager Program Is Associated with Better Outcomes in Incident Hemodialysis Patients
Joseph A. Kahn, Patrick Bridge, John W. Larkin, Hao Han, Sheetal Chaudhuri, Len A. Usvyat, Terry Ketchersid, Franklin W. Maddux.
Fresenius Medical Care North America, Waltham, MA.

Background: The Renal Care Coordinator (RCC) Program places chronic kidney disease (CKD) case managers in the Nephrology Practice to co-manage late stage CKD (4 and 5) patients for an optimal outpatient start to Renal Replacement Therapy (RRT). This program is performed through both physical and virtual RCCs. We compared outcomes in patients starting hemodialysis (HD) who were previously enrolled in the RCC program and those who were not.

Methods: We compared outcomes in patients enrolled into the RCC program versus patients considered to have a ‘Timely Referral’ for dialysis (i.e. were followed in a

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Th-Po994

Extracellular Overhydration Measured by Multifrequency Bioelectrical Analysis Is Associated with Increased Postdialytic Systolic Blood Pressure in Hemodialysis Patients

Jae Yeul Park, Seok-hyung Kim, Ah Ran Choi, Kyung Eun Lee, Hae-yung Kim, Hoon Young Choi, Sung-Kyu Ha, Hyeong cheon Park

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Background: Postdialytic hypertension is associated with increased morbidity and mortality for hemodialysis (HD) patients. Recent studies suggest that increased postdialysis extracellular water (ECW) volume may account for the rise in postdialysis systolic blood pressure (PDSBP). The aim of this study was to assess the relationship between volume status and PDSBP in HD patients.

Methods: Volume status assessments were performed after mid-week HD using multifrequency bioelectrical impedance (BIA, Inbody S10) in supine position. Demographic and routine biochemical data were collected and pre- and post-dialysis B-type natriuretic peptide (BNP) level was measured (Triage BNP test, Alere).

Results: We enrolled clinically stable 99 HD patients from 3 dialysis centers. Patients were divided into 3 groups based on fluid overload defined by pre-dialysis systolic blood pressure (PDSBP) criteria (≥130 mmHg or ≥110 mmHg or ≥90 mmHg). The mean age was 55.1 ± 13.3 years in hypertensive, 58.3 ± 13.2 years in stable, and 65.2 ± 7.7 years in hypotensive group. Postdialysis BNP was 267.8 ± 251.1 pg/ml in hypertensive, 66.0 ± 92.9 pg/ml in stable, and 9.2 ± 21.9 pg/ml in hypotensive group. There were no differences in gender, dialysis prescriptions, and subjective global assessment score among the patient groups. The ECW/TBW ratio was significantly higher in the hypertensive group and positively correlated with PDSBP and delta BNP. The only independent risk factor affecting PDSBP was ECW/TBW ratio after dialysis.

Conclusions: HD patients who demonstrate increased in PDSBP should have their volume status reassessed and target dry weights adjusted using BIA, with emphasis on increased the ECW/TBW ratio.

TH-Po950

Novel Phosphate Binder, Ferric Citrate Hydrate, Can Reduce Serum Phosphate Levels and Doses of Erythropoiesis Stimulation Agents in Japanese Patients on Hemodialysis

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Nephrology, Nagoya Kyoritsu Hospital, Nagoya, Japan; Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

Background: Ferric citrate hydrate (FC) has been available in Japan as a phosphate binder for patients on dialysis (HD) since 2014 although its effects have not been evaluated in detail in such patients. The present study aimed to determine the effects of FC on serum phosphate levels and anemia control in patients on HD.

Methods: Thirty-eight outpatients (mean age, 62.5 ± 5 years; male, n = 28 [73.7%]; mean HD vintage, 7.2 ± 6 years; hypertension, n = 29 [76.3%]; diabetes, n = 19 [50.0%]; secondary hyperparathyroidism, n = 15 [39.5%]) on maintenance HD were treated with FC for six months to control hyperphosphatemia. Serum concentrations of phosphate, calcium, hemoglobin, and ferritin levels, transferrin saturation (TSAT), and weekly epoetin (EPO) doses were evaluated.

Results: Mean phosphate levels were significantly decreased from 7.05 ± 1.11 to 6.19 ± 0.91 (p < 0.0001), 6.14 ± 1.16 (p < 0.05) and 6.01 ± 1.11 (p < 0.005) mg/dL at one, three and six months, respectively. Calcium, hemoglobin and ferritin levels did not significantly differ during the same periods. Transferrin saturation was significantly increased (26.7 ± 10.9% vs. 20.0 ± 9.3%, p < 0.05) and the weekly EPO dose was significantly decreased (2750 ± 2699 vs. 6801 ± 7406 IU/week, p < 0.05) after six months of FC therapy.

Conclusions: FC can decrease serum phosphate levels and the weekly EPO dose. Therefore, FC is useful for treating hyperphosphatemia and renal anemia in Japanese patients on HD.

TH-Po951

Geographic Variation of Potentially Avoidable Readmissions in Hemodialysis Patients

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Background: In 2011 in the United States, 36.3% of prevalent hemodialysis patients were readmitted within 30 days of an index hospitalization. These rates are approximately twice that of the general U.S Medicare population. While some readmissions to hospital are unavoidable, it is probable that a substantial number could be prevented. In the present study, we describe inter-state variability in 30-day potentially avoidable readmissions (PAR).

Methods: The United States Renal Data System (USRDS) was used to identify prevalent hemodialysis patients (vintage >90 days) with acute hospitalizations in 2008. Exclusion criteria were transfer to rehabilitation or skilled nursing facility, unknown dialysis start date, and renal function recovery. PAR were identified using a validated, computerized algorithm (SHARP), and displayed geographically by state in map software (MapInfo).

Results: 250,606 index hospitalizations were identified, with 37% readmissions within 30 days (n = 84,279). Nationwide, 24% of index hospitalizations were followed by a 30-day PAR (64.9% of all readmissions) (n= 59,803). PAR ranged from 12% to 51% by state. The figure shows the geographic distribution of potentially avoidable readmissions.

Conclusions: There is inter-state variability in PAR among chronic hemodialysis patients, and that may be related to regional differences in practice patterns or patient demographics. Further characterization of risk factors associated with PAR is the focus of our ongoing research.

TH-Po952

Unravelling the Relationship Between Mortality, Hyponatremia, Inflammation and Malnutrition in Hemodialysis Patients: Results from the International MONDO Initiative

Marije J.E. Dekker, Daniëlle Marcelli, Bernard J. Canaud, Constantijn Konings, Karel M. Leunissen, Nathan W. Levin, Jochen G. Raimunn, Frank van der Sande, Len A. Usvyat, Peter Kotanko, Jeroen Kooman, Catharina Hospital Eindhoven; Maastricht Medical Center; Fresenius Medical Care; Renal Research Inst.

Background: Hyponatremia is a risk factor for mortality in hemodialysis patients. However, it is not well known to which extent comorbidities, such as malnutrition, fluid overload and inflammation are related to hyponatremia and influence the association between hyponatremia and outcomes.

Methods: We studied 8892 patients from the European subset of the MONDO Initiative. Nutritional and fluid status were assessed by multifrequency bioimpedance spectroscopy. Based on pre-dialysis fluid status, fluid depletion was defined as an extracellular water volume < -1.0L and fluid overload > +2.5L. Malnutrition was defined as a lean tissue index below the 10th percentile of age- and gender matched healthy controls. Hyponatremia and inflammation were defined as serum sodium levels < 135 mEq/L and C-reactive protein levels >10 mg/L, respectively.

Results: Hyponatremia was predicted by the presence of malnutrition (odds ratio (OR) 1.48 (95%CI 1.30-1.69)) and inflammation (OR 1.44 (95%CI 1.26-1.64)), but not by fluid depletion (OR 1.38 (95%CI 0.98-1.93)) or fluid overload (OR 0.99 (95%CI 0.85-1.14)). Malnutrition (hazard ratio (HR) 1.39 (95%CI 1.23-1.58)), inflammation (HR 2.31 (95%CI 2.04-2.62)), fluid overload (HR 2.17 (95%CI 1.90-2.47)) and hyponatremia (HR 1.63 (95%CI 1.39-1.90)) were independent predictors for all-cause mortality.

Conclusions: In hemodialysis patients hyponatremia is associated with malnutrition, inflammation and malnutrition but not with deranged fluid status. Hyponatremia maintained predictive for all-cause mortality after correction for malnutrition, inflammation and fluid status abnormalities. Hyponatremia may aid efforts to identify hemodialysis patients at increased risk of death.
Hyperkalemia is a major problem in dialysis patients. It is associated with increased risk of cardiac arrhythmias and sudden cardiac death. However, few studies have examined frequency of hyperkalemia episodes in a large population of dialysis patients. We present a characterization of the magnitude of hyperkalemia prevalence in a large hemodialysis population and examine the role of interdialytic interval in its occurrence.

Methods: We derived annual cohorts of hemodialysis patients (2007-2010) from linked DaVita and USRDS databases. Included patients were those receiving thrice-weekly hemodialysis. On a monthly basis, hyperkalemia case was defined as a serum potassium level greater than or equal to 5.5 mEq/L. Hyperkalemia prevalence was calculated as the proportion of dialysis patients with at least one episode of hyperkalemia during a given month. We examined the association between serum potassium levels and mortality risk, adjusting for demographic and clinical factors in time-dependent Cox proportional hazards models.

Results: Hyperkalemia defined as serum K ≥5.7 mEq/L was associated with an increased risk of mortality (adjusted hazard ratio [AHR] 1.1, 95% CI 1.01-1.28, P = 0.037, compared to K ≥5.0 mEq/L) after adjustment for demographic and clinical factors in time-dependent Cox proportional hazards models; the AHRs increased progressively as the threshold for hyperkalemia rose (AHRs 1.09 for K=5.7 mEq/L, 1.13 for K=5.8 mEq/L, 1.20 for K=5.9 mEq/L, and 1.28 for K=6.0 mEq/L). The pattern of the point estimates was similar for cardiovascular mortality, although the results did not reach statistical significance (AHRs 1.09 for K=5.7 mEq/L, 1.13 for K=5.8 mEq/L, 1.20 for K=5.9 mEq/L, and 1.28 for K=6.0 mEq/L).

Conclusions: Hyperkalemia is associated with all-cause mortality beginning at K ≥5.7 mEq/L, with mortality risk point estimates increasing in ordinal fashion through K level ≥6.0 mEq/L. A similar pattern was observed in the point estimates for cardiovascular mortality. This study may have identified a threshold at which point serum K becomes dangerous.
TH-PO956

A Multicenter, Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial of Nalbuphine ER Tablets for the Treatment of Uremic Pruritus: Baseline Population Characteristics Vandana S. Mathur,1 Jayant Kumar,2 Paul W. Crawford,1 Howard Halt,1 Thomas Sciascia.1 1Mathur Consulting, Woodside, CA; 2Trevi Therapeutics, New Haven, CT, 1Renal Medicine Associates, Albuquerque, NM; 1Bios-statistics, Edireign Consulting, Wilmington, DE, 1Research by Design, Evergreen Park, IL.

Background: Uremic pruritus (UP) afflicts 30-40% of hemodialysis patients (HDP) and is associated with greater use of ESA and antibiotics. UP is hypothesized to be centrally-mediated via the reduction in endogenous κ/µ opioid ligand ratio. Nalbuphine ER tablet (NAL), a κ-opioid agonist and µ-opioid antagonist, is being developed for treatment of UP.

Methods: 373 HDP with moderate or severe UP (Numerical Rating Scale, NRS itch intensity scores ≥4.5) were randomized to blinded placebo or NAL (60 or 120 mg BID) X 8-wks.

Results: Worsening itch intensity by baseline NRS quartile was monotonically associated with impaired QOL on all instruments as well as with sleep onset latency, anxiety, and depression, but not with age, gender, BMI, ethnicity, itch duration, IPITH, URR, or Kt/V. Black race appeared to be associated with higher NRS.

Conclusions: In addition to the 1st endpoint hypothesis that NAL will reduce itch intensity, the apparent associations between itch intensity and QOL measures at baseline warrant examination by treatment. Unblinded results will be presented.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

TH-PO957

International Variation of Characteristics of Health Literacy and Its Association with Mortality in Dialysis Kerri L. Cavanaugh,1 Mia Wang,1 Ken Walliston,1 Russell Rothman,1 Ali AlSahow,1 Patricia De Segueraa,1 Takeshi Haraguchi,1 Brian Bieber,1 Bruce M. Robinson,2 Ronald L. Pisoni,3 Francesca Tenori,1,2 1Vanderbilt Univ; 2Arbor Research; 3Jahra Hospital; 4Hospital Infanta Leonor; 5Fukushima Medical Univ.

Background: In patients receiving hemodialysis (HD), low health literacy (LHL) has been associated with greater use of emergency care, more hospitalizations and higher mortality. Little is known about the characteristics of LHL in HD patients outside of the United States.

Methods: A total of 11,476 DOPPS participants completed the Brief Health Literacy Screen (BHLS) [0-12]. Descriptive statistics were performed overall and by country. Participant characteristics were examined between three health literacy categories using mixed, GEE, and multinomial logistic models. Cox models were applied to examine effects of study phase, country, and facility clustering.

Conclusions: LHL prevalence across countries may be in part explained by cultural differences as well as health care systems. Vulnerable patients are at highest risk of LHL, and LHL is an independent predictor of mortality. Further examining by country the role of health system practices may help to overcome LHL-related barriers to patient engagement and improve outcomes in hemodialysis.

Funding: Pharmaceutical Company Support - The DOPPS Program is supported by Amgen, Kyowa Hakko Kirin, AbbVie Inc., Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. Additional support for specific projects and countries is also provided in Canada by Amgen, BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support); in Germany by Hexal, DGN, Shire, WiNe Institute; for PDPSS in Japan by the JSPD. All support is provided without restrictions on publications.

TH-PO958


Background: Hemodialysis patients are frequently subject to Gram-positive infections including Staphylococcus aureus and Methicillin-resistant Staphylococcus aureus (MRSA). Vancomycin is an antibiotic of choice in this population to treat these infections. The objective of this project was to validate the performance of a pre formatted individual prescription protocol of vancomycin in its capacity to reach target vancomycin serum concentrations of 10 to 30 mg/L for Gram-positive infections and 15 to 20 mg/L for MRSA infections.

Methods: The records of 84 patients diagnosed with end-stage renal disease undergoing a 4-hour, three times weekly high-flux hemodialysis treatment were analyzed retrospectively. All patients received vancomycin according to a weight-based dosing protocol between 2011 and 2014. Patients < 70 kg received a 1000 mg loading dose followed by a 500 mg maintenance dose at dialysis session. Patients between 70 and 100 kg received a 1500 mg loading dose followed by a 750 mg maintenance dose. Patients > 100 kg received a 1500 mg loading dose followed by a 1000 mg maintenance dose.

Results: We collected and analyzed 189 dosages of 84 patients. For all assays, 95.2% achieved levels between 10 and 30 mg/L and 50.3% achieved levels between 15 and 20 mg/L. Stratified by weight categories, for the 10 to 30 mg/L target, 93.3% of patients < 70 kg, 100% of patients between 70 and 100 kg and 89.5% of patients > 100 kg achieved the target serum concentrations (mainly below), 61.3% of patients between 70 and 100 kg achieved the target serum concentrations and 31.6% of patients > 100 kg achieved the target serum concentrations (mainly below, but not below 30 mg/L).

Conclusions: The vancomycin weight-based dosing protocol achieved target serum concentrations of 10 to 30 mg/L in 95.2% of patients. However, because half the dosages of patients < 70 kg were below the target of 15 to 20 mg/L, vancomycin bolus and maintenance doses should be adjusted upward in this subgroup. No dose change is suggested in the other subgroups.

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

TH-PO959

Trends in Incident ESRD Counts Initiating Dialysis in Freestanding Facilities Have Regional Variation David T. Gilbertson,1 Peer Kidney Care Initiative Investigators.1 1CDBG, MRF, Minneapolis, MN; 2Peer Kidney Care Initiative.

Background: Overall rates of incident end-stage renal disease (ESRD) patients initiating dialysis in freestanding units have stabilized, and the growth in counts of incident ESRD patients began to slow by the beginning of this decade. We assessed trends in incident ESRD counts from 2004–2011, overall and geographically by the 9 US Census Divisions.

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Methods: Data were ascertained from the Centers for Medicare & Medicaid Services ESRD database. For annual incident cohorts, we identified patients with their first outpatient dialysis within 3 months of initiating chronic dialysis in a freestanding facility.

Results: Yearly counts increased through 2010, with an average annual percent increase of 2.7% from 2004 to 2011. Between 2009 and 2011, this average percent increase was relatively unchanged (0.6%). However, there were region-to-region differences, with increased New England Census Division experiencing the largest proportionate decrease in incident patients between 2009 and 2011, while the contiguous Middle Atlantic division averaged the highest increase during the same period by 2011.

Conclusions: Overall trends in dialysis incidence reveal substantial geographic variation that has not been explained, suggesting that an assessment based on overall U.S. counts may mask important regional differences. Whether these trends will continue in the face of increasing diabetes rates, an aging population and shifts in social demographical changes is uncertain and will require more detailed analysis.

Funding: Pharmaceutical Company Support - Financial support for Peer is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc. (DCI), DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renal Ventures Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care. In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, Minnesota, Private Foundation Support

TH-P0960

Association of Intradialytic Hypoxemia with Hospitalization and Mortality:Results from a Large U.S. Hemodialysis Cohort

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Background: While intradialytic hypoxemia is recognized since the early days of hemodialysis (HD), its associations with hard clinical outcomes have not yet been assessed.

Methods: We analyzed arterial oxygen saturation (SaO2) data obtained by Crit-Line™ monitor (CLM) in chronic HD patients treated between 1/2012 and 1/2015. An individual 6-month baseline with at least 10 CLM measurements preceded a 12-month follow-up. Prolonged intradialytic hypoxemia (PIH) was defined as SaO2 ≤ 90% for more than 2 hours. Cox proportional hazards analysis with adjustment for age, gender, race, vintage, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), diabetes, albumin, hemoglobin, erythropoietin (EPO) dose, neutrophil-to-lymphocyte ratio, interdialytic weight gain, post-HD systolic blood pressure, and ultrafiltration rate. We conducted Cox proportional hazards analysis with adjustment for age, gender, race, vintage, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), diabetes, albumin, hemoglobin, erythropoietin (EPO) dose, neutrophil-to-lymphocyte ratio, interdialytic weight gain, post-HD systolic blood pressure, and ultrafiltration rate.

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listed for renal transplant and 10.1% received a renal transplant. With matching for age, sex and race, overall mortality rates were higher in scleroderma cases than controls (22.3 Vs. 15.5 per 100 person-years, \( P < 0.001 \)). Overall rates of listing for renal transplant (8.4 Vs. 8.5 per 100 person-years, \( P = 0.92 \)) and rates of transplantation (4.1 Vs. 4.3 per 100 person-years, \( P = 0.66 \)) were similar in scleroderma cases and controls.

Conclusions: The incidence of ESRD from scleroderma appears to have declined in the United States since 1995. Mortality rates on RRT are higher in scleroderma cases than controls (1.5 vs. 0.8 listings/100 person-years, \( P = 0.03 \)); however, transplantation rates were not different (4.1 vs. 4.3/100 person-years, \( P = 0.96 \)). Overall rates of listing for renal transplant and receiving a renal transplant were as likely in scleroderma patients as matched controls.

**TH-PO964**

**Prevalence and Mortality Associations of Protein- Energy Wasting Syndrome Criteria in Maintenance Hemodialysis Patients**

*G. Wei, 1 Xiaorui Chen, 1 Kalani L. Raphael, 1,2 Syndrome Criteria in Maintenance Hemodialysis Patients Prevalence and Mortality Associations of Protein- Energy Wasting* 0.1

**Methods:** The prevalence of International Society of Renal Nutrition and Metabolism panel PEW criterion (listed in the table) at the 12 m follow-up visit were examined. Subsequent mortality associations were examined in Cox models adjusted for demographics, duration of ESRD, Kt/V and flux groups, smoking and alcohol use.

**Results:** There were 632 deaths / 3390 yrs of follow-up. The prevalence of PEW criterion varied widely: 0% for low body fat% to 64% for low DEI (figure).

**Conclusions:** As the prevalence and mortality associations of protein-energy wasting (PEW) syndrome criteria in the MHD population are not well established, we examined these in 1480 MHD pts in the HEMO Study, a multi-center RCT to examine the effects of dialysis dose and dialyzer flux on mortality.

**Funding:** NIDDK Support

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**TH-PO965**

**Primary Care Physician Involvement in the Care of Chronic Dialysis Patients in the U.S.**

*Vahakn B. Shahinian, Deanna Chyn, Yi Li, John Z. Ayanian, Richard Hirth, William H. Herman, Rajiv Saran. Univ of Michigan.*

**Background:** Current health reform efforts aimed at improving quality and value center around delivery of good primary care. However, national patterns of primary care physician (PCP) involvement along with a nephrologist in the care of chronic dialysis patients are unknown.

**Methods:** Patients on chronic dialysis during 2010-11 with Medicare as the primary insurer were identified using US Renal Data System (USRDS) data. PCP involvement was defined based on a claim for an outpatient (non-dialysis) visit with a physician specializing in family practice, general internal medicine or geriatrics. Patients were characterized with respect to two aspects of preventive care: influenza vaccination and diabetes care.

**Results:** The sample included 179,645 patients, 8,272 of whom were diabetic. In 2010, 59% of patients had evidence of PCP involvement based on 1 outpatient visit. Patients with PCP involvement were older and more likely to be female, white and with diabetes as cause of ESRD (Table). Rates of vaccination and diabetes care were higher in those with PCP involvement, even after adjustment (ORs: 1.48 [1.45-1.51] for vaccination and 1.53 [1.48-1.58] for a composite of diabetes care).

**Conclusions:** Even under the loosest definition of PCP involvement, over one quarter of dialysis patients have no evidence of PCP involvement. Patients with PCP involvement have higher rates of preventive care, but further study should examine the impact on outcomes and costs.

**Funding:** NIDDK Support

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**TH-PO966**

**Are We Choosing Wisely? A Study of Colon Cancer Screening Practices Among Dialysis Patients in the United States**

*Christopher A. Carlos, 1 Chi-yuan Hsu, 1 Meda E. Pavkov, 1 Nilka Rios Burrows, 1 Vahakn B. Shahinian, 2 Rajiv Saran, 2 Neil R. Powe, 1 Kirsten L. Johansen. 3 Univ of California, San Francisco, San Francisco, CA; 2Univ of Michigan, Ann Arbor, MI; 3Centers for Disease Control and Prevention, Atlanta, GA.*

**Background:** Because estimated net gains in life expectancy are very small, the American Society of Nephrology recommended against routine cancer screening in asymptomatic dialysis patients. We aimed to determine how often colon cancer screening is performed in the U.S. and whether colon cancer screening is targeted toward healthier dialysis patients. **Methods:** We performed a retrospective cohort study of patients aged ≥50 years on dialysis between January 1, 2007 and September 30, 2012 using data from the United States Renal Data System (USRDS). Using multivariable Cox regression models, patients were divided into quartiles based on the risk of death and the likelihood of receiving a kidney transplant and, according to these quartiles of risk, we then assessed the likelihood of colon cancer screening (CCS) by fecal occult blood testing, sigmoidoscopy or colonoscopy from Medicare claims data.

**Results:** Of 391,616 patients, 13% received CCS over a median follow-up of 1.5 years (interquartile range 0.7-2.9). Screening was most common in patients with the lowest mortality risk (16%), compared with 9% of those with the highest mortality risk (HR 1.33;
Severe Sepsis Hospitalizations in Those on Maintenance Dialysis – National Trends and Outcomes

Ankit Sakhuja,1 Kianoush Banaei,2 Hatem Amer,2 Robert C. Albright,2 Nephrology, Univ of Michigan; 2Nephrology and Hypertension, Mayo Clinic.

Background: Severe sepsis (SS) is a life-threatening condition requiring early diagnosis and management. Incidence of SS is increasing in general population (GP) and mortality is declining; however, epidemiology and outcomes of SS have not been well studied in those on maintenance dialysis (MD). We designed this study to look at incidence and outcomes of SS in those on MD.

Methods: Using Nationwide Inpatient Sample database we included all hospitalizations (age ≥20 yr) with SS based on ICD-9-CM codes of severe sepsis, septic shock or blood stream infection with organ dysfunction from 2005 to 2010. Those on MD were identified based on ICD-9-CM codes. Age adjusted incidence of SS and mortality in subgroups was calculated by direct standardization to 2000 standard US population. Linear regression was used to assess trends over time and logistic regression to assess independent effect of MD on mortality.

Results: Of estimated 5,000,152 (95% CI: 4,798,520-5,201,784) hospitalizations with SS, 6.4% were on MD. Unadjusted incidence of SS was 145.4/1000 in MD compared to 3.5/1000 in GP with incidence rate ratio 40.9 (95% CI: 40.8-40.9). Age adjusted incidence of SS seems to be increasing in both subgroups though trend was not significant in MD (Fig 1).

Conclusions: Our findings suggest that screening was appropriately targeted to dialysis patients with longer life expectancies and away from those with the lowest chances of receiving kidney transplantation.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO967

Unadjusted in-hospital mortality is higher in MD (30.3% vs 26.2%; p<0.001). Age-adjusted mortality is decreasing in both subgroups though trend was not significant in MD. Age-adjusted mortality continues to be higher in MD (Fig 1). MD is an independent risk factor for mortality with OR 1.26 (95% CI: 1.23-1.29).

Conclusions: Hospitalizations with SS are over 40 times more common in MD. Mortality is higher in MD and being on MD is an independent predictor of mortality in those admitted with SS. Though incidence of SS seems to be increasing, there is a trend towards decrease in mortality even in MD.

TH-PO968

Trends in Colorectal Cancer Screening in U.S. End-Stage Renal Disease Population

Kevin C. Abbott,1 Chyng-Wen Fwu,2 Paul L. Kimmel,1 Paul W. Eggers.1 Div of Kidney, Urologic Hematologic Diseases, NIDDK, NIH, Bethesda, MD; 2Social & Scientific Systems, Inc., Silver Spring, MD.

Background: Screening for colorectal cancer (CRC) has been recommended for those over 50 years old. Medicare coverage of CRC screening began in 2000. Dialysis patient care is shared by many practitioners, perhaps leading to therapeutic nihilism and insufficient screening. CDC data show almost 2/3 of patients at risk report CRC screening. We determined rates of CRC screening in ESRD hemodialysis (HD) patients, compared to a 5% Medicare sample, and to assess secular trends.

Methods: We used data from the 2001-2011 USRDS to describe trends in percentages of HD patients receiving CRC screening tests per year. We limited our study population to patients with Medicare Part A and B as primary payer to ensure complete Medicare claims data for CRC screening. Current Procedural Terminology /Healthcare Common Procedure Coding System (CPT/HCPCS) codes identified Medicare physician and supplier billing data for screening: colonoscopy (G0105 and G0121), sigmoidoscopy (G0104), and fecal-occult blood test (FOBT; G0107, G0328, and 82270). We compared HD data to a 5% Medicare sample.

Results: Overall, the proportion of HD patients having CRC screening decreased from 6.1% annually in 2001 to 3.5% in 2011 due to decreased use of FOBT. There was a persistent increase in the proportion of patients with colonoscopy or sigmoidoscopy for CRC screening in the 11-year study period, from 0.3% to 1.0% annually. In most years, male, black and age 50-75 patients were more likely to receive colonoscopy or sigmoidoscopy than female, white, and other age subgroups. In 2006, the most recent available comparable year, CRC screening in HD patients was less than that of the general Medicare population; 0.8% vs. 1.6% annually for colonoscopy and sigmoidoscopy, 6.0% vs. 8.1% including FOBT.

Conclusions: Screening for CRC in ESRD HD patients is less frequent than in the general Medicare population, and considerably less than CDC recommendations. Differences in ascertainment methods (CDC uses self-report) may account for most of the disparity from CDC estimates.

Funding: NIDDK Support

TH-PO969

Increasing Prevalence of Withdrawal from Dialysis: Trends from 2004-2011

James B. Wemore,1 Peer Kidney Care Initiative Investigators.2 CDRG, MMRF; 2Peer Kidney Care Initiative.

Background: Voluntary withdrawal from dialysis, which frequently occurs when a patient perceives dialysis as having become unduly burdensome, is an area of increasing interest. How early withdrawal, defined as that occurring within 1 year of dialysis initiation, has changed over the past decade has not been fully explored.

Methods: Patients initiating dialysis between 2004 and 2011 were selected from the Centers for Medicare & Medicaid Services End-Stage Renal Disease (ESRD) database. Information on withdrawal was ascertained from the ESRD Death Notification Form by the presence of code 104 (“withdrawal”) in the 1st or 2nd position. The unadjusted cause-specific monthly mortality rate (deaths per 100 pt-years) was calculated for patients initiating in each year.

Results: Annual incident counts ranged from 87,174 (2004) to 100,665 (2011). Overall, during the first year of dialysis, the withdrawal rate was highest soon after initiation, peaking at month 2 for all years except 2004. Rates then decreased until approx. month 9, stabilizing through month 12. Additionally, early rates more than tripled over the study period, from 1.9 per 100 pt-years at month 2 in 2004 to 5.9 in 2008 to 6.4 in 2011.
Conclusions: Withdrawal rates are high in the weeks immediately after dialysis initiation, a pattern more marked in recent years. Because patients who withdraw soon after initiation may be suboptimal dialysis candidates, future work should focus on determining whether a tailored approach, designed to identify individual patient goals and present the risks and benefits of dialysis and viable alternatives such as conservative care, might provide optimal patient-centric care.

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc., DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renal Ventures Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care. In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, MN., Private Foundation Support

TH-PO970


Background: Fluid overload in patients on conventional hemodialysis is a frequent complication associated with increased hospitalizations, cardiovascular morbidity and all-cause mortality. There are multiple patient and physician-related factors that lead to fluid overload. Individualizing dialysate sodium prescription and minimizing the sodium gap are potential modifiable risk factors.

Methods: We performed a cross-sectional study on 111 prevalent stable conventional hemodialysis patients at the McGill University Health Center. The associations of sodium gradient with various hemodialysis parameters of fluid status including interdialytic weight gain percentage (IDWG%), ultrafiltration (UF) rate, blood pressure (BP), interdialytic hypertension and intradialytic hypertension were analyzed.

Results: The mean serum sodium gradient was 4.6 ± 3.6 mEq/L. with a mean pre-dialysis sodium of 142.0 ± 3.0 mEq/L. There was a direct correlation between sodium gradient and interdialytic weight gain percentage (p=0.49, p<0.01) as well as ultrafiltration rate (p=0.44, p<0.01). The average sodium gradient was significantly higher in patients with IDWG > 3% (6.36 vs. 3.16 mEq/L, p<0.01) and in patients with UF rate > 10ml/kg/h (6.01 vs. 4.23 mEq/L, p=0.03). In a univariate logistic regression model, a higher sodium gradient was associated with interdialytic weight gain percentage (OR 3.6 mEq/L, p<0.01) and in patients with UF rate > 10ml/kg/h (6.01 vs. 4.23 mEq/L, p=0.03). There was a direct correlation between sodium gradient and blood pressure (pre-dialysis or post-dialysis) or number of antihypertensive medications.

Conclusions: A higher sodium gradient was associated with significant increases in IDWG and UF rate which are associated with poor outcomes. Sodium gradient was not associated with interdialytic hypertensive episodes. With the parameters we measured in this study, it appears that individualizing dialysate sodium prescription to minimize sodium gap leads to less fluid overload in conventional hemodialysis patients.

TH-PO971

Calcific Uremic Arteriolopathy: Mortality Outcomes with and without Sodium Thiosulfate Therapy Chamberlain L. Obialo, Alexander Quarshie. Dept of Medicine, Morehouse School of Medicine, Atlanta, GA; Clinical Research Center, Morehouse School of Medicine, Atlanta, GA, Venezuela.

Background: Calcific uremic arteriolopathy (CUA) or Calciaphaxis is commonly seen in patients with end stage kidney disease (ESKD) and carries a high mortality risk. There is no definitive therapy for this condition but promising results have been reported in patients treated with intravenous sodium thiosulfate (STS). However, the mortality advantage of therapy with STS over therapy without STS remains unknown.

Methods: We retrospectively reviewed our ESKD patient’s records over a 10-year period and identified 45 biopsy confirmed cases of CUA. Associations between patients who received STS therapy and those who did not and various categorical end points were assessed using the Pearson chi-squared tests while differences in continuous end points were examined using Mann-Whitney-U tests. Survival analysis utilized Kaplan-Meier plots. All statistical tests were two-sided, and level of significance set at 0.05.

Results: The mean age of the 45 cases was 63, 60% female, mean body mass index was 34 and mean dialysis vintage was 4 years. Of the 45 cases, 23 (51%) received STS while 22 (49%) did not. The mean level of serum albumin, phosphorus and parathyroid hormone was 2.8 g/dl, 6.7 mg/dl and 989 pg/dl respectively. One –year mortality was 22% in STS vs. 50% in no STS cases, p = 0.05. The overall survival of the patients over the 2- year study period was significantly superior in the recipients of STS than in those who did not receive STS, p = 0.03.

Patients who did not receive STS were also more likely to have major surgeries than those who received STS, 86% vs. 52%, p = 0.01.

Conclusions: Sodium thiosulfate therapy appears to confer both short term and long term survival advantage over no STS. We encourage hospitals and dialysis companies to procure and make this agent more available to physicians.

Funding: Clinical Revenue Support

TH-PO972

Effect of High-Dose and High-Flux Hemodialysis on Markers of Inflammation in the HEMO Study Kristen L. Nowak1, Tom Greene,2, J. Alan Ying,2 Alfred K. Cheung,2 Michel Chonchoel.1 1Univ of Colorado Denver; 2Univ of Utah.

Background: Hemodialysis treatment induces markers of inflammation, which could affect clinical outcomes. This study sought to determine whether high-dialysis dose and high-flux dialysis would improve markers of inflammation compared with standard dialysis dose and low flux dialysis.

Methods: The HEMO Study was a randomized multicenter study of the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum high sensitivity C-reactive protein (hs-CRP, pre-specified primary outcome for this set of analyses) and interleukin-6 (IL-6) were measured in stored serum samples in 1,846 HEMO participants. For each inflammatory marker we used a joint multi-state modeling approach to estimate the proportion of patients in 5 ordered states (S) over 3 annual assessments while accounting for mortality: S1=deceased (score=0); S2=alive in highest quartile (score=1); S3=alive in 2nd quartile (score=2); S4=alive in 3rd quartile (score=3); and S5=alive in lowest quartile (score=4). The mean rank was computed over 3 yrs of follow-up and compared between the randomized groups.

Results: Randomized patients had high rates of coexisting conditions: 45% had diabetes, and 80% had a history of cardiac disease. Characteristics of the patients in the two dose groups were similar, as were the characteristics of those in the two flux groups. The state distribution of hs-CRP in each year by dose (KTV) group and by flux group for hs-CRP are shown in Figure 1.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Comorbidity data source may impact performance evaluation. The impact is larger for smaller groups, and may increase with prevalent patients included.

Funding: Pharmaceutical Company Support - DaVita Clinical Research, DaVita HealthCare Partners Inc., Denver, Colorado

TH-PO974

Thematic Analysis of the Medical Records of a National Cohort of Patients Who Initiated Maintenance Dialysis: 2000-2009

Susan P.Y. Wong,1 Elizabeth Vig,2 Nilka Rios Burrows,2 Chuan-fen Liu,1 Desmond Williams,3 Paul L. Hebert,1 Ann M. O’Hare.1 1Univ of Washington; 2Center for Disease Control.

Background: Little is known about how decisions to initiate dialysis take shape in clinical practice.

Methods: We performed a qualitative thematic analysis of the medical records of patients who initiated maintenance dialysis to understand factors that impact decisions to initiate maintenance dialysis as they occur in clinical context. We analyzed key care processes, patient-provider interactions and patient and/or provider concerns and considerations relevant to the decision to initiate dialysis as documented in the electronic medical records of a national random sample of patients for whom the decision to initiate maintenance dialysis was made at the Department of Veteran Affairs between 2000 and 2009 (n=1,691).

Results: We identified three dominant, overlapping themes pertaining to the decision to initiate dialysis: 1) dialysis initiation as process, which describes the decision to initiate dialysis as integrated with other treatment decisions and unfolding over time rather than an isolated decision occurring at a fixed point in time; 2) sources of momentum for dialysis initiation, which describes factors that appeared to hasten the process of dialysis initiation and included hospitalization for acute illness and efforts to optimize patients’ clinical status for future medical interventions; and, 3) push-pull dynamics between patients and providers, which describes the sometimes adversarial relationship between patients and providers during the process of dialysis initiation in which patients were often portrayed by providers as “resistant” to dialysis initiation while providers appeared paternalistic and safety conscious in their approach towards treatment decisions.

Conclusions: Our analysis of the medical record underscores the complexity of treatment decisions about dialysis initiation in real-world clinical settings and supports a re-conceptualization of dialysis initiation as a process that unfolds over time rather than as a discrete treatment decision occurring at a fixed point in time.

Funding: Other U.S. Government Support, Veterans Administration Support

TH-PO975

Trends in 30-Day Readmission Rates in Dialysis Patients During an Era of Medicare Payment Policy Changes, 1996-2012

Allan J. Collins,1 Peer Kidney Care Initiative Investigators.2 1MRBF; 2Peer Kidney Care Initiative.

Background: High hospital readmission rates, which may indicate inadequate quality of care and result in unnecessary expenditures, have been a recent focus for Medicare. Medicare has enacted payment-related policy changes: freezing the inpatient payment rate (1997), expanding “disproportionate share” hospital payments (early 2000s), tying

isCRP did not differ significantly between dose (p=0.83) or flux groups (p=0.53). Similar results were obtained for IL-6.

Conclusions: Over 3 years, neither high-dose nor high-flux dialysis exhibited a beneficial effect on markers of inflammation.

TH-PO973

Comorbidity Data Source May Impact SMR/SHR Calculation

Jianmeng Liu,1 Mahesh Krishnan,2 Jincheng Zhou,1 Kimberly M. Nieman,1 Yi Peng,1 David T. Gilbertson.1 1CDRG, MMRF, Mpls, MN; 2DaVita Healthcare Partners, Denver, CO.

Background: Standardized mortality and hospitalization ratios (SMRs and SHRs) are used to measure dialysis facility performance, with adjustment for demographics and comorbidities derived from the end-stage renal disease (ESRD) Medical Evidence (ME) Report. Sensitivities are low for ME-based comorbidities. We investigated the effect on SMR and SHR calculations by comparing ratios adjusted for claims-based comorbidities.

Methods: Using the USRDS ESRD database, we included US hemodialysis patients who initiated dialysis July 1-December 31, 2006-2010, had Medicare as primary payer, were aged ≥ 66 years, and had no prior transplant (TX). Patients were followed from dialysis initiation to the earliest of death, TX, modality change, or 1 year. SMRs and SHRs were calculated for patients in for-profit/non-profit and rural/urban facilities for ME-based and claims-based comorbidity, separately. Cox models were used for expected number of deaths and piecewise Poison models for expected number of hospitalizations. Agreement of comorbidity between the two sources was measured by a kappa statistic.

Results: 73,950 incident hemodialysis patients were included. Kappas for comorbidity agreement were low, less than 0.5, except for diabetes (0.77). Percent of patients with claims-based comorbidity was similar for for-profit and non-profit facilities; ME-based comorbidity was lower for for-profit facilities. Differences between ME-based and claims-based SMRs/SHRs were statistically significant. Compared with ME-based SMR/SHR, claims-based ratios decreased 0.9%/0.6% for for-profit and 1.0%/0.7% for urban facilities and increased 3.4%/2.8% for non-profit and 5.9%/4.1% for rural facilities.

Conclusions: Representing presenting author.
reimbursement for outpatient hemodialysis services to the number of monthly visits (2004), introducing the new Medicare prospective payment system (2011), and instituting the “hospital payment penalty” (2012). Given evidence demonstrating links between these changes and readmission rates in the general population, we sought to examine changes in 30-day readmission rates in dialysis patients 1996–2012.

Methods: Data were obtained from the Centers for Medicare & Medicaid Services End-Stage Renal Disease database. Dialysis patients were assessed for discharges from short-term or critical access hospitals. Thirty-day readmission rates were calculated, without adjustment for differences in patient case-mix or hospital characteristics.

Results: All-cause readmission rates increased modestly over the period studied except for 2012. The nadir was 32.8% in 1998; the rate increased to 34.6% in 2005, fell to 34.1% in 2009, and peaked at 34.8% in 2010. Discharge data in the first 6 months of 2012 showed further decrease (32.8%). In comparison, other studies show that the rate in the general Medicare population was relatively stable 2007-2011 (19.0%), and decreased in 2012 (18.4%).

Conclusions: Thirty-day readmission rates were substantial in dialysis patients compared with general Medicare patients, possibly reflecting case-mix. How public policy changes may have affected potentially avoidable readmissions should be more fully explored. Cause-specific readmission rates might provide a better reflection of quality of care and should be examined.

Funding: Pharmaceutical Company Support - Financial support for Peer is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc. (DCI), DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renal Ventures Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care.

In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, Minnesota. Allian Collins, MD, FACP, is the Executive Director of Peer. Allan Collins serves as a co-investigator on Phase I and II studies for DaVita Clinical Research., Private Foundation Support

TH-PO976

The Impact of Volume Status on Nocturnal Hypoxia in Patients Undergoing Maintenance Hemodialysis Farhanah Yousaf, Mitesh K. Patel, Sherbeth Marie C. Young, Chaim Charytan, Alla Goldberg, Bruce S. Spinowitz. New York Hospital Queens, Flushing, NY.

Background: Hemodialysis patients experience changes in volume status according to hemodialysis schedule. Excess fluid volume may shift to the neck upon assuming a recumbent position during dialysis leading to engorgement of peripheral venules. We explored the impact of volume status on nocturnal hypoxia in the hemodialysis population.

Methods: Following local IRB approval, adult hemodialysis patients who were undergoing regular chronic hemodialysis (HD) for at least 3 months were consented to complete two nights of nocturnal oximetry using Pulsox 300i wristwatch. HD night was defined as the night of HD treatment whereas non-HD night was defined as the night on which no HD was performed. The first hour of recording was deleted in efforts to capture oximetry reading from sleep time only. Motion artifacts and aberrant data were also excluded from the analysis. Oxygen desaturation index (ODI) was defined as the number of desaturations ≥ 3% from baseline lasting ≥ 10 seconds, per hour. Paired t-test was used to compare HD and non-HD night related data.

Results: Twenty HD patients (11 males and 9 females) aged 54 ± 13 years with a mean body mass index of 25.5 ± 4.6 kg/m² and neck circumference of 38.4 ± 5.8 cm participated in the study. Mean ODI was 21.2 ± 21.1 on HD night versus 20.0 ± 19.8 on non-HD night (p=0.6) with a mean interdialytic weight gain of 1.9 ± 1.3 kg. The lowest recorded mean saturation was 76.2 ± 10 % on HD night versus 73.5 ± 11 % on non-HD night (p<0.3). Eleven of 20 patients, with a mean interdialytic weight gain of 2.1 ± 1.5 Kg, experienced worsening of ODI on non-HD night (16.9 ± 17.9) versus HD night (11.6 ± 13.8) [p=0.008]. Meanwhile, nine patients, with an mean interdialytic weight gain of 1.5 ± 0.9 Kg, exhibited improvement in ODI on non-HD night (23.8 ± 22.4) versus HD night (32.9 ± 23.1) [p=0.04].

Conclusions: Volume status alone does not explain HD to non-HD variation in nocturnal hypoxemia seen in ESRD population. Both central and obstructive mechanisms are likely involved. Additional research is warranted to further explore this phenomenon and develop preventive strategies.

TH-PO977

Hospital Readmission within 30 Days of Discharge Among Adults Receiving Dialysis Lorien S. Dalrymple,1 Barbara A. Grimes,2 Patrick S. Romano,1 Yi Mu,1 Dahn V. Nguyen,1 Kirsten L. Jhansohn,1,2 UC Davis; UCSF; UC Irvine; San Francisco VA.

Background: Hospital readmission is common in adults receiving dialysis. Few studies have examined the timing or causes of 30-day hospital readmission.

Methods: We used the USRDS to examine adults initiating dialysis Jan 2009 through Dec 2010 who had Medicare as the primary payer. The cohort was followed from day 90 of dialysis for up to one year; with censoring for death, renal recovery or transplant. We classified the principal cause of the index hospitalization and hospital readmission using Clinical Classification Software.

Results: Our cohort consisted of 103,381 patients. During follow-up, 50,639 patients experienced 89,728 index hospital admissions; 5% resulted in in-hospital death. Of the 85,284 live hospital discharges, 25,792 (30%) were associated with 30-day readmission. The median time to readmission was 11 [5, 19] days. Leading causes of readmission by cause of index hospitalization are in Table 1.

Table 1. Causes of 30-Day Readmission

<table>
<thead>
<tr>
<th>Cause of Index Admission</th>
<th>Leading Cause</th>
<th>2nd Leading Cause</th>
<th>3rd Leading Cause</th>
<th>4th Leading Cause</th>
<th>5th Leading Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause N=89728</td>
<td>Complication of device, implant or graft</td>
<td>Septicemia</td>
<td>CHF</td>
<td>DM</td>
<td>HTN</td>
</tr>
<tr>
<td>Complication of device, implant or graft N=14195</td>
<td>Septicemia</td>
<td>DM</td>
<td>CHF</td>
<td>HTN</td>
<td></td>
</tr>
<tr>
<td>Septicemia N=6409</td>
<td>Septicemia</td>
<td>Complication of device, implant or graft</td>
<td>DM</td>
<td>Pneumonia</td>
<td>CHF</td>
</tr>
<tr>
<td>HTN N=5380</td>
<td>HTN</td>
<td>Complication of device, implant or graft</td>
<td>CHF</td>
<td>DM</td>
<td>Fluid and electrolyte disorders</td>
</tr>
<tr>
<td>CHF N=3232</td>
<td>CHF</td>
<td>HTN</td>
<td>Complication of device, implant, graft</td>
<td>Fluid and electrolyte disorders</td>
<td>Septicemia</td>
</tr>
<tr>
<td>DM N=4986</td>
<td>DM</td>
<td>Complication of device, implant or graft</td>
<td>Septicemia</td>
<td>HTN</td>
<td>Complications of surgical procedures or medical care</td>
</tr>
</tbody>
</table>

*HTN: Hypertension with complications and secondary hypertension; CHF: Congestive heart failure - nonhypertensive; DM: Diabetes mellitus with complications

For the 5 most common causes of hospitalization, the principal cause for readmission was in the same category as the initial admission, accounting for 18-32% of readmissions.

Conclusions: Thirty-day hospital readmission in Medicare recipients on dialysis is frequently leading to causes related to the initial admission.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc.

TH-PO978

Racial/Ethnic and Age Differences in Cause-Specific Deaths Among U.S. Dialysis Patients Alison J. Yu,1 Keith C. Norris,2 Alfred K. Cheung,1 Guofen Yan.1 Univ of Southern California; 2 UCLA; 3 Univ of Utah; 4 Univ of Virginia.

Background: Recent research reported that Hispanics have the lowest all-cause mortality, African Americans (AAs) intermediate, and Whites the highest among U.S. dialysis patients over 30 years old. The objective of this study is to examine whether this risk pattern varied depending on the cause of death.

Methods: The study included 1,255,640 adult incident dialysis patients between 1995 and 2010 in the USRDS, with no prior kidney transplantation. We examined 5 major cause-specific deaths: cardiovascular (CVD), infection, malignancy, others, and unknown. Cause-specific hazards for each cause-specific death were compared among AAs, Hispanics, and Whites for overall and stratified by age groups.

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

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Results: After adjustment for multiple covariates (Table), compared with Whites, in all age groups, Hispanics consistently had lower risks of cause-specific deaths for all major causes examined (HRs<1), while AAs also had lower risks except for the cause of infection, for which AAs had significantly higher risks in age groups of <50 and >80 years (HRs from 1.07-1.94).

Table. Adjusted cause-specific hazard ratios (HRs) for AAs and Hispanics vs. Whites

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>CVD</th>
<th>Infection</th>
<th>Malignancy</th>
<th>Others</th>
<th>All-cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>0.99* 0.52</td>
<td>1.94 0.81</td>
<td>0.52 0.60*</td>
<td>1.06* 0.62</td>
<td>1.17 0.60</td>
</tr>
<tr>
<td>31-40</td>
<td>0.85 0.61</td>
<td>1.51 0.55* 0.82 0.65</td>
<td>0.75 0.63 0.97 0.68</td>
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<tr>
<td>41-50</td>
<td>0.74 0.60</td>
<td>1.07 0.79 0.75 0.66</td>
<td>0.59 0.56 0.79 0.63</td>
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<tr>
<td>51-60</td>
<td>0.69 0.63</td>
<td>0.83 0.71 0.86 0.61</td>
<td>0.54 0.56 0.72 0.64</td>
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<tr>
<td>61-70</td>
<td>0.74 0.70</td>
<td>0.84 0.81 0.82 0.62</td>
<td>0.50 0.59 0.73 0.69</td>
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<td>71-80</td>
<td>0.78 0.78</td>
<td>0.98 0.90 0.92 0.70</td>
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<tr>
<td>&gt;80</td>
<td>0.84 0.84</td>
<td>1.07 1.01* 1.06* 0.89*</td>
<td>0.57 0.65 0.83 0.83</td>
<td></td>
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</tr>
</tbody>
</table>

Note: all significant at p<0.05 except the ones indicated by *.

Conclusions: The racial difference observed in all-cause mortality, in which Hispanics have the lowest risk, AAs intermediate, and Whites the highest, was also noted for major cause-specific deaths in most age groups, except for the cause of infection. Both younger and older AAs are at the greatest risk of death due to infection. Further studies are needed to explore the specific reasons responsible for the higher risk of infection-related death in AAs.

Funding: NIDDK Support

TH-PO979
Dialysis Therapy and Mortality in Older Heart Failure Patients with Advanced Chronic Kidney Disease: The Kaiser Permanente MATCH Study
David Lan, Sijie Zheng, Sharina Belani, Jingrong Yang, Thida Tan, Juan Daniel Ordonez, Susan Kim, Alan S. Go. Kaiser Permanente Northern California.

Background: Heart failure (HF) and chronic kidney disease (CKD) often coexist and those with both have much worse outcomes than having either alone, with limited data to guide optimal management. We evaluated the outcome of dialysis therapy in a diverse elderly cohort with HF and advanced CKD.

Methods: In Kaiser Permanente Northern California, a large integrated healthcare system, we identified members ≥70 years with HF and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² between 2008-2012 and no prior renal replacement therapy, cancer, cirrhosis or organ transplant. Through 2013, we identified patients who started chronic dialysis and individually matched controls who were alive on the dialysis start date of the matched case along with age, gender, diabetes status, and high-dimensional propensity score to start dialysis. Demographics, clinical features and drug use were obtained from electronic records. We calculated rates of death through 2013 and examined the impact of dialysis on mortality using Cox regression.

Results: We identified 334 eligible HF-CKD cases who initiated dialysis and 899 matched control HF-CKD patients. Mean age was 80.1±8.7 yrs, with 51% women, 33% black and 72% diabetic. Case and control patients were well-matched across characteristics, except for controls being less likely to be Hispanic or have proteinuria, or to receive alpha or calcium channel blockers or thiazide diuretics; and more likely to have prior intracranial bleed, liver disease, dementia and higher blood pressure, hemoglobin and mean eGFR (16.4 vs. 12.0 ml/min/1.73 m²). Incidence of death was 32 per 100 p-y in combined case and control patients. Among matched patients, after further adjustment for residual differences in patient features, dialysis was independently associated with a 47% lower rate of death (hazard ratio 0.53, 95%CI:0.41-0.67).

Conclusions: In older adults with HF and advanced CKD, dialysis was independently associated with a lower mortality. Randomized trails are needed to determine the net outcomes of dialysis related to both length and quality of life in the elderly with HF and advanced CKD.

Funding: Private Foundation Support

TH-PO980
Gender, Poverty, and Dialysis Mortality in Adults with Sickle Cell Disease

Background: Chronic dialysis patients with sickle cell disease (SCD) have increased risk of mortality compared with the general US dialysis population. The contributions of gender and neighborhood poverty to dialysis mortality in SCD patients are largely unknown.

Methods: Using USRDS data, we linked all US adults with SCD who initiated dialysis between 1995-2012 with zip-code level US Census neighborhood data. We performed multivariable Cox regression models with adjustment for age, dialysis type, BMI, and diabetes status to compare mortality between men and women, stratified by neighborhood poverty level. Neighborhoods with ≥20% of households living below the federal poverty level. Neighborhoods with ≥20% of households living below the federal poverty level.

Results: We included 334 eligible HF-CKD cases who initiated dialysis and 899 matched control HF-CKD patients. Mean age was 80.1±8.7 yrs, with 51% women, 33% black and 72% diabetic. Case and control patients were well-matched across characteristics, except for controls being less likely to be Hispanic or have proteinuria, or to receive alpha or calcium channel blockers or thiazide diuretics; and more likely to have prior intracranial bleed, liver disease, dementia and higher blood pressure, hemoglobin and mean eGFR (16.4 vs. 12.0 ml/min/1.73 m²). Incidence of death was 32 per 100 p-y in combined case and control patients. Among matched patients, after further adjustment for residual differences in patient features, dialysis was independently associated with a 47% lower rate of death (hazard ratio 0.53, 95%CI:0.41-0.67).

Conclusions: In older adults with HF and advanced CKD, dialysis was independently associated with a lower mortality. Randomized trials are needed to determine the net outcomes of dialysis related to both length and quality of life in the elderly with HF and advanced CKD.

Funding: Private Foundation Support

TH-PO981
Peritoneal Dialysis (PD) Patient Outcomes Under the Dialysis Prospective Payment System (PPS)
Marc Turement, Regina M. Baker, Jeffrey Pearson, Chad M. Cogan, Parma Mukhopadhyay, Elizabeth L. Cope. Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: The use of PD was expected to be incentivized by the expanded Medicare PPS that was implemented in 2011. There is early evidence under the PPS of additional incident ESRD patients and dialysis facilities using PD (Hirth et al 2013; Turement et al 2014). More widespread PD use could have implications for PD outcomes due to potential changes in PD selection or in the experience of dialysis providers with PD. This study assessed PD patient outcomes before and after the new PPS was implemented.

Methods: This study included n=36,582 incident ESRD patients for whom PD was identified as the intended initial dialysis modality on the CMS ESRD Medical Evidence Form during 2008-12. We evaluated 1-year PD technique failure and PD patient mortality using data from Medicare claims, the Standard Information Management System, CROWNWeb, and the CMS Death Notification Form. PD technique failure was ascertained when hemodialysis was used for at least 60 days.

Results: Selection of PD increased from 5.8% to 8.4% of incident patients between 2008 and 2012 (see Figure).

Trends in PD Modality and One-Year PD Patient Outcomes, by Year of Incidence, 2008-2012

*Demonstrator excludes patients receiving transplants within one year and patients with unknown modality at one year.

Conclusions: Men with SCD who live in poor neighborhoods were at highest risk of death. Efforts to address socioeconomic barriers may be an important target for improving survival in this population.

Funding: NIDDK Support, Other NIH Support - NHLBI
During this period, 1-year PD technique failure decreased from 18.8% to 16.1% of patients and 1-year PD patient mortality decreased from 9.4% to 8.6% (see Figure). Outcomes were relatively stable or improving across patient age, race, and Hispanic ethnicity subgroups and for patients in both urban and rural areas.

Conclusions: In the context of expanding PD use under the new PPS, there is no early evidence of worsening overall PD patient outcomes or of growing disparities in PD patient outcomes by demographic group or by urban/rural location. Instead, there were lower levels of PD technique failure and PD patient mortality in the initial years of the new payment system.

Funding: This study was supported by National Institute on Minority Health and Health Disparities (NIH-NIMHD).

TH-PO982

Cognitive Impairment and Mortality in Adults on the Kidney Transplant Waitlist

Background: Older adults with poor cognitive function are at increased mortality risk. It is unclear whether ESRD patients of all ages with cognitive impairment are at increased mortality risk of while on the kidney transplant (KT) waitlist.

Methods: 918 ESRD patients being evaluated for and waitlisted for KT (no previous listings) at Johns Hopkins were enrolled in a prospective cohort study (11/2009-5/2014). The Modified Mini Mental Status (MMS), a test of global cognitive function (range 0-100, higher scores represent better function) was assessed at KT evaluation. Global cognitive impairment was defined as MMS score<80). Mortality risk by MMS score and cognitive impairment (separately) was estimated using an adjusted Cox proportional hazards model; participants were censored at the waitlist removal, time of KT or administrative end of follow-up.

Results: At KT evaluation, the mean (SD and range) age was 54 (14; 18-86), 57% were male, and 46% were African American. The mean (SD and range) MMS score was 82.6 (11, 47-100) and 52% were classified as having cognitive impairment. 45 participants died over an average of 1.7 years of follow-up. Mortality risk was greater for adults on the KT waitlist who had worse MMS scores (1 point decrease in MMS score: HR=1.05, 95% CI: 1.02-1.08, P=0.003) and those with cognitive impairment (HR=2.51, 95% CI: 1.70-3.71, P<0.001) were at increased mortality risk.

Conclusions: The results support the hypothesis that MMS should be included in KT patient evaluations, in addition to MDRD and other risk scores. Cognitive impairment may be a predictor of mortality for KT waitlist patients.

Funding: This research was supported by an unrestricted grant from the American Society of Transplantation (AST) and National Institute of Diabetes and Digestive and Kidney Diseases (K01DK094853). The authors and Johns Hopkins declare no conflicts of interest.

TH-PO984

Who Makes the Best Exit Site: Nephrologist or Surgeon? Vaibhav S. Keskar, Mollura, B. Bliany, Brian Blew, Jeffrey Weiten, Brendan McCormick. The Ottawa Hospital, Univ of Ottawa, Ottawa, ON, Canada.

Background: Buried peritoneal dialysis (PD)catheters are placed months before dialysis is needed and the exit site is created at the initiation of dialysis by the nephrologist. In contrast, the exit site of an unburied catheter is created by the surgeon at the time of insertion. Our PD unit uses both methods of catheter placement. We undertook this study to compare the outcomes of the two methods of exit site creation.

Methods: The charts of all patients who initiation PD between Jan 2012 and Dec 2013 were reviewed. At each clinic visit, exit sites were graded by the PD nurse into standard predefined groups: perfect, good, equivocal and infected. Primary outcome was the frequency of perfect exit sites at 6, 12, and 24 months after initiation of PD. Secondary outcomes were exit site infections, peritonitis and technique failure due to exit site infection.

Results: 119 patients started PD during the period of interest and 114 remained on PD at 12 months. 52 patients had buried catheters exteriorized at the time of starting PD (group A) and 62 patients had unburied catheters (Group B). Group A had more males (71% vs 48%), had higher mean age (65±14 vs 59±15) and had most of the patients as incident dialysis patients. Diabetic nephropathy was the most common underlying disease in either group (61.53% and 51.61%). Group B had a higher frequency of perfect exit sites at 2 months but this difference disappeared by 6 and 12 months. There was a trend towards more exit site infections in Group A but this did not translate into more technique failure.

Conclusions: Buried catheters are less likely to have perfect appearance at two months compared to unburied catheters; however this is no longer significant at six and 12 months. The trend towards more exit site infections with buried catheters suggests that there may be clinical consequences of the tissue trauma at time of exteriorization. Consideration should be given to the use of prophylactic antibiotics at exteriorization.

TH-PO985


Background: Peritonitis, tunnel and catheter exit site (ESI) infections are the most serious complications of peritoneal dialysis (PD). We studied the effect of antibiotic ointment (EUDRAC: 2009-016835-36) on catheter-related infections (CRIs) and morbidity.

Methods: Allocation was stratified in blocks of 4:1 ratio. Ointment containing 2% colistin, tobramycin, amphotericin B and 4% vancomycin or normal saline were applied to the CSE over 1 year. Follow-up period was 3 months after the last dose. Exit site infection (ESI) was defined as erythema, edema or local pain with purulent secretion and positive culture. Antibiotic therapy was given according to local protocols.

Results: 140 patients were included, 6 didn’t meet entry criteria. Characteristics and dialysis parameters of the 65 in the control group (CG) and 69 intervention group (IG) patients were comparable.

Conclusions: Antibiotic ointment significantly reduced the incidence of ESI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Mean study duration was 0.6 (IG) vs 0.6 (CG) years (ns). 26 episodes of CR1 (11 ESL, 4 tunnel, 11 peritonitis) occurred in the CG and 12 in the IG (3 ESL, 0 tunnel, 9 peritonitis) (p<0.001). Etiology of ESI was Staphylococcus aureus (x7), Corynebacterium spp., Pseudomonas aeruginosa, E. coli, Serratia spp., coagulase-negative S. (x2) and 1 negative culture in the CG and S. aureus (x1), 1 Gram-negative bacillus and 1 negative culture in the IG. Systemic or topical antibiotics were given for ESI in 11 (CG) and 2 patients (IG) (p=0.01), respectively. Hospital admissions were 23 (CG) and 15 (IG). Local side effects were significantly increased in the IG.

Conclusions: Local prophylaxis with a broad-spectrum antimicrobial ointment is associated with a significant reduction in ESI and systemic antibiotic use without associated bacterial resistance. Significant local side effects were observed.

Funding: Private Foundation Support

TH-PO986

Association Between Plasma Fibroblast Growth Factor-23 and Carotid Artery Atherosclerosis in Peritoneal Dialysis Patients

Nanmei Liu, Jimin Hospital of Shanghai.

Background: We investigate the association between plasma fibroblast growth factor-23 (FGF-23) levels and carotid artery atherosclerosis of 125 stage 5 chronic kidney disease (CKD5) patients, who are doing continuous ambulatory peritoneal dialysis (CAPD) at renal dialysis of Shanghai Jimin Hospital in China.

Methods: A retrospective cohort study of individuals 15 years of age and older, divided into two cohorts according to carotid intima-media thickness (CIMT): CIMT normal cohort (CIMT<0.9mm) and CIMT thickening cohort (CIMT³0.9mm). Plasma FGF-23 concentrations were determined by ELISA. CIMT thickness and atherosclerotic plaques were measured by carotid ultrasound.

Results: Of the 125 PD patients, the CIMT was thickened in 82 patients (65.6%). Compared with the CIMT normal patients, plasma FGF-23 concentration was significantly increased (p<0.01) in the CIMT thickening cohort (Table 1). Linear regression analysis discovered an obvious positive correlation between plasma FGF-23 and CIMT (r=0.416, P=0.006) (Table 2). Multiple regression analysis indicated that plasma FGF-23 level was independently associated with plasma FGF-23 and CIMT (β=0.421, t=2.607, P<0.01) (Table 3).

Conclusions: The level of plasma FGF-23 was positively correlated with CIMT and played an important role in development of carotid artery atherosclerosis in peritoneal dialysis patients.

Funding: Government Support - Non-U.S.

TH-PO987

Atherogenic Index of Plasma Is Associated with Insulin Resistance in Non-Diabetic Peritoneal Dialysis Patients

MieJune Lee, 1 Jae Eun Um, 2 MiEun Wu, 1 Tae Ik Chang, 1 Tae-Hyun Yoo. 1 'Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; 2 'Brain Korea 21 PLUS, Severance Biomedical Science Inst, Yonsei Univ College of Medicine, Seoul, Korea; 3 'Dept of Internal Medicine, NHIC Ilsan Hospital, Gyeonggi-do, Korea.

Background: Insulin resistance (IR) is an independent risk factor for cardiovascular morbidity and mortality. Although many factors including uremia, chronic inflammation, and abnormal adipokine levels are known to contribute to the development of IR, the role of pro-atherogenic lipoprotein on IR remains unknown in peritoneal dialysis (PD) patients. Therefore, we investigated the independent association between pro-atherogenic lipoprotein and IR in non-diabetic PD patients.

Methods: We conducted a cross-sectional study in 75 non-diabetic PD patients. Pro-atherogenic lipoprotein was assessed by the atherogenic index of plasma (AIP, log transformed triglyceride to high-density lipoprotein cholesterol ratio). IR was determined by homeostatic model assessment-IR (HOMA-IR). Patients were divided into the higher and lower HOMA-IR group according to the median value of HOMA-IR. Independent association between AIP and HOMA-IR was ascertained by multivariate linear regression analysis.

Results: The mean age of the patients was 52.1±11.2 years, 35 patients (46.7%) were male. The mean value of AIP was 0.38±0.33 and the median value of HOMA-IR was 1.58 (interquartile range, 0.88 to 2.76). AIP was significantly greater in the higher HOMA-IR group (0.50±0.27 vs. 0.53±0.32, P=0.001). AIP was negatively correlated with systolic blood pressure (r=-0.32, P=0.005) and log adiponectin (r=-0.42, P=0.001) and positively correlated with sagittal abdominal diameter (r=0.25, P=0.033), residual renal function (r=0.29, P=0.012), serum albumin (r=0.26, P=0.026) and log HOMA-IR (r=0.54, P<0.001). Independent multiple regression analysis of AIP (β=0.251, P<0.001) was independently associated with HOMA-IR after adjustment for confounding factors.

Conclusions: Pro-atherogenic lipoprotein abnormality determined by high AIP might be implicated with development of IR in non-diabetic PD patients.

TH-PO988

Reducing Mortality in CAPD Patients by Statin

Yong-kwu Lee, Tae Ik Chang, Sug kyun Shin. Nephrology Div, Dept of Internal Medicine, National Health Insurance Corporation, Ilsan Hospital, Goyang, Korea.

Background: Patients who are on CAPD (Continuous Ambulatory Peritoneal Dialysis) shows higher serum LDL cholesterol and Triglyceride compared to patients who are on hemodialysis. But higher cholesterol level does not seem to effect on raising mortality or cardiovascular morbidity and mortality. On the contrary, lower serum cholesterol level in CAPD patients tends to raise mortality and morbidity due to poor nutritional status.

Methods: This study is a retrospective study designed to evaluate the effect of cholesterol level, statin on CAPD outcome and mortality. Patients who were on peritoneal dialysis for at least 6 months since March 1st, 2000 were included. A total of 467 patients were enrolled in this study. Patients’ biological parameter, biochemical parameter and morbidity/mortality during CAPD maintenance period were collected.

Results: Patients whose initial cholesterol level were above 240 mg/dL shows significantly low CAPD failure rate compared to patients whose initial cholesterol level were below 200 mg/dL (OR=0.469, P=0.049). Patients whose average LDL-cholesterol during CAPD period were over 100mg/dL showed significantly higher mortality compared to patients whose initial LDL-cholesterol level were below 100mg/dL (OR=1.848, P=0.024).

Patients whose compliance to statin during CAPD period was over 80% showed significantly low mortality compared to patients who did not take statin during CAPD period (OD=0.556, P=0.020). Patients showed no significant difference in mortality due to total cholesterol, HDL cholesterol levels and patients showed no significant difference in CAPD failure due to HDL/LDL cholesterol, statin usage.

Conclusions: In CAPD patients, serum total cholesterol level should be targeted higher than HD or CKD patients. On the contrary, similar to HD or CKD patients, Statin should be administered and LDL cholesterol should be lowered during CAPD period to lower mortality. To identify the difference in cholesterol mechanism of CAPD patients further, in depth study over adequate cholesterol level in CAPD patients needs to be proceeded.

TH-PO990

Using Daily Remote Biometric Monitoring in Peritoneal Dialysis

Suje G Lee, 1 Manya Magnus, 2 Neal Sikk, 1 1 Medicine, George Washington University, Washington, DC; 2 Epidemiology and Biostatistics, George Washington University, Washington, DC; 3 Emergency, George Washington Univ, Washington, DC.

Background: Peritoneal dialysis(PD) requires self-monitoring with daily blood pressure(BP), weight, & physical examination. Patients(Pts) don’t always perform procedures or record results. We aim to determine associations between daily remote biometric monitoring(RBM) & clinical and pt satisfaction outcomes.

Methods: Pts were provided with BP monitoring equipment & scale which were capable of announcing the results, transmitting the results via Bluetooth technology to a hub located in the pt’s home & via 2G/3G cellular signal to a Telehealth call center. PD nurses viewed results or alerted to abnormal results.

Results: 300 subjects(subjects) from 10 PD units were followed over at least 12 months. Demographics include male (56%), African American(AA)62%), & median age 56 yrs (IQR 44-64) and 1.86 yrs on dialysis (IQR 0.62-3.73). AA subs were more likely to use than non-AAA(69% vs 55%; p<0.05). 51% of subs used RBM, with 66% consistently using the equipment. RBM was associated with reduced risk of hospitalization (Coef -0.27, SE 0.10, p=0.006). Subs became increasingly less likely to breach any upper or lower alert threshold (OR 0.995, p=0.004). Subj satisfaction of RBM equipment for BP monitoring was 87% & scale 90%. Rural exceeded non-rural subjs in utilizing RBM (OR 4.77, 95% CI 1.34-16.98, p<0.02). Use of RBM was associated with improved perception of confidence with self-care requirements of PD easier to collect measurements (OR 2.69, 95% CI 1.52-4.76, p<0.001); more secure in their measurements (OR 3.28, 95% CI 1.71-6.26, p<0.001); getting more support from their PD doctors and nurses (OR 2.05, 95% CI 1.01-4.12, p<0.05).

Conclusions: RBM was associated with increased frequency, accuracy, and confidence of measurements to medical personnel, enhanced perception of autonomy and confidence in measurements, & reduction of hospitalizations & out of range measurements for BP. RBM was acceptable & satisfactory to PD pts. RBM offers additional tools to support PD pts in maintaining their measurement regimens & reduce negative health outcomes.

Funding: Other U.S. Government Support

TH-PO990

Impact of Patient-Centric Automated Peritoneal Dialysis User-Interface on Operator Learning and Confidence

Catherine Firanek, Mary Gellens, James A. Sloand. Medical Affairs, Baxter Healthcare, Deerfield, IL.

Background: Automated peritoneal dialysis (APD) is an underutilized therapy for patients with end-stage renal disease (ESRD). The perception patients may not be able to manage their own treatment setups comes into play in choice of this treatment modality. Improvements to cycler technology may help to further simplify therapy for patients.
Reducing barriers to uptake. This study aimed to determine whether a cycler-embedded, patient-centric interface offered an enhanced user experience compared to a conventional APD cycler.

Methods: 30 study participants (ages 29-84, mean 50 yrs, 67% male) diagnosed with ESRD were randomized into 2 groups using cycler with patient-centric user interface with advanced technology in development and a conventional APD cycler. Participants evaluated cycler on 2 non-consecutive days using a different cycler each day. Each participant was given a brief orientation, setup task, training session, break, followed by a setup task and questionnaire. Study results were analyzed via Fisher’s exact, Mann-Whitney and Exact binomial tests.

Results: The cycler with patient-centric user interface and advanced technology (in development) scored better on reduced reliance on printed instructions (p=0.001). Patients committed fewer deviations on the cycler in development vs the conventional cycler (2 of 19 vs 14 of 19 respectively) after training (p=0.004), including disinfecting hands (p=0.02) and line handling (p=0.01), and were more confident that they set up the cycler according to specifications (p=0.043). The new cycler scored higher in overall preference among study participants: The cycler with a patient centric user interface was rated easier to learn (p=0.005) and to use (p=0.016), preferable to use (p=0.03), and users felt more confident in choosing the new cycler at home compared to conventional cycler (p=0.004).

Conclusions: A cycler with embedded, patient-centric interface was rated higher in terms of overall reliance on instructions, task competency, ease of use and learning, preference and overall confidence of using the cycler. These findings indicate that APD cycler development could lead to increased user confidence and comfort.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO991
Single-Site Trans-Umbilical Peritoneal Dialysis Catheter Insertion Mangalakumar Veerasingam
Nephrology, KMCH, Coimbatore, Tamilnud, India.

Background: Traditional laparoscopic peritoneal dialysis catheter placement requires two ports insertion and this could lead to complications like leak and hernia at the port sites. We describe a novel approach of using single-site trans-umbilical ports that is associated with small scar (less than 1cm) and reduced complications.

Methods: Under general anesthesia, pneumoperitoneum was created as per standard method. One 10mm and one 5mm port was inserted through trans-umbilical route to guide peritoneal dialysis catheter insertion. Hernial orifices were inspected and if there was any adhesion present that was released to facilitate free fluid movement. The catheter was inserted through a small incision 1 inch below umbilicus. The catheter was positioned in the pouch of Douglas using lap instrument passed through the trans-umbilical port. The other end of catheter was tunneled in the standard manner and brought out through the exit site and the titanium adaptors were fixed as usual. To prevent the migration of catheter from the pelvic cavity a trans-facial loop was placed around the catheter (freely mobile but remains in pelvis). Omentum was folded and pulled upwards to the left upper guardant and fixed to anterior abdominal wall using a trans-facial loop. The latter prevented the omentum from wrapping dialysis catheter and causing malfunction. Then the port site was closed in three layers (Video available).

Results: 10 cycler undergoing cycler insertion with this approach (Male 7, Female 3) and the mean follow up period is 11 months. None of them developed leak or catheter migration or any mechanical complication that might require catheter reposition or change.

Conclusions: Combined method of Single-site port placement, omentopexy and loop fixation of intra-abdominal segment of catheter offers the following advantages -small incision; hence risk of leak when catheter was used early after placement is low. The risk of hernia through port site is reduced and small scar will be welcome to image conscious patients. If there was any adhesion present that could be released with minimal trauma to peritoneum. Placement of a loop around the catheter prevented catheter migration. Omental wrapping was prevented by fixing this in the upper quadrant by trans-facial loop.

TH-PO992
Peritonitis and Survival following PD Catheter Insertion in Infants Joshua Zaritsky, Coral D. Hanevold, Troy Richardson, Jonathan Rodean, John P. Lawlor, Raymond P. Quigley, Alicia Neu, Bradley Warady. SCOPE Collaborative, CHA, Overland Park, KS.

Background: Chronic peritoneal dialysis (PD) is the dialysis modality of choice for children. However, there are limited outcome data in those who undergo PD catheter (cath) insertion in the 1st year of life. Using data from the Children’s Hospital Association Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (ESRD) Collaborative (SCOPE), we examined peritonitis rates and survival in 156 infants who had a PD cath placed in the 1st yr of life.

Methods: Data on pt demographics, PD cath characteristics, peritonitis risk factors and outcomes from 157 cath insertions from 29 North American pediatric dialysis centers were reviewed and analyzed using chi square test for association or a Wilcoxon rank-sum test.

Results: In hospital and overall peritonitis rates during the 1st year post cath insertion were 1.73 and 0.76 per pt-year, respectively. Gram + organisms were responsible for 38.7% of infections (figure); 28% were culture negative. Polycystic kidney disease and pulmonary hypoplasia were more frequent in infants with peritonitis, whereas anuria did not differ between groups (table). Use of a curled catheter or plastic adaptor, nephrectomy prior to or concurrent with cath insertion, and G-tube insertion after cath placement were more common in pts with peritonitis, while number of cuffs, surgical technique, cath use within 14 d and cath revision did not differ between groups. Infants with peritonitis had longer initial hospital stays and lower survival compared with those without peritonitis.

Conclusions: This large cohort of infants with ESRD, who found a high rate of peritonitis and identified several risk factors associated with peritonitis. Given that peritonitis was associated with increased initial hospital stay and mortality, attention to the potentially modifiable factors is needed.

TH-PO993
Risk Factors for All-Cause Unexpected Hospitalization After Peritoneal Dialysis Catheter Implantation Z Li, Zita C. Abreu,1 Joanne M. Bargman.2 1Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China; 2Nephrology, Toronto General Hospital Univ of Toronto, Toronto, ON, Canada.

Background: Implantation of the peritoneal dialysis catheter (PDC), usually an elective procedure, may necessitate unexpected hospitalization due to multiple co-morbidities and inherent instability of the end-stage renal disease patient. This information is important for administrative planning for a PD program. However, information on hospitalization after PDC implantation is limited and details about the reason for hospitalization are lacking.

Methods: We performed a prospective cohort study in consecutive patients who underwent PDC implantation at a single institution from 2007 to 2013. Clinical characteristics of enrolled patients, technique of the implantation procedure and all-cause unexpected hospitalization and morbidity within 14 days after implantation were analyzed.

Results: A total of 246 patients receiving 252 PDC implantations during the 6 years were studied. After 39 procedures (15.5%), patients had an unexpected hospital stay due to operative complications (33.3%), worsening of comorbid disease (35.9%), or a single-night hospital stay for observation (30.8%). Compared to discharged patients, the unexpected hospitalization ones were older (P=0.001), had higher rates of previous episodes of heart failure (P<0.006) and heart disease (P<0.001), had more use of general anesthesia (P=0.046), had more added procedures during the implantation (P=0.02) and had more episodes of flow obstruction and peritonitis (P=0.012 and P=0.001). Multivariable logistic regression showed that age, cardiac morbidity, use of general anesthesia, PDC flow problems and peritonitis after implantation were independent predictors of all-cause unexpected hospitalization.

Conclusions: For the first time, our study has analyzed the rate of unexpected hospitalization after PDC implantation and identified the salient risk factors. Increased focus to identify patients at greatest risk for hospitalization, evaluation of processes of care, and implementation of preventive strategies may be helpful to reduce unplanned hospitalization after catheter insertion.
TH-PO994

Early Mechanical and Infective Complications in First Time Blind, Bedside, Midline Percutaneous Tenckhoff Catheter Insertion with Ultra Short Break-in Period: Setting New Standards

Zuying Xiong, 1 Gui Santosh Varughese, 1 Ninoo G. George, 2 Santosh Varughese. 1 Nephrology, Christian Medical College, Vellore, Tamil Nadu, India; 2 Nephrology, Bilirobh Hospitals, Chennai, Tamil Nadu, India.

Background: There are no large studies that have looked into ultra-short break-in period with blind, bedside,midline approach of Tenckhoff catheter insertion.

Methods: 294 consecutive adult patients underwent catheter insertion for chronic peritoneal dialysis at our centre from January 2009 to December 2013. Those with history of midline laparotomy scars and hernias were referred for open surgical insertion. 245 patients (86.3%) underwent the percutaneous and 39 patients (13.7%) underwent surgical insertions.

Results: The mean break-in period for the percutaneous group (PG) was 2.68 ± 2.63 days and for the surgical group (SG) was 11.19 ± 6.96 days, p < 0.001. Poor catheter outflow was present in 22 (9%) of PG and in 4 (10.3%) of SG (p = 0.80). Primary catheter non-function was present in 24 (9.8%) of the PG and in 4 (10.3%) of the SG (p = 0.73). Catheter survival at one year was 164/241 (89.1%) in the PG. The various outcomes are:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Percutaneous N=295</th>
<th>Surgical N=39</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed Catheter Insertion,n(%)</td>
<td>20(8)</td>
<td>0</td>
<td>0.74</td>
</tr>
<tr>
<td>Poor outflow,n(%)</td>
<td>22(9)</td>
<td>4(10.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Dialysate leak,n(%)</td>
<td>16(6.5)</td>
<td>6(15.4)</td>
<td>0.055</td>
</tr>
<tr>
<td>Mesenteric tear,n(%)</td>
<td>20(8)</td>
<td>0</td>
<td>0.74</td>
</tr>
<tr>
<td>Paralytic ileus,n(%)</td>
<td>0</td>
<td>1(2.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Exit site bleeding,n(%)</td>
<td>1(0.4)</td>
<td>0</td>
<td>0.69</td>
</tr>
<tr>
<td>Early peritonitis,n(%)</td>
<td>3(1.2)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Overall early mechanical complications,n(%)</td>
<td>40(16.3)</td>
<td>11(28.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Primary catheter non-function,n(%)</td>
<td>24(8.9)</td>
<td>4(10.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Mortality,n(%)</td>
<td>68/241(28.2)</td>
<td>17/364(47.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Catheter survival at one year,n(%)</td>
<td>164/184(89.1)</td>
<td>29/358(82.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Median patient survival(n)</td>
<td>45/95(UL:28.5-57.5)</td>
<td>35/95(UL:24-46)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Figure: Relevance of systolic blood pressure to vascular events and cause-specific mortality, by prior vascular disease or raised troponin.

Conclusions: The significantly shorter break-in period and smaller wound incisions reduce hospitalization and the need for bridging hemodialysis as well as having good patient and catheter outcomes.

TH-PO995

Comparing Outcomes of Percutaneous Peritoneal Dialysis Catheter Insertion by Nephrologist versus Open Surgical Insertion – Large Single Centre Experience

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Background: Several studies suggest that percutaneous insertion of peritoneal dialysis (PD) catheters by nephrologists improves the uptake of PD. Percutaneously inserted PD catheters have the advantage of being less invasive, removing the need for general anaesthetic, reducing hospital stay, facilitating acute PD, therefore making PD more accessible. There are only a few small studies directly comparing the outcomes of patients who have had a percutaneous versus open method of implantation, with some suggesting poorer outcomes. We retrospectively reviewed data on all patients who had a percutaneous or open surgical PD catheter inserted between August 2011 and December 2014 at a single renal centre, to identify the patients who developed an exit site infection (ESI) or episode of PD peritonitis within two and four weeks of catheter insertion. We also looked at patients who developed a functional catheter problem requiring manipulation or replacement of the catheter within the first year. Chi-squared test was used to assess statistical significance.

Results: 276 PD catheters were inserted in the said time period. 152 were inserted percutaneously and 124 with open surgery. There were less ESI (at 2 weeks - 2.6% versus 4.3%) and PD peritonitis within two and four weeks of catheter insertion. We also looked at patients with PD catheters requiring manipulation or replacement within the first year due to a functional problem was comparable in the percutaneously inserted catheters (9.2% versus 12.9%; p=0.327). There were no major complications in the form of visceral perforation or major haemorrhage in either method.

Conclusions: In our study, it was found that infected related complications were better with percutaneous PD catheter insertion and mechanical failure rate was comparable to open surgical PD catheter insertion. In our practice we have found that percutaneously inserted PD catheters are a safe means of increasing patient access to PD, enabling more patients to have a home-based therapy.

TH-PO996

Shared Decision-Making in Chronic Kidney Failure: The Retrospective Analysis of First Stage PD Patients in Germany

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Background: To date, little is known about the extent to which patients with chronic kidney failure feel involved in decision-making regarding the life-changing dialysis treatment. Previous studies on mortality yielded equivalence of peritoneal (PD) and hemodialysis (HD). However, only 5% of the patients in these studies were HD patients, although many patients are eligible for both options and entitled to receive unbiased counselling.

Methods: In a nationwide multicenter study with federal funding (“CORETH-project”), we surveyed 781 patients on dialysis since 6 to 24 months with regard to their rating of shared decision-making (SDM) with their physician concerning the choice of renal replacement therapy. We used the “Shared Decision-Making Questionnaire” (Kriston et al. 2010), which is a highly reliable and well accepted measure. Furthermore, patients indicated the dominating reason for choosing their treatment as well as their treatment satisfaction (TS).

Results: Data were compared between propensity score-matched groups of patients (nPD=nHD=246).

Conclusions: Our findings highlight awareness for an unbiased nephrological counselling-culture and provide indications for a successful SDM-process when choosing dialysis modality. According to the results, an effective SDM can pave the way for dialysis patients’ quality of life and treatment success.

Funding: Government Support - Non-U.S.

TH-PO997

Depression and Cognitive Impairment in Peritoneal Dialysis: A Multi-Center Cross-Sectional Study

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Background: Depression and cognitive impairment have been identified as independent risk factors for mortality in peritoneal dialysis (PD) patients. The relationship between depression and cognitive functions in PD patients was investigated in this multi-center cross-sectional study.

Methods: Study design: multi-center cross-sectional study. Setting & Participants: A total of clinically-stable 458 patients who performed PD for at least 3 months from 5 PD units were included in this study. Only 5% of the patients in Germany choose PD, even though many patients are eligible for both options and entitled to receive unbiased counselling. Measurements: Global cognitive function was measured by using the Modified Mini-Mental State Examination (3MS), specific cognitive function by executive function, immediate memory, delayed memory, visuospatial skill and language ability by subtests of Repeatable Battery for the Assessment of Neuropsychological Functioning. Depression was diagnosed if the depression severity index <0.5 by using Zung’s Self-rating Depression Scale.

Results: The prevalence of depression and cognitive impairment evaluated by 3MS were 52% and 28.4% respectively. Patients with mild or moderate/severe depression had higher prevalence of global cognitive impairment, executive dysfunction, impaired immediate and delayed memory. After adjusting for demographic, comorbidity data and clinical parameters, depression scores were independently associated with lower scores of 3MS, immediate and delayed memory, and language ability, and longer completion time of tests. Even mild depression and HD independently predict higher risk of CI, executive dysfunction, impaired immediate and delayed memory after multivariable adjustments.

Conclusions: Even mild depression plays an important role in global and specific cognitive functions in PD patients.

Funding: Government Support - Non-U.S.
Proposed Model for the Care of Hospitalized Peritoneal Dialysis Patients

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Background: Peritoneal dialysis (PD) has been prescribed throughout the United States, yet the optimal model of care for hospitalized PD patients remains unknown. With a growing interest in home modalities and emphasis on quality, it is imperative that we identify an effective and efficient way to care for this patient population during hospitalization.

Methods: We describe a model successfully implemented at Vidant Medical Center (VMC) in 2008. Prior to this date, the primary hospital nurses performed PD care. Due to the high risk, low volume nature of inpatient PD, this resulted in inconsistent care as well as decreased physician, nursing, and patient satisfaction. In 2008, an inpatient PD nursing team was created. This team, consisting of nephrology nurses with specialized PD training, is managed by VMC’s self-maintained dialysis unit. Staffed with 2 nurses during the day and at night, they provide 24/7 care throughout the hospital, including the ICU and ED. Responsibilities include patient education, exit site care, catheter flushes, and all manual and automated PD exchanges. Upon discharge, the outpatient unit is contacted to ensure appropriate transition back to the outpatient setting.

Results: This model provides several benefits: 1) PD treatments are consistently completed and charted, 2) Increased physician, nursing, and patient satisfaction, 3) Continuity of care, and 4) Cost reduction (personnel and supplies). Since inception, this team has grown to 13 nurses. During FY2014, 2568 (1572 adult / 996 pediatric) PD treatments were performed, the majority CAPD. To ensure appropriate utilization of nursing resources, most are cross-trained to perform hemodialysis.

Conclusions: In conclusion, the creation of a specialized nursing team has been instrumental in optimizing the care of our hospitalized PD patients. This sustainable model provides effective, efficient care and should be considered for implementation by hospitals providing PD services.

Elderly Peritoneal Dialysis Compared with Elderly Hemodialysis Patients and Younger Peritoneal Dialysis Patients: Competing Risk Analysis of a Korean Prospective Cohort Study

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1 Internal Medicine, Seoul Nat’l Univ College of Medicine, Seoul, Republic of Korea; 2Internal Medicine, Seoul Nat’l Univ Boramae Medical Center, Seoul, Republic of Korea; 3Internal Medicine, Kyungpook Nat’l Univ School of Medicine, Daegu, Republic of Korea.

Background: The outcomes of peritoneal dialysis (PD) in elderly patients have not been thoroughly investigated. We aimed to investigate the clinical outcomes and risk factors associated with PD treatment in PD elderly patients.

Methods: We conducted a prospective observational nationwide adult end-stage renal disease (ESRD) cohort study in Korea from August 2008 to March 2013. Among incident patients (n=830), patient and technical survival rate, quality of life, and Beck’s Depression Inventory (BDI) scores of elderly PD patients (≥65 years, n=95) were compared with those of PD patients aged ≤49 years (n=205) and 50~64 years (n=192); and elderly hemodialysis (HD) patients (n=315). The patient death and technical failure were analyzed by cumulative incidence function.

Results: The patient survival rate of elderly PD patients was inferior to that of younger PD patients (P<0.001). However, the technical survival rate was similar (P=0.097). Compared with elderly HD patients, the patient survival rate did not differ according to dialysis modality (P=0.987). Elderly PD patients showed significant improvement in the BDI score compared with the PD patients aged ≤49 years (P=0.003). Low albumin, hemoglobin, and low residual renal function were significant risk factors for the PD patient survival; and peritonitis was a significant risk factor for technical survival.

Conclusions: The overall outcomes were similar between elderly PD and HD patients. PD showed the benefit in BDI and quality of life in the elderly. Additionally, the technical survival rate of elderly PD patients was similar to that of younger PD patients. Taken together, PD may be a comparable modality for elderly ESRD patients.

Phosphorus Control and Phosphate Binder Pill Burden During Real-World Use of Sucroferric Oxycitrate in Peritoneal Dialysis Patients

Linda H. Ficociello, Vidhya Parameswaran, Mark Costanzo, Claudy Mullon, Franklin W. Maddux, Robert J. Kossman. Fresenius Medical Care North America (FMCNA), Waltham, MA.

Background: Achieving serum phosphorus (sPhos) control can be a challenge for dialysis patients (pts). This retrospective database analysis examined the real-world effectiveness of sucroferric oxycitrate (SO), an iron-based phosphate binder (PB), in adult peritoneal dialysis (PD) pts.

Methods: A cohort of PD pts prescribed SO as part of routine clinical care at FMCNA clinics was analyzed. Pts had 1 sPhos measured during SO and had been previously treated with sevelamer, calcium acetate, calcium carbonate or dual therapy. Changes in sPhos, serum calcium (sCa), intaphyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and PB pill counts per day (PPD) were assessed 3-months before SO (baseline) and 3-months after SO (follow-up).

Results: Pts (n=328) were, on average, 53 years old, with a dialysis vintage of 3.9 years. At baseline, 56% of pts used sevelamer, 29% calcium acetate, 11% calcium carbonate, and 5% dual therapy. Pts in-range increased from 13.5 to 23.8% (76% increase). Mean sPhos decreased from 6.92 to 6.67 mg/dl, P<0.001. PB PPD was reduced from 8.4 to 3.8 pills (4.6 fewer pills, P<0.001). There was no significant change in sCa (9.1 to 9.0 mg/dl) or iPTH (335 to 555 pg/ml). TSAT and FER increased from 35.4 to 36.6% and 752.1 to 814.9 mg/ml, respectively.

Conclusions: This was accomplished with a mean of 3.8 pills per day, a reduction of 4.6 pills (P<0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

Laparoscopic Findings of Visceral Peritoneal Injury in Patients Treated with Neutral pH Peritoneal Dialysis Solution

Yudo Tanno, Naena Matsuo, Izumi Yamamoto, Yasuyuki Nakada, Ichiro Obikado, Keitaro Yokoyama, Takashi Yokoo. Div of Kidney and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.

Background: Encapsulating peritoneal sclerosis (EPS) is caused by a visceral peritoneal lesion, i.e., intestinal tract adhesion and encapsulation, it is important to evaluate changes in the visceral peritoneum. It has been reported that there was a decreasing trend of peritoneal injury with the use of PD solution with neutral pH as compared with acidic pH in the histopathological evaluation of the parietal peritoneum; however, there is no report evaluating changes in the visceral peritoneum, which is essentially important and should be evaluated. We previously reported laparoscopic approach for evaluation of EPS (KI 2012) in patients treated with PD solution with acidic pH. In this study, we examined macroscopic findings of the visceral peritoneum in patients treated with neutral pH solution alone for 4 years or more by laparoscopy.

Methods: I9 patients underwent laparoscopy at the time of PD catheter removal. Duration of PD in these patients was 64±18.8 months. Clinically, none of these patients had developed EPS by the time of the investigation. The findings of both parietal and visceral peritoneal tissues were categorized according to color changes, presence of neovascularizations and adhesions.

Results: It was found that longer the duration of PD, the worse the peritoneal injury. Although changes in the parietal and visceral peritoneum had heterogeneous distributions, the changes in the visceral peritoneum were milder, showing a discrepancy with the findings of the parietal peritoneum. As compared with laparoscopic findings in patients treated with PD solution with acidic pH, the degree of color changes, presence of neovascularizations, and adhesions were all mild, however, severe adhesions were noted in patients with a history of PD peritonitis.

Conclusions: Although changes in the visceral peritoneum resulting from the use of PD solution with neutral pH show a decreasing trend as compared with acidic pH, there is a certain level of peritoneal change, suggesting the possibility of progression of peritoneal deterioration by long-term continuous use.

TH-PO1002

“Composite” Encapsulating Peritoneal Sclerosis: A New Presentation in a Long Time of Renal Replacement Therapy

Valerio Vizzardi. O.U. of Nephrology, Spedali Civili and Univ of Brescia, Brescia, Italy.

Background: Encapsulating peritoneal sclerosis (EPS) is the more dangerous complication of peritoneal dialysis (PD). The EPS can occur during PD (classic EPS), after kidney transplantation (TX) or rapid shift to hemodialysis (HD) as the mode of renal replacement therapies (RRTs).

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

Underline represents presenting author.

328A
Peritonitis Rates Among African Americans and Caucasians Undergoing Peritoneal Dialysis Patients with Peritonitis

**Background:** Severe and prolonged peritonitis leads to peritoneal membrane failure and is the most common cause of technique failure in patients treated with peritoneal dialysis (PD). Recent studies reported that delta neutrophil index (DNI), which reflects the fraction of circulating immature granulocytes in the blood, is a practical severity marker of infection. This study investigated whether DNI could be a predictive marker of catheter removal in PD patients with peritonitis.

**Methods:** Patients treated with PD peritonitis at Severance Hospital between January 2012 and January 2015 were enrolled. Demographic data, clinical, and laboratory parameters including DNI were collected at the time of peritonitis. DNI was calculated by automatic analyzer.

**Results:** A total of 125 PD peritonitis episodes in 92 patients were investigated. The mean age was 59 ± 12.0 years and 55 (44.0%) were male. PD catheter was removed in 31 (24.8%). The median value of DNI in patients underwent PD catheter removal was significantly higher compared to that of patients who maintained PD catheters (DNI interquartile range, 3.30 (0.0-65.0) vs. 0.70 (0.0-22.5), P = 0.001). DNI is significantly associated with percentage of segmented neutrophil (r = 0.28) and serum albumin (r = -0.32), and dialysate leukocyte counts (r = 0.20), but not with C-reactive protein (CRP) levels (r = 0.08). Multivariate logistic regression analysis revealed that DNI was an independent predictor for PD catheter removal in patients with PD peritonitis (odds ratio = 1.08, 95% confidence interval = 1.01-1.12, P = 0.04) after adjustment for serum albumin, CRP, leukocyte count of dialysis effluent, and septic shock. The area under the ROC curve (AUC) of DNI for PD catheter removal was 0.69 (P = 0.001), whereas the AUC of dialysate leukocyte count was not statistically significant (0.52, P = 0.70).

**Conclusions:** DNI levels reflected the severity of PD peritonitis. Higher levels of DNI could be an independent predictor for PD catheter removal in patients with PD peritonitis.

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**TH-PO1004**

Peritonitis Rates Among African Americans and Caucasians Undergoing Peritoneal Dialysis

**Background:** African Americans (AA) are under-represented in the prevalent peritoneal dialysis (PD) population in the United States. There is relatively little conclusive data to explain the cause of this. One explanation is that AA may have higher rates of peritonitis than Caucasians leading to increased technique failure. This study aimed to determine if differences between AA and Non-AA rates of peritonitis at the University of Alabama at Birmingham Home Dialysis existed.

**Methods:** This is a single-center retrospective cohort analysis of data from November 2012 to November 2014. Baseline demographics as well as data on peritonitis episodes were analyzed. Peritonitis rate was defined as the absolute number of distinct peritonitis episodes divided by the number of patient months at risk. Relapsing peritonitis episodes were excluded. Chi-square analysis was used to compare baseline categorical variables and independent t test to compare length of time on dialysis. Rates of peritonitis were analyzed by Fischer exact test. Peritonitis free survival, hospitalization free survival and technique failure were analyzed by log rank comparison of Kaplan Meier curves.

**Results:** A total of 920 cases and 2607 controls were identified. There were a total of 70 failures, 31 (44.3%) related to infectious complications, 22 (31.4%) to non-infectious complications (e.g. obstruction, leaks), 8 (11.4%) to inadequate dialysis, and 9 (12.9%) to miscellaneous factors. Overall survival at 36 months was 78.81%. Covariates significantly affecting technique failure include prior HD (1.83; 1.14–2.92), non-infectious complications (1.82; 1.28–2.59), DM (1.62; 1.00–2.63), HIV (2.52; 1.01–6.24), peritonitis (1.94; 1.29–3.12), and exit site infections (1.79; 1.09–2.92). Previous abdominal surgeries (90; 0.758–1.08) and BMI (1.005; 0.971–1.04) were not significantly associated with failure.

**Conclusions:** This is one of the largest single center studies of its type from a US PD program. It shows excellent 3 year PD technique survival, better than reported in similar studies. Our results confirm that diabetes mellitus, PD related infections, and non-infectious mechanical problems are independent risk factors for PD technique failure. Conversely, BMI, abdominal surgeries, and demographic characteristics such as race and gender do not have significant association and should not be considered barriers to PD initiation.

**Funding:** Clinical Revenue Support

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**TH-PO1006**

Effect of Early Peritonitis on Clinical Outcomes

**Background:** Infection is a source of significant morbidity and mortality for peritoneal dialysis (PD) patients. Previous studies suggest that early peritonitis is associated with shorter technique survival; however these studies are limited by small samples, restricted generalizability, and a lack of standardized definitions. We used data from a large dialysis database to determine if the timing of the first peritonitis episode is associated with adverse clinical outcomes.

**Methods:** US and Canadian data from 1996 to 2005 in the Baxter POET (Peritonitis, Organisms, Exit sites, Tunnel infections) database was analyzed. Patients who developed peritonitis within 6 months of PD initiation were identified as cases. Controls were patients whose first peritonitis occurred after 6 months. Patients who never developed peritonitis or who were on PD for less than 6 months were excluded. Patients were censored at the clinical endpoint, transfer to hemodialysis, or death.

**Results:** There were 920 cases and 2607 controls were identified.

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

Underline represents presenting author.

329A
Testing the Impact of BMI on Mortality Among PD Patients. Data of hazard ratios and 95% confidence intervals (CIs) were obtained for respective BMI groups provided by each study. We performed meta-regression analysis using unrestricted maximum likelihood model.

**Results:** The Medline, EMBASE, and the Cochrane library search provided a total of 3,047 articles. After screening of all titles, 513 abstracts were selected. Finally, 9 cohort studies with 33,090 patients were included in the final analysis. Log hazard ratio for all-cause mortality showed a trend negatively associated with increasing four square root of BMI (slope coefficient: -0.1976, 95% CI [-0.4110 to 0.0118, p = 0.0695].

### TH-PO1007

**Underweight Predicts Technical Failure: A Retrospective Cohort Study of Incident Peritoneal Dialysis Patients**

Xiaoxuan Huang, Xiuqin Zeng, Qing Wang, Zibo Xiong, Yumei Liao, Zuying Xiong. Div. of Nephrology, Peking Univ Shenzhen Hospital, Shenzhen, Guangdong, China.

**Background:** Technical failure is more common in peritoneal dialysis (PD) than in hemodialysis. High body mass index (BMI) increases mortality in the general population, but it may improve survival in hemodialysis patients. In PD patients, yet, reports regarding the association of BMI with technical survival are scarce and remain controversial.

**Methods:** In this retrospective cohort study, 348 incident PD patients (aged 48.2 ± 15.5 years, 62% men) at Peking University Shenzhen Hospital from 2000 to 2014 were included. BMI was calculated with height and weight first recorded within 2 to 6 months after initiation of PD. Patients were categorized according to the World Health Organization index (BMI) on mortality among peritoneal dialysis (PD) patients. We examined the effect of BMI on patient and technique survival in a prospective, incident PD cohort at a single center.

**Methods:** Subjects who started PD between 2000 and 2012 were enrolled in the study. Demographic and laboratory data were prospectively collected. Patients were categorized into four BMI groups: obese, >25 kg/m²; overweight, 23.1–24.9 kg/m²; normal, 18.5–22.9 kg/m² (reference category); and underweight, <18.5 kg/m². Patient and technique survival were compared using Cox proportional hazards model.

**Results:** A total of 632 incident PD patients were included in final analysis. The median follow-up period was 40 months (interquartile range, 19–64 months). In Kaplan–Meier survival curve, patient survival was not statistically different among all BMI categories (p = 0.641, by log-rank test). The hazard ratio (HR) adjusted for age, sex, diabetes, comorbidities, albumin, hemoglobin for patient survival was not significant among BMI groups (p = 0.837). In contrast, technique survival was significantly poorer in obese patients than in patients having a normal BMI (p = 0.029, by log-rank test). The HR for technique failure was significantly greater for obese PD patients in comparison with the reference category [1.8, 95% confidence interval (CI): 1.2 to 2.6; p = 0.008]. The reasons for technique failure included recurrent peritonitis (34%), inadequate dialysis (17%), mechanical problem (17%), and refractory exit-site tunnel infection (11%) in obese patients.

**Conclusions:** In our PD patients, patient survival was similar in all BMI categories. Therefore, obese patients should not be discouraged from receiving PD purely on the basis of BMI. However, technique survival was significantly poorer for obese PD patients. Further study is warranted to improve technique survival in obese patients.

### TH-PO1010

**Phosphate Clearance in Peritoneal Dialysis: Residual Renal Function and Dialysis Modality**

Carmen Gonzalez corvillo, Mariangeles Rodriguez Perez, Alejandro A. Suarez benjumea, Nuria Areste, Mercedes Salgueira lazo. Nephrology, Virgen Macarena-Rocio, Sevilla, Spain.

**Background:** Evaluate urinary and peritoneal excretion of phosphate and related factors in peritoneal dialysis (PD). Analyze phosphate clearance depending on PD modality and peritoneal membrane type.

**Methods:** Observational study, in a sample of 375 PD patients. Mean age 60 (±14) years, 24% patients on APD (16=CPD, 8=NIPD) 13 on CAPD. Mean Kt/V: 2.04 ± 0.6. Mean residual renal function (RRF): 6.3 ± 4 ml/min. Transmembranous peritoneal transport: 6 high (6H), 26 high-average (6A) and Slow-average (LA). Renal and peritoneal phosphate clearance (ultrafiltration and diffusion) was analyzed. Urinary and dialysate P and creatinine clearance was measured. Serum PTH was measured.

**Results:** In PD patients, BMI was inversely associated with mortality as in HD patients. Other outcomes such as cardiovascular death, peritonitis incidence, and technical failure will be additionally evaluated.

**Conclusions:** In PD patients, BMI was inversely associated with mortality as well as in HD patients. Other outcomes such as cardiovascular death, peritonitis incidence, and technical failure will be additionally evaluated.

### TH-PO1008

**The Association Between Body Mass Index and Mortality in Peritoneal Dialysis Patients**

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**Background:** Unlike the general population, a higher body mass index (BMI) was consistently found to be a strong predictor of decreased mortality in patients with end-stage renal disease who receive maintenance hemodialysis (HD). This phenomenon has been referred to as the “Obesity paradox” or “reverse epidemiology.” Similar tendency has been observed in several studies with peritoneal dialysis (PD) patients, but the studies have reported conflicting results. We conducted this study to evaluate the association between BMI and all-cause mortality in PD patients.

**Methods:** A systematic search was conducted for published studies in Medline, EMBASE, and the Cochrane library databases from 1970 to April 2015. We identified studies evaluating the impact of BMI on mortality among PD patients. Data of hazard ratios and 95% confidence intervals (CIs) were obtained for respective BMI groups provided by each study. We performed meta-regression analysis using unrestricted maximum likelihood model.

**Results:** We performed meta-regression analysis using unrestricted maximum likelihood model. The Medline, EMBASE, and the Cochrane library search provided a total of 3,047 articles. After screening of all titles, 513 abstracts were selected. Finally, 9 cohort studies with 33,090 patients were included in the final analysis. Log hazard ratio for all-cause mortality showed a trend negatively associated with increasing four square root of BMI (slope coefficient: -0.1976, 95% CI [-0.4110 to 0.0118, p = 0.0695].

**Conclusions:** Our results suggest that patients with early peritonitis had a significantly higher peritonitis rate than controls (1.26 and 0.67 episodes per patient per year, p<0.001). Early peritonitis was also associated with shorter technique and patient survival.

### TH-PO1009

**Is Obesity a Poor Prognostic Factor in Incident Peritoneal Dialysis Patients?**

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**Background:** Obesity is associated with an increased risk of death in the general population. Previous studies have demonstrated a discrepancy in the impact of body mass index (BMI) on mortality among peritoneal dialysis (PD) patients. We examined the effect of BMI on patient and technique survival in a prospective, incident PD cohort at a single center.

**Methods:** Subjects who started PD between 2000 and 2012 were enrolled in the study. Demographic and laboratory data were prospectively collected. Patients were categorized into four BMI groups: obese, >25 kg/m²; overweight, 23.1–24.9 kg/m²; normal, 18.5–22.9 kg/m² (reference category); and underweight, <18.5 kg/m². Patient and technique survival were compared using Cox proportional hazards model.

**Results:** A total of 632 incident PD patients were included in final analysis. The median follow-up period was 40 months (interquartile range, 19–64 months). In Kaplan–Meier survival curve, patient survival was not statistically different among all BMI categories (p = 0.641, by log-rank test). The hazard ratio (HR) adjusted for age, sex, diabetes, comorbidities, albumin, hemoglobin for patient survival was not significant among BMI groups (p = 0.837). In contrast, technique survival was significantly poorer in obese patients than in patients having a normal BMI (p = 0.029, by log-rank test). The HR for technique failure was significantly greater for obese PD patients in comparison with the reference category [1.8, 95% confidence interval (CI): 1.2 to 2.6; p = 0.008]. The reasons for technique failure included recurrent peritonitis (34%), inadequate dialysis (17%), mechanical problem (17%), and refractory exit-site/tunnel infection (11%) in obese patients.

**Conclusions:** In our PD patients, patient survival was similar in all BMI categories. Therefore, obese patients should not be discouraged from receiving PD purely on the basis of BMI. However, technique survival was significantly poorer for obese PD patients. Further study is warranted to improve technique survival in obese patients.

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

Underline represents presenting author.

330A
Results: Mean total P clearance=480±192mg/d. Mean renal P clearance=286±201mg/d and mean non-renal P clearance=246±148mg/d (mean clearance through UF=22±15mg/d [0.6%]) and by D 194=85±24hr[91%]. Mean urinary and dialysate P Cr were 40±15 and 0.59±0.24 Mean WPCI=31.4±13.1L/week. Mean serum P 4.9±1mg/dl and PTH294±166pg/ml 86.8% of patients were on Selevcre and 22%calcium based binders.45%were on vitD vita minD(r=0.87p<0.001) Positive correlation between peritoneal P clearance and UF(r=0.45p<0.004) as well as between RRF and P renal elimination(r=0.83 p<0.001) was observed. WPCI was higher in patients on CAPD than on APD(r=39.4±7 vs 21.1±13L/week p<0.05)being the main differences subjected to continuous vs discontinuous modality(CAPD vs US.CAPD was more protective that is why preservation of RRF is crucial. There is a correlation between peritoneal D(r=0.87p<0.001).

Influence Outcomes?

TH-PO1012

Proteinuria at PD Initiation May Predict Residual Renal Function Loss in the Automated Peritoneal Dialysis Patients Using Biocompatible Solution Yoshifumi Hamasaki, 1 Kenti Doi, 2 Rei Isshiki, 3 Haruki Kume, 3 Masaoi Nangaku, 4 Eisei Noiri, 5 1Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; 2Emergency and Critical Care Medicine, The Univ of Tokyo, Tokyo, Japan; 3Urology, The Univ of Tokyo, Tokyo, Japan.

Background: Residual renal function (RRF) has a significant impact on the prognosis of dialysis patients. Peritoneal dialysis (PD), especially using biocompatible PD solution (BPDS) with neutral-pH and reduced glucose degradation products, has advantageous to protect the RRF (Kidney Int. 2009; 75:206-211). It is still unclear whether factors predicting RRF loss in the PD patients using BPDS. We investigated the relationship between clinical parameters at PD initiation and the change of RRF in the PD patients using BPDS.

Methods: The data from patients who started PD as their first dialysis modality from 2001 to 2014 at The University of Tokyo Hospital were collected retrospectively. All patients were treated by automated PD (APD) using BPDS. To identify predictors of RRF decline, we analyzed data including clinical parameters measured at PD initiation. Residual GFR was calculated as the average of 24-hour urinary urea and creatinine clearances. The rates of urine volume and residual GFR decline were calculated by the least squares linear regression formula. The outcome of dialysis modality change was defined as switching APD to hemodialysis (HD) or combined therapy of PD and HD due to RRF loss.

Results: 96 patients were analyzed in this study. On multiple regression analysis, the decline rates of urine volume and residual GFR were significantly correlated with proteinuria at PD initiation. When patients were divided into two groups according to urinary protein level, Kaplan-Meier analysis revealed the lower proteinuria group had higher persistence rate of APD and lower rate of dialysis modality change (Log rank p = 0.01 and 0.04, respectively). On ROC analysis, urinary protein predicted the need of dialysis modality change within 2 years after PD initiation with statistical significance (AUC [95% CI]=0.78 [0.66-0.90]).

Conclusions: Proteinuria at PD initiation may predict RRF loss and the need of dialysis modality change in the PD patients using BPDS.


Background: Although urgent start (US) peritoneal dialysis (PD) and traditional start (TS) PD have similar outcomes, it is not known if differences in outcomes exist based on race. The objective of this study was to determine if differences in PD outcomes exist when stratified based on race and type of PD start.


Background: In-center HD and PD are the 2 most common types of dialysis utilized in US. Few studies have examined characteristics of patients who changed dialysis modality. Kaiser Permanente Northern California is an integrated health care delivery system with 3.7 million members. We retrospectively examined the characteristics and disease burden of patients who switched from HD to PD.

Methods: Retrospective examination of EMR from Jan 2009 – Oct 2014. Disease burden was assessed by internally developed comorbidity score point, which predicts negative outcomes in the next 12 months, based on documented comorbidities and hospitalizations.

Results: From 2010-2014, dialysis population in our integrated health system increased from 4005 to 4491 patients, and PD population grow from 621 to 1033. In this period, 11% patients of initiated dialysis occurred within a year after dialysis initiation. 8% of HD patients switched to PD and 24% of PD patients switched to HD. Majority of patients who switched from HD to PD do so within 6 months of initiation. They have less comorbidities than those who stay on HD. They have a higher comorbidity score when they switch to PD but lower than repeated switchers who switched from PD to HD. They were younger than those remaining on PD. Most patients who switched from PD to HD did so within a year. They have more comorbidities than those who stay on PD and have a higher comorbidity score when they switch to HD, even higher than the repeat score of those who switch from HD to PD. The difference in co-morbidity scores between the first and second measurement is higher for the PD to HD pattern. They have similar age to those who didn’t switch.

Conclusions: Patients who switched from HD to PD remain at approximately the same comorbidity score before and after switch. Comorbidity scores of patients who switched from PD to HD significantly increased, suggesting that change was influenced by decline in their overall condition. In our patient population, the switch from HD to PD is likely a patient’s decision, while the switch from PD to HD may be due to inability to continue PD.

Impact of Pre-Dialysis Immunosuppressive Treatment Time on Infectious Complications and Survival of Systemic Lupus Erythematosus (SLE) Patients on Peritoneal Dialysis Junbao Shi, 1,2 Joanne M. Bargman. 1,2 Dept of Nephrology, Peking Univ Third Hospital, Beijing, China; 1Div of Nephrology, Univ Health Network, Toronto General Hospital, Toronto, ON, Canada.

Background: SLE patients on peritoneal dialysis (PD) have a significant risk of infectious complications and poor outcomes. However, few studies have examined the relationship between pre-dialysis exposure to immunosuppressive (IS) therapy and the outcomes of PD. The objective of this study was to investigate whether pre-dialysis IS treatment influences the infectious complications and outcomes of SLE patients on PD.

Methods: Twenty-six SLE patients were treated with PD in a major academic centre from May 1996 to May 2014. Demographics, diagnostic tests and IS treatment, comorbidity indices, biochemistry and clinical data upon initiation of PD and hospitalization, infective complications, hospitalizations and clinical outcomes during the study period were collected. Three years was chosen as the discriminant between longer and shorter duration of IS therapy.

Results: Two patients were lost to follow-up during the study period. Therefore, a total 24 patients were included for analysis. The SLE patients with longer duration of pre-dialysis IS (>7) were older than patients with shorter pre-dialysis IS (≤7) (8.6±1.2 vs 7.1±1.7, P<0.05), but there were no significant differences in sex, race, PD duration, PD sub-modality and biochemistry between the two groups (P>0.05). Seven patients died during the follow-up period and all the deaths were from the group with longer-pre-dialysis IS time (P<0.05). Three patients died from infections, two patients from cardiovascular disease, and two had sudden death at home. However, there were no significant differences in the incidence of other infectious or hospitalization, infective complications, hospitalizations and clinical outcomes during the study period were collected. Three years was chosen as the discriminant between longer and shorter duration of IS therapy.

Conclusions: SLE patients undergoing PD with longer pre-dialysis exposure to IS drugs have a greater mortality that appears to be related to both infectious and noninfectious causes. Although incident to PD, they should be considered a high-risk subgroup.
examined to 1) compare mass transfer-area coefficients (MTACs) for urea, creatinine and glucose during fast and standard PETs and 2) use those parameters to predict PD therapy prescription adequacy.

**Methods:** Data from 104 PD (41 CAPD, 63 APD) patients who underwent a 4-hour standard PET and an overnight exchange with the same glucose concentration were used to determine PD prescription adequacy parameters. Calculated MTAC values for standard PET were compared with those for fast PET by using only data obtained at 4-hours during the standard PET and assuming a 200 mL residual volume in the prior exchange. The calculated membrane parameters were used to predict net ultrafiltration (UF), urea Kt/V and creatinine clearance (CCr), and those predictions of therapy adequacy were also compared with the mean of 3 actual measurements of net UF, Kt/V and CCr for each patient.

**Results:** Median urea, creatinine and glucose MTACs were 20.9, 10.1, and 9.1 mL/min during standard PET, and 21.0, 10.1 and 9.0 mL/min during fast PET; the corresponding membranes were fast-dissolved MTFAs for urea, creatinine and glucose were 0.6, 0.3 and 0.6 mL/min. Comparing predictions using standard fast PET, 81% of net UF were within 150 mL, 94% of Kt/V were within 0.1/wk and 93% of CCr were within 2 L/wk. The percent of predicted and actual measured values of net UF within 300 mL, Kt/V within 0.2/wk and CrCl within 8 L/wk were 64%, 63% and 77% for standard PET and 38%, 64% and 77% using fast PET; these differences were not statistically significant.

**Conclusions:** These results suggest that the predictions of PD therapy adequacy using PD Adequate are clinically equivalent when either fast or standard PET is employed. **Funding:** Pharmaceutical Company Support - Baxter Healthcare Corporation

**TH-PO1016**

The Loss of Residual Diuresis Increases in Erythropoietin in PD Patients

**Background:** Anemia in ESRD is attributed to impaired erythropoietin formation due to erythropoietin and iron deficiency. The accelerated clearance of erythropoiesis may at least partially be due to enhanced erythropoiesis, a suicidal death of erythrocytes characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine (PS) externalization at the erythrocyte (RBC) surface. Exposed PS is recognized by macrophages that engulf and degrade the affected cells. Little is known about mechanisms underlying enhanced erythropoiesis in ESRD. At least in theory, erythropoiesis may be stimulated by some uremic toxins. The present study investigated erythropoiesis in peritoneal dialysis (PD) patients.

**Methods:** 46 PD patients (31 M, mean age: 64±14yrs) and 17 healthy subjects (CTR) were enrolled. All measurements were made in isolette RBCs. PS exposure was estimated from FITC-Annexin V binding by flow cytometric.

**Results:** 27 patients were treated with CAPD and 19 with APD. The mean length of treatment was 39±29months. The PS externalization on surface was significantly higher in PD patients than in CTR (2.6% ± 1.6% vs. 0.8 ± 0.6%, P < 0.05). The mean percentage of eryptosis showed no significant differences between patients with (n=18) and without diabetes, treated with CAPD or APD and with a negative or positive (n=18) history of peritonitis. Eryptosis showed significantly lower levels in PD patients with residual diuresis (n=23) than in patients without (3.7%, 2.6-5.6 vs. 3%, 1.5-6.1, P=0.03). A significant negative correlation was observed between percentage of eryptosis and Body Mass Index (BMI) (r=0.39, P=0.05). There was no statistically significant relationship between erythropoiesis and months of PD, urea, albumin, creatinine, or urine volume.

**Conclusions:** In conclusion, erythropoiesis has been shown to be significantly higher in PD patients than CTR. Our data suggest that the type and the length of PD treatment do not enhance erythropoiesis. On the contrary, the loss of residual diuresis leads to a significant increase of eryptosis. The residual diuresis may contribute to the elimination of potential uremic toxins that induce increased erythropoiesis. **Funding:** Private Foundation Support

**TH-PO1017**

The Pattern of T Helper Lymphocytes Has No Clinical Implications in Peritoneal Dialysis Patients

**Background:** Anemia in ESRD is attributed to impaired erythropoietin formation due to erythropoietin and iron deficiency. The accelerated clearance of erythropoiesis may at least partially be due to enhanced erythropoiesis, a suicidal death of erythrocytes characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine (PS) externalization at the erythrocyte (RBC) surface. Exposed PS is recognized by macrophages that engulf and degrade the affected cells. Little is known about mechanisms underlying enhanced erythropoiesis in ESRD. At least in theory, erythropoiesis may be stimulated by some uremic toxins. The present study investigated erythropoiesis in peritoneal dialysis (PD) patients.

**Methods:** 46 PD patients (31 M, mean age: 64±14yrs) and 17 healthy subjects (CTR) were enrolled. All measurements were made in isolette RBCs. PS exposure was estimated from FITC-Annexin V binding by flow cytometric.

**Results:** 27 patients were treated with CAPD and 19 with APD. The mean length of treatment was 39±29months. The PS externalization on surface was significantly higher in PD patients than in CTR (2.6% ± 1.6% vs. 0.8 ± 0.6%, P < 0.05). The mean percentage of eryptosis showed no significant differences between patients with (n=18) and without diabetes, treated with CAPD or APD and with a negative or positive (n=18) history of peritonitis. Eryptosis showed significantly lower levels in PD patients with residual diuresis (n=23) than in patients without (3.7%, 2.6-5.6 vs. 3%, 1.5-6.1, P=0.03). A significant negative correlation was observed between percentage of eryptosis and Body Mass Index (BMI) (r=0.39, P=0.05). There was no statistically significant relationship between erythropoiesis and months of PD, urea, albumin, creatinine, or urine volume.

**Conclusions:** In conclusion, erythropoiesis has been shown to be significantly higher in PD patients than CTR. Our data suggest that the type and the length of PD treatment do not enhance erythropoiesis. On the contrary, the loss of residual diuresis leads to a significant increase of eryptosis. The residual diuresis may contribute to the elimination of potential uremic toxins that induce increased erythropoiesis. **Funding:** Private Foundation Support

**TH-PO1018**

Dialysate Losses of Vitamin 25(OH)D in a Cohort of Patients Treated with Peritoneal Dialysis

**Background:** Peritoneal dialysis (PD) is associated with 25(OH) vitamin D deficiency. To our knowledge, there are no cohort studies about 25(OH) vitamin D dialysate losses in PD. Objective: To characterize 25(OH) vitamin D losses in peritoneal effluent (PE) and their relation with changes in serum 25(OH) vitamin D levels during 4 months in a cohort of incident PD patients.

**Methods:** 52 patients with <6 mths but >1 mth on PD were invited from 2011 to 2014. Those with severe infections, hospitalizations, and oral intake of D3 or D2 during follow up were excluded. Basal vitamin 25(OH) D in 24h PE and serum were measured. After 4 months, a 2nd assessment was performed. The principal outcome was the change in serum vitamin 25(OH) D levels.

**Results:** 43 patients were included, 22 (51%) men, median age was 39y (Intercuartile range [IQR] 31-62), 29 (68%) had diabetes and 29 (67%) had some degree of renal residual function during all study. After 4 months of PD initiation, all patients had vitamin 25(OH) D levels <20ng/mL, 13 of them with levels less than 10 ng/mL.

**Characteristics:**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n=43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum 25(OH)D, ng/mL</td>
<td>14.2 (10.3-20.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peritoneal effluent 25(OH)D, ng/mL, losses, mg/day</td>
<td>13 (9.2-17)</td>
<td><em>Not measurable at this timepoint</em></td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>521 (343-845)</td>
<td>0.6</td>
</tr>
<tr>
<td>Ca, mg/dL</td>
<td>9.2 (8.5-9.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>P, mg/dL</td>
<td>4.9 (3.6-6.1)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The mean decrease of vitamin 25(OH)D levels was 5.8 ng/mL/6 months (IQR 2.9-9.3 ng/mL). Basal PE losses in mg/day and delta in serum vitamin 25(OH)D D had a significant correlation

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Conclusions: High efficient losses of vitamin 25(OH)D are observed in patients on PD and may explain very low levels observed during follow up in this cohort.  

Funding: Government Support - Non-U.S.

TH-PO1020  
Peritoneal Protein Excretion Was Lower in Nocturnal Intermittent Peritoneal Dialysis as Compared with Continuous Ambulatory Peritoneal Dialysis Not Associated With Peritoneal Transport Status in the Same Individual  
Hironori Nagasawa,1 Anayama Mariko,2 Yasushige Makino, Masaki Nagasawa. Dept of Nephrology, Shinonoi General Hospital, Nagano, Japan.

Background: Recent studies have reported that peritoneal protein excretion (PPE) during peritoneal dialysis (PD) therapy is associated with cardiac disease and patient survival. However, little is known regarding the extent to which PPE can be influenced by PD prescription or peritoneal transport status.

Methods: The aims of this study were to compare PPE in the same individual with different PD prescriptions of either continuous ambulatory PD (CAPD) or nocturnal intermittent PD (NIPD), and to evaluate the correlation between PPE and dialysate to plasma creatinine ratio (D/P Cr). Seventeen patients, of whom 58.8% were male, were included in the study. A peritoneal equilibrium test was performed and the amount of total protein (TP) loss in the dialysate was measured during CAPD or NIPD in the same patient.

Results: The mean age of the patients was 59.4 ± 18.0 years, body mass index was 21.5 ± 3.4, serum TP (s-TP) was 5.8 ± 0.8 g/dL, serum albumin (s-Alb) was 3.0 ± 0.7 g/dL, C-reactive protein (CRP) was 0.4 ± 0.7 mg/dL, and D/P Cr was 0.76 ± 0.15. During NIPD therapy, PPE was correlated with peritoneal clearance (γ = 0.63, p = 0.006), efficient volume (γ = 0.69, p = 0.002), and PPE to efficient volume ratio (γ = 0.80, p = 0.000), but not with s-TP, s-Alb, CRP, or D/P Cr. During CAPD therapy, PPE was negatively correlated with s-TP (γ = -0.62, p = 0.007) and s-Alb (γ = -0.58, p = 0.014), positively correlated with efficient volume (γ = 0.50, p = 0.037) and PPE to efficient volume ratio (γ = 0.72, p = 0.001), but not with CRP or D/P Cr. On comparing NIPD and CAPD, there was no difference in efficient volume (7341 mg vs. 7209 mg, respectively); however, both PPE and PPE to efficient volume ratio were significantly lower during NIPD than during CAPD [5586 mg vs. 7779 mg (p = 0.004) and 0.74 mg/mL vs. 1.09 mg/mL (p = 0.004), respectively].

Conclusions: The current study demonstrated that PPE and PPE to efficient volume ratio were lower during NIPD than during CAPD in the same individual, independent of s-TP, s-Alb, CRP, or D/P Cr. On comparing NIPD and CAPD, there was no difference in efficient volume (7341 mg vs. 7209 mg, respectively); however, both PPE and PPE to efficient volume ratio were significantly lower during NIPD than during CAPD [5586 mg vs. 7779 mg (p = 0.004) and 0.74 mg/mL vs. 1.09 mg/mL (p = 0.004), respectively].

Funding: Government Support - Non-U.S.

TH-PO1022  
Relation of Central and Brachial Blood Pressure to Volume Status in Peritoneal Dialysis Patients  
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Background: Euvolemia is an important predictor of outcome in peritoneal dialysis (PD), but chronic subclinical volume overload occurs frequently in PD patients. Even though volume overload is associated directly with hypertension, blood pressure (BP) not always reflect volume overload. Central BP has been shown to be a better predictor for target organ damages compared with brachial BP in general population. In this study, we evaluated comparative values of central BP and brachial BP for determining volume status in PD patients.

Methods: We enrolled 52 prevalent PD patients, and accessed volume status using Body Composition Monitor (BCM). Central BP was estimated using radial artery tonometry, and brachial BP measurement at office and 24-hour ambulatory blood pressure monitoring (ABPM) were performed. Volume overload was defined as an overhydration (OH) >1L. Results: Average office central systolic BP (<50BP), office brachial systolic BP (oSBP), and ambulatory brachial systolic BP (24-oSBP) were 139.8±26.3, 140±19.2, and 142.5±22.0 mmHg, respectively. In overall, 41 (78.8%) patients were in volume overload status. A stronger association of central BP with volume overload compared with brachial BP was observed in the receiver operating curve analysis (area under the curve (AUC) of cSBP, oSBP, and 24-oSBP were 0.87±0.06, 0.78±0.09, and 0.83±0.06 respectively). In multivariate analysis adjusted for age, sex, PD vintage, diabetes, and cardiovascular disease, the odds ratio (OR) for central BP (OR 1.110; 95% CI 1.019-1.210) was higher than those for brachial BP (OR 1.085; 95% CI 1.014-1.161 for 24-oSBP and OR 1.094; 95% CI 1.021-1.173 for 24-oSBP).

Conclusions: Office central BP was more strongly related to volume status than out-of-office ambulatory brachial BP as well as office brachial BP, suggesting that central BP was more valuable than brachial BP in assessing volume status in PD patients.

Funding: Government Support - Non-U.S.

TH-PO1023  
Novel Regimen for Intraperitoneal Cefazolin and Ceftazidime in Peritoneal Dialysis Patients  
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Background: Current guideline suggested that intraperitoneal (IP) antibiotics should be administered only in a long peritoneal dialysis (PD) dwell (>6 hours), which is not always practical because the long dwell might result in low ultrafiltration and volume overload. The objectives of this study were to develop a novel regimen for IP antibiotics in short dwell (<2 hours) during the automated PD cycling and examine the dialysate and plasma level of the most used empirical antibiotics for PD-related peritonitis, cefazolin and ceftazidime.

Methods: In the novel regimen, cefazolin and ceftazidime (20 mg/kg each) were added in a 5-liter bag of 2.5% dextrose PD fluid which was placed on the warmer of the PD machine without last fill or additional dwell. Cefazolin and ceftazidime concentrations of the most used empirical antibiotics for PD-related peritonitis, cefazolin and ceftazidime. The novel regimen for IP cefazolin and ceftazidime in short dwell (<2 hours) during the automated PD cycling could provide adequate dialysate and plasma level of the most used empirical antibiotics for PD-related peritonitis, cefazolin and ceftazidime. The novel regimen for IP cefazolin and ceftazidime in short dwell (<2 hours) during the automated PD cycling could provide adequate dialysate and plasma level of the most used empirical antibiotics for PD-related peritonitis, cefazolin and ceftazidime.

Conclusions: Six PD patients without peritonitis were participated in the study. Dialysate cefazolin and ceftazidime concentrations were high throughout the PD session in all patients (26-360 mg/L). Plasma cefazolin and ceftazidime exceeded the minimal inhibitory concentration (MIC) for susceptible organisms (8 mg/L) in 2 hours (cefazolin 28.5±8.0 and ceftazidime 12.5±3.4 mg/L at 2 hours), peak at 10 hours (51.1±14.1 and 23.0±5.2 mg/L) and then sustained well above the MIC at 24 hours (42.0±9.8 and 17.5±3.1 mg/L).

Conclusions: The novel regimen for IP cefazolin and ceftazidime in short dwell (<2 hours) during the automated PD cycling could provide adequate dialysate and plasma concentration and would become a standard regimen for peritonitis in PD patients already using PD cycling machine as well as those who temporarily need shorter dwells during peritonitis due to increasing peritoneal solute transport.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author.
TH-PO1024

Is Automated Peritoneal Dialysis Better Than Continuous Ambulatory Peritoneal Dialysis in Quality of Life, Depression, and Renal Treatment Satisfaction? A Prospective Multicenter Propensity-Matched Study
Sun-Hee Park,1 Hee-Yeon Jung,1 Sukyoung Lee,1 Ji-Young Choi,1 Se-Hee Yoon,1 Jang-Hee Cho,1 Chan-Duck Kim,1 Yong-Lim Kim.1 Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; 2Internal Medicine, Konyang Univ, Daejeon, Republic of Korea.

Background: Health-related quality of life (HRQOL) is an important variable in the selection of dialysis modality among incident dialysis patients. However, relative superiority in HRQOL between automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD) are not clearly known. The objective of this study was to compare HRQOL, depression, and renal treatment satisfaction over time between APD and CAPD patients.

Methods: Incident patients initiating APD and CAPD were prospectively enrolled from nationwide multicenters in Korea. HRQOL, depression, and renal treatment satisfaction were assessed at 1 and 12 months after the start of dialysis by Kidney Disease Quality of Life Short Form 36 (KDQOL-36), Beck’s Depression Inventory (BDI), and Renal Treatment Satisfaction Questionnaire (RTSQ), respectively. The mean changes of scores in APD and CAPD were compared by propensity score matching analysis.

Results: All 260 incident patients starting peritoneal dialysis (PD) from 11 centers were included in this study. A total of 170 patients were matched from 208 patients who completed all questionnaires and did not change PD modality during the 1-year follow-up period. The total scores at 1 month showed better HRQOL for APD than CAPD patients in symptom, patient satisfaction, pain, and social function domains. No differences were observed between the two groups in total scores of KDQOL-36 at 12 months. However, CAPD patients had a significantly greater improvement in symptom and health status domains. A significant improvement also occurred in BDI and RTSQ in CAPD patients.

Conclusions: APD is not better than CAPD in HRQOL, depression, and renal treatment satisfaction during initial first one year on dialysis. The relative positive effect of CAPD compared with APD on improvement of HRQOL, depression, and renal treatment satisfaction was confirmed.

TH-PO1025

Thyroid Functional Disease and Mortality in a National Peritoneal Dialysis Cohort
Connie Rhoe,1 Vanessa A. Ravel,1 Elani Streja,1 Rajnish Mehrotra,2 Steven B. Kim,1 Jianxi Wang,1 Danh V. Nguyen,1 Steven M. Brunelli,1 Csaba P. Kovesdy,1 Gregory Brent,1 Kamyar Kalantar-Zadeh,1 UC Irvine; 2UW; 3DaVita Clin Research; 4UTHSC; 5UCLA.

Background: Peritoneal dialysis (PD) patients have a high prevalence of thyroid dysfunction which may be due to 1) peritoneal effluent losses (vast majority of thyroid hormone is protein-bound) and 2) frequent exposure to povidone-iodine cleaning agents leading to iodine-induced hypo- and hyperthyroidism. In the general population thyroid dysfunction is associated with higher risk of cardiovascular (CV) disease and death. There has not been study of the association between hypo- or hyperthyroidism defined by TSH with mortality in PD patients.

Methods: We examined the association of thyroid functional status with all-cause mortality in a 5-year national cohort (1/2007-12/2011) of PD patients with at least one TSH measure. Thyroid functional status was defined as: hyper-, eu-, and hypothyroidism (TSH <0.5, 0.5-5, >5mIU/L). We examined time-dependent and baseline thyroid function to determine short- and long-term exposure–mortality associations, respectively, using Cox models with 3 adjustment levels: unadjusted, case-mix, and case-mix+laboratory adjusted.

Results: Among 1484 patients, 7% and 18% had hypo- and hyperthyroidism, respectively. In time-dependent analyses, hypo- and hyperthyroidism were each associated with higher mortality risk in all 3 Cox models (ref: euthyroidism). In baseline analyses, hypothyroidism was associated with higher death risk in unadjusted and case-mix models, but associations were attenuated to the null in case-mix+laboratory models.

Conclusions: Time-dependent hypo- and hyperthyroidism were each associated with higher mortality, suggesting short-term risk in PD patients. Further studies are needed to determine if CV pathways are implicated, and if thyroid-modulating therapies ameliorate mortality in this population.

Funding: NIDDK Support, Private Foundation Support

TH-PO1026

A Tale of APOL1 Mutation and Parvovirus Infection
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Introduction: We present a case of a first trimester pregnant woman with nephrotic range proteinuria and fetal demise in the setting of an acute parvovirus infection. Kidney biopsy revealed collapsing FSGS, and exome sequencing revealed mutations in APOL1. The relationship between Parvovirus and FSGS is one that clinicians might overlook, and perhaps may play a more prominent role in these progressive cases especially with APOL1 mutations.

Case Description: 37 yo Caribbean female presented at 8 weeks gestation with progressive swelling. Her daughter developed fifth’s disease one month prior. On presentation her BP was 146/95, HR 77 with pitting edema. Her creatinine was 6.3, BUN 43, albumin 1.5, and spot ptt/crt 20.8. Parvovirus PCR was 2000 copies. Biopsy demonstrated collapsing FSGS secondary to Parvovirus B19 [Fig 1A 1B]
The hope was that this injury would improve with improvement in titers, so IVIG was started. A follow up PCR showed improvement to 200 copies but she remained nephrotic with proteinuria of 20-60g. Re-biopsy revealed significant scarring and dialysis was initiated [Fig 1C]. Patient is now being evaluated for transplant. Given the unusual severity of this case, and her possible African ancestry, a genetic susceptibility to podocyte injury was entertained. Whole exome sequencing identified the patient to have two APOL1 risk alleles.

**Discussion:** Parvovirus has been linked with collapsing FSGS, and in one study viral PCR was detected in 78% of kidney tissue with this diagnosis. The combination of B19 infection and APOL1 mutation likely made our patient particularly susceptible to injury. Our case raises the question of how often subclinical parvovirus infection may be involved in collapsing FSGS, and highlights how sudden and devastating it can be to the life of a prior healthy woman.

**TH-PO1027**

**Podocyte Myeloid Bodies without Confirmed Genetic Mutation in a Female: Fabry’s Disease?**

**Case Description:** A 46 year-old Hispanic woman was evaluated for proteinuria. She was asymptomatic with no prior medical history or family history, and no exposure to silica, amiodarone, or hydroxychloroquine. Her exam was unremarkable: no neuropathy, skin changes, or corneal dystrophy. Scr was 0.6 mg/dL, UA 2+ protein with P/C ratio of 1.94 g/g. Biopsy revealed diffuse enlargement of the podocytes with a foamy cytoplasmic appearance and on EM, prominent podocyte lamellated lipid inclusions with foot process effacement and minimal endothelial deposits.

**Introduction:** Fabry’s disease (FD) is a X-linked lysosomal storage disorder caused by deficient alpha-galactosidase activity. A renal variant has been described with the R363H mutation. Due to random X-chromosomal inactivation, heterozygous females can present a diagnostic challenge. We report a case with a renal limited presentation, biopsy findings characteristic of FD but a negative whole blood DNA analysis.

**Case Description:** A 29-year-old female presented with proteinuria of 20-60 g. Renal biopsy revealed significant scarring and dialysis was initiated. She represented two weeks later, with a serum creatinine of 2.97 mg/dL and 9 grams of proteinuria on 24 hours collection and serum albumin of 2.2. She was initially fluid resuscitated, however, creatinine increased to 5.2 mg/dL and he became oliguric. Urine microscopy was without casts and serology markers were negative. Renal biopsy was performed that showed an interstitial nephritis with eosinophil rich infiltration and severe edema. Amongst other histological findings, there was dense tubulointerstitial fibrosis with tubular atrophy and hyaline casts. There was a positive Periodic Acid-Schiff (PAS) staining. The patient was treated with high dose (2mg/kg) steroid and oral diuretics. Renal function has returned to his prior baseline and he has subnephrotic proteinuria.

**Discussion:** This describes a case of nephrotic syndrome and interstitial nephritis related to the monoclonal antibody, Iplimumab. Interstitial nephritis has been extensively described with this drug before. 1However, this is the first case to our knowledge of the administration of ipilimumab leading to acute kidney injury from interstitial nephritis and severe proteinuria from diffuse podocyte foot process effacement. Prompt recognition of this presentation is necessary to preserve renal function.

**TH-PO1030**

**Kappa Light Chain-Associated Crystal-Storing Tubulopathy, Podocytopathy, and Histiocytosis in GI Tract, in a Patient with Multiple Myeloma Mishifumi Yamashita, 1,2 Albert Q. Lam, 1,2 Joseph V. Bonventre, 1,2,3 Vanesa Bijoj, 1,2 Pathology, Brigham and Women’s Hospital, Boston, MA; 1 Renal Disease, Brigham and Women’s Hospital, Boston, MA; 2,3 Harvard Medical School, Boston, MA.**

**Introduction:** Multiple myeloma manifests with variety forms of kidney disease, such as amyloidosis, cast nephropathy, and light chain deposition kidney disease. Among them, crystal-storing disease is a rare entity. We report an interesting case of a patient with examedulillary IgGk multiple myeloma, who presented with crystal-storing histiocytosis in GI tract, and subsequently developed crystal-storing tubulopathy and podocytopathy.

**Case Description:** A 60-year-old man with type 2 DM and HTN was found to have a 1 cm largeecal polyp on screening colonoscopy in 2009. The polyp showed diffuse infiltration by a plasma cell neoplasm and crystal-storing histiocytosis with k light chain (LC) restriction. At that time, the patient showed intact bone marrow, normal renal function and proteinuria of 0.5 g/24h. He was subsequently closely followed with endoscopy, SREP, and renal function tests. In 2014, he developed nephrotic range proteinuria (~4g/24h), slightly rising Cre to 1.12 mg/dL, and increased serum free k LC (216 mg/L). Kappa biopsy was performed, revealing many proximal tubular epithelial cells containing PAS-positive crystalline material in the cytoplasm. The glomeruli were unremarkable except for mild mesangial expansion. No significant immune deposits were present in glomeruli or tubulointerstitium, but there was slightly stronger background IF reactivity for k LC than l LC on frozen tissue sections. IF studies on prostate-digested paraffin sections revealed strong k LC reactivity of the materials aggregated in the tubular epithelial cells and podocytes, while l LC was negative. EM revealed extensive intracytoplasmic accumulation of crystalline material of rhomboid and rectangular shapes in proximal tubular epithelial cells and podocytes.

**Discussion:** LC-associated crystal-storing disease is a rare kidney disease. To our knowledge, this is the first reported case of coexisting crystal-storing tubulopathy, podocytopathy, and histiocytosis in the GI tract in a patient with multiple myeloma.
Paraneoplastic Tumor-induced Osteomalacia (TIO) in Small Cell Carcinoma: First Report of Positive Immunostaining for Fibroblast Growth Factor-23 in Small Cell Carcinoma

TH-PO1035

Paraneoplastic Tumor-induced Osteomalacia (TIO) in Small Cell Carcinoma: First Report of Positive Immunostaining for Fibroblast Growth Factor-23 in Small Cell Carcinoma

TH-PO1031


Introduction: Chronic lymphocytic leukemia (CLL) has been associated many glomerular disorders. Rarely, it has been associated with amyloidosis either as the sole clone responsible, or in association with a plasma cell clone possessing the same light chain. Though the co-existence of clonal plasma cells and CLL is known, the temporal association of this patient's nephrotic syndrome secondary to amyloid-lambda light chain due to a small lambda-restricted plasma cell population, temporally associated with a relapse of a kappa-restricted CLL.

Case Description: A 66 year-old male, diagnosed with kappa-restricted CLL in 2009 achieved complete remission after 6 cycles of fludarabine, cyclophosphamide and rituximab. 5 years later, he presented with foamy urine, generalized swelling, and weight gain. Serum creatinine was 1.1. Initial spot urine protein / creatinine ratio showed proteinuria of 5g/g which later increased to 10g/. During the previous year serum albumin fell from 3.6 to 2.6 to 5.7 mg/dL over the preceding year. His CD4+ T-cell count was 514 and his viral load never reached detectable levels. Only for preemptive renal transplantation. She received a 0-antigen mismatched deceased donor renal allograft with uneventful post-transplant course. Allopurinol dose was increased to 600 mg daily with complete resolution of disabling visual symptoms. Allograft function has been excellent with nadir creatinine of 0.82 and urine microscopy negative for DHA crystals.

Discussion: APRT deficiency is a autosomal recessive purine metabolism disorder where adenosine is oxidized by xanthine dehydrogenase to 2,8–dihydroxyadenine (2,8-DHA), forming insoluble urinary crystals, nephrolithiasis, nephrotic syndrome and renal failure. Literature reveals diagnosis of APRT deficiency is rare before kidney transplantation. Delay in diagnosis and xanthine oxidase inhibitor treatment predisposes to recurrent disease in renal allograft, with allograft loss in over 25% cases. Though APRT is ubiquitous in all cells, extrarenal symptoms are uncommon in affected individuals. Our patient presented with crystalline keratopathy resolving completely after kidney transplantation.

Case Description: 41 y/o Caucasian female with recurrent 2,8-DHA nephrolithiasis since age 23 was maintained on Allopurinol. Clinical course was significant for obstructive uropathy requiring multiple stent placements; continued decrement in renal function and blood pressure. Temporal association of this patient's nephrotic syndrome secondary to amyloid-lambda light chain due to a small lambda-restricted plasma cell population, temporally associated with a relapse of a kappa-restricted CLL.

Discussion: Though the co-existence of clonal plasma cells and CLL is known, the temporal association of this patient’s nephrotic syndrome secondary to amyloidosis from a unique plasma cell clone expressing a different light chain supports the hypothesis that, in CLL, sharing the same microenvironment as non-tumor cells may activate bystander B-cells to express free light chains and in this case lead to amyloidosis.

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Minimal Change Disease Diagnosing Relapsing Mantle Cell Lymphoma
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Introduction: Glomerular lesions are linked with hematologic malignancies, with minimal change disease (MCD) commonly associated with Hodgkin’s lymphoma. Diagnosis of the underlying hematologic disorder often precedes development of the glomerulopathy; however, in rare cases, MCD precedes discovery of the lymphoma by several months. We present a case of a new onset nerosis and AKI in association with undetected relapsing mantle cell lymphoma (MCL).

Case Description: A 74 y/o man with history of stage IV mantle cell lymphoma in remission developed AKI and new onset edema. Chemotherapy completed 1 year prior to presentation induced complete remission on bone marrow and follow-up PET scans. On presentation he denied B symptoms, had no new lymphadenopathy, and only noted decreased appetite. The patient was edematous and hypertensive. Serum cr was 2.4 mg/dl up from 1.3 mg/dl. High-grade, non-quantifiable urine protein was noted by the lab. Urine sediment was remarkable for numerous granular casts, oval fat bodies, and few uric acid crystals. Serum uric acid was 13.2 mg/dl. Therapy for tumor lysis syndrome was instituted due to concern for relapsing lymphoma in the setting of AKI. However, PET/CT scan was completely normal with no evidence for lymphoma. Furthermore, LDH was within normal limits. Kidney biopsy revealed normal glomeruli on light microscopy with acute tubular injury. EM revealed global effacement of foot processes. A diagnosis of MCD with focal tubular injury was made and steroid therapy was started. Peripheral flow cytometry and later a bone marrow biopsy confirmed a 23% tumor burden compatible with relapsed MCL.

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Introduction: Bevacizumab (BCZ), an inhibitor of vascular endothelial growth factor (VEGF), is approved for the treatment of various cancers. We are reporting a case of BCZ induced acute kidney injury (AKI) with proteinuria (PTN) and thrombotic microangiopathy (TMA) and providing a summary of evidence after systematic review of reported cases in literature.

Case Description: A 57-year-old Caucasian woman with no history of kidney disease presented with abdominal pain 4 weeks after completing most recent cycle of BCZ (first dose 3 weeks before hospitalization) for colon cancer. She presented with new onset of hypertension (HTN), diffusely tender abdomen and a significantly low hemoglobin of 4.6 g/dl. A non-contrast CT showed hemorrhagic pancreatitis. Her serum creatinine at presentation was 2.93 mg/dl (baseline: 0.5 mg/dl). Further workup showed platelets of 60,000/µL, lactate dehydrogenase of 510 mg/dl and LDH of 947 U/L. Peripheral blood smear showed 3 schistocytes/hpf. Urinalysis was positive for protein and 4 RBCs/hpf. 24 hour urine had 2.1 gms of protein. Hepatitis panel, ANCA and SPEP were negative. ADAMTS 13 activity was normal. Based on clinical diagnosis of AKI, PTN and TMA related to BCZ, the drug was discontinued and patient was managed conservatively without plasma exchange (PE). The creatinine gradually improved to 1.5 mg/dl while platelet count and hemoglobin returned to baseline at discharge.

Discussion: We identified 24 cases reported in literature with mean age of 62 years. All patients presented with AKI and PTN with 61% being nephrotic range. The onset of PTN ranged from 2 weeks to 28 months after initiation of BCZ. HTN occurred among 62% while TMA among 57% of patients. Most of the patients had partial or complete recovery of AKI and PTN with only 1 patient progressing to end-stage renal failure on dialysis ranging from 2 to 33 months. The causative mechanism of nephrotoxicity is thought to be related to low free VEGF levels leading to endothelial dysfunction and podocytopathy. Treatment includes withholding the drug if PTN exceeds 2g/day or permanent discontinuation for nephrotic syndrome and ACEI or thiazide diuretics for treatment of HTN. Drug induced TMA with normal ADAMTS 13 levels rarely requires PE.

5-Oxoprolinuria: A Rare Cause of High Anion Gap Metabolic Acidosis due to Acetaminophen Ingestion
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Introduction: Acquired 5-oxoprolinuria is a rare cause of high anion gap metabolic acidosis due to excessive acetaminophen ingestion. It largely goes unrecognized because an assay for 5-oxoproline is not widely available. The malnourished and chronically ill women with history of chronic acetaminophen ingestion are commonly affected. Acetaminophen levels are rarely in toxic range.

Case Description: A 57-year-old woman with a history of adipsis dolorosa was admitted for acute osteomyelitis. She was chronically taking acetaminophen containing pain medication. Her hospital course was complicated by anion gap metabolic acidosis and cardiorespiratory failure. Her acetaminophen level was not elevated. Usual causes of anion gap acidosis were ruled out. Finally, a urine organic acid screen showed elevated 5-oxoprolinuria levels. Acetaminophen containing pain medication was stopped, she was given IV hydration and sodium bicarbonate. Her anion gap metabolic acidosis would quickly resolve.

Discussion: Acute and chronic acetaminophen ingestion can lead to high levels of 5-oxoprolinuria. The pathophysiology behind acquired 5-oxoprolinuria has been mostly explained by reduced glutathione in prior case reports. 5-oxoprolinuria is an intermediate in the gamma-glutamyl pathway, the metabolic cycle responsible for creating glutathione and shunt amino acids into the cysteol. When glutathione levels are diminished, feedback inhibition ceases, causing an overproduction of 5-oxoprolin. Sepsis, amongst others etiologies, have been implicated in glutathione depletions. 5-oxoprolinuria clinically presents with altered mental status. One of the key aspects of diagnosing this disorder is the detection of 5-oxoprolin in urine. N-acetylcysteine may be an effective treatment that acts to restore intracellular glutathione levels. Extracellular fluid expansion with dextrose containing saline promptly improves symptoms. In conclusion, 5-oxoprolinuria should be considered in any patient with unexplained metabolic acidosis and recent acetaminophen ingestion. Overlooking the diagnosis can be costly.

Severe Tubulointerstitial Nephritis with Lymphoid Follicles in Sjögren’s Syndrome
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Introduction: Patients with Sjögren’s syndrome (SS) are at increased risk for the development of lymphoma. They present state of immunologic and lymphoid hyperactivity in SS may predispose patients to the development of lymphoid neoplasm. However, biopsy specimens from some of these patients do not meet histologic criteria for frank malignancy. We report a rare case of severe tubulointerstitial nephritis with lymphoid follicles in SS.

Case Description: A 66-year-old woman, who had developed general malaise for a few years, was admitted to our hospital, because of the rapid rise in the serum creatinine levels. Laboratory data showed calcium 10.2 mg/dl (8.9-10.7 mg/dl), phosphorus 4.7 mg/dl (2.5-4.6 mg/dl), alkaline phosphatase 2784 units/L (0-120 units/L), intact PTH 5707.8 pg/ml (12-65 pg/mL). She underwent tracheostomy and four-gland parathyroidectomy with autotransplantation in the subcutaneous abdominal tissue. Biopsy of the left maxillary bone revealed osteitis fibrosa consistent with renal osteodystrophy.

Discussion: Hyperparathyroidism can cause extraosseous calcification in arteries, joints, and viscera. Osteitis fibrosa cystica is characterized by increased bone turnover caused by secondary hyperparathyroidism. The prevention of a positive phosphate balance is the mainstay of treatment of high-turnover bone disease.

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Scleroderma renal crisis was diagnosed according to the pathology result. Lisinopril 20 mg once daily was started, but the patient continued deteriorating leading to hemodialysis.

**Discussion:** Recognizing the early signs of kidney injury is important to initiate the treatment scleroderma renal crisis(SRC). Physicians should suspect for SRC once patients have signs of acute kidney injury regardless of elevated blood pressure or creatinine.

**TH-PO1042**

**Acetaminophen Associated 5-Oxoproline Acidosis in an Anuric End-Stage Renal Disease Patient**

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**Introduction:** Also known as pyroglutamic acid, 5-oxoproline is an intermediary in glutathione antioxidant metabolism. Reports of acetaminophen associated 5-oxoproline high-anion gap metabolic acidosis (HAGMA) has been slowly growing in the literature but remains under recognized in clinical practice.

**Case Description:** A 57 year old male with anuric end-stage renal disease (ESRD) was admitted for confusion and hypotension secondary to sepsis from infected lower extremity ulcer, poor oral intake, and excessive peritoneal dialysis. Laboratory evaluation revealed a depressed bicarbonate level of 17 mEq/L and an elevated albumin-corrected anion gap of 30 mEq/L. Despite correction of an elevated L-lactate with fluid resuscitation and antibiotics, his HAGMA persisted. An exhaustive investigation was unable to find a convincing etiology including commonly attributable organic acids, D-lactate, paraproteinemia, toxic exposures, and medications. Further inquiry revealed a protracted course of therapeutic acetaminophen ingestion with a weighted average daily dose of 1.3 grams in the four weeks leading to presentation. Serum 5-oxoproline was elevated to >100.0 nmol/mL (normal range 6.0-10.0 nmol/mL). Serum acetaminophen was undetectable. All acetaminophen containing medications were subsequently stopped. His clinical course improved with supportive care and he was discharged home. After 5 weeks of acetaminophen cessation, his serum 5-oxoproline normalized to 27.1 nmol/mL with anion-gap and bicarbonate levels returning to baseline.

**Discussion:** To our knowledge, we report the first case of acetaminophen associated 5-oxoproline acidosis in an anuric ESRD patient. Risk factors are thought to be related to glutathione deficiency which in turn favors the 5-oxoproline pathway of the γ-glutamyl cycle and results in accumulation. These risk factors include reactive acetaminophen metabolites, alcohol abuse, malnutrition, sepsis, renal dysfunction, and liver disease. As an under recognized entity in clinical practice, 5-oxoproline should be considered in adults with unexplained HAGMA and the above risk factors.

**TH-PO1043**

**Renal Amyloidosis Associated with Apolipoprotein C-II Deposition**

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**Introduction:** A 62-year-old female with no family history of renal disease presented with a creatinine at 2.3 mg/dL and hypertension. Baseline creatinine was 1.2 mg/dL one year prior to presentation and she had 1+ proteinuria on urinalysis 3 years earlier. Serologic workup was negative for ANA, C3, C4, hepatitis B and C, HIV and SLE. A renal biopsy was performed by direct sequencing of apolipoprotein C-II and showed mutation in patient and a Novel Foxp3 Mutation

**Discussion:** Apolipoprotein C-II is a component of very low density lipoprotein and readily aggregates in lipid free conditions to form homogenous amyloid fibrils due to their intrinsic structure. To the best of our knowledge, this is the first case of apolipoprotein C-II renal amyloidosis. This case highlights the importance of performing DNA sequencing of exons of interest and LCMS on known amyloidogenic proteins to accurately diagnose and type the renal amyloidosis, which is critical for prognosis, treatment and genetic counseling.

**TH-PO1044**

**Membranous Nephropathy in a Young Child with IPEX-Like Phenotype and a Novel Foxp3 Mutation**

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**Introduction:** Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome typically presents with heterogeneous manifestations. The syndrome is characterized by numerous auto-immune diseases due to dysfunction in the Foxp3 gene, which plays a critical role in maintaining immune tolerance.

**Discussion:** Membranous nephropathy in a young child with IPEX-like phenotype and a novel Foxp3 mutation is a rare and important case of membranous nephropathy in a young child with IPEX-like phenotype and a novel Foxp3 mutation.
**TH-PO1045**

**Acute Rejection of a Kidney Transplant in a Patient with Common Variable Immunodeficiency Syndrome**

**Omar Moussa Al Nimri,1 Rakesh Malhotra, Paisit Pauksakon, Beatrice P. Concepcion. Vanderbilt Univ Medical Center, Nashville, TN.**

**Introduction:** Common Variable Immunodeficiency (CVID) is a primary immunodeficiency characterized by hypogammaglobulinemia. Clinical manifestations include recurrent bacterial infections, autoimmune disorders, chronic lung disorders, hepatitis and lymphoma. We report a case of a patient with known CVID whose post-transplant course was complicated by acute cellular and humoral rejection which ultimately led to graft loss.

**Case Description:** A 44 y.o. male with ESRD was diagnosed in 11/2010 with CVID after developing peritonitis. He had a history of recurrent sinopulmonary infections and pneumococcal pneumonia. Immunoglobulin levels were undetectable and B and NK cell numbers normal. He was treated with monthly IVIG infusions. In 3/2012, he underwent living unrelated kidney transplantation (KT). Immunosuppression consisted of basiliximab, methylprednisolone (MP), FK, MMF and prednisone. Baseline creatinine (Cr) post KT was <1.2 mg/dl. A renal biopsy revealed membranous nephropathy with mild mesangial proliferative involvement. His main concern for patients with CVID undergoing KT was the risk of the induction of CVID syndrome. He had chronic renal failure and was on dialysis for 9 months at the time of KT.

**Discussion:** To our knowledge, this is the first reported case of a patient with diagnosed CVID on maintenance IVIG who then underwent KT. The main concern for patients with CVID undergoing KT is the risk of the induction of CVID syndrome. However, this case illustrates that rejection can occur and adequate immunosuppression remains essential. Balancing immunosuppression with the risk of infection can be quite challenging in this patient population, making them high risk for transplantation.

**TH-PO1046**

**Reverse Pseudohyperkalemia in a Patient with Non-Hodgkins Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia**

**Paisit Paueksakon, Beatrice P. Concepcion.**

**Case Description:** A 14-month-old male with a history of failure to thrive (FTT), eczema (5 months old), with cough and wheezing for 4 months. Pertinent findings on physical exam included weight <25th percentile, length 105th percentile, BP 103/83 mmHg, and diffuse wheezing. Laboratory evaluation showed normochromic normocytic anemia, WBC 7.1 K/mm3, platelets were 154 K/mm3. His serum was 195 mg/dl, elevated serum glucose 303-326 mg/dl, normal serum calcium-creatine ratio 0.25, low Cr 43 μmol/l and C 4.7 mg/dl, and negative ANA and anti DNA. Thyroid function tests were normal; islet cell antibodies were elevated at 80 (normal <1.2). A renal biopsy revealed membranous nephropathy with mild mesangial proliferative changes. Upon further evaluation, he was found to have fat malabsorption and numerous food allergies. Genetic sequencing identified a novel missense mutation, c.767T>C leading to substitution of the highly conserved amino acid threonine with methionine at position 256 in the Fgpl3 gene. This mutation was predicted to be deleterious by in silico analysis thereby indicating the likelihood of CVID syndrome. Of note, Fgpl3 protein expression was borderline low. The patient was treated with prednisone and tacrolimus with partial resolution of extra-renal symptoms, improvement in proteinuria and is currently awaiting bone marrow transplant.

**Discussion:** Infants with IPEX syndrome usually present with auto-immune enteropathy, FTT, eczema, type 1 diabetes mellitus and thyroid dysfunction. Renal involvement is rare and includes proteinuria, hematuria and renal insufficiency. Some children with novel mutations may have partial features as seen in this case. A diagnosis of IPEX should be considered in any male infant or young child with proteinuria in association with systemic features of autoimmunity.

**TH-PO1047**

**An Unusual Presentation of Fibromuscular Dysplasia**

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**Introduction:** Fibromuscular dysplasia typically presents in middle aged women, often with hypertension. Depending on which arteries are involved, patients may present with transient ischemic attack, stroke [carotid artery FMD], or intractable hypertension [renal artery FMD]. We report an atypical case of fibromuscular dysplasia (FMD) in a male, that presented with renal infarction and no other symptoms.

**Case Description:** The patient is a 47yo male with no significant past medical history, including no history of Ehlers-Danlos syndrome or Marfan’s syndrome, who developed sudden left flank pain while driving. No urinary symptoms. No tenderness on exam. The pain was so severe that he went to a local ER. Initial evaluation notable for BUN 10 mg/dl, Cr 1.06 mg/dl, urinalysis negative for blood, protein, and white blood cells. CT angiography revealed sealed bleeding consistent with FMD at the distal main renal artery at the junction of the bifurcating branches, and tapered narrowing and occlusion most likely caused by spontaneous dissection with intramural hematoma, with upper pole infarct.

**Discussion:** This case is notable because the FMD occurred in a male, and because renal infarction is a rare presentation of FMD. The actual cause of the infarction is most likely arterial dissection, with or without peripheral emboli.

**Funding:** Clinical Revenue Support

**TH-PO1048**

**Clotting Filter Might Be an Early Clue to Fat Embolism Syndrome: Case Report and Literature Review**

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**Introduction:** Non traumatic causes of Fat Embolism Syndrome (FES) have been reported with bone marrow transplantation, osteomyelitis, pancreatitis, alcoholic fatty liver, and with liposuction. Etiology likely is fat particles entering the circulation with damage to capillary beds. Regardless of the mechanism initiating fat embolism, the end result is an intense inflammatory response. In the lungs, this induces lung injury that is indistinguishable from ARDS. FES can cause cerebral edema with raised intracranial pressure along with multi-organ failure and AKI.

**Case Description:** We present a 40-year-old African American lady who underwent non-myeloablative bone marrow transplant for Myelodysplastic anemia. One week after engraftment she developed sudden onset of respiratory distress leading to a cardio-respiratory arrest. She developed ARDS, multiple organ dysfunction syndrome and CVVH was initiated for oliguric AKI and Metabolic acidosis. Soon after initiating CVVH her filter clogged with white, creamy plaque which cleared after 2 successive filters. Patient met Gurd and Wilson’s criteria for diagnosis of Fat Embolism Syndrome. She had abundance of...
inflammatory cells on Broncho alveolar lavage including neutrophils and macrophages. Oil
Red-O stain (stain for lipid) was performed to quantify macrophages displaying positivity. The
initial Prep yielded 5 of 5 and the repeat prep yielded 11 out of 12 macrophages positive
for Oil-Red-O. CT brain was performed which revealed large acute strokes with midline
shift compatible with subdural herniation. No cerebral blood flow was identified on nuclear
scan and patient was declared brain dead and terminally weaned.

Discussion: With the absence of specific tests or criteria the diagnosis of FES is
dependent on the clinical acumen of the physician. Lipid inclusion in 30-70% of
macrophages / inflammatory cells is most suggestive of FES. Only proven treatment is
supportive care. We present that a clotting filter might be an earlier step to diagnose
fat embolism syndrome and sending the filter for pathological analysis looking for lipid
laden inflammatory cells is a less invasive approach as compared to quantification using
Broncho-alveolar lavage.

TH-PO1049
Fatal Hyponatremia with Glycine Solution During Hysteroscopy – Proposal for New
Mechanisms of Hyponatremia and Cerebral Edema
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Introduction: We report a fatal case of severe symptomatic hyponatremia and cerebral
edema following hysteroscopy.

Case Description: 39 y/o woman underwent 70 mins hysteroscopic myomectomy, 6L of
glycine solution used for distension, without documented deficits. 3 hours later she
developed pulmonary edema. Hyponatremia of 117mEq/L first noted 4 hours post surgery,
baseline normal sodium. Course further complicated by agitation, vomiting, lethargy due
to cerebral edema confirmed on CT. Cerebrospinal fluid pressure 270 mm H20. Post-op day 3
she also developed central diabetes insipidus. Remained brain dead, extubated and died after 12
days.

Discussion: Hyponatremia with glycine is iso-osmolar occurring as a result of dilution
effect since glycine is retained in extra-cellular fluid before its metabolism by glycine
cleavage enzyme. Two mechanisms with our postulated explanation: 1) How does cerebral
edema develop with iso-osmolar hyponatremia? 2) Why is hyponatremia often
more severe than predicted? Proposed mechanisms: 1) Glycine can cross blood brain
barrier (BBB) by passive diffusion, as shown in rats and cats. Sodium, however, does not exit
brain via BBB as sodium transport across BBB occurs only inward. With glycine toxicity,
glycine accumulates in the brain cells after crossing BBB followed by water resulting in
brain edema. Possibility of glycine metabolism to ammonia leading to cerebral edema
cannot be ruled although high levels were not seen in our case.

TH-PO1050
Cytomegalovirus-Induced Atypical Hemolytic Uremic Syndrome After Renal
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Introduction: Atypical hemolytic uremic syndrome (aHUS) may occur as de novo
disease and recurrence of primary renal disease in kidney transplant recipients. Causes of
de novo HUS includes immunosuppressive drugs, ischemia reperfusion injury, acute humoral
rejection, and viral infections. Some patients have a genetic susceptibility to the disease
from underlying mutations in the complement regulatory proteins. Cytomegalovirus (CMV)
has been rarely reported as a trigger for de novo post-transplant aHUS.

Case Description: A 61 year old male underwent deceased donor kidney transplant for
ESRD from presumed FSGS. 1 year following transplant he was admitted with profound
diabetes and weight loss due to CMV colitis and high grade CMV viremia (410,462 copies/ml).
His immune suppression was reduced and he was discharged home on oral valganciclovir
with near resolution of symptoms. He was re-admitted 1 week later with nausea, abdominal
pain, and acute kidney injury (Creatinine of 3.8 mg/dL, baseline of 1.8 mg/dL). His repeat
CMV viral load was significantly better at 70,000 copies/ml. Labs were suggestive of
microangiopathic hemolytic anemia. Hb 8 g/dL, platelets 58 K/uL, LDH 586 U/L, aHUS
(>20 mg/dL, and ADAMTS13 activity <67%). He received 4 sessions of plasmapheresis
without improvement and required initiation of dialysis. Histologic features of acute and
subacute endothelial injury, including segmental fibrin thrombosis of 2 arterioles were present on
transplant kidney biopsy. His aHUS genetic panel revealed several mutations in different
genes. aHUS serum activity was identified. He was started on eculizumab. His hemolysis labs
improved and he was taken off dialysis.

Discussion: CMV infection by way of endothelial injury can provoke aHUS in kidney
transplant recipients and possibly be enhanced by genetic predispositions. Postulated
mechanism of CMV-endothelial injury include increased leakage and platelet adhesion,
endothelial expression of Von Willebrand factor, E-selectin, vascular cell adhesion
molecule-1, and intercellular adhesion molecule-1. In our case, the aHUS process was
halted by use of eculizumab.

TH-PO1051
Acute Interstitial Nephritis from Anti-PD-1 Therapy with Pembrolizumab in Two
Patients with Advanced Non-Small Cell Lung Cancer
Heidi Mac G. Timbol, Anushree C. Shirali. Internal Medicine, Section of
Nephrology, Yale Univ School of Medicine, New Haven, CT.

Introduction: Immune checkpoint inhibition with monoclonal antibodies (mAb)
targeted against programmed cell death receptor 1 (PD-1) is an emerging immunotherapy
for various cancers. Pembrolizumab, an anti-PD-1 mAb, is being used in clinical trials with
promising anti-tumor responses, but renal-specific adverse events are not clear. We report
2 cases of acute interstitial nephritis (AIN) in patients who received Pembrolizumab for
advanced non-small cell lung cancer (NSCLC).

Case Description: Two female patients, both 69 years of age, with metastatic NSCLC
were seen in outpatient nephrology clinic for acute kidney injury (AKI). Both patients
were enrolled in a clinical trial with Pembrolizumab, and their cases had been complicated
previously by auto-immune adenalitis. On labs, Patient A had an increase in creatinine to
2.1 mg/dL prior to cycle 16, up from a baseline of 0.9 mg/dL. Patient B had a creatinine
peak of 1.9 mg/dL after cycle 6, up from a baseline of 1.1 mg/dL. Medications were
significant for long-standing pantoprazole use in both patients. Urine sediment showed
many WBC clumps without casts or RBCs. Renal ultrasound was unremarkable. Variable
expansion with normal saline and cessation of potential nephrotoxins failed to reverse renal
dysfunction in either case. Each patient underwent CF-guided renal biopsy, which showed
diffuse AIN. Steroid therapy with prednisone 60 mg/day with a slow taper was started and
creatinine improved to baseline.

Discussion: These two cases highlight a new association between AIN and
Pembrolizumab, which to the best of our knowledge has not been previously reported.
While both patients were on pantoprazole therapy prior to their AKI, this medication
was not new. Rather, the time course of AKI best fits with initiation of pembrolizumab.
Additionally, their pre-existing drug-related auto-immune adenalitis suggests a possible
auto-immune component to AIN from anti-PD-1 therapy. With increasing use of these
agents, clinicians should maintain a high index of suspicion for AIN as a cause of AKI and
have a low threshold for kidney biopsy to confirm diagnosis and initiate early treatment.

TH-PO1052
Concurrent Anti-PLA2R and ADAMTS 13 Inhibitor – Coincidence or a Clue to
Pathogenicity? 1 Laith Al-Rabadi,1 Moshe Shashar,1 Parikshit Duriseti,2 Ami Patel,1 Aala
Jaberri,1 Ashish Upadhyay,1 Joel M. Henderson,1 Vipul C. Chitalia,1 David J. Salam,1 Laurence H. Beck.1
Internal Medicine, Section of Nephrology, Yale Univ School of Medicine, New Haven, CT.

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a hematologic
emergency associated with a decrease in ADAMTS13 activity, most often due to the presence
of an inhibitor. Severe proteinuria is an unusual feature of TTP. The concurrent presence
of an inhibitor. Severe proteinuria is an unusual feature of TTP. The concurrent presence
of anti-PLA2R and ADAMTS13 inhibitor has never been previously reported until now.

Case Description: Herein, we present a case of a 70 year old male who presented with
generalized anasarca. Physical exam was remarkable for BP 180/100, and 2+ peripheral
edema. Workup revealed Hgb 7.4, Pts 46, Creatinine 1.45, LD 742 and undetectable
haptoglobin. His peripheral smear showed many schistocytes. These findings were
consistent with thrombotic microangiopathy. Urine analysis showed 2+ blood, 3+ protein.
Examination of the urinary sediment revealed oval fat bodies, and some RBCs. The patient
was initiated on plasma exchange and prednisone (1 mg/kg). Further studies revealed a serum
albumin of 2.2 and urine protein/Cr of 9. Kidney biopsy showed features of membranous
nephropathy with many subepithelial deposits flanked by new basement membrane material
(spikes). The deposits were immunoreactive for PLA2R, with IgG1 but no IgG4 reactivity.
In addition, there was moderately severe arterial and arteriolar sclerosis and segmentally
prominent double contour formation in the glomeruli. These vascular changes suggest a
primary form of endothelial injury and consistent with chronic thrombotic microangiopathy.
VWF protease activity came back as less than 3% with an elevated inhibitor titer of 1.3
BU. Anti-PLA2R was detected in the urinary at a titer of 40.3 IU/ml. Both were exclusively of the
IkG1 subtype by western blotting, atypical of the usual IgG4 predominance for both autoimmune
disorders.

Discussion: Although prednisone, plasmapheresis, and supportive therapy have
thus far stabilized both diseases, rituximab would be our first choice for more definitive
treatment of these concurrent autoimmune disorders. This unique case may help to further
our understanding of the mechanistic pathways underlying both of these clinical entities.
Cathryn J. Byrne

Introduction: Microparticles were seen on EM. Podocytes at the subepithelial aspect of the basement membrane, with deposition of spherical material. No electron dense deposits were found. Immunofluorescence was negative other than trace IgM and C3 reactivity along the peripheral capillary walls and in the mesangium. The majority of cases do not contain electron-dense deposits, nor do they show any reactivity with IgG. Here we present the first reported case of PIG in a patient of African descent.

Case Description: A 58 year old Africa female from Ghana with history of systemic lupus erythematosus presented to the nephrology clinic for the evaluation of proteinuria. She has more than 8L/day. Her urine osmolality increased to 444 mOsm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After augmentation, the patient reported ingestion of an excessive amount of melatonin for insomnia, but no other medications. She received DDAVP for 4 days with complete resolution of hypernatremia and polyuria.

Discussion: Extensive literature review revealed that rat studies show melatonin regulates the glomerular filtration of both sodium and water. It stimulates sodium tubular transport in the proximal tubules but its receptor or action on the distal tubule is unknown. Most patients with melatonin overdose have been less than 24 years old. It has been suggested that melatonin overdose could lead to fatal outcome. This is the first case of melatonin overdose in a 66-year-old man with a history of hypertension, hyperlipidemia, and diabetes.

Diabetes Insipidus Induced by Excessive Intake of Melatonin

Rahul N. Pawan, Savneek S. Chugh, Amy R. Patel.

Introduction: Melatonin is produced by the pineal gland and regulates the sleep-wake cycle in humans. Specific over the counter melatonin formulations can be used to treat circadian rhythm-related sleep disorders and age-related insomnia. Acute intoxication of melatonin and its deleterious effects have rarely been reported.

Case Description: A 24 year old female, with no known medical history, was brought to the hospital for altered mental status and possible drug overdose. Her vital signs were a Tmax of 101.8 F, HR 170, BP 150/103, and a pulse oximetry of 98% on 2L NC. On physical exam, she had mildly dilated and sluggish pupils. Due to an altered sensorium, she was intubated for airway protection. Initial lab tests showed a sodium of 140 mEq/L, potassium 3.9 mEq/L, chloride 113 mEq/L, bicarbonate 25 mEq/L, BUN 8 mg/dL, and a creatinine of 0.6 mg/dL.

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Discussion: Extensive literature review revealed that rat studies show melatonin regulates the glomerular filtration of both sodium and water. It stimulates sodium tubular transport in the proximal tubules but its receptor or action on the distal tubule is unknown. Most patients with melatonin overdose have been less than 24 years old. It has been suggested that melatonin overdose could lead to fatal outcome. This is the first case of melatonin overdose in a 66-year-old man with a history of hypertension, hyperlipidemia, and diabetes.
Virology screen, immunology screen, urine culture, urine PCR, DSA, Cyclosporin levels and renal ultrasound were normal with no change in patients haemodynamic status. Hence a kidney biopsy was performed to identify the cause, which showed evidence of calcification with surrounding inflammation with no evidence of rejection. Her steroid dose was transiently increased due to the inflammation seen on the biopsy and all her calcium and hydroxychloroalcalcerol supplements were suspended, which lead to recovery of her renal function to baseline.

Discussion: Our patient had mild hypercalcemia prior to parathyroidectomy with a stable renal function and following parathyroidectomy patient developed renal dysfunction despite similar levels of calcium, which can only be explained by iatrogenic calcium supplementation based on the renal biopsy. Perhaps routine monitoring of urinary calcium may help us guide the amount of calcium given to such patients and aiming for lower levels of calcium post parathyroidectomy rather than normal levels may prevent such phenomenon.

TH-PO1059

Severe Ketaoid Acidosis After Bariatric Surgery in a Patient Treated with Canagliflozin

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Introduction: Euglycemic diabetic ketoacidosis is relatively uncommon and is usually caused by starvation and a lack of caloric intake. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been very recently implicated as a cause of severe ketoacidosis. We report a case of severe euglycemic DM ketoacidosis induced by a combination of SGLT-2 inhibitor use and low caloric intake after bariatric surgery. While withdrawal of canagliflozin, its effect on glycosuria persisted for 7 days. Considering long biological effect of SGLT-2 inhibitors, they should be stopped weeks before a bariatric surgery to avoid ketoacidosis.

Current presentation due to poorly controlled DM-2. Ten days prior to his hospitalization, he underwent gastric sleeve bypass surgery and was discharged on post-op day 1. Upon admission to the ICU, his physical exam was benign except for a PR 108/min, RR 29/min, and a normal BP 128/69 mmHg. ABG showed pH 6.9, pCO2 13mmHg, pO2 99mmHg, bicarbonate 5mg/dL. His anion gap was 37, and serum glucose 152 mg/dL, with normal kidney function. Urine toxicology and blood levels of lactic acid and blood glucose were normal. Urinalysis revealed pH 5.0, glucose >1000 mg/dL, and ketones\textgreater;150 mg/dL. During the first day, he received 150 mg of sodium bicarbonate; his canagliflozin was held. He was intubated and started on a regular insulin drip along with 5% dextrose solution. He remained intubated for an insulin drip for 3 days, received 5-10 L of normal saline and extensive electrolyte replacement; blood glucose never exceeded 200 mg/dL while glycosuria persisted until day 7. C-peptide increased from 0.29 to 2.26 mg/L. Once anion gap was closed and patient stabilized, he was extubated and weaned off the insulin drip.

Post-procedure, we present a new case of severe euglycemic DM ketoacidosis induced by canagliflozin and his effect on glycosuria persisted for 7 days. Considering the long biological effect of SGLT-2 inhibitors, they should be stopped weeks before a bariatric surgery to avoid ketoacidosis.

TH-PO1060

Severe Hypercalcemia in Erdheim-Chester Disease: A Rare Clinical Scenario


TH-PO1061

APOL1 Polymorphisms in Deceased Donors and Primary Glomerular Disease Post-Kidney Transplant: First Case Report

Pratik B. Shah, Alexander C. Wiseman, James E. Cooper. Renal Diseases and Hypertension, Univ of Colorado Medical Center, Aurora, CO.

Introduction: Genetic polymorphisms in APOL1 (G1/G2) are associated with glomerular disease and ESRD. An emerging issue is whether screening for APOL1 (G1/ G2) should be performed in living or deceased kidney donors.

Case Description: A 46-year-old Caucasian male with a history of SLE received a deceased donor kidney transplant. The deceased donor was a 12-year-old African American male. 9 months post-transplant, he presented with acute kidney injury following an elective dental procedure. On post-op day 0, his SCR was 7.9 mg/dL, with spot UPC of 2 g/L Cr, platelet count of 58000, LDH of 2022 U/L, haptoglobin of <14 mg/dl. The patient did not recover kidney function. The patient's acute kidney injury was attributed to collapsing glomerulopathy in the setting of immune mediated microangiopathy or rejection. Plasma CMV PCR was positive at 234000 copies/ml. The patient ultimately did not recover kidney function. The patient's acute kidney injury was attributed to collapsing glomerulopathy in the setting of acute CMV infection. The patient's deceased donor DNA was analyzed for APOL1 risk variant genotyping and was positive for two APOL1 risk variants: compound heterozygosity for APOL1 G1, c.1024A>G; p.Ser342Gly and APOL1 G2 c.1164delTTATAA. The sister kidney from the same deceased donor had been transplanted to a 63 year old female with ESRD from diabetes. Six months post-transplant, she had new onset proteinuria of 2.5 g/d, and a renal biopsy demonstrated focal segmental glomerulosclerosis (FSGS). Her renal function and proteinuria remain stable 12 months post transplant.

Discussion: To our knowledge, this is the first case report of high risk variant APOL1 in a deceased donor with subsequent primary glomerular disease in both the recipients. This suggests that deceased kidney donor APOL1 genotyping may be informative in predicting graft outcomes. This also highlights the important question of whether routine screening of African American donors for high risk APOL1 variants before renal transplant is warranted. This consideration must be balanced against the significant limitations in kidney availability.

TH-PO1061

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TH-PO1062

Atypical HUS in an Infant due to a Novel Gene Mutation
Mohamed Alejari1, Robin Amy Krensford1, M. Khurrum Faizan2. 1Rhone Island Hospital; 2Hasbro Children’s Hospital; 3Hasbro Children’s Hospital.

Introduction: Atypical HUS (aHUS) is a rare genetic renal disease associated with over-activation of the alternative pathway of complement. A variety of mutations have been described in the complement pathways genes in patients with aHUS. We report a case of aHUS due to a novel mutation in the factor B (CFB) gene.

Case Description: 10 months old Caucasian girl who presented with diaphoresis, vomiting, and swelling in her extremities and face for 2 weeks preceded by an episode of cough, runny nose with non-bloody diarrhea. Upon presentation her BP was 150/90 mm Hg. Lab data showed WBC 16.4 × 10^9/L, PLT 1x10^11/L, BUN 46 mg/dL, creatinine 0.3 mg/dL, LDH 632 IU/L, normal ADAMTS13 and C3 level 7.9 mg/dL. Urine revealed 32RBC/hpf with proteinuria, Urine Protein Creatinine ratio 19 g/g. Peripheral blood smear revealed schistocytes. Stool was negative for Shiga toxin. Clinical presentation was suggestive especially of aHUS and patient was treated with Eculizumab. She had worsening anasarca with neck edema, requiring a tracheostomy after failed intubation. She required RRT for volume management during her hospital course after failing diuretics. Renal biopsy showed acute and chronic thrombotic microangiopathic changes consistent with aHUS. Genetic testing revealed a novel mutation in the complement Factor B gene in the region of binding to Von Willebrand factor. It also showed a heterozygous deletion of CFBR1 and CFHR4. Patient recovered renal function 3 weeks after presentation. C3 remained low after recovery of renal function. RRT was stopped after two weeks and she was discharged on ACEI with Eculizumab every 2 weeks.

Discussion: Gain of function mutations in CFB are extremely rare in aHUS and occur in only 1% to 2% of cases of familial aHUS. There is increased C3b affinity and form hypercatabolic C3 convertase that is resistant to dissociation, thus increasing C3b formation. Anti C5 Antibody Eculizumab has revolutionized the care of aHUS, improving the overall prognosis of these patients. This case is the first case reported with this novel CFB gene mutation. No long term data available regarding the outcomes of aHUS with Eculizumab therapy.

TH-PO1063

Oxymorphone-Induced Thrombotic Microangiopathy and Acute Kidney Injury

Introduction: Intravenous (IV) administration of oral oxymorphone represents an emerging pattern of drug abuse with increasing popularity and unforeseen adverse consequences. Here, we present a case of IV Oxymorphone abuse associated with thrombotic microangiopathy (TMA) and acute kidney injury (AKI).

Case Description: A 32-year-old man with a history of IV drug abuse presented with non-healing left arm wound. Physical examination was unremarkable except for a left non-healing left arm wound. A variety of mutations have been described in the region of binding to V on Willebrand factor. It also showed a heterozygous deletion in only 1% to 2% of cases of familial aHUS. There is increased C3b affinity and form hypercatabolic C3 convertase that is resistant to dissociation, thus increasing C3b formation. Anti C5 Antibody Eculizumab has revolutionized the care of aHUS, improving the overall prognosis of these patients. This case is the first case reported with this novel CFB gene mutation. No long term data available regarding the outcomes of aHUS with Eculizumab therapy.

Discussion: This patient presented with TMA, acute kidney injury, and normal serum ADAMTS13 activity. His urine oxymorphone was positive and he admitted to IV abuse of oxymorphone. Serum complement levels were normal as were all other investigations. ADAMTS13 level was >100%. Kidney biopsy showed evidence of TMA supported by glomeruli filled with focal extravasated and crenated RBCs. Immunofluorescence (IF) was negative for immune complex deposition but C4d staining was positive. Conservative management including platelet transfusion, without plasma exchange, was followed by stabilization of renal function.

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TH-PO1067
IgG4 Mediated Isolated Reteroperitoneal Fibrosis Causing Obstructive Uropathy in a Patient with Subclinical Ankylosing Spondylitis
A. H. Morgan, V. Aggarwal. Internal Medicine/ Nephrology Div, SUNY Upstate Medical Univ, Syracuse, NY.

Introduction: Reteroperitoneal fibrosis is a rare manifestation of systemic autoimmune disease, characterized by the presence of inflammatory and fibrotic retroperitoneal tissue that often encases the ureters causing obstructive uropathy. Idiopathic retroperitoneal fibrosis is currently being recognized as IgG4-related disease. We report a case of histologically confirmed IgG4 related retroperitoneal fibrosis in a patient with subclinical Ankylosing spondylitis. This association has been rarely reported.

Case Description: A 70 year old male with PMH of HTN, diabetes and baseline creatinine of 1.2 mg/dl presented with weakness, vomiting and decreased urine output. Physical examination was unremarkable. Further evaluation revealed serum creatinine of 13.3 mg/dl and BUN=110 mg/dl. He also has mild hyperkalemia and anion gap metabolic acidosis. Urine analysis was negative for protein or RBC cast. A CT scan of the abdomen and pelvis, showed retroperitoneal mass, Aortitis, ankylosis of SI joint bilaterally with osseous fusion and bilateral mild hydronephrosis. Bilateral nephrostomy tubes were placed with excellent urine output as well as improvement of creatinine to baseline in 48 hours. He subsequently had a CT guided biopsy of the retroperitoneal mass. Histopathology revealed dense fibrous tissue with significant IgG4 positive plasma cell infiltrate. Immunohistochemical workup showed elevated level of IgG4 as well as positive HLA-B27. Hence this obstructive uropathy was confirmed to be due to IgG4 related retroperitoneal fibrosis. He also met the clinical and imaging criteria for Ankylosing spondylitis. Treatment with oral corticosteroids was initiated by rheumatology.

Discussion: Our hypothesis is that the patient had a subclinical Ankylosing Spondylitis which triggered IgG4 mediated disease that lead to retroperitoneal fibrosis which caused bilateral obstructive uropathy. Hence role of ankylosing spondylitis in development of idiopathic retroperitoneal fibrosis by IgG4 mediated mechanisms warrants further consideration and for nephrologists to be aware of this rather unusual presentation.

TH-PO1068
IgG4-Related Tubulo-Interstitial Nephritis with Low Complement C4, Circulating Immune Complexes and an Elevated IgG4, Presenting as Unilateral Hydronephrosis and Prostatitis
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Introduction: IgG4-Related Disease is characterized by infiltrates of IgG4-positive plasma cells and eosinophils in different organs and is a rare cause of tubulointerstitial nephritis (TIN) and idiopathic retroperitoneal fibrosis.

Case Description: A 67 year old white male had a creatinine increase from 0.90 to 2.06 mg/dl. He had fatigue and dyspnea. Complement C3 was normal, C4 low 0.06 g/l, C1Q-BA 28% (>50%), but ANA/ENA, Anti Jo1, ANCA, HBV, HCV and M-protein were negative. IgG 3.0 g/dl (N 0.8-1.4 g/l). Urine showed 3 RBC/HFP, protein 0.36 g/l, albumin 61 mg per 24h. On ultrasound both kidneys were 13 cm with right sided hydronephrosis and 300 ml urinary retention. CT-Urography showed obstruction of the right ureter at the iliac artery. A bladder catheter and ureteral stent did not improve renal function. A MAG-3 IV injection showed a non-functioning right kidney without hydronephrosis on ultrasound. After revision, the CT showed soft tissue surrounding the aorta and the right iliac artery. A kidney biopsy showed TIN with a dense infiltrate of IgG4-positive plasma cells and eosinophils with impressive fibrosis, a vein showed obliterator phlebitis, consistent with IgG4-related TIN. The patient was treated with prednisone 40 mg daily and after 1 week he reported a dramatic clinical improvement, his creatinine decreased to 1.7 mg/dl.

Discussion: Hydronephrosis first dominated the clinical picture, delaying diagnosis, but the low C4, positive C1Q-BA and large kidneys suggested IgG4-related TIN. We found only one report of IgG4-related TIN with hydronephrosis, but that was after uterine tract tuberculosis. Rare cases were reported of IgG4-related segmental ureteritis or prostatitis without TIN and the cases of IgG4-related TIN had no hydronephrosis. The present case is the first with coincident biopsy-proven IgG4-related TIN, ureteral obstruction and prostatitis. Hydronephrosis does not exclude, but may be part of IgG4-related disease.

TH-PO1069
Monoclonal Light Chain Proximal Tubulopathy with Unique Ultrastructural Microtubular Inclusions

Introduction: Renal disease related to monoclonal gammopathies is common and varied. An uncommon lesion is proximal light chain tubulopathy (PLCT), which may present with Fanconi syndrome (FS) and variable degrees of renal failure. Most have ultrasonic (US) findings of proximal tubule damage with crystalline inclusions of Ig λ's within proximal tubular cells (FTS). A minority of PLCT do not have crystals; these may have LC restrictions. We describe a patient with a rare finding: PLCT with light chain (LC)-related microtubular inclusions.

Case Description: 74 year old man had progressive CKD over 2 years with serum creatinine rising from 1.3 to 3.4 mg/dl. A serum M spike, 1.0 g/dl of Igλs, was present. Urine protein, 1200 mg/day, contained 13% albumin, and 45% M spike of IgGκ. No findings of FS. Renal biopsy abnormalities were limited mainly to the proximal tubules (PT). The PT’s were bright red on trichrome stain and showed granular cytoplasmic changes and marked cell shedding with red stain with PAS. On immunofluorescence, the LC's were strongly stained 3-4+ for total Ig κ, IgG, IgM, IgA and λ were negative. On EM, non-branching microtubules, ranging in size from 26–36 nm were membrane bound within PT lysosomes. No amyloid filaments or crystalline structures were seen. Bone marrow subsequently showed a 1 grade B cell lymphoma with clonal λ B cells and small population of κ plasma cells.

Discussion: Two large biopsy reports of monoclonal renal disease found PLCT to be very uncommon, 0.5 – 4%. Most have findings of crystalline inclusions, less without crystals. To our knowledge, there are only 2 other cases with inclusions similar to our findings. We describe two cases of monoclonal immune deposition causing membranous nephropathy in SLE.

TH-PO1070
IgG1-kappa Monoclonal Membranous Nephropathy Associated with Systemic Lupus Erythematosus
Stephen W. Roderer, Anjali A. Satoskar, Tibor Nadasy, Isabelle Ayoub, Brad H. Rovin, Samir Parikh. The Ohio State Univ, Columbus, OH.

Introduction: Monoclonal gammopathy of renal significance is a recently described condition in which monoclonal protein is found in the kidney but often without a circulating clone. It has not been seen with SLE. We describe two cases of monoclonal immune deposition causing membranous nephropathy in SLE.

Case Description: Case 1: An 18 year old female with SLE developed nephrotic syndrome with 4g/d proteinuria and normal serum creatinine. Immunofluorescence (IF) on renal biopsy showed diffuse IgG1-kappa staining in the mesangium and along the capillary loops. Lambda staining was negative. Electron microscopy showed a low grade B cell lymphoma with clonal κ B cells and small population of κ plasma cells.

Case 2: A 38 year old female with SLE developed proteinuria of 2.5g/d and microscopic hematuria. Similar to case 1, IF on renal biopsy showed diffuse granular IgG1-kappa deposition in the mesangium and along the capillary loops. Lambda staining was negative. EM revealed monomeric κ light chains without subepithelial electron-dense deposits. Workup for a systemic monoclonal gammopathy, including urine and serum immunofixation and serum free light chains was negative. A diagnosis of IgG1-kappa monoclonal membranous nephropathy associated with SLE was made. She was started on an ACEi and prednisone with improvement in proteinuria from 2.5g/d to <0.5g/d.

Discussion: These 2 cases represent a newly described form of monoclonal membranous nephropathy associated with SLE. In both cases the monoclonal protein was restricted to the kidney. The pathogenesis is unclear but may be due to autoreactive B-cells producing an abnormal clone locally in the kidney. The clinical significance must still be elucidated but it may impact treatment and long-term outcomes so clinicians caring for SLE patients should be aware of this association. Further, these patients may develop a systemic monoclonal gammopathy, so close monitoring is necessary.
Discussion: This is the second reported case of necrotizing and crescentic glomerulonephritis associated with IgG1-κ anti-GBM IgG. It is unknown if this disease is driven by an underlying autoimmune process or monoclonal gammopathy. Both cases are atypical for classic anti-GBM disease due to their relapsing nature.

TH-PO1072
First Reported Case of Collagenofibrotic Glomerulopathy in a Patient with Multiple Myeloma

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Introduction: Collagenofibrotic glomerulopathy is an extremely rare idiopathic glomerular disease characterized by abnormal accumulation of atypical spiraled and frayed type III collagen fibrils in mesangial and subendothelial areas, and elevated serum procollagen III and hyaluronan levels. Proteinuria (commonest feature), edema, hypertension, and occasional progression to ESRD are commonly seen. We report the first published case of Collagenofibrotic glomerulopathy in Multiple Myeloma.

Case Report: A 54 year old male with recent history of IgG kappa Multiple Myeloma (May 2011); with underlying CKD stage 3 and baseline Creatinine at 2 mg/dl, in remission status-post autologous stem cell transplant (January 2012) and on Lenalidomide maintenance therapy, presented with proteinuria of 4g. Kidney biopsy revealed nodular and Focal glomerulosclerosis with IF weakly (+) for IgG, IgA, IgM, C3, C4, Clq, kappa and lambda light chains with +3 staining for IgM and Clq. EM showed patchy foot process effacement with massive deposition of collagen-III fibers. The weak and non-specific staining, along with massive collagen-III fiber deposition fitted with the description of Collagenofibrotic glomerulopathy, and made an immune-mediated kidney injury less likely.

Discussion: Discussion: Collagenofibrotic glomerulopathy is an extremely rare disease characterized by massive intraglomerular atypical type III collagen fiber deposition. Proteinuria is the cardinal manifestation of this disease. Clinically, patients present with edema and hypertension and often progress to ESRD. Etiology and pathogenesis remains elusive. Most cases are seen in Japan and an autosomal-recessive mode of inheritance has been described. Definitive diagnosis is established by identifying collagen-III fibrils by IF and EM with special staining. No specific treatment is available unfortunately.

TH-PO1073
Severe Acute Kidney Injury (AKI) with Organomegaly in a 17 Days Old Newborn: When Pathology Makes the Difference

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Introduction: Acute tubulointerstitial nephritis (ATIN) is a significant cause of AKI in children and is often due to allergic drug reactions or infections. Diagnosis of ATIN is usually clinical and renal biopsy not routinely performed.

Case Description: A previously healthy 17 days old baby presented with decreased oral intake, vomiting and oliguria. His first laboratory results showed an elevated creatinine (2 mg/dl) and thrombocytopenia (platelets 18x10^4/L). His urinalysis was abnormal (proteins 12 g/L). His chest and abdominal CT revealed multiple abscess formations in the right lung and liver. A skin biopsy was consistent with drug-induced GTIN caused by T-cell lymphoma. Although CHOP chemotherapy induced remission of lymphoma and disappearance of multiple abscesses, his renal function was not recovered. At 6 days of age, a renal biopsy was performed and showed a massive and polymorph infiltrate with destruction of tubular structures [Fig.1, A-B]. Ischemic glomerulitis, double glomerular membranes and mesangial oedema [Fig.1, C-D] were observed. Administration of steroids was followed by improvement of his renal function and cessation of diuresis after 6 days. The patient has been disease-free since.

Fig 1: Renal biopsy in a newborn with severe AKI

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

Renal biopsy findings were consistent with severe ATIN. The most likely etiology for his AKI was drug induced. This patient was started on prednisone medication and a follow-up cytopathology revealed a left grade III vesicoureteral reflux.

Discussion: ATIN is rare in neonates and usually drug-induced. This is the first report of a renal biopsy-proven AKI in a neonate. Even if procedural risks of a renal biopsy are not negligible, it can make the difference in certain cases by dictating appropriate management.

TH-PO1074
AL Lambda Amyloidosis in Kidney Transplant Allograft as a Cause of Massive Nephrotic Syndrome with AKI

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Introduction: This interesting case showed AL lambda amyloidosis in kidney transplant allograft as a cause of nephrotic syndrome with AKI. 51 year old African American female with history of ESRD secondary to APOD s/p DDKT in Oct 2010 with Thymoglobulin induction, maintained on 3 drug immunosuppression including tacrolimus, mycophenolate and prednisone with baseline creatinine of 1.5, presented with anasarca and orthostatic hypotension. Her serum albumin was 1.2mg/dL. She underwent extensive investigations including Echo, transplant allograft ultrasound all of which came back unremarkable. She has sudden onset sub nephritic range proteinuria in Aug 2013 which progressed to nephrotic range in Feb 2014. She has 34g of protein on a 24h urine collection 90% of which was albumin. Her UPCR gradually got worse from 10 to 32 with worsening in serum Cr from 1.5 to 5.5. She has poor response to IV Lasix with albumin infusion and has severe orthostatic symptoms. Her SPEP and UPAP were negative. Urine IFE was also negative. Urine IFE showed lambda light chain. Serum free light chain showed elevated lambda levels. Due to worsening and explosive proteinuria with worsening anasarca renal allograft biopsy was done that showed lambda AL amyloidosis involving glomeruli, arterioles and arteries along with light chain proximal tubulopathy. Congophilic casts consistent with light chain cast nephropathy. Pt underwent bone marrow biopsy that did not show MM. She was treated with bortezomib combined with cyclophosphamide and dexamethasone and has good response with improvement in orthostatic hypotension, serum albumin level and lambda light chain got normal.

TH-PO1075
Granulomatous Interstitial Nephritis Caused by T-Cell Lymphoma

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Introduction: Granulomatous tubulointerstitial nephritis (GTIN) occurs 0.5-1.3% in renal biopsy samples. Granuloma is basically caused by type IV allergy; T cell mediated mechanism against drug, foreign bodies and microorganisms such as Mycobacterium. We here present, a rare case of GTIN associated with T cell lymphoma.

Case Description: Sixty-year-old man with uncontrolled diabetes complained right chest pain. Chest and abdominal CT showed multiple abscess formations in the right lung and liver. A skin biopsy was consistent with drug-induced GTIN caused by T-cell lymphoma. Light microscopy showed diffuse interstitial inflammatory infiltrates predominantly with mononuclear cells including some atypical cells, which invaded tubular basement membrane resulting impaction of these cells in the tubular lumina. Since drug induced lymphocyte stimulation test (DSLST) was positive for TAZ/PIPC, we once diagnosed as drug induced GTIN in this patient. Despite stopping antibiotics, his renal function was not recovered. Meanwhile, atypical lymphoid cells were detected in the urine cytology and serum soluble IL2 receptor was significantly increased. Immunohistochemistry revealed hypercellularity of mononuclear atypical lymphocytes stained with T-cell markers, CD3 and CD5, and then diagnosed as GTIN caused by T-cell lymphoma. Although CHOP chemotherapy induced remission of lymphoma and disappearance of multiple abscess formation, the kidney dysfunction was unimproved.

Discussion: The case reminds us T-cell lymphoma as an additional cause of GTIN.

TH-PO1076
Pauci-IgG Glomerulonephritis and Excherichia Coli Bacteremia: A Mere Coincidence or a True Causal Association?

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Introduction: Antineutrophil cytoplasmic antibody (ANCA) associated vasculitides are systemic autoimmune diseases affecting small to medium sized blood vessels. Pauci-immune necrotizing glomerulonephritis (GN) is one of the manifestations. Triggering factors for ANCA associated vasculitides are not well-defined. Systemic infections have been implicated in the pathogenesis.

Case Description: A 67 year old patient was admitted to the hospital from a nursing home for a Foley catheter associated Excherichia coli (E. colli) urinary tract infection & bactemia along with septic shock and acute kidney injury/septic shock with a peak serum creatinine (Cr) of 3.8mg/dL. She had recently been hospitalized for subarachnoid hemorrhage that was treated conservatively and her serum Cr at that time was 0.9mg/dL.

Discussion: This is the second reported case of necrotizing and crescentic glomerulonephritis associated with IgG1-κ anti-GBM IgG. It is unknown if this disease is driven by an underlying autoimmune process or monoclonal gammopathy. Both cases are atypical for classic anti-GBM disease due to their relapsing nature.
She promptly responded to standard treatment of septic shock and her serum Cr improved to 1.6 mg/dl on discharge. Ten days later, she was readmitted to the hospital after a follow up visit to her primary physician where a routine blood work showed her serum Cr to be elevated to 6.8 mg/dl. Urine sediment revealed several RBCs and few granular casts. Anti-myeloperoxidase antibody was positive with a titer of 1:640. Other serological tests were negative. Her renal function declined further and she was initiated on hemodialysis. A renal biopsy was consistent with pauci-immune necrotizing and crescentic GN. She was treated with steroids, intravenous cyclophosphamide and plasmapheresis following which she came off dialysis & her serum Cr stabilized around 1.8 mg/dl.

Discussion: Anti-LAMP-2 antibodies, a subtype of ANCA antibodies directed against lysosome-associated membrane protein-2 (LAMP-2) have been reported in patients with pauci-immune necrotizing GN, often in coexistence with anti-PR3 & anti-MPO antibodies. Infections with bacteria that express the bacterial adhesin FimH (mostly E. coli), which has 100% homology with the human LAMP-2 epitope, are believed to trigger autoimmunity via molecular mimicry. In our patient, the onset of ANCA positive necrotizing GN in a close temporal association with E. coli bacteremia suggests a possible causative relationship.

TH-PO1077
Cryoglobulinemic Vasculitis and Glomerulopathy Associated with Chronic Lymphocytic Leukemia
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Introduction: Cryoglobulinemia manifests as ischemic or occlusive vasculopathy with or without renal involvement. Early stage Chronic lymphocytic leukemia (CLL) has not been reported with vasculitic lesions as its first manifestation. We report a rare case of Stage I CLL with cutaneous, renal and cerebral lesions due to monoclonal Type I cryoglobulinemia.

Case Description: A 60 year-old woman presented with abdominal pain due to peritoneal hematoma from a ruptured right gonadal artery, which was embolized. Labs included eukocytosis, anemia with mild azotemia. Flow cytometry was consistent with CLL. The patient was readmitted with a serum creatinine of 11.2 mg/dl and proteinuria and required hemodialysis. There were extensive lesions on her lower extremities and a necrotic left forearm ulcer. Renal biopsy revealed membranoproliferative glomerulonephritis with deposition of IgG kappa light chain cryoglobulins as intraluminal hyaline deposits (Figure 1), infiltrates consistent with CLL and thrombi in intrarenal arteries. Biopsy was complicated by hematoma leading to left nephrectomy. Plasmapheresis was initiated for myeloma cast nephropathy.

The pathophysiology of GN in CLL is possibly due to glomerular deposition of immune complexes and/or paraproteins. Review of the literature reveals a small number of cases of MN associated with CLL and cryoglobulinemia.

Discussion: Vasculitic presentations, bleeding or thrombotic and/or renal failure in the setting of CLL may be manifestations of cryoglobulinemia. Because of potential rapid progression, as in this case, regular urinalysis and testing for cryoglobulins should be considered in all stages of CLL, with possible renal biopsy when cryoglobulinemia and proteinuria are detected.

TH-PO1078
PGNMD in a Patient with Hepatitis C
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Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMD) is infrequently associated with hematological disease but more commonly presents like an immune-complex glomerulonephritis. Few have reported cases associated viral infections such as hepatitis C. We report a case of PGNMD in a patient with active HCV infection.

Case Description: A 56 year-old male with refractory hepatitis C (post treatment with interferon and Ribavirin), HTN and coronary artery disease presented with rising creatinine (peak 5.3 mg/dl) from baseline (0.9 ml/dl a year ago) and no kidney disease in family. He reported months of progressive fatigue, dyspnea on exertion, nausea, vomiting, and dark urine. He endorsed chronic Buprenorphine use for leg pain. On examination BP was normal with clear lungs and no edema. Urinalysis revealed blood but minimal proteinuria with urine protein to creatinine ratio of 0.5 g/g and albumin 4.2 g/dl. Complements were low (C3 83 mg/dl, CH50 <10 U/ml). HCV-RNA quantification was 1.7 million copies. SPEP, plasma light-chains, ANA, ANCA, Anti GBM, HIV, Hep B serologies were normal. Bone survey was negative. Renal biopsy revealed diffuse linear staining of glomerular basement with monoclonal IgG1/Kappa immunoglobulin and endocapillary focal glomerulonephritis, chronic interstitial nephritis with ATN. Renal function did not improve until Prednison was initiated, down to 3.3 mg/dl. Cyclophosphamide was started after discussion with his gastroenterologist. Antiviral therapy has been delayed until further improvement of renal function.

Discussion: We report a case of PGNMD associated with HCV. There are 2 other reports of HCV associated PGNMD however with membranous glomerulonephritis pathologic. 30% of PGNMD patients have some heavy- and light-chain isoform as the glomerular deposits. Membranoproliferative (57%) or endocapillary proliferative (35%) are the most two common histological variants. Nase et al in a series of 32 patients reported after an average of 30.3 months of follow-up, 38% had complete or partial recovery, 38% had persistent renal dysfunction, and 22% progressed to ESRD. Viral infection such as HCV associated immune disorders could be implicated in the pathogenesis. Currently, there is no consensus regarding the management of this entity.

TH-PO1079
Myeloma Cast Nephropathy with Acute Renal Failure, Skin Rash, Eosinophilia, and Low Complement C4 Level
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Introduction: We here report myeloma cast nephropathy with skin rash, eosinophilia and low complements which is a very atypical presentation of this renal condition.

Case Description: A 53y Caucasian female was admitted with 3 day confluent erythematous skin rash, acute renal failure with sCr 17.6 with a normal baseline renal function of sCr 0.7 mg/dL. Five days prior, she was prescribed cephalexin for root canal infection. Initial diagnosis of acute interstitial nephritis was made but patient didn't respond after stopping antibiotics and steroid course trial, urine exam showed WBC clumps and no casts. Serological biomarkers were done and reported Negative ANA, ANCA, cryoglobulins, Hepatitis B, Hepatitis C and HIV. Complement C4 was low with normal C3. Patient’s laboratory workup showed normocytic normochromic anemia and pseudohyponatremia per osmolality check, SPEP and SFLC ordered and was positive for M-spike with free light chain analysis showing predominant Lambda more than 4 g/L. Renal biopsy showed myeloma cast nephropathy.

Bone marrow biopsy confirmed MM with 80% plasma cell. Patient received bortezomib +dexamethasone + cyclophosphamide chemotherapy and her renal function completely improved after being dialysis dependent for about 12 weeks. Patient is being evaluated for BM transplant after chemotherapy response.

Discussion: Multiple Myeloma can cause renal damage in many ways which sometimes can be misleading and very uncharacteristic. Up to our knowledge, this presentation is quite uncommon in literature and hence we suggest including myeloma related kidney injury in such clinical presentation.

TH-PO1080
A Rare Case with ANCA-Related Necrotizing Glomerulonephritis without Nephritic Features or Systemic Vasculitis
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Introduction: We report an atypical and unusual case of ANCA necrotizing glomerulonephritis with no significant nephritic features or systemic vasculitic picture.

Case Description: A 78 year-old African American female with history of controlled hypertension was admitted with diagnosis of pneumonia and renal failure and was treated empirically with antibiotics. Despite antibiotic treatment, she had persistent leukocytosis and anemia which was ruled out by negative WBC scan and CT chest. Urine had pre-renal pattern and urinalysis was bland twice. Renal ultrasound was unremarkable except for hyperechoic kidneys. Despite aggressive hydration for 10 days, renal function continued to worsen. Patient was never oliguric. Serum biomarkers were checked due to unexplained renal failure which reported negative hepatitis B, C and HIV as well as normal Complement C3, C4, ANA, dsDNA and antiphospholipid panel. Normal SPEP with no M spike. UPEP showed faint IGG monoclonal band in the ALPH-2 region. SFLC was negative. Bone marrow biopsy showed normal cellularity. Although patient had no obvious systemic vasculitic features, but due to renal failure and persistent non-specific respiratory symptoms, ANCA was checked and was positive for anti-MPO antibodies. Renal biopsy showed pauci-immune acute necrotizing glomerulonephritis (Figure 1) with negative Anti-GBM and immune fluorescence. Patient was treated with cyclophosphamide, high dose steroids and plasmapheresis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Discussion: The patient had advanced necrotizing GN but never developed nephritic or systemic vasculitic features and UA was persistently bland. The probability of diagnosing ANCA associated GN based upon above clinical presentation was significantly low, making this an unusual case.

TH-PO1081
Bilateral, Multifocal Renal Tumors Diagnosed as Birt-Hogg-Dubé Syndrome Confirmed by Genetic Analysis

Introduction: Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant disorder characterized by skin fibrofolliculomas, pulmonary cysts and spontaneous pneumothorax, and renal cancers. The syndrome is caused by germline mutations of the FLCN gene located in 17p11.2 encoding folliculin. The risk of renal cancer is seven times higher in BHD patients. Bilateral, multifocal and chromophobe renal cell carcinoma is characteristic of renal cancers in BHD. Among about 110 pathogenic mutations reported in BHD, only twenty six of them have been associated with renal cancer. In this study, we described a case of 50-year-old woman with chromophobe renal cell carcinoma who had c.1557delT mutation in the FLCN gene which is novel in BHD-associated renal cancer.

Case Description: A 50-year-old woman presented with flank pain. A CT scan of abdomen showed multifocal tumors in both kidneys. To differentiate the origin of the tumors, a chest CT and a whole body PET-CT were carried out, although there was no other lesion except a few lentiform cysts at basal lungs. Histologic evaluation through a needle biopsy revealed that the mass was chromophobe type renal cell carcinoma. The patient underwent nephrectomy. Given multifocal distribution of the renal cell carcinoma, we suspected an inherited form of kidney cancer. Although she denied any specific familial history, the cystic change of both lungs and chromophobe renal cell carcinoma pointed towards the possibility of BHD. DNA sequencing of the entire FLCN gene identified a heterozygous c.1557delT mutation in exon 14 [p.Phe(TTT)519Leu(TTA)fs*18].

Discussion: Once multifocal renal masses are diagnosed as renal cell carcinoma, histologic subtype, family history and other clinical features should be considered to recognize familial renal cancer syndromes. Multifocal chromophobe renal cell carcinoma should prompt genetic test for BHD even in a patient without typical skin lesion. In our patient, c.1557delT mutation was found out which has been first reported in BHD-associated renal cancers.

TH-PO1082
The First Case of Steroid Responsive Renal Involvement of Mycosis Fungoides without Sezary Syndrome

Introduction: Mycosis fungoides (MF) is a mature T cell non-Hodgkin lymphoma with presentation in the skin but with potential involvement of the nodes, bloods and viscera. Renal lymphomatous involvement in MF has received limited attention. We present a rare case of moderate dose steroid responsive lymphomatous renal involvement with acute renal injury which occurred in solitary kidney.

Case Description: A 59-year-old man presented with fever, right flank pain with a rise of creatinine 10.54mg/dL one month prior being 1.4mg/dL. He had donated his left kidney 10 years ago. He had recurrent pruritic rash before MF was diagnosed by skin biopsy, 4 years prior to his presentation, he received several different course of chemotherapy, including cyclophosphamide, Adriamycin, vincristin, and prednisone (CHOP), alpha-interferon. Ultrasound revealed normal echogenicity with right kidney 14 cm. Urinalysis showed protein 1+, WBC cast and no hematuria. He was treated first with antibiotics in case of acute pyelonephritis. He deferred started within two days, however, his renal function kept declining. Hemo-dialysis was performed. On the 6th day, Renal biopsy was performed. Renal biopsy showed that numerous atypical lymphocytes with hyperchromatic, indented, variably sized nuclei were infiltrated in the tubulointerstitium. After treatment with methylprednisolone 40mg, level of creatinine improved up to baseline.

Discussion: To our knowledge, this is the first report of steroid responsive renal involvement of MF. Renal involvement in non-Hodgkin lymphoma has been reported, including AKI, glomerulonephritits, and infiltration of renal parenchyma by lymphoma cell. Renal manifestations of MF are especially rare and there are only few cases published to date. But there has been no case which showed steroid response except this case.

TH-PO1083
A Case of Cryoglobulinemic Nephropathy with Successful Childbirth After Recurrent Episodes of Nephrotic Syndrome During Pregnancy

Case Description: A 35-year-old woman was admitted to our hospital because of massive proteinuria that developed during the third pregnancy. The previous two pregnancies had been terminated because of similar episodes of nephrotic syndrome. No history of hypertension was observed, but during the course she presented cryoglobulinemia, a high titer of RF and low serum complements. The renal biopsy performed 10 days after the third termination revealed MPGN-like lesions with lobulation in glomeruli, double contour of GBM, endotheliosis, and moderate mesangial cell proliferation. Immunofluorescence study showed IgG, IgA, IgM, C3, C4, and Clq all positive mainly along the glomerular capillaries, and subendothelial deposits were confirmed by EM, thus she was diagnosed as cryoglobulinemic nephropathy. Because the histologic findings of repeated renal biopsy were not improved two months after the disappearance of proteinuria, treatment with 30 mg/day of PSL was started, followed by intravenous cyclophosphamide 6 times and plasma exchange, since she had a desire for baby. Finally at the fourth pregnancy, she bore a healthy baby weighing 2.342kg at vaginal delivery at 36 weeks despite of recurrent appearance of nephrotic syndrome. After delivery, she was given 30 mg/day of PSL and proteinuria subsided.

Discussion: We experienced a rare case of the type III cryoglobulinemic nephropathy that repeatedly developed nephrotic syndrome during pregnancy, but finally bore a baby after immunosuppressive therapy. The pathogenesis of pregnancy-induced nephrotic syndrome in cryoglobulinemia in this patient was not known, aggressive treatment may be helpful for ameliorating nephropathy, leading to successful delivery.

TH-PO1084
A Case of Glomerular Lipidosis with Type III Hyperlipoproteinemia Exhibiting Nephrotic Syndrome

Case Description: A 77-year-old woman was admitted to our hospital because of nephrotic-range proteinuria. She was diagnosed as chronic thyrotoxic 8 years before, after which she started to have levothyroxine and remained uneventful. Three weeks before coming to our hospital severe edema developed rapidly, and she gained 10 kg of body weight in 6 months. Laboratory examinations showed nephrotic syndrome with mild renal dysfunction (s-Alb 2.1 g/dL, urinary protein 7.97 g/gCr, s-Cr 0.95 mg/dL), marked hypothyroidism (TSH 45.2 µIU/mL, Free T4 0.83 ng/mL). Genetic test for APOE revealed homozygosity of apoE2 and immunoelectrophoresis for lipoprotein showed type III hyperlipoproteinemia. Renal biopsy revealed the presence of intracapillary lipid thrombi and foam cells; electron microscopy demonstrated lipid droplet accumulated mainly in mesangial cells, whereas podocytes, endothelial cells and tubular cells were rather unremarkable. Immunofluorescence studies showed no significant deposits in glomeruli. Intense lipid-lowering therapy with Statin for 1 month, the patient’s nephrotic-range proteinuria subsided. She was discharged with good condition.
Discussion: We report here a case of glomerular liposudosis associated with type III hyperlipidemia. The nephrotic syndrome was unexpected but the hyperlipidemia with glomerular lipid accumulation would have a pathogenic role for glomerulopathy, but other factors might be involved in causing nephrotic syndrome.

TH-PO1085
Successful Treatment of Crescentic Glomerulonephritis (GN) in Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS) Ramchandar Bakhtian, Mark G. Parker. Nephrology, Maine Medical Center, Portland, ME.

Introduction: HUVS is a rare autoimmune systemic disorder characterized by chronic urticaria, low complements and extracutaneous organ involvement. Kidney involvement is not uncommon (50% of cases), usually of benign nature. The glomerular injury pattern varies from mesangial proliferation to membranoproliferative glomerulonephritis (MPGN). Crescentic MPGN in HUVS is rare; only six cases have been reported in world literature, many with poor outcomes. We present a case of crescentic GN successfully treated with substantial remission.

Case Description: A 55-year-old Caucasian female with a previous episode of hives was admitted to hospital with features of both acute nephritic and severe nephrotic syndrome. She had 6 months history of persistent hives, fatigue, fevers, arthralgia, self-limited recurrent angioedema episodes, and generalized lymphadenopathy. Lymph node biopsy displayed reactive hyperplasia. Her serum creatinine was 4 mg/dl, urine protein to creatinine ratio was 23, serum complement levels were 1.0 mg/dl and C3 < 100 mg/dl, 10x the normal values for a case of HUVS. Serologic workup was positive for vWF and ANA at titer of 1:80. Anti-dsDNA, cryoglobulins, anti-SSA, anti-SSB, chronic hepatitis panel, and workup for paraproteinemia were all negative. C3 and C4 levels were normal. An ANA positive HUVS was confirmed. Renal biopsy revealed immune complex crescentic MPGN with IgG, IgA, IgM, C3 and C4 deposits on immunofluorescence. Treatment was started initially with high dose glucocorticoids followed by addition of mycophenolic acid and losartan. Her systemic symptoms and acute kidney injury resolved completely. Nephrotic syndrome improved slowly. After 6 months of therapy her proteinuria decreased to 4.5 g/kg per day with serum albumin increased to 3.8 g/dl.

Discussion: Crescentic GN associated with HUVS appears to convey a poor renal prognosis. Based on available information in five of six reported cases, three progressed to end stage renal disease; one had near complete renal recovery and another had partial recovery with persistent nephrotic range proteinuria. Relatively good outcome in our case may aid to our understanding of this uncommon and newly recognized disease process.

TH-PO1086
An Unusually Early Presentation of Pre-Eclampsia David Bennett, Renu Regunathan-Shenk, Maya K. Rao. Medicine, Div of Nephrology, Columbia Univ Medical Center, New York, NY.

Introduction: Pre-eclampsia affects approximately 3-6% of pregnancies in the United States. It is defined as new onset hypertension and proteinuria in pregnancy. By definition, it occurs after 20 weeks gestation. However, earlier cases have been reported in the literature. Case Description: The patient is a 45 y/o woman, 16 weeks + 4 days pregnant with a previous episode of hives. She presented to the hospital with high blood pressure (BP 193/122), 1+ upper extremity edema, 2+ lower extremity edema, and 12 g of protein on 24hr urine collection. On labs, Cr 0.85, 3+ protein on UA (previously normal), hemoglobin 12.2, WBC 14k, platelets 202, SPEP, UPEP, and Kappa and Lambda Light Chain levels were negative. Platelet count 202, LDH 334 (elevated), and indirect bilirubin 0.2. AST, ALT, and Alkaline phosphatase were normal. The patient underwent a kidney biopsy which demonstrated subacute glomerular thrombotic microangiopathy with prominent endothelitis, characteristic of pre-eclampsia. Termination of pregnancy was advised and performed. On post-discharge follow-up, spot urine protein-to-creatinine ratio (in mg/mg) decreased to 1.52 after ~1.5 months, 0.32 after ~3.5 months, and 0.13 after ~6 months. BP improved as well and she is now off antihypertensives.

Discussion: This patient had multiple risk factors for pre-eclampsia including age, multiparity, obesity, IVF, and ovum donor pregnancy. Although kidney biopsies are associated with a higher complication rate in pregnant women, they often change management, as was the case for this patient. Given this case and others reported in the literature, the gestational age criteria for the diagnosis of pre-eclampsia should be reconsidered.

TH-PO1087
A Case of Autosomal Dominant Polycystic Kidney Disease and C3 Glomerulonephritis Conor Patrick Moran, Mamoun S. Elawad. Dept of Nephrology, Altnagelvin Hospital, Western Health and Social Care Trust, Londonderry, United Kingdom.

Introduction: Autosomal Dominant Polycystic Kidney Disease, (AD-PKD), is the most common form of inherited renal disease. Proteinuria has been reported, however, nephrotic range proteinuria and nephrotic syndrome are rarely reported in the literature. Only 30 cases of patients with AD-PKD and polycysticulopathy have been reported. The most common have been FSGS and Membranous Nephropathy. Two cases of Mesangioproliferative Glomerulonephritis and one case of Membranoproliferative Glomerulonephritis have been reported.

Case Description: We present a 47 year old female with Autosomal Dominant Polycystic Kidney Disease with C3 Glomerulonephritis. The patient had been under regular and remarkable Nephrology clinic follow-up for many years. She was admitted to our hospital with a history of left sided chest pain and new onset of proteinuria. On examination she presented to with new proteinuria, (Urinary ACR 375.4mg/mmol), and evidence of C3 hypocomplementemia, (0.3 g/L, normal: 0.8-1.7 g/L). Kidney function was newly impaired, (Creatinine 118, eGFR: 45.3 mL/min/1.73m2). C3 Nephritic factor was normal and ANA and Anti-dsDNA were negative. ACE inhibition was performed. Renal biopsy showed markedly enlarged and lobulated glomeruli with marked endocapillary proliferation. Widespread thickening of the glomerular basement membranes, (GBM), with numerous double contours was observed. Immunofluorescence revealed strong granular positivity for C3 along the GBM with some focal mesangial C3. There was some IgM, but no IgG, in the GBM. In July 2014, there was no clinical response to ACE inhibition. Corticosteroids were commenced, (Prednisolone 1mg/kg), which achieved partial remission, (urinary ACR fell from 650.3mg/mmol to 79.7 mg/mmol), however, in August 2014 she developed nephrotic syndrome requiring aggressive diuretic therapy. Addition of ACE inhibition induced complete remission of proteinuria, (UA CR 25-30 mg/mmol), with normalisation of C3 levels. Renal function remains stable.

Discussion: In a disease where CKD progression is predictable, glomerular pathology can accelerate this decline and histology should be sought. This is the second reported case of AD-PKD associated with Membranoproliferative C3 Glomerulonephritis in the literature to date.

TH-PO1088

Introduction: Achieving maturity is quite a challenge for women with chronic kidney disease (CKD). Pregnant patients with CKD of any stage but especially stages 3–4 are at increased risk for fetal loss, prematurity and pre-eclampsia.

Case Description: We present a case of a 31 year old pregnant female with a past medical history of CKD stage 3B secondary to medullary cystic disease (MCD) who presented with acute kidney injury at 31 weeks gestation. Her other co-morbidities include a history of diabetes and idiopathic thrombocytopenia (ITP). On admission, the patient had a creatinine of 2.32 mg/dl and was found to have 7 gm proteinuria. During this pregnancy, her baseline creatinine was 1.6-1.8 mg/dl and prior to pregnancy she had baseline proteinuria of 2 gm. Given her elevated creatinine and degree of proteinuria, there was concern that the patient could have pre-eclampsia. A management dilemma occurred and it was unclear whether the patient should have an emergency C-Section for questionable pre-eclampsia.

Discussion: Given the patient's diagnosis, any lung exam was normal. Her exam was notable for BP 193/122, 1+ upper extremity edema, 2+ lower extremity edema, and bibasilar crackles on lung exam. On labs, Cr 0.85, 3+ protein on UA (previously normal), with 3 RBC's and 6 WBC's, ~12g of protein on 24hr urine collection, and serum albumin 3.8 g/dl. CT of chest was normal. A team effort along with fetal monitoring can help differentiate pre-eclampsia from other conditions of CKD, ITP, and MCD. After a multidisciplinary meeting with the obstetrician, nephrology, and hematologist occurred, it was felt that the patient truly did not have pre-eclampsia. A key decision was made and was not induced. Her AKI was attributed to volume depletion and progression of CKD. Her creatinine eventually declined to 1.9-2 mg/dl and her proteinuria decreased to 3-5 grams. The patient is now 34 weeks pregnant and her renal function has been maintained.

Discussion: Our case highlights that in patients with multiple co-morbidities and CKD, the diagnosis of pre-eclampsia can be challenging. Incorrectly labeling a patient as pre-eclamptic can lead to pre-term delivery and risks to the fetus. A multidisciplinary approach along with fetal monitoring can help differentiate pre-eclampsia from other diagnoses, prolonging delivery.
steroids. Given renal fibrosis and comorbidities, no further therapies were pursued. Repeat EGD showed improved duodenal lesions after steroids, however renal function declined and the patient required dialysis.

**Discussion:** IgA nephropathy historically recurs post-KT but rarely impacts graft survival. De novo HSP with significant nephritis is infrequently described and treatment strategies are lacking. Additional data with this disease remain unestablished. Interestingly MMF is used for severe HSP in children. Whether lack of MMF maintenance contributed to HSP in our patient remains unknown.

**TH-PO1090**  
Harvoni Induced Acute Interstitial Nephritis  
Jyotsana Thakkar, Kenan D. Jhaveri, Rimda Wanchoo.  
Nephrology, North Shore-LIJ Hospital, NY.

**Introduction:** Harvoni is a new combination pill consisting of ledipasvir with sofosbuvir approved by FDA in October 2014 for the treatment of chronic Hepatitis C genotype 1 virus infection. No cases of Acute Kidney Injury (AKI) have been reported with this agent thus far. We report the first case of Harvoni associated biopsy proven acute interstitial nephritis (AIN).

**Case Description:** A 64 year old AA female with chronic Hepatitis C, hypertension, diabetes mellitus came to our clinic for evaluation of AKI superimposed on chronic kidney disease. Laboratory data revealed serum creatinine of 2.24 mg/dl (baseline Cr 1.5 mg/dl), hypoalbuminemia (3.2 gm/dl) with a spot urine protein/ creatinine ratio of 3.3 (baseline of 1). Her AKI coincided with peripheral eosinophilia. Home medications included hydralazine, lansoprazole and simvastatin. She had recently completed eight weeks of treatment for Hepatitis C with Harvoni and her most recent viral load was undetectable. She denied using any NSAID, antibiotics, PPI or herbal supplements. Physical exam was normal. AKI workup revealed negative ANCA, normal complement, normal serum free immunoglobulin light chain ratio and negative ANA panel.

Patient underwent kidney biopsy. Light microscopy showed 11 glomeruli, 3 were globally sclerosed, 3 had cellular crescents with mesangial nodular matrix expansion and moderate tubular atrophy. Interstitium showed moderate fibrosis with severe lymphocytic inflammation. Immunofluorescent microscopy was normal and electron microscopy showed diffusely thickened glomerular membrane and moderately effaced foot processes. A final diagnosis of acute interstitial nephritis with chronic diabetic nephropathy was made. Her clinical picture, pathology findings and time course of renal impairment coincided with Harvoni use and is suggestive of Harvoni induced AKI. She was initiated on steroid therapy and advised to stop further use of Harvoni. Her renal function is stable with no further deterioration after stopping offending agent.

**Discussion:** Harvoni has a cure rate of up to 94-100% in patients with Hepatitis C genotype 1. We report first case of biopsy proven AIN with Harvoni. Hepatologists and nephrologists need to be aware of the potential side effect of this novel agent.

**TH-PO1091**  
Thrombotic Microangiopathy Secondary to Smoldering Myeloma: A Form of MGRS  
Jyotsana Thakkar, Rimda Wanchoo, Kenan D. Jhaveri.  
Nephrology, North Shore-LIJ Hospital, NY.

**Introduction:** Thrombotic microangiopathy syndrome (TMA) is not a usual presentation of paraproteinemic diseases. We report a case of TMA secondary to smoldering myeloma presenting as monoclonal gammopathy of renal significance (MGRS).

**Case Description:** A 64 year old AA female with chronic Hepatitis C, hypertension, diabetes mellitus with her most recent viral load was undetectable. She denied using any NSAID, antibiotics, PPI or herbal supplements. Physical exam was normal. AKI workup revealed negative ANCA, normal complement, normal serum free immunoglobulin light chain ratio and negative ANA panel.

Patient underwent kidney biopsy. Light microscopy showed 11 glomeruli, 3 were globally sclerosed, 3 had cellular crescents with mesangial nodular matrix expansion and moderate tubular atrophy. Interstitium showed moderate fibrosis with severe lymphocytic inflammation. Immunofluorescent microscopy was normal and electron microscopy showed diffusely thickened glomerular membrane and moderately effaced foot processes. A final diagnosis of acute interstitial nephritis with chronic diabetic nephropathy was made. Her clinical picture, pathology findings and time course of renal impairment coincided with Harvoni use and is suggestive of Harvoni induced AKI. She was initiated on steroid therapy and advised to stop further use of Harvoni. Her renal function is stable with no further deterioration after stopping offending agent.

**Discussion:** Harvoni has a cure rate of up to 94-100% in patients with Hepatitis C genotype 1. We report first case of biopsy proven AIN with Harvoni. Hepatologists and nephrologists need to be aware of the potential side effect of this novel agent.

**TH-PO1092**  
A Case of Leukocyte Chemotactic Factor 2 Associated Amyloidosis  
Nadia Badeg, Saeed Kamran Shaffi.  
Nephrology, Univ of New Mexico.

**Introduction:** Leukocyte chemotactic factor 2-associated amyloidosis (LECT2) is a newly described form of nonhereditary amyloidosis. The disease usually presents with chronic kidney disease and bland urinary sediment with variable degrees of proteinuria. We describe a case of a young Hispanic female who presented with nephrotic syndrome without renal insufficiency.

**Case Description:** A 40 year old Hispanic female with history significant for uncontrolled type 2 diabetes, hypertension and rheumatoid arthritis, was referred to renal clinic for evaluation of nephrotic syndrome. Physical examination revealed peripheral and bilateral lower limb edema. Pertinent diagnostic data are shown in figure 1.

**Figure 1: Diagnostic Data**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis</td>
<td>Normal</td>
</tr>
<tr>
<td>Urine microscopy</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.5</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>1.4</td>
</tr>
<tr>
<td>SLEP</td>
<td>Normal</td>
</tr>
<tr>
<td>Urine protein/creatinine</td>
<td>&gt;1.2mg/dl</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>&gt;1.2mg/dl</td>
</tr>
<tr>
<td>Serum albumin</td>
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<td>Serum albumin</td>
<td>1.4</td>
</tr>
<tr>
<td>SLEP</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Renal ultrasonad**

Renal biopsy showed extensive amyloidosis involving the glomeruli, interstitium and arterioles. Immunofluorescence was negative for immunoglobulins and amyloid associated protein. Proteomic typing of the amyloid revealed ALECT2 associated amyloidosis. The patient was started on lansoprazole and simvastatin, but her proteinuria failed to improve and she had progressive deterioration of renal function. Two years later, she developed ascites and elevated liver enzymes. Her presentation was concerning for hepatic amyloidosis; therefore, she was transferred to a liver transplant center for further evaluation.

**Discussion:** Based on two large renal biopsy series, LECT2 accounts for 2.5-2.7% of all cases of renal amyloidosis. In a multicenter study involving 72 patients with renal ALECT2, 92% were Hispanic, 2.8% were below the age of 50 and 91.4% had a serum creatinine > 1.2mg/dl. One third had nephrotic range proteinuria, but only 10% of all patients presented with nephrotic syndrome. Pathogenesis is not clear. It is postulated that inflammatory processes lead to excessive production of an amyloidogenic variant of ALECT2. Accurate identification of the amyloid protein is essential as disease modifying treatments are available for certain types of amyloidosis.

**TH-PO1093**  
Complement Polymorphisms in Patients with Thrombotic Microangiopathy Associated with Intraavenous Abuse of Oral Formulation of Extended-Release Oxyomorphine (OPANA-ER)  
Joe Ghara, Lukas Haragiss, Satish Kumar.  
Nephrology, Univ of Oklahoma Health Science Center, Oklahoma City, OK.

**Introduction:** In 2012, the CDC reported 15 cases of unexplained renal failure and thrombotic microangiopathy (TMA) in which all patients reported dissolving and intravenously injecting an oral preparation of oxymorphone (OPANA) prior to presentation. Since then, 30 additional cases have been reported in the U.S. The mechanism of IV Opana-associated TMA is unclear. ADAMTS13 levels were normal. We report two patients with genetic polymorphisms of complement system proteins as a possible mechanism for Opana-associated TMA.

**Case Description:** Two patients, a 26 yo WM (Pt 1) and a 38 yo WM (Pt 2) presented with unexplained renal failure (serum creatinine 8.2 and 4.6 mg/dl respectively) in the setting of IV Opana Abuse. Both displayed a hematological constellation of microangiopathic hemolytic anemia, thrombocytopenia, consumed haptoglobin and elevated LDH. Both patients had normal INR/PT/PTT, ADAMTS13 (both > 55%) and fibrinogen levels. ANA, HIV, and hepatitis profiles were negative. Renal biopsy showed intermediate sized vessels with a thrombotic microangiopathy in both patients. Both received plasmapheresis for 5 days. Hematological microangiopathy resolved in Pt 2 but persisted in Pt 1. Both remained dialysis dependent. Genetic studies for complement-mediated HUS demonstrated both to be positive for a heterozygous polymorphism (IVSP-78 G>A) within an intron of the membrane cofactor protein (MCP/CD 46) and for a homozygous polymorphism (p.His402Thr) in the complement factor H (CFH). In addition, both patients had an additional CFH polymorphism (p.Val621Le; Pt 1 homozygous, Pt 2 heterozygous).

**Discussion:** Our patients suggest a 2 bit mechanism for IV Opana-associated TMA. Both had polymorphisms in complement system proteins MCP and CFH with a potential predisposition for complement-mediated HUS. The MCP/CD 46 polymorphism has been shown to be enriched in patients with complement-mediated HUS. Polymorphisms in complement system proteins could cause hyperactivation and dysregulation of the complement system and provide a genetic predisposition for thrombotic microangiopathy, with IV Opana abuse acting as a trigger.
Acute Kidney Injury due to an Excessive Dose of Rivaroxaban

Case Description: A 45 y/o man presented to his physician's office with abdominal pain. Computed tomography (CT) of the abdomen was done and thrombosis of the portal, splenic, and mesenteric vein was identified. He was admitted to the hospital and discharged on warfarin 10 mg b.i.d. A week later he was given a prescription for rivaroxaban 20 mg tab and told to take 1 tablet daily. He mistook it for 2 tablets daily. After 5 days, he noticed painless gross hematuria for several days. He reported to his physician's office and his serum creatinine had increased to 2.7 mg/dl from a baseline of 1.5. He had a previous history of stroke and hypertension. He was evaluated with 2 years prior CT (revealed with course of warfarin), hypertension, and diabetes. His medications included metformin, glipizide, gemfibrozil, valsartan, sitagliptin, and rivaroxaban. His vital signs were normal. Physical examination showed splenomegaly but was otherwise unremarkable. Urinalysis revealed many red blood cells with trace proteinuria. The urine protein to creatinine ratio was 257 mg. Serologies were negative and there was no evidence of intravascular hemolysis. Antiphospholipid antibodies were negative as was a hypercoagulable work-up. A bone marrow biopsy was unremarkable and paroxysmal nocturnal hemoglobinuria was ruled out. Renal dopplers were normal for renal vein thrombosis. Renal function remains stable after 3 months. Renal biopsy was not performed in the setting of required anticoagulation and likely diagnosis of anticoagulant related AKI.

Discussion: WRN is a newly recognized form of AKI in the setting of excessive anticoagulation due to rivaroxaban. This appears to be the first reported case of a WRN-like AKI due to the NOAC rivaroxaban, and was likely caused by inadvertent doubling of the patient's dose. WRN can often be irreversible and in this patient as well no renal recovery was evident at 3 months.

Irreversible Acute Kidney Injury due to Oxalate Nephropathy from Intravenous Vitamin C

Case Description: High doses of vitamin C are widely used in alternative medicine for treatment of cancer, viral illness and fatigue. Vitamin C is metabolized to oxalic acid in the body. High doses of vitamin C have the potential to cause hyperoxaluria, nephrolithiasis and oxalate nephropathy. We report a patient who developed severe, irreversible, acute kidney injury due to acute oxalate nephropathy from high dose intravenous vitamin C.

Case Discussion: A 30 year old man with a history of hypertension, hypothyroidism, and mild pancytopenia, presented to a wellness clinic with fatigue and weight loss. He had a normal metabolic profile except hypercalcemia (corrected Ca, 12 mg/dl). He received IV vitamin C 30 g/d for 7 days. Serum creatinine was 1.3 mg/dl prior to Vitamin C administration. One month following treatment, he was admitted to our hospital with serum Cr 9.1, Na 110, K 3.1, Cl 70, CO2 16, BUN 152, Glucose 131, Ca 8.4, Uric Acid 1.21, CPK 175, Phos 11.9, and Protein 6.1. Urine sediment was normal. Urine vitamin C level was 40. An abdominal CT with IV contrast revealed diffuse mesenteric and retroperitoneal lymphadenopathy with hepatosplenomegaly and ascites. Liver was without cirrhosis. A renal ultrasound revealed normal sized, echogenic kidneys. Serum free light chains and serum and urine protein electrophoresis were normal. A renal biopsy revealed diffuse acute tubular injury and abundant tubular calcium oxalate deposits consistent with acute oxalate nephropathy. Bone marrow biopsy was normal and culture negative. A lymph node biopsy demonstrated diffuse T Cell Lymphoma. Patient was started on dialysis and remained dialysis-dependent at least follow up.

Discussion: Our patient developed severe, irreversible acute kidney injury from high dose intravenous vitamin C. The hypercalcemia was likely a contributing factor for the extensive deposition of calcium oxalate crystals in the kidney. A literature search identified 2 previous reports of oxalate nephropathy from intravenous vitamin C. High dose vitamin C is a common component of alternative medical regimens for cancer and other illnesses. We urge caution in using high dose vitamin C especially in patients with pre-existing renal insufficiency or hypercalcemia.

Atypical Hemolytic Uremic Syndrome (aHUS) due to a Novel Sequence Variation of Diacylglycerol Kinase Epsilon (DGKE)

Case Description: Anti-HUS is a congenital disease characterized by hemolytic anemia, thrombocytopenia, and organ dysfunction (e.g. renal failure). Genetic alterations resulting in uncontrolled activation of the complement system are found in 50-60% of aHUS cases. Recently, mutations in DGKE have been associated with aHUS. The DGKE gene encodes an intrinsic signaling alterations in the signaling pathways controlling endothelial and platelet procoagulant tendency and podocyte function can also lead to aHUS. Patients with DGKE-associated disease tend to present at earlier age, have nephrotic range proteinuria, fail to respond to plasma exchange, and may develop renal failure, but do well after renal transplantation.

Case Discussion: We identified a novel homozygous sequence variation c.134AC>A, p.N448K in the kinase active site domain of DGKE in a family with aHUS. The index case presented at 1 year of age with nephrotic range proteinuria and hypertension. Renal biopsy showed tubular flaring of the tubules and collapse of the basement membranes by oncogenes like BCR-ABL or ALCAM. At age 10, she does not have thrombocytopenia, schistocytes, abdominal or CNS manifestations, as typically noted in patients with complement-mediated aHUS. Genetic testing was resent to identify mutations previously not available for this family treatment. The patient also carries heterozygous sequence variation ADAMTS13 c.3287G>A, p.R1096H, associated with decreased ADAMTS13 function and is heterozygous for CFHHR5. Subsequently, a younger sister presented with hypertension, hematuria and nephrotic range proteinuria. The symmetric sister is also homozygous for the same mutation in DGKE and is heterozygous for CFHR5, but lacks the ADAMTS13 variant. Parents and siblings with heterozygous DGKE variants are healthy.

Discussion: This is the first reported case of a kinase active site domain of DGKE associated with aHUS. Additional studies are needed to determine the impact of DGKE mutations on the clinical course of patients with aHUS and their appropriate management.

Membranoproliferative Glomerulonephritis with Mixed Cryoglobulinemia in Patients with Autoimmune Hepatitis

Case Description: Case 1: A 56 year old female presented with microscopic hematuria (6-10 RBC), proteinuria (6.9 g) and acute kidney injury (creatinine 1.5 mg/dL). Her renal function deteriorated requiring hemodialysis treatment. Serum IgG/Mg cryoglobulins. Kidney biopsy showed mesangial proliferation, protein thrombi within capillary loops, reduplication of GBM and mesangial interpositioning, consistent with cryoglobulinemic MPGN. She was treated with plasma exchange and rituximab. Case 2: A 18 year old female presented with proteinuria (1.7 g), hematuria (44 RBC) and serum creatinine 0.8 mg/dl. Mixed type III cryoglobulins consisting of IgG/Mg were detected in the serum. Kidney biopsy revealed mesangial hypercellularity, reduplication of GBM with subendothelial, mesangial and scattered subepithelial deposits. She was treated with plasma exchange, one dose of 1000 mg intravenous cyclophosphamide and 1 gram of rituximab 4 weeks later. Treatment led to the disappearance of cryoglobulins and normalization of urinary findings and resolution of AKI. Case 2: 18 year old female presented with proteinuria (1.7 g), hematuria (44 RBC) and serum creatinine 0.8 mg/dl. Mixed type III cryoglobulins consisting of IgG/Mg were detected in the serum. Kidney biopsy revealed mesangial hypercellularity, reduplication of GBM with subendothelial, mesangial and scattered subepithelial deposits. She was treated with plasma exchange, one dose of 1000 mg intravenous cyclophosphamide and 1 gram of rituximab 4 weeks later. Treatment led to the disappearance of cryoglobulins and normalization of urinary findings. Serologic tests at presentation are presented in table 1.
**Discussion:** There has been a high risk of urethral malignancies associated with Chlamydaharb-aristolochic acid exposure with 40 - 45% of these patients developing multifocal high grade transitional cell carcinoma leading to a suggestions for either prophylactic bilateral native nephrectomy and ureterectomy at the time of renal transplantation or screening cystoscopic every 6 months to identify early stage urethral carcinoma. Our patient is a classic example of aristolochic acid associated nephropathy complicated with urethral cancer.

**TH-POI099**

**Anti-Tumor Necrosis Factor Therapy – A Trigger for Anti-Glomerular Basement Membrane Disease**

Carlos Antonio Cortes Sanchez, Hector R. Cordova, Krystahl Z. Andujar. Medical Service, VD Caribbean Health System, San Juan, PR.

Introduction: Tumor necrosis factor (TNF) has a key pathological role in diseases such as rheumatoid arthritis (RA). Vasculitis and other autoimmune diseases have been associated with the use of anti-TNF agents such as Adalimumab.

Case Description: A 73-year-old man with RA, Hypertension, Diabetes Mellitus type 2 and Non-Hodgkin’s Lymphoma in remission for 3 years complained of decreased urine output, dark urine, poor appetite, weight loss and peripheral edema for three weeks. He was on chronic low dose Prednisone and Adalimumab intermittently during the previous 21 months. Physical exam revealed bilateral lower extremity pitting edema but no skin lesions. Laboratories showed a serum creatinine of 9.5mg/dL (baseline of 1.5mg/dL). Urinalysis exhibited many RBC’s, proteinuria (2+) and pyuria without casts. The clinical picture suggested acute glomerulonephritis. Hemodialysis (HD) was started.

<table>
<thead>
<tr>
<th>Test</th>
<th>Upon Admission</th>
<th>After Plasmapheresis</th>
<th>After Reexposure to Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>1.80 Speckled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3/C4</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-GBM (&lt; 1.0 AI)</td>
<td>7.9</td>
<td>2.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Atypical PANCA (&lt; 1.20)</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>P-ANCA (&lt; 1.20)</td>
<td>1.20</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>MPO (&lt; 1.0 AI)</td>
<td>4.6</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>C-ANCA (&lt; 1.20)</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>ProUAb (&lt; 1.0 AI)</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>ASO Titer</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serology tests were compatible with Anti-Glomerular Basement Membrane Disease. Alveolar hemorrhage was not present. Plasmapheresis therapy decreased anti-GBM titers but there was no recovery of renal function. The patient continued using Adalimumab after discharge. He later returned with hemoptysis due to alveolar hemorrhage, which resolved after the discontinuation of Adalimumab. The patient remained HD-dependent.

Discussion: The temporal association of the illness with anti-TNF therapy and worsening of symptoms upon reexposure suggest an etiologic role of Adalimumab in the development of Anti-GBM Disease in our patient receiving anti-TNF therapy should have renal function closely monitored to allow early detection of this infrequent but life-threatening side effect.

**TH-POI100**

**Severe Pauci Immune Crescentic Glomerulonephritis Mimicking ANCA Related Vasculitis Caused by Clinically Silent Dental Abscess Leading to Bacterial Endocarditis**

Anil K. Chunduri, Maria Saleem Khan, Anthony Alvarado, Tibor Nadasy, Lee A. Hebert. Nephrology, OSUMC, Columbus, OH.

Introduction: Severe crescentic GN is usually categorized based on the cause if it is Anti GBM or IC mediated disease. However, it is not widely appreciated that some instances of pauci immune GN are actually the result of severe occult systemic infections. We present a case of severe pauci immune crescentic GN whose initial assessment for infection was negative. The patient was assumed to have idiopathic AA V and was treated with high dose corticosteroids. These findings are rarely common, if ever, associated with AA V.

Case Description: 55 year old male with PMH of CAD presented to an outside hospital with fatigue. Initial labs revealed Hb: 7.6g/dL, WBC: 2.8 K/µL, Pt: 44 K/µL, Cre: 2.26 mg/dL. Infectious work up was negative. Autonomic workup revealed: ANA positive (1:40), Anti GBM (<2), Anti PR3 (0.6), ANCA and Anti MPO: negative. C3: 77mg/dL, C4: 16.9 mg/dL (wnl). Cystoglobin (<5), Urine PC ratio was 1.2. Further workup included a bone marrow biopsy and kidney biopsy, which was suggestive of pauci-immune crescentic and necrotizing GN. He received treatment with steroids and was discharged on steroid taper. His creatinine upon discharge was 1.5 mg/dL. On follow up his creatinine was elevated to 3.5 mg/dL. He was transferred to our institute. Repeat Infectious work up revealed streptococcus viridans bacteremia, tricuspid and aortic valve endocarditis. A panoramic radiograph of his teeth showed periapical abscess. He was subsequently diagnosed with infection related acute pauci-immune crescentic necrotizing GN. Unfortunately this patient remained dialysis dependent at the time of discharge.

**Discussion:** It is well established but not widely appreciated that severe pauci-immune crescentic GN can be the direct result of infection. Thorough investigation is warranted even if the initial infectious workup is negative, if the patient does not have a positive response to conventional therapy to improve morbidity and mortality.

**TH-POI101**

**POEMS Syndrome with Cast Nephropathy**

Amanda K. Hall,1 Josephine Abraham,2 Monica Patricia Revelo Penafiel,1 Frederic Clayton.1 ‘Div of Nephropathy and Hypertension, Univ of Utah, Salt Lake City, UT; ‘Div of Pathology, Univ of Utah, Salt Lake City, UT.

Introduction: POEMS syndrome(Polynephropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) is a plasma cell disorder with peripheral neuropathy and any of the following features osteosclerotic bone, Castleman’s disease, increased levels of serum vascular endothelial growth factor(VEGF), organomegaly, endocrinopathy, edema or skin changes. We report a case of POEMS presenting with acute renal failure due to cast nephropathy.

Case Description: A 63-year-old Caucasian female presented with a 3 month history of increasing weakness and was diagnosed with chronic inflammatory demyelinating polyneuropathy. She was also noted to have new onset diabetes mellitus and hypothyroidism. She was treated with intravenous immunoglobulin(IVIG) with minimal response. She was admitted with acute renal failure initially thought to be secondary to IVIG, progressive weakness, and shortness of breath. Serum beta 2 microglobulin was elevated and kappa/lambda ratio was abnormal with Bence-Jones proteinuria. Renal biopsy was deferred as the patient developed respiratory failure, subarachnoid hemorrhage, and a left middle cerebral artery stroke. Comfort measures were initiated. Bone marrow biopsy confirmed multiple myeloma with 20% clonal plasma cells. She was treated with an不受限制 hepatomegaly, splenomegaly, and peripheral nerve demyelination with active axonal loss. Renal examination showed cast nephropathy with monoclonal kappa light chains.

These features are characteristic of POEMS given the multiple myeloma with neuropathy, organomegaly, rash and new onset diabetes mellitus and hypothyroidism.

Discussion: POEMS is a paraneoplastic syndrome associated with plasma cell dyscrasia. Polynephropathy with plasma cell disorder should prompt evaluation for POEMS as outcomes have been excellent with diagnosis and treatment.

**TH-POI102**

**Acute Interstitial Nephritis Associated with a New Breast Cancer Chemotherapy Regimen**

Cory Handelsman,1 Michael T. Tanoue,2 Amy Kwon,2 Steven Salvatore,3 Jeffrey I. Silberzweig.5 ‘Div of Nephrology, Weill Cornell Medical College; 1Dept of Medicine, Weill Cornell Medical College; 2Dept of Pathology, Weill Cornell Medical College, New York, NY; 5The Rogosin Inst, New York, NY.

Introduction: Acute interstitial nephritis (AIN) as a direct consequence of chemotherapy is infrequently described. A recent review implicated ifosfamide, tyrosine kinase inhibitors, and pemetrexed as culprits in this process. We describe a case of AIN related to the recently approved chemotherapy regimen of pertuzumab, trastuzumab, and docetaxel for HER-2 positive metastatic breast cancer. While diarrhea, rash, and pruritis are well-known side effects, this report is the first to show AIN as a consequence of this combination regimen.

Case Description: A 69-year-old woman recently diagnosed with HER-2 positive breast cancer and treated with six cycles of neoadjuvant pertuzumab, trastuzumab, and docetaxel was hospitalized for acute kidney injury after two days of diarrhea and vomiting. Admission labs demonstrated leukocytosis to 26,000/uL, serum creatinine of 5.9 mg/dL (baseline of 1.55 mg/dL), and elevated anion gap metabolic acidosis with a lactic acid of 4.5 mmol/L. Urinalysis showed pyuria with occasional granular casts. Fractional excretion of sodium was 1.88%. Renal sonogram showed normal renal cortical kidney with no evidence of hydroureter or calculus. Infectious workup, including blood, urine, and stool studies, was unrevealing. Despite aggressive hydration and resolution of diarrhea and vomiting within 48 hours, her renal function worsened; her creatinine peaked at 9.0 mg/dL on hospital day 3. She was non-oliguric throughout the admission. A renal biopsy revealed moderate, diffuse acute and subacute, interstitial inflammation characterized by lymphocytic infiltration with moderate eosinophilia and diffuse tubular injury. Some endothelial injury

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

Underline represents presenting author.

351A
was present as well. The patient was diagnosed with AIN related to combination chemotherapy with docetaxel, pertuzumab, and trastuzumab.

**Discussion:** This is the first documented case of AIN related to combination chemotherapy with docetaxel, pertuzumab, and trastuzumab.

**TH-PO1103**

**Sarcoidosis-Lymphoma Syndrome Presenting with Severe Refractory Hypocalcemia**

Osita O. Okechukwu, Barry M. Wall, Elvira Gosmanova, Deepak Pandkanti, Nephrology Div, UTHSC, Memphis, TN; Nephrology Section, VAMC, Memphis, TN.

**Introduction:** Sarcoidosis-lymphoma syndrome (SLS) is rare. Sarcoidosis (S) usually precedes lymphoma (L) by many months. Constitutional symptoms and hilar lymphadenopathy are suggestive of an initial manifestation of SLS. We report a SLS case presenting with severe acute hypercalcemia and acute kidney injury (AKI).

**Case Description:** Case Report: A 70 yr-old Caucasian male was hospitalized with symptoms of generalized weakness, poor oral intake, and altered mental status. Examination was significant for dry mucous membranes, depressed mental function, evidence of bilateral pleural effusions, mild ascites, and 2cm well-delineated hyperpigmented erythematous plaques on anterior chest wall. Laboratory findings included a corrected serum Ca 19.4mg/dL (2 months prior: 9.3mg/dL), ionized Ca 2.3mmol/L, BUN 56mg/dL, serum creatinine 2.5mg/dL (baseline 1.4mg/dL), and mild anemia. Further work up revealed suppressed PTH (0.2pg/mL), normal LFT, T3, T4, urine electrophoresis, calcium, creatinine, ACE, CEAs, PSA, and TSH. A workup diagnosis of hypercalcemia of malignancy was made. Intrahepatic and pelvic soft tissue showed increased activity on PET scan. MRI abdomen revealed a mass suspicious for lymphoma. Following biopsy, the patient was treated with prednisone. Two weeks later, her symptoms had fully resolved and her serum was present as well. The patient was diagnosed with AIN secondary to chemotherapy and nephropathy can be a late complication of chronic pancreatitis leading to CKD and ESRD.

**Discussion:** Calcium oxalate in the GI tract, combined with increased colonic mucosal permeability, malabsorption may increase free fatty acids that competitively inhibit the formation of prostanoids (Prostaglandin biosynthesis) and lead, with the aim of stopping the inflammatory cascade.

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

**Underline** represents presenting author.
Discussion: This case illustrates the potential effectiveness of denosumab for the treatment of hypercalcemia refractory to bisphosphonates. Denosumab is a human monoclonal antibody against RANK-Ligand (RANKL) whose use has previously been described for management of hypercalcemia, but required multiple infusions. Recognition of this additional treatment, with effectiveness from a single infusion, is critical in managing refractory hypercalcemia, as the only other known option is hemodialysis. Increasing availability of options for management of refractory hypercalcemia may allow patients to avoid complications associated with hemodialysis.

TH-PO1108
Collapsing and NOS Focal Segmental Glomerulosclerosis (FSGS): Progression Along a Spectrum or Different Diseases? Suzanne L. Katsanos, Patrick H. Nachman, JulieAnne G. McGregor, Volker Nickeleit. UNC Kidney Center, Chapel Hill, NC.

Introduction: Minimal change disease (MCD) and some variants of FSGS (tip lesion and not otherwise specified NO) are thought to represent a histologic spectrum of a same autoimmune pathogenic process (Habib, R. Proceedings IXth Int Conf of Neph.). This contention has never been proven, however. Some cases of MCD are thought to be “unsampled” FSGS. A “transition” from MCD to FSGS is common in steroid-resistant forms (Tejani, A. Nephron 39). It has been proposed that collapsing FSGS is pathogenically and clinically distinct from other FSGS variants based on morphology, demographics, severity of nephrotic syndrome, and renal prognosis. The etiology has not been identified but viral agents, drugs, and cyclosporine toxicity have all been proposed.

Case Description: We present the case of a 37-year-old African American male with a complicated course of nephrotic syndrome. He was diagnosed with biopsy-proven MCD when 9 years old. He was treated with steroids followed by chlorambucil and then cyclophosphamide over the next several years. He was in complete remission off therapy for about 2 years until he re-presented with increased edema, proteinuria (3.8 g/dl), hypoalbuminemia, and acute kidney injury (AKI). A repeat biopsy (23 glomeruli) showed FSGS NO. He was treated with steroids followed by mycophenolate mofetil and cyclosporine, resulting in complete remission. 7 years later, he developed edema, proteinuria (21 g/dl) and AKI. Repeat biopsy showed 25 glomeruli demonstrating segmental tuft collapse, activation of endothelial cells, and segmented marked activation and crowding of podocytes consistent with collapsing FSGS. HIV, hepatitis B, and hepatitis C were negative.

Discussion: The transition from MCD to FSGS NO is common in the literature. However, the transition from FSGS NO to collapsing FSGS is rarely reported. This patient’s case raises questions about this transition from NO to collapsing variant. Glomerular undersampling is unlikely given 25 glomeruli were examined each time. This could represent a progressive, patient-related pathogenetic process versus a de novo lesion (either related to a viral infection or medication, for example).

TH-PO1109
Lymphoma Associated Monoclonal Cryoglobulinemia in a Patient with Hepatitis C Sangeeta Mutnuri, Marjan Afrozouan, Hania Kassem.1 Dept of Nephrology, UTMB, Galveston, TX; 2 Dept of Pathology, UTMB, Galveston, TX.

Introduction: We present a case of type I cryoglobulinemia and membrandeproliferative glomerulonephritis (MPGN) in a patient with hepatitis C infection (HCV), leading to the diagnosis of a marginal zone lymphoma.

Case Description: A 47 year-old male with HCV and hypertension presented with two month duration of shortness of breath and decreased urine output. On examination he was hypertensive (blood pressure: 183/111 mm of Hg), had lung crackles, lower extremity edema and hepatosplenomegaly. Laboratory tests were significant for pancytopenia, hypoalbuminemia and an elevated creatinine of 2.8mg/dl (0.8mg/dl four months ago). Urine exam revealed red blood cell (RBC) casts, dysmorphic RBC’s and nephrotic range proteinuria (9.5 g/ml). Immunohistochemistry revealed elevated rhamatoid factor, hyycopomponentemia and cryoglobulinemia. These findings led to a suspicion of HCV induced cryoglobulinemic glomerulonephritis. Kidney biopsy was performed revealing MPGN type III with deposits. Fluorescence microscopy favored Kappa monoclonal. Electron microscopy of the deposits was consistent with cryoglobulins. Serum immunoelectrophoresis also confirmed IgM/Kappa monoclonality. As HCV is more commonly associated with polycymal cryoglobulinemia this finding of monoclonality prompted a search for malignancy. A bone marrow biopsy showed lymphoid aggregates including rare low-endothelial marginal zone lymphocytes. He was initiated on rituximab/dexamethasone based regime. The creatinine trended down to 1.87 mg/dl.

Discussion: Monoclonal cryoglobulinemia is related to lymphoproliferative diseases whereas HCV is associated with polyclonal cryoglobulinemia. This case stresses the importance of differentiating between the two entities especially in patients with co-existing disorders. Making this crucial distinction helps predict the underlying etiology and treatment.

TH-PO1110

Introduction: IgG4-related kidney disease (IgG4-RKD) usually presents as tubulointerstitial nephritis with IgG4-positive plasma cell (PC) infiltration and serum IgG4 elevation. IgG4-RKD has characteristic histological findings called storiform fibrosis and polyclonal IgG4-positive PC infiltration. Storiform fibrosis has been rarely described for management of hypercalcemia, but required multiple infusions. Recognition of this crucial distinction helps predict the underlying etiology and treatment. Here we report a patient diagnosed with lupus nephritis (LN) with IgG4-negative IgG4-RKD.

Case Description: A 59-year-old Japanese man was referred to our hospital with chest pain and mild proteinuria. Thoracic biopsy was performed for abnormal lung shadow and interstitial pneumonia was diagnosed. Although ANA titer was elevated to 2560-fold, anti-DNA, anti-Sm, and anti-SS-A/B antibodies were all negative. Serum C3 and C4 levels and complement activity were decreased. Serum IgG and IgE levels were elevated, but serum IgG4 level was within normal limits. On contrast-enhanced CT, multiple low-density lesions were observed in kidney. Renal biopsy findings revealed lymphoplasmacytic infiltration with storiform fibrosis and small numbers of eosinophils. Immunostainings revealed CD138+ or IgG4-positive PC infiltration without IgG4-positive PC. Immunofluorescence microscopy disclosed granular mesangial positivity for a “full-house” pattern. Electron microscopy disclosed mesangial and subendothelial dense deposition accompanied with virus-like particles. We diagnosed this patient with IgG4-negative IgG4-RKD and LN (ISS/RPS II). After administration of 20 mg prednisolone, laboratory data was drastically improved.

Discussion: To our knowledge, this is the first report of a patient with LN and IgG4-negative IgG4-RKD. IgG4-negative IgG4-RKD may be a chronic burnout phase of IgG4-RKD. Further studies gathering similar cases would be needed to clarify whether or not IgG4-negative IgG4-RKD is included in a category of IgG4-RKD.

TH-PO1111
A Case of Acute Phosphate Nephropathy in a Kidney Transplant Recipient Hetal Shah, M. Lee Sanders, Kelly A. Birdwell, Anthony J. Langone, Paist Paukeasakon, Beatrice P. Concepcion. Vanderbilt Univ Med Center, Nashville, TN.

Introduction: Acute phosphate nephropathy has been described after large doses of phosphate, typically in laxatives and bowel cleansing preparations. We present a case of acute phosphate nephropathy in a kidney transplant recipient who was taking oral phosphorus supplementation for hypophosphatemia.

Case Description: A 26 year-old man with a living related donor kidney transplant in 2011 complicated by recurrent IgA nephropathy with a baseline creatinine of 1.9 mg/dl presented with nausea, vomiting, diarrhea, fatigue and elevated creatinine. Two weeks prior to presentation, he had been started on K-Phos-Neutral 500 mg three times a day for a total of 1500 mg/day of oral phosphorus (iPTH) was 58 pg/mL. He soon after developed diarrhea and ten days later developed nausea and vomiting. He was found to have a creatinine of 10.4 mg/dl, phosphorus 9.7 mg/dl, calcium 9.6 mg/dl and iPTH 761 pg/ml. Urinalysis showed a urine pH of 5, no red blood cells and trace protein. Renal biopsy was performed, and pathology revealed 30 foci of intratubular calcium crystals with associated acute tubular injury involving 30-40% of tubular profiles, along with known reoccurrence of IgA nephropathy. The patient underwent acute hemodialysis for oliguric acute kidney injury. Given the high serum phosphorus, he was dialyzed for four consecutive days until phosphorus level was less than 4 mg/dl and did not rebound. Patient was discharged requiring intermittent hemodialysis for an additional three weeks until he demonstrated renal recovery. His new baseline creatinine is 2.2 mg/dl and he has remained off hemodialysis.

Discussion: Hypophosphatemia is common in kidney transplant recipients. Although rare, acute phosphate nephropathy can occur in the setting of phosphorus repletion. This patient also had multiple risk factors, including baseline renal dysfunction, volume depletion and angiotensin receptor blocker use. Acute phosphate nephropathy can potentially lead to irreversible loss of renal function. While no specific treatment exists, in this case, aggressive hemodialysis to decrease serum phosphorus may have played a role in this patient’s eventual renal recovery.

TH-PO1112
Unusual Membranous Nephropathy in a Patient with Lupus Iheanyichukwu Ogu, Julia Lewis, Agnes B. Fogo. Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.

Introduction: Membranous nephropathy (MN) is an immunologically mediated glomerular disease. Distinguishing between primary and secondary MN is important in guiding diagnosis and treatment. We present a case of a patient with systemic lupus with pathologic features in a repeat biopsy suggestive of primary MN.
Case Description: A 32 year old African American woman presented in 1998 with nephrotic range proteinuria (IgG, edema and serum creatinine 0.6). She had negative work up for secondary causes including lupus. Renal biopsy showed mild matrix expansion, diffuse global basement membrane (GBM) spikes, preserved tubulointerstitial compartment; fine granular IgG(3+), C3(1+) IgM(trace), C1q(trace), IgA(negative) capillary loop staining with focal mesangial IgM and C3 staining; numerous subepithelial deposits, 90% foot process effacement, and unremarkable endothelial cells. She was started on an angiotensin receptor blocker but was lost to follow up. In 2011 she was diagnosed with lupus and in July 2014, had proteinuria (1.9g). Repeat renal biopsy showed persistent MN with features concerning for lupus, with reticular aggregates, mildly increased mesangial matrix and cellularity, and 20% interstitial fibrosis. After referral to our clinic, additional testing on the 1998 biopsy (fig. 1.2) showed diffuse global capillary wall IgG(I+2), IgG2(I+2), IgG3(negative), IgG4(I+2), PLAR2(negative); and the 2014 biopsy (figs. 3.4) showed diffuse global granular capillary wall IgG(I+2), IgG2(I+2), IgG3(negative), IgG4(I+2) and PLAR2 near global(I+2) granular capillary loop staining.

Discussion: The PLAR2 staining and the dominance of IgG4 currently are consistent with primary MN. The negative PLAR2 in 1998 may indicate early disease or epitope change. The mesangial deposits are nonspecific and could possibly represent a low grade with primary MN. The negative PLA2R in 1998 may indicate early disease or epitope change.

TH-POI113
A Case of Proliferative Glomerulonephritis with Monoclonal IgG Deposits Exhibiting Marked Nephrotic Syndrome Who Responded Well to the Renin-Angiotensin System Blockade
Yoshihiko Ishihiguchi, Hideki Inoue, Tomoaki Onoue, Yutaka Kakizoe, Yuichiro Izumi, Takashige Kuwabara, Takuo Miyoshi, Masatake Adachi, Yushi Nakayama, Masashi Mukoyama. Nephrology, Kumamoto Univ Hospital, Kumamoto, Japan.

Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a recently recognized entity of glomerulonephritis caused by glomerular deposition of monoclonal IgG. The clinical and pathological features, treatment and prognosis of this entity remain elusive.

Case Discussion: A 79-year-old woman was admitted to our hospital due to hematuria and marked nephrotic-range proteinuria. Her serum creatinine level was 0.75 mg/dL and urinary protein excretion was 20.8 g/gcreatinine. Renal biopsy showed a membranoproliferative feature without nodular formation. Immunofluorescence study showed capillary and mesangial deposits of IgG, C1q and C3. Moreover, IgG-kappa deposits were strongly stained and IgG3 deposits were restrictedly stained for IgG heavy-chain lambda ratio. These findings were consistent with the diagnostic criteria for PGNMID.

Considering her age and tolerability, we started monotherapy with angiotensin II receptor blocker. This case showed drastic reduction in proteinuria with stable renal function within several months after the treatment with the renin-angiotensin system (RAS) blockade alone.

Discussion: We report here an exceptional case of PGNMID associated with the membranoproliferative feature successfully treated with RAS blockade alone, without steroids or other immunosuppressive agents. Further studies are needed to clarify clinical spectrum and prognosis of this newly described disease entity.

TH-POI114
Brexitumab Induced Renal Steatosis – The Hint Is in the Urine
Akhil Heads, Ronald J. Falk, Abhijit V. Kshirsagar. UNC Kidney Center, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.

Introduction: We describe the onset of acute kidney injury (AKI), lipodystrophy and multi-organ steatosis after the use of Brexiutumab, a monoclonal antibody targeting CD30, in patients with recurrent Hodgkin Lymphoma (HL).

Case Discussion: A 61 year old female with recurrent HL, treated with Brexitumab 180mg (4 and 2 weeks prior to admission), was admitted with a 1-month history of nausea and vomiting. She was found to have AKI, creatinine 1.7 - baseline 0.9 mg/dL, elevated liver enzymes (AST 324, ALT 282 U/L), a urine protein/creatinine ratio of 1.0g with a total creatinine of 1.75 and 32 mg/dL. Urine microscopy revealed numerous free fatty droplets and fatty casts (8g), edema and neutrophilic infiltration of the glomerular capillary wall, showing a maladaptive polarization light. Sudan black dye demonstrated positive staining indicating non-cholesterol fat in the urine.

PET/CT imaging did not show malignancy, but revealed severe fatty infiltration of multiple organs not present 4 months earlier. The patient was hospitalized and the patient died on hospital day #6. An autopsy revealed hepatosplenomegaly with severe steatosis, fatty infiltration of the pancreas and proximal renal tubular epithelial cell macro/microvesicular steatosis with intra-glomerular lipiduria.

Conclusion: The development of AKI, lipodystrophy and multi-organ steatosis after 2 doses of Brexitumab is concerning for a drug-induced injury. Sudan dye attaches to neutral lipids and is helpful in distinguishing the 2 categories of lipids. Only 2 weeks after the last dose of Brexitumab, the patient was found to have new fatty infiltration and a subsequent autopsy revealed intra-glomerular lipidosis. The first histologic feature was steatosis was the presence of fat bodies in the urine. Typically, charged lipids have the appearance of a maltese cross under polarizing light, while neutral lipids do not refract polarized light in this manner.

TH-POI115
Pheochromocytoma: An Unusual Cause of Thrombotic Microangiopathy
Yoshihiko Ishihiguchi, Hideki Inoue, Tomoaki Onoue, Yutaka Kakizoe, Yuichiro Izumi, Takashige Kuwabara, Takuo Miyoshi, Masatake Adachi, Yushi Nakayama, Masashi Mukoyama. Nephrology, Kumamoto Univ Hospital, Kumamoto, Japan.

Introduction: Hypertensive disorders during pregnancy result in substantial maternal and fetal morbidity. Pheochromocytoma in pregnancy is extremely rare with a reported frequency of 0.002% and 50% maternal and fetal mortality.

Case Description: A 25 year old female, 26 weeks of gestation with gestational diabetes presented with antenatal hemorrhage, confusion and uncontrolled hypertension with BP 145/95 mmHg. Investigations revealed hemoglobin 9 g/dL, platelets 760000/microliter, serum creatinine 2.4 mg/dL, LDH 245U/L, AST 300U/L, ALT 390U/L, urine dipstick protein 1+. Ultrasound confirmed abrupt placenta and intrauterine death of fetus needing emergency surgical evacuation. She developed intraoperative hypotension needing multiple blood transfusions and ventilatory support. Her renal function worsened needing initiation of hemodialysis. Septic and hemolytic work up were negative. She had paroxysmal episodes of uncontrolled hypertension and flash pulmonary edema needing frequent rescue hemodialysis and parenteral antihypertensives. Renal doppler was negative for renal artery stenosis. CAT scan showed left adrenal mass. Plasma normetanephrine was elevated at 1223 pg/ml suggestive of pheochromocytoma. BP was stabilized with four drugs and surgical resection of the tumor was done. A wedge kidney biopsy showed thrombotic microangiopathy (TMA). The tumor histopathology confirmed pheochromocytoma, positive for chromogranin and synaptophysin staining. Post operative, her creatinine stabilized at 1.6 mg/dL, BP and glucocorticoid status returned to normal.

Discussion: Discussion: Pheochromocytoma in pregnancy is an extreme rarity with a frequency of 0.002%. It is often mistaken for other hypertensive disorders of pregnancy. This is the first case report of a patient with acute kidney injury in pregnancy from TMA secondary to pheochromocytoma. Patient made good renal recovery after resection of the tumor.

TH-POI116
Immune Reconstitution Inflammatory Syndrome and Hypercalcemia with Acute Kidney Injury following Antiviral Therapy
Carolina Garcia, Kelly H. Beers, Catherine Miranda, Kamran Karimi, Yezina T. Nigatu, Nand K. Wadhwa. Nephrology/Medicine, Stony Brook Medicine, Stony Brook, NY.

Introduction: Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory disorder with paradoxical worsening of preexisting infections following HAART in HIV-infected individuals. We describe a case of IRIS following Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir) resulting in hypercalcemia.

Case Discussion: A 33 year-old woman with acquired immunodeficiency syndrome (AIDS) who had been on Stridhild for two months presented to the ED with acute kidney injury with a serum creatinine of 2.93 mg/dL and Ca of 15.2 mg/dL. Her CD4 count was 145 u/L and viral load 35 copies/mL. Four months prior, she was treated with amphotericin for cryptococcal lung infection and Cryptococcemia. One month prior, a right lower lobe metastasis was found and surgical resection of the tumor was done. A wedge kidney biopsy showed thrombotic microangiopathy. A CAT scan showed left adrenal mass. Plasma normetanephrine was elevated at 1223 pg/ml suggestive of pheochromocytoma. BP was stabilized with four drugs and surgical resection of the tumor was done. A wedge kidney biopsy showed thrombotic microangiopathy (TMA). The tumor histopathology confirmed pheochromocytoma, positive for chromogranin and synaptophysin staining. Post operative, her creatinine stabilized at 1.6 mg/dL, BP and glucocorticoid status returned to normal.

Discussion: Discussion: Pheochromocytoma in pregnancy is an extreme rarity with a frequency of 0.002%. It is often mistaken for other hypertensive disorders of pregnancy. This is the first case report of a patient with acute kidney injury in pregnancy from TMA secondary to pheochromocytoma. Patient made good renal recovery after resection of the tumor.
Discussion: IRIS is thought to be due to increased T-lymphocyte proliferation after HAART in AIDs patients. IRIS typically manifests as a granulomatous inflammation. Corticosteroids are treatment of choice in IRIS in the setting of excess 1.25 (OH)3. D3 was low suggesting possible other mechanisms.

TH-POI117
IgA-Dominant Postinfectious Glomerulonephritis: A Case Series
Pranjal Sharma,1 Anitha Vijayan,2 Tingting Li.2
1Dept of Internal Medicine, Renal Div, Washington Univ in St. Louis, St. Louis, MO; 2Dept of Internal Medicine, Renal Div, Washington Univ in St. Louis, St. Louis, MO.

Introduction: IgA dominant post-infectious glomerulonephritis (PIGN) is a distinct clinicopathologic entity that typically occurs in diabetic patients and in association with a recent or active staphylococcal infection. Patients usually present with hematuria, proteinuria, and ACR. Renal pathology shows an immune complex glomerulonephritis with various light microscopic patterns and IgA-dominance or co-dominance with IgG on immunofluorescence. Here we report the clinical characteristics and outcomes of 10 patients with IgA dominant PIGN.

Case Description: After obtaining approval from the local IRB, retrospective, single-center review of data was performed and 10 patients with IgA dominant PIGN were identified.

Majority was white males, and 6/10 were diabetic. Eight patients had a Staphylococcal infection and one had active Hep C infection. Only 3/10 had low complements, 6/10 required RRT and 4 developed ESRD, of which 2 died at 2 and 5 months after initiation of RRT. Five were left with varying degree of CKD and one was lost to follow up. Three patients were treated with immunosuppression in addition to antibiotics-all had significant improvement in renal function; one patient who was initially RRT-dependent was able to come off dialysis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infection</th>
<th>Hema-</th>
<th>Proteinuria</th>
<th>Peak S</th>
<th>Cr</th>
<th>RRT</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hep C</td>
<td>N/N</td>
<td>Y</td>
<td>7.5</td>
<td>1.6</td>
<td>No</td>
<td>CKD</td>
</tr>
<tr>
<td>2</td>
<td>MSSA</td>
<td>L/L</td>
<td>Y</td>
<td>0.6</td>
<td>6.9</td>
<td>Y</td>
<td>CKD</td>
</tr>
<tr>
<td>3</td>
<td>MRSA/Pseu-</td>
<td>N/N</td>
<td>Y</td>
<td>1.16</td>
<td>1.9</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>MSSA</td>
<td>N/N</td>
<td>Y</td>
<td>6.5</td>
<td>5</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>MRSA</td>
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<td>Y</td>
<td>3.7</td>
<td>10.9</td>
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</tr>
<tr>
<td>6</td>
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<tr>
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<td>MRSA/RE</td>
<td>N/N</td>
<td>Y</td>
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<td>Y</td>
<td>ESRD</td>
</tr>
<tr>
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<td>N/N</td>
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<td>6.5</td>
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<td>Died</td>
</tr>
<tr>
<td>9</td>
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<td>3.9</td>
<td>No</td>
<td>CKD</td>
</tr>
<tr>
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<td>Y</td>
<td>2.8</td>
<td>5.2</td>
<td>No</td>
<td>CKD</td>
</tr>
</tbody>
</table>

N=Normal; L=Low; Y=Yes

Table 1. Clinical features and outcomes of pts with IgA-dominant PIGN

Discussion: IgA-dominant PIGN is an increasingly recognized disorder that occurs most commonly in diabetic patients with Staphylococcal infections. Overall renal prognosis is poor. Treatment with immunosuppression in addition to antibiotics may be considered.

TH-POI118
Hematuria in a Young Female: This Was a Hard Nut to Crack

Introduction: Flank pain with hematuria usually indicates urolithiasis but in its absence, renal vascular abnormalities should be considered.

Case Description: A 27-year old female with history of sickle cell trait, was admitted for hematuria. She had flank pain at the end of her urine stream but did not associate fever, chills or dysuria. She was treated with ciprofloxacine for presumed UTI but due to weakness she presented to our hospital. Her vital signs were stable and had a normal physical examination. Her hemoglobin was 8.1 g/dL and creatinine was 1.5 mg/dL with urine microscopy evident for 3 plus proteinuria with >25 RBC/hpf and >50WBC/hpf. Her total protein to creatinine ratio was 2 and had a negative urine culture. She had normal complement, ANA screen and negative serology work up for autoimmune disease. Renal ultrasound (US) showed 10 cm (right) X 9.5 cm (left) kidneys. Her non-contrast CT abdomen and cystoscopy was non-diagnostic. To further evaluate her hematuria she underwent renal US with Doppler which showed narrowing of the left renal vein at the level of the superior mesenteric artery (SMA) with a peak velocity gradient greater than 10:1, consistent with left renal vein compression and a “water- cather” syndrome (NCS). She subsequently underwent exploratory laparotomy with evidence of aortic and SMA scalping compression of renal vein at its confluence with inferior vena cava (IVC). The IVC and left renal vein were explored and evidence of aortic and SMA scissoring compression of renal vein was noted. The usual course of treatment for NCS is hemodialysis (HD), 5 sessions of HD was performed with improvement of 39% in Cr. However, patient’s anti-GBM titer was negative! Electron microscopy showed thickening of GBM and no T cell aberrancy or B cell monoclonality. A kidney biopsy revealed pauci-immune necrotizing CGN. Electron microscopy (EM) showed no deposits or fibrillary or tubular structures in the glomeruli. The patient was treated with hemodialysis (HD), 5 sessions of plasmapheresis and oral cyclophosphamide for 3 months. He responded to treatment with near complete resolution of his symptoms and near normalization of kidney function.

Discussion: Pauci-immune CGN is associated with either microscopic polyangiitis or granulomatosis with polyangiitis. These can present as RPGN and have either a positive MPO or PR3 ANCA but have no deposits on immunofluorescence and EM. CGn in particular is a disease with distinct immune pathogenesis, has distinct immune deposits in glomerular capillaries and fibrillary and tubular structures on EM. Our case was an unusual combination of 2 different pathologically and pathogenically distinct disease entities. To our knowledge this is the first reported case with these unusual manifestations.

TH-POI119
Fibrillar Glomerulonephritis Presenting as Rapidly Progressive Crescentic Glomerulonephritis
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1Dept of Nephrology, Veterans Affairs Medical Center, Shreveport, LA; 2Dept of Nephrology, LSU School of Medicine, Shreveport, LA.

Introduction: Fibrillar glomerulonephritis is a rare disease of unclear etiology, known to be associated with malignancy, autoimmune disorders, lymphoplasmacytic disorders and hepatitis C. It is seen in 0.5 to 1.0% of native kidney biopsies.

Case Description: We report a case of a 62 year old Caucasian male veteran who had a past medical history of hepatitis C, hyperlipidemia, s/c coronary bypass, multiple colon polyps with colectomy and CKD stage 3. Patient, on a routine follow up appointment, was noted to have rapid worsening of kidney function, with creatinine increase from baseline of 1.4-1.8 up to 3.2 mg/dL. He was also noted to have 24 RBCs per HPF on urine microscopy. Urine protein:creatinine ratio was 4.5. Hepatitis C related membranous glomerulonephritis (GN) was high on the differential list. Hepatitis B and HIV serologies were negative. Complement and cryoglobulins, ANCA and serum protein electrophoresis were all within normal limits. Patient underwent kidney biopsy, which showed crescentic GN, with linear pattern immunoglobulin deposition along the GBM (glomerular basement membrane) on light microscopy and immunofluorescence suggestive of anti-GM disease. However, patient’s anti-GM titer was negative! Electron microscopy showed thickening of GBM due to fibrillary deposits. Similar fibrillary deposits were also seen in the mesangium, with haphazard distribution of fibrils measuring about 15 mm, consistent with fibrillar GN. Congo red stain for amyloid was negative. Patient was also found to have a 2.8 x 2.5 cm well- circumscribed solid & cystic mass in right kidney on ultrasound, suspicious for renal cell carcinoma (RCC). A fine needle aspiration of the mass yielded cells consistent with RCC.

Discussion: Fibrillar GN is known to be associated with malignancy. It can rarely present clinically as rapidly progressive, crescentic GN, and masquerade as anti-GM disease on immunofluorescence. Electron microscopy and serologic workup are needed to clinch the definitive diagnosis.

TH-POI121
Paucci-Immune Necrotizing Crescentic Glomerulonephritis as the First Manifestation of Chronic Lymphocytic Leukemia Relapse
J Saadi Imam,1 Monia E. Werlang,1 Tatiana A. Thorn,2 Nabeel Aslam.1
1Dept of Medicine, Division of Internal Medicine, Mayo Clinic, Jacksonville, FL; 2Dept of Medicine, Div of Nephrology, Mayo Clinic, Jacksonville, FL.

Introduction: The association between hematological malignancy and auto-immune disease is a well-documented phenomenon. Chronic lymphocytic leukemia (CLL) patients have 5-10% risk of developing autoimmune cytopenias, and a rare subset of these CLL patients have autoimmune complexes antibodies (ANA, anti-GBM) with the setting of vasculitis. Here, we present a case of a patient with treated CLL whose relapse was identified by the new diagnosis of ANCA-associated paucci-immune glomerulonephritis.

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

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This was an unexpected learning case that shows that the occurrence of diabetic nephropathy may correlate more with presence and not the intensity or duration of hyperglycemia. Further studies are needed to elucidate this phenomenon.

TH-PO1124
Case of Catastrophic Antiphospholipid Syndrome Treated with Plasma Exchange
Takeyuki Takamura, Tetsuhiro Furuya, Tetsuharu Oku, Kenichiro Kitamura. Third Dept of Internal Medicine, Univ of Yamashita.

Introduction: Catastrophic antiphospholipid syndrome (CAPS) is characterized by diffuse vascular thrombosis, leading to multiple organ failure within a few days and resulting to poor prognosis. Antiphospholipid syndrome (APS) is an autoimmune thrombotic syndrome with recurrent thrombosis and occurs in both artery and vein, and from large to micro vessels. CAPS is also defined as a fetal variant of APS and develop thrombosis of three different organ systems with histopathologic evidence of multiple small vessel occlusions and high titters of antiphospholipid antibodies. Treatment for CAPS has not been established, and intensive anticoagulation or immunosuppressive therapy is carried out.

Case Description: A 68-year-old female who had been diagnosed as lupus erythematosus and APS complicated with multiple cerebral infarctions and treated with 5 mg of oral prednisolone. After her admission, she developed de novo cerebral infarction and colonic perforation with ischemic enteritis. Following a partial colectomy, she developed gram-negative bacteremia, subsequently, multiple strokes, non-ST elevation myocardial infarction, renal failure, and pathological findings with multiple thrombi. These clinical findings indicated that patient’s features were consistent with CAPS. She was maintained with anti-bacterial agent, anticoagulant, and prednisolone. However, since renal failure and anuria had continued, she was treated with plasma exchange (PE) and hemodialysis. Thereafter the volume of urine output was gradually increased and her renal function was recovered.

Discussion: We report a case of CAPS with multiple organ failure and successfully treated with anticoagulant, prednisolone, and PE. The clinical manifestation of CAPS depends on the release of inflammatory cytokines from the affected organs by thrombosis and small vessel occlusion. Our patient’s successful course could be attributed to beneficial role of PE through the removal of excessive inflammatory cytokines.

TH-PO1125
Acute HIV in a HIV-Naïve Patient During Primary HIV Infection and High Viral Load
Amit Durr.

Introduction: A hitherto healthy 42 yo AA male felt chilly 6 days earlier. He took a NyQuil and skipped next day’s shift for body aches/GI cramps. He improved but again felt bad by HS, 48h later. Next AM in a local ER, his UA showed WBC/RBC, 3+ protein, and a SG of 1.030. Physical exam, chest X-ray, contrast abdominal CT, and eGFR, were normal. His HIV panel worked full capacity again, but got admit 48h later after a brief syncopy.

Case Description: Viral signs: T 103°F, BP 100/60 mm Hg, and HR 76 bpm. He had transient mild diastolic. Serum albumin (A1b) was 2.1 g/dl, creatinine (cr) 2 mg/dl, and WBC 103/ml. UA had WBC/RBC and <0.5 g/dl protein. UA was 21 mmol/L. His urine protein was <12 g/24h. CRP was <2 (<0.5 mg/dl), and ESR 50 mm/h. CRP was 8717 U/l and h笔者 = 48h. He BCP, and HIV-1/2 Ab screens were (-), but the HIV-2A4 gen. He had >3>106 HIV copies/ml, and 213 CD4+ cells/ml. US showed normal-sized kidneys, no obstruction, but some cortical echogenicity. His HIF first proved for 72h, but then rose to 8 mg/dl in 1w. Dialysis and HAART were initiated. By then he had edema and A1b was 1.2 g/dl. Renal biopsy showed collapsing GN, podocyte hypertrophy/hyperplasia, microcystic tubular dilations, 3+ acute tubular injury, 2+ patchy (mostly lymphocytic) infiltration with focal tubulitis, and no signs of chronicity. Prednisone was added. He seroconverted (HIV-1) 2w after his first chills.

Discussion: Of the case reports of primary renal HIV infection only 2 had biopsy-proven HIV. One was HIV Ab (+) but was EIA but not by Western blot, and had 700,000 HIV copies/ml (Szabo S et al. 2002). The other was HIV Ab (+) by EIA but not by Western blot, and had 70,000 HIV copies/ml (Szabo S et al. 2002). Both had advanced RF and already other infections. Our patient had normal eGFR until his acute HIV infection. The high HIV load alone, not replication, is the sole likely cause for HIV, consistent with the view that a direct toxic effect of the HIV gene product on podocyte dedifferentiation, since viral particle endocytosis readily occurs in podocytes (as their normal filter cleaning role?), but lack of HIV entry receptors precludes local replication (Khatua AK et al. 2010).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
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356A
FR-PO001
A Case of Hypercalciemia with Renal Failure: Renal Sarcoid?

Introduction: Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by noncaseating granulomas in involved organs. Renal involvement occurs in 35-50%, manifested by hypercalciuria, hypercalcinosis, and nephrolithiasis. Granulomatous interstitial nephritis is the most typical histological finding, usually in the setting of systemic disease and rarely in the absence of extrarenal sarcoid.

Case Description: A 54 y/o male presented with AKI superimposed on CKD and severe hypercalciuria (Calcium 13.5 mg/dL, Creatinine 2.8 mg/dL). Six months prior he had a kidney stone removed at which time his creatinine was 2.4 mg/dL with Ca=1.7 mmol/L but no further work up was performed. He was taking no medications and complained of back pain. Physical exam was unremarkable. A CT scan was negative for nephrolithiasis but no further work up was performed. He was aggressively treated with IV NS and then Lasix with minimal improvement in the creatinine or the serum calcium. Work up for hypercalciuria included normal serum and urine immunofixation, negative PPD, normal PSA and normal skeletal survey. 25 Hydroxyvitamin D 27.8 ng/ml (30-95 ng/mL), PTH suppressed at <3 pg/ml, total 1, 25 HydroxyVitamin D 79 pg/ml (18-72 pg/ml), Angiotensin Converting enzyme 82 (9-77 U/L). A formal ophthalmologic exam and PFTs were normal. A diagnostic kidney biopsy was performed.

Discussion: The diagnosis of sarcoid interstitial nephritis was strongly suggested by the renal biopsy given that other causes of granulomatous were ruled out. The patient was started on prednisone 60mg/d with rapid resolution of the hypercalciemia and slow improvement in renal function (Creatinine 2.9 mg/dL). A slow steroid taper over 1 year is planned.

FR-PO002
Pediatric Chronic Refractory SIADH: Use of Tolvaptan
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Introduction: The syndrome of inappropriate antidiuretic hormone (SIADH) is the most common cause of euvoletic hyponatremia in hospitalized patients, and standard therapies can be limited in their effectiveness. Arginine vasopressin receptor antagonists (AVR-A) oral tolvaptan and intravenous conivaptan have been FDA approved in adults, but reports on long-term use in pediatrics are lacking. We report on the dosing and safety of chronic AVR-A treatment in two patients with chronic SIADH. Dosing regimen was extrapolated from current pediatric and adult literature.

Case Description: Case A is a 13 year old, 43.5 kg female with a 12-year history of chronic A VR-A treatment in two patients with chronic SIADH. Dosing regimen was extrapolated from current pediatric and adult literature.

Initial treatment included fluid boluses with NS, bicarbonate drip and broad-spectrum antibiotics for suspected sepsis. Further history revealed that patient had MMA and then IV fluid was changed to D20NS with insulin drip. He was started on special formula feed for MMA. Daily peritoneal dialysis was continued. Serum ammonium, β-hydroxybutyrate and lipase levels were normal. Blood and stool cultures grew salmonella enteritidis and antibiotics were switched to iv ciprofloxacin and metronidazole. With assistance from metabolic specialist, nephrologist and endocrinologist, patient was treated successfully.

Discussion: MMA is a rare autosomal recessive disorder (incidence of 1:48,000), caused by deficiency of methylmalonyl-CoA mutase or its cofactor, cobalamin. It is associated with anion gap metabolic acidosis, hypoglycemia, ketonuria and hyperammonemia. Metabolic decompensation can occur during episodes of increased catabolism such as prolonged fasting. Treatment of acute illness includes, providing hydration with high caloric supplementation, stopping all protein intake for 1-2 days and reintroduction of a low protein diet later. Severe acidosis may require dialysis.

FR-PO003
Methylmalonic Acidemia: An Unexpected Consult for an Adult Nephrologist: A Case Report
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Introduction: Organic acidemia are caused by deficiencies of enzymes involved in the breakdown pathways of amino acids, fatty acids and carbohydrate metabolism. Methylmalonic academia (MMA) is a heterogeneous group of disorders of impaired metabolism of methylmalonic acid. We present a patient with MMA who was admitted with severe metabolic acidosis.

Case Description: A 21 year old male with past medical history of end stage renal disease on peritoneal dialysis, chronic pancreatitis, diabetes mellitus and coeliac disease presented to emergency room with diarrhea. He denied fever, abdominal pain and vomiting. He was hypotensive. Laboratory tests showed metabolic acidosis with anion gap of 33 mMol/L and absence of leukocytosis. Arterial blood gas result was pH:7.38, pCO2: 18 mmHg, paO2: 108 mmHg and HCO3: 10 mMol/L. Patient was kept NPO and acidosis worsened the next day.

Discussion: MMA is a rare autosomal recessive disorder (incidence of 1:48,000), caused by deficiency of methylmalonyl-CoA mutase or its cofactor, cobalamin. It is associated with anion gap metabolic acidosis, hypoglycemia, ketonuria and hyperammonemia. Metabolic decompensation can occur during episodes of increased catabolism such as prolonged fasting. Treatment of acute illness includes, providing hydration with high caloric supplementation, stopping all protein intake for 1-2 days and reintroduction of a low protein diet later. Severe acidosis may require dialysis.

FR-PO004
Congenital Pituitary Stalk Interruption Syndrome (PSIS) Newly Diagnosed in Case of Hyponatraemia in the Elderly.
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Introduction: There are many diseases that cause hyponatraemia. Among them, adenohypophysis (AI) is important due to its urgency. We present an extremely rare case of elderly-onset AI in congenital PSIS, which is highly suggestive of the mechanism of AI progression.

Case Description: A hyponatremic episode (Na 117 mEq/L) occurred in a 76 year-old Japanese man in conjunction with common cold. Laboratory analyses revealed a low serum cortisol level. He was short-statured, had no hair growth on his axilla and pubis, and had unusual pale pigmentation in skin. He presented with gynecostasia and microopenis. CT scan revealed anorchism. He was not mentally retarded. Serum hormonal analyses showed AI, hypothyroidism, growth hormone deficiency, hypogonadism and hyperprolactinemia. Set of CTH/TRH/GRH/LHRH stimulation test disclosed hypothalamic panhypopituitaryism. Brain MRI visualized severely pressured 2-mm thick pituitary, but not the pituitary stalk, indicating PSIS.

Discussion: We concluded that his PSIS was not an acquired but a congenital anomaly based on his episode of intrathecal growth retardation and anorchism in the light of embryology. In PSIS patients, the functions of pituitary are sometimes maintained even if partially, although hypophyseal portal vessel snaps apart. This is because hypothalamic hypopituitarism occurs through the superior hypophyseal artery (SIIA), the nutrient artery of both hypothalamus and pituitary. In this case, the echogram of the internal carotid artery, from which SHA branches showed severe atherosclerosis. We speculate that the progression of atherosclerotic changes impaired the blood flow of SHA and then decreased the conversion of LH and FSH into anterior pituitary hormones. This transformation could be additionally supported by the prolonged fasting. Treatment of acute illness includes, providing hydration with high caloric supplementation, stopping all protein intake for 1-2 days and reintroduction of a low protein diet later. Severe acidosis may require dialysis.

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FR-PO005

A Family Case of Hyopparathyroidism, Deafness, and Renal Dysplasia Syndrome with a Novel Mutation of GATA3
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Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT), a major cause of end-stage renal disease in children, often present as a systemic disorder with extrarenal symptoms. Extrarenal symptoms and family history are helpful in the genetic diagnosis of CAKUT. We report here a family case of hypoparathyroidism, deafness, and renal dysplasia syndrome (HRD) with a novel mutation of GATA3.

Case Description: Soon after birth, a female patient was diagnosed as having bilateral cystic dysplastic kidneys by renal ultrasonography. She also had hearing impairment at the infancy. She received peritoneal dialysis at the age of 3 years and received a cadaveric kidney transplant at the age of 10 years. When she was 14 years old, she visited the emergency department because of acute abdomen. Detailed examinations showed hypertelorism associated with vaginal atresia. Branchio-oto-renal syndrome was considered as her diagnosis based on her hearing impairment, bilateral cystic dysplastic kidneys, and normalcalcemia. However, we suspected that she had an HRD syndrome because we found that her mother had hypoparathyroidism after determining a detailed family history. Genetic analysis was approved by the central ethics board of Tokyo Women’s Medical University and Kobe University. This analysis showed a novel mutation, c. 1013G>T (C338F) of GATA3, the causative gene for HRD syndrome.

Discussion: Our patient did not show any symptoms of hypoparathyroidism. However, based on the family history, we performed a genetic analysis and found a novel mutation of GATA3. She was then diagnosed with atypical HRD syndrome. Therefore, determining a detailed family history is important in the precise diagnosis of CAKUT patients.

FR-PO006

Hypocomplementemic Urticarial Vasculitis Syndrome Resistant to Corticosteroid and Plasma Exchange Therapy
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Introduction: We present a case of HUVS resistant to corticosteroid and plasma exchange.

Case Description: A 36-year-old Japanese man with the history of diffuse panbronchitis, eczema, cutaneous vasculitis, and kidney dysfunction. Percutaneous kidney biopsy was performed at the hospital, and the diagnosis was non-IgA mesangial proliferative glomerulonephritis. In spite of the administration of angiotensin II receptor blocker, progressive kidney dysfuction was evident. Then he was transferred to our hospital 4 months later. He also had a history of urticarial rash on his leg and pigmentation was evident at the time of transfer. Urticular rash revealed 3+ proteinuria and 3+ hematuria, and urinary sediment showed red blood cells of 50-99/high power field. Urinary protein/creatinine (Cr) ratio was 2.9 g/gCr. Blood tests revealed a serum Cr level of 2.4 mg/dL, complement (C) 3 level 18 mg/dL, and C4 level 23 mg/dL. We performed kidney biopsy again, and found membranoproliferative glomerulonephritis with crescents. Since additional blood test revealed serum anti-C1q antibodies of 51,965 U/mL, the diagnosis of HUVS was made. We treated him with methylprednisolone pulse therapy followed by oral prednisolone, but his kidney function was unchanged and he developed bacterial pyelonephritis. Next, we added plasma exchange and a temporary decrease in proteinuria accompanied by a decrease of serum anti-C1q antibody level. But his kidney function did not recover, and the level of anti-C1q antibody raised again.

Discussion: HUVS is a systemic vasculitis with urticarial rash, hypocomplementemia, and anti-C1q antibodies. Effective and specific treatment for HUVS has not been established. Although corticosteroid and plasma exchange showed temporal efficacy, it was impossible to suppress the progressive kidney dysfunction in this case.

FR-PO007

Acquired Fanconi Syndrome in a Patient with Acetaminophen Overdose
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Introduction: Acquired Fanconi syndrome is described in patients receiving antiretrovirals, aminoglycosides, platinum compounds and with proximal tubulopathies due to light chain disease/paraproteinemias. We describe a case of acetaminophen induced acute tubular necrosis (ATN) presenting as Fanconi syndrome with hypophosphatemia, normoglycemic-glucosuria, aminoaciduria, and uric acid, potassium and bicarbonate wasting.

Case Description: A 35 year old woman with borderline personality disorder, depression, alcohol abuse, multiple suicide attempts, and previous acetaminophen overdose was transferred from outside hospital with fulminant hepatic failure secondary to acetaminophen poisoning. Nephrology was consulted for metabolic acidosis and AKI. On exam she was oriented to person only and following minimal commands. She had acute fulminant hepatic failure as evidenced by transaminase elevations, encephalopathy, and coagulopathy. On presentation her serum creatinine was 2.95 which rose over the next 3 days to 9.06. Initial blood gas was consistent with metabolic acidosis and respiratory compensation. Serum potassium (K) was low (2.9-3.5) despite large doses of K supplements. Her K requirements abated when bicarbonate supplementation was discontinued. Acetaminophen level was elevated on transfer at 21 and urine drug screen was positive for opiates and benzodiazepines; toxic alcohols were negative. Serum uric acid was <1.5 mg/dL and phosphorus <1 mg/dL. Glucose was 1-2+ on urinalysis with normal blood glucose. The following amino acids were elevated in her urine: aspartic acid, beta alanine, citrulline, gamma amino acid butyric acid, glutamic acid, leucine, ornithine, proline, taurine and valine. This was a non-specific pattern of generalized aminoaciduria consistent with proximal tubulopathy and acquired Fanconi syndrome. The patient subsequently recovered renal function and the proximal tubulopathy resolved.

Discussion: It is common for nephrologists to be aware that ATN (in this case acetaminophen induced) can lead to acquired Fanconi syndrome and proximal tubulopathy which seem to resolve as ATN resolves. Aggressive treatment with bicarbonate supplements can exacerbate urinary K wasting and should be avoided.

FR-PO008

Spontaneous Remission of Non-Parasitic Chyluria
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Introduction: Chyluria is a medical condition characterized by the presence of chyle in the urine. The disease is most prevalent in South East Asian countries mostly caused by parasitic (Wuchereria bancrofti) infections. Chyluria presents as a cloudy milk-colored urine accompanied by systemic symptoms such as weight loss, fatigue, and rarely, flank pain from retained clots.

Case Description: A 72 year-old woman presented to Nephrology clinic complaining of milky urine (Figure 1) and painless hematuria with clots for two months as well as twenty-pound weight loss. Physical exam was unremarkable. Cystoscopy and urine cytology were unremarkable. Serum albumin was 3.2 g/dL. A urinalysis showed 3+ protein and 50 red blood cells per HPF. Urine sediment had no dysmorphic cells or casts. A 24-hour urine collection revealed 8.8 grams of protein. Chyluria screen was positive for chylomicrons and triglycerides. Midnight blood smears were negative for filarial parasites. Urine culture was negative for mycobacteria or schistosomas. Serologic studies including IgG western blot for cisticercus and IgG ELISA for filariasis were negative. The rapid plasma reagin (RPR) was also negative. Imaging for a lymphatic leak by lymphocintigraphy was unrevealing. The patient was managed conservatively and underwent spontaneous remission with disappearance of chyluria several months of her initial diagnosis.

Discussion: The most common cause of chyluria is parasitic infection with granulomatous diseases or structural etiologies less frequently encountered. Sclerotherapy of the renal pelvis is the definitive treatment. Idiopathic chyluria as shown in this case is rare. Conservative management of idiopathic disease may be warranted due to the possibility of spontaneous remission.

FR-PO009

Rebound Hypertension and Hypokalemia After Stopping Drospherenone
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Introduction: Drospheronone is the fourth generation oral contraceptive with antimineralocorticoid effects, which are reported to be generally mild. There have been several warnings issued for drospheronone, in relation to adrenal insufficiency and hyperkalemia. But, no reports thus far of the rebound effects like hypertension (HTN) and
hypokalemia, following the discontinuation of the medication, especially after prolonged use. Re-introduction of low dose spironolactone and screening for other causes of nephrotic syndrome was also recommended. For more information, see the reference.

**Case Description:** A 54-year-old Indian woman, previously normotensive, noted severe proteinuria of 3.1 g/day on presentation to the emergency department, where she was also noted to have mild hypokalemia of 3.1 mmol/L. Given the rather new onset of severe HTN and hypokalemia, work-up for secondary causes of HTN was done, which revealed normal aldosterone level (9 ng/dL), low plasma renin activity (PRA) (0.15 ng/mL/hr) and high aldosterone/PRA ratio (60). Looking back into her history, it was noted that the timing of symptoms was closely related to discontinuing Yasmin® (Ovral®) due to elevated estradiol and 3 mg drospirenone), which she was taking for over 6 yrs. She was thought to have rebound effect with relatively excess mineralocorticoid activity, precipitated by the abrupt discontinuation of drospirenone. With the introduction of low dose spironolactone, her symptoms significantly improved.

**Discussion:** Drospirenone (an analogue of spironolactone), which has antimineralocorticoid and antiandrogenic activities similar to endogenous progesterone, counteracts the estrogen-mediated stimulation of the renin-angiotensin-aldosterone system (RAAS). Due to these effects, it has the potential to decrease blood pressure and also cause hyperkalemia. At a dosage that suppresses ovulation, drospirenone induces mild natriuresis, which is followed by compensatory stimulation of the RAAS (comparable to a low sodium diet). When the prolonged ongoing suppression for the RAAS is removed, there might be a potential rebound effect with (relatively) high aldosterone state, resulting in sodium retention, leading to HTN. Spironolactone appears to be useful in this situation.

FR-PO010

**Acthar Induced Hypokalemic Metabolic Alkalosis**

**Inman Qayyum,** Neil W. Lyman. Dept of Nephrology, St. Barnabas Medical Center, Livingston, NJ.

**Introduction:** Acthar, an ACTH formulation from porcine pituitary gland, is an effective therapy for Membranoproliferative Glomerulonephritis (MGN). A rare adverse effect of hypokalemic alkalosis was observed in our patient. We present a report of an 84 y/o Caucasian female who developed severe hypokalemia and metabolic alkalosis with Acthar therapy, and concomitant diuretic use.

**Case Description:** The patient presented with severe bilateral leg edema. Lower extremity doppler was negative for DVT. Echo revealed normal EF. UA showed 4+ protein, 3+ red blood cells and trace proteinuria. She was started on a regimen of Acthar 80 units 2x/week. 35 days later, she was readmitted for worsening renal function and proteinuria. Serum creatinine was 1.99 mg/dL (baseline 1.34 mg/dL). Albumin was 2.3 g/dL. Workup for malignancy and concomitant diuretic use.

**Discussion:** Despite the presence of normal factor H and I levels, treatment with Eculizumab is effective for complement mutation. Our patient had a homozygous deletion of CFIHR3-CFIHR1, which has previously been linked to aHUS. CFIHR3-CFIHR1-deficient plasma is thought to contribute to defective regulation of complement activation on the cell surface and occurs despite the presence of normal factor H and I levels. Treatment with Eculizumab is effective and should be started promptly as disease can be halted and chronic damage limited.

FR-PO001

**Polycthemia in a Patient with Bartter’s Syndrome and Medullary Nephrocalcinosis**

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**Introduction:** Bartter’s syndrome is a tubular salt wasting disorder presenting with severe hypokalemic alkalosis, hyperkalemia, and hyperparathyroidism with normal blood pressure. Medullary nephrocalcinosis in this disorder is an infrequent finding and is usually unrecognised. Polycythemia is an unusual presentation in patients with renal diseases, but has been described in literature among patients with nephrotic syndrome and distal tubular acidosis. It is noteworthy, however, that reports on secondary erythrocytosis among patients with Bartter’s syndrome is lacking. The exact mechanism for the polycythemia is unclear, although erythropoietin levels include hypoxia-induced nephrocalcinosis causes stimulation of oxygen receptors thus increasing erythropoietin secretion, and stimulation of prostaglandin production may be contributory.

**Case Description:** A 27 year-old Filipino male with recurrent bouts of severe hypokalemic alkalosis since childhood presenting as bilateral lower extremity weakness necessitating recurrent hospital admissions was diagnosed with Bartter’s syndrome based on metabolic alkalosis, hypokalemia, hyperkalemia, slight hyponatremia with normal serum calcium and magnesium levels. He had normal blood pressure and no frank hypercalcuria. His creatinine was elevated and his ultrasound revealed normal sized kidneys with bilateral nephrocalcinosis. He had elevated hemoglobin of 190 g/L, slight leukocytosis with no thrombocytosis. JAK2 mutation was negative and a bone marrow biopsy revealed mildly hypercellular marrow with trilineage hematopoiesis, hematopoiesis for which polycythemia was ruled out. Findings were consistent with a reactive marrow. He underwent as needed phlebotomy and was maintained on potassium replacement, spironolactone and an ace-inhibitor.

**Discussion:** Polycythemia in a patient with Bartter’s syndrome and medullary calcinosis is a rare entity with very limited data in literature. The mechanism leading to secondary erythrocytosis, as well as nephrocalcinosis among patients with Bartter’s syndrome remains uncertain. Clinicians should be aware of potential complications of this disorder so as to institute appropriate management.

FR-PO002

**Homoeozygous Deletion of CFIHR3-CFIHR1 as a Cause for Atypical Hemolytic Uremic Syndrome in a Patient with Systemic Lupus Erythematosus**

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**Introduction:** Thrombotic microangiopathy (TMA) is a rare but devastating condition associated with systemic lupus erythematosus (SLE). In SLE, renal TMA is typically associated with the anti-phospholipid syndrome (APS) or TTP. Here we report a case of atypical hemolytic uremic syndrome (aHUS) associated with SLE that was confirmed by complement genetic studies and treated successfully with Eculizumab.

**Case Description:** A 21 year old African American female with a history of SLE and class II-V lupus nephritis was hospitalized after presenting with AKI, thrombocytopenia (TCP), and a microangiopathic hemolytic anemia (MAHA). Initial lab values revealed a serum creatinine of 3.5 mg/dL, platelet count of 58, hemoglobin of 7.3, and LDH of 1484. Plasmapheresis and IV soludemol was started empirically for presumed TTP and SLE flare. ADAMTS13 enzyme activity was normal and APS antibodies were negative. There was no improvement and the patient was started on dialysis. The patient required multiple blood transfusions as TCP and MAHA persisted. A kidney biopsy was performed and findings were consistent with severe TMA. The patient was empirically started on Eculizumab and after the first dose, TCP improved rapidly, with a platelet counts increase from 27% to 170K. Complement mutation studies were obtained and revealed a homoeozygous deletion of CFIHR3-CFIHR1 genes. The patient continued on Eculizumab, and after 4 months she recovered renal function and was liberated from dialysis.

**Discussion:** This is the first report of aHUS associated with SLE in a patient with an identified complement mutation. Our patient had a homoeozygous deletion of CFIHR3-CFIHR1, which has previously been linked to aHUS. CFIHR3-CFIHR1-deficient plasma is thought to contribute to defective regulation of complement activation on the cell surface and occurs despite the presence of normal factor H and I levels. Treatment with Eculizumab is effective and should be started promptly as disease can be halted and chronic damage limited.

FR-PO013

**A Novel Mutation in KLHL3 Gene Causes Familial Hyperkalemic Hypertension**

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**Introduction:** Familial hyperkalemic hypertension is an autosomal dominant disorder where mutations in the thiазide-sensitive NaCl co-transporter (NCC) cause salt-dependent hypertension. Implicated genes include WNK1, WNK4, KHL3 and CUL3. These lead to increased activity of the NCC in the distal nephron, excessive chloride and sodium reabsorption, and volume expansion. We describe a disease causing variant in KLHL3 not previously reported in the literature.

**Case Description:** An 18 year-old man with no prior medical history presented with an incidental finding of serum potassium of 7.3mmol/L. He was hypertensive with blood pressure 150/90mmHg. His mother, maternal uncle and grandmother also had a history of early onset hypertension and unexplained hyperkalemia.

**Discussion:** His labs showed serum sodium 139mMol/L, chloride 103mMol/L, creatinine 83mMol/L. His arterial blood pH was 7.37 with bicarbonate 21. Plasma renin activity was suppressed at 0.2ng/ml/H and his serum aldosterone was raised at 534.4pmol/L. The last 24-hour urinary sodium reabsorption, leading to HTN. Spironolactone appears to be useful in this situation.

**Discussion:** The association of Bartter’s syndrome with medullary calcinosis and secondary erythrocytosis is a rare entity with very limited data in literature. The mechanism leading to secondary erythrocytosis, as well as nephrocalcinosis among patients with Bartter’s syndrome remains uncertain. Clinicians should be aware of potential complications of this disorder so as to institute appropriate management.
FR-PO014
Renal Failure Run A-FUowl: Disseminated Histoplasmosis  Eileen Smith, Rajeev Raghavan, Sreedhar A. Mandayam. Baylor College of Medicine, Houston, TX.

Introduction: In patients with fever of unknown origin (FUO) and glomerulonephritis, Histoplasma capsulatum should be considered.

Case Description: A 37-year-old man presented to the hospital with 3 weeks of fatigue, 15-pound weight loss, intermittent chest pain, dyspnea on exertion and 3 day history of erythematous pruritic rash on his neck. PMH included congenital aortic stenosis with AVR, complicated by endocarditis requiring repeat AVR. Physical exam found splenomegaly and a lacy erythematous rash on the neck and torso. On admission, creatinine was 3.15 mg/dL (baseline 1.17, last year) with gross hematuria, and new pancytopenia. Initial work-up for glomerular disease was non-diagnostic. He developed persistent cyclical fevers to 102°F during his hospital stay. Blood cultures, tagged WBC scan and TEE were negative. Kidney biopsy showed numerous electron-dense deposits suggestive of Membrano-Proliferative Glomerulonephritis. Further history revealed that the patient regularly cleaned a chicken coop. An infectious work-up found the patient to be strongly positive for the Histoplasma capsulatum urinary antigen. With itraconazole for histoplasmosis and concomitant steroid therapy for glomerulonephritis, he defervesced and his creatinine improved to 1.4 mg/dL.

Discussion: Infection Related Glomerulonephritis (IRGN) is an immune-mediated disease caused by non-renal pathogens. The incidence is higher in developing countries: for example, per 100,000 individuals, the incidence of cases per year is 39 in India and 0.78 in the United States. It is believed that sub-clinical IRGN is common and underdiagnosed. In a study of 1012 kidney biopsies, 10% had evidence of disease, such as subepithelial humps. Hematuria is present in >80% of cases, and patients usually present with Nephritic Syndrome. Endemic mycoses as a cause of glomerular disease in humans are rare. An infection due to H. capsulatum can result from inhalation of aerosolized spores after disruption of chicken droppings harboring the fungus. We suspected endocarditis given his cardiac history, and kidney biopsy findings also supported infection. However, the splenomegaly, FUO, and exposure to fowlis (FUOwuls) established the diagnosis.

FR-PO015
Next Generation Sequencer Driven Exome Analyses Identified a MCKD1 Family with New Mutation Before VNTR Of MUC1 DNA Sequence, Suffering From Mucosal Dysfunctions  Satoshi Yamamoto,1 Jun-Ya Kaimori,1 Masaki Hatanaka,2 Naotsu Ichiguchi,1 Shiro Takahara,1 Hiromi Rakugi,1 Yoshitaka Isaka.1
1Dept of Advanced Technology of Transplantation, Osaka Univ School of Medicine, Osaka, Japan; 2Dept of Genetic Medicine & Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

Introduction: Hereditary tubulo-interstitial nephritis (h-TIN) is characterized by family history, bland urine, normal size kidney, hyperuricemia, renal fibrosis and gradual renal function loss. MCKD1 type h-TIN is also recognized by the difficulty to identify mutant sequence by conventional Sanger Sequencer or next generation sequencing, because the cystine insertion mutation locates in the GC rich valuable number tandem repeat (VNTR) region. The mutant MUC1 DNA sequence is supposed to produce truncated type protein, which is inferred to be trafficked to the cell membrane. Because of the difficulty of identification, there may be lots of unknown symptoms in MCKD1.

Case Description: We identified 5 hereditary TIN patients in a family, three of those are on hemodialysis and one is under dialysis, and the other was CKD. The C2D2 patient was 23 y.o female, whose renal function is gradually reducing for 10 years. Now her serum creatin is over 3. Her renal MRI images showed normal size kidneys with no cysts. The patients are suffering from mucosal dysfunctions including GI ulcer, sinusitis, and dysphagia. We analyzed genome DNA sequence of hereditary TIN family by next generation sequeencer driven trio exome analyses. They revealed that the 2 bp deletion mutation were located before VNTR. Interestingly, consequently produced mutant MUC1 cysts. The patients are suffering from mucosal dysfunctions including GI ulcer, sinusitis, renal fibrosis and gradual renal function loss. MCKD1 type h-TIN is also recognized by the difficulty to identify mutant sequence by conventional Sanger Sequencer or next generation sequencing, because the cystine insertion mutation locates in the GC rich valuable number tandem repeat (VNTR) region. The mutant MUC1 DNA sequence is supposed to produce truncated type protein, which is inferred to be trafficked to the cell membrane. Because of the difficulty of identification, there may be lots of unknown symptoms in MCKD1.

Discussion: We could identified the totally new mutation sequence of MCKD1 family, because it located before the GC rich VNTR sequence of MUC1. The newly identified mutant protein showed the almost same a.a. repeats sequence, suggesting these repeat sequence is implicated in the pathophysiology of MCKD1 type h-TIN.

Funding: Government Support - Non-U.S.

FR-PO016
Propofol-Induced Hyperkalemia in a Hemodialysis Patient  Ibrahim M. El-Ali, Chandana Shekar, Sathak Virmani, Ruchir D. Trivedi. Dept of Medicine, Div of Nephrology, Univ of Connecticut Health Center, Farmington, CT.

Introduction: Propofol induced hyperkalemia and propofol infusion syndrome are well described in the intensive care literature. Propofol induced sudden cardiac arrest, however, may be under recognized. We report a case in which a large bolus of propofol was associated with an acute increase in serum K+ precipitating potentially fatal cardiac arrhythmia.

Case Description: A 58 y/o male on maintenance hemodialysis (HD), having missed 2 HD sessions, presented with altered mental status and hyperkalemia. Patient required intubation for airway protection. Serum K+ was 8.2 mEq/L and confirmed with repeat of 8.8 mEq/L. Propofol bolus was used as premedication for intubation followed by infusion at 20 mcg/kg/min. Ventricular fibrillation and cardiac arrest ensued soon after propofol bolus. Patient was managed with repeated calcium chloride bolus totaling 10 grams and urgent hemodialysis. Post-HD Serum K+ level was 4.3 mEq/L. Repeat K+ 10 hours after HD, with other parameters being changed, was 7.1 mEq/L, increasing to 7.9 mEq/L within the next hour. Cardiac monitor showed widening QRS interval. No concurrent evidence of hemolysis, DIC or rhabdomyolysis. No exogenous K+ was given. HD was re-initiated emergently to avoid recurrent cardiac arrhythmias. Propofol was discontinued with no recurrence of hyperkalemia.

Discussion: Direct mitochondrial respiratory chain inhibition similar to mitochondrial myopathy is the most plausible explanation for propofol infusion syndrome (PRIS); a rare but significant adverse effect of propofol. Impaired mitochondrial fatty acid metabolism leads to lactic acidosis causing trans-cellular potassium shifts to ECF resulting in hyperkalemia. Rapid rise of serum K+ is more closely correlated with onset of arrhythmia than absolute K+ levels. Propofol bolus can also cause sudden worsening of hyperkalemia via depressed beta adrenoceptor-agonist effect and acute transcellular shift of potassium. This complication can be fatal in ESRD patients who may have baseline hyperkalemia. Hence, propofol should only be used with extreme caution in ESRD patient population on HD.

FR-PO017
A CuriousSLE Tangled Case: Systemic Lupus Erythematosis as the Unifying Diagnosis for Fibrillary Glomerulopathy and Toxic Epidermal Necrolysis  Kawan A. Swain, Hao Liu, Volker Nickeleit, Patrick H. Nachman. Nephrology, Unv of North Carolina at Chapel Hill, Chapel Hill, NC.

Introduction: Fibrillary glomerulopathy is a rare cause of glomerular disease. Most cases are idiopathic but can be associated with autoimmune diseases.

Case Description: 58 y/o Caucasian male with a past history of hypertension presented a week after developing an acute erythematous rash associated with fever, encephalopathy, and AKI. The rash was preceded by a month history of intermittent night sweats, fever, and joint pain. The desquamating rash encompassed ~30% BSA with mucosal involvement. Skin biopsy revealed acute vascular interface dermatis consistent with toxic epidermal necrolysis (TEN). Labs showed pancytopenia without evidence of hemolysis. Serum Cr was 2.14 mg/dL (recently 0.9) and urine Protein/Cr was 1.1g. Urine microscopy showed numerous acanthocytes and a few RBC casts. Serologies revealed low C3 and C4, positive ANA 1:640 and ENA screen, but negative ANCA, cryoglobulins, infectious work up and antibodies to ds-DNA, Sm, RNP, Ro/SSA, La/SSB, Jol and Se70. A kidney biopsy showed acute tubular injury and mild mesangial and endothelial proliferation without crescents or tuft necrosis. Immunofluorescence revealed diffuse 1-2+ staining for IgG, IgA, IgM, C3, C1q, kappa and lambda in the mesangium and capillary walls. Electron microscopy showed mesangial and capillary deposits with 20nm non-branching fibrils. Congo red stain was negative and IgG subclass stain did not reveal monoclonality. The findings were classified as a fibrillary glomerulonephritis. After initial methylprednisolone pulse, treatment with oral prednisone and mycophenolate mofetil resulted in resolution of rash, encephalopathy, and recovery of renal function and cell counts. The unifying diagnosis is new onset SLE, with TEN (possibly precipitated by naproxen) and fibrillary glomerulopathy.

Discussion: This case illustrates an uncommon presentation of an immune complex mediated fibrillary glomerulopathy consistent with SLE in an older male patient who presented with TEN. SLE has been rarely implicated as a cause of SJS/TEN when associated with initial photodistribution, absence of genital involvement, and a prolonged course.

FR-PO018
An Unusual Case of Renal Failure in an Adult: “Prune Belly Syndrome”  Antonio Medaura, Jeffrey D. Wallach, Sudhanshu Jain. Nephrology, Harlem Hospital Center, New York, NY.

Introduction: Prune Belly Syndrome is a rare congenital disease characterized by hypoplastic abdominal wall musculature, severe urinary tract dilatation and bilateral undescended testes. The complete syndrome is seen only in males affecting 3.8 per 100,000 live births. While the cause is unknown several aspects suggest an influence of genetic factors. Very few patients survive adulthood and all of them progress to ESRD.

Case Description: A 25-year-old male from Burkina Faso presented with a 10-year history of fever, rigors and right-sided flank pain. On exam he was found to have an empty scrotum and a distended bladder. He reported history of several urinary tract infections and urological surgeries during childhood. He was found to have azotemia (Sr. creatinine 10.8 mg/dl and BUN 82 mg/dl) and an eGFR of 8 ml/ min/ 1.73m2. Urinalysis was cloudy with 2+ protein, 3+ leucocyte esterase, 2-5 WBC's and moderate bacteria. Urine culture was sterile with an acute increase in serum K+ precipitating potentially fatal cardiac arrhythmia. 58 y/o male on maintenance hemodialysis (HD), having missed 2 HD sessions, presented with altered mental status and hyperkalemia. Patient required intubation for airway protection. Serum K+ level was 4.3 mEq/L. Repeat K+ 10 hours after HD, with other parameters being changed, was 7.1 mEq/L, increasing to 7.9 mEq/L within the next hour. Cardiac monitor showed widening QRS interval. No concurrent evidence of hemolysis, DIC or rhabdomyolysis. No exogenous K+ was given. HD was re-initiated emergently to avoid recurrent cardiac arrhythmias. Propofol was discontinued with no recurrence of hyperkalemia.
survive until adulthood or they are already ESRD. The findings in our report. This diagnosis in a 25 year old is rare, as most patients do not need of further studies, it may be worthwhile to empirically treat with azithromycin for to be considered when there is a high rate of ammonia production. And while we are in need of further studies, it may be worthwhile to empirically treat with azithromycin for ureaplasma infection in so called “idiopathic hyperammonemia”.

He received intravenous antibiotics and improved clinically.

Discussion: Although lower urinary tract and kidney malformations account for 40% of childhood ESRD it is a rare cause of kidney failure in adults. Mutation in the HNF1β gene and homozygous loss-of-function mutation of muscarinic receptor M3 (CHRM3) were described. CHRM3 is the major receptor mediating urinary bladder contraction upon micturition. These patients have normal urethral patency on cystogram and detrusor hyporeflexia with high residual volumes after micturition seen on cystometry, identical to the findings in our report. This diagnosis in a 25 year old is rare, as most patients do not survive until adulthood or they are already ESRD.

FR-PO019
How ‘Idiopathic’ Is Idiopathic Hyperammonemia? Esso Georges, Kavitha Vellanki. Nephrology, Loyola Univ Medical Center, Maywood, IL.

Introduction: Idiopathic hyperammonemia is characterized by progressive elevations in serum ammonia of unknown etiology, ultimately leading to cerebral edema and death. It is a rare fatal syndrome described in transplant setting; lung transplant recipients having the highest risk. Calcineurin inhibitors are thought to play a role but the exact mechanism is not known. Here we report an unusual case of severe hyperammonemia that has been linked to donor transmitted Ureaplasma infection.

Case Description: A 59 yr old Hispanic man with idiopathic pulmonary fibrosis received bilateral lung transplant at our center. His induction regimen included thymoglobulin and methylprednisolone and was maintained on tacrolimus, mycophenolate and prednisone. Despite all these measures, ammonia levels remained persistently elevated at > 1700 µg/dL (Figure 1) and patient expired within 4 days. At autopsy, bronchoalveolar lavage (BAL) of bilateral lung weighed positive for Ureaplasma urealyticum. On further testing, donor’s pre- transplant BAL was positive for the same organism. Lysis of urea by Ureaplasma generates free ammonia and when left untreated, can cause hyperammonemia. But the rise in serum ammonia levels of such a magnitude despite aggressive dialysis is unheard of.

Discussion: In conclusion; underlying infection with urea splitting organisms need to be considered when there is a high rate of ammonia production. And while we are in need of further studies, it may be worthwhile to empirically treat with azithromycin for Ureaplasma infection in so called “idiopathic hyperammonemia”.

FR-PO020
Pelvocalyceal Leakage on Ethanol Sclerotherapy for Recurrent Infected Renal Cyst in ADPKD Eunyoung Lee, Joo-Hark Yi, Sang-Woong Han, Ho-Jung Kim. Division of Nephrology, Dept of Internal Medicine, Hanyang Univ Guri Hospital, Guri-si, Gyeonggi-do, Republic of Korea.

Introduction: Though sclerotherapy has been commonly considered as a valid and safe therapeutic option for symptomatic renal cysts, it’s effectiveness in recurrent infected renal cyst in autosomal dominant polycystic kidney disease (ADPKD) is rarely reported.

Case Description: A 76-year-old woman with ADPKD was again admitted by infected (L1) renal cyst (7.3 cm) on ultrasonography (US) with similar episode, 1 yr ago. She presented with a fever, dysuria and left CVA tenderness. Despite clinical and laboratory improvement with sensitive antibiotics against Klebsiella pneumonia for 14 days, the size of the infected renal cyst was paradoxically enlarged (8.9 cm) on follow-up US. Thus, percutaneous catheter was inserted for drainage and after 1 wk, tubogram showed no evidence of dye leakage (figure1-A). Following complete clinical recovery, absolute ethanol sclerotherapy was performed to prevent further recurrent cyst infection. However, she complained of severe burning pain in low abdomen at the beginning of the procedure. Tubogram dye was shown in pelvocalyceal system and ureter (figure1-B). Sclerotherapy was immediately stopped and saline irrigation was followed. Then, percutaneous catheter was removed into the cyst for further draining, and double-J catheter was inserted at ureteropelvic junction to prevent a ureteral stricture. Then, she underwent uneventful hospital course, and discharged on hospital day 42.

Discussion: Infected renal cyst wall, despite clinical recovery, could consist of already damaged tissue that may be easily broken by ethanol. Through this unexpected adverse complication, we learned that cyst ablation therapy with ethanol may not be an appropriate modality to prevent recurrent renal cyst infection in ADPKD.

FR-PO021
A CD2AP Mutation (p.T374A) Associated with Cognitive Decline and Focal Segmental Glomerulosclerosis in Young Adulthood Dmitry Tsvetkov,1 Yoland Marie Anistan,1 Christian Harteneck,2 Maik Gollasch.1 1Charité Univ Medicine Berlin, Nephrology/Intensive Care, Experimental and Clinical Research Center (ECRC) and Max Delbrück Center for Molecular Medicine, Berlin, Germany; 2Dept of Pharmacology and Experimental Therapy, Inst of Experimental and Clinical Pharmacology and Toxicology, Eberhard Karls Univ Hospitals and Clinics, and Interfaculty Center of Pharmacogenomics and Drug Research, Univ of Tübingen, Tübi.

Introduction: Mutations in CD2-associated protein (CD2AP) gene have been identified in patients with focal segmental glomerulosclerosis (FSGS); however, reports of CD2AP mutations remain scarce.

Case Description: We performed Sanger sequencing in a 32-year old patient with steroid-resistant FSGS presented with a nephrotic syndrome (proteinuria >3.5 g/day). The patient reported that his mother and his only brother also have a kidney disease. Neurological examination showed a remarkable cognitive decline within the last 5 years. Therapy with steroid and low-intermediate doses of cyclosporine A led to a persistent reduction of proteinuria. Serum creatinine levels and glomerular filtration rate (eGFR) did not decline during this treatment.

Discussion: Our patient displayed mild cognitive decline, a phenotypic characteristic not previously associated with CD2AP-associated FSGS. His proteinuria was remarkably reduced by treatment with cyclosporine A. Our findings expand the genetic spectrum of CD2AP-associated disorders and broaden the associated phenotype with the co-occurrence of cognitive decline. Our case shows that cyclosporin A is a treatment option for CD2AP-associated nephropathy.

FR-PO022
Acute Motor and Sensory Axonal Neuropathy-Associated Syndrome of Inappropriate Antidiuretic Hormone Secretion Weeraporn Srisang,1 Aumyot Prongdong,1 Pavis Laengvejakul,2 Camilo Pena,1 Mustafa G. Aly,1 Sorot Phisitkul.1 1Internal Medicine, TTUHSC; 2Neurology, TTUHSC.

Introduction: SIADH is associated with various conditions including Guillain-Barre’ syndrome (GBS). We report a case of SIADH associated with acute motor and sensory neuronal nephropathy (AMSAN), a variant of GBS.
FR-PO023

Severe Renal Osteodystrophy as a Result of Fanconi Syndrome
Rabie L. Adams-Eldred, Charles W. Heilig.

Introduction: Fanconi syndrome is a disease of the proximal renal tubules in which glucose, amino acids, uric acid, phosphate, bicarbonate and other substances are not reabsorbed and lost in the urine.

Case Description: 22 year old African American female with an autosomal dominant Fanconi syndrome. Her disease is clinically manifested by severe rickets and short stature. Her short stature has not responded to growth hormone. She has multiple stress fractures, and she amebulates with a walker. Her disease is manifested chemically by generalized aminoaciduria, hyperchloremic metabolic acidosis, hyperphosphaturia, glucosuria, bicarbonaturia, and proteinuria. Her life compliance with the medication has been poor. She has a gastoentero tube for medications administration. Her medications include Calcium Carbonate, Neutrase-Phos, Rocaltol, Polycitanz and Zantac.

Her physical examination showed: Height 98.5 cm, weight 15.8 kg, blood pressure 106/57, pulse 80. She can stand up with hips flexed and her trunk slightly forward because of the anterior and lateral bowing of the femurs. She has significant ankle prominence, and she has good range of motion. Extremities: Have severe ricket changes. Lower extremities are deformed with prominent femur curve bilaterally. The rest of her exam was unremarkable.

Urinary analysis showed glucose 100 mg/dL, ketones 40 mg, blood trace, pH 7, protein greater than 300 mg. Chemistries showed, Sodium 134, potassium 3.4, bicarbonate 13, chloride 114, glucose 142, BUN 5, creatinine 0.6, calcium 7.9, phosphorus 3.8. Osmolality 268. Alkaline phosphatase 865. White count 7.3, hemoglobin 14, hematocrit 41.3, platelets 385. 162 (normal 0-80 mcg/dl). She was treated with a carbohydrate based diet and avoidance of medications known to precipitate an acute attack.

Discussion: AIP results from a deficiency of PBG deaminase, leading to accumulation of ALA. ALA forms a complex with GSH and a precipitate. The constellation of recurrent abdominal pain and explanation of SIADH in a young menstruating female led to the diagnosis of AIP. Studies sent for AIP demonstrated elevated urine total porphyrin 3,374 (normal 0-300 mmol/24 hr), urine porphyrin 115 (normal 0-4 mg/24hr), 5-aminolevulinic acid (ALA)-delta 79.8 (normal < 7mg/24hr), and RBC protoporphyrin 68 (normal 0-80 mcg/dl). She was treated with a carbapenem based diet and avoidance of medications who present with failure to keep with the replacement of these substances secondary to compliance of use of the patient, adverse permanent skeletal effects might result from that.

FR-PO024

A Case of Solute Diuresis
Muhammad K. Qaseem, Elizabeth A. Gilliams, James L. Bailey.

Introduction: Polyuria is a common manifestation of many primary medical disorders. Here we present a case of ASLD with altered mental status and later developed polyuria.

Case Description: A 24-year old male with history of ASLD was admitted to the Intensive Care Unit (ICU) for altered mental status with an ammonia level of 347mcmol/L. He was started on Ammonia Scavenger therapy with Ammonia (arginine, Na-benzoate and 2-keto-4-methyl-2-oxopentane). On hospital day 3 he developed hypokalemia, hypernatremia and polyuria of 5L. His labs are listed below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day-1</th>
<th>Day-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na=140 mmol/L</td>
<td>Na=148 mmol/L</td>
<td></td>
</tr>
<tr>
<td>K=3.8 mmol/L</td>
<td>K=2.6 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Cl=112 mmol/L</td>
<td>Cl=118 mmol/L</td>
<td></td>
</tr>
<tr>
<td>CO2=20 mmol/L</td>
<td>CO2=26 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Creatinine=0.68 mg/dL</td>
<td>Creatinine=0.5 mg/dL</td>
<td></td>
</tr>
<tr>
<td>BUN=3 mg/dL</td>
<td>BUN=2 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Urinary Ammonia=347 mcmol/L</td>
<td>Urinary Ammonia=47 mcmol/L</td>
<td></td>
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</tbody>
</table>

Urine studies showed urine Sodium of 253mmol/L, urine Potassium of 59mmol/L, urine chloride of 175 mmol/L, urine anion gap of 137, urine osmolality of 63 mOsm/kg and urine Creatinine of 63 mg/dL with a 5.3L of urine in 24 hours. He was receiving 2%Normal Saline, Ammonium and Total Parenteral Nutrition (TPN). It was recommended to decrease the dose of ammonium to decrease the non-measured anions in the urine,stoping ½normal saline and change the TPN to have less solute load. With these interventions his urine output and hypokalemia improved to almost back to normal.

Discussion: Argininosuccinate Lyase (ASLD) activity results in the breakdown of argininosuccinic acid to arginine and fumarate. ASLD can result in severe hyperammonemia. Treatment of acute decompensations with hyperammonemia involves discontinuing oral protein, using intravenous arginine and ammonia scavenging therapy. Polypurina in ASLD could be due to different mechanisms such as low BUN leading to poor urine concentrating ability with loss of free water or due to solute diuresis. Our patient’s high urine osmolality and high urine sodium indicated a mechanism other than Diabetes insipids. After the solute content was decreased his urine osmolality decreased significantly along with his urine output. Hypokalemia also improved. Management of solute diuresis in this case was to reduce the solute intake of the patient but first and foremost requires an accurate diagnosis.
Serum Hypokalemia in a Hemodialysis Patient

Maria M. Costa, 1
department of Nephrology, University of Alabama at Birmingham, Birmingham, AL

Patient: A 58-year-old male on chronic hemodialysis presented with complaints of feeling unwell, weight loss, and frequent diarrhea for at least one month. On admission, his medical history included hypothyroidism, prostate cancer, and bipolar disorder on lithium for 40 years.

Methods: A comprehensive laboratory evaluation revealed normal serum sodium, blood urea nitrogen, and creatinine. The patient had an intravenous doxycalciferol dose of 8.6 mg/dL; serum albumin of 3.2 gm/dL, PTH of 352 pg/mL, 25OH-Vitamin D2 <4 ng/mL, 25OH-Vitamin D3 12 ng/ml, and phosphorus of 6.3 mg/dL.

Results: The intravenous doxycalciferol dose was increased to 12 mg/dL with a plan to increase it further if needed. His intravenous doxycalciferol dose was increased to 8.6 mg/dL on day 3 and increased to 12 mg/dL on day 5.

Conclusions: The patient developed acute respiratory failure requiring intubation shortly after albuterol nebulizer treatment. He was also receiving Dexamethasone (Corticosteroid) and an inhaled anticholinergic agent (Ipratropium bromide) for chronic obstructive pulmonary disease. It is possible that the patient's hypocalcemia may have contributed to the developme
Discussion: Vasopressin does not usually result in hypotension when used in management of shock. Possible explanations include lack of renal responsiveness secondary to sepsis, hypoperfusion, acute kidney injury, or lack of intake of hypertonic fluids. In this case, the patient developed marked hypotension in setting of preserved renal function.

FR-PO032
Hyperkalemia Secondary to Octreotide Use in a Patient with Normal Kidney Function

Dron P. Bhandari, Jyotsana Thakkar, Hitesh H. Shah. Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY.

Introduction: Octreotide, a somatostatin analogue works by reducing blood levels of a variety of hormones (e.g. growth hormone, insulin) and chemical messengers (e.g. gastrin, vasoactive intestinal peptide). Octreotide therefore has been used as an effective medication for the treatment of sulphonylurea-induced hyperglycemia, acromegaly, VIPoma and carcinoid syndrome. Octreotide-induced hyperkalemia has rarely been reported in the literature. We report a patient with normal renal function who developed hyperkalemia secondary to octreotide use.

Case Description: A 70-year-old male with long standing history of DM (since 20 years), HTN, and metastatic neuroendocrine pancreatic cancer was referred by his oncologist for evaluation of severe hyperkalemia (serum potassium level of 6.6 mmol/L). Patient was diagnosed with pancreatic neuroendocrine tumor approximately 2 years prior to his presentation for which he underwent Whipple procedure. He was also receiving imprisonment-induced hyperkalemia due to the restoration of HAART. In patients with HIV and AIDS with history of granulomatous disease, it is important to monitor for hypercalcemia when initiating HAART therapy or adjusting therapy.

FR-PO034
Hypocalcemia in Severe Malnourishment, and Acute Pancreatitis Veils Vitamin D Intoxication


Introduction: Although vitamin D has a wide therapeutic index, a routine use of high doses of vitamin D intake can cause toxicity. We report a case with severe hypocalcemia likely due to malnutrition and pancreatitis related to alcoholism followed by hypercalcemia from vitamin D toxicity.

Case Description: A 43 year-old woman with alcoholism was admitted with rhabdomyolysis and alcohol induced acute pancreatitis. On initial examination she was in moderate distress with altered mental status and diffuse abdominal pain. Her blood pressure was 102/67 mmHg, heart rate 136/min and temperature 38.3°C. Her lab data revealed WBC 54.71 x 10^9/L, Hb 16.9 g/dL, PLTs 186 x 10^9/L, serum Na 129 mEq/L, K 3 mEq/L, bicarbonate 19 mEq/L. BUN 32 mg/dL and creatinine 1.3 mg/dL. The initial amylase, lipase, calcium and Mg were 1.7 mg/dL, CPK 1089 IU/L and albumin 2.9 g/dL. She received intravenous Ca, Mg, K and phosphorus in addition to oral supplements. On day 4, her serum Ca was 8.7 mg/dL, albumin 2.5 g/dL, phosphorus 4.0 mg/dL and K 3.9 mmol/L without any supplement. Her serum Mg remained low and continued to receive oral and intravenous Mg supplements. Serum Ca was not checked between days 9-14 of her hospitalization. On day 15, her serum Ca was 12.8 mg/dL, ionized Ca 6.4 mg/dL, vitamin D 25OH 370 ng/ml, vitamin D 1-25 OH 149 pg/ml and intact PTH 11.8 pg/ml. Her TSH, T4, ACE and vitamin A levels were normal. Her 24 hours urine revealed Na 140 mEq/L, K 70 mEq/L, creatinine 1110 ng/L, UN 41.4 g/L, Ca 462 mg/L, Mg 403 mg/L, phosphorus 931 mg. She admitted taking vitamin D 50,000 units daily for many months for her psoriasis on her own. Her hypercalcemia was treated and her serum calcium stabilized over one week to 9.4 mg/dL while her vitamin D 25OH and vitamin D 1-25OH remained elevated over the next 6 weeks.

Discussion: Her unusual presentation of hypocalcemia masked vitamin D toxicity till she resumed regular nutrition. Her hypocalcemia was likely related to malnutrition due to chronic alcoholism and possible calcium deposition due to acute pancreatitis. With proper nutrition during her hospitalization and improvement of her underlying condition led to hypocalcemia due to vitamin D toxicity.

FR-PO035
Re-Defining the Speed Limit in Osmotic Demyelination Syndrome? Malriukh Rizvi, Rebecca D. Monk. Nephrology, Univ of Rochester Medical Center, Rochester, NY.

Introduction: Osmotic demyelination syndrome (ODS) is a severe, debilitating, possibly fatal neurological condition that results from rapid correction of severe chronic hyponatremia. Imaging reveals central pontine myelinolysis (CPM). Potential added risk factors for ODS include Sodium (Na+) < 120 mmol/L, alcoholism, malnutrition and liver transplanted. Current recommendations advise raising serum sodium by less than 9 mmol/L in 24 hours. We present a case of ODS in a patient presenting with severe hypotremena corrected at a maximum rate of 8mmol/L in 24 hrs.

Case Description: A 37 year old man with a history of alcohol abuse was sent in to the hospital by police after a car accident for jaundice. He endorsed two weeks of worsening jaundice and right upper quadrant (RUQ) pain. Admission vital signs were stable. Physical exam revealed marked jaundice, abdominal distention and RUQ pain. Work up revealed severe alcoholic hepatitis with cirrhosis and metabolic derangements including a Na of 105 mmol/L, chloride of 69 mmol/L, urea nitrogen of 45 mg/dL, creatinine of 2.13 mg/dL with unknown baseline. 5% saline with ddA VP was initiated for caution correction of severe chronic hyponatremia. Imaging reveals central pontine myelinolysis (CPM). Potential added risk factors for ODS include Sodium (Na+) < 120 mmol/L, alcoholism, malnutrition and liver transplant. Current recommendations advise raising serum sodium by less than 9 mmol/L in 24 hours. We present a case of ODS in a patient presenting with severe hypotremena corrected at a maximum rate of 8mmol/L in 24 hrs.

Discussion: A 43 year-old woman with alcoholism was admitted with rhabdomyolysis and alcohol induced acute pancreatitis. On initial examination she was in moderate distress with altered mental status and diffuse abdominal pain. Her blood pressure was 102/67 mmHg, heart rate 136/min and temperature 38.3°C. Her lab data revealed WBC 54.71 x 10^9/L, Hb 16.9 g/dL, PLTs 186 x 10^9/L, serum Na 129 mEq/L, K 3 mEq/L, bicarbonate 19 mEq/L. BUN 32 mg/dL and creatinine 1.3 mg/dL. The initial amylase, lipase, calcium and Mg were 1.7 mg/dL, CPK 1089 IU/L and albumin 2.9 g/dL. She received intravenous Ca, Mg, K and phosphorus in addition to oral supplements. On day 4, her serum Ca was 8.7 mg/dL, albumin 2.5 g/dL, phosphorus 4.0 mg/dL and K 3.9 mmol/L without any supplement. Her serum Mg remained low and continued to receive oral and intravenous Mg supplements. Serum Ca was not checked between days 9-14 of her hospitalization. On day 15, her serum Ca was 12.8 mg/dL, ionized Ca 6.4 mg/dL, vitamin D 25OH 370 ng/ml, vitamin D 1-25 OH 149 pg/ml and intact PTH 11.8 pg/ml. Her TSH, T4, ACE and vitamin A levels were normal. Her 24 hours urine revealed Na 140 mEq/L, K 70 mEq/L, creatinine 1110 ng/L, UN 41.4 g/L, Ca 462 mg/L, Mg 403 mg/L, phosphorus 931 mg. She admitted taking vitamin D 50,000 units daily for many months for her psoriasis on her own. Her hypercalcemia was treated and her serum calcium stabilized over one week to 9.4 mg/dL while her vitamin D 25OH and vitamin D 1-25OH remained elevated over the next 6 weeks.

Discussion: Her unusual presentation of hypocalcemia masked vitamin D toxicity till she resumed regular nutrition. Her hypocalcemia was likely related to malnutrition due to chronic alcoholism and possible calcium deposition due to acute pancreatitis. With proper nutrition during her hospitalization and improvement of her underlying condition led to hypocalcemia due to vitamin D toxicity.
**FR-PO036**

A Case of Axenfield-Rieger Syndrome Presenting with Elevated Serum Bicarbonate

**Rudrick V. Ledesma, Maureen E. Brogan, Venkata Buddharaju, Rahul N. Pawar, Rajat Lamba. Westchester Medical Center, NY.**

**Introduction:** Elevated serum bicarbonate can be often misdiagnosed as metabolic alkalosis leading to improper management. Chronic respiratory acidosis caused by central hypventilation can lead to elevated bicarbonate secondary to renal compensation. We present a case of central hypventilation caused by cerebello-ponsine lesion in a patient with Axenfield-Rieger syndrome (ARS).

**Case Description:** A 25 yo man with PMH of glaucoma, developmental delay, schizoaffective disorder sent to the ED for respiratory failure. He was seen earlier in renal clinic for observation of elevated serum bicarbonate. He was complaining of fatigue and insomnia. Arterial blood gas was done and showed a pH of 7.30, pCO2 of 79, P02 of 63 and HCO3 of 38.9. He was eventually admitted for further management. While in the hospital, he continuously needed bilevel positive airway pressure. Chest ultrasound showed little to no movement of his diaphragm. EMG was negative. PFT was suboptimal as he wasn’t able to follow the instructions. MRI brain showed a mass on his right cerebello-ponsine angle. He was also diagnosed with ARS during his hospital stay. The mass was resected and progressive improvement was observed in his respiratory status. He was eventually weaned off bilevel positive airway pressure and was discharged home without any need for respiratory support.

**Discussion:** Elevated serum bicarbonate can often pose a diagnostic challenge. Evaluation should start with an ABG which would differentiate a primary metabolic alkalosis from a renal compensation of respiratory acidosis. Differential diagnoses for respiratory acidosis include central hypventilation, primary lung pathology, neuromuscular disease and airway pathology. Central hypventilation could be secondary to lesions in the respiratory center. ARS presents as a spectrum of developmental disorders resulting from abnormal migration and differentiation of neural crest cells with both occular and systemic manifestations. The region in the brain that are most affected are forebrain and pituitary gland. Our case is interesting as he had ARS with epidermoid cyst which we believe has led to central hypventilation and elevated bicarbonate as compensatory mechanism.

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**FR-PO037**

Signet-Ring Cell Carcinoma Presenting as Frequency of Urination

**Haya Waseem Siddqui, Daniel E. Carl, Todd W. Gehr. Nephrology, Virginia Commonwealth Univ, Richmond, VA.**

**Introduction:** Urinary tract obstruction may occur at any site in the urinary tract and is important to recognize early since it is readily reversible if quickly corrected.

**Case Description:** 45 year old male with obesity, history of gastric bypass surgery, hypertension and obstructive sleep apnea who presented to our institution for evaluation of frequency of urination. He developed progressively worsening frequency of urination, occurring every hour during the day and night for 3 months prior to presentation. During this time, his serum creatinine was 1.6 mg/dL. He had been seen multiple times by an Urologist and Primary Care Providers outside our institution, and was diagnosed with prostatitis despite negative urine cultures and no pyuria. During the work up, an outpatient CT scan revealed mild bilateral hydrourereter and mild left hydronephrosis. Furthermore, an office cystoscopy revealed diffuse inflammatory cystitis of the bladder and no definitive bladder lesion. Over the ensuing 3-4 weeks, he developed acute kidney injury with a serum Cr that peaked at 6mg/dL. This prompted an admission to an outside facility. He was again found to have mild bilateral hydrourereter, however, ureteral stents were attempted, but unsuccessful. A repeat cystoscopy revealed severely inflamed bladder tissue with no visualized bladder biopsy. The patient was transferred to VCU for placement of percutaneous bilateral nephrostomy tubes by interventional. He had successful stent placement by IR followed by post obstructive diuresis treated with intravenous fluid hydration in the form of saline. His AKI improved as he continued his progression of subsequent imaging. His serum Cr improved to 1.3 mg/dL and repeat CT scan with intravenous contrast was obtained for staging which showed circumferential bladder wall thickening with asymmetric soft tissue prominence along the right anterior dome most consistent with bladder neoplasm. Outside pathology report was consistent with signet cell carcinoma of bladder.

**Discussion:** Signet-ring cell carcinoma a rare bladder tumor can result in acute kidney injury secondary to bilateral ureteral obstruction.

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**FR-PO038**

A Case of Tenofivir-Induced Nephrotoxicity


**Introduction:** Tenofivir (TFV) is a nucleotide reverse-transcriptase inhibitor used for treatment of HIV and hepatitis B. Most studies suggest TFV has only a modest effect on estimated glomerular filtration and severe nephrotoxicity is uncommon. We describe a case of severe renal failure and mitochondrial tubulopathy related to TFV.

**Case Description:** A 55 year old woman with HIV on TFV for several years, presented with vomiting and abdominal pain for 4 days. Physical exam was unremarkable. Laboratory data showed BUN 65 mg/dL, creatinine 9.07 mg/dL (baseline: normal), bicarbonate 12 mmol/L, glucose 137 mg/dL, HIV RNA: 21 copies/mL and CD4: 292 cells/µL, glycosuria and proteinuria (1575/24 hours). Serologic tests for autoimmune diseases were negative. Kidney biopsy showed proximal tubule (PT) injury and eosinophytic oval cytoplasmic inclusions on trichrome stain (fig. a) with no definite glomerular or mesangial abnormalities. Electron microscopy (EM) showed PT cells with cytoplasmic swelling, loss of membrane integrity, accumulation of enlarged dysmorphic mitochondria with intra-crystalline matrix approach to the loss of cristae (fig. b) consistent with mitochondrial injury (MI) seen in TFV nephrotoxicity. Despite discontinuing TFV, she remained dialysis dependent.

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**FR-PO039**

A Case of Severe Hypomagnesaemia in a Patient Treated with Trastuzumab

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**Introduction:** A case of invasive ductal carcinoma that was treated with chemotherapy including Trastuzumab found to have severe hypomagnesaemia requiring very aggressive repletion strategies.

**Case Description:** A 36 y/o non-alcoholic female with past medical history of hypertension well controlled on diet therapy, was diagnosed with invasive ductal carcinoma of the breast requiring initiation of chemotherapy with docetaxel and carboplatin with Trastuzumab. She received a total of 6 cycles of chemotherapy every three weeks and Trastuzumab 2gm weekly infusion after completion of chemotherapy, the dose of Trastuzumab was increased to 6gm per infusion every three weeks. Her serum magnesium level which was 2.1mg/dl in the beginning of chemotherapy was noted to be low at 0.5mg/dl when she presented with generalized weakness to the hospital six months into the treatment. At this time, she had completed her chemotherapy 2 months ago and now on Trastuzumab only. She was on lasix and proton pump inhibitors at that time, both of which were stopped immediately. However her serum magnesium remained low between 0.6-1.0 mg/dl persistently for next few months requiring intravenous infusions every week. On repeated testing, fractional excretion of magnesium remained high indicating renal wasting. Although patient was hypokalemic initially, it corrected immediately after stopping loop diuretics and remained normal ruling against tubulopathies such as Gitelman or Bartter syndrome. She remained hypomagnesemic despite completing one year course with Trastuzumab. She is receiving once a week intravenous infusions of magnesium sulphate and oral supplements three times a day and serum magnesium remains at 0.4-1.0 mg/dl persistently for next few months requiring intravenous infusions every week. As the patient had metabolic alkalosis it was unlikely that the patient had other EGFR inhibitor with Cetuximab used in colon cancer and Erlotinib used in lung cancer, but not reported in patients taking Trastuzumab, especially after escalating to higher doses.

**Discussion:** Trastuzumab is a human epidermal growth factor (HER-2) inhibitor which belongs to the family of epidermal growth factor receptor (EGFR). EGFR is involved in increasing the magnesium absorption in the distal nephron by increasing the transcription of the genes regulating TRPM6 channels. Hypomagnesaemia has been well reported in other EGFR inhibitor with Cetuximab used in colon cancer and Erlotinib used in lung cancer, but not reported in patients taking Trastuzumab, especially after escalating to higher doses.

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**FR-PO040**

Capecitabine Induced Acquired Barter’s-Like Syndrome

**Eric A. Kirk, Jennifer Thompson, Juan Carlos Q. Velez, Nithin Karakala. Nephrology, MUSC, Charleston, SC.**

**Introduction:** Many forms of chemotherapy carry a risk of electrolyte abnormalities. Capecitabine is an antimetabolite of the fluoropyrimidine carbamate class of chemotherapeutic agents. Phase I and II trials have reported hypomagnesaemia, hypocalcemia with capecitabine and temozolomide developed back spasms and was found to have severe hypokalemia (2.4mmol/L), hypomagnesemia (0.7mg/dL), hypocalcemia (6.4mg/dL) and metabolic alkalosis (bicarbonate 30mmol/L) in the absence of vomiting or diarrhea 5 weeks after starting a 2 week course of capecitabine (1400mg/m² divided twice daily). She had evidence of renal salt wasting with sodium 256.5mEq, potassium 51.8 mEq and calcium 50mg/m in a 24 hour urine collection. No evidence of hypoparathyroidism, with intact PTH 67.3pg/mL, 1,25 hydroxy vitamin D was 33pg/mL. Further capecitabine therapy was withheld. 24 hr urine collection was completed 1 week later with decreased renal loss of sodium, potassium and calcium and normalization of electrolytes.

**Case Description:** We present a case of life threatening hypokalemia caused secondary to capecitabine. As the patient had metabolic alkalosis it was unlikely that the patient had Fanconi as described in some cases reports. Our case is unique as this patient developed a combination of hypokalemia, hypocalcemia, hypomagnesaemia and metabolic alkalosis.
caused by capcitabine. The patient exhibited Barter’s like physiology with increased renal loss of calcium, magnesium, and sodium and evidence of metabolic alkalosis. Unlike the proximal tubulopathy associated with capcitabine, the pathophysiology of acquired Barter’s with is unknown but could be caused by direct inhibition of apical NaKCC or ROMK, or activation of the calcium sensing receptor on the basolateral surface in the thick ascending loop of Henle.

FR-PO401
Uncommon Case of Severe Hypercalcemia After Renal Transplantation 

Rapeepat Lekkham, Gitana Bradauskaite. Nephrology, Einstein Medical Center, Philadelphia, PA.

Introduction: Following renal transplantation, hypercalcemia is frequently caused by persistent hyperparathyroidism, but other causes should be kept in mind. We report a case of hypercalcemia after renal transplant from unregulated extrarenal 1,25-dihydroxyvitamin D synthesis from disseminated tuberculosis and cryptococcosis.

Case Description: The patient was a 59-year-old male with unknown etiology of ESRD who received a living unrelated kidney transplant. He was stable on low dose immunosuppressive agents for history of BK virus infection. At 10 months post-transplant, the patient diagnosed with disseminated cryptococcosis with granulomatous mesenteric mass and positive cryptococcal antigen. High dose oral fluconazole was started. 10 days later, he readmitted with severe hyponatremia, severe hypercalcemia (corrected serum Ca peak at 14.72 mg/dL) and acute renal failure (serum Cr peak at 5.8 mg/dL from baseline 1.6 mg/dL). The iPTH level was suppressed to 2.8 pg/mL. The serum 1,25(OH)D level was elevated and levels of 25(OH)D fell. Serum phosphate rose and ALP levels were elevated. PTH-related peptide was negative. Serum immunoreactive phosphatidylinositol binding protein 3 was elevated. He also had a positive acid-fast bacillus (AFB) sputum. CT head revealed a well-defined 1.4 cm skull base lesion with calcified granuloma at lung base. Culture from lung biopsy showed strongly positive for Mycobacterium Tuberculosis. Anti-tuberculosis drugs were started and mycophenolate mofetil was held. Elevated calcium levels were unresponsive to calcitonin, fluoride, nor did it diuretic. After his sputum AFB became negative, the oral prednisone was increased to 60mg/day. Hypercalcemia and hyperphosphatemia normalized upon one month follow up and remained stable until finished 6 months course of anti-tuberculosis drugs and the creatinine returned to baseline.

Discussion: Unlike persistent hyperparathyroidism, underlying diseases of PTH independent hypercalcemia after renal transplantation like a granulomatous disease can lead to significant morbidity and mortality. Early recognition and prompt treatment is necessary.

FR-PO402
Treatment of Malignancy-Associated Hypercalcemia with Low Calcium

Hemodialysis Yields Significant Benefits for Cancer Patient 

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Introduction: Hypercalcemia of malignancy can be fatal. In literature, primary hyperparathyroidism is rarely described in the setting of malignancy. We describe a case of malignancy-related severe hypercalcemia that was refractory to standard therapy with low Ca HD.

Case Description: A 56 year-old male presented with 3 weeks of weakness and confusion. CT head revealed a 1.4 cm skull base lesion. Urine microscopy revealed pigmented granular casts. He was placed on an oral prednisone at 60mg/day. His serum Ca peaked at 14.7 mg/dL. Despite calcium-sparing diuretics, the patient developed refractory hypercalcemia. He was started on low Ca HD. Thereafter, his Ca and PTH levels were successfully managed with low Ca HD. Calcium levels were maintained between 7 and 10 mg/dL with low Ca HD. He tolerated the dialysis without adverse events. His mental status improved.

Discussion: Underline represents presenting author.

FR-PO404
Viral Inclusions Excluding BK: Case Report of JC Virus Renal Allograft Nephropathy

Deanne Leonard,1 Cherisse M. Cortese,1 Xochiquetzal J. Geiger,1 Lynn D. Cornell,2 Jane Hata,1 Mary B. Prendergast.1 1Mayo Clinic, Jacksonville, FL; 2Mayo Clinic, Rochester, MN.

Introduction: JC virus, a DNA polyomavirus, infects 70-80% of asymptomatic adults with clinical significance in immunocompromised hosts; known for causing progressive multifocal leukoencephalopathy, a fatal disease resulting in demyelination from infected oligodendrocytes. The paucity of data on JC virus nephropathy makes it essential to report this case.

Case Description: 76 year old male with diabetes mellitus and end stage renal disease underwent a deceased donor kidney transplant with basiliximab induction and a standard steroid taper. He experienced self-limited diarrhea with negative work up. Maintenance immunosuppression included mycophenolate mofetil, prednisone and tacrolimus, with levels 4.5-8.2. Serum CMV PCR was negative. Year 1, serum creatinine: 1.4 mg/dL, urine protein to creatinine ratio 0.05 gm, negative urinary analysis. Allograft biopsy: normal glomeruli, 5% tubular atrophy, mild tubulitis not meeting criteria for rejection and several large medullary viral inclusions but minimal plasma cells, 4D negative.

Discussion: We report a unique case of JC viral inclusions that was treated successfully with renin-angiotensin system inhibition and renal allograft preservation.

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

366A
FR-PO045
Successful Treatment of Anti-Angiotensin II Type 1 Receptor Antibodies Associated with Refractory Antibody-Mediated Rejection and Acute Cellular Rejection in Kidney Transplantation: A Case Report

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Introduction: Angiotensin II type 1 receptor (AT1R) antibody has been proved that it can be detrimental to kidney allograft. Similar to HLA-antibody, patients who have AT1R antibody are at risk for rejection and poor allograft outcome. There is no standard treatment in this situation but the aim is to remove pathologic antibodies and suppress antibodies production. Outcomes after treatment are unsatisfactory and not well established. Herein we present a successful treatment kidney transplant patient who experienced AT1R antibody associated rejection.

Case Description: A 50-year-old male with hypertension and ESRD underwent a disease donor kidney transplantation using a graft from acute kidney injury donor with peak serum creatinine of 1.24 mg/dl. No intraoperative complication occurred, urine flow rate of 300 ml/hr was observed immediate postoperative but abruptly decreased to 20 ml/hr at 8 hours posttransplantation. Acute rejection was suspected, thus allograft biopsy was done. The histopathological findings were compatible with acute cellular rejection combined with antibody-mediated rejection (ABMR). AT1-R antibody was detected at level of 15.0 µ/ml. Anti-rejection therapies were offered with steroid, IVIG, plasmapheresis, anti-thymocyte globulin and rituximab. At 8 weeks posttransplantation, rejection was well controlled with stable serum creatinine of 1.5 mg/dl.

Discussion: Although AT1R antibody associated rejection has rarely been reported, the outcomes after rejection are unsatisfactory. Early detecting rejection and rapid antibody removal seem to be the most effective treatment that prolong allograft function in present time. There are limited and controversial data about long term graft survival by treating patient with angiotensin receptor blocker.

Funding: Government Support - Non-U.S.

FR-PO046
Hemodiafiltration for Hepatic Encephalopathy Induced by Budd-Chiari Syndrome in a Patient with End-Stage Kidney Disease

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Introduction: Budd-Chiari Syndrome (BCS) is defined as portal hypertension caused by obstruction of the inferior vena cava at the liver. Severe BCS induces hepatic encephalopathy and has known to be exacerbated during hemodialysis (HD) treatment. Hemodiafiltration (HDF) has been proposed be effective for some dialysis-related complications due to better removal of middle sized uremic toxins and preservation of plasma osmolality, compared with HD. Here, we present a patient with BCS who developed hepatic encephalopathy after progression of BCS, which was ameliorated by HDF.

Case Description: The patient was a 36-year-old woman complaining of a consciousness disorder. She was diagnosed with BCS as a consequence of antiphospholipid antibody associated complications due to better removal of medium sized uremic toxins and preservation of plasma osmolality, compared with HD. Here, we present a patient with BCS who developed hepatic encephalopathy after progression of BCS, which was ameliorated by HDF.

Case Description: The patient was a 36-year-old woman complaining of a consciousness disorder. She was diagnosed with BCS as a consequence of antiphospholipid antibody associated complications due to better removal of medium sized uremic toxins and preservation of plasma osmolality, compared with HD. Here, we present a patient with BCS who developed hepatic encephalopathy after progression of BCS, which was ameliorated by HDF.

Discussion: Although AT1R antibody associated rejection has rarely been reported, the outcomes after rejection are unsatisfactory. Early detecting rejection and rapid antibody removal seem to be the most effective treatment that prolong allograft function in present time. There are limited and controversial data about long term graft survival by treating patient with angiotensin receptor blocker.

Funding: Government Support - Non-U.S.

FR-PO047
De Novo Lupus Nephritis in a Stable Kidney Transplant Recipient

Laura Panarey, Karthik M. Ranganaga, Aliden Michael Doyle. Div of Nephrology & Hypertension, Drexel Univ Hahnemann Hospital, Philadelphia, PA.

Introduction: De Novo Lupus Nephritis (LN) is an exceedingly rare complication in kidney transplant recipients. We present a case of histoplasmosis induced clinical manifestations of SLE. The scarcity of autoimmune disease in this population is not fully understood, but has been attributed to the maintenance immunosuppression used to prevent allorejection and rejection.

Case Description: Herein we present a 55-year-old woman with post streptococcos glomerulonephritis and HTN; 28 years status-post living-related kidney transplant. The patient had no personal or family history of autoimmune disease at time of transplant. Three years ago, she began complaining of episodic carpo-pedal spasm and scleritis; laboratory abnormalities included mildly low albumin and stable IgA proteinuria. Medications were stable and no potentially provocative antigens, vaccines or transfusions, were given during this period. Immunosuppression included cyclosporine and low dose prednisone. Seven months ago, the patient developed malar rash and hemo-proteinuria prompting immunological studies and kidney allograft biopsy. Anti-nuclear, double stranded DNA, Smith and histone antibodies were all strongly positive with low serum complement levels. Serum creatinine increased by 0.5 mg/dl; from baseline; urine protein to creatinine ratio revealed nephrotic range proteinuria peaking at 9.6 grams. Immunofluorescence revealed granular “full house” pattern, C4d negative; Electron microscopy revealed intramembranous deposits. The patient was treated with high dose prednisone, continued cyclosporine and addition of mycophenolate mofetil.

Discussion: Although rare, de novo auto-immune disease should be considered for transplant patients despite maintenance immunosuppression.

FR-PO048
Atypical Hemolytic Uremic Syndrome Allograft Outcome in the Post Eculizumab Era

Laura Panarey, Karthik M. Ranganaga, Aliden Michael Doyle. Division of Nephrology & Hypertension, Drexel Univ Hahnemann Hospital, Philadelphia, PA.

Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is an exceedingly rare etiology of renal failure; forms of HUS are often linked to underlying viral illness or particular classes of immunosuppression in transplant recipients. Exceedingly rare are genetic etiologies of aHUS for which transplantation is undesirable due to very high recurrence rates of disease.

Case Description: Herein we describe a case of misdiagnosis; 78 year old man initially diagnosed with rapidly progressive glomerulonephritis (RPGN) by kidney biopsy developed anuria necessitating hemodialysis. The patient had no family history of kidney disease. Immunological work-up negative for Anti-nuclear or cytoplasmic antibodies; complement remained within normal limits. Patient received a living-unrelated kidney transplant from a 40 year old healthy donor. Standard induction soludemol and thymoglobin. Initiation of maintenance calcineurin inhibitor (CNI), steroid, antithymabote. Favorable outcomes were observed, creatinine 1.77 mg/dl and urine output upon discharge. One week post transplant, patient was observed to have increased creatinine, peak 4mg/dl, not amenable to discontinuation of CNI or typical offending agents; prompting renal biopsy. Histologically Thrombotic Microangiopathy (TMA), C4d - observed and deemed comparable to native biopsy slides. Laboratory studies confirmed aHUS: (-) ADAMST13; low lactate dehydrogenase, elevated haptoglobin; peripheral smear hithocytes. Negative viral studies including Shiga toxin. Pt was treated with high dose soludemol, plasma exchange and eculizumab; resolution of kidney function, creatinine 1.88 mg/dL, month after discharge. One month later, the patient developed anuria necessitating hemodialysis. The patient had no family history of kidney disease; 28 years status-post living-related kidney transplant. The patient had no personal or family history of autoimmune disease at time of transplant. Three years ago, she began complaining of episodic carpo-pedal spasm and scleritis; laboratory abnormalities included mildly low albumin and stable IgA proteinuria. Medications were stable and no potentially provocative antigens, vaccines or transfusions, were given during this period. Immunosuppression included cyclosporine and low dose prednisone. Seven months ago, the patient developed malar rash and hemo-proteinuria prompting immunological studies and kidney allograft biopsy. Anti-nuclear, double stranded DNA, Smith and histone antibodies were all strongly positive with low serum complement levels. Serum creatinine increased by 0.5 mg/dl; from baseline; urine protein to creatinine ratio revealed nephrotic range proteinuria peaking at 9.6 grams. Immunofluorescence revealed granular “full house” pattern, C4d negative; Electron microscopy revealed intramembranous deposits. The patient was treated with high dose prednisone, continued cyclosporine and addition of mycophenolate mofetil.

Discussion: Although rare, de novo auto-immune disease should be considered for transplant patients despite maintenance immunosuppression.

FR-PO049
An Unusual Manifestation of Disseminated Histoplasmosis in a Renal Transplant Patient

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Introduction: Disseminated histoplasmosis is rare but can develop in immunocompromised patients. High recurrence rates of disease.

Case Description: The patient is a 42-year-old man with ESRD secondary to unclear etiology, who had a living related renal transplant from his cousin 4 years ago in Mexico. He was born in El Salvador, moved to California at age 7, and had traveled to Mexico and Cuba (last travel 1 year ago). His post-transplant course was complicated by antibody mediated rejection and borderline acute cell mediated rejection 2 years ago, for which he was successfully treated with IVIG, plasma exchange, and rituximab. His medication included tacrolimus, MMF, and prednisone. He presented with 2-3 weeks of fever and mild abdominal pain after unsuccessful treatment with ciprofloxacin. He had fever of 38.7
Case Description: A 46-year-old white male with previous renal stones and recurrent urinary infections underwent a right nephrectomy and subsequent renal transplantation due to failure of the remaining kidney. Five years post-transplant, an abdominal ultrasound scan was performed due to recurrent urinary infections and ongoing pyuria. This was reported as normal, but he later developed a discharging sinus in his left flank. A CT scan revealed a left solitary pulmonary mass, which was diagnosed as Mycobacterium avium complex (already dropped), but antibiotics did not relieve symptoms. In addition, he exhibited a left solitary pulmonary mass, which was diagnosed as Mycobacterium avium complex (MAC) infection by lung needle biopsy. Cystoscopy and retrograde pyelography revealed hemorrhagic cystitis and right ureteral stenosis, where a catheter was placed. Viral PCR test was performed for differentiating hemorrhagic cystitis, and adenovirus was detected both in urine and in blood. Symptoms and abnormal findings on CT were improved by the placement of a catheter and the decrease of tacrolimus dosage.

Discussion: Diuretic challenge may be useful to differentiate hydropnephrosis from obstructive nephropathy. The presence of vesicoureteral reflux and the absence of obstruction are associated with an increased risk of recurrent pyelonephritis.

FR-PO053

A Case of Hydronephrosis due to Adenovirus Hemorrhagic Cystitis following Peripheral Blood Stem Cell Transplantation for Malignant Lymphoma

INTRODUCTION: Hemorrhagic cystitis is a rare complication of hematopoietic stem cell transplantation (HSCT) and is associated with mortality [1]. Adenovirus is a well-known etiologic agent of hemorrhagic cystitis. We report a rare case of adenovirus hemorrhagic cystitis in a patient following HSCT.

CASE DESCRIPTION: A 50-year-old male, who had undergone SCT 4 months ago for the treatment of nasal-type extranodal NK/T cell lymphoma and received tacrolimus as prophylaxis for graft-versus-host disease, developed fever, right back pain and dysuria. Computed tomography (CT) showed perirenal and periureteral fat heterogeneity and dilation of the right ureter. He was diagnosed as pyelonephritis caused by ureteral stones (already dropped), but antibiotics did not relieve symptoms. In addition, he exhibited a left solitary pulmonary mass, which was diagnosed as Mycobacterium avium complex (MAC) infection by lung needle biopsy. Cystoscopy and retrograde pyelography revealed hemorrhagic cystitis and right ureteral stenosis, where a catheter was placed. Viral PCR test was performed for differentiating hemorrhagic cystitis, and adenovirus was detected both in urine and in blood. Symptoms and abnormal findings on CT were improved by the placement of a catheter and the decrease of tacrolimus dosage.

Discussion: Differential diagnoses were urothelial carcinoma, recurrence of malignant lymphoma, retroperitoneal fibrosis and disseminated MAC disease. Urine cytology result was negative for malignancy. Gallium scintigraphy excluded recurrence of malignant lymphoma. Fat heterogeneity disappeared after catheter placement, suggesting that malignant lymphoma and retroperitoneal fibrosis were unlikely. MAC was not detected from blood and urine cultures. Clinical course and laboratory data indicated that inflammation of adenoviral hemorrhagic cystitis spread to the right ureter, leading to ureteral stenosis and hydronephrosis in an immunocompromised patient after SCT.

FR-PO054

Unusual Case of Thrombocytopenia in a Dialysis Patient

INTRODUCTION: Thrombocytopenia is a frequent complication in patients on dialysis. It can be due to various causes such as infection, drugs, and autoimmune disorders. Here we report an unusual case of thrombocytopenia in a dialysis patient due to heparin induced thrombocytopenia (HIT).

CASE DESCRIPTION: An 81-year-old female started on HD 2 months prior for progressive CKD was sent to the ED for excessive bleeding around the tunneled catheter site and a platelet (PLT) count of 27 K/uL. When she was first started on inpatient HD, she was found to be thrombocytopenic and heparin autoantibodies were weakly positive so she was started on argatroban. At the 1st outpatient HD unit, her PLT count increased to 200 K/uL. After transferring to a 2nd outpatient HD center, her PLT count, once again, dropped to 27 K/uL, along with recurrent bleeding at the catheter site. This prompted investigation of heparin exposure as a cause, but it was revealed that the patient never received heparin during any of her treatments. Despite being restarted on argatroban, her PLT count remained in the 20 K/uL range. The trombonin release assay was negative. It was noted that the hospital and the 2nd outpatient unit both used a F160NR dialyzer, different from the dialyzer used in the first outpatient unit. With the suspicion of a possible dialyzer reaction, the membrane was switched from F160NR to Gambro Revaclear. Her PLTs increased to 125 K/uL in 4 days. Discharge medications indicated that the patient must use a Revaclear dialyzer. A week later, repeat PLT count was noted to be 200 K/uL.

Discussion: This case demonstrates a rare dialyzer reaction, in which a specific dialyzer membrane leads to severe thrombocytopenia and bleeding. It has been postulated that complement activation might have a role, but this patient had normal complement levels.
FR-PO054
Calcium Free Dialysis for Hypercalcemic Crisis
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Introduction: Hypercalcemic crisis, a potentially life-threatening condition, has been defined as a calcium of 14 mg/dL or more with evidence of multi-organ dysfunction including cardiovascular, renal or CNS involvement. We describe a case of hypercalcemic crisis due to primary hyperparathyroidism treated with low calcium/calcium free dialysis.

Case Description: A 62 year old healthy man was brought by his wife to the ED for lethargy, worsening confusion over 3 days, weight loss and constipation. On exam, he was hemodynamically stable, had flat jugular veins and dry mucous membranes. His corrected calcium was 23.58 mg/dL with a creatinine of 3.60 mg/dL. He was aggressively hydrated with normal saline and received a total of 2 doses of Calciumtrin 240 IU IM with no improvement in his mental status or in his calcium levels. He was then given Denosumab 60 mg SQ and underwent a 3 hour session of low calcium dialysis (Ca bath 1.0 mEq/L). During the treatment, he was given NS boluses in addition to his maintenance NS 250 cc/hr to avoid hypotension. He subsequently underwent 3 additional treatments (Treatments 2 and 4- using calcium free dialyse and Treatment 3- using Ca 1.0 mEq/L) that were well tolerated. Following his 2nd treatment, his mental status improved significantly. After his 4th treatment, his calcium was 12.26 mg/dL. His intact PTH level was 1324 pg/mL. A Sestamibi thyroid scan showed a large left parathyroid mass. The patient underwent surgical resection of a 13 cm parathyroid adenoma after which his calcium normalized to 9.8 mg/dL. His clinical course and a blood pressure trend during hemodialysis is reported below.

Discussion: Calcium free dialysis and the use of low calcium dialysate was tolerated with no hemodynamic instability. Aggressive hydration is important to maintain tolerability. It can be safely used as a bridge to definitive surgical treatment in the setting of primary hyperparathyroidism.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
proliferative was held. His exam was unremarkable except for an exophytic gingival lesion on his right mandible. His function was at baseline. Imaging revealed increased lung and liver nodularities with bulky lymphadenopathy. An axillary lymph node biopsy was performed and was consistent with Kaposi sarcoma (HHV8+). Tacrolimus was stopped and the patient was transitioned to the mTOR inhibitor: sirolimus. He was initiated on liposomal doxorubicin for extrarenal, cutaneous metastatic disease after four cycles. His renal function remained stable on sirolimus and prednisone.

Discussion: Post-transplant malignancies are common and constitute a major burden. Adjustment of immunosuppression is the mainstay of therapy in these cases. It is standard of care to switch from calcineurin inhibitors to sirolimus upon the diagnosis of Kaposi sarcoma. However, there’s no literature regarding chemotherapy in transplant-associated Kaposi sarcoma. Most of the available data is from the AIDS population that we extrapolated to our patient. His bulky disease triggered us to explore aggressive therapy. Combination chemotherapy and sirolimus seem to be a good therapeutic strategy that should be considered in cases of disseminated post-transplant Kaposi sarcoma.

FR-PO058

Warfarin-Related Nephropathy in a Kidney Transplant Patient Nadeen J. Khoury,1 Gilbert W. Moeckel,2 Mark A. Perazella. 1Nephrology, Yale Univ, New Haven, CT; 2Dept of Pathology, Yale Univ, New Haven, CT.

Introduction: Anticoagulant-related nephropathy is a new entity manifesting as AKI as the setting of excessive anticoagulation. Initial cases were related to warfarin use; however, more recently AKI is reported with direct thrombin inhibitors. We present biopsy-proven warfarin-related nephropathy (WRN) in a transplant patient on anticoagulation for atrial fibrillation with INR<2.

Case Description: A 69 y old man with hypertension, atrial fibrillation (on warfarin), T2DM and ESRD s/p living unrelated kidney transplant with baseline sCr 2.0 mg/dl (on cyclosporine, mycophenolate and prednisone) presented with nausea, vomiting and abdominal pain. Acute cholecystitis was diagnosed and percutaneous cholecystostomy drainage performed. Initial labs revealed leukocytosis and AKI on CKD with sCr 2.7 mg/dl. INR was 1.8. Urinalysis revealed 3+blood, 2+ protein with 179 RBCs/HFPE, urine sediment 1-2 RBC casts/LPEF. Transplant kidney ultrasound was unremarkable. Complements were normal. Urine microscopy demonstrated persistent RBC casts and kidney biopsy was performed. Acute tubular injury with numerous occlusive RBC casts suggestive of WRN was observed. Kidney function slowly improved but sCr remained above baseline upon discharge. Warfarin was resumed due to high stroke risk.

Discussion: Our patient’s presentation with AKI in the setting of acute cholecystitis raised the possibility of sepsis-induced AKI. However, the presence of microscopic hematuria and numerous RBC casts suggested a glomerular process. Biopsy suggested WRN developing in the setting of CKD and anticoagulation. Our case is somewhat unusual given the INR<2. Most cases of WRN have an INR>3. However, the patient had risk factors that have been linked to WRN including CKD, diabetes mellitus and hypertension. Interestingly, INR levels several months prior were all consistently below 2 yet the patient had 2 bleeding episodes requiring hospitalizations (GI bleed and thigh hematoma) suggesting an underlying bleeding predisposition. It is reasonable to consider WRN in cases of unexplained AKI with RBC casts in a patient with INR<3 in the presence of other risk factors and bleeding tendency.

FR-PO059

Successful Preemptive Kidney Transplantation Using Rituximab Induction in a Young Patient with Focal Segmental Glomerulosclerosis and Overt Nephrotic Syndrome – Case Report Aurelius Kolonko, Grzegorz Piecha, Andrzej Wieczek. Dept of Nephrology, Transplantation and Internal Diseases, Medical Univ of Silesia, Katowice, Poland.

Introduction: Focal segmental glomerulosclerosis (FSGS) recurs in 30% of patients receiving their first kidney transplant and often leads to graft loss. In the past, patients with FSGS and overt nephrotic syndrome were rarely transplanted, mostly due to the worries about its relapse. Rituximab (RTX), an anti-CD20-specific monoclonal antibody, was previously reported to be a valuable option in resistant nephrotic syndrome and in relapsing FSGS after second kidney transplantation. Hereby, we present a successful first kidney transplantation of a young patient with FSGS and full-blown nephrotic syndrome, treated with RTX induction.

Case Description: The patient is a 24-year-old woman, who developed nephrotic syndrome at the age of 4. FSGS was confirmed early by renal biopsy. However, the presence of microscopic hematuria and numerous RBC casts suggested a glomerular process. Renal function was at baseline. Imaging revealed increased lung and liver nodularities with bulky lymphadenopathy. An axillary lymph node biopsy was performed and was consistent with Kaposi sarcoma (HHV8+). Tacrolimus was stopped and the patient was transitioned to the mTOR inhibitor: sirolimus. He was initiated on liposomal doxorubicin for extrarenal, cutaneous metastatic disease after four cycles. His renal function remained stable on sirolimus and prednisone.

Discussion: Post-transplant malignancies are common and constitute a major burden. Adjustment of immunosuppression is the mainstay of therapy in these cases. It is standard of care to switch from calcineurin inhibitors to sirolimus upon the diagnosis of Kaposi sarcoma. However, there’s no literature regarding chemotherapy in transplant-associated Kaposi sarcoma. Most of the available data is from the AIDS population that we extrapolated to our patient. His bulky disease triggered us to explore aggressive therapy. Combination chemotherapy and sirolimus seem to be a good therapeutic strategy that should be considered in cases of disseminated post-transplant Kaposi sarcoma.

FR-PO060

Black Appearing Peritoneal Effluent Manjumitha Ramachia, Carol Motes Headley, Geeta G. Gyanamlani, Adnan Naseer, Barry M. Wall. Nephrology, Veterans Affairs Medical Center, Memphis, TN.

Introduction: Endoscopic tattooing with India ink is a useful and safe tool for localizing small colorectal lesions. Case Description: 60 year old man with End Stage Renal Disease due to Lupus Nephritis with continued Ambulatory Peritoneal Dialysis (CAPD), developed black effluent from the peritoneal dialysis drain bag following screening colonoscopy. Findings included an ulcerated tumor occupying 25% to 49% of the colon circumference. There was no evidence of bleeding and multiple forceps biopsies were taken. The tumor area was marked with tattoos using 3 injections (5 ml each) of India ink. He resumed CAPD and noticed his dialysate effluent was “black”. He presented to the ER with nausea, vomiting and black colored peritoneal fluid. Examination revealed a mildly tender abdomen without rebound or guarding. Vitals were stable and he was afebrile. CT scan of abdomen revealed subcutaneous free intraperitoneal fluid. His peritoneal dialysis. Peritoneal effluent cell count was elevated at 0.619 K/ul and WBC count of 5.5 K/ul. Her presentation was consistent with peritonitis (cloudy dark gray/black peritoneal effluent and elevated cell count). empiric antibiotics were initiated with vancomycin, cefepime and metronidazole. Within 48 hours the peritoneal effluent was clear (cell count down to 0.105 K/ul). The effluent culture grew Escherichia coli and Providencia Staurtii. Dialysate remained normal. At the time of partial colectomy performed one month later, dark dye was still visible on mesenteric transverse colon, but no abscesses was identified.

Discussion: Complications associated with India ink tattooing include abscesses, inflammatory pseudotumor, focal peritonitis and peritoneal staining, most of which have been attributed to inadequate dilution or sterilization of the India ink. Dye spillage into the peritoneal cavity has been reported to occur at a rate between 2.4% and 13%. This occurrence has been attributed to injection technique (deep), and the possibility of transmural penetration of the dye. In our patient, the coagulation use, Angiolydiasis and malignancies. Also medications like Sodium-polystyrene-sulfonate can cause direct mucosa damage. We report a case of GIB in Hemodialysis-patient attributed to Sevelamer-induced colonic-ulceration.

Case Description: 56Y/O ESRD-Hemodialysis patient with multiple comorbidities including hypertension, systolic cardiac dysfunction, Atrial fibrillation, H/o Breast Cancer s/p mastectomy/chemo(05),presented to the hospital with passage of bright red blood per rectum,accompanied with syncope and shortness of breath. Her medications included Amiodarone, Aromasin, baby-Aspirin, Carvedilol, Diltiazem, Pantoprozole, Sevelamer, Vincalecite. Her clinical examination was unremarkable(including neurologic exam)except for palp. Orthostatic vital signs not checked due to dizziness, Significant labs findings were:hemoglobin-5.7/mg/dl, Serum Potassium-5.5mg/L,BUN and Serum-Creatinine-40mg/dl respectively and INR-1.1. CT head- no acute abnormalities, Mesenteric angiom-no source identified, Endoscopic-Gastro-duodenoscopy- normal, colonoscopy- no active bleeder, multiple diverticulosis1. Bleeding scan showed activity near the hepatic flexure. She underwent emergent right-hemicolecetomy for the continued bleeding. Pathology report showed metastatic Carcinoma involving proximal Colon. Colon-Mucosa inflamed and ulcerated,cluster of organophilic Fish scale like crystals suggestive of Sevelamer crystals were noted in colonic mucosa. Patient improved post surgery.

Discussion: There is only handful of literature on the Sevelamer colonic toxicity. This case highlight the fact that with widespread use of sevelamer in dialysis patient, physicians should be aware of this entity. Our understanding of Sevelamer-associated mucosal injury is limited and there are no known prevention strategies available.

FR-PO062

Successful Eculizumab Therapy in De Novo Atypical Hemolytic Uremic Syndrome in a Renal Transplant Recipient Adil Mohammad Nazarak, Matthew Edey, Martin Chanayireh, Sunil Bhandari. 1Internal Medicine/ Nephrology, Wayne State Univ, Detroit, MI; 2Internal Medicine/ Nephrology, Indiana Univ Ball Memorial Hospital, IN.

Introduction: End stage kidney disease patients experience significant morbidity and mortality. One common complication in this population is Gastro-intestinal bleeding(GIB). Potential causes of GIB in terrace in transplant recipients include anticoagulation use, Angiolydiasis and malignancies. Also medications like Sodium-polystyrene-sulfonate can cause direct mucosa damage. We report a case of GIB in Hemodialysis-patient attributed to Sevelamer-induced colonic-ulceration.

Case Description: 370A

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author. 370A
required multiple blood transfusions. Her trough tacrolimus level was raised at 22 ng/l. Stool microscopy and culture was negative for shiga-toxin producing bacteria. Blood film showed red cell fragments; serum lactate dehydrogenase was raised at 752 u/L. ADAMTS-13 activity was normal. Renal biopsy was consistent with thrombotic microangiopathy. Complement genetic analyses (factors H, I, B and MCP tested) did not reveal any pathogenic mutations. Anti-factor H antibody was negative. She was treated, first with four cycles of plasma exchange and then commenced on ecuclizumab at 900mg infusion weekly for first four doses and then 1200mg fortnightly. Her renal and anemia parameters rapidly normalised.

Discussion: Eculizumab has been used successfully in treatment of aHUS in our patient who had developed this condition de novo. Uncertainties still remain regarding the duration of treatment and long-term efficacy.

FR-PO065

BK Nephropathy in Allogeneic Stem Cell Transplant Recipient without Thrombotic Microangiopathy and Graft-Versus-Host Disease: A Unique Observation

Rima N. Paj,1 Maria del Pilar Fernandez,2 Jai Prakash Babu Thippaiah Jagedonahalli,2 William F. Glass,2 Sairah Ahmed,2 Ala Abudayeh2

1Section of Nephrology, UT MD Anderson Cancer Center; 2Nephrology and Hypertension, UT-Houston Medical School; 3Pathology, UT-Houston Medical School; 4Dept of Stem Cell Transplantation, UT MD Anderson Cancer Center.

Introduction: BK virus is emerging as an important pathogen in allogeneic stem cell transplant (SCT) recipients and more prevalent in patients of Graft versus Host Disease (GVHD) and Thrombotic microangiopathy (TMA). Due to immunosuppression, different drugs and/or drug combinations have been associated with BK nephropathy such as tacrolimus. BK virus causes chronic kidney disease, ureteral stenosis and hemorrhagic cystitis in stem cell transplant patients leading to increase mortality and long hospital stay. We present a unique case of BK nephropathy that has occurred in patient who was asymptomatic and without any co-infections, TMA, or GVHD. The patient was tapered off tacrolimus which showed improvement in the BK viral urine and serum load.

Case Description: A 31-year-old female with history of Acute Myeloid Leukemia (AML) underwent an allogeneic stem cell transplant a year ago. Patient was treated with 4 cycles of Fludarabine, IDArubicin, CYTarabin (FIA) and sorafenib regimen. Post-transplant course was complicated by GVHD of gastrointestinal tract and skin (Grade I) Patient was maintained on tacrolimus and later tapered off. She remained asymptomatic; however, kidney function worsened with elevated creatinine at 1.8. BK Serum viral Load of 10,800 was seen. Therefore, renal biopsy was done which was consistent with BK nephritis. With limited effective therapeutic options, immunosuppression by tacrolimus was tapered off and Leflunomide was started showing a decrease in viral load and creatinine stabilizing to 1.37.

Discussion: A definitive diagnosis of BK nephritis is confirmed with a kidney biopsy. BK nephropathy is an important and often overlooked cause of chronic kidney disease in allogeneic stem cell transplant patients. This case report helps to recognize the much needed development of guidelines in detection and treatment of BKV for early intervention.

FR-PO066

Pharmacokinetics and Total Removal of Fosfomycin in a Patient with Chronic Kidney Failure Undergoing Haemodialysis

Julius Schmidt, Jan T. Kielstein. Nephrology, Medical School Hannover, Hannover, Germany.

Introduction: Fosfomycin shows bactericidal activity against various gram-positive, gram-negative and anaerobic pathogens, including antibiotic resistant S. aureus. However, dosing of fosfomycin in critically ill patients undergoing renal replacement is based on scarce data.

Case Description: A female chronic dialysis patient (76 years, BMI 20) was admitted to our hospital due to distinct drowsiness. Computed tomography of the lumbar spine unveiled spondyloïdosis of the thoracic vertebrae T11/12. A punch biopsy of the affected bone region showed focal osteomyelitis. As the patient was allergic to penicillin, antibiotic therapy with cimidamycin and fosfomycin sodium (8 g per day, 3 g before, 5 g after IHD session) was initiated. Maximum plasma concentration after the 3 g infusion was 496 mg/L. IHD led to a distinct reduction of fosfomycin plasma levels of 61%, with a dialyzer clearance of 75 ml/min. The total amount of fosfomycin in the total collected dialysate was 2430 mg. Cmax after the additional administration of 5 g of fosfomycin after IHD treatment was 467 mg/L.
Tumoral Calcinosis – A Rarely Seen Complication in Dialysis Patients

**Case Description:**
Case: 50-year-old female with end-stage renal disease secondary to hypertension presented for evaluation of painful left shoulder mass. She has been on dialysis for 12 years. She has multiple painful swellings on her hands, elbow, and feet. Stated that her shoulder mass appeared 2 years ago and has progressively increased in size. Also complained of excruciating pain causing trouble carrying out her daily activities. Her surgical history significant for a right neck dissection for a neck mass, parathyroidectomy and a thyroid lobectomy.

**Introduction:**
Tumoral calcinosis is characterized by solitary or multiple painless, periarticular soft-tissue calcium deposits. Tumoral calcinosis was first described by Giard and Duret in 1898 and 1899. There are two categories, a familial variant also called Teutschlaender disease and secondary tumoral calcinosis also called Uremic tumoral calcinosis.

**Case Description:**
Secondary tumoral calcinosis is associated with high serum Ca X P in dialysis patients, secondary or tertiary hyperparathyroidism, aluminium intoxication and vitamin D overload. These lesions are painless but massive swellings can cause mechanical limitation, pain and neurovascular symptoms due to compression of adjacent structures. Management includes dietary phosphate restriction, noncalcemic phosphate binders, intense dialysis with a low-calcium dialysate and calcimimetics. Surgical excision is indicated in symptomatic lesions. Parathyroidectomy recommended in patients with persistently elevated PTH levels. Tumoral calcinosis resolves after successful renal transplantation.

**Discussion:**
Fosfomycin dosing guidelines in dialysis patients are based on publications from the 1970s and 1980s. These publications indicate a high elimination of fosfomycin during hemodialysis with a dialyzer clearance of 60 ml/min. Modern dialysis even exceeds these clearance rates, as seen in this case report (75 ml/min). The large amount of fosfomycin in the total spent dialysate indicates the need for an additional dose after dialysis therapy. About 97% of the administered dose of fosfomycin was found in the dialysate. This suggests that intermittent hemodialysis can decrease fosfomycin serum levels beyond ranges, where minimal inhibitory concentrations in bone spicula can be achieved. Therefore, fosfomycin dosage after hemodialysis seems crucial to provide sufficient drug concentrations.

**FR-PO067**

**Tumoral Calcinosis – A Rarely Seen Complication in Dialysis Patients**

Lathašia Raakesh, Raakesh Hassan, Christopher C. Wong, Chong Parke.

**Nephrology, Univ of Southern California, Los Angeles, CA.**

**Introduction:**
Tumoral calcinosis is characterized by solitary or multiple painless, periarticular soft-tissue calcium deposits. Tumoral calcinosis was first described by Giard and Duret in 1898 and 1899. There are two categories, a familial variant also called Teutschlaender disease and secondary tumoral calcinosis also called Uremic tumoral calcinosis.

**Case Description:**
Case: 50-year-old female with end-stage renal disease secondary to hypertension presented for evaluation of painful left shoulder mass. She has been on dialysis for 12 years. She has multiple painful swellings on her hands, elbow, and feet. Stated that her shoulder mass appeared 2 years ago and has progressively increased in size. Also complained of excruciating pain causing trouble carrying out her daily activities. Her surgical history significant for a right neck dissection for a neck mass, parathyroidectomy and a thyroid lobectomy.

**Discussion:**
Secondary tumoral calcinosis is associated with high serum Ca X P in dialysis patients, secondary or tertiary hyperparathyroidism, aluminium intoxication and vitamin D overload. These lesions are painless but massive swellings can cause mechanical limitation, pain and neurovascular symptoms due to compression of adjacent structures. Management includes dietary phosphate restriction, noncalcemic phosphate binders, intense dialysis with a low-calcium dialysate and calcimimetics. Surgical excision is indicated in symptomatic lesions. Parathyroidectomy recommended in patients with persistently elevated PTH levels. Tumoral calcinosis resolves after successful renal transplantation.

FR-PO068

**Palate Nodule in a Hemodialysis Patient: A Long and Winding Road Until Diagnosis**
Precil Diego Miranda de Menezes Neves,1 Ramaiane Aparecida Bridi,2 Rosilene M. Elias,1 Fabio Luiz de Menezes Montenegro,1 Rosa M.A. Moyes,1,3 *Nephrology, Univ of Sao Paulo, Sao Paulo, Brazil; ‘Univ Nove de Julho-UNINOVE, Sao Paulo, Brazil.

**Introduction:**
Secondary hyperparathyroidism (SHPT) is a common condition in end-stage renal disease patients. We highlighted a complication that usually affects long bones, a brown tumor (BT). We report a case of a patient with SHPT, with a palate nodule, which diagnosis investigation led to a BT of maxilla.

**Case Description:**
A 25-years-old female, previously hypertensive, who returned to hemodialysis after her kidney transplant failure. She was referred to our CKD-MBD service with a 3-month history of a progressively enlarging submucosal nodule with hard consistency on her posterior left palate. The mass was painful since the beginning, and presented progressive growth. She had no fever, neither consumptive symptoms nor palpable lymph nodes. Before coming to our service, she was referred to a maxillofacial surgery service, where a computed tomography (CT) and a biopsy were requested, as no initial suspected diagnosis was done. CT disclosed a lytic bone lesion located in alveolar process of maxilla, measuring 3.0 X 2.5cm, and damaging the superior molar roots, producing a bulging in the left maxillary sinus, nasal cavity and palate. Microscopy view evidenced the presence of multinucleated giant cells among ovoid and fusiform mesenchymal cells, large amount of hemorrhage and trabecular of lamellar bone tissue, being compatible with Brown Tumor. On review of her case, she confirmed that Sevelamer 1.6g thrice a day, but the administration of Vitamin D analogs was not possible due to hyperphosphatemia. Her serum intact Parathormone levels were 1,500pg/ml, Vitamin D 36ng/ml, ionized calcium: 4.8mg/dl, phosphorus: 6.1mg/dl. Technetium sestamibi parathyroid scan revealed hyperperactive glands at both superior thyroid lobes and at the low cervical region. The patient was submitted to total parathyrectomy, and the lesion is progressively decreasing despite of other modalities of treatment.

**Discussion:**
Brown Tumors must be kept in mind as a differential diagnosis in patients with SHPT even when these lesions are located in unusual sites such as the maxilla.

FR-PO069

**A Case of Levofloxacin Toxicity Treated with Continuous Venous-Venous Hemofiltration**
Karl Berthold Pembaur, Jennifer Thompson, Nithin Karakala.

**Nephrology, MUSC, Charleston, SC.**

**Introduction:**
Levofloxacin is a commonly prescribed antibiotic. Multiple adverse events such as central nervous system and cardiovascular toxicity have been described. Cardiovascular toxicity, namely QT prolongation when present can be particularly dangerous and requires urgent management. Aside from stopping the drug there is paucity of data regarding other urgent treatment modalities such as CRRT when potential toxicity is suspected.

**Case Description:**
A 53-year-old African American female with a history of ESRD on peritoneal dialysis (PD) for 2 years was admitted for concern of levofloxacin toxicity. She had been admitted to an outside hospital and discharged approximately 1 week prior to presentation with a levofloxacin prescription for presumed bronchitis. During initial evaluation, she admitted to taking levofloxacin 500 mg every 8H for the preceding 5 days. She admitted she had been performing PD every other day as she was concerned she was volume depleted. After 3 days she developed nausea, vomiting, left heel pain, left hand tremor, and palpitations. She had not performed peritoneal dialysis since the onset of her symptoms. Her initial physical exam was consistent for left hand tremor and Achilles tendon tenderness. Her QTc upon initial evaluation was 534. Serum levofloxacin level was ordered and a decision was made to start continuous venous-venous hemofiltration (CVVH) to increase clearance of levofloxacin. CVVH was stopped after clinical recovery of her symptoms and normalization of QTc. Her initial levofloxacin level was 36.65 mcg/ml (normal therapeutic range 4-12 mcg/ml) and sevoflurane were followed for the duration of treatment every 12 hours. Below is a graphical trend of her levofloxacin levels.

**Discussion:**
Levofloxacin toxicity represents a unique and dangerous clinical challenge. This case report shows successful and effective treatment of critical toxicity with the use of CVVH.

FR-PO070

**Utility of Cystatin C in the Setting of Urinoma**
Lilian Saro-Nune1,4, Amrei Auferheide,2 Alan Perlman,1,2 *Nephrology, Weill Cornell Medical College, NY, NY; ‘Rogosin Inst, NY, NY; ‘Technical Univ, Munich, Germany.

**Introduction:**
Urinomas (i.e. presence of urine outside of the urinary tract) are common in the setting of urologic/pelvic surgery. Due to the resorption of extravasated urinary constituents such as urea nitrogen and creatinine, determination of renal function is typically confusing and often leads to the false impression of acute renal failure, a situation referred to as pseudo-renal failure. We describe the superior precision of cystatin C (CysC) vs serum creatinine (Scr) in estimating renal failure in a patient with urinoma.

**Case Description:**
79 yo M with a history of urinary retention requiring a chronic indwelling Foley catheter presented with catheter obstruction leading to bladder rupture and apparent acute renal failure. Presenting Scr was 5.8mg/dl (baseline 1.5mg/dl). A cystogram was consistent with urinoma. Treatment of the bladder leak consisted of urinary catheter replacement and he maintained urine output of > 2L/24H for several days. Scr decreased to 2.9mg/dl. A second episode of catheter obstruction subsequently occurring resulted in a significant increase of the extraperitoneal bladder leak and acute rise of creatinine to 4.6mg/dl. After placement of a larger catheter, his Scr decreased to 1.7mg/dl. During the second episode of urine leakage, simultaneous CysC levels were obtained. In contrast to
the marked variation of SCr during the onset and resolution of the urinoma, CySc levels demonstrated declining moderating from 3 mg/dL to 2.0 mg/dL during onset, followed by return to near baseline level of 1.7 mg/dL upon catheter replacement. CySc based eGFR values using CKD-EPI demonstrated similar relative stability, decreasing from 39 to 29 mL/min during the recurrent bladder rupture, followed by an increase to 36 mL/min after Intervention. In contrast, the eGFR decline based upon SCr-based CKD-EPI equation was notably labile declining from 20 to 11 mL/min during episode then increased to 38 mL/min with treatment.

Discussion: These findings imply superiority of CySC over SCr in estimating renal function in patients with urinoma and pseudo-renal failure. Discordant estimates of eGFR between CySC and SCr may be indicative of urinoma.

FR-PO071
Two Cases of Nonocclusive Mesenteric Ischemia Triggered by Intradialytic Hypotension
Siwadon Pitukweerakul, Praveen Ratanasrimetha, Soo Ryeong Ryoo, Kyung Soo Kim.

Introduction: Among dialysis patients, non-occlusive mesenteric ischemia (NOMI), defined as diffuse intestinal ischemia without any organic blood vessels occlusion, is rare (10%-15% of all patients) but has a very high mortality (50%-90%). The factors associated with mortality from this disease include age, diabetes, hypertension, intradialytic hypotension, atherosclerosis, medications, etc. Early diagnosis and treatment are important for improving survival in patients with this disease.

Case Description: We here report two cases of NOMI, who were triggered by hypotension during hemodialysis.

Case 1: A 52-year-old woman who had a low left ventricular ejection fraction after myocardial infarction showed intradialytic prolonged hypotension. On physical examination, he was hypotensive with diffuse abrupt abdominal tenderness. The laboratory investigation showed a high white blood cell count of 20,000. Case 2: A 88-year-old woman on maintenance hemodialysis for 5 years had hemorrhagic shock. On examination, she was also hypotensive with mild abdominal tenderness. The laboratory investigation showed a high white blood cell count of 16,000. We performed multiple detector computed tomography (MDCT) and found patent mesenteric vessels in both cases. Subsequent surgical procedure revealed the necrosis of terminal ileum in case 1 and autopsy revealed necrosis of cecum in Case 2. Finally, we diagnosed them as having NOMI. The former underwent surgical procedure and was discharged alive from the hospital but the latter was dead.

Discussion: Considering the fact that NOMI is very high mortality disease, early diagnosis must be important. However, a diagnosis of this disease is very difficult because clinical manifestations are nonspecific. We speculated that the profile of hemodialysis is very similar to that of risk factors, therefore, we should evaluate patients who showed intradialytic hypotension with abdominal pain using multiple detector computed tomography.

FR-PO072
Aggressive Renal Cell Carcinoma in a Renal Allograft
Hafiz Ali Sroya, Antonia Harford. Nephrology, UNM, Albuquerque, NM.

Introduction: Kidney cancers arising in renal allografts are very rare and most publications focus on cancers in native kidneys of transplant recipients. We are reporting a case of a renal cell carcinoma (RCC) arising 14 years post-transplant.

Case Description: A 46-years old man with a history of ESRD due to diabetic nephropathy underwent hemodialysis for one year prior to receiving a Living Un-Related Renal Transplant from his brother –in-law, a 36 yo healthy male in 2001. The patient had immediate graft function post-transplant and was maintained on MMF, Cyclosporine and Prednisone. He underwent renal allograft biopsy in 2004 for a gradual decline in renal allograft function; this biopsy showed chronic transplant glomerulopathy. The patient had very gradual decline in renal allograft (CKD G3B1) until Jan 2015, when he developed mild lower abdominal pain over several weeks. Imaging including abdominal US and CT revealed a 14 X 12 X 12 cm mass arising from the transplant kidney with extensive regional adenopathy involving the right common iliac vein and IVC with evidence of lung metastasis. Biopsy showed RCC, clear cell type with extensive necrosis. The venous involvement precluded surgical excision. The patient was treated with sunbimib. Several weeks later, he developed extensive bilateral pulmonary embolism treated with heparin infusion. IVC filter was placed at this time, with initiation of low dose warfarin. He demonstrated increasing modestly from a very gradual decline during period then increased to 38 mL/min with treatment.

Discussion: Considering the fact that NOMI is very high mortality disease, early diagnosis must be important. However, a diagnosis of this disease is very difficult because clinical manifestations are nonspecific. We speculated that the profile of hemodialysis is very similar to that of risk factors, therefore, we should evaluate patients who showed intradialytic hypotension with abdominal pain using multiple detector computed tomography.

FR-PO073
A Case of Acute Allograft Rejection Combined with BK Virus-Associated Nephropathy
Bernice Kim, Soo Ryeong Ryoo, Kyung Soo Kim. Div of Nephrology, Dept of Internal Medicine, Dongguk Univ Ilsan Hospital, Goyang, Republic of Korea.

Introduction: Rejection and BK virus-associated nephropathy (BKVAN) are major causes of renal allograft dysfunction. Treatment can be difficult when both conditions coexist, because potent immunosuppression is required in acute rejection and reduction of immunosuppressive agents is essential in BKVAN. We present a case of acute allograft rejection combined with BKVAN.

Case Description: A 41-year-old man with end stage renal disease because of hypertensive nephrosclerosis received a deceased donor renal transplantation. Immunosuppressive therapy was started with mycophenolate mofetil, tacrolimus, antibody-mediated rejection was diagnosed. Plasmapheresis was initiated and intravenous immunoglobulin (IVIG) and rituximab were administered. After 10 days of treatment, sCr was decreased to 1.5 mg/dL. Additional episodes of sCr elevation occurred and more sessions of plasmapheresis and IVIG administration were done, but sCr was elevated to 2.48 mg/dL on POD 67. Decay cells were detected on urine cytology and high levels of vituria and viremia were found on polymerase chain reaction for BK virus DNA. On second kidney biopsy, findings of acute cellular rejection were noted and viral inclusion bodies in tubular epithelium were seen, suggestive of BKVAN. For treatment of BKVAN, reduction of immunosuppressive agents was initiated in addition to the treatment of acute rejection. Steroid pulse therapy was done in regard of acute cellular rejection. Despite therapy, his renal function did not recover completely and sCr was elevated to 3.2mg/dL on POD 138.

Discussion: It is difficult to treat when BKVAN and acute rejection coexist. In our patient, IVIG and leflunomide was administered and immunosuppression was reduced for BKVAN while steroid pulse therapy was performed for acute rejection, but his allograft function deteriorated. Studies are required to optimize the management of these difficult cases.

FR-PO074
Decreased Ultrafiltration in an End-Stage Renal Disease Patient with Sickle Cell Anemia: A Potential Strategy to Facilitate Kidney Transplantation
Ekamol Tantisattamo, Siwadon Pitukweerakul, Praveen Ratnasirimetha, Nephrology, Northwestern Univ; 1Presence St. Francis Hospital, Evanston; 2Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.

Introduction: Sickle cell crisis (SC) leads to mortality and morbidity in sickle cell anemia (SCA) patients. V olume depletion is a common precipitating cause. Volume overload may require increasing ultrafiltration(UF). We report a case of SCA woman with acute kidney injury (AKI) who suffered from recurrent episodes of SC and acute hemolytic anemia requiring blood transfusions after hemodialysis(HD) was initiated. She became more sensitized from blood transfusions. Decreased UF reduced episodes of SC and blood transfusions.

Case Description: A 39-year-old African American woman with a longstanding history of SCA presented with a severe episode of SC complicated by AKI requiring chronic HD 5 years ago. Since starting HD, she had more episodes of SC from once a year up to every other month and required more blood transfusions. She presented for a pre-kidney transplant evaluation. Her panel reactive antibody(PRA) increased from 28 and 0 to 44 and 10, for class I and II, respectively. Upon interview, she has HD 3 times/week. Her estimated dry weight was 62 kg and intradialytic weight gain was 2-2.3 kg. She sometimes had dialytic hypotension with BP of 90s/50s. As concern for over UF being a potential cause of volume depletion and subsequently precipitating SC, the UF was decreased. She had fewer episodes of SC and blood transfusions. She remained on the kidney transplant waiting list with this HD prescription and stable hemoglobin.

Discussion: Our patient presented with more frequent episodes of SC after HD initiation. Intradialytic hypotension indicates intravascular volume depletion which subsequently precipitating SC and hemolytic anemia. Volume management in SCA patients with ESRD is challenging and critical to avoid intravascular volume depletion. SC and acute hemolytic anemia may be surrogate markers of over UF. Avoiding over fluid removal can prevent SC, acute hemolytic, and blood transfusion which potentially increases immunological barrier for kidney transplantation from sensitization.

FR-PO075
Recurrent Catastrophic Antiphospholipid Syndrome Treated with Eculizumab in a Peritoneal Dialysis Patient
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Introduction: Catastrophic Antiphospholipid Syndrome (CAPS) is a severe variant of Antiphospholipid Syndrome (APS), a systemic autoimmune disease characterized by recurrent thrombosis and/or venous thromboses in presence of elevated titers of antiphospholipid antibodies (aPL). These autoantibodies, promote thrombosis by activating endothelial cells and platelets. We describe a case of a clinical remission in recurrent CAPS via inhibition of terminal complement with Eculizumab in a Peritoneal Dialysis (PD) patient.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Case Description: A 48-year-old man has shown recurrent CAPS characterized by diffuse rash, fever, heart, kidneys, liver and lung involvement confirmed by positivity of aPL. Angiography revealed a bilateral subclavian arterial thrombosis, a right iliac arterial stenosis that was treated with a stent and a left renal arterial occlusion. The patient’s renal function was decreased until End Stage Renal Disease, secondary to chronic thrombotic microangiopathy, and PD therapy was started. During 16 months, our patient presented 8 recurrent episodes of disease with pulmonary involvement characterized by multiple alveolar hemorrhages in concomitance with liver necrosis (biopsy proven) and myocardial ischemia. The patient was treated with high-dose pulse corticosteroids (methylprednisolone 500 mg intravenous (IV) every 6 h for 3 days followed by prednisone (1 mg/kg/day), plasma exchange (5 series with a total of 74 sessions), IV immunoglobulin (400 mg/kg/day for 5 days), IV Rituximab (initial therapy and maintenance after 6 months), clopidogrel, aspirin and anticoagulation. Despite this standard therapy, we did not observe a sustained remission. As no improvement of the literature, we propose to administer Eculizumab, a monoclonal antibody against complement C5, that blocks and prevents the generation of the proinflammatory and proinflammatory molecules C5a and membrane attack complex C5b-9. The patient has been in remission with long-term Eculizumab treatment and anticoagulation therapy, without further thrombotic events during 1 year of follow-up. Funding: Private Foundation Support.

FR-PO076

A Case Report of Post-Transplant Lymphoproliferative Disorder in Kidney Allograft
Dina Abdelwahab, Nadeen J. Khoury, William S. Asch. Div of Nephrology, Yale Univ, New Haven, CT.

Introduction: Renal tumors are rare in transplanted kidneys. Nephrectomy is the traditional approach for renal masses. We are reporting a renal mass that was found to be a post-transplant lymphoproliferative disorder in the renal allograft which we chose to biopsy instead of using traditional surgical resection.

Case Description: A 63 year old female with past medical history of renal cell carcinoma diagnosed as a small mass by right nephrectomy, ESRD secondary to MPGN status post living donor kidney transplant presented with abdominal pain, fever and diarrhea. Ultrasound of renal allograft showed a solid mass measuring 4.8x5.6x4.3 cm in the upper pole of the transplanted kidney which was predominantly homogenous with internal vascularity. MRI revealed a 6.2 x 4.9 x 6.5 cm mass with solid enhancing and non-enhancing components within the transplanted kidney concerning for renal cell carcinoma. Given her previous history of RCC there was an increased concern for recurrence. Nephrectomy would have been the traditional approach but that would have meant sacrificing her allograft and initiating hemodialysis. The mass was biopsied and pathology revealed post-transplant lymphoproliferative disorder. Microscopic description showed a small kidney portion with tubules and glomeruli overrun by a dense lymphoid infiltrate. Immunohistochemical stains revealed that the large atypical cells were positive for CD20, CD21, MUM-1 and CD30 but negative for CD3, CD43 and CD138. C-myc stained approximately 10-20% of cells and Ki-67 30-40%. In situ hybridization for Epstein Barr virus encoded RNA (EBER) was positive. Patient received 6 cycles of R-CHOP, follow-up MRI showed decrease in mass size.

Discussion: The biopsy of renal tumors for the diagnosis of small masses has not been widely adopted despite recent safety reports with advanced techniques and physician’s expertise. It has been shown to be safe and reliable and should be considered in all patients with small masses especially in transplanted kidneys to decrease the risk of unnecessary surgical intervention.

FR-PO077

Renal Replacement Therapy for Severe Hyponatremia (PNA 99mEq/L), Using 5% Dextrose Solution Infusion Method
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Introduction: Dialysis therapy for patients with severe hyponatremia poses risk of myocardial ischemia, dysrhythmia and cerebral edema. To prevent rapid correction, low sodium dialysate or filtration fluid can be used; however, dialysate sodium concentration needs to be changed frequently as patient’s serum sodium concentration rises. Instead of using low sodium dialysate, infusion of 5% dextrose solution during dialysis can be used to adjust the serum sodium concentration. We conducted a study to examine the safety and efficacy of CVVH using 5% dextrose solution infusion method.

Case Description: A 46-year-old woman presented to the emergency department with cardiogenic shock for AMI with rupture of the papillary muscle. Her medical history included hypertension and dyslipidemia in good pharmacological control. On 9th March TAH had been implanted in order to replace the lost heart function. From the day of admission to ICU, the patient developed oliguric AKI and CRRT was started. Subsequently, the patient was switched to four times a week haemodialysis. To maintain an appropriate circulating volume for the operation of cardiac device, atrial filling pressures were maintained between 5-5.5 mmHg and 6.0-6.5 mmHg in the right and left atrium respectively. At the same time it was decided to record the change of hematocrit which the patient was subjected during the dialysis sessions (via Blood Volume Monitor (BVM)) in order to identify the critical BVM value for the functioning of the cardiac device. In this way we were able to manage the patient’s dialysis sessions even once he was discharged from the hospital with the portable version of TAH.

Discussion: This patient received dialysis therapy four times a week in order to maintain a more constant and weight constant till March 2015, when he underwent to combined heart and kidney transplantation. To the best of our knowledge this is the longer case of continuous dialysis therapy in a patient with total artificial heart. Total Artificial Heart is currently not a valid therapeutic option for those patients waiting for heart transplantation even for long periods of time.

FR-PO079

Severe Varicella Zoster Virus Encephalitis and Retinal Necrosis in a Renal Allograft Recipient
Jean Luc Franck, Srijita Mukherjee, Tina Thomas, Sharon M. Graves. Nephrology, Emory Univ, Atlanta, GA.

Introduction: Varicella zoster virus infection (VZV) has devastating potential complications and should be considered more often for testing by clinicians. Our case reflects the need to maintain a higher degree of suspicion for VZV by clinicians treating the immunosuppressed population.

Case Description: A 31-year-old man underwent living related renal transplantation in 2008 for chronic glomerulosclerosis. The clinical course was uneventful until January 2015, when he was diagnosed with grade 1A rejection after admitting to four months of nonadherence to his prescribed immunosuppressant regimen, consisting of tacrolimus, mycophenolate mofetil, and prednisone. The rejection was addressed with pulse IV steroids and resumption of his oral immunosuppressant regimen. Over the next four months, the patient sought medical attention for worsening and persistent occipital headache. Lumbar puncture was performed and suggested a viral etiology.MRI imaging was performed and revealed a large cerebellar infarct and diffuse vasculitis. Upon transfer to our institution, the patient underwent emergent neuroradiologic evaluation for positive TAH and was found to have a large subdural hematoma with compressive mass effect. Polymerase chain reaction (PCR) testing in the cerebrospinal fluid was positive for VZV. The patient was started on acyclovir and steroids for treatment of VZV encephalitis and diffuse vasculitis. Ophthalmologic evaluation revealed retinal necrosis of the left eye, with PCR testing of the anterior chamber fluid also positive for VZV. After 4 weeks of acute care, the patient is currently in rehabilitation.

Discussion: Varicella Zoster Virus infection requires timely diagnosis and treatment for positive outcomes in the immunosuppressed patient. Clinical presentation can vary dramatically, from subtle rash to encephalitis. Therefore, clinicians caring for immunosuppressed patients should more routinely consider VZV as part of the differential diagnosis. Our case raises several questions including consideration for lengthening duration of VZV prophylaxis in allograft recipients and consideration for resuming VZV prophylaxis when resuming immunosuppression after extended periods of nonadherence.

FR-PO080

Hemodialysis Related Acute Thrombocytopenia During Pregnancy
Nikulkumar Chaudhari, Belinda Bun Jin, Anjali Acharya. Dept of Nephrology, Jacobi Medical Center, Bronx, NY.

Introduction: Thrombocytopenia is not uncommon during pregnancy. It could be multifactorial and range from a mild asymptomatic condition to severe thrombocytopenia with fetal effects.

Case Description: A 29 year old woman with hypertension, CKD-IV from primary FSGS, presented at 10th week of gestation. Intravenous heparinization had to be initiated at 20th gestation week. Thrombocytopenia developed as described in the table below.

<table>
<thead>
<tr>
<th>Time (Weeks of Pregnancy)</th>
<th>Platelet Count (x10^9/L)</th>
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<tbody>
<tr>
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<tr>
<td>2</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Patient was not on antiplatelet agents and panel for HIT antibodies was negative. Patient remained asymptomatic throughout hospitalization. Hematological evaluation ruled out all routine causes of thrombocytopenia during pregnancy such as gestational thrombocytopenia, preeclampsia, HELLP, TTP/ITP and autoimmune causes. Given the chronological correlation of platelet decrease and hemodialysis it was concluded that thrombocytopenia was caused by the peritoneal dialysis. Patient was switched from a Fresenius dialyzer opting to Exeltra 210 high flux dialyzer.

Discussion: Complement activation, anti-coagulation use, exposure of blood to the roller pump, dialysis tubing, micro-bubbles, and use of cellulose membrane are potential causes of dialysis related thrombocytopenia. In addition, sterilization techniques have shown to have a differential impact. A major difference between the two dialyzers used was the technique of sterilization. Electron beam radiation used in the Fresenius dialyzer might affect membrane integrity or physical properties that could lead to platelet activation, aggregation, or adsorption causing thrombocytopenia, which is not seen with gamma sterilization. Thrombocytopenia is an important, if rare, complication of hemodialysis that should be considered in the differential diagnosis of thrombocytopenia in pregnancy. Dialysis associated thrombocytopenia may occur despite the use of biocompatible membranes.

FR-PO081
A Rare Case of Nephrocalcinosis Caused by Hereditary Renal Hypouricaemia

Three Months After Kidney Transplantation
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Introduction: Renal hypouricaemia (MIM: 220150) is a syndrome that involves a defect in urate transporter (URAT1) for urate reabsorption at the brush border of the proximal tubule. Nephrocalcinosis and exercise-induced acute renal failure are two major complications affecting renal function. A C889T mutation in SLC22A12 encoding URAT1 is the rare mutation in Japanese. Here we report a rare case of nephrocalcinosis caused by hereditary renal hypouricaemia three months after kidney transplantation.

Case Description: A 41-year-old man had undergone living-related kidney transplantation because of Henoch–Schönlein purpura nephritis. Three month protocol biopsy showed several localized nephrocalcinosis determined by either von kossa or de Galantha’s stain (staining for urate crystals). The evaluation for nephrocalcinosis showed hypouricaemia at 1.9 mg/dl with a high fractional excretion of uric acid at 26.8% (normal range, 6–10%). DNA direct sequencing followed by restriction fragment length polymorphism showed that both the recipient and donor were heterozygous for C889T.

Discussion: This case illustrates that severe allograft rejection, confirmed on histopathological and molecular level, can in rare cases present with pronounced lymphadenopathy.

FR-PO083
Prevnar 13 Associated Immune Thrombocytopenic Purpura in a Renal Transplant Recipient
Sagar Gupta, Daniel C. Brennan, Renal, WashU, St. Louis, MO.

Introduction: ACIP recommends all adults with immunocompromising conditions should receive PCV13 to prevent invasive disease caused by 13 serotypes of S.pneumoniae. We describe here a case of ITP associated with Prevnar13 administration in a renal allograft recipient, which is the first reported case of its kind.

Case Description: A 77 year old Caucasian male presented with chief complaint of increased bruising at insulin injection sites for one week. There was no history of fever, abdominal pain, diarrhea, bleeding episodes, neurological deficits, new medications or insect bites. He had ESRD secondary to hypertension and DM2. He received a living unrelated kidney allograft 22mo ago. He was on tacrolimus, MMF, prednisone, MMF later discontinued indefinitely due to BK viremia. Family history was non-contributory. Medications included allopurinol, ASA, statin, bacitracin, carvedilol, insulin glargine and aspart, prednisone and tacrolimus. He received Prevnar13 1 month ago. Exam showed normal vital signs and petechial rash in the areas of insulin injections. Lab testing resulted in Fb 11.7, WBC 7.7 (baseline) and platelet 3000 (baseline 140). BUN 31 and Cr 5.0 (baseline). PT/PTT, LDH and haptoglobin were normal. No schistocytes seen. Infectious workup was negative and ADAMTS-13 activity result at 102%. The isolated thrombocytopenia was diagnosed as ITP and was attributed to the Prevnar 13 vaccine. He was started on pulse methylprednisolone, IVIG. He received 6 units platelets with counts increasing to 94000, later discharged on a prednisone taper. Weekly blood counts showed improvement to his baseline of 140,000 in 3 weeks.

Discussion: PCV13 contains the S. pneumoniae serotypes’ capsular polysaccharide covalently linked to an immunogenic carrier protein resulting in a T cell–dependent antigen. This is a T helper-cell response. The pathogenesis of ITP involves antibody production driven by CD4-positive helper T cells reacting to platelet surface glycoproteins. Antibodies formed during viral or bacterial infections may also cross-react with normal platelet membrane proteins (a form of molecular mimicry). Isolated cases of ITP have been reported but are relatively rare. Our case is further unique to occur in a pt on immunosuppression with a calcineurin inhibitor and corticosteroids.

FR-PO084
Placement of a Tunneled Hemodialysis Catheter in the Superior Vena Cava for Multiple Central Venous Occlusions
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Introduction: A tunneled hemodialysis catheter is essential for dialysis access when the use of a functioning arteriovenous fistula is not possible. In extreme situations of multiple central venous occlusions, it remains a challenge to establish durable vascular access. Unconventional routes to the central veins are typically used. We successfully performed placement of a tunneled hemodialysis catheter in the superior vena cava (SVC) with fluoroscopic guidance in a hemodialysis patient with multiple central venous occlusions due to repeated catheterization. We report on a feasible option for hemodialysis patients with multiple central venous occlusions.

Case Description: A 49-year-old diabetic male who had been diagnosed with ERSD one year prior came to our medical center because of temporary catheter occlusion. CT venography revealed obstruction of the bilateral brachiocephalic, internal jugular and the common femoral veins, and central venography showed occlusion of the bilateral internal jugular and internal iliac veins. Guided by ultrasound, a percutaneous transhepatic route, as described by Duncan et al[9], was developed, which was applied to SVC venography and provided access for a 5F indwelling catheter, which was used to locate the distal end of
the SVC (Figure 2A). The puncture point of the skin was beneath and 0.5–1.0 cm outside of the sternum and head of the sternoclavicular joint and the direction of the subcutaneous tunnel was along the distal end of the SVC, which was marked by a 5F indwelling catheter. Under fluoroscopic guidance, a micro-21G needle (Cook) was used to puncture the stumps of occlusion of the SVC, with the needle in the needle tip in the right atrium (Figure 2D). CT showed that the needle did not enter the chest.

Funding: Clinical Revenue Support

FR-P0085
Crystal Nephropathy in a Kidney Transplant Recipient due to Excessive Consumption of Oxalate Rich Diet and Vitamin C

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Introduction: Acute kidney injury due to crystal nephropathy has been reported mainly in patients with gastrointestinal (GI) malabsorption or GI surgery. We present a rare case of crystal nephropathy in the kidney transplant recipient (KTR) without obvious GI risk factors.

Case Description: 68 year old obese female, who is living-unrelated KTR for five years, with a stable post-transplant course and a baseline serum creatinine (scr) of 1.1 mg/dl, presents to our hospital with tiredness and diarrhea for one week. She had extensive work up in the past for chronic diarrhea which is described as “soft stool”. 24 hour fecal fat, serum amylase and serum lipase were normal. Upon presentation, scr was 7.1 mg/dl which prompted us to perform an allograft kidney biopsy demonstrating multiple oxalate crystals deposited in the renal tubules. Reviewing her history further revealed that she was consuming 3 gm vitamin C (over the counter) daily for the last one month. Her preferred diet always consisted of oxalate rich foods (spinach). Renal functions improved in one month (scr 2mg/dl) with hydration, discontinuation of vitamin C, and changes in dietary habits. Urine studies obtained after one week of treatment showed normal urine calcium, low urine oxalate and citrate.

Discussion: Oxalate nephropathy can occur from hyperoxaluria due to ingestion of oxalate rich diet or substances which metabolize to oxalate like vitamin C or from enteric causes like malabsorption. In our patient, we ruled out enteric causes and determined oxalate nephropathy was secondary to ingestion of oxalate rich diet and excess vitamin C. Cレンノー functions improved with modification of diet, hydration and discontinuation of offending agents. Although vitamin C and high oxalate diet are rare causes of oxalate nephropathy in patients with normal renal function, it may cause significant nephropathies in KTR. KTR patients therefore, should follow low oxalate diet and avoid excessive vitamin C even with normal renal functions to avoid development of crystal nephropathy.

FR-P0086
The Conundrum of Dry Weight in a Pregnant Dialysis Patient


Introduction: The frequency of pregnancy in women of child bearing age who are on dialysis ranges from 0.3–1.5% per year. When a dialysis patient does become pregnant, nephrologists become extra vigilant to ensure a successful outcome for both mother and child. An important question that often arises is how to adjust a patient’s dry weight as pregnancy progresses.

Case Description: We present a case of a 23 year old pregnant dialysis patient who was admitted to the hospital with shortness of breath at 26 weeks gestation. She had a past medical history of a miscarriage, hypertension, and a failed deceased donor renal transplant. At her outpatient dialysis unit, she was being dialyzed 6 times per week. Her dry weight was increased by 1.5 kg during the first trimester and during the second trimester by 1 pound a week to account for normal pregnancy weight gain. On this admission, her weight was 113.5 kg and her estimated dry weight was 114 kg. Her vital signs on admission revealed that she was mildly hypertensive with a blood pressure of 150/94 and her oxygen saturation was 90% on room air. After other etiologies were excluded, it was determined that the patient’s hypertension and hypoxia were due to volume overload despite the patient being below her expected dry weight. A fluid monitor was placed on her and she was monitored for consecutive days with a net ultrafiltration of 7 liters. There were no signs of fluid distress during volume removal on the monitor. A uterine artery doppler was also performed and showed no signs of hypeperfusion to the fetus during dialysis. Subsequently, the patient’s shortness of breath and hypoxia resolved. Upon discharge, her new dry weight was 108 kg, which was 6 kg below her expected dry weight. The patient delivered a baby weighing 5.4 lbs at 37 weeks with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively.

Discussion: In a pregnant dialysis patient, it is difficult to distinguish between normal pregnancy weight gain and extra fluid. A fetal monitor and uterine artery doppler during dialysis are useful tools that nephrologists can employ to titrate ultrafiltration goals. Better volume management in turn could avoid pre-term delivery.

FR-P0087
A Rare Cause of AKI in a Renal Transplant Recipient

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Case Description: We present a 66 year-old African American woman who underwent pre-emptive living related donor kidney transplant for ESRD secondary to DMII and hypertension. She had immediate graft function and was discharged on the fourth post-operative day with Na 136 mEq/L, K 3.5 mEq/L, Cl 102 mEq/L, creatinine 1.3mg/dl and urine pH 7.0. Baseline renal biopsy was normal. Her medications on discharge included Prograf, Cellexpect, Prednisone, Bactrim, Valcyte and sodium bicarbonate. She presented 10 days later with complaints of nausea, and vomiting as many as 10 times. Serum chemistries revealed the following: Na 136 mEq/L, K 5.0 mEq/L, Cl 95 mEq/L, and total CO2 20 mEq/L, consistent with a high-anion gap metabolic acidosis (AG 21). Serum creatinine was 1.3 mg/dl and urinalysis revealed a urine pH of 7.5, pyuria and bacteriuria. Urine culture grew E. Faecalis and renal transplant ultrasound was normal. She was started on IV antibiotics and IV fluids. On IV antibiotics and stay in the hospital, her chemistries revealed her anion gap metabolic acidosis had resolved, with total CO2 rising to 27 mEq/L. However, serum creatinine increased to 1.8 mg/dl, and continued to rise further despite treatment. A renal allograft biopsy was performed. Microscopic examination of the biopsy revealed widespread nephrocalcinosis with calcium-phosphate deposition. PTH at the time was 255 pg/mL, Ca 8.5 mg/dl, iPO4 4.1 mg/dl and fractional excretion (FE) of Ca 0.15%, FEiP29%, and urine anion gap was 29.

Discussion: We propose that our patient had developed post-transplant RVT, given the presence of the non-anion gap metabolic acidosis, low K, and urine pH of 7.0 in the immediate post-transplant period. Positive urine anion gap is suggestive of decreased ammonium excretion (although it should be confirmed with measurement of the urine osmolal gap and urinary P,CO2). The combination of high urine pH, as a consequence of bicarbonate administration and decreased bicarbonate reabsorption, in conjunction with hyperparathyroidism and consequent increase phosphate excretion, provided the perfect medium for calcium phosphate precipitation.

FR-P0088
A Rare Case of Rabbit Anti-Thymocyte Globulin Induced Disseminated Intravascular Coagulation

Vasanthi Balaraman,1,2 Anup Patel.1 1Dept of Renal Transplant, Saint Barnabas Medical Center, Livingston, NJ; 2Dept of Nephrology, Newark Beth Israel Medical Center, Newark, NJ.

Introduction: Rabbit anti-thymocyte globulin (RATG) is a purified polyclonal immunoglobulin used for induction therapy in renal transplantation. Adverse effects include cytokine release syndrome, leukopenia, thrombocytopenia and serum sickness. We report a rare case of renal transplant recipient who developed severe coagulopathy and post-operative bleeding in whom RATG was used for induction.

Case Description: A 61 year old female with end stage renal disease received a deceased donor renal transplant. RATG (2 mg/kg) was initiated intraoperatively. Over the ensuing 2 hours, the patient became hemodynamically unstable with excessive bloody output from the surgical site drain. Exploration of the renal transplant revealed diffuse oozing from surrounding tissues but no bleeding from the arterial or venous anastomosis. Labs revealed an elevated prothrombin time of 27.0 sec, thrombin time of 36.4 sec, INR of 0.5, platelet count greater than 575,000/ml, reduced fibrinogen level of 135 mg/dl and platelet count of 66000/cmm. The RATG infusion was stopped. Multiple units of packed red blood cells, platelets, fresh frozen plasma and cryoprecipitate were transfused. There was persistent bloody output. A reexploration revealed persistent diffuse oozing which required packing of the transplant bed. On postoperative day 4, the patient’s condition improved.

Discussion: We suspect Disseminated Intravascular Coagulation(DIC) may be secondary to RATG in our case. The donor biopsy showed no evidence of DIC. Other causes including calcineurin inhibitors, hyperreactive rejection and sepsis were ruled out. Only a few case reports of RATG induced coagulopathy exist in the literature. Weber el al reported 12 hematopoietic stem cell transplant patients having coagulopathy after using RATG therapy. These cases had elevated D-dimer, tissue factor, thrombin-antithrombin III complex, and thrombomodulin, but had no bleeding, thrombocytopenia or vaso-occlusive complications. We contemplate that DIC is a rare but potential life threatening complication of RATG induction and awareness of this potential complication is important.

FR-P0089
A Page Transplant Kidney

Supreet Sethi, Shalini Bumb, Scott Leonard Sanchez. Div of Nephrology, Dept of Internal Medicine, Duke Univ Health System, Durham, NC.

Introduction: Page kidney occurs by extrinsic compression of the renal parenchyma from a hernia or a mass, leading to activation of the renin-angiotensin-aldosterone system and resulting in systemic hypertension.

Case Description: A young-adult male, with ESRD of uncertain etiology underwent living related kidney transplantation 3-months prior to presentation. His post-transplant serum creatinine (Scr) stabilized at 1.3-1.5mg/dl. He was maintained on a drug immunosuppressive regimen including tacrolimus, prednisone and mycfortic. The patient presented to the hospital with pain over allograft site and low grade fever.He reported an altercation with a family member without clear direct trauma to his right lower quadrant graft. The patient was emergently brought to blunt trauma center. Initial lab workup revealed elevated white blood cells, with normal hemoglobin, platelets, electrolytes, bilirubin, liver function tests, creatinine and blood pressure. Hemoglobin was hypotensive with blood pressures in the 170-180/100-110 mm Hg range. Labs revealed a Scr of 4.1mg/dl, potassium of 5.7mmol/L, hemoglobin of 10.8g/dl from a baseline of 12g/
BLA Colored Dialysate: A Rare Complication of Peritoneal Dialysis due to Biliary Peritonitis

**Introduction:**
We report a rare complication of black colored dialysate in a patient with ESRD on peritoneal dialysis (PD) with acute cholecystitis.

**Case Description:**
A 73 year old man was undergoing peritoneal dialysis for ESRD secondary to obstructive uropathy. He presented with black discoloration of his PD effluent. The patient had a history of previous cholecystectomy due to extrahepatic bile duct rupture or due to gall bladder rupture in patients without ESRD. There are few reports of biliary peritonitis due to intrahepatic bile duct rupture secondary to obstructive uropathy. An acute fluid bilirubin level of >6 mg/dl with an ascitic fluid/serum bilirubin ratio of >1.0 has been shown to correlate with choleperitoneum. The black colored PD effluent in our patient represented a biliary leak likely from increased permeability of the gallbladder wall or microperforation in the setting of non-perforated cholecystitis or from an unidentified intrahepatic bile duct rupture. In conclusion black colored PD effluent should prompt investigation for gall bladder disease and/or pancreatitis. Peritoneal fluid and serum bilirubin levels and lipase levels can aid in making a diagnosis.

**Discussion:**
Dark colored dialysate has been reported in hemorrhagic and non-hemorrhagic pancreatitis. Acute bile leak or choleperitoneum is a recognized complication of cholecystectomy due to extrahepatic bile duct rupture or due to gall bladder rupture in patients without ESRD. There are few reports of biliary peritonitis due to intrahepatic bile duct rupture spontaneously and in the setting of cholecystitis. An acute fluid bilirubin level of >6 mg/dl with an ascitic fluid/serum bilirubin ratio of >1.0 has been shown to correlate with choleperitoneum. The black colored PD effluent in our patient represented a biliary leak likely from increased permeability of the gallbladder wall or microperforation in the setting of non-perforated cholecystitis or from an unidentified intrahepatic bile duct rupture. In conclusion black colored PD effluent should prompt investigation for gall bladder disease and/or pancreatitis. Peritoneal fluid and serum bilirubin levels and lipase levels can aid in making a diagnosis.

**Case Description:**
A 41 year old woman with ESRD from lupus nephritis, received living related renal transplant 9 years ago; admitted with hemoglobin of 5.6 g/dl with normal WBC count and platelet count. Patient had well-functioning allograft with serum Cr of 1.5 There was no evidence of joint swelling, rash, or alopecia. Hepatitis B, C, HIV, tuberculosis, RBC, WBC, or urine analysis. Serum Protein was 4.9 g/dl; Albumin 2.7 g/dl. LDH, haptoglobin, DS, DNA,ANA,ANCA,4T,hepatica B,C,HSV, Parvo virus PCR, EB PCR, free kappa/Lambda were normal. MCV was 95.9 fL. Peripheral smear showed many normal lymphocytes with normal count. Serum creatinine was 0.58 mg/dl. Hemoglobin was 11.6 g/dl. Albumin was 2.2 g/dl. Total bilirubin was 0.1 mg/dl but absence of erythroid precursors. Flow cytometry revealed increased NK 56(-), CD3 +, CD8 +, CD19 +, CD56 +. Renal allograft Ultrasound, CT Chest and CT abdomen were normal. This patient had her last epogen in 2003 and anti-EPO antibody induced PRCA though possible but absence of erythroid precursors. False negative for EPO antibody.

**Discussion:**
We present a case of PRCA in a renal transplant recipient due to NK cell lympho proliferative disorder which was successfully treated with ATG.

**FR-PO002**
New-Onset Diabetes After Transplantation in a Pediatric Patient with Congenital Anomalies of the Kidney and Urinary Tract: The Role of Hepatocyte Nuclear Factor 1ß

**Introduction:**
Congenital anomalies of the kidney and urinary tract (CAKUT) are the most frequent cause of end-stage renal disease (ESRD) in children. New-onset diabetes after transplantation (NODAT) is one of the major complications following kidney transplantation (KTx). Mutations of hepatocyte nuclear factor 1ß (HNF1ß), a transcriptional factor important for development and maturation of the liver, may cause a multi-system disorder, including CUKAT, diabetes, liver dysfunction. We report a pediatric patient with renal hypodysplasia carrying a novel mutation of HNF1ß who developed NODAT and liver dysfunction.

**Case Description:**
The patient was a 14-year-old girl. She was diagnosed with bilateral hypodysplastic kidney in the newborn period. At the age of 3 years, she received living-related KTxs from her mother preemptively. At the age of 4 years, a steroid pulse for acute rejection resulted in development of diabetes mellitus (NODAT). At the age of 13 years, she complained of acute right flank pain and fever. Laboratory data showed elevated transaminase levels and computed tomography showed malformation of the bile duct. The causes of NODAT were initially thought to be steroid and tacrolimus. However, based on her clinical features, including CUKAT, NODAT, and liver dysfunction, screening for a mutation of HNF1ß was performed. Her peripheral blood lymphocytes were used, primary HNF1ß expression was induced followed by reverse transcriptase-polymerase chain reaction. A total of 11 exons of HNF1ß were sequenced using a standard PCR amplification and direct sequencing protocol. The patient was found to be a heterozygous for a homozygous splicing mutation of HNF1ß, c.344+2T>C.

**Discussion:**
CUTK is the leading cause of ESRD in children and CUKAT is the most frequently mutated gene of CUKAT. Therefore, the contribution of HNF1ß mutations to the development of NODAT appears to be large in the field of pediatric KTxs. An oral glucose tolerance test and screening for HNF1ß mutations may be advisable before KTxs in CUKAT patients.

**FR-PO003**
Acute Kidney Injury from Biopsy Proven Oxalate Nephropathy in a Combined Kidney and Lung Transplant Recipient

**Introduction:**
Acute oxalate nephropathy (AON) is a rare, but well-reported cause of acute kidney injury (AKI) in patients with cystic fibrosis (CF) after lung transplant. We report the only known case of late onset of AON in a transplanted kidney in a combined kidney and lung transplant patient without CF after undergoing medical and surgical management of infective endocarditis.

**Case Description:**
A 62 year old Caucasian male with a remote history of Hodgkin’s disease complicated by radiation-induced pulmonary fibrosis and aortic stenosis underwent a simultaneous double lung transplant and bioprosthetic aortic valve replacement (AVR) in February 2013. His post operative course was complicated by recurrent bronchopneumonias secondary to MSSA requiring prolonged oxacillin as well as ESRD secondary to presumed uncorrected acute tubular necrosis (ATN). The patient subsequently underwent a successful living unrelated kidney transplant from his wife in October 2014 with baseline creatinine of 1.4 mg/dl. Unfortunately, he developed E. faecalis bacteremia secondary to urosepsis and subsequent finding of multi-valvular endocarditis with superior vena cava involvement. This was treated with a prolonged antibiotic course, but recurrent admissions thereafter for CHF and community AKI necessitated a redo AVR along with mitral valve replacement and tricuspid valve repair, “Commando Procedure” on 3-9-2015. Immediate post-operative AKI occurred and was thought due to ATN given the presence of muddly brown casts on sediment exam along with hemodynamic instability requiring temporary intra- and post-operative vasopressor support. Amuric AKI persisted for four weeks leading to a surveillance kidney biopsy to investigate for superimposed rejection. Notable histologic findings were tubular injury consistent with ATN, but more prominent was that of extensive calcium oxalate deposits consistent with AON.

**Conclusion:**
In summary we report the first known case of AKI due to AON in a lung and renal transplant recipient after infective endocarditis requiring prolonged antibiotics and the Commando heart procedure. Though the clinical presentation mimics ATN it is important for clinicians to include AON in the differential diagnosis.
mice results in a concentrating defect in part related to a reduction of AVPR2 expression. As Pax2 and PTIP expression increased in PKD2, Pax2 and PTIP localize to the inner medulla, we hypothesized that Pax2 and PTIP are required for AVPR2 expression.

**Methods:** In IMCD-3 cells with control, Pax2 or PTIP depletion, we determined Pax2 and AVPR2 expression by the mRNA and protein level in response to normal and elevated osmolality. By ChIP analysis, we identified sites of Pax2 and PTIP enrichment on the AVPR2 promoter and determined changes in histone modifications, PolII occupancy in both IMCD and in murine medulla tissues.

**Results:** Pax2 mRNA peaks 8 hours after an increase in osmolality, Pax2 protein peaks at 30 minutes and returns to baseline 2 hours.33% of the HMT activity zone localized to a 100 bp fragment of the AVPR2 promoter, resulting in increases in activation marks, recruitment of PolII to this locus and an increase in gene expression in both cell lines and murine kidney. We identify the minimal promoter that Pax2 binds to and drives expression of the AVPR2 locus. Deletion of this 100 bp region of DNA results in lack of gene expression in the absence and presence of Pax2. Deletion of PTIP results in loss of gene expression even though Pax2 localizes to the promoter region, as histone activation marks are not increased and PolII is not recruited to this locus.

**Conclusions:** Thus, Pax2 and PTIP both regulate the expression of AVPR2 in the murine inner medulla and in cells derived from this tissue. Pax2 provides the locus specificity for PTIP recruitment of the HMT activating complex and gene expression.

**Funding:** NIDDK Support

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**FR-PO095**

Adenine Downregulates NKCC2 and AQP2 in the Rat Kidney and Causes Early Nephrogenic Diabetes Insipidus

**Background:** Long-term feeding of adenine is extensively used to develop animal models of chronic renal failure with metabolic features resembling those observed in humans. However, the mechanisms by which adenine induces renal failure are poorly understood.

**Methods:** In this study, we examined the early effects of adenine (ADN) feeding on water metabolism and renal function in rats placed in metabolic cages. Rats were fed control diet or diet supplemented with 0.25% or 0.50% ADN, or 0.50% adenosine ad libitum with free access to deionized water, and monitored daily for food intake, water balance and urine osmolality, and euthanized for blood an kidney collections after 7 days. The results demonstrated that adenine-fed rats exhibited a sharp polyuria and polydipsia and decreased urine osmolality as early as 3 days, and the magnitude of these effects is dose-dependent. Further, ADN caused a significant reduction in food intake and body weight at 0.50% but not at 0.25%. None of these physiologic parameters were altered by adenine treatment. dDAVP treatment induced a significant increase in urine osmolality in control but not in ADN-treated rats. Immunoblotting experiments demonstrated a sharp reduction in AQP2/actin ratio in rats fed 0.50% ADN (65%), but expression of AQP2/actin ratios were reduced in control (75%) and in rats fed 0.25% ADN (50%). Analysis of kidneys of adenine-treated vs. control animals. The results also demonstrated that the abundance of NKCC2/actin proteins ratio was reduced to zero in the kidney outer medulla of adenine-fed rats vs. control rats. Blood chemistry of adenine-fed rats was normal except for a significant 3.8-fold increase in BUN, as compared to control rats. When rats were fed adenine diet supplemented with 7% NaCl, their BUN was corrected to normal level, with no change in food intake and body weight, but still exhibited a significant reduction in urine osmolality.

**Conclusions:** In conclusion, adenine acts on renal tubules as a signaling molecule and causes nephrogenic diabetes insipidus, likely by directly downregulating NKCC2 and AQP2 in the kidney. The combination of renal fluid loss and decreased food intake likely plays an important role in the development of early acute renal injury that progresses to chronic kidney disease in long-term periods of adenine treatment.

**Funding:** NIDDK Support, Clinical Revenue Treatment

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**FR-PO096**

AMPK Activation Increases Urine Concentrating Ability in a Rat Model of Congenital Nephrogenic Diabetes Insipidus

**Background:** The urine concentration mechanism is primarily regulated by vasopressin which activates NKCC2 and urea transporters to generate a hypertonic interstitium that permits osmoregulation and resorption of AQP2. Congenital nephrogenic diabetes insipidus (NDI) is caused by vasopressin V2 receptor (V2R) mutations. Present treatment options for NDI are limited. We studied AMPK as an alternative pathway to stimulate transporters involved in urine concentration.

**Methods:** Tolaptan (10 mg/kg/day), a selective V2R antagonist, was given by oral gavage to rats for 4 days, +/- metformin (800 mg/kg/day). Urine volume and osmolality were measured daily. Following sacrifice, kidneys were dissected into inner medulla tip, base and outer medulla, and UT-A1, AQP2, and NKCC2 were analyzed by Western blot. Immunoblotting was used to localize AQP2, pAQP2, pAMPK, and NKCC2.

**Results:** Tolaptan was used to produce a rat model of NDI. Urine volumes of tolaptan-treated rats increased 105% within 24 h. Metformin was used to stimulate AMPK as a candidate NDI treatment. Metformin decreased urine volume by 110% back to control levels in 3 days. Urine osmolality in control rats was normalized with tolaptan, with no change in base. Meloxicam significantly increased the ratios of pAQP2 and pAMPK to total AQP2 in IM tip (44% and 40%, respectively). Ibuprofen increased the ratio of pAQP2 to total AQP2 in IM tip but did not affect pAMPK/AQP2 total. Both NSDAs increased pAQP2 and pAMPK ratios in tip and base. Meloxicam increased UT-A1 levels in IM tip, but not base. NR3a, present in rat IM tip and base, was significantly increased in the melanocim and melanocin treated IM base (37% and 20%, respectively), but unchanged in IM tip. AQP2 and UT-A1 abundances were decreased both in wild type (AQP2: to 76%; UT-A1: to 62%) and NR3a-/- mice (AQP2: to 52% UT-A1: to 75%). Outer medullary AQP2 and UT-A1 by 61% in tolvaptan treated rats (p<0.05). IM tip AQP2 was also increased 44% but failed to reach statistical significance (p=0.057). In contrast, IM base UT-A1 and AQP2 protein levels were not changed with AMPK stimulation. Outer medullary NKCC2 abundance was increased 117% with AMPK stimulation in control rats (p=0.004) but not in V2R-blocked rats. Immunochemistry showed that AQP2 and p-AQP2Ser256 appear to be localized on the cell membrane with acute and chronic AMPK stimulation, both in control and V2R-blocked rats.

**Conclusions:** AMPK stimulation in V2R-blocked rats is able to reduce the urine concentrating defect by increasing UT-A1 and AQP2. These results indicate that specific AMPK pathway activators might provide a promising treatment for congenital NDI.

**Funding:** NIDDK Support

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**FR-PO097**

HYAL2 Disruption Leads to Impaired Urinary Dilution Capacity in Mice

**Background:** Hyaluronan (HA) is a hyaluronosylglycan present in high amount in the inner medulla of the kidney but almost absent in the cortex. Hyaluronidase 2 (HYAL2) is one of the two major hyaluronidases acting synergistically to degrade HA. Recently, it has been shown that HYAL2 mice display HA accumulation in the kidney. Renal HA content is known to vary with hydration status. Therefore, our study was set up to characterize the renal excretory capacities and renal water handling in response to water deprivation and acute water loading in HYAL2 mice.

**Methods:** Experiments were performed in HYAL2 mice and in their wild-type controls. After appropriate acclimation, water deprivation was performed during 24 hours. The capacity to excrete a water load was tested on an hourly basis for the next 6 h after i.p. injection of 2 ml of sterile water. Diuresis and urinary osmolality were measured. HA concentration was measured in the kidney tissue and its distribution through the different kidney regions was assessed. HYAL2 mice was examined using immunohistochemistry. Expressions of aquaporin 2 (AQP2) and p-Ser 256 AQP2 were also assessed using immunohistochemistry and immunoblotting.

**Results:** After water deprivation, HYAL2 mice showed the same ability to concentrate urine as wild-type HYAL2+/- mice. On the other hand, HYAL2 mice had a significant delay in the diuretic response induced by an acute water load. As for renal HA content, HYAL2 mice maintained higher HA concentration than HYAL2+/+ mice after both water deprivation and acute water loading. HA was present around tubules in all kidney zones including cortex. In HYAL2 mice, kidney AQP2 and p-Ser 256 AQP2 expressions were increased after water deprivation and decreased after acute water loading to the same extent in KO and WT mice.

**Conclusions:** HYAL2 deficiency and/or increased renal interstitial HA delays the diuretic response to acute water loading without any increase in plasma AVP or collecting duct AQP2 expression.

**Funding:** NIDDK Support, Clinical Revenue Treatment

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**FR-PO098**

Phosphorylated AQP2 and NR3a Reduce NSAID-Induced Urine Concentration Defect

**Background:** Vasopressin increases urine concentration through activation of aquaporin-2 (AQP2) in the collecting duct. Nonsteroidal anti-inflammatory drugs (NSAIDs) block PGE2 synthesis, and may suppress AQP2, producing a urine concentrating defect. NSAIDs can regulate cellular Ca2+ entry and may influence AQP2 trafficking.

**Methods:** We treated rats with a nonselective NSAID, ibuprofen, and a COX-2-selective NSAID, meloxicam, daily for 2 weeks. We assessed urine osmolality and volume, and monitored p-AQP2s by Western blotting. NR3a-/- mice were used to examine if NR3a has a protective role.

**Results:** Both NSAID-treated rats showed an overall decrease in AQP2 and UT-A1 mouse. However, the beneficial effects of NR3a may reflect the altered Ca2+ entry that could be limiting dephosphorylation of AQP2 and promoting improved water homeostasis.

**Funding:** NIDDK Support, Government Support - Non-U.S.
FR-PO099

The Role of Klotho in Renal Sodium and Water Transport
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Background: Klotho (Kl), a transmembrane protein hormone, counteracts aging. Aging is often paralleled by dehydration, which could promote age-related disorders, because it decreases renal Kl protein abundance, as well as increasing plasma osmolarity, antidiuretic hormone (ADH), aldosterone, and 1,25 vitamin D. ADH and aldosterone decrease Kl transcription in HEK293 cells and are elevated in the sera of Kl knockout mice. We explored the effects of Kl deficiency on renal transporters.

Methods: 8-12 week old male Kl+/−, Kl−/− and Kl−/− mice (n=6/group) were fed standard mouse chow and given access to tap water. We evaluated serum levels of Na, K, Cl, Mg, creatinine and urea. We immunoblotted for sodium/hydrogen exchanger isoform 3 (NHE3), renal outer medullary potassium channel (ROMK), the Na-K-2Cl cotransporter (NKCC2), alpha subunit of the epithelial sodium channel (αENaC) and aquaporin 2 (AQP2) in kidney membrane fractions; and for phosphorylated glycosynse synthase kinase 3 beta (pGSK3β) in cytoplasmic fractions.

Results: Data are mean±SEM.

<table>
<thead>
<tr>
<th>Kl+/−</th>
<th>Kl−/−</th>
<th>p&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>25.1±3.4</td>
<td>24.5±3.0</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>148±0.6</td>
<td>144±0.6</td>
</tr>
<tr>
<td>Cl (mEq/L)</td>
<td>4.60±0.2</td>
<td>4.2±0.1</td>
</tr>
<tr>
<td>Mg (mg/dl)</td>
<td>114±1.4</td>
<td>111±1.5</td>
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<tr>
<td>Urea (mg/dl)</td>
<td>50.5±3.3</td>
<td>52.0±2.1</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.11±0.0</td>
<td>0.1±0.0</td>
</tr>
<tr>
<td>NHE3*</td>
<td>55.1±1.1</td>
<td>92.5±2.2</td>
</tr>
<tr>
<td>ROMK*</td>
<td>99.3±2.4</td>
<td>93.4±1.7</td>
</tr>
<tr>
<td>AQP2*</td>
<td>97.5±1.1</td>
<td>97.8±1.4</td>
</tr>
<tr>
<td>pGSK3β*</td>
<td>99.0±0.4</td>
<td>98.3±0.7</td>
</tr>
</tbody>
</table>

Conclusions: In Kl knockout mice, there seems to be normal regulation of NKCC2 and trafficking of AQP2 to the apical plasma membrane in response to ADH. However, Kl knockout mice present reduced sensitivity to elevated plasma aldosterone levels with no increase in oENaC or ROMK protein expression. A lack of Kl can deregulate the adaptive response. (FAPESP).

FR-PO100

Urine Aquaporin-2: Improvement in ELISA Measurements by Alkaline Pre-Treatment and Mechanisms of the Secretion
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Background: Vasopressin-regulated water channel, aquaporin 2 (AQP2) is excreted in urine in the form of extracellular vesicles (mostly exosomes). Urine AQP2 has been measured in many clinical water-balance disorders as a potential biomarker for diagnosis. However, basic permeable support and excretion of AQP2 to the medium was measured.

Methods: Human urinary samples from healthy subjects were measured by a sandwich ELISA. Effects of maneuvers to disrupt the exosome membranes mechanically (freezing and thawing at different temperatures) and chemically (treating with alkali and detergents) on permeability and excretion of AQP2 to the medium was measured.

Results: 1. Urine samples stored at 4°C or -80°C did not show significant AQP2 values in ELISA, whereas those stored at -25°C for more that 2 weeks provided the values. Urine samples treated with 0.4N NaOH/0.5% Triton X-305 showed the consistent and comparable values to those stored at -25°C, indicating the need of disruption of the exosome membranes. 2. Supernatans of 200000g ultracentrifugation contained less than 0.5% of AQP2 of original urine samples. 3. In the culture, AQP2 concentration was more than 10 times higher in apical medium compared to basalolateral, and apical AQP2 excretion was stimulated with 3h-incubation of 10-3 forskolin and 100mM NaCl.

Conclusions: Almost all urine AQP2 is enclosed in exosomes, and pre-treatment of alkaline NaOH allows consistent ELISA measurements. Mechanisms of urinary excretion of AQP2 can be examined in culture system.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical, Government Support - Non-U.S.

FR-PO101

Inhibition of EGFR Activity Increases Aquaporin 2 Phosphorylation and Increases Water Reabsorption in Lithium Treated Mice
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Background: Impairment of vasopressin (VP) receptor type 2 signaling in the kidney is detrimental to water homeostasis. However, strategies targeting cAMP signaling to treat diseases associated with water balance have so far been unsuccessful in humans, prompting a search for alternative pathways that modulate AQP2 trafficking.

Methods: The effect of erlotinib (Erl) oral gavage in a lithium induced nephrogenic diabetes insipidus mouse model was analyzed by measuring urine volume and osmolarity. The effect of Erl on aquaporin 2 trafficking and expression in kidneys was studied by immunostaining and western blot analyses. EGF and Erl regulation of AQP2 trafficking and phosphorylation were studied using selected kinase inhibitors and phospho-specific antibodies on AQP2-expressing LLC-PK1 cells.

Results: Erl alone had only a subtle effect on AQP2 trafficking, but it exerted a significant antagonizing effect on VP-induced AQP2 phosphorylation and membrane accumulation. Conversely, erlotinib (Erl), an EGFR inhibitor, led to a VP-independent increase of apical AQP2 accumulation in collecting ducts, and significantly reduced urine volume by more than 40% after 4 days of treatment in lithium-induced NDI mice. Erl enhanced AQP2 plasma membrane localization in cells by increasing AQP2 ectosity and decreasing endocytosis. This effect was cAMP, cGMP, and PKA independent. Despite apparently bypassing cAMP pathways, Erl resulted in AQP2 phosphorylation accumulation in a dose dependent manner at series 256, an essential step in VP-induced AQP2 membrane accumulation. We propose that EGF has a tonic inhibitory effect on VP action, and that relief of such inhibition enhances AQP2 phosphorylation and results in membrane accumulation.

Conclusions: We showed a crosstalk between EGF and VP in the modulation of AQP2 trafficking. EGFR inhibition increases AQP2 membrane expression bypassing the canonical VP/AMPK/PKA pathway and ameliorates lithium-induced NDI in mice. This study improves our understanding of the diversity of mechanisms that regulate water reabsorption in the body, and uncovers a novel pathway for potential therapeutic targets for NDI.

Funding: NIDDK Support

FR-PO102

ChIP-seq Analysis of Genomic Binding Sites for the Transcription Factor E11 in mckPkd Cells
Hyun Jun Jung, Viswanathan Raghrum, Jae Wook Lee, Mark A. Knepper. Systems Biology Center, NHLBI, NIH.

Background: Collecting duct cells selectively express a number of transport proteins (aquaporins and ion channels) vital to water and electrolyte balance. Previous studies of tissue-specific gene expression in collecting duct cells have implicated E11 family transcription factors (TFs)(Yu et al. PNAS 2009;106:2441). We integrated data from prior proteomics and transcriptomics studies of mouse mckPkd cells using Bayes’ Rule to create a probability-based ranking of all known TFs with regard to likelihood of a role in collecting duct-specific gene expression. Among the top-ranked TFs were several E11 family TFs including E11i.

Methods: To identify genomic binding sites for E11i in mckPkd cells, we carried out ChIP-seq analysis using an antibody successfully employed in the Mouse ENCODE Project. The mckPkd cells were treated with the vasopressin analog dDAVP (100µM) for 24 hr prior to crosslinking and chromatin immunoprecipitation (ChIP) (n=3). DNA libraries were prepared from immunoprecipitated DNA and sequenced using an Illumina HiSeq 2000 sequence to identify TF-enriched genomic regions. Control ChIP was carried out with nonspecific IgG.

Results: The analysis (MACS peak-calling software) identified >2000 binding sites seen in all three replicates and not seen in IgG-only controls. The identified sites mapped to the top-ranked TFs were several E11 family TFs including E11i.

Conclusions: The analysis (MACS peak-calling software) identified >2000 binding sites seen in all three replicates and not seen in IgG-only controls. The identified sites mapped to the top-ranked TFs were several E11 family TFs including E11i. ChIP-seq Analysis of Genomic Binding Sites for the Transcription Factor E11i in mckPkd Cells

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

379A
Deletion of Aquaporin 11 in Transgenic Mice prior to Post-Natal Day 12 Results in Proximal Tubule Injury and Cyst Formation  
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**Background:** AQPII is expressed in the proximal tubule (PT). Neutato AQPII KO mice show PT vacuolization and cyts, resulting in renal failure and death. This study examined whether AQPII deficiency at any stage of kidney development is important for PT injury and cyst formation; 2) if cyts are closed structures or dilations of PT; 3) the role of metabolic challenges on PT injury and cyst formation.

**Methods:** Tamoxifen-inducible AQPII KO mice were generated. Deletion of AQPII at post-natal (PN) day 2, 4, 6, 8, 10, 12 or 21 was investigated alongside neonate total AQPII KO mice. PT cell vacuolization and tubular cyts were observed only in mice where AQPII gene disruption was instigated before PN day 12. AQPII gene deletion after PN week 3 did not result in PT injury or cyst formation. Similar to deletion before PN 2 or 6, maximal PT injury was induced (1600 h) on PN day 21 induced AQPII KO mice or total neonatal AQPII KO mice resulted in PT cytoplasmatic vacuoles but not cyts. IP injection of biotinylated-dextran (10kDa) in adult, neonatally induced AQPII KO mice revealed endocytotic uptake in both cytosolic and PT epithelium. Thus apparent cyts were continuous with PT hence representing PT dilations. This was confirmed by serial sectioning and digital 3-D tracing of PT cyts in adult, neonatally induced AQPII KO mice. Electron microscopy of PT in kidneys from adult neonatally induced AQPII KO mice revealed dilated RER and extensive autophagosomes. Deletion of AQPII from PN 12 leads to PT cell injury and severe PT tubular dilatation. 2) AQPII gene deletion after full kidney development results in normal PT morphology, and only present with PT injury in response to metabolic challenges. 3) Apparent cyts represent PT dilations and are not closed cyts. Conclusion: AQPII deficiency prior to PN day 12 sensitizes PT cytos of the developing kidney to cellular injury and causes severe PT dilations thus revealing a novel mechanism for PT cyst formation.

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

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Involvement of NADPH Oxidase 2 in the Kidney Injury of Aquaporin-11 KO Mouse  
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**Background:** Aquaporin-11 (AQPII), the latest member of the AQ family to be described, is an intracellular AQ. Several in vivo studies have shown that AQPII deficiency causes kidney injury characterized by the formation of multiple cyts. Recently, this kidney injury was reported to be related to the production of reactive oxygen species (ROS). However, the underlying molecular mechanism is largely unknown.

**Methods:** In this study, we examined the mechanism by which AQPII deficiency induces ROS production using PCR array, real-time PCR, immunoblotting, and immunohistochemistry techniques. Also, a pathway analysis was performed with the results from the gene expression analysis.

**Results:** Immunohistochemistry studies showed that the number of 8-hydroxy-2'-deoxyguanosine-positive cells in renal interstitium was increased in AQPII KO mice in comparison with control mice. In parallel, immunoblotting analysis revealed increased levels of renal protein carbonylation in the KO mice. The NADPH oxidase (NOX) enzyme family is important sources of ROS and so far, six members (NOX1, NOX2, NOX3, NOX4, DUOX1, DUOX2) have been identified in mouse. Among them, real-time PCR analysis showed that renal NOX2 mRNA level was markedly increased in the KO mice. Furthermore, mRNAs for the assembly factors (p40phox, p47phox, p67phox) for NOX2 in the kidney were dramatically up-regulated in the KO mice. Immunoblotting analysis revealed that renal NOX2 protein expression was significantly increased in the KO mice. Immunohistochemistry showed that NOX2-positive cells were observed in renal interstitium.

**Conclusions:** These data strongly suggested that increased ROS production in AQPII KO mice was mediated by NOX2, leading to the kidney injury.

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Intracellular Vacuoles in the Kidney of AQPII Null Mice May Simulate the Cisplatin Nephrotoxicity  
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**Background:** Nephrotoxicity is a major side effect of cisplatin in chemotherapy. Despite years of research, the mechanism underlying cisplatin nephrotoxicity remains unclear and effective renal protective approaches during chemotherapy are still unavailable. Pathophysiological mechanisms of cisplatin nephrotoxicity is characterised by intracellular vacuoles in the proximal tubule which are very similar to the kidney phenotype of AQPII null mice before the polycyst development. We speculated that cisplatin may inhibit the function of AQPII to induce intracellular cytos.

**Results:** As the primary target of cisplatin (Casp12) in cisplatin nephrotoxicity has been reported in the literature (J Am Soc Nephrol. 16: 1985, 2005), the expression of Casp12 was examined by real-time PCR in the kidney of AQPII null mice with intracellular vacuoles, i.e. two weeks after birth. Casp3/Casp7 for apoptosis were not induced, while Casp12 for ER stress and inflammation were strongly induced by 9 folds and Casp8 for inflammation by 6/7.5 folds. We next examined the effect of cisplatin on AQPII expression in the kidney. The real-time PCR showed the decrease of AQPII expression by half in mice kidney at three days after 20 mg/kg BW i.p. cisplatin with almost normal renal function. When AQPII hetero-mice were challenged with the same cisplatin treatment, the renal parameters were increased: (hetero/wild) BUN 159.1±3.4 mg/dl, Cr 0.33±0.17 mg/dl, UA 3.13±0.2 mg/dl. We next searched for the interventions which enhance AQPII expression in the kidney. The increase of AQPII expression was observed by thiazide diuretics and by 3 times i.p. of 1g/kg BW 1,2-dichloro-propane. The increase of AQPII mRNA expression was observed in the next day after 3 times i.p. of the treatment.

**Conclusions:** The expression of AQPII may play an important role in the development of cisplatin nephrotoxicity. The enhancing the AQPII expression in the kidney will be a renoprotective strategy in cisplatin nephrotoxicity.

**Funding:** Government Support - Non-U.S.
FR-PO108
RNA-seq Profiling of the Cortical Collecting Duct in Vasopressin Escape
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Background: Vasopressin escape is a protective mechanism that limits hyperosmolality in the syndrome of inappropriate antidiuresis (SIADH). RNA-seq, we investigated transcriptomic changes in microdissected cortical collecting duct (CCD) of rats undergoing vasopressin escape.

Methods: Male Sprague-Dawley rats (120-160 g) were placed on continuous dDAVP (5 ng/hr) infusion for 5 days, and received either a high water load (50 mL/d, "escape") or a normal water load matching insensible losses plus urine output (25 mL/d, "control"). Rats were sacrificed at day 1, 2, and 4 mm of CCDs were collected by manual microdissection. RNAs were processed into cDNA libraries and 50-bp paired-end reads were obtained using an Illumina platform. Reads mapping to Ensembl genes were counted for differential-expression analysis.

Results: Sequence depths were 40-65 million reads, with 80% of reads mapping to Ensembl genes. At day 2, 180 transcripts were downregulated and 339 transcripts were upregulated at a false discovery rate < 0.1. Consistent with increased water excretion in vasopressin escape, transcripts of aquaporin-2 and aquaporin-3 were significantly downregulated at day 1, 2, and 4. Among downregulated transcripts were transcription factors (Hes1, Hmx2, Hoxb5, Hoxb6, Hoxb7, Jun, and Fox3) and a cyclin-dependent kinase inhibitor (Cdkn1b). Among upregulated transcripts were proteins involved in cell division, such as centromere proteins (Cepma, Cenpl, Cenplp, and Cenpf); cyclins (Ccn2, Ccnb2 and Ccnb1), a cyclin-dependent kinase (Cdk1), components of DNA replication machinery (Pol31 in DNA polymerase complex; Mcm2, Mcm3, Mcm4, Mcm6, and Mcm7 in MCM replicative helicase complex; Orc5 in origin recognition complex); polo-like kinase 1 (Plk1); and forkhead box protein M1 (Foxm1). GO terms related to cell division were enriched in upregulated transcripts ("cell cycle phase", adjusted p=8x10^-24; "mitosis", 2x10^-19).

Conclusions: RNA-seq revealed that increased rate of cell division may be an activated mechanism involved in remodeling of the CCD to restore water homeostasis as a part of the adaptation to SIADH.

Funding: Other NIH Support - Division of Intramural Research, NHLBI Projects ZIA-HL001285 and ZIA-HL006129

FR-PO109
Silencing of the Kinome Identifies a Novel Modulator of Aquaporin-2 Trafficking
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Background: Arginine vasopressin (AVP)-dependent water reabsorption requires the redistribution of aquaporin-2 (AQP2) from intracellular vesicles into the plasma membrane of renal principal cells. Despite identification of several proteins participating in the control of AVP-dependent AQP2 trafficking, the molecular mechanisms underlying the AQP2 redistribution are largely unknown. The aim of this study was to identify proteins controlling the localization of AQP2 and thereby to elucidate molecular mechanisms underlying the AQP2 translocation.

Methods: We established a large-scale siRNA screening using mouse collecting duct cells, stably expressing human AQP2. The expression of 719 kinases was knocked down and the AQP2 localisation was analysed by automated immunofluorescence microscopy. Among overexpressed in HEK293 cells, the mutant SGLT2 transporter is not efficiently translocated to the basolateral membrane due to reduced affinity urate facilitatory transporter in kidneys. Here, we show that MCT12 resides on basolateral membranes of proximal tubules. Patients with MCT12 mutation exhibit reduced plasma levels and increased fractional excretion of guanidinoacetate but not glucosuria. A heterozygous mutation (c.643C>A; p.Q215X) in the creatine transporter gene MCT12 (also known SLC16A12) was recently identified as the cause of a syndrome with juvenile cataracts, microcornea and glucosuria in a single family. While the MCT12 mutation co-segregated with the eye phenotype, poor correlation with the glucosuria phenotype questioned a pathogenic role of the mutation in the kidney.

Conclusions: Here we show that MCT12 functions as a low affinity urate facilitatory transporter in kidneys.

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FR-PO111
Mouse Monocarboxylate Transporter 9 Functions as a Urate Transporter
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Background: Monocarboxylate transporter 9 (MCT9) is expressed in kidney, testis and retinal pigment epithelium (RPE). MCT9 is of particular interest due to its unique localization. Here, we suggested, for the first time, that MCT9 functions as a low affinity urate facilitatory transporter in kidneys.

Funding: Government Support - Non-U.S.

FR-PO112
Mutation in the Creatine Transporter MCT12 Causes Low Plasma Level and Increased Fractional Excretion of Guanidinoacetate but Not Glucosuria
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Background: A heterozygous mutation (c.643C>A; p.Q215X) in the creatine transporter gene MCT12 (also known SLC16A12) was recently identified as the cause of a syndrome with juvenile cataracts, microcornea and glucosuria in a single family. While the MCT12 mutation co-segregated with the eye phenotype, poor correlation with the glucosuria phenotype questioned a pathogenic role of the mutation in the kidney.

Methods: We undertook a detailed phenotypic investigation of the index family and performed complementary in vitro studies.

Results: Here we show that MCT12 resides on basolateral membranes of proximal tubules. Patients with MCT12 mutation exhibit reduced plasma levels and increased fractional excretion of guanidinoacetate, but normal creatine levels, suggesting that MCT12 may function as a guanidinoacetate transporter in vivo. However, functional studies in Xenopus oocytes revealed that MCT12 transports creatine but not its precursor guanidinoacetate. This indicates that impaired MCT12-mediated cellular efflux affects guanidinoacetate homeostasis indirectly, e.g. by an increase of the cellular creatine concentration, which is known to inhibit guanidinoacetate synthesis. Genetic analysis revealed a separate, hitherto undescribed heterozygous mutation in SGLT2 (c.265G>A; p.A97T) in the family that segregated with the renal glucosuria phenotype. When overexpressed in HEK293 cells, the mutant SGLT2 transporter is not efficiently translocated to the plasma membrane and displays greatly reduced transport activity.

Conclusions: Our data indicate that MCT12 functions as basolateral exit pathway for creatine in the proximal tubule. Heterozygous mutation of MCT12 affects systemic levels and renal handling of guanidinoacetate. Furthermore, our data reveal the presence of a digenic syndrome in the index family with simultaneous MCT12 and SGLT2 mutation. Thus, glucosuria is not part of the MCT12 mutation syndrome.

Funding: Government Support - Non-U.S.
Weitao Huang, L. Lee Hamm, Kathleen S. Smith.

Background: NaDC1 reabsorsbs filtered citrate (Cit); thus its regulation is important in preventing calcium nephrolithiasis. Importantly NaDC1 reabsorbs other Krebs cycle intermediates such as succinate (Suc) and αKG. Recently Suc and αKG have been found to activate TLR4 in paracrine signaling as their luminal presence stimulates distal nephron G-protein coupled receptors GPCR93 and GPCR99 respectively. Luminal Suc via GPCR99 has been found to stimulate renin release; while αKG via GPCR99 stimulates bicarbonate secretion by type B intercalated cells. The purpose was to determine whether knockout of NaDC1 produces hemodynamic or urine pH changes that might be anticipated by activation of these receptors.

Methods: Adult NaDC1 KO, heterozygous (Het), and wild-type mice (WT), under normal or acid diet for 72 hr, were studied using standard clearance techniques. After anesthetization diet measurements of hemodynamics, renal AngII and lead to severe in renal hypertrophy. Urine, blood and tissue were collected for measurement of Cit, Suc, αKG, and αKG.

Results: NaDC1 KO produced 2, 4, and 10-fold increases in normal urine, Cit, Suc, and αKG, respectively. There was substantial residual reabsorption of Cit and Suc in KO mice, indicating other transporters involved in reabsorption of these substrates. Despite the increase in normal urine there was no significant increase in urine pH (normal or acid diet); in fact on normal diet urine pH was lower in KO mice (5.14 ± 0.04 vs 5.90 ± 0.13 WT; p < 0.001). The lower urine pH in KO mice on normal diet may be a response to the loss of potential bicarbonate in the form of increased Krebs cycle intermediate excretion. There was no change in the ability of KO mice to excrete ammonia. In regard to potential hemodynamic effects mediated by NaDC1 KO and increased urine Suc, no change in MAP was determined comparing WT, Het or KO either on normal or acid diet.

Conclusions: In sum, NaDC1 is responsible for significant reabsorption of filtered αKG and Suc, but knockout of NaDC1 does not impair acid-base homeostasis or BP changes on normal or acid diets.

Funding: NIDDK Support

FR-PO114

The Ablation of Dendritic Cells Prevents the Upregulation of the Intrarenal Renin-Angiotensin System and Renal Sodium Transporters in Response to Angiotensin II and High Salt Diet

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Background: Blood pressure depends on the renal sodium reabsorption mediated by the tubular transporters that are modulated in the intrarenal renin-angiotensin-aldosterone system (iRAS). Angiotensin II (AngII) and a high salt diet (HS) cause hypertension (HT) and the upregulation of the iRAS and sodium transporters. Our previous studies showed that the ablation of Dendritic Cells (DCs) in mice prevented the development of HT in response to AngII+HS. In the present study, we evaluated if the ablation of DCs alters the modulation of the iRAS and tubular sodium transporters by AngII+HS.

Methods: CD11c+ DOG mice, selective loss of DC (CD11c+ cells after Diphtheria Toxin (DT) injection, received vehicle, AngII+HS (AngII, 450 mg Kg−1 day−1 NaCl in drinking water, 1.5% NaCl), or AngII+HS (DT, 8ng/kg d) during 14 days; Paired WT mice received vehicle, AngII+HS or AngII+HS+DT. We measured blood pressure (days 0, 4, 8, 14), and at day 14 we harvested tissues to measure the abundance of renal DCs (MHC-II+) and αENaC. Using qRT-PCR and Western blot.

Results: The injection of DT prevented the development of HT in response to AngII+HS only in CD11c+ DOG mice. CD11c+ DOG and WT mice showed increased abundance of DCs in the cortex (perfusate). Only the CD11c+ DOG mice showed a sharp reduction of renal DCs after DT injection. Both, in WT as in CD11c+ DOG mice the administration of AngII+HS increased the iRAS (in fold of induction: Angiotensinogen, 1.5; Angiotensin converting enzyme, 1.9; and Angiotensin II receptor type I, 5), NHE3, NCC and αENaC increased significantly by AngII+HS+DT. Furthermore, DT did not affect to influence the upregulation of L-NAMe. iRAS in L-NAMe mice had similar (p=0.84) SBP (145±5mmHg) as the Sham+L-NAMe group (146±4mmHg, n=6) after 2 weeks. Relative heart weights were also similar (p=0.45) between L-NAMe+HS (4.9±0.2) and Sham+L-NAMe treated mice (4.8±0.3mg/g BW).

Conclusions: Our data suggests that the full pressor response on AngII is dependent on the spleen. However, the effect of the spleen appears to be independent of renal hypertension. Moreover, the protective effect of the spleen is specific to AngII-dependent HTN and does not appear to be generalizable to all mouse models of hypertension. Further studies are needed to understand the physiological link between lymphoid-bearing organs and hypertension.

Funding: NIDDK Support

FR-PO116

Salt Overload Promotes Severe Renal Injury and Activates AngII, Renal NF-κB and Other Components of Innate Immunity in a Model of Arterial Hypertension


Background: Hypertension (HTN) develops in rats that received the NaF inhibitor pyrroldinedithiocarbamate (PDTC) during lactation. High salt (HS) and uninephrectomy (UNx) exacerbate HTN, increase renal AngII and lead to severe in renal injury. Here, we further investigated the mechanisms of renal injury and the effect of Losartan (L) in this model.

Methods: Munich-Wistar pups received PDTC (PDTC) or no treatment (C) during lactation. At 10 wks of age, all rats underwent UNx and were divided in: C, normal salt diet (NS); PDTC, given NS; PDTC+HS, given HS; PDTC+L-NAME, given HS and L, 50 mg/kg/d. After 3 mo, we assessed: tail-cuff pressure (TCP, mmHg), glomerulosclerosis (GS), collagen content and collagen synthesis. We investigated the mechanisms of renal injury and the effect of Losartan (L) in this model.

Results: In PDTC mice, renal injury caused by HS+UNx involves activation of renal NF-κB, macrophages (Mo) and lymphocytes (Ly), cells/mm2, TLR4 and nuclear NF-κB (nC) and serum IL-6 (ng/mL).

In PDTC+L-NAME mice, renal injury caused by HS+UNx involves activation of renal AngII and innate immunity, including the NF-κB system. FASEB J. CPQNP.

FR-PO117

Interleukin-6 Inhibitation Attenuates Hypertension and Proteinuria in Dahl Salt-Sensitive (SS) Rats

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Background: The infiltration of T lymphocytes in the kidney accompanies hypertension and proteinuria. In Dahl SS rats, pharmacological or genetic reduction of T cells attenuates hypertension and renal damage in SS rats fed high salt. An examination of the infiltrating T cells in the kidney demonstrated that interleukin 6 (IL-6) mRNA levels are >50-fold higher in T cells isolated from the kidney in comparison to circulating T cells. IL-6 is a pro-inflammatory cytokine which positively correlates with hypertension in humans.

Methods: We infused splenectomized rats with interleukin-6 (IL-6) or vehicle intraperitoneally for 14 days after induction of HTN. Heart weight/body weight (H/W) ratios were calculated and kidney leukocyte infiltration was analyzed by flow cytometry.

Results: Mice with prior SPLX+AngII had significantly lower (P<0.05) TCP at both week 1 (148±7) and week 2 (135±7) as compared to Sham+AngII (174 and 173±7mmHg). Similarly, splenectomized mice had significantly smaller (P<0.007) H/W (4.3±0.6) as compared to Sham+AngII treated mice (5.2±0.4mg/g BW). Interestingly, no difference was observed in renal CD45+T (8.2±3 vs 10.6±1x104 cells/g, P=0.64) or CD3+ T-cell infiltration (8.8±0.2 vs 9.6±0.1x104 cell/g, P=0.64) between the Sham+AngII and SPLX+AngII treated mice, respectively. Furthermore, splenectomy did not appear to influence the upregulation of L-NAMe. SPLX+L-NAMe mice had similar (P=0.84) SBP (145±5mmHg) as the Sham+L-NAMe group (146±4mgHg, n=6) after 2 weeks. Relative heart weights were also similar (P=0.45) between splenectomy+L-NAMe (4.9±0.02) and Sham+L-NAMe treated mice (4.8±0.3mg/g BW).

Conclusions: Our data suggests that the full pressor response on AngII is dependent on the spleen. However, the effect of the spleen appears to be independent of renal hypertension. Moreover, the protective effect of the spleen is specific to AngII-dependent HTN and does not appear to be generalizable to all mouse models of hypertension. Further studies are needed to understand the physiological link between lymphoid-bearing organs and hypertension.
Methods: Experiments were performed to assess the potential role of IL-6 in Dah SS hypertension by administering anti-IL-6 neutralizing antibody (anti-IL-6; 4 µg/day, IP; R&D Systems, Minneapolis, MN) or normal goat IgG control (4 µg/day, IP) for 11 days. Results: The MAP and urine protein excretion rates (Upro) were similar between the groups of SS rats (n=13-16/group) when fed low salt (0.4% NaCl) chow. Following 11 days of high salt (4.0% NaCl) treatment, the rats receiving anti-IL-6 demonstrated significantly lower in the treated vs the control group (954±133 mg/day vs 1802±336 mg/day). Moreover, the increase in MAP following 11 days of 4.0% NaCl intake was significantly attenuated in treated (MAP=138±3 mmHg) vs the control group (MAP=151±4 mmHg). The Upro was also significantly attenuated in treated (193±17 mg/day) vs control group (252±20 mg/day). To investigate mechanisms of action, a flow cytometry analysis of infiltrating immune cells in the kidney (n=4-5/group) was performed. The total number of leukocytes (CD45+) was significantly lower in the treated vs the control (14.2±1.7x10^6 vs 21.6±2.8x10^6 cells/kidney). The total number of monocytes and macrophages (CD11b+) was significantly lower in the treated vs the control group by 31%. The total number of T cells and T regulatory cells were not different among the groups.

Conclusions: The present studies indicate that IL-6 may participate in the development of SS hypertension and end-organ damage by mediating the infiltration of leukocytes into the kidney.

FR-PO118
High Salt Affects Toll-Like Receptor-Induced Gene Expression in Macrophages
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Background: High dietary salt intake is a major risk factor for cardiovascular disease. A high-salt (NaCl) diet increases NaCl concentrations in the skin. In the skin, macrophages respond to high NaCl by the osmosensitive transcription factor NFAT5 and promote NaCl efflux via lymph vessels. Other effects of NaCl on local macrophages have remained largely elusive. Therefore, we investigated whether evidence suggests that NFAT5 also regulates multiple Toll-like receptor (TLR)-induced genes such as NOS2, TNF, and IL6 in macrophages, independently of osmotic stress. We aimed to investigate the effects of NaCl-generated hypertonicity on the expression of these genes in TLR-activated macrophages.

Methods: We simulated the hypertonic skin microenvironment by culturing macrophage-like RAW 264.7 cells in NaCl-induced hypertonic media (340-480 mMosm/kg) and compared this with normotonic media (320 mMosm/kg). After 1 to 24 hours of stimulation with lipopolysaccharide (LPS) or Zymosan A, a TLR2 ligand, we measured nitric oxide production (2-fold), NOS2 mRNA (3-fold) and NOS2 protein expression (2.25-fold) in LPS- and Zymosan A-stimulated cells. In contrast, equiosmolar mannitol or urea did not affect p65 in vascular smooth muscle cells.

Results: NaCl significantly and dose-dependently increased nitric oxide (NO) production (2-fold), NOS2 mRNA (3-fold) and NOS2 protein expression (2.25-fold) in LPS- and Zymosan A-stimulated cells. In contrast, equiosmolar mannitol or urea did not affect expression levels. NaCl also increased LPS-induced p38 phosphorylation and total NFAT5 protein expression. Similarly, NaCl increased TNF mRNA expression 1.25-fold. Remarkably, NaCl significantly downregulated LPS-induced expression of CCL5 (4-fold), IL6 (2.4-fold) and IL12b mRNA (3.5-fold).

Conclusions: Elevated concentrations of NaCl, comparable with those found in the skin after high dietary salt intake, amplify expression of NOS2 and TNF in TLR-stimulated macrophages. This effect is likely mediated via p38 and NFAT5. Increases in NOS2 and TNF mRNA expression. Similarly, NaCl increased TNF mRNA expression 1.25-fold. LPS- and Zymosan A-stimulated cells. In contrast, equiosmolar mannitol or urea did not affect p65 in vascular smooth muscle cells.

FR-PO119
Indoxyl Sulfate Uptake Activates Protein Kinase Cdelta in Human aortic smooth muscle cells
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Background: Chronic kidney disease (CKD) is considered major causes of death in cardiovascular disease (CVD) patients. Prorenin receptor (PRR) is significantly expressed in the human smooth muscle cells. In this study we aimed to clarify the role of indoxyl sulfate (IS), a uremic toxin, in PRR activation in rat aorta and human aortic smooth muscle cells (HASMCs).

Methods: CRD rats and IS-administrated rats were subjected for in vivo experiments. Human aortic smooth muscle cells (HASMCs) was treated with or without indoxyl sulfate (IS).

Results: Immunohistochemistry showed increased expression of PRR and renin/ prorenin in aorta of CRD rats and IS-administrated rats compared with normal rats. IS elevated the expression of PRR and prorenin in HASMCs. N-acetylcyesteine, an antioxidant, and diphenylethenesindamin, an inhibitor of nitric oxide synthase, attenuated the expression of PRR and prorenin in HASMCs.

Conclusions: IS promotes aortic expression of PRR and renin/prorenin through OAT3-mediated uptake, production of reactive oxygen species, and activation of AhR and NFκB p65 in vascular smooth muscle cells.

FR-PO120
Role of Skin and Endothelial Surface Layer Heparan Sulfates in Blood Pressure Regulation
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Background: Besides the skin, the endothelial surface layer (ESL) contains many glycosaminoglycans (GAGs) that can osmotically inactivate Na+ and may affect blood pressure (BP). EXT genes regulate heparan sulfate (HS) polymerization, the predominant ESL GAG. In mice with heterozygous loss of EXT1 and EXT2 (EXT), and wildtype (WT) mice, we investigated the role of HS in the skin and ESL in BP regulation after an acute and chronic NaCl load.

Methods: We investigated BP effects of a 7-d normal (0.3%), NSD, and high (8.0%) HSD NaCl diet, with tail cuff measurements, and an acute 1.8% NaCl load (8 µl/g) with intracardiac measurements. We used intravital microscopy to estimate ESL thickness in ~40 µm crenaster vessels on both diets. We used high performance liquid chromatography-mass spectrometry to measure skin HS disaccharide concentration.

Results: Baseline BP was equal in WT and EXT mice (p=0.9), with no difference between NSD and HSD. Relative to WT, acute NaCl infusion increased BP in EXT mice (p<0.02), while heart rate remained equal (p=0.5). After a NSD and HSD, EXT mice had a 78% reduction of ESL thickness compared to WT mice (Fig A). HSD increased ESL thickness in WT, especially in 20-40 µm vessels, but not in EXT mice (Fig BC). Skin HS concentration and sulfation patterns were equal between diets in WT mice (Fig DE). On NSD, EXT mice had more highly sulfated HS compared to WT (Fig DE). EXT mice on a HSD had the highest skin HS concentration, of which most were low-sulfated.

Conclusions: An intact ESL is pivotal to prevent a BP increase during acute NaCl excess. Skin GAGs may be particularly important to prevent detrimental NaCl effects on the long-term, especially when the ESL is damaged by NaCl exposure.

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FR-PO121
Functional and Dynamic Microcompartmentation of Cav-1/TRPV4/KCa Channels in Caveolae of Endothelial Cells
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Background: Cav-1 activated K+ channels (Kv channels) play an important role in the endothelium-dependent hyperpolarization and regulation of vascular tone and blood pressure. For activation, Kv needs to colocalize with Cav-1 in caveolae. In endothelial cells under static condition. Mechanical stimulation of cells via exposure to shear stress led to a partial de-novo colocalization of K Cav-3.1 with Cav-1 and TRPV4. It has been proposed that Kv channels and Cav-1 form functional units and may affect blood pressure. We show that TRPV4 and small-conductance K Cav-2.3 are enriched in caveolae of human microvascular endothelial cells. Using immunoprecipitation, immunocytochemistry and superresolution microscopy, we found a caveolae-dependent association between Cav-1, TRPV4 and small conductance K Cav-2.3, but not intermediate conductance K Cav-3.1, in endothelial cells under static condition. Mechanical stimulation of cells via exposure to shear stress led to a partial de-novo colocalization of K Cav-3.1 with Cav-1 and TRPV4. In a mouse model of genetic Cav-1 deficiency, we found significantly reduced K Cav-3.1-mediated currents as determined by patch-clamping in carotid artery endothelial cells (CAEC). We conclude that Cav-1^-/- mice compared to wildtype. Functionally, Cav-1^-/- mice were less responsive to shear stress and acetylcholine.
FR-PO122

Adenosine A1 Receptor Exacerbates Water-Sodium Retention in Deoxycorticosterone Acetate-Salt Hypertensive Mice

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Background: Water-sodium retention is the key change in salt sensitive hypertension. Adenosine A1 receptor (A1AR) engages in tubuloglomerular feedback; its activation is followed by increased secretion of atrial natriuretic peptides (ANP) in the heart. We aim to study the function of A1AR in water-sodium retention.

Methods: DOCA-salt hypertensive model was established by removal of left kidney, implantation of a DOCA pellet (200mg, 60-day release), and feeding with high salt diet (8%NaCl). Arterial blood pressure and heart rate were measured by tail-cuff method. Urine samples were collected using metabolic cage. The CD73 (an adenosine synthetase), A1AR, ANP and Corin (a protease cleaves pro-ANP, producing ANP) mRNA expression were measured by real-time PCR.

Results: Wildtype DOCA-salt mice showed higher blood pressure (124.7±20.3 vs. 105.8±14.1 mmHg, P<0.01), slower heart rate (562.0±90.8 vs. 681.5±90.1, P<0.01), and increase in 24h urine output (3606.0±2359 vs. 1399±752 ml, P<0.001). The adenosine pathway was activated in DOCA-salt mice evidenced by increased CD73 (2.22 and 17.7 times increased expression in kidney and heart, P<0.034 and 0.001) and A1AR expression (2.54 and 11.12 times increased expression in kidney and heart, P=0.032 and 0.009). The cardiac mRNA expression of ANP and Corin were also significantly higher in DOCA-salt mice (176.67 and 30.93 times increased expression, P=0.030 and 0.005). The A1AR+ mice showed no significant changes in blood pressure or heart rate between DOCA-salt and sham group. The elevation in 24h urine output (7003±3742 vs. 3606±2359 ml, P=0.031) and 24h sodium excretion (1464.5±860.0 vs. 1479.7±48.9 mmol/d, P=0.028) was more prominent compared to wildtype DOCA-salt mice. There was no change in either ANP or Corin mRNA expression.

Conclusions: A1AR may exacerbate water-sodium retention in salt sensitive hypertension. The reduction in glomerular hyperperfusion and hyperfiltration through tubuloglomerular feedback possibly outweighs the up-regulation of Corin and subsequent ANP expression.

FR-PO123

Dietary Fructose Increases Renal Sympathetic Nerve Activity in Response to High Salt Diet in Awake Freely Moving Rats

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Background: High consumption of fructose containing foods is increasingly prevalent. Fructose is associated with metabolic syndrome including hypertension. Fructose upregulates renal Na and Cl transport and induces neuroexocytosis, both of which may increase blood pressure. Here we tested the hypothesis that fructose-fed rats fed a high salt diet will have higher plasma renin activity (PRA), renal sympathetic nerve activity (RSNA) and mean arterial pressure (MAP) than glucose-fed rats on similar diet.

Methods: Male Sprague Dawley rats were instrumented for telemetric MAP and RSNA measurements. They were placed on 20% glucose (GF) or 20% fructose (FF) in their drinking water and 0.4% NaCl diet for 10 days then switched to 4% NaCl diet with further monitoring. RSNA recordings were obtained using LabChart 7 Pro. Rats were also subjected to air jet stress and nasopharyngeal reflex testing.

Results: Baseline integrated RSNA did not differ between GF and FF rats. RSNA decreased in GF rats to 0.961 ± 0.182 mV/sec after high salt diet. In contrast, integrated RSNA increased from 1.199 ± 0.245 to 1.600 ± 0.231 mV/sec after high salt intake in FF rats (P < 0.05). Air jet stress and nasopharyngeal reflex responses in MAP and RSNA in GF rats were as expected and brief but in FF rats both responses were significantly greater and sustained for a longer period of time. High salt suppressed. PRA by only 40% in FF rats: 2.05 ± 0.27g Ang I/ml/hr (high salt) vs 3.48 ± 0.45 ng Ang I/ml/hr (baseline; P < 0.05).

Conclusions: We found that the expected suppression of RSNA by high salt diet is completely reversed into stimulation with high fructose diet. The suppression of PRA by high salt diet is blunted and the response to acute stressors enhanced, thus suggesting increased RSNA is a critical component of fructose-induced salt-sensitive hypertension.

Funding: NIDDK Support, Veterans Administration Support
Results: At baseline systolic BP were similar in CNTF-KO and WT mice (119±2 vs.124±1 mmHg). CNTF deficiency significantly attenuated BP increase under Ang II infusion (week 1: 139±3 vs. 153±3 mmHg; week 2: 151±5 vs. 168±4 mmHg; n=19; P<0.01). Strikingly, in the CNTF-KO group significantly less animals died of cardiovascular causes (4.2% (KO)) vs. 29.2% (WT) P<0.05). In accordance, end organ damage (cardiac hypertrophy, renal vascular fibrosis and tubulo-interstitial damage) was attenuated in the CNTF-KO group. In the isolated perfused kidney, pressor response to Ang II was significantly attenuated in CNTF-KO mice. Administration of CNTF (0.5nM) nearly restored the Ang II dependent pressor response. This effect was mediated through a JAK2/STAT3 dependent pathway as static (0.1µM), a selective STAT3 inhibitor abolished the CNTF induced increase in pressor response in kidneys of CNTF-KO. On cellular basis, CNTF induced phosphorylation of STAT3 and MYPT in VSMCs.

Conclusions: Better survival and less end organ damage strongly suggest that CNTF has a major impact on blood pressure regulation. CNTF seems to modulate the Ang II induced vasoactivity via a JAK2 / STAT3 dependent mechanism. Thus, CNTF might qualify as therapeutic target in hypertension.

Funding: Government Support - Non-U.S.

FR-PO127
Angiotensin II AT1 Receptor Potentiates Prostaglandin E2 Vasconstrictor Effects Maria Palazzo Kraemer, Fred S. Lamb, Richard M. Breyer. 1

Background: Prostaglandin E2 (PGE2) is a key modulator of blood pressure and arterial tone. It usually has vasodepressor effects however under certain circumstances can act as a vasoconstrictr. Recent reports have articulated that sub-threshold concentrations of KC1 and phenylephrine augment PGE2-mediated constriction in rat femoral arteries, however the effects of angiotensin II (Ang II) on PGE2-mediated contraction are unknown.

Methods: Wire myography was performed on femoral arteries isolated from WT or EP deficient mice. Ang II had no effect on mouse femoral arteries at doses up to 1 µM. Pretreatment of arterial rings with 1 nM Ang II potentiated PGE2-evoked constriction in a dose dependent manner (AUCmax: 1.78±0.33, AUCMax 22.27±9.820, P<0.05). To identify the relevant E-Prostanoid (EP) receptor, femoral arteries from EP1, EP2, and EP3 receptor null mice were tested. Arteries isolated from EP1- and EP2- but not EP3- mice responded to PGE2 after Ang II priming. Pretreatment of arterial rings with 1 µM losartan, an AT1 angiotensin receptor antagonist, blocked PGE2-induced constriction in both WT and EP deficient mice.

Results: PGE2 had no effect on mouse femoral arteries at doses up to 1 µM. Pretreatment of arterial rings with 1 nM losartan, an AT1 angiotensin receptor antagonist, blocked PGE2-induced constriction in both WT and EP deficient mice.

Conclusions: The renin-angiotensin system plays a key role in the maintenance of cardiovascular and renal homeostasis, primarily via appropriate activation of the angiotensin II type 1 receptor (AT1R). On the other hand, exaggerated activation of AT1R signaling would exert detrimental effects, such as various aging-related diseases including renal dysfunction. We previously identified an AT1R-associated protein (ATRAP/Agrap), which is a molecule directly interacting with the AT1R. The accumulating results indicate that ATRAP exerts functionally selective inhibition on exacerbated AT1R activation in response to pathological stimuli. The present study was performed to investigate pathophysiological significance of ATRAP in aging-related phenotypes by employing systemic ATRAP-knockout mice (ATRAP-KO mice).

Methods: ATRAP-KO mice and their wild-type control mice (WT mice) were fed the standard diet and maintained until death to estimate their life spans. Their growth (body weight change and appearance) and physiological parameters (blood pressure, cardiac index, water and lipid metabolism) were also analyzed. Furthermore, aging-related organ damages in the hearts, aortas and kidneys were examined in young (3 to 4 months old) and aged (22 to 25 months old) mice in both groups.

Results: There was no difference in the growth between two groups. In addition, ATRAP-KO mice and their controls did not show any evident difference in terms of physiology, aging-related orgaion damages, and glucose and lipid metabolism. Furthermore, aging-related organ damages in the hearts, aortas and kidneys were examined in young (3 to 4 months old) and aged (22 to 25 months old) mice in both groups.

Conclusions: In the present study, ATRAP-KO mice showed accelerated renal fibrosis with shortened life span. Therefore, ATRAP deficiency seems to exacerbate the aging-related renal fibrosis and to inhibit the longevity.

FR-PO130
Effects of Deficiency of Angiotensin Receptor-Binding Molecule on Blood Pressure Regulation in Chronic Kidney Disease Ryu Kobayashi, Kouchi Tamura, Hiromichi Wakui, Akinoibou Maeda, Kengo Azushima, Sona Hak, Ryu Kobayashi, Masato Ohsawa, Yoshitoyo Toya, Satoshi Umemura. Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan.

Background: The renin-angiotensin system plays a key role in the maintenance of cardiovascular and renal homeostasis, primarily via appropriate activation of Ang II type 1 receptor (AT1R). On the other hand, exaggerated activation of AT1R signaling would exert detrimental effects, such as promoting various aging-related diseases including chronic kidney disease (CKD). We previously identified an AT1R-associated protein (ATRAP/Agrap), which is a molecule directly interacting with the AT1R. Accumulating results indicate that ATRAP exerts functionally selective inhibition on exacerbated AT1R activation in response to pathological stimuli. The present study was performed to investigate pathophysiological significance of ATRAP in aging-related phenotypes by employing systemic ATRAP-knockout mice (ATRAP-KO mice).

Methods: ATRAP-KO mice and their wild-type control mice (WT mice) were subjected to 5/6 nephrectomy (Nx) as CKD model. To examine the effects of ATRAP deficiency, blood pressure and other parameters were measured in ATRAP-KO mice and WT mice after 5/6 Nx.

Results: At baseline, blood pressure was similar in ATRAP-KO and WT mice. In ATRAP-KO mice, blood pressure increased from 2 to 8 weeks after 5/6 Nx and was significantly higher than that in WT mice (ATRAP-KO vs WT; systolic blood pressure at 4 weeks after 5/6 Nx, 124±2 mmHg vs 107±1mmHg, P<0.01). With respect to the mechanism of elevated blood pressure in ATRAP-KO mice after 5/6 Nx, plasma volume was significantly higher in ATRAP-KO mice than in WT mice after 5/6 Nx, in spite of no significant difference in creatinine clearance between two groups after 5/6 Nx.

Conclusions: Although ATRAP-KO mice show similar blood pressure and renal function with WT mice in normal condition, ATRAP-KO mice exhibited significantly
increased blood pressure and plasma volume after 5/6 Nx compared with WT mice. Therefore, endogenous ATRAP may exert a protective function against pathological blood pressure elevation in CKD.

FR-PO131
In Vivo Action of Angiotensin II Type 1a Receptor in Renal Injury Induced by Deoxycorticosterone Acetate-Salt Hypertension: Mikako Hisamichi,1 Atsuko Remori,1,2 Takeshi Sugaya,1 Daisuke Ichikawa,1 Kenjiro Kimura,1 Yugo Shibagaki,11 Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan; 2Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki, Japan; 3Dept of Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: The AT1a receptor plays a major role in the renal action of Ang II and is expressed in vascular smooth muscle cells of the afferent arterioles. In this study, we investigated the morphological change in deoxycorticosterone acetate (DOCA)-salt hypertensive rats and confirmed the in vivo function of the AT1a receptor against renal damage due to hypertension.

Methods: To examine urinary L-type fatty acid binding protein (L-FABP) as an indicator of tubulointerstitial damage, we used both L-FABP clearance studies and phase contrast MRI to confirm the in vivo function of the AT1a receptor against renal damage due to hypertension.

Results: In the DOCA salt hypertensive model with L-FABP+/- AT1a +/+ (DOCA), slight expansion of the glomerular area and tubulointerstitial damage were observed, but no glomerular sclerosis. In the AT1a knockout mice administered DOCA-salt (L-FABP+/- AT1a -/- DOCA mice), glomerular sclerosis with expansion of the mesangial area was found, and the degree of tubulointerstitial damage was more severe compared to L-FABP+/- AT1a +/+ DOCA mice. L-FABP+/- AT1a +/+ DOCA mice and L-FABP+/- AT1a -/- DOCA mice. This renal damage induced in the L-FABP+/- AT1a -/- DOCA mice was significantly attenuated by reduction of blood pressure using Hydralazine. Activation of the AT1a receptor may contribute to myogenic response of the afferent arteriole involved in the renal autoregulatory mechanism.

Conclusions: In conclusion, kidneys without AT1a receptors exhibited an increased vulnerability to hypertension, and therefore activation of the AT1a receptor inhibited the transmission of the elevated systemic pressures to the glomeruli.

FR-PO132
Renal Blood Flow and Oxygenation During Renin-Angiotensin-Aldosterone System Activation – Two Sides of the Same Coin? Rene van der Bel,1 Aart J. Nederveen,2 Bram F. Coolen,2 Wouter V. Potters,2 Hein J. Verberne,2 Lütfett Vogt,1 Erik Stroes,1 C.T.P. (Paul) Krediet,1 Internal Medicine, AMC, Univ of Amsterdam, Netherlands; 2Radiology, AMC, Univ of Amsterdam, Netherlands.

Background: In chronic kidney disease, renal hypoxia and renin-angiotensin-aldosterone system (RAAS) activation may augment each other. Although renal oxygenation (RO) measured by Blood Oxygen Level Dependent (BOLD) MRI is not correlated to Glomerular Filtration Rate (GFR), recent data suggest that RO relates to inter-individual variation of RAAS activity. Further explore this we measured the effects of Angiotensin II (Ang-II) on renal blood flow (RBF) and RO in healthy subjects.

Methods: After a 30 min baseline phase, 8 healthy volunteers (age 19-22 years) were subjected to continuous Ang-II infusion at 0.3, 0.9 and 3.0 ng/kg/min for 12 minutes per dose. RO and RBF were assessed by BOLD and phase contrast MRI, respectively (Ingenia, 3.0T, Philips Healthcare). Off-line, R2* values were calculated for cortex and medulla, on mono-exponential fitting to multi-echo 2-dimensional fast-field-echo data (TR 140 ms; FA 70°; TE 2 ms; DTE 5 ms; 16 echoes; voxel 1.2 mm² by 4 mm). RBF was calculated in the proximal renal artery after manual vessel segmentation. During a second visit (n=6), GFR and Effective Renal Plasma Flow (ERPF) were measured by 133mTechnetium Tc 99m-HMPAO (Tc-99m-HMPAO) renal scintigraphy.

Results: Mean arterial blood pressure increased from 83.0±2.85 at baseline to 91.3±3.76 mmHg (p<0.002). RBF decreased dose dependently from 11.1±2.08 to 8.05±1.02 (p=0.02) ml/min/100g tissue. GFR and ERPF both decreased (10±7.1%, p=0.016; 24±4.5%, p<0.001). RBF and ERPF measurements strongly correlated (R=0.75, p<0.001). There was a trend towards a cortical R2* increase of 7.2±5.37% (p=0.041); medullar R2* did not change. Cortical DPP-4 and DRBF inversely correlated (R=0.42, p=0.044). Cortical DPP-4 and AGFR correlated (R=0.48, p=0.017).

Conclusions: Ang-II causes a dose dependent DRBF. The observed DRO seem to differ between cortex and medulla. Only for the cortex BOLD may provide an index of tissue perfusion.

FR-PO133
Chloride Contributes to Hypertension and Renal Injury in Aldosterone-Salt Treated Rats: Takahiro Yamauchi, Shigehiro Doi, Toshihiko Doi, Kensei Sasaki, Toshinori Ueno, Ayunami Nakashima, Takao Masaki. Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Aldosterone-salt treatment is known to induce renal inflammation and platelet aggregation. Hypertension is a development of these changes as well as elevated EMT markers. In addition to sodium, chloride has recently been reportedly to be involved in renal damage, raising the possibility that sodium-bicarbonate may ameliorate renal injury and hypertension in aldosterone-salt treated rats. Further, the aldosterone-salt group compared with the NaHCO3-aldo-salt group, 1) drinking 1% NaCl solution with aldosterone infusion (NaCl-aldosterone treated group), 2) drinking 1% NaHCO3 solution with aldosterone infusion (NaHCO3-aldosterone treated group), and 3) drinking water with vehicle infusion. Blood pressure levels were measured at -70°; min TE 2 ms; DTE 5 ms; 16 echoes; voxel 1.2 mm² by 4 mm). RBF was calculated in the proximal renal artery after manual vessel segmentation. During a second visit (n=6), GFR and Effective Renal Plasma Flow (ERPF) were measured by 133mTechnetium Tc 99m-HMPAO (Tc-99m-HMPAO) renal scintigraphy.

Results: In the NaCl-aldosterone group had higher blood pressure levels than the NaHCO3-aldosterone group. Protein expression of eNOS and PdGf in the membrane fraction was also increased in the NaCl-aldosterone group compared with the NaHCO3-aldosterone group. In addition, the NaCl-aldosterone group had high protein levels of NCC and phosphorylated NCC in the whole protein and membrane fractions. On the other hand, the expression of inflammatory (C3D, CD68, IL17A, IL-23 receptor) and fibrotic markers (α-smooth muscle actin, collagen I) were greater in the NaCl-aldosterone group.

Conclusions: These findings suggest that chloride plays an important role in the development of NaCl-aldosterone-induced hypertension and renal injury.

FR-PO134
RAGE-DNA Aptamer Improves Aldosterone-Induced Renal Injury Possibly via Inhibition of Rac1-MR Axis in Mice with Hypertensive Nephropathy: Kensei Taquchi,1 Sho-ichi Yamagishi,1 Yuichi Higashimoto,2 Yosuke Nakayama,1 Katsuhiko Asanuma,2 Seiji Ueda,1 Kei Fukami.1 Div of Nephrology; Dept of Medicine; 2Dept of Pathophysiology and Therapeutics of Diabetic Vascular Complications; Dept of Chemistry, Kurume Univ School of Medicine, Kurume, Japan; 3Div of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Background: Advanced glycation endproducts (AGEs) stimulate the generation of reactive oxygen species (ROS) and subsequently enhance various intracellular pathways through the interaction with receptor for AGEs (RAGE). Although AGEs-RAGE axis has been mainly investigated in diabetic nephropathy, its pathophysiological role in hypertensive nephropathy (HN) is unknown. In addition, recent evidence has suggested that aldosterone (aldo)-mineralocorticoid receptor (MR) system plays a crucial role for the pathogenesis of HN. In this study, we examined whether AGEs-RAGE system could interact with aldo-MR axis in deoxycorticosterone acetate (DOCA)-induced HN in mice. Further, we explored the inhibitory effects of DNA-aptamer directed against RAGE (RAGE-aptamer) on aldosterone-induced renal injury in HN. Methods: Uninephrectomized 8-week-old C57Bl6/J male mice were divided into three groups; 4% salt diet (control), 4% salt diet with DOCA (50mg), and DOCA with hydralazine (Hyd). RAGE-aptamer constructed by SELEX method was continuously administrated with osmotic mini pump.

Results: DOCA elicited-UAE was independent of blood pressure. Renal ROS generation, RAGE protein expression and plasma carboxymethyl lysine (CML) levels were elevated in DOCA/salt mice. RAGE was co-localized MR in podocytes by immunohistochemical analysis. Further, RAGE-bound Rac1 activation and MR overexpression were observed in DOCA/salt mice. DOCA-elicited increase in UAE, renal ROS generation and RAGE expression, plasma CML levels were improved by RAGE-aptamer independent of blood pressure. Interestingly, RAGE-aptamer suppressed GTP-bound Rac1 activity and MR overexpression in DOCA/salt mice.

Conclusions: AGEs-RAGE axis and Rac1-MR pathway could be correlated with each other, which could lead to podocyte injury in HN. RAGE-aptamer may be a novel therapeutic strategy for the progression of HN.

FR-PO135
Dipeptidyl Peptidase-4 Inhibitor Ameliorates the Aldosterone-Induced Renal Fibrosis: Kang-Yung Peng, Vincent Wu. Dept of Internal Medicine, National Taiwan Univ, Taipei, Taiwan.

Background: Renal fibrosis is considered a common outcome of a wide variety of chronic kidney diseases with diverse causes. However, no antifibrotic agent has been approved in clinical practice yet. In this study, we examined the effect of dipeptidyl peptidase-4 (DPP-4) inhibitor on aldosterone-induced fibrosis by aldosterone.

Methods: Human proximal tubular epithelial cells (HK2) were used to examine the inhibitory effect of DPP-4 inhibitor on aldosterone induced epithelial-mesenchymal transition (EMT). Besides, aldosterone infusion mice were used to evaluate the effect of DPP-4 inhibitor, linagliptin, on aldosterone induced renal fibrosis. Expression of TGF-β, OPN and molecules involved in EMT were examined using western blot and immunohistochemistry. Renal fibrosis was determined by Masson's trichrome staining.

Results: In vitro studies showed that aldosterone significantly increases the expression of TGF-β, OPN and markers of EMT in HK2 cells, while these effects were abolished in that treated with DPP-4 inhibitor. Similarly, the aldosterone-infused mice exhibited severe kidney fibrosis. The expression of TGF-β, OPN, vimentin and α-SMA were induced by aldosterone, and oral DPP-4 inhibitor ameliorated the kidney fibrosis and lessened the increase in fibrotic proteins without significant changes in blood pressures.

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Hypertension: Basic
Poster/Friday

**FR-PO136**
G-Protein-Coupled Receptor 40 Mediates the Regulation of Epithelial Sodium Channel by Epoxyeicosatrienoic Acid Signaling

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**Background:** Epoxyeicosatrienoic acid (EET) plays diverse functions including cellular proliferation, anti-inflammation and vasorelaxation. Although it has been demonstrated that EET also regulate epithelial sodium channel (ENaC), the potential functional receptor mediating the biological effect of EET has remained elusive. In the present study, we investigated the role of GPR40 mediating ENaC regulation of EET in mouse cortical collecting duct (M1-CCD) cell line.

**Methods:** M1-CCD cells were cultured with aldosterone in the absence or presence of 14,15-EET. In addition, M1-CCD cells treated with aldosterone were cultured in the absence or presence of GW9110, a GPR40 antagonist.

**Results:** The mRNA and protein of ENaC-a and GPR40 were endogenously expressed in the M1-CCD cells as well as the cortical collecting ducts of murine kidney. Treatment with aldosterone increased the protein expression of ENaC-a and mineralocorticoid receptor (MR). These changes were abolished by 14,15-EET treatment, and treatment with 14,15-EET increased the phosphorylation of ERK1/2. Inhibition of GPR40 by treatment with GW9110 enhanced the aldosterone-induced upregulation of ENaC-a and MR, while decreased ERK1/2 phosphorylation.

**Conclusions:** In conclusion, EET inhibits aldosterone-induced ENaC activation by the inhibition of MR and activation of ERK1/2. GPR40 inhibition augmented the aldosterone-induced ENaC activation by the activation of MR and inhibition of ERK1/2. These findings suggest that GPR40 mediate the ENaC regulation by EET signaling.

**FR-PO137**
The Extra Renal Effect of Hydrochlorothiazide on Systemic Blood Pressure: Role of Vasodilation in Volume Depleted States

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**Background:** Thiazides are specific inhibitors of the Na⁺-Cl⁻ cotransporter (NCC) in the distal nephron, and the most commonly used diuretics for the treatment of mild arterial hypertension, vascular stiffness, vasoconstrictor and endothelium-dependent and independent vascular dysfunction. Thiazides are at increased risk of hypotension and kidney hypoperfusion subsequent to systemic vasodilatation by HCTZ.

**Methods:** Methods: Balance studies were performed in age/sex-matched wild type and NCC deficient mice. The blood pressure was measured using computerized tail cuff method. Cardiac functions were analyzed by echocardiography.

**Results:** Hydrochlorothiazide (HCTZ) significantly reduces systemic blood pressure when NCC KO mice are volume-depleted and their renin-angiotensin system (RAS) is activated, however, it had no effect on blood pressure of salt replete NCC KO mice. The reduction in blood pressure in salt depleted animals was dramatic, happened within hours after HCTZ and occurred in the absence of any increase in salt excretion, indicating its extra-renal origin. Echocardiography showed no significant changes in cardiac output in response to HCTZ. The antihypertensive effects of HCTZ were abrogated in the presence of a blocker of large conductance Ca++-activated K+ (BK) channels, Paxilline. Western blots demonstrated significant enhancement of BK expression in vascular system of salt depleted, NCC-deficient mice.

**Conclusions:** Our results indicate that vasocostriction secondary to RAS activation amplifies the extra-renal hypotensive action of HCTZ through vasodilatation irrespective of the status of its renal target. Patients on a combination diuretic regimen such as furosemide and HCTZ are at increased risk of hypotenston and kidney hypoperfusion subsequent to systemic vasodilatation by HCTZ.

**Funding:** Veterans Administration Support, Government Support - Non-U.S.

**FR-PO138**
Mitochondrial Oxidative Stress-Activated Renal Local RAS Promotes the Expression and Function of NCC in Proteinuric Kidney Disease

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**Background:** The fluid retention and hypotenston are common complications of kidney diseases, whose pathogenic mechanisms remain elusive.

**Methods:** Kidney tissues from mice subjected to albumin overload via i.p injection for 12 days and renal biopsy specimens were analyzed.

**Results:** Following albumin overload, we found a striking increase of Na⁺-Ci cotransporter (NCC) expression by 2.3-fold in mouse kidneys determined by Western blotting and qRT-PCR. To evaluate NCC function in these mice, NCC inhibitor hydrochlorothiazide (10mg/kg) was administered via a single i.p injection. In agreement with NCC upregulation, the response to hydrochlorothiazide was significantly enhanced in albumin overloaded mice. Considering the established role of renin-angiotensin system (RAS) in regulating sodium transporters, we examined key components of RAS and found a striking elevation of angiotensinogen (AGT) and angiotensin converting enzyme (ACE) by 2-3 folds in line with enhanced urinary AngII excretion. In proteinuric mice, we also observed 4-fold upregulation of NCC and remarkable stimulation of ACE detected by immunohistochemistry in accord with significantly increased urinary Ang II output. To further investigate the role of RAS in NCC upregulation, we did primary culture of renal tubular cells and observed that albumin directly increased NCC paralleled with significant induction of AGT, ACE, and Ang II. Strikingly, administration of specific ACE inhibitor captopril to the cells remarkably abolished albumin-induced enhancement of NCC and RAS components. Additionally, albumin overload significantly reduced superoxide dismutase (SOD2) by 60%, and administration of a SOD2 mimic (MnTBAP) entirely abolished the stimulation of NCC; AGT, and ACE in mice with albumin overload.

**Conclusions:** The findings demonstrated an important role of albuminuria in upregulating NCC expression in a mitochondrial oxidative stress-initiated stimulation of renal local AGT/ACE/AngII, which may contribute to the fluid retention and hypertension in proteinuric kidney disease to some extent.

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

**FR-PO139**
Prophylactic and Therapeutic Tenapanor Are Vascular Protective in a Rat Model of CKD

*AstraZeneca R&D, Malmö, Sweden; 1Plato Biopharma Inc., Denver, CO.*

**Background:** Tenapanor (AZD1722), an inhibitor of the Na⁺-H⁺ exchanger NHE3, reduces absorption of gut sodium and phosphate. It is being developed for renal and congestive-related indications.

**Methods:** 6/6 nephrectomized Sprague Dawley rats were fed 4% NaCl chow to induce salt-sensitive arterial hypertension. Oral tenapanor (1 mg/kg/day) was initiated either at the start of NaCl intake (prophylactic; Px) or 2 weeks later (therapeutic; Tx), and was administered for up to 6 weeks. Disease controls (DCs; vehicle-treated) and healthy controls (HCs; sham operated, normal chow) were included to enable assessment of disease progression. Systemic hemodynamics and urinary and plasma biomarkers were assessed every 2 weeks. Ex vivo vascular function (isometric tension recording) or arterial stiffness (pulse wave velocity) was evaluated at 2 and 6 weeks. Ex vivo vascular function (isometric tension recording) or arterial stiffness (pulse wave velocity) was evaluated at 2 and 6 weeks.

**Results:** Compared with DCs, rats in the Px and Tx groups had reduced urinary albumin, sodium and phosphorus excretion (p<0.05), and looser stools. Systolic, diastolic and mean BP increased in DCs but were normalized in the Tx group. Disease controls (DCs; vehicle-treated) and healthy controls (HCs; sham operated, normal chow) were included to enable assessment of disease progression. Systemic hemodynamics and urinary and plasma biomarkers were assessed every 2 weeks. Ex vivo vascular function (isometric tension recording) or arterial stiffness (pulse wave velocity) was evaluated at 2 and 6 weeks.

**Conclusions:** Tenapanor reduced absorption of gut sodium and phosphate. It is being developed for renal and congestive-related indications.

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

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

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387A
Conclusions: Tenapanor prevented most of the maladaptive consequences in a rat model of renal insufficiency-induced salt-sensitive arterial hypertension and CKD. The benefit of Tx treatment was similar to that elicited by Px use, suggesting disease modification. Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO140

Urinary Exosome Profiling in Thiazide Induced Hyponatremia
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Background: Thiazides are one of the most widely used and cost-effective class of anti-hypertensive medication. Thiazide-Induced Hyponatremia (TIH) is one of their major adverse effects and the leading cause of drug-induced hyponatremia requiring hospitalization. A priori TIH must result from excessive saliuresis and/or water reabsorption. The water and electrolyte transporter composition of urinary exosomes (UE) reflects their cellular origin and are a promising way to study renal dysfunction. This study assessed the expression of AQP2 and NCC in the UE of TIH patients.

Methods: 100 patients admitted to hospital with severe TIH donated urine samples during acute TIH and at 2 months post TIH cessation. Matched normotensive controls were recruited both on and off thiazides (groups 1 & 2 respectively). UE from a representative sample of each patient group were isolated and AQP2 and NCC were evaluated by Western blotting and Nanoparticle Tracking Analysis (NTA). AQP2 and NCC expression was normalized by urinary creatinine. Immunoblots were also corrected for total protein and results expressed as units of optical density/Ucr.

Results: Westerns showed that UE expression of AQP2 was higher in cases during acute TIH compared to convalescent (32.93 vs 28.71, P=0.01) and compared to control groups 1 & 2 (15.61 and 15.09 respectively, P=0.001). NCC expression was lower in TIH patients acutely compared to convalescent (17.72 vs 31.86, P=0.03) and compared to both control groups (30.32 and 31.17, P=0.05). NTA also demonstrated increased AQP2 expression in acute & convalescent UE.

Conclusions: This study highlights the utility of UE analysis to probe the molecular pathophysiology of TIH. Increased AQP2 and reduced NCC expression suggests that TIH results from increased water reabsorption and sodium wasting in the distal nephron. TIH studies may further understand of renal physiology and inform the design of new thiazide medicines less prone to cause hyponatremia. Funding: Government Support - Non-U.S.

FR-PO141

Epigenetic Modulation of Renal Arterioles Induced by DOCA-Salt Loading in Mice
Hiroki Snap, Kazutoshi Miyashita, Masaaki Sato, Kentaro Fujii, Aika Hagiwara, Masanori Tamaki, Hiroshi Itoh. Internal Medicine, School of Medicine, Keio Univ, Tokyo, Japan.

Background: The relationship between salt intake and development of hypertension is familiar; however, the mechanism for the onset has not been fully revealed. Our previous report showed that the medial hypertrophy of renal arterioles after transient salt loading in spontaneous hypertensive rat caused lasting elevation in blood pressure. The present study investigated the significance of epigenetic modulation of the gene expressions which are relevant to the medial hypertrophy after transient salt loading.

Methods: Male 6 week old C57B6 mice were implanted deoxycorticosterone acetate (DOCA) pellets and given drinking water containing 1% NaCl for 2 weeks for generation of salt-induced hypertension. The blood pressure was measured by a tail-cuff method during and after the transient salt loading. Histological examinations of the kidneys were performed during and after the salt loading. Gene expressions in the kidney such as matrix metalloproteinases (MMPs), which promote the medial hypertrophy, were quantified. Epigenetic modulation of the genes were analyzed.

Results: Transient salt loading caused elevation in blood pressure during the loading period. Blood pressure after stopping salt-loading was also significantly higher than that before salt loading. Salt loading caused medial hypertrophy of renal arterioles, and it remained after stopping salt loading, as to cause lasting renin elevation. Real time PCR revealed that MMP2 and MMP9 were increased during the salt loading. CNGN5, CHP and p300, which are histone acetyltransferases, were elevated. Sir1, Sir3, HDAc1 and HDAc3, which are histone deacetylases, were decreased. Histone H3K9 and H4K16 acetylations in the MMP2 gene were enhanced by the salt loading.

Conclusions: The lasting medial hypertrophy and renin elevation after transient salt loading were suggested to be caused by the increased expression of MMPs along with augmented histone acetylations by the salt loading. Increased expressions of acetyltransferases along with decreased expressions of Sirs and HDAcs by transient salt loading would be involved in the enhancement of the histone acetylations.

FR-PO142

Radio-Frequency Catheter-Based Renal Denervation in Hypertensive Sheep with Chronic Kidney Disease Impairs Responses to Hemorrhage
Reetu R. Singh,1 Karen M. Moritz,2 Kate M. Denton. 1Physiology, Monash Univ; Clayton, VIC, Australia; 2School of Biomedical Sciences, The Univ of Queensland, St. Lucia, QLD, Australia.

Background: Renal sympathetic nerves medulate kidney function and blood pressure (BP). Trials using catheter-based renal denervation (cDXN) in hypertensive patients yielded results both in support of and, against its efficacy in lowering BP. A critical question is whether cDXN has adverse consequences, in situations of clinical challenge, such as hemorrhage in denervated patients where intact nerves would be required. This study examined consequences of cDXN 1) on BP and renal function and 2) on reflex activation of sympathetic nerve activity (SNA) in hypertensive sheep with chronic kidney disease (CKD).

Methods: Sheep with established hypertension and renal dysfunction (CKD group) with an appropriate control group were used. At 10 months of age, some animals underwent cDXN (CKD-cDXN) and control-cDXN while the remaining underwent sham procedure (CKD-intact; control-intact). At 2 months post-cDXN, BP, renal function, and plasma renin activity (PRA) were assessed before, during and after hemorrhage (20% blood volume withdrawn over 15 minutes).

Results: CKD sheep had higher BP compared to all groups but CKD-cDXN sheep had similar BP to control sheep. Basal renal function was not further reduced. In response to hemorrhage, BP fell in all groups but the greatest decrease occurred in CKD-cDXN. In Control-intact sheep this fall in BP gradually recovered, associated with increase in PRA reflecting an increase in reflex SNA. In contrast, in Control-cDXN and CKD-cDXN groups, PRA did not increase and BP did not recover reflecting an absence of increase in reflex SNA.

Conclusions: cDXN effectively reduced BP at 2 months post-cDXN in previously hypertensive sheep but had no effect on renal function. However, the lack of reflex activation of neural mechanisms observed during hemorrhage suggest, that cDXN may impair a patient’s ability to adequately respond to physiological challenges. Funding: Government Support - Non-U.S.

FR-PO143

Interleukin-10 Mediates the Renoprotective Properties of Mesenchymal Stem Cells-Derived Extracellular Vesicles in Porcine Metabolic Syndrome and Renal Artery Stenosis
Alfonso Eirin,1 Xiang-yang Zhu,1 Christopher M. Ferguson,2 Scott Riester,3 Andre J. Van Wijnen,4 Amir Lerman,5 Lilach O. Lerman.1,3 Div of Nephrology and Hypertension, Mayo Clinic; 2Orthopedic Surgery, Mayo Clinic; 3Cardiovascular Diseases, Mayo Clinic, Rochester, MN.

Background: Mesenchymal stem/stromal cells (MSCs) are immunomodulatory and have unique potential to restore the renal microvasculature, but may generate safety concerns. MSC-derived extracellular vesicles (EVs) emerged as a novel non-cellular alternative. Using a swine model of metabolic syndrome (MetS) superimposed on renal artery stenosis (RAS) we tested whether intrarenal injection of EVs attenuates renal injury and if this capacity is mediated by their cargo of the anti-inflammatory cytokine IL-10.

Methods: MetS pigs were studied after 16 weeks of RAS untreated or treated 4 weeks earlier with a single intrarenal delivery of labeled EVs harvested from autologous MSCs (2.5x10^5/Kg) with or without pre-silenced IL-10 (IL-10 knock-down). Lean and MetS Sham served as controls (n=7 each). Single-kidney renal blood flow (RBF) and glomerular filtration rate (GFR) were studied in vivo, and microvascular architecture (micro-CT) and fibrosis ex vivo.

Results: EVs were detected in the stenotic-kidney 4 weeks after injection. RBF and GFR, which increased in MetS compared to Lean, fell in MetS-RAS, but improved in EV-treated pigs (Table). EVs also improved cortical microvascular density and renal fibrosis (Figure). Yet, these renoprotective effects were blunted in pigs treated with IL-10 depleted EVs.

Conclusions: Intrarenal delivery of MSC-EVs improves renal structure and function in chronic experimental MetS+RAS, partly mediated by their cargo of IL-10. These observations suggest that EV-based regenerative strategies might be useful for patients with MetS+RAS.

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FR-PO144

Role of Mitochondrial Dysfunction and ROS Production in Ang II-Induced NLRP3 Inflammasome Activation

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Background: The type 1 angiotensin (AT1) receptor plays an important role in maintaining blood pressure. Previous studies suggested that the activation of immune responses by angiotensin (Ang) II during hypertension may aggravate renal damage. NLRP3 inflammasome activation promotes renal inflammation and contributes to chronic kidney disease. Further investigation should be performed to explore the correlation between the RAS and NLRP3 inflammasome activation, and possible mechanisms.

Methods: C57BL/6 AT1R-/- and NLRP3-/- mice underwent left nephrectomy followed 1 week for recovery. Blood pressure measurements were recorded at baseline and following 4 weeks of chronic Ang II or saline infusion. At the end of the experiment, the kidney were harvested and fixed. AT1R sRNA and mitoTEMPO treatment were before performed after the Ang II stimulation in HK2 cells. The expression levels of NLRP3 inflammasome and mitochondrial dysfunction were measured.

Results: Ang II significantly induced kidney injury and NLRP3 inflammasome activation. Mitochondria swelling and fragmentation were observed by transmission electron microscope. AT1-/- blocked Ang II-induced hypertension, inhibiting the mitochondrial dysfunction and NLRP3 expression. Deficiency of NLRP3 attenuated kidney injury in hypertension with no significant influence to blood pressure. In vitro studies showed that Ang II stimulation increase the mitochondrial damage and NLRP3 activation in dose- and time- dependent manner. AT1R silence effectively blocked Ang II-induced damage. MitoTEMPO attenuated the activation of NLRP3 inflammasome through clearance of reactive oxygen species (ROS). Moreover, Ang II-induced mitochondrial dysfunction was markedly inhibited by silencing of NLRP3.

Conclusions: Ang II stimulation induces NLRP3 inflammasome activation through AT1a receptor. Ang II-induced NLRP3 activation is mediated by mitochondrial dysfunction, with overproduction and accumulation of ROS. NLRP3 inflammasome activation plays an important role in kidney injury, and blocking it can be a potential therapeutic target for hypertension-associated kidney damage.

Funding: Other NIH Support - National Science Foundation of China

FR-PO145

The Endoplasmic Reticulum Stress Inhibitor 4-Phenylbutyric Acid Prevents the Development of Essential Hypertension in Young Spontaneously Hypertensive Rats

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Background: Essential Hypertension is the leading global risk factor for premature death. This complex multifactorial disease has no known cause and has been shown to contribute to the progression of chronic kidney disease (CKD). Mechanistically both Endoplasmic Reticulum (ER) stress and the Unfolded Protein Response (UPR) have been implicated in the pathobiology of this disease. A small molecular chaperone, Endoplasmic Reticulum (ER) stress and the Unfolded Protein Response (UPR) have been implicated in the pathobiology of this disease. A small molecular chaperone, 4-phenylbutyric acid (4-PBA), is known to inhibit ER stress. In our previous studies, we found that 4-PBA is able to lower blood pressure in animal models of hypertension. It remains unclear however if ER stress is a cause of hypertension or a consequence.

Methods: Young spontaneously hypertensive rats (SHR) were used in this study and Wistar Kyoto (WKY) rats were used as its normotensive control. High blood pressure begins to develop in the young SHR at 4-weeks of age. Radio-telemetry transmitters (HE-X1 transmitter, Data Sciences International) were implanted to monitor blood pressure development, heart rate and ECG activity in both SHR and WKY. SHR and WKY were both randomized into 4-PBA (1 g/kg/day) or vehicle groups at 4-weeks of age to determine if ER stress inhibition would prevent the development of hypertension. Resistance vessels, such as mesenteric arteries and renal arteries were collected after 8 weeks and analyzed for specific ER stress markers using real-time polymerase chain reaction (RT-PCR).

Results: 4-PBA treatment significantly lowered systolic, diastolic and mean arterial pressures in the SHR rats, but not in the WKY rats. 4-PBA treatment also significantly attenuated pre-hypertensive tachycardia in the SHR. Additionally, 4-PBA significantly prevented the expression of UPR markers CHOP and GRP78 in SHR resistance blood vessels.


FR-PO146

Macrophage Endothelin-B Receptors Clear Endothelin-1 and Regulate Blood Pressure

Necerni Dhaun. Queen’s Medical Research Inst, University of Edinburgh.

Background: Hypertension is common. Its cause remains unclear in the majority of those affected. Recent data suggest that macrophages (MΦ) contribute to, and protect from, hypertension. Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor with additional pro-inflammatory properties. The effects of ET-1 on MΦ biology are well studied.

Methods: To examine the interactions between the ET and MΦ systems we administered incremental doses of intravenous ET-1 to C57Bl12-diphtheria toxin receptor (DT) expressing mice given diphtheria toxin (DT) and to untreated control mice to create on model of endothelial injury. The type 1 angiotensin (AT1) receptor has a specific role in ET-1 clearance. We investigated the role of the Mϕ ET receptor in ET-1 mediated endothelial dysfunction. We also cultured bone marrow derived MΦ (BMDM) from both mice and human monocytes in vitro. Finally, we examined BP and the ET system in patients receiving MΦ depleting and non-depleting therapy.

Results: MΦ depletion or loss of function – C11b-DTR mice given DT and LysMΔMΦ mice – were not associated with a difference in baseline BP or endothelial dysfunction. In both, administration of ET-1 resulted in an exaggerated hypertensive response compared to controls. At a dose of ET-1 1nmol/kg the maximal change in BP was ~20-fold in MΦ deficient mice compared to control groups. In vitro, mouse BMDM and human MΦ possess both ETa and ETb receptors. Whereas stimulation of mouse and human MΦ with exogenous ET-1 did not polarize MΦ to a classical or alternative phenotype, both displayed chemokinesis to ET-1. This was reduced by selective ETa, and completely blocked when both ETa and ETb receptor mediated dynamin-dependent endocytosis present in both murine and human MΦ. Finally, patients receiving MΦ depleting therapy we show that BP is higher and the ET system more activated than those receiving non-depleting therapies.

Conclusions: Overall, these data suggest that MΦ and ET-1 may play an important role in BP control and potentially have a critical role as a therapeutic target in hypertension.

FR-PO147

Role of the Myeloid Endothelin-B Receptor in Angiotensin II Mediated End-Organ Damage


Background: Hypertension is common and in the majority of cases its cause remains unknown. Recent interest has focused on the role of macrophages (Mø) in blood pressure (BP) regulation. Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor mediating its effects through two receptors – the endothelin-A receptor (ET_a) and endothelin-B (ET_b) receptor. The ET_b receptor has a specific role in ET-1 clearance. We investigated the role of the Mø ET_b receptor in a model of angiotensin II (ANG)-mediated end-organ damage.

Methods: Mø ET_b receptor deficient mice (LysMΔMΦ) and controls were exposed to Ang II infusion for 6 weeks under a high salt diet. We assessed BP via telemetry, cardiac structure and function and endothelial function by Doppler ultrasound, end-organ injury and plasma and urine ET-1.

Results: At baseline, components of BP did not differ between groups and increased similarly with Ang II. Whereas after 6 weeks of Ang II LysMΔMΦ and controls had similar left ventricular hypertrophy and cardiac insufficiency, endothelial function was better in LysMΔMΦ at both baseline and after Ang II (% dilation of basilar artery in response to CO2: LysMΔMΦ vs. controls: 7.5±1.1% vs. 5.8±0.9%, p<0.01; at 6 weeks: 11.4±1.0% vs. 9.0±0.7%, p<0.01). Baseline renal function and proteinuria did not differ between groups. After Ang II, LysMΔMΦ showed similar renal function compared to controls but less proteinuria (urine albumin: creat, mg/mmol: 208:10 vs. 530:25, p<0.01), glomerulosclerosis (34±2 vs. 61±4%, p=0.03), mesangial expansion (14±2% vs. 28±2%, p<0.01) and fewer renal Mø compared to controls (F4/80 staining per high power field, LysMΔMΦ vs. controls: 1.1±0.7 vs. 3.2±0.5%, p<0.02), although similar levels of CD3' T cells. Plasma ET-1 was no different at baseline but increased more in LysMΔMΦ with Ang II vs. controls after 6 weeks Ang II: 3.7±0.7 vs. 1.4±0.2pg/ml, p<0.03). Urine ET-1 was similar baseline and 6 weeks.

Conclusions: Deletion of the Mø ET_bR is associated with a blunting of the effects of systemic Ang II infusion as reflected by less endothelial dysfunction, reduced inflammation and end-organ damage. The mechanisms for these effects are the focus of ongoing research.
FR-PO148
A Novel Reduced Uterine Perfusion Pressure (RUPP) Model of Preeclampsia in Mice
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Background: Preeclampsia (PE) is a pregnancy-related hypertension with proteinuria that typically develops after 20 weeks of gestation. PE is caused by a reduction in uterine blood flow due to abnormal trophoblast invasion of the spiral arteries. The ischemic placenta releases anti-angiogenesis factors such as sFlt-1, leading to maternal hypertension and proteinuria. The reduced uterine perfusion pressure (RUPP) model is widely used in rats, but not in mice, hindering the clarification of genetics of PE. The aim of the present study is to establish a novel PE model using an improved RUPP method in mice.

Methods: As shown in the Figure 1, uterine vessels of pregnant ICR mice were ligated at 14.5 dpc, and BP, renal phenotype and pregnancy outcome were analyzed.

Results: RUPP in mice increased blood pressure. B.B' ligation mice showed increased urinary albumin excretion, mesangial expansion and endotheliosis as shown by the reduction of glomerular open capillary area. RUPP increased the risk of miscarriages and premature deliveries, and significantly reduced fetal weights at 18.5 dpc compared to those of sham mice.

Conclusions: We developed a novel RUPP mouse model that recapitulates the phenotype of PE. This model is expected to be useful for investigating pathogenesis of PE and evaluating its new therapies.

FR-PO149
Sildenafil Treatment Is Protective against Progression of Renal Injury in the Preeclamptic Dahl Salt Sensitive Rat
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Background: Preeclampsia, a hypertensive disorder of pregnancy, is characterized by transient glomerular damage and increased risk for kidney disease later in life. Recent studies in our lab have identified the Dahl salt sensitive (Dahl S) rat on a 0.3% NaCl diet as a spontaneous model of superimposed preeclampsia. We hypothesized that sildenafil treatment would result in an improvement in renal function during the preeclampsia pregnancy exhibited by the Dahl S rat.

Methods: Female Dahl S rats (n=4-9) were mated, and rats were randomly divided into control and sildenafil treated groups. Sildenafil was administered to the treated group via food on gestational days 10-20 at a dose of 50 mg/kg/d. Rats were placed in metabolic cages on gestational day 19 for 24 hr urine collection, and blood and tissues were harvested on gestational day 20. Urinary protein excretion, nephron excretion, and plasma and urinary creatinine concentrations were measured by Bradford assay, Exocell ELISA, and the picric acid method, respectively. Kidney sections were stained with Mason’s trichrome, and glomeruli were measured (n=20 per rat) and analyzed using Nikon software.

Results: Sildenafil treatment significantly improved renal function, as observed in the increase in creatinine clearance and corresponding decrease in plasma creatinine (Table, *p=0.05 vs control). Treated rats exhibited less renal injury, with a significant decrease in proteinuria and nephritis during late pregnancy (Table). Histological analysis showed that the treated rats did not exhibit glomerulomegaly during pregnancy compared to the untreated controls (Table).

Conclusions: This study provides preclinical evidence that sildenafil prevents the progression of renal injury during preeclampsia.

FR-PO150
Recessive Mutations of the Interaction Partners, TENC1, DLC1 or MAG2, Cause Nephrotic Syndrome in Humans
Shazia Ashraf,1 Jia Rao,1 Merlin Airik,1 Svjetlana Lovric,1 Jennifer A. Lawson,1 Weizhen Tan,2 Karolin Sadowksi,1 Werner Lukas Pabst,1 Daniela A. Braun,1 Heon Yung Gee,1 Richard P. Lifton,12 Martin Zanker,1 Friedhelm Hildebrandt.1,4 1Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 2Inst of Human Genetics, Univ of Medicine, New Haven, CT; 4Inst of Human Genetics, Univ Hospital Magdeburg, Magdeburg, Germany; *HHMI.

Background: Identification of monogenic causes of nephrotic syndrome (NS) has furthered the understanding of its pathogenesis. However, many genes and disease mechanisms remain unknown.

Methods: We performed homozygosity mapping (HWM) and whole exome sequencing (WES) in individuals of consanguineous families with NS to identify the underlying mutations. To identify additional families, we performed microfluidic PCR (Fluidigm Access Array™) and next generation sequencing (NGS) to screen worldwide cohort of ~2000 individuals with severe NS.

Results: By WES in consanguineous family A1358, we identified a homozygous missense mutation (p.R292Q) in the TENC1 (Tensin-2) gene in an amino acid residue conserved since Ciona intestinalis. By microfluidic PCR and NGS, we detected additional mutations in TENC1 in three unrelated families with NS. Later, we also discovered mutations in 2 different families with NS in DLC1 gene, a known binding partner of TENC1. Interestingly, most of the individuals with TENC1 or DLC1 mutations had steroid sensitive NS or histologically showed biopsy of MCNS. Furthermore, in 2 families with NS and neurological impairment, we identified 2 different homozygous truncating mutations in MAG2 gene. Deficiency of Tenc1 or Mag2 has been previously shown to cause NS in mice. By Co-IP, we now show that TENC1 and DLC1 interact with MAG2 in HEK293T cells and these interactions are abrogated in one of the MAG2 mutant. Knockdown of TENC1, DLC1 or MAG2 in cultured podocytes exhibited an altered podocyte migration rate. Immunofluorescence microscopy showed that TENC1 and DLC1 colocalize with phosphotyrosine at the focal adhesions in cultured human podocytes.

Conclusions: We, thus, identified mutations of TENC1, DLC1 and MAG2 as three novel single-gene causes of NS revealing a potential new pathogenic pathway for NS.

Funding: Other NIH Support - DK076683

FR-PO151
Mutation of DHTKD1 Can Cause Nephrotic Syndrome with Neurological Impairment and Ketoacidic Aciduria
Weizhen Tan,1 Shazia Ashraf,1 Svjetlana Lovric,1 Jia Rao,1 Merlin Airik,1 David Schaprio,1 Daniela A. Braun,1 Heon Yung Gee,1 Martin Zanker,1 Friedhelm Hildebrandt.1,4 1Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 4Inst of Human Genetics, Univ Hospital Magdeburg, Magdeburg, Germany; *Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Steroid-resistant nephrotic syndrome (SRNS) is the second most frequent cause of end-stage kidney disease in children. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis. However, additional genes and disease mechanisms remain obscure. To identify a new causative gene for SRNS with neurological impairment, we combined homozygosity mapping (HWM) and whole human exome sequencing (WES).

Methods: In two siblings (of consanguineous parents) with SRNS, neurological impairment, and ketoacidic aciduria, HM yielded 8 segments of homozygosity by descent at an average size of ~485 Mb. We performed WES in both siblings to identify the underlying single-gene disease-causing mutation.

Results: WES in this consanguineous family detected a homozygous missense mutation (p.Val296Met) in the DHTKD1 (dehydrogenase E1 and transtetikolase domain containing 1) gene in an amino acid residue that is evolutionary conserved to prokaryotes (Saccharomyces cerevisiae). The mutation segregated with the affected status in this family and was absent from the 1,000 genomes project and Exome Aggregation Consortium (ExAC) databases. DHTKD1 functions as a 2-oxoglutarate-dehydrogenase E1 component and plays an important role in energy production in mitochondria through the tricarboxylic-acid cycle. Mutations in DHTKD1 have previously been identified as cause of 2-aminoadipic and 2-oxoaciduria via impaired turnover of decarboxylation 2-oxoadipate to glutaryl-CoA. [1] Danhauser K. et al., Am J Hum Genet, 91:1088-1087, 2012.

Conclusions: We identified a recessive mutation of DHTKD1 as a novel single-gene cause of SRNS with neurological impairment and ketoacidic aciduria. Further genetic and functional studies will shed light on the involvement of this protein in the pathogenesis of NS and will provide a further step in understanding the disease mechanism.

Funding: Other NIH Support - R01-DK076683, Private Foundation Support

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390A

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<th>Nephriticuria (mg/g day)</th>
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Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support
FR-PO152

Genes Encoding Nuclear Pore Outer Ring Components NUP85, NUP107, and NUP133 Are Mutated in Patients with Nephrotic Syndrome Svetlana Lovric,1 Weizhen Tan,2 David Schapira,3 Shazia Ashraf,1 Daniela A. Braun,1 Jia Rao,1 Richard P. Lifton,4 Heon Young Gee,4 Friedhelm Hildebrandt,1,5 1Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 2Dept of Genetics, Yale Univ School of Medicine, New Haven, CT; 3Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Steroid resistant nephrotic syndrome (SRNS) almost invariably progresses to end-stage kidney disease. Although more than 30 single-gene causes of SRNS are known, a large proportion of SRNS remains unexplained. Recently, mutations in genes encoding proteins of the nuclear complex (NPC), NUP93 and NUP205 were identified as novel causes of nephrotic syndrome. Study of these genes has implicated SMAD signaling in the pathogenesis of nephrosis.

Methods: To identify additional novel causes of nephrotic syndrome, we performed a candidate screen of 17 nuclear pore complex (NPC) genes in an international cohort of >900 individuals with SRNS with microfluidic multiplex PCR (Fluidigm AccessArray®) and next generation sequencing (illumina Miseq®).

Results: In two families we identified two homozygous missense mutations, p.A477V and p.R645W, (conserved to S. cerevisiae) in the NPC outer ring protein NUP85. We then sequenced the exons of 1,000 additional families in genes encoding other outer ring proteins and found mutations in NUP107 (1 family, p.Y889C, conserved to C. elegans) and NUP133 (2 families, p.S974R and p.R231G, p.L1055S, conserved to D. rerio). Although the structure resolution of the NPC 3D complex is incomplete, we modeled the interacting portions of the Y-subcomplex proteins NUP107 and NUP133. Two of the mutations, p.S974R in NUP133 and p.Y889C in NUP107, are located in the interacting alpha helixs between the two proteins. 5 of 6 families demonstrated FSGS on biopsy.

Conclusions: As a novel cause of SRNS we identified mutations in 3 different NPC outer ring proteins NUP85, NUP107, and NUP133 that form an integral part of the Y-subcomplex. Further functional studies are needed to illuminate how the defect of NPC contributes to the pathogenesis of nephrotic syndrome.

 Funding: Other NIH Support - DK076683

FR-PO153

Defining the Genetic Epidemiology of a Phenotypically Well-Characterized Adult-Onset Focal and Segmental Glomerulosclerosis Cohort Moumita Baruah,1 Daniel C. Catran,1 Heather N. Reich,1 Michelle A. Hladunewich,6 Mark Leung,2 Weili Li,3,4 Andrew D. Paterson,5 York P. Pei.1

Background: Genetic epidemiology underpins an understanding of human disease and identifies new biological pathways. The genetic landscape of focal and segmental glomerulosclerosis (FSGS), a common cause of kidney disease, is unknown.

Methods: To gain insight into the genetic epidemiology of FSGS, we performed exome sequencing on adult-onset FSGS cases and family members. The sequencing data was interrogated using the Exome Variant Server and compared against the Exome Aggregation Consortium (ExAC) to identify the most recurrent variants.

Results: We identified diagnostic variants for FSGS in 4 genes in 5/31 families (16%): TRPC6, INF2, LAMA5, and ADCK4. These mutations were enriched in the right tail of the age at diagnosis distribution, suggesting that genes involved in renal development predispose to FSGS.

Conclusions: FSGS is a complex genetic disease with highly penetrant genes and a large number of cases in which the underlying genetic etiology remains unknown.

 Funding: Private Foundation Support

FR-PO154

A Novel Mouse Mutant with a Point Mutation in Laminin α5 Exhibits Chronic Nephrotic Syndrome Sara Falzone1, Thomas Nicol,1 Cheryl Scudamore,2 Frederick W.K. Tam,2 Charles D. Pusey,3 Jeffrey H. Miner,1 Steve Dm Brown,1 Paul K. Potter,1 1Mammalian Genetics Unit, MRC Harwell, Harwell, Oxfordshire, United Kingdom; 2Mary Lyon Centre, MRC Harwell, Harwell, Oxfordshire, United Kingdom; 3Renal Science, Imperial College, London, United Kingdom; 4Renal Div, Washington Univ, St. Louis, MO.

Background: Diseases associated with ageing pose an increasing social and financial burden on society and represent an imperative for research in the biomedical sciences. We are undertaking the first large-scale project to investigate the interaction between genetic variation and the pleiotropic effects of ageing, employing random mutagenesis and phenotyping to generate new models of late onset or age-related disease.

Methods: Mouse mutants are being aged to 18 months and undergo comprehensive phenotyping across a wide range of disease areas at several time points throughout the life of the mice. To date we have identified lines with a variety of late onset phenotypes which are being characterised in detail.

Results: Mutant mice were identified at 6 months of age with elevated creatinine and urea levels, which reached end stage renal failure at approximately 10 months of age. Mapping and whole genome sequencing identified a LAMA5 nonsense mutation in the L4a domain of LAMA5. Time course studies of LAMA5 homozygotes showed reduced serum albumin (18.0 ± 1.2 vs 24.9 ± 3.1 g/l, mean SD) and proteinuria from 12 weeks of age with a gradual loss of renal function over time. Affected mice also have significantly elevated cholesterol levels and a progressive nephropathy leading to diffuse glomerular fibrosis, dilated protein filter tubules and pigment deposition suggesting this is a model of nephrotic syndrome. The mutation does not affect expression of the LAMA5 protein within the glomerular basement membrane.

Conclusions: We have identified a novel mouse mutant with a missense mutation LAMA5 resulting in nephrotic syndrome. Recent patient sequencing data suggests LAMA5 mutations are associated with focal segmental glomerulosclerosis. The model does not affect expression of the LAMA5 protein within the glomerular basement membrane.

 Funding: Government Support - Non-U.S.

FR-PO155

Exome Sequencing Suggests a Role for Nephrin Number in FSGS Adile Mitrotti,1 David Fasel,1 Yifu Li,1 Monica Bodria,1 Landino Allegri,1 Gerald B. Appel,1 Jai Radhakrishnan,1 Loreto Gesualdo,4 Gian Marco Ghiggeri,5 Richard P. Lifton,1 Ali G. Ghiravi,1 Simone Sanna-Cherchi.1,2 Medicine, Columbia Univ Medical Center, New York, NY; 3Genetics, Yale, New Haven, CT; 4Medicine, Univ of Parma, Parma, Italy; 5Medicine, Univ of Bari, Bari, Italy; 1Medicine, Gaslini Children Hospital, Genova, Italy.

Background: Exome sequencing is a powerful tool to identify disease-causing mutations. Identification of novel genes for dominant FSGS has proven difficult.

Methods: We performed exome sequencing in 41 patients from 31 families affected by FSGS. Exome sequencing was conducted on Illumina HiSeq2500. Annotations were conducted with semi-automated scripts developed in the lab.

Results: We detected diagnostic variants for FSGS in 4 genes in 5/31 families (16%): TRPC6, INF2, LMX1B, and LAMB2. We detected two variants of unknown significance in FSGS-associated genes (EMP2, INP2). We detected 7 variants in additional 6 patients associated with late-onset FSGS that predispose to different kidney diseases when mutated (LAMA5, COL4A4, FRA51, FREM1, FREM2, UMOD). While these conditions can represent phenocopies of FSGS, it is possible that genes involved in renal development predispose to proteinuria and adaptive FSGS.

 Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Analysis of the remaining 20 families (65%) did not reveal any gene with rare segregating mutations present in multiple independent families.

Conclusions: Mutations in genes known to be associated to FSGS are identified in a small proportion of cases. Mutations with focal segmental glomerulosclerosis in genes involved in GNB3 and kidney development can result in defects that present as FSGS. These findings can point to a correct genetic diagnosis and the identification of mutations in genes involved in CAKUT suggests that glomerular sclerosis could be the manifestation of a maladaptive reaction to reduced glomerular mass from phenocopies of FSGS.

 Funding: NIDDK Support, Private Foundation Support
Role of CD2AP Mutations in Steroid Nephrotic Syndrome Revisited – New Insights from Next Generation Sequencing
Ania B. Koziel, Katrina Soderquest, Andrey S. Shaw, Michael A. Simpson

FR-PO157

Chemical Chaperone 4-PBA Is Not Nephroprotective in Experimental Podocin Nephropathy
Janja Tamara Włodkowski, Manoucheh Tabatabaeifar, Geza De Mollet, Corinne Antignac, Franz J. Michaeli

Results:
Conclusions:

FR-PO158

Prominent Renal Complications in the c.80A>G in MMACHC Gene
Mansoureh Tabatabaeifar, Yun-Zhen Qu, Zhao Cui, Ming-Jiang Wang

FR-PO159

The Susceptible Human Leukocyte Antigen Class II Genes and the Encoding Acidic Residues on Major Histocompatibility Complex Molecules to Primary Membranous Nephropathy
Li-Jun Xia, Zhen Qu, Zhao Cui, Gang Liu, Jun-Hua Liao, Ming-hui Zhao

Results:

FR-PO160

Somatic Mosaicism and Variant Frequency Detected by Next Generation Sequencing in X-Linked Alport Syndrome
Naohiro Kamiyoshi, Kandai Nozu, Tomohiko Yamamura, Takeshi Ninchoji, Yuko Shimah, Koichi Nakashima, Norisighe Yoshikawa, Kazumoto Iijima

Methods:

Results:

Background:

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: De novo variants can occur even in asymptomatic male cases of XLAS resulting in mosaicism, with important implications for genetic counseling. This is the first study to show a tendency between the variant allele frequency and disease severity in male XLAS patients with somatic mosaic variants in COL4A5. Although this is a very rare status of somatic mosaicism, further analysis is needed to show this correlation in a larger population.

FR-PO161

A New Non-Invasive Method to Examine Collagen α5(IV) Expression Using Plucked Hair Follicles: Analysis of an X-Linked Alport Family with a Novel COL4A5 Splice Region Variant Andrew F. Malone, Steven Daniel Funk, Jeffrey H. Minze. Renal Div; Dept of Medicine, Washington Univ, St. Louis, MO.

Background: Alport syndrome is a hereditary disease caused by mutations in COL4A5 in 85% of cases. Many different mutation types in this gene have been described. Levels and patterns of type IV collagen deposition are variable in the glomerular basement membranes of Alport kidneys. As COL4A5 is also expressed in the skin, we sought to characterize COL4A5 deposition in the basement membrane of plucked hair follicles from a family with a novel COL4A5 variant as a way of confirming the functional significance.

Methods: Whole-exome sequencing was done on the proband of a family with biopsy (renal and skin)-confirmed Alport syndrome. Sanger sequencing was performed on all affected family members and a married-in unaffected individual. Immunofluorescence microscopy was performed on whole mount and sectioned hair follicles co-stained with monoclonal antibodies to collagen α2 and α5(IV). Staining intensity between males and females, affected and unaffected, was analyzed.

Results: Family WU1 is a 3 generational family with chronic kidney disease secondary to Alport syndrome. Affecteds are in each generation, and both males and females are asymptomatic. Whole-exome sequencing of affected individual 3232 revealed a novel splice region variant c.1780-6T>G in COL4A5. There were no other potentially pathogenic variants found in COL4 or other podocyte genes. This variant was confirmed by Sanger sequencing and segregated with disease. Reduced and abnormal expression of COL4A5 protein was confirmed in affected family members by immunofluorescence microscopy of hair follicles.

Conclusions: We confirmed linkage of a novel splice region variant in COL4A5 to Alport syndrome in a family with a typical X-linked inheritance pattern; this variant may be pathogenic. We developed and validated a new approach to characterize the expression of COL4A5 protein using immunofluorescence microscopy of plucked hair follicles. Furthermore, we demonstrated variability of COL4A5 expression between patients in this family, suggesting intermitting failure of splicing and/or variable lyonization in females. Funding: NIDDK Support

FR-PO162

X-Linked Alport Dogs Demonstrate Mesangial Filipodial Invasion of the Capillary Tuft as an Early Event in Glomerular Damage Sabrina D. Clark,1 Mary B. Nabity,1 Rachel Cianciolo,1 Brianna M. Dufek,1 Dominic E. Cosgrove,1 Veterinary Pathobiology, Texas A&M Univ, College Station, TX; 1Veterinary Biosciences, The Ohio State Univ, Columbus, OH; 2Genetics, Boys Town National Research Hospital, Omaha, NE.

Background: X-linked alport syndrome (XLAS), caused by a mutation in the type IV collagen COL4A5 gene, accounts for approximately 80% of the cases of human Alport syndrome. Dogs with XLAS have a similar clinical progression. Prior studies in autosomal Alport mice demonstrated early mesangial cell invasion as the source of laminin 211 in the glomerular basement membrane (GBM), leading to proinflammatory signaling. Thus far, these findings have not been confirmed in a large animal model.

Methods: XLAS dogs and unaffected littermates were monitored with serial kidney biopsies at 2, 4, 6, and 12 months of age. V orinostat treatment induced hyperacetylation of kidney lysine residues. This was associated with reduced albuminuria, decreased aSMA protein expression, and reduced gene expression of inflammatory cytokines.

Results: In silico drug repurposing identified vorinostat as a potential therapeutic agent. Treatment with voriostat induced hyperacetylation of kidney lysine residues. This was associated with reduced albuminuria, decreased aSMA protein expression, and reduced gene expression of inflammatory cytokines. Further studies will better define the mechanisms underlying the protective effect of this novel therapy.

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

FR-PO164

KCTD1 Mutations in Scalp-Ear-Nipple (‘Finlay-Marks’) Syndrome: A Further Cause of Thin Basement Membrane Nephropathy Dongmao Wang,1 Peter Diakumis,2 Melanie Bahlo,2 Deb J. Colville,1 Judith A. Savige.1 Medicine, The Univ of Melbourne (Parkville, Melbourne, VIC, Australia; 2Bioinformatics, WEHI, Melbourne, VIC, Australia.

Background: Scalp-Ear-Nipple syndrome is an ectodermal dysplasia, with a scalp defect, dislocated ears and absent breasts. It results from mutations in KCTD1, a potassium channel gene, which encodes KCTD1, a K+ channel subunit. It causes renal disease. Currently there are few effective therapies for AS. Therefore we applied a novel therapeutic approach to AS, drug repurposing of the putative therapy showed that vorinostat exerts a renoprotective effect. Further studies will better define the mechanisms underlying the protective effect of this novel therapy.

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

FR-PO165

Podocyte Globotriaosylceramide (GL3) Accumulation in Fabry Disease Is Influenced by Age and Genotype Bezhad Najafian,1 Camilla Tøndel,2 Einar Fang1, Rohan John,3 York P. Pei,3 James W. Scholey.2 1Inst of Medical Science, Univ of Toronto, Canada; 2Dv of Nephrology, Univ of Toronto, Canada; 3Internal Medicine, Chonnam National Univ Medical School, Korea; 4Pathology, Univ of Toronto, Canada.

Background: Alport Syndrome (AS) is a hereditary nephropathy caused by mutations in genes that encode type IV collagen, leading to progressive injury and eventually end-stage renal disease. Currently there are few effective therapies for AS. Therefore we applied a novel therapeutic approach to AS, drug repurposing of the putative therapy showed that vorinostat exerts a renoprotective effect. Further studies will better define the mechanisms underlying the protective effect of this novel therapy.

Funding: Private Foundation Support, Government Support - Non-U.S.
density \( V[GL3/Podo] \) was estimated and correlated with age and GLA mutation. The latter, on average, for 38 of these patients, included 35 classical, 2 cardiac variant (N215S) and one late onset (R363H) mutation. Patients over 65 years of age had 38 deaths, 21 of these were ERT treated patients, and 17 of the deaths were in patients over 65. There were 44 patients, ages 37-50 with low V[GL3/Podo] (r=0.03, p=0.02), included patients with N215S (n=2) and R363H mutations and one patient whose GLA mutation was unavailable. V[GL3/Podo] directly correlated with urine albumin creatinine ratio (r=0.50, p<0.001) and foot drop in males younger than 30 years. Volume density of podocytes per glomerulus was inversely correlated with age (r=-0.69, p<0.001) across the age range with no plateauing, suggestive of continuous podocyte loss.

Conclusions: The fraction of podocyte cytoplasm filled with GL3 inclusions increases with age up to about age of 30 in Fabry males with classical GLA mutations and associated with podocyte injury and albuminuria. Plateauing of podocyte GL3 volume density after age of 30 is suggestive of a threshold beyond which GL3 accumulation may not be compatible with podocyte survival. The clinical progression of Fabry nephropathy beyond age 30 in FD males with classical mutations could be reflected in other podocyte parameters such as podocyte hypertrophy and/or loss. Thus further studies are underway to explore these possibilities.

Funding: NIDDK Support, Pharmaceutical Company Support - Sanofi

FR-PO166
Outcomes of Patients Over 65 in the Canadian Fabry Disease Initiative Study
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Background: The Canadian Fabry Disease Initiative (CFDI) is a multicentre prospective study of outcomes with enzyme replacement therapy (ERT) in Fabry disease. ERT has been shown to be of benefit in reducing Fabry cardiac and renal disease. There is uncertainty as to the benefits of ERT in older patients. We compared outcomes of ERT in patients over 65 years of age with the overall CFDI population.

Methods: Patients are reviewed every 6-12 months as to clinical status. ERT is provided every 2 weeks according to national guidelines with intravenous dose agalsidase alpha (0.2 mg/kg) or agalsidase beta (1.0 mg/kg). Cardiovascular risk factor modification is promoted with use of ASA, statins and ACEI/ARB. Clinical outcomes are defined as stage 5 CKD, stroke/TIA, acute deafness, cardiac arrest, CHF, arrhythmia, unstable angina, MI, PTCA, pacemaker/ICD, AVR/CABG and death.

Results: As of Jan 2015, 429 subjects were enrolled. There were 51 patients over 65 yrs, 68.6% female, and 60.8% on ERT with mean age 71.8 yrs. There were no differences in mean age, cardiac variant genotype, or time in the CFDI between those on ERT and those not. Compared with patients not on ERT, those on ERT had lower CGFR, greater proteinuria and higher LVM at both baseline and 6 y later. Three patients not on ERT had 5 clinical events, prevalence 15%, no deaths with clinical event rate of 1/345 patient years. Twenty patients on ERT had 5 deaths, 38 clinical events, prevalence 64.5% and clinical event rate of 1.9/3 patient years. Death was more likely in females 21% vs. males 8.3%. Patients over 65 had greater prevalence of cardiac indications for ERT than the overall CFDI population. Time to first clinical event was earlier in those on ERT (p=0.003).

Conclusions: Older patients with Fabry disease continue to have clinical events, mainly cardiac, despite ERT but appear to be living longer. Use of the Canadian Fabry Disease guidelines appears to successfully target high-risk older patients. ERT use in this subgroup appears to be of benefit.

Funding: Pharmaceutical Company Support - Genzyme, a Sanofi Company Shire Inc, Government Support - Non-U.S.

FR-PO167
A Founder Haploype of APOE-Kyoto Mutation Associated with Lipoprotein Glomerulopathy
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Background: Lipoprotein glomerulopathy (LGP) is a rare dominant inherited kidney disease with incomplete penetrance, histological characterized by the formation of intraglomerular lipoprotein thrombi. Their main clinical manifestation includes proteinuria, diastolic hypertension, microalbuminuria and hyperlipidemia. Intraglomerular lipoprotein thrombi. CCX168 was compared with the currently available agent. Our previous study revealed the largest population of LGP from a county 200 kilometer near Chengdu city, in Sichuan province, China. All these patients shared APOE-Kyoto mutation in e3 allele, which suggests that the APOE-Kyoto mutation allele associated with LGP in the narrow country was identical, suggesting that mutation is common in chinese patients through a founder effect. And patients didn’t have a common haplotype of counterpart APOE allele as the asymptomatic carriers, which association with the onset of LGP isn’t known. To the new haplotype 32 of APOE4, its clinical value isn’t clear now.

Results: Eleven Pregnancies in Four Women with Atypical Hemolytic Uremic Syndrome
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Background: Pregnancy activates the maternal alternative pathway of the complement system due to presentation of paternal antigens. In females with atypical Hemolytic Uremic Syndrome (aHUS) – a disease of the complement regulatory proteins and C3 – each pregnancy can trigger life-threatening disease episodes.

Methods: Data were collected from patients with aHUS, enrolled in the Viennese TMA Cohort. Pregnancies occurred between 2002 and 2015. Results: We report 11 pregnancies in 4 women (table 1). Two had an established diagnosis of aHUS prior to the first pregnancy (case 2 and 3). Case 1 presented with end-stage renal disease due to TMA (biopsy-proven) 12 months after her first delivery and case 4 presented postpartum after her uncomplicated first delivery. In 8 pregnancies females received preventive plasma infusions (Pl, 200-1600 mL) 2 to 4 weeks apart. After kidney transplantation case 1 received a maintenance therapy (Pls once a month), which was intensified during the II. pregnancy to every other week. Two pregnancies (case 1 II., case 3 III.) are currently ongoing without evidence of a disease flare so far. Nine pregnancies went without any complication and the offspring are healthy. One pregnancy (case 3 III., without Pls) resulted in an intraternal fetal death at gestation week 36, but without signs of TMA in the mother.

FR-PO169
Orally Administered Complement 5a Receptor Inhibitor CCX168 Development in Atypical Hemolytic Uremic Syndrome
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Background: The orally administered complement 5a receptor (C5aR) inhibitor CCX168 is in Phase 2 development for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, atypical hemolytic uremic syndrome (aHUS), and IgA nephropathy. The anaphylatoxin C5a is a potent neutrophil attractant involved in neutrophil priming and activation as well as inducing endothelial cell injury. The latter causes increased neutrophil and platelet adhesiveness, leading to thrombosis, one of the hallmark signs of aHUS. We report here progress in the aHUS program.

Methods: In an ex vivo thrombus formation system, serum from aHUS patients induces thrombus formation on microvascular endothelial cells. CCX168 was compared with the anti-C5 antibody eculizumab and soluble complement receptor 1 (SCR1) in this assay. Results: CCX168 resulted in a dose-dependent inhibition of thrombus size.
Whole Exome Sequencing Identifies Mutations in TUBAL3 as a Novel Cause of Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)

**FR-POI171**

**Whole Exome Sequencing Identifies Mutations in TUBAL3 as a Novel Cause of Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)**

**Asaf Vivante,1,4 Jan Jakob Schulz,1 Shirlee Shril,1 Julian Jakob Schulz,1 Stefan Kohl,1 Daw-yang Hwang,1 Eliah O. Kehinde,4 Richard P. Lifton,1 Martin Zenker,1 Friedhelm Hildebrandt.1,3**

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**Background:** Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of end-stage kidney disease in children. The morphogenesis of kidney and urinary tract is modified by genetic mutations that lead to CAKUT. Identifying these mutations will not only provide deeper insights on disease mechanisms but also aids in improving diagnosis. TUBAL3 was identified as a potential candidate gene for causing CAKUT.

**Methods:** Homozygosity mapping with whole exome sequencing (WES) was performed in 20 consanguineous families with CAKUT from India. Homozygous recessive mutations within the homozygous region were further evaluated as the strongest candidates. Furthermore, we screened an additional cohort of 900 patients with CAKUT for additional mutations with a barcoded array based multiplex exon PCR (48X48 Fluidigm Access Array™) followed by next generation sequencing (Illumina MiSeq™). All identified mutations were confirmed by Sanger sequencing.

**Results:** A homozygous truncating mutation (p.Tyr179*) in the gene TUBAL3 was identified in the consanguineous Indian family A3838 using WES. We then independently detected another mutation homozygously (p.Gly106Ser) in the gene TUBAL3 in a family A1347 of Kurdish descent. TUBAL3 (Tubulin, alpha-like 3) is a protein coding gene and is very conserved across species. Tubulin is the major constituent of microtubules.

**Conclusions:** We identified recessive mutations in TUBAL3 as a novel single-gene cause of CAKUT. Further genetic information and functional studies will help understand disease mechanisms and the role of TUBAL3 in the pathogenesis of CAKUT.

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**FR-POI170**

**Whole Exome Sequencing Reveals Mutation of PAPLN as a Novel Cause of Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)**

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**Background:** Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in children. Knowledge from animal models suggests that single gene mutations in genes governing kidney and urinary tract development may lead to CAKUT in humans. However, the genetic pathogenesis of human CAKUT remains mostly elusive.

**Methods:** To identify novel monogenic causes of CAKUT we applied homozygosity mapping with whole exome sequencing (WES) to 36 families with CAKUT. Then we investigated a worldwide cohort of ~1,600 families with CAKUT with a barcoded array based multiplex exon PCR (48X48 Fluidigm Access Array™) and next generation sequencing (Illumina MiSeq™). Results: In a consanguineous family with isolated CAKUT we detected a homozygous protein truncating mutation (p.Arg480*) in the PAPLN gene by WES. PAPLN encodes papillin, a component of the extracellular matrix (ECM) that plays a role in ECM development and interacts with ADAMTS metalloproteases. Papillin contains several thrombospondin type 1 domains homologous to ADAMTS-1, in which mutations lead to very distinct CAKUT phenotype in mice.

**Conclusions:** We identified a recessive truncating mutation in PAPLN as a novel monogenic cause of CAKUT, suggesting that CAKUT in humans may result from disruption of ECM degradation and turn over.

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**FR-POI172**

**Association of PAX2 and Other Gene Mutations with the Clinical Manifestations of Renal Coloboma Syndrome**

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**Background:** Renal coloboma syndrome (RCS) is characterized by kidney hypoplasia or dysplasia and abnormality of the optic nerve. Diagnosis of RCS is based on the morphological examination of the kidney, ophthalmologic findings, and family history. Approximately 170 cases with PAX2 gene mutations have been reported in cases with RCS worldwide. However, around 50% cases of RCS have no mutation in PAX2 gene.

**Methods:** To investigate the incidence and effects of mutations of PAX2 and 25 related genes, 26 patients with RCS were screened using next-generation sequence analysis, and candidate mutations were confirmed using Sanger sequencing. The correlation between mutations and clinical manifestation was evaluated.

**Results:** Thirty patients, including two family cohorts (n = 5 and 2), 19 patients with sporadic RCS, and 4 coloboma only control cases were evaluated in the present study. Screening the sequences of PA2X and 22 other genes identified 46 nonsynonymous single nucleotide changes and 9 indels. Among these candidate gene abnormalities, eleven PA2X mutations, including four novel mutations, were confirmed using Sanger sequencing, as well as mutations in CHD7, SALL4, KIF26B, and SIX4. A SALL4 mutation was detected in one patient, and CHD7, KIF26B, and SIX4 mutations were detected in another patient, of which KIF26B mutation is novel. Kidney function and proteinuria were more severe in patients with PA2X mutations than in those without themutation. Moreover, the coloboma score was significantly higher in patients with PA2X gene mutations. Three out of five patients with PA2X mutations had focal segmental glomerulosclerosis diagnosed from kidney biopsies.

**Conclusions:** Our data indicate that PA2X mutation is a key mutation in RCS and may make a major contribution to the pathogenesis of kidney and eye abnormalities. However, other factors and gene mutations may play a role, and further human and animal studies will be required to define the mechanism of pathogenesis of RCS.

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

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**FR-POI173**

**Whole Exome Sequencing Identifies a Mutation in TTC25 as a Novel Monogenic Cause of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)**

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**Background:** Congenital anomalies of the kidney and urinary tract (CAKUT) cover a wide range of renal malformations which account for most cases of pediatric CKD. So far more than 30 monogenic CAKUT-causing genes have been identified. However, for most cases the underlie genetic cause is still unknown.
Methods: To identify causative genes for CAKUT we investigated consanguineous families with CAKUT by applying whole exome sequencing (WES) combined with homozygosity mapping.

Results: In one family we detected a homozygous loss-of-start mutation in the gene TCT25 (tetratropicopeptide repeat-containing 25). This mutation (c.Met1Thr; c.2T>C) was present in an affected child that had a posterior urethral valve, vesicourethral reflux and bilateral hydrourephrosis. TCT25 plays a role in ciliogenesis, proencreatin cilia function and signal transduction in the sonic hedgehog pathway (Hayes, J. M. et al., 2007. Dev. Biol. 312: 115; Xu Y et al., 2015. PLOS ONE 10(4): e0124378). The latter has been shown to coordinate bladder as well as urethra formation in mice (Haraguchi R et al., 2007. Development 134(3):525; Haraguchi R et al., 2012. PLOS ONE 7(1): e42245).

Conclusions: By WES and homozygosity mapping we identified TCT25 as a novel monogenic CAKUT-causing gene if mutated.

Funding: NIDDK Support

FR-PO174
Phenotypic Analysis of a Cohort of Patients with Hepatocyte Nuclear Factor 1 Beta (HNF1β) Mutations and Correlation with Established Scoring Systems
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Background: Hepatocyte nuclear factor 1 beta (HNF1β) mutations may lead to a wide spectrum of clinical phenotypes including developmental defects of the kidney, pancreas, liver, and Mullerian duct. HNF1β mutations account for Renal Cysts and Diabetes (RCAD) syndrome. We reviewed patients with known HNF1β mutations to determine the range of phenotypes and identified if these patients would have been detected based on established scoring systems.

Methods: We selected patients who had been screened for HNF1β mutations from 2009 to 2014 within our hospital. Serum magnesium, potassium, urate and creatinine levels were noted as well as renal morphology based on imaging. All positive and negative patients for HNF1β mutations had their phenotypes quantified and correlated with published HNF1β scoring systems and screening criteria.

Results: 135 patients were screened over 5 years. The cohort included 17 patients from 10 families with confirmed HNF1β mutations. The majority of these patients had CKD stage 3, with a mean creatinine of 144 μmol/L. Only 35% of mutation positive patients had both renal cysts and diabetes. 57% of patients had hyponatremia, 50% of the patients had hyperuricemia and 4 patients had clinical symptoms of gout with 75% of these patients noted as well as renal morphology based on imaging. All positive and negative patients for HNF1β mutations had their phenotypes quantified and correlated with published HNF1β scoring systems and screening criteria.

Conclusions: The majority of patients with HNF1β mutations demonstrated hypomagnesaemia (50%), hyperuricaemia (53%) and deranged liver function tests (59%). RCAD remains a misnomer and patients with HNF1β mutations have a wide phenotypic spectrum, with only one third having renal cysts and diabetes. The use of a HNF1β scoring/ screening system will help to improve detection rates.

FR-PO175
CTNS Gene Mutations and Variants in Adult Hemodialysis Patients
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Background: Nephropathic Cystinosis (NC), a rare, systemic, autosomal recessive disease due to CTNS gene mutations causes end-stage renal disease (ESRD). While most cases of NC are recognized in infancy (95%), late-onset NC with ESRD is rare but might be under-diagnosed. NC is rarely diagnosed in African-Americans (AA). Objective: To identify CTNS mutations and possible pathogenic variants (A) in a representative sample of NC patients (pts) in the US.

Methods: Genomic DNA was extracted from whole blood from 4007 adult hemodialysis pts from the Davita biorepository. Fluidigm’s Access Array IFC was used for the CTNS target enrichment. Enriched DNA was sequenced on the HiSeq 2500 using 2 x 100bp read length.Reads were mapped to the human genome version hg19 using the BWA aligner. Mutations and A were called using both GATK and Sambtools and confirmed by Sanger sequencing.

Results: 16 pts had homozygous (HoZ) and 52 pts had compound heterozygous (HTZ) CTNS sequence Δ. 1/6 pts had a known diagnosis of NC (W138X). In HoZ pts, 6 had known mutations in CTNS (V421S/C were AA) consistent with NC. 9 had upstream promoter mutations (UMP) (7 with -294C>T and 2 with -295G>C, a mutation locus with known disease association), and 3 of these pts were AA. In 52 HTZ CTNS sequence Δ, 2 AA pts had UPM. The other 50 had combinations of changes in the CTNS coding sequence & promoter region.

Conclusions: The unexpected frequency of CTNS gene mutations & Δ suggest that late-onset NC may be underrecognized in ESRD. These CTNS alterations need further study to determine pathogenicity and association with NC. In addition, CTNS mutations & Δ in AA sub-population signals a need for evaluation for a diagnosis of late onset nephropathic cystinosis in ESRD.

Funding: Pharmaceutical Company Support - Raptor Pharmaceuticals

FR-PO176
Sixteen Monogenic Genes Cause 20% of Early-Onset Urinary Stone Disease
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Background: Urinary stone disease (USD) is a prevalent condition that affects 10-15% of adults in their lifetime. It is associated with high morbidity due to colicky pain, the necessity for surgical intervention, and sometimes progression to chronic kidney disease. In recent years, multiple monogenic causes of USD have been identified. However, the prevalence of each monogenic gene has yet to be systematically studied in a pediatric urinary stone cohort.

Methods: To determine the percentage of cases that can be explained molecularly by mutations in 1 of 30 known urinary stone genes, we conducted a high throughput exon sequencing analysis in an international cohort of consecutively recruited individuals from three renal stone clinics. The cohort consisted of 143 individuals under 18 year of age, with nephrolithiasis (n=123) or isolated nephrocalcinosis (n=20).

Results: We detected likely causative mutations in 16 of 30 analyzed genes, leading to a molecular diagnosis in 20% (n=29 of 143) of affected individuals. 14 of the 32 detected mutations were not previously described as disease causing (43%). We show that mutations in recessive genes are more likely to cause infantile onset disease, whereas mutations in dominant genes are more likely to manifest later.

Conclusions: We present the first exclusively pediatric cohort examined for monogenic causes of urinary stone disease, and our data demonstrates that important therapeutic and preventative measures may result from mutational analysis in individuals with early-onset USD.

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FR-PO177
Mild Inhibition of Alanine-Glyoxylate Aminotransferase Translation as a Possible Treatment of Primary Hyperoxaluria Type I
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Background: Primary hyperoxaluria type 1 (PH1) is a kidney stone disease, often leading to ESRD, caused by absence, deficiency or mistargeting of the liver peroxisomal alanine-glyoxylate aminotransferase (AGT), encoded by AGT. The most frequent mutation G170R, responsible for 30% of PH1 cases in Caucasians, results in aberrant mitochondrial localization rather than catalytic inactivity. Modulating AGT maturation and folding has long been perceived as a therapeutic approach. Yet, numerous attempts over the years failed to rescue AGT mutants. We propose mild translational inhibition as a novel approach to improve folding and localization of AGT mutants.

Methods: The antihelminthic FDA-approved drug emetine, was used as a translation inhibitor. To ensure selective and specific discrimination between the mitochondrial (major) and the peroxisomal (minor) subpopulations of mutated AGT we developed the GlowAGT assay based on the recently described self-assembled split GFP approach.

Results: Using GlowAGT, WT-AGT but not G170R-AGT was detectable by GFP fluorescence, although both variants were visible by indirect immunofluorescence. Long-term treatment with low concentrations of emetine showed statistically significant increase of fluorescent subpopulation of G17OR-AGT. GFP fluorescence was exclusively co-distributed with the peroxisomal staining in all cases.

Conclusions: We have developed and applied successfully GlowAGT as a unique self-assembly split-GFP-based assay for detecting peroxisomal subpopulation of AGT. Using GlowAGT we show that mild translation inhibition by emetine is a novel therapeutic approach for PH1 caused by AGT misfolding/mislocalization.
FR-PO178

Functional Analysis of CLCNKB Mutations Causing Bartter Syndrome Type III Yohan Bignon,1 Mathilde Keck,1 Stéphane Lourdel,1 Rosa Vargas-Pousou,2 Jacques Teulon,1 Olga Andrini.1 (Metabolisme et Physiologie Renales, Centre de Recherche des Cordeliers, UPMC, Paris, France; 2Dept of Human Genetics, Hopital Europeen Georges Pompidou, Univ Paris 5, Paris, France.)

Background: Bartter Syndrome type III is a human autosomal recessive disease characterized by salt wasting, hypokalemic metabolic alkalosis and secondary hyperaldosteronism. Therefore, patients affected by Bartter syndrome type III display polyuria, polydipsia, dehydration, nephrocalcinosis and failure to-thrive. The disease is caused by inactivating mutations in the CLCNKB gene encoding for the CIC-Kb Cl- channel that is present in the distal nephron, where it mediates the basolateral step of Cl- absorption [2]. In this study, we investigated the functional consequences of five previously reported pathogenic CIC-Kb missense mutations (A204T, A210V, P216L, G424R, G437R [3]).

Methods: We characterized the electrical activity, total protein expression, surface expression and subcellular localization of mutated forms of CIC-Kb in X laevis oocytes and mammalian cell lines.

Results: Currents produced by G424R and G437R CIC-Kb channels were reduced by 50%, in proportion to membrane targeting without any change in total protein abundance. A210V and P216L mutants did not produce any current but their membrane insertion was only partially reduced (50-80%). Protein abundance of A210V was decreased by half. Conversely, that of P216L was comparable to WT CIC-Kb, suggesting that the P216L mutation was inherited from a healthy parent.


Funding: Government Support - Non-U.S.

FR-PO179

Changes in Urologic and Medical Treatment of Cystinuric Patients Over Time Caroline Prot-Bertogne,1 Said Lebbah,1 Michel Daoud,1 Isabelle Tostivint,4 Olivier Traxer,2 Bertrand Knebelmann,4 Marie Courbebeisse.1 (Physiology, APHP, Georges Pompidou European Hospital, Paris, France; 2Biostatistics, AP-HP, Necker Hospital for Sick Children, Paris, France; 3Urology, AP-HP, Necker Hospital for Sick Children, Paris, France; 4Nephrology, AP-HP, Pitîé-Salpêtrîere Hospital, Paris, France.)

Background: Cystinuria is the most common monogenic nephro lithiasis disorder, but few studies have described its urological and medical treatment in a large cohort.

Methods: We retrospectively collected data from 442 French cystinuric patients. Clinical and laboratory data, urological and medical treatments were described. A mixed-effects logistic regression model was used to estimate the effects of urinary pH, urinary specific gravity, and cysteine-binding thiol agents (CBT) on the risk of cystine crystalluria.

Results: The median follow-up [min-max] was 15.8 years [0.1-65.6]. The average annual rate of surgical procedures increased with time (P<0.001). During the period 2000-2004, 73.3% of patients had at least one flexible ureteroscopy, versus 23.2% after 2005 (P<0.001). CBT were prescribed for 55.3% of patients. Prescription of tiopronin increased over time with no significantly patients (P<0.001). At least one side effect was recorded in 23.7% of patients treated with tiopronin, and 30.2% of patients treated with D-penicillamine (P<0.23). Increasing urinary pH and decreasing urinary specific gravity significantly reduced the risk for a patient to have a cystine crystalluria whereas D-penicillamine and tiopronin did not reduce this risk. The estimated probability of cystine crystalluria was 45%, 38%, 31% and 25% for an urinary pH of 6.5, 7.0, 7.5 and 8 and was 32%, 31% and 16% for an urinary specific gravity of 1015, 1010 and 1005.

Conclusions: The number of urological interventions and the prescription of tiopronin has increased over time. We show for the first time that D-penicillamine and tiopronin don’t impact cystine crystalluria although inducing frequent adverse effects in the same proportions. Urinary pH above 7.5 and morning urinary specific gravity below 1005 should be the goals of medical therapy.

Funding: Government Support - Non-U.S.

FR-PO180

Defect of Interdependent Membrane Targeting and Endocytosis of Cubilin and Amnionless Leads to Imerslund-Gräsbeck Syndrome Tomohiro Udagawa,1 Ken-ichiro Miura,1 Akihiko Saito,1 Yutaka Harita,1 1Pediatrics, Graduate School of Medicine, The Univ of Tokyo, Bunkyo-ku, Tokyo, Japan; 2Applied Molecular Medicine, Niigata Univ Graduate School of Medical and Dental Sciences, Chuo-ku, Niigata, Japan.

Background: Imerslund-Gräsbeck syndrome (IGS) is an autosomal recessive disorder characterized by low-molecular-weight proteinuria and megaloblastic anemia. IGS is caused by mutations of either cublin (CUBN) or amnionless gene (AMN). Cublin forms protein complex with amnionless (cubam complex) and functions as the receptor-mediated endocytotic machinery.

Methods: A six-year-old boy with history of megaloblastic anemia was diagnosed with IGS because of low-molecular weight proteinuria. Whole-exome sequencing identified novel missense mutations, one each in CUBN and AMN. The CUBN mutation was de novo and the AMN mutation was inherited from a healthy parent.

Results: Renal biopsy showed translocation of amnionless from the apical membrane to the cytoplasm of proximal tubular cells. Using cultured cells, the mechanism of membrane trafficking of cubam and the effect of the mutations were analyzed. Although wild-type cubilin and amnionless were interdependently targeted to the cell membrane, the CUBN or AMN mutation abrogated membrane expression and endocytosis without affecting the interaction between cubilin and amnionless. Coexpression of amnionless induced maturation of cubilin protein, and the modification were identified by stable isotope labeling using amino acids in cell culture (SILAC)-based quantitative mass spectrometry. Notably, the CUBN mutation completely abrogated the amnionless-dependent glycosylation of cubilin. Tunicamycin or substitution of several Asn residues to Asp abrogated membrane targeting of cubam without affecting cubilin and amnionless interaction, further supporting a role of cubin glycosylation.

Conclusions: Our results demonstrate that digenic heterozygosity can lead to IGS and suggest that interdependent membrane trafficking of cubam complex mediated by posttranslational modification is crucial for the renal and intestinal absorption.

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FR-PO181

Metabolic Control of Nephron Progenitor Cell Renewal and Differentiation Anna Abrams, Jiao Liu, Zubaadia R. Saffiedeen. Pediatrics, Tulane Univ, New Orleans, LA.

Background: Nephron progenitor cells (NPC) availability and differentiation potential determine nephron endowment. Emerging data from embryonic stem cells and other developing systems emphasize the significance of energy metabolism in cell fate determination. Systemic metabolic dysfunction such as hyperglycemia alters neural and adipocyte stem cell fate. Nephron deficit in kidneys of diabetic mothers (idm) is known; however the effect on NPC and nephrogenesis under maternal hyperglycemia are unknown. Metabolic parameters of renewing NPCs are also unknown. Based on published stem cell data, we hypothesized that NPC self-renewal and differentiation are balanced by energy metabolism.

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

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Methods: a. Fetal kidneys were exposed to maternal hyperglycemia using Streptozotocin (STZ). The kidney sections were immunostained to detect apoptosis (active caspase3) in the CM (Six2 and NCAM) and nascent neprons (Lef1 and NCAM). b. Glycerolysis was inhibited ex vivo in E12.5 kidneys by pharmacological inhibition of PFKFB3 (YN1 5-25Sm). c. Glycerolysis and oxidative phosphorylation were measured in NIDDK Support, Other NIH Support - NHEMGS.

Results: a. CM of P0 kidneys of STZ-treated females showed increased apoptosis and reduction in nascent nephron number (Lef1+ and NCAM+). Glycerolysis inhibition resulted in a smaller dispersed CM, accelerated but not ectopic differentiation of the NPC with up to a 50% increase in Lhx1+ nascent nephrons 24-48h post-treatment, and decreased CitEd expression by QPCR in isolated NPC. UB tip and branch numbers were unchanged. Thus, increased nephrogenesis was independent of UB branching. Expression of Wnt4 was unchanged. c. Conditional deletion of p53 in NPC also resulted in dispersed CM, depletion of the CM, increased Lhx1+ NPC independent of apoptosis, and hypoplastic kidneys with fewer nascent nephrons. Isolated mutant cells showed reduced basal oxygen consumption rate and decreased maximal respiratory capacity. Accordingly, the mutant cells exhibit a significant, nearly two-fold decrease in ATP (P<0.005, n=3).

Conclusions: Our data are consistent with the idea that the metabolic status of the NPC is a critical determinant of NPC renewal and differentiation.

Funding: NIDDK Support, Other NIH Support - NHEMGS

FR-PO182
Prolene Receptor Signaling Promotes Nephron Induction During Mouse Kidney Development Renfang Song,1 Graeme James Preston,1 Laura R. Kidd,2 Ihor V. Yosypiv,1 1Pediatrics, Tulane Univ, New Orleans, LA; 2Pathology, Tulane Univ, New Orleans, LA.

Background: Deficient nephrogenesis is the major factor contributing to congenital renal hypoplasia (RHD), one of the leading causes of childhood end-stage kidney disease. Nephron induction is driven by reciprocal interactions between progenitor cells of the cap mesenchyme and the uretic bud (UB).

Methods: To determine the potential role of the prolene receptor (PRR) in nephrogenesis, we generated mice with a conditional deletion of the PRR in Six2-positive nephron progenitors of the cap mesenchyme and their epithelial derivatives (Six2CreER).

Results: Inactivation of PRR in nephron progenitors caused a marked decrease in the number of developing nephrons, severe congenital RHD with collapsed glomeruli and an enlarged Bowman’s space (such as those seen with a collapsing FSGS), podocyte foot process effacement and early postnatal death within 48 hours from birth. UB branching was greatly reduced, likely secondary to decreased nephrogenesis. Reduced congenital nephron endowment resulted from premature depletion of nephron progenitor cell population due to impaired progenitor cell proliferation and loss of normal morphogenic inductive response to canonical Wnt/b-catenin signaling within the metanephric mesenchyme. At 2 months of age, heterozygous Six2CreER mice exhibited focal glomerulosclerosis, decreased kidney function and massive proteinuria.

Conclusions: Collectively, these results are consistent with a cell-autonomous requirement for the PRR within nephron progenitors for progenitor maintenance, induction of nephrogenesis, normal kidney development and function. Thus, PRR is a potential candidate for future genetic screening studies in patients with congenital RHD and proteinuric kidney disease.

FR-PO183
Functional Dissection of Enhancers for Bmp7 in Kidney Development Taro Tsujimura,1,2,3 Osamu Takase,1,2,3 Masao Namagaki,1 Keichi Hishikawa,1,2,3 1Advanced Nephrology and Regenerative Medicine, The Univ of Tokyo Hospital, Tokyo, Japan; 2Div of Nephrology and Endocrinology, The Univ of Tokyo Hospital, Tokyo, Japan; 3Div of Tissue Engineering, The Univ of Tokyo Hospital, Tokyo, Japan.

Background: Bmp7 is a critical player in the kidney development, as shown by its severe retardation in the KO mice of the gene and their subsequent perinatal lethality due to the malfunction. Previous studies identified two potential enhancers for the Bmp7 expression in the developing kidney around the locus: one residing inside the 1st intron of Bmp7 for expression in the developing ureteric bud; the other located downstream of the 3' end of Bmp7, which is rather active in the metanephric mesenchymal cells. Consistently, Bmp7 is also expressed in these two distinct domains. However, neither the requirement of these elements nor the noise of Bmp7 secreted from these different cell types for the kidney development has been uncovered so far. In this study, we aimed to characterize the roles of the two enhancers to better understand the cis-regulation of Bmp7 and the kidney development.

Methods: We established and analyzed homoyzogous mice carrying a large genomic deletion of the downstream region of Bmp7 including the mesenchymal enhancer.

Results: We found that they have significantly smaller body size than their wild type littermates, although they are viable unlike the KO mice of Bmp7. We previously showed that the same deletion also disrupts the topological partition of the chromatin conformation between the Bmp7 domain and the neighboring one of another developmental gene, Tjoc2p, resulting in a merger between them (Tsujimura et al. PLoS Genetics 2015). Interestingly, upon deletion, we scored significant up-regulation of Tjoc2p in the kidney probably by the loss of the intron enhancer.

Conclusions: These results suggest that the endogenous genomic context guarantees robustness in the regulation of the kidney development by linking the more important ureteric bud enhancer to Bmp7 tightly. The differential roles of the two enhancers will be further discussed based on the histological and functional analysis of the kidney in the homoyzogous deletion mice.

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FR-PO184
BMP7 Regulates Expansion of the Postnatal Nephron Mary E. Tautzieni,1 Seymou Rosen,2 Jordan A. Kreidberg. 1,3,4 1Dept of Medicine, Boston Children’s Hospital, Boston, MA; 2Dept of Pathology, Beth Israel Deaconess Medical Center, Boston, MA; 3Dept of Pediatrics, Harvard Medical School, Boston, MA; 4Harvard Stem Cell Inst, Cambridge, MA.

Background: The factors that regulate the expansion of nephrons after their initial induction and differentiation are largely unknown. Bone morphogenic protein 7 (BMP7) is a crucial factor driving proliferation and self-renewal of nephron progenitor cells during the development of the embryonic kidneys. In this study we investigated potential role for BMP7 as a regulator of post-induction nephron growth and differentiation.

Methods: The Bmp7 gene was conditionally mutated in progenitor cells using Six2-GFP/Cre. Kidneys from mutant and control mice were analyzed using a novel approach to identify proximal tubule expansion as an indicator of nephron growth in the postnatal mouse.

Results: Kidneys of Bmp7 conditional mutant mice were smaller with reduced numbers of nephrons. Bmp7 was expressed in developing nephron tubules of control kidneys and was absent from mutant kidneys. Proximal tubule growth, as determined by computationally measuring the area of lectin-stained proximal tubules in postnatal kidneys, was reduced in mutant kidneys. However, the proximal tubule area per glomerulus was increased in mutant kidneys, indicating that those nephrons that were induced underwent hypertrophy. Proliferation, as defined by Ki67+ nuclei per LTL. Islet cells within the proximal tubule compartment, was initially greater in mutants but declined by P10.

Conclusions: Loss of Bmp7 in progenitors leads to low nephron number. Bmp7 appears to be an important driver of postnatal nephron expansion. This phenotype is similar to oligomeganephropnia and may be used to understand the basis for nephron hypertrophy in low nephron number situations.

Funding: NIDDK Support

FR-PO185
Grainyhead-Like 2 (Grhl2) Regulates Collecting Duct Barrier Function, Aquaporin 2 Expression and Urinary Concentration Christian Hinze,1,2 Janett Ruffert,1,2 Katharina Walentin,1 Max Werth,1 Jonathan M. Barash,3 Andong Qiu,4 Kerim Mutig,1 Sebastian Bachmann,1 Kai M. Schmidt-Ott,1 1Dept of Nephrology, Charité-Universitätsmedizin, Berlin, Germany; 3Max Delbrueck Center for Molecular Medicine, Berlin, Germany; 4Div of Nephrology, Columbia Univ, New York; 5Dept of Anatomy, Charité-Universitätsmedizin, Berlin, Germany; 6Urological Research Laboratory, Charité-Universitätsmedizin, Berlin, Germany.

Background: Osmotic homeostasis is tightly regulated by the kidney and its collecting ducts which form tight barriers, thereby maintaining steep concentration gradients and allowing transcellular reabsorption of water via aquaporins. The transcription factor grainyhead-like 2 (Grhl2) is highly expressed in renal collecting ducts. Using cultured collecting ducts, we recently showed that Grhl2 regulates epithelial barrier formation and lumen expansion via a target gene set comprising the transcription factor Ovo-like 2 (Ovol2), the small GTPase Rab 25 (Rab25) and the tight junction component claudin 4 (Cldn4). The role of Grhl2 in the collecting duct in vivo is unknown.

Methods: To investigate the role of Grhl2 in the renal collecting duct, we generated a collecting duct-specific knockout with Hoxb7-Cre; Grhl2fl/fl mice, which exhibit a deletion of Grhl2 protein in most cells of the collecting duct. The molecular and cellular alterations in their kidneys and their response to water deprivation were analyzed.

Results: Transcriptional profiling of Hoxb7-Cre; Grhl2fl/fl mice kidneys and control littermates showed deregulation of Ovol2, Rab25 and Cldn4, but also differential expression of Aquaporin 2 (Aqp2). Following water deprivation, Grhl2-deficient mice displayed significantly lower urinary osmolality at 6 hours (P=0.001) and 24 hours (P=0.04) when compared to control mice. Moreover, Grhl2-deficient mice had more than 35% more urine volume during the first 24 hours in response to water deprivation when compared to controls (P=0.005).

Conclusions: Our data indicate that Grhl2 critically participates in water homeostasis, epithelial barrier function and Aqp2 expression. This might be of relevance to diseases involving defective renal responses to water deprivation.

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FR-PO186
Loss of the Transcription Factor Tcf21 in the Renal Stroma Leads to Polyuria and Defects in Tubular Development Shintaro Idg,1 Yoshio Maczawa,1 Rizalda P. Scott,2 Tucker Onay,1 Kana Id,1 Minori Takemoto,1 Koutaro Yokote,1 Susan E. Quaggin. 2 1Clinical Cell Biology and Medicine, Chiba Univ Graduate School of Medicine, Chiba, Japan; 2Feinberg Cardiovascular Research Inst and Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.

Background: Renal stromal cells serve as a supportive framework for nephrons and the collecting duct network, produce erythropoietin, and contribute to renal fibrosis when they undergo myofibroblast-like transformation. Tcf21/Pod1 is a BHLL transcription factor
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FR-PO187

Genetic Deletion of Cyclooxygenase-2 Impairs Glomerular Slit Diaphragm Formation During Late Stages of Kidney Development

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Background: Renal cyclooxygenase-2 (COX-2) expression is necessary for normal glomerular development. Impaired COX-2 activity has been associated with decreased expression of vascular endothelial growth factor (VEGF), a vascular growth factor of significant importance for glomerular capillary development. Therefore experiments were designed to test the hypothesis that COX-2 expression supports glomerular development through stimulation of capillary loop formation.

Methods: Kidney tissue was collected from a developmental series of COX-2 knock-out (KO) mice and wild-type littersmates (WT).

Results: Renal COX-2 expression showed developmental regulation with significantly higher COX-2 expression at postnatal (P) days 1 and P7 than at any later time points (P14, P21 and P40). Quantitative unbiased stereology at P28 showed significantly reduced glomerular number in COX-2 KO mice compared to WT littersmates (8188 ± 781 and 12251 ± 454 glomeruli/kidney respectively, P=0.0001). Subcapsular accumulation of small and immature glomeruli was seen in COX-2 KO mice whereas glomeruli deeper in the cortex towards the medullary region appeared normal. Tissue abundance of VEGF, angiotensin-1 and -2 mRNAs was significantly reduced in COX-2 KO mice compared to WT at P7. By electron microscopy at P28, immature subcapsular glomeruli showed normal appearance of fenestrated endothelial cells but severe podocyte foot process effacement and absence of mesangial cells. Normal morphology was confirmed in glomeruli deeper in the cortex. At P7, COX-2 KO mice showed reduced expression of slit diaphragm proteins nephrin and podocin but not synaptopodin compared to WT.

Conclusions: In summary, deletion of COX-2 leads to decreased renal expression of VEGF, and reduced capillary formation. This may result in abnormal capillary development and severe podocyte foot process effacement and impaired expression of slit diaphragm proteins. In conclusion, COX-2 activity is necessary for normal podocyte function and slit diaphragm formation during late stages of kidney development.

Funding: Private Foundation Support

FR-PO188

Functional Cross Talk Between Tyrosine Phosphorylation of Crumbs Homolog 2 and Mechanistic Target of Rapamycin Complex 1 in Developing Podocyte

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Background: Mutation of crumbs homolog 2 (CRB2) is a novel cause of congenital nephrotic syndrome in humans that is linked to functional changes in the epithelial cell ultrastructure; however, how CRB2 functions in podocyte development is unknown. Other isoform: CRB2

Methods: MDCK cells expressing mouse full-length CRB2 or mutated-CRB2 lacking tyrosine phosphorylation site were established. Specific antibodies against CRB2 intracellular domain (mCRB2Ab) (tyrosine phosphorylation site (pY-CRB2Ab)) or tyrosine phosphorylation site/pY-CRB2Ab were generated. The samples from cultured cells and rat kidneys were subjected to Western blot study and immunofluorescence microscopy.

Results: Int-CRB2Ab determined CRB2 to locate at the apicobasal membrane in wild-CRB2 cells. Specificity of pY-CRB2Ab was confirmed by using samples from mutated-CRB2 cells and wild-CRB2 cells treated with protein tyrosine phosphatases inhibitor. Int-CRB2Ab identified that CRB2 expression commenced at the comma-shaped body stage, observed in the apical side of glomerular epithelium. CRB2 in the S-shaped body was still visible at the apical side of immature podocytes, then translocated along the lateral side of early distal tubule. CRB2 was observed in the podocyte foot processes. In contrast, phosphorylation of CRB2 was determined faintly in immature podocyte at the S-shaped body stage, intensely at the interstage of podocyte and then dropped sharply at stage of mature podocyte. Expression of CRB2 at the mature stage, but was not in immature podocyte. Finally, mTORC1 in mutated-CRB2 cells was activated more than that in wild-CRB2 cells.

Conclusions: CRB2 tyrosine phosphorylation may regulate energy system of developing podocytes through suppressing excessive mTORC1 activation.

FR-PO190

Epithelial Cell Fate in the Nephron Tubule Is Mediated by the etv5a Transcription Factor During Zebrafish Kidney Development

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Background: Kidney development requires the differentiation and organization of discrete nephron epithelial lineages, however the genetic and molecular pathways involved in these events remain poorly understood. The embryonic zebrafish kidney, or pronephros, provides a simple and useful model to study nephrogenesis.

Methods: The pronephros is comprised of two types of epithelial cells: transportive and multi-ciliated cells (MCCs). Transportive cells occupy distinct tubule segments and are characterized by expression of solute transporters, while MCCs function in fluid propulsion and are dispersed in a “salt-and-pepper” pattern in the tubule. Epithelial cell identity is related in a dynamic way between Notch signaling pathway and retinoic acid (RA) signaling, where RA promotes MCC fate by inhibiting Notch signaling in renal progenitors, where Notch activity acts downstream to trigger transportive cell formation and restrict MCC identity. Previous research has shown that etv5a and its ETS family members are required for ciliogenesis in other zebrafish tissues.

Results: Here, we mapped etv5a expression to renal progenitors that occupy domains where MCCs later emerge. Thus, we hypothesized that etv5a is required for ciliogenesis of MCCs in the nephron. etv5a loss of function produced a decline of MCC number and reduced expression of the MCC markers odf3b and centrin, where rescue experiments partially restored wild-type MCC number. In epistatic studies, exogenous RA treatment expanded the etv5a domain, indicating that etv5a acts downstream of RA. Additionally, treatment with exogenous RA partially rescues the reduced MCC phenotype after loss of etv5a. FISH shows that both of two types of probe (etv5a and odf3b) increased etv5a expression, while overexpression of Notch using a transgenic line reduced the etv5a domain, suggesting Notch acts upstream to inhibit etv5a.

Conclusions: Taken together, these findings provide novel insights about the mechanisms of epithelial cell development during nephrogenesis.

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FR-PO191

Emx1 Is Essential for Distal Segment Development During Nephrogenesis

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Background: Vesicle kidneys are comprised of functional subunits called nephrons that typically have three basic pars: a renal corpuscle, a tubule with proximal and distal segments, and a duct. The developmental pathways that establish nephron segment identities from renal progenitors remain poorly understood.

Results: In summary, deletion of COX-2 leads to decreased renal expression of VEGF, and reduced capillary formation. This may result in abnormal capillary development and severe podocyte foot process effacement and impaired expression of slit diaphragm proteins. In conclusion, COX-2 activity is necessary for normal podocyte function and slit diaphragm formation during late stages of kidney development.

Funding: Private Foundation Support

Funding: NIDDK Support
Methods: The zebrafish embryo forms a simple two-nephron pronephric kidney that possesses anatomic and functional homology with human nephrons. emx1 is a homeobox gene that, along with its paralog emx2, is known for playing essential roles in brain development. While both genes are expressed in the pronephros, their roles in nephrogenesis have not been established. Using whole mount in situ hybridization, we found that emz1 and emz2 were dynamically expressed in renal progenitors, and became localized to the distal and proximal tubules, respectively.

Results: In knockdown studies, emz1 morphants formed a normal distal domain, marked by clcnk, but within it formed an expanded distal early (DE) segment, marked by slc2a5. These data suggest that emz1 is essential to promote the DL, and may restrict the DE and/or negotiate the site of the DE/DL boundary. Furthermore, emx2 expression is responsive to changes in retinoic acid (RA), which is essential to induce proximal segments and repress distal segments during nephrogenesis. RA treated embryos had a restricted emx1 domain and expanded emx2 domain, while exposure to the RA biosynthesis inhibitor DEAB conversely expanded emz1 and restricted emz2 expression. These data suggest that RA signaling acts upstream of both genes in renal progenitors, positively regulating emz2 and negatively regulating emz1.

Conclusions: Future studies will define the role of emx2, independently explore emx1/nephrogenesis, and examine the relationship of these emz genes to other factors, such as zic3b, that have been shown recently identified to be components of the gene regulatory networks that direct nephron segmentation. Preliminary data looking at factor interactions suggest that emx genes may be located downstream of them or work independently.

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FR-PO196
Enalapril Treatment Modulates Lymphangiogenesis and Fibrogenic Machinery in the Developing Rat Kidney
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Background: The renin angiotensin system plays a pivotal role in both renal development and progressive renal disease. Lymphangiogenesis occurs during normal organ development and pathological processes. In this study, we aimed to investigate the effect of angiotensin II inhibition on the expression of fibrogenic-related molecules and lymphatic vessels in the developing rat kidney.

Methods: Newborn rat pups were treated with enalapril (30 mg/kg) or vehicle for 7 days after birth. We investigated the intrarenal expression of fibroblast growth factor (FGF)-1, FGF-2, FGF receptor (R)-1, fibroblast-specific protein (FSP)-1, intercellular adhesion molecule-1, toll-like receptor (TLR)-2, and TLR-4 with Western blotting and immunohistochemistry at postnatal day 8. For the determination of lymphatics, the lymphatic vessel markers of vascular endothelial growth factor (VEGF)-C, VEGFR-3, and podoplanin were assessed. For detection of cell proliferation and collagen fibers, Ki-67 and Sirius red stainings were performed.

Results: In the enalapril-treated group, intrarenal FGF-1, FGF-2, FGF-1 and VEGF-C protein expression were decreased, compared to the controls (P < 0.05). Immunohistochemistry for the lymphatic vessel markers of VEGF-C, VEGFR-3, and podoplanin showed reduced lymphatic immunostainings in the enalapril-treated kidneys. However, FSP-1 expression was prominent in the interstitium and glomeruli in enalapril-treated kidneys. While cell proliferation was reduced in the enalapril-treated group, collagen deposition was enhanced in the enalapril-treated kidneys (P < 0.05). Intercellular adhesion molecule-1, toll-like receptor (TLR)-2, and TLR-4 protein expression showed no differences between the two groups.

Conclusions: Enalapril treatment during postnatal 7 days may induce perturbations in FGF/VEGF signals, cell proliferation, and lymphangiogenesis required for renal development and maturation and activate in part the fibrogenic machinery in the developing rat kidney.

FR-PO197
The Effect of Prenatal Hypoxia and a Postnatal High Salt Diet on Renal Structure in the Aged Mouse
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Background: Chronic fetal hypoxia leads to growth restriction and increased risk of adulthood disease. This study examined the long-term renal outcomes of offspring prenatally exposed to hypoxia, and whether a postnatal high salt diet could exacerbate impairments.

Methods: Pregnant CD1 mice were housed in a hypoxic chamber (12.0% O2; N=8, HYP) or control (21% O2; N=8, CON) environment from embryonic day (E) 14.5 to birth (E21.5). A subset of male offspring was randomly allocated to a control diet (0.2% NaCl; N=8, CON) or high-salt diet (5% NaCl; HS) from 10 weeks of age. Blood pressure was measured at 12 months of age and kidneys were collected. Kidney sections were examined for nephron number, glomerulosclerosis, interstitial fibrosis, renal vascular remodeling, and α-SMA staining of CON kidneys was confined to vascular vessel markers of vascular endothelial growth factor (VEGF)-C, VEGFR-3, and podoplanin were assessed. For detection of cell proliferation and collagen fibers, Ki-67 and Sirius red stainings were performed.

Results: In the enalapril-treated group, intrarenal FGF-1, FGF-2, FGF-1 and VEGF-C protein expression were decreased, compared to the controls (P < 0.05). Immunohistochemistry for the lymphatic vessel markers of VEGF-C, VEGFR-3, and podoplanin showed reduced lymphatic immunostainings in the enalapril-treated kidneys. However, FSP-1 expression was prominent in the interstitium and glomeruli in enalapril-treated kidneys. While cell proliferation was reduced in the enalapril-treated group, collagen deposition was enhanced in the enalapril-treated kidneys (P < 0.05). Intercellular adhesion molecule-1, toll-like receptor (TLR)-2, and TLR-4 protein expression showed no differences between the two groups.

Conclusions: Enalapril treatment during postnatal 7 days may induce perturbations in FGF/VEGF signals, cell proliferation, and lymphangiogenesis required for renal development and maturation and activate in part the fibrogenic machinery in the developing rat kidney.

FR-PO199
A Perinatal Switch in Iron Utilization Determines Postnatal Chronic Kidney Disease
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Background: Iron deficiency affects 2 billion people world-wide and is a threat to embryonic and early postnatal development. Periconceptual maternal iron deficiency (PM-ID) results in hypoxic postnatal kidneys but it is not clear whether PM-ID causes cell-lineage or cell-stage specific hypoxia, nor which species of iron is involved.

Methods: We investigated a model of dietary iron deficiency and a deficiency of the transferrin receptor, TIR1 (cellular transferrin receptor, iron deficiency, ATF-ID) in different cell lineages using a novel TIR1-knockout construct.

Results: Severe PM-ID depleted both TIR and NTBI (non-transferrin bound iron) resulting in severe hypoxia postn. Despite iron deficiency, anephric, even anemia during gestation, whereas the overall structure of ureteric bud was maintained. Midle PM-ID resulted in surviving but severe postnatal postn. kidney hypoxia, disruption of the growth of the proximal tubule and TALH and increased mortality before weaning. To determine the mechanism of hypoxia we examined mesenchymal, ureteric and stromal ATF-ID with different Cre drivers. Mesenchymal ATF-ID (Six2Cre or KspCre) demonstrated increased demand for transferrin by the time of birth, resulting in worsening proximal tubule hypoxia, remarkable cystic transformation and interstitial fibrosis, and even anephria (Prox3Cre) before birth, the timing of which coincided with accelerated segment-specific growth. The combination of ATF-ID and PM-ID further worsened nephron development. In contrast, the collecting ducts (HoxB7Cre) and stroma (Foxd1Cre) did not depend on transferrin.

Conclusions: In sum, NTBI supported prenatal and postnatal stromal and ureteric development and the initial stages of metanephric development, whereas Tf iron was required for perinatal maturation of the nephron. Tf-iron depletion resulted in hypoxia, cysts, fibrosis, the timing and specificity of which was the result of a sequence of utilization of NTBI followed by Tf-iron. We propose that a perinatal switch in the mechanism of iron utilization governs the compartmentalization of the kidney and reflects changing cellular control of iron delivery. Iron deficiency is a cause of CKD.

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FR-PO200
Troyn/TNFRSF19 Marks a Progenitor/Cell Stem Population in the Kidney
Kees Schutgens, 1,2 Maarten B. Rookmaaker, 1 Robert Vries, 3 Marianne C. Ohmann, 1

Background: Segment committed stem cells play a crucial role in renal development and regeneration. Identification of these stem cells is an important step towards the development of new diagnostic and therapeutic strategies for renal diseases. In this study, we evaluated Troy, an adult stem cell marker in other organs, as a marker for segment committed stem cells in the developing and adult kidney.

Methods: Renal Troy expression was assessed during embryonic development and adult turnover using Troy-GFP mice. The contribution of Troy+ cells to renal development and turnover was investigated using in vivo lineage tracking after Troy-GFP-CreERT2/Rosa-LacZ. Daughter cells were identified using immunohistochemistry for tubular segment-specific markers. In addition, in vitro stem cell capacity was assessed by a sphere-forming assay.

Results: During embryonic development Troy+ cells were present in the ureteric bud [1A], whereas in adult kidney Troy+ cells were present in the papilla. After p1 induction, Troy+ cells gave rise to tubular structures by clonal expansion that persisted up to 2 years after induction [1B-1E]. Immunohistochemistry revealed predominant co-staining with iron markers in Troy+. Troy+ cells contributed to clonal, collecting duct formation after cessation of nephrogenesis. Finally, Troy+ cells had a higher in vitro sphere forming capacity than Troy- and Troy+ cells [1F-1H].
Preserved Nephrogenesis following Partial Nephrectomy in Early Neonates
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Background: The labeling-retaining cell (LRC) approach is a reliable way to identify adult stem cells. To identify the best labeling time for adult renal stem cells, we administered BrdU in different periods of the kidney development.

Methods: A pulse of BrdU was administered at different periods during E11.5-20.5, respectively, covering the whole process of the kidney development. The adult kidney were examined the distribution of BrdU-positive cells. A subtotal nephrectomy (Nx) was induced in adult mice to observe the response of BrdU-retaining cells to injury.

Results: In adult kidneys, the distribution of BrdU-retaining cells was heterogeneous with different BrdU-labeling time. With BrdU labeled at E11.5-13.5, lots of BrdU-positive cells were located in the papilla and inner medulla, only few scattered in the proximal tubules. With BrdU labeled at P9, lots of cells in the inner medulla and outer medulla could retain the immunoreactivity of BrdU. With BrdU labeled at P9, 11.5, the distribution of BrdU-positive cells was mainly in the outer medulla, few in the cortex inner medulla, no longer in the papilla. With BrdU labeled at P12.5-14.5 and P15.5-17.5, lots of BrdU-positive cells were in the outer medulla, but no longer in the papilla or inner medulla. With BrdU labeled at P18.5-21.5, BrdU-positive cells were only found in the cortex. The proximal tubules were the only nephron segments stably containing few BrdU-retaining cells after a chase period of six months. After Nx in adult mice, BrdU-positive cells were more significantly increased in the cortex near the incision edge. BrdU-positive cells mainly distributed in the proximal tubules at the site of injury. Some BrdU-positive cells did not express PCNA, even though numerous PCNA-positive cells were found near the incision edge of kidney. In contrast, originally retained abundant BrdU-positive cells in the outer medulla and inner medulla significantly reduced and disappeared rapidly in the vicinity of incision.

Conclusions: The locations of LRCs were different if BrdU was administered in different periods of kidney development. Most of BrdU-retaining cells were quiescent, few of them in the proximal tubule and papilla may be the renal progenitor cells.

FR-PO202
BrdU Labeling Adult Renal Stem Cells in Development Kidney
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Background: The labeling-retaining cell (LRC) approach is a reliable way to identify adult stem cells. To identify the best labeling time for adult renal stem cells, we administered BrdU in different periods of the kidney development.

Methods: A pulse of BrdU was administered at different periods during E11.5-20.5, respectively, covering the whole process of the kidney development. The adult kidney were examined the distribution of BrdU-positive cells. A subtotal nephrectomy (Nx) was induced in adult mice to observe the response of BrdU-retaining cells to injury.

Results: In adult kidneys, the distribution of BrdU-retaining cells was heterogeneous with different BrdU-labeling time. With BrdU labeled at E11.5-13.5, lots of BrdU-positive cells were located in the papilla and inner medulla, only few scattered in the proximal tubules. With BrdU labeled at P9, lots of cells in the inner medulla and outer medulla could retain the immunoreactivity of BrdU. With BrdU labeled at P9, 11.5, the distribution of BrdU-positive cells was mainly in the outer medulla, few in the cortex inner medulla, no longer in the papilla. With BrdU labeled at P12.5-14.5 and P15.5-17.5, lots of BrdU-positive cells were in the outer medulla, but no longer in the papilla or inner medulla. With BrdU labeled at P18.5-21.5, BrdU-positive cells were only found in the cortex. The proximal tubules were the only nephron segments stably containing few BrdU-retaining cells after a chase period of six months. After Nx in adult mice, BrdU-positive cells were more significantly increased in the cortex near the incision edge. BrdU-positive cells mainly distributed in the proximal tubules at the site of injury. Some BrdU-positive cells did not express PCNA, even though numerous PCNA-positive cells were found near the incision edge of kidney. In contrast, originally retained abundant BrdU-positive cells in the outer medulla and inner medulla significantly reduced and disappeared rapidly in the vicinity of incision.

Conclusions: The locations of LRCs were different if BrdU was administered in different periods of kidney development. Most of BrdU-retaining cells were quiescent, few of them in the proximal tubule and papilla may be the renal progenitor cells.

FR-PO203
Tissue-Specific Transport and Injury Response in Kidney Tubules Derived from Human Pluripotent Stem Cells
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Background: Human pluripotent stem cells (hPSCs) can differentiate into cells expressing markers of kidney proximal tubules, but the functional capacity of these structures remains poorly understood. We developed a new, adherent, 3D culture system to evaluate transport and injury characteristics in hPSC-derived kidney tubules, compared to undifferentiated hPSCs.

Methods: hPSCs sandwiched in extracellular matrix were maintained in pluripotency-sustaining media to form undifferentiated cavitated spheroids (SOX2+OCT4+), or differentiated with growth factors into nephron progenitor cells (PAX2+SIX2+) and subsequently proximal tubules (LTL+LRP2+). hPSC spheroids or differentiated tubules were incubated with small molecule fluorescent probes to monitor transport into lumens, such as nephrotoxic chemicals to assess nephrotoxicity and kidney injury molecule-1 (KIM-1).

Results: Kidney tubule lumens selectively accumulated rhodamine-dextran (RD) and fluorescein methotrexate (MTX) transport cargos. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA, significantly reduced cargo accumulation. When treated with the nephrotoxic compounds gentamicin or cisplatin, 70% of hPSC-derived proximal tubules expressed KIM-1 at the apical/luminal surface. In contrast, the lumens of undifferentiated hPSC spheroids did not accumulate RD and MTX, nor express KIM-1 after toxic injury with cisplatin or gentamicin.

Conclusions: hPSC-derived kidney tubules are capable of transport and injury responses, which are characteristic of kidney proximal tubules and distinct from undifferentiated hPSC epithelia. The accessibility of this system to small molecules and live-cell microscopy enables rapid and real-time visualization of transport processes and testing of molecular pathways. KIM-1 expression in hPSC-derived kidney tubules may provide a quantifiable standard with which to predict human nephrotoxicity. Our findings introduce a framework in which to evaluate the functionality of hPSC-derived kidney epithelia, prior to transplantation into ESRD patients.

Funding: NIDDK Support, Private Foundation Support
many of these disadvantages could potentially be overcome. To this end we have been attempting to develop a protocol to produce proximal tubule-like cells from human iPSCs with xenobiotic transport capabilities.

Methods: Human iPSCs were differentiated into the intermediate mesoderm (IM) using Wnt and retinoic acid activation (CHIR99021 and TTNBP). Cells were further differentiated using combinations of different growth factors.

Results: The derived cells exhibited cobblestone morphology and expressed certain proximal tubule proteins such as claudin-2. Additionally, the cells can be maintained for up to 4 weeks in culture. Preliminary results demonstrate the ability of the differentiated cells to form functional organoids (Di-10-ASP) and organic anions (6-CF) and to extrude p-glycoprotein substrates (calcium-AM).

Conclusions: While further characterization will be needed, the initial results are promising, indicating that proximal tubule-like cells derived from iPSCs could be a new tool for screening the nephrotoxic potential of compounds.

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

FR-PO205
The Direct Differentiation Method of Renal Tubular Cells by Synthetic mRNAs of Transcription Factors Identified from TF-Inducible Human ES Bank. Ken Hiratsuji,1 Toshiaki Monkawa,1 Shintaro Yamaguchi,2 Ryuji Morizane,1 Shigeru B.H. Ko,2 Minoru S.H. Ko,2 Hiroshi Itoh.1 1Dept of Internal Medicine, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan; 2Dept of System Medicine, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan.

Background: To find transcription factors which promote differentiation towards renal tubular cells, we utilized the human ES line s with doxycycline-controllable transcription factors (TF-inducible hES bank). To establish the differentiation method of renal tubular cells, we transfected the synthetic human mRNA of the target transcription factors into human ES cells.

Methods: We performed exhaustive search for DNA microarray data after TF induction in the hES bank, and analyzed them in silico to find the specific transcription factors, which expressed in kidney epithelial cells. We synthesized the synthetic human mRNA of the target transcription factors. By using the lipofection method, we transfected the synthetic mRNA of target transcription factors to human ES cells, and cultured them. The morphological changes, mRNA expressions, and protein expressions were analyzed.

Results: Some candidate transcription factors, which expressed in human kidney epithelial cells, were identified by in silico analysis. We successfully made synthetic mRNA of candidates of transcription factors. Five days after the transfection of the synthetic mRNA to human ES cells, we were able to observe characteristic morphological changes in the differentiated cells. The mRNA expression of OSR1, ITGAS, AQP1, and MEGALIN were increased. Moreover, the protein expression of AQP1 and LTL were also detected in the differentiated cells.

Conclusions: We identified specific transcription factors for differentiation toward kidney (especially, proximal tubular cells), and demonstrated that the differentiation of proximal tubular cell phenotype from human ES cells by a novel method using synthetic mRNA.

FR-PO206
Differentiation of Human iPSC into Functional Podocytes. Caroinka Rauch,1 Anja Wilmes,1 Elisabeth Feifel,1 Georg Kern,1 Paul Jennings,2 Gerhard Gstraunthaler.1 1Innsbruck Medical Univ; 2Innsbruck Medical Univ; 3Innsbruck Medical Univ; 4Internal Medicine, Rush Univ Medical College, Chicago, IL.

Background: Podocyte injury and subsequent loss of glomerular integrity is a major cause for chronic kidney disease (CKD). Two-thirds of patients with CKD suffer from disorders that arise from the glomerulus, mainly due to podocyte injury. Podocytes are highly specialized cells with a complex cytoarchitecture composed of foot processes that form the glomerular filtration barrier. The study of the molecular processes of glomerular injury is hampered by the fact that cultured primary podocytes have a limited capacity to divide and are difficult to maintain. However, generation of pluripotent stem cells (induced PSCs) from somatic cells allows the possibility of a new source of human cells. The high differentiation capacity of iPSCs would potentially enable the establishment of differentiation protocols for iPSC-derived podocytes which can overcome the burden of primary podocytes in culture.

Methods: To this end we applied and optimized a previously published protocol for podocyte differentiation (Song et al., 2012; PMID: 23029522). Human iPSCs are grown in differentiation media for ten days, containing growth factors known to be important for in vitro podocyte differentiation, BMP-7, activin A, and retinoic acid. Conditionally immortalized human podocyte cultures served as controls.

Results: After three days in differentiation media, iPSCs showed a clear podocyte morphology with podocyte foot processes. To further prove the state of podocyte differentiation, expression of specific podocyte markers was examined via immunofluorescence. Marked expression of the podocyte specific markers podocin and synaptopodin could be successfully verified on differentiated iPSCs. In addition, iPSC-derived podocytes showed significant release of VEGF into the culture medium. Finally, doxorubicin, a podocyte specific toxin, was highly toxic to these cells with an IC50 of 1.5 μM after 48h.

Conclusions: Podocytes generated from iPSCs have far reaching applications in disease modelling, tissue engineering, drug screening and discovery, and toxicity testing. Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO207
Sourcing of Renal Tubular Epithelial Cells from Human Stem Cell-Derived Kidney Organoids. Elijah Weber,1 Benjamin S. Freedman,2 Jonathan Himmelstreich,1 Edward J. Kelly.1 1Pharmaceutics, Univ of Washington, Seattle, WA; 2Nephrolgy, Univ of Washington, Seattle, WA; 3Kidney Research Inst, Univ of Washington, Seattle, WA.

Background: Human pluripotent stem cells (hPSCs) provide a self-renewing, reproducible source of kidney cells for laboratory investigation and regenerative medicine approaches. Several groups have tested the potential of hPSC-derived renal tubular epithelial cell (RTECs) to grow and maintain differentiation in 2D and 3D cultures, compared to primary RTECs from adult kidneys.

Methods: hPSCs were treated with growth factors to promote differentiation in nephroblast progenitor cells (PA2/SIX2) and subsequently proximal tubules (LTL, ZO1, LR2). RTECs purified from tubular organoids were re-plated on tissue culture plates with or without extracellular matrix. RTECs were analyzed for proliferation, kidney-specific marker expression, and their capacity to seed a ‘kidney on a chip’ 3D microphysiological system (MPS).

Results: RTECs purified from hPSC organoids grew to confluent monolayers in minimal RTEC growth media on extracellular matrix. hPSC-derived RTECs resembled primary RTECs morphologically. Marker immunofluorescence analysis revealed that purified hPSC-RTECs possessed ZO1 + tight junctions and reacted with LTL. Sub-cultivation was limited to 2-3 passages, after which hPSC-RTECs underwent epithelial-to-mesenchymal transition and senesced. In a 3D MPS, hPSC-derived RTECs formed tubular structures comparable to primary RTECs. Immunofluorescence staining demonstrated positive signals for the tubule transporters SGLT2 and OAT3 as well as the epithelial markers CD113 and E-cadherin.

Conclusions: We have shown that hPSC-RTECs can propagate in vitro and maintain their differentiated characteristics, with morphology and markers similar to primary RTECs. hPSC-RTECs are grown in a 3D MPS, they maintain an epithelial phenotype and express membrane transporters essential for functions including glucose reabsorption and organic anion secretion. This system establishes a platform in which to optimize hPSC-RTEC expansion and function in a 3D, microfluidic context, with relevance for human disease modeling in vitro and for the development of regenerative therapeutics.

Funding: Other NIH Support - UHSTR000504, Other U.S. Government Support

FR-PO208
Genome-Wide Methylation Analysis of Epigenetic Memory in Human Kidney Derived iPSC Cells. Osamu Takase, Tsuji Tsuchijima, Masao Nakagawa, Keichi Hishikawa. Dept of Advanced Nephrology and Regenerative Medicine, The Univ of Tokyo, Tokyo, Japan.

Background: Epigenetic memory such as DNA methylation signature of iPSCs derived from parental cells was reported to determine the differentiation fate of the iPSCs (Nature 2012). Last year, we reported the result of kidney specific induction protocol (Nature Comm, 2013) by using two different kinds of human iPSCs established from human fibroblast (F-iPS) and human kidney epithelial cells (K-iPS), and demonstrated more efficient induction of markers of kidney development (WT-1, Pax-1, Sall-1) and differentiation (AQP-1, Nephrin) in K-iPS as compared with F-iPS cells.

Methods: In this study, we performed a genome-wide methylation analysis of K-iPS and F-iPS cells, and tried to clarify the mechanism of kidney lineage specific induction of human iPSCs.

Results: Among 27,578 sites, we focused on high CpG promoter location (GC>0.55, Cpg>0.75). 56 genes such as Kid1 and SOD2 were strongly methylated in F-iPS than in K-iPS. 47 genes such as KCNK12 and GATA4 were strongly methylated in K-iPS than in F-iPS. 23 markers of kidney development were strongly methylated in F-iPS than in K-iPS cells (P<2.36 vs 2.1; Sall-1 vs 2.87 vs 4.3). However, the marker of differentiation was strongly methylated in K-iPS (AQP-1: 1.7 vs 1.1).

Conclusions: These results demonstrate that epigenetic memory in parental cell determine the induction of human iPSC cells toward kidney lineages, and the role of key genes in kidney lineage specific induction will be discussed.

Funding: Government Support - Non-U.S.

FR-PO209
Mechanism of Kidney Repair in the Omentum-Kidney Model – Tubulogenesis and Differentiation of Free-Lying WT-1 Cells to Podocytes Occurring in the Fusion Zone. Ignacio Garcia-Gomez,1 Krishnamurthy P. Gudelithhil,2 Peter D. Hart,2 Jose A.L. Arruda,2 Ashok K. Singh.2 1Hektoen Inst of Medicine, Chicago, IL; 2Div of Nephrology, Univ of Illinois at Chicago, Chicago, IL; 3Kidney Research Inst of Medicine, Rush Univ Medical College, Chicago, IL.

Background: When activated omentum was fused to the injured kidney it induced glomerular repair and ameliorated chronic kidney disease (Garcia-Gomez et al JASN 2014). The fusion zone between the omentum and the injured kidney was highly proliferative (high Brd uptake), with abundant free-living nephron progenitor WT-1 cells. In this study, we examined the fusion area to further understand the mechanisms of repair in this model.

Methods: In 5/6 surgically nephrectomized polyethylene glycol intraperitoneally to activate the omentum and fuse to the injured kidney. Nephrectomized rats with complete omentectomy were used as control. Kidney tissues were examined 1-3 weeks after injury by histology and immunofluorescence (Pax-2, WT-1 and podocalyxin).
E15 embryonic rat kidney served as control for immune-staining. Two-week fusion zone tissue and tissue far from fusion zone, control and normal was quantified for mRNA for selected developmental genes (WT-1, Wnt-4, Pod1, Lim1, HNF-6, BMP-7) by RT-PCR.

Results: We found that the fusion zone tissue showed proliferation and expansion of collecting ducts, as evidenced by intense staining for Pax2, in a pattern similar to that seen in E15 embryonic rat kidney. Further, several islands of WT-1 cells in the fusion zone differentiated to podocytes, as judged by co-expression of podocalyxin. mRNA for Wnt-4 and WT-1 increased by 10-20 folds and mRNAs for other developmental genes increased by 2-5 folds in the fusion zone. Control tissue did not show the above changes.

Conclusions: The fusion zone tissue between the injured kidney and omentum appears to be a highly active tissue with proliferation and differentiation of kidney progenitor cells (WT-1, Pax-2, podocalyxin) taking place, and thus providing a healing environment to the injured kidney.

Funding: Private Foundation Support

FR-PO210


Background: Mesenchymal stromal cells (MSCs) are immunomodulatory cells and have shown beneficial effects in kidney disease. It has previously been shown that human perivascular stromal cells (PSCs) from several different organs share characteristics of bone marrow derived MSCs (bmMSC), however, at the same time there are tissue specific properties. We hypothesized that human kidney derived PSCs (hkPSCs) are, due to tissue specific imprinting, more potent in kidney repair compared to bmMSCs and sought to find a novel clinical grade isolation method.

Methods: Human transplantation grade kidneys (n=3) were digested with continuously 5% platelet lysates and cells were selected for plastic attachment and NG2 cell enrichment (fig A). Culture was continued until spindle shaped cells appeared (kPSCs) and were compared to bmMSCs between passages 5-10.

Results: hkPSCs have comparable marker expression, cytokine excretion patterns, vascular stabilization and immunosuppressive capacity compared to bmMSCs. hkPSCs showed a distinct gene expression profile including an increased expression of HexD11, a homeobox factor important in nephrogenesis. In a wound scratch assay, kidney epithelial wound healing with conditioned medium of hkPSCs was significantly faster and after 7 hours approx. 80% closure was seen with hkPSC conditioned medium, which was only 40% with bmMSC supernatant (p<0.01) (fig B, C).

Conclusions: Here we show a novel, clinical grade isolation method of hkPSCs and compared these cells to bmMSCs. hkPSCs showed a distinct expression profile and are able to enhance kidney tubular epithelial wound healing to a greater extent than bmMSCs. These cells are a promising new cell therapeutic candidate to explore for treatment of kidney disease.

Funding: Government Support - Non-U.S.

FR-PO211


Background: Atherosclerotic renal vascular disease (ARVD) induces microvascular loss and interstitial inflammation, ultimately leading to ischemic injury. Mesenchymal stem cells (MSCs) can induce angiogenesis, decrease inflammation, and limit apoptosis in experimental animals. Aging and co-morbid conditions may blunt these properties in older human subjects. This study tested the hypothesis that hypoxic preconditioning of adipose tissue-derived MSCs would modify expression of MicroRNAs (miR) associated with MSCs survival, angiogenic, and anti-inflammatory properties.

Methods: MSCs obtained from subcutaneous tissue of 7 patients with ARVD (Age 75.3±4) were cultured under normoxic or hypoxic conditions (1%) for 4 days. Hypoxic MSCs were returned to normoxia thereafter. Levels of the pro-survival and pro-angiogenic factors vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF) were measured in the supernatant by ELISA. Expression of miRs- 210, 21 and 145 in MSCs was measured by quantitative rt-PCR and apoptosis by flow cytometry for Annexin V.

Results: Hypoxic conditions increased VEGF and IGF (p<0.05) in MSC supernatant, but had no effect on apoptosis.

FR-PO212


Background: Atherosclerotic renovascular disease (ARVD) reduces blood flow (RBF) and GFR, and amplifies kidney hypoxia and inflammation. Adipose-derived mesenchymal stem cells (aMSCs) improve renal function in swine ARVD, in part by improving cortical micro-vascularization, but their safety and efficacy in humans are unknown. We report initial results from a pilot study of unilateral intra-arterial administration of low dose of autologous aMSCs in human subjects with ARVD under an FDA-approved IND.

Methods: Seven patients (Age 75.3±4) with severe ARVD were studied during fixed Na+ diet and ACE/ARB Rx before and 3 months after unilateral arterial injection of 2x10^5 autologous aMSC/kg. Stenotic-kidney (SK) cortical and medullary perfusion, volume and RBF were measured using multidetector CT and GFR by iohalamate clearance. SK deoxyhemoglobin levels (R2*) and fractional hypoxia were measured by 3T BOLD-MRI. Stenosis levels of neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor (TNF-α) were also measured.

Results: All patients tolerated aMSC without adverse effects. SK cortical volume and whole kidney RBF increased after three months (Figure 1), as did measures of tissue oxygenation, whereas no changes observed in the contralateral untreated kidneys (CLK) (data not shown). SK GFR did not change, nor did renal vein levels of TNF-α, MCP-1, or NGAL.

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Underline represents presenting author.

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

**405A**

**Stem Cells**

### FR-PO213

**Cell Therapy with Serelaxin Promotes Angiogenesis and Anastomosis which Is Critical for the Preservation of Vascular Integrity After Kidney Injury**

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**Background:** We previously reported that the combination of mesenchymal stem cells (MSCs) and serelaxin (Rln) attenuates ureteral obstruction (UUO)-induced fibrosis. However the affect on endothelial cell regeneration is yet to be elucidated. Here we tested the hypothesis that a mechanism of repair after fibrosis is induced via endothelial anastomosis and sprouting in the presence of MSCs and Rln.

**Methods:** Live cell imaging of human bladder endothelial cells (HBECs) and umbilical vein endothelial cells (HUVECs) in tube forming assays were conducted with MSC-conditioned media and Rln (1-100ng/mL) to observe their affects on anastomosis. Spheroid assays determined the effects of MSC and Rln on HBECs and HUVECs sprouting in vivo. Proliferation of HBECs and HUVECs in the presence of MSCs and Rln was investigated. A qPCR for angiogenic genes was performed on MSCs cultured with or without Rln (100ng/mL). Endothelial integrity was visualized using CD31 protein localization in kidneys from mice 3, 5 and 7 days after UUO, with or without MSCs Rln (n=4-6/group).

**Results:** Anastomosis of HBECs was modulated in the presence of MSC-conditioned media and Rln with tube number and branch length increased compared to control. HUVECs readily formed sprouts in culture, which was enhanced when both Rln and MSCs were present. The migration capacity of MSCs towards injured HBECs was significantly increased when Rln was added. Rln induced the expression of angiogenic genes from the MSCs. Immunofluorescent microscopy of CD31 determined a decrease of endothelial integrity in a time-dependent manner in vivo. However the administration of MSCs and Rln preserved the vasculature.

**Conclusions:** These results suggest that both anastomosis and sprouting is enhanced only when both MSCs and Rln are used in combination. This may be in part due to Rln-induced release of angiogenic factors from MSCs which may aid in revascularization of the fibrotic kidney.

_Funding:_ Private Foundation Support, Government Support - Non-U.S.

### FR-PO214

**Effects of Adipose Derived Stem Cells in a Model of Chronic Renal Hypoxia**

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**Background:** Chronic renal artery stenosis causing chronic hypoxia may lead to irreversible damage of the kidney with progressive deterioration of renal function. Due to reduced regenerative abilities of the kidney, mesenchymal stem cells (MSC) emerge as an alternative therapy. The aim of this study was to investigate the effects of MSC, isolated from adipose tissue (ASC) on renal fibrogenesis induced by chronic renal artery stenosis.

**Methods:** Left renal artery of male Wistar rats was partially occluded and ASC were injected through caudal vein. ASC were characterized by their immunophenotype/multipotentiality. To analyze the migration and retention time, labeled ASC were injected 6 weeks after renal occlusion (RO) and analyzed 24, 48, 72 hours or 15 days after injection by flow cytometry. Caudal systolic blood pressure (SBP) was weekly estimated. Renal function and tissue gene expression levels of collagen I (Col I), Fibronectin (FN) and TGF-β were determined by qPCR, 6 weeks after renal artery occlusion in the following groups: Sham; Stenotic control (StC), receiving PBS i.v.; Stenotic + ASC (StC + ASC). ASC were injected 3 and 5 weeks after RO i.v.

**Results:** After 48 hours cells were retained in both kidneys, stenotic and contralateral followed by heart and lung. After 15 days the presence of ASC decreased significantly in the lungs and heart but they were still present in the kidneys. StC animals showed progressive increase in SBP while the StC + ASC rats had a stabilization of SBP with no further increase after RO injection. Plasma ANP levels were similar among groups except developed proteinuria which was reduced by ASC treatment. There was an increase in the expression of Coll, FN and TGFβ in the stenotic kidney (cortex and medulla) which was reversed by ASC treatment.

**Conclusions:** In conclusion ASC prevented further increase in SBP and reduced the expression of molecules induced-fibrosis. ASC migration and retention in the clipped and contralateral kidneys can be potentially beneficial to restore damaged tissue and preserve the function of the contralateral kidney.

_Funding:_ Government Support - Non-U.S.

### FR-PO215

**Therapeutic Effects of Erythropoietin Producing Kidney Mesenchymal Stem Cell Derived Microparticles on Anemia in Chronic Kidney Disease Mice**

*Hoon Young Choi,*1 Mirae Lee,1 Yung Yi Kang,1 Sang-Kyu Ha,2 Hyeong Cheon Park.1

1Research Institute of Medical Science, Kangnam Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea; 2Dept of Internal Medicine, Gyeongsang University College of Medicine, Daegu, Korea.

**Background:** Progression of chronic kidney disease (CKD) results in aggravation of erythropoietin (EPO)-dependent anemia. Microparticles (MPs) shed from kidney mesenchymal stem cells (KMSC) have been demonstrated to confer protective effects against acute kidney injury and kidney fibrosis via transfer of messenger RNA. Previous studies have demonstrated improved renal function by EPO transduced MSC. We investigated whether MPs derived from EPO producing KSMC can exert therapeutic effects on anemia in CKD mice.

**Methods:** Mouse model of CKD and renal anemia was induced by the electrocoagulation of right renal cortex and sequential left nephrectomy. Six weeks post-nephrectomy, CKD and anemia was confirmed via blood urea nitrogen (BUN) and hemoglobin measurements as well as renal histology. Stable human EPO-producing KMSC (EPO-KMSC) and their MPs isolated by differential ultracentrifugation were injected intraperitoneally into established CKD mice and followed for 2 weeks (EPO-KMSC: 1×10⁶ per mice, MP: 2×10⁶ per mice). BUN and hemoglobin were evaluated and degree of renal tubulointerstitial damage was examined for 2 weeks after CKD.

**Results:** EPO secretion from EPO-KMSC was confirmed to sustain over 4 weeks in vitro and RT PCR reviewed the presence of EPO mRNA within MPs. Injected EPO-KMSC-derived MPs were demonstrated within tubulointerstitial area. Animals that received EPO-KMSC and MPs demonstrated significantly lower BUN levels compared to CKD control mice (60±2, 62±7 vs. 83±7 mg/dL, P<0.05, respectively). Importantly, hemoglobin levels were significantly higher in CKD mice treated with EPO-KMSC and MPs compared to CKD control mice (11.7±0.1, 11.3±0.5 vs 9.9±0.7 mg/dL, P<0.05, respectively).

**Conclusions:** The use of EPO secreting KMSC is a viable strategy for cell therapy in renal anemia. Our results suggest that EPO-KMSC derived MPs as well as EPO-KMSC can improve renal function and renal anemia in CKD mice.

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

### FR-PO216

**Transplantation of Human Embryonic Mesenchymal Stem Alleviates Lupus Nephritis in MRL/lpr Mice**

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**Background:** Compared with bone marrow derived MSC, embryo-derived MSC have greater expansion and differentiation potentials. T helper cell 17(Th17) and interleukin (IL-17) is closely related to the occurrence and development of Lupus. The glial cell-derived neurotrophic factor (GDNF) which is closely related to the kidney development is found to be a kidney protection factor and can increase the renal protective effects of stem cells as well. Perserin (PS) is a member of the family of GDNF and also involves in the kidney development. We investigated the effects of human embryonic MSC (iMSC) in lupus nephritis in MRL/lpr mice.

**Methods:** The MRL/lpr mice were divided into 2 groups: Control, iMSC group. iMSC were injected at one dose of 1×10⁶/200ul twice (at the 16th, 19th weeks of age) through tail vein. Mice were sacrificed at 24 weeks of age.

**Results:** Multi-treatment of iMSC was able to increase the survival, decrease the levels of 24-h proteinuria, and anti-double-stranded DNA (dsDNA) antibody. +MSC treatment showed significant improvement of renal index. Both iMSC and Intestinal inflammatory cell infiltration in MRL/lpr mice. iMSC treatment also inhibited Th17 cell differentiation in spleen and decrease the serum level of IL-17. The level of GDNF and PSP was increased in renal of iMSC treatment MRL/lpr mice.

_Funding:_ Private Foundation Support, Government Support - Non-U.S.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
These findings indicated that hMSCs transplantation might be a therapeutic potential of hASC.

Methods: Twenty male Sprague-Dawley rats were divided into four groups: Control, GM (140 mg/kg/day, ip for 10 days), GM-TMSCs (1 x 10^7 cells, intravenous injection at 1 day after the 1st GM injection) and T-MSC group. To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26 red fluorescence before infusion. Measurement of BUN, Cr, proteinuria and histologic analysis including TUNEL staining were performed on 16 days of GM injection. Effect of T-MSC on renal tubular cells was also evaluated using a tranwell co-culture system of NRK cells and T-MSC. Intracellular ROS was analyzed by measuring NOX activity, H₂O₂, generation, NOx mRNA expressions with DCF-DA staining.

Results: PKH-26-labeled T-MSCs were observed in renal tubular cells in GM-TMSCs group. The infusion of T-MSCs preserved renal function with a decrease in proteinuria. T-MSCs also accelerated renal tubular dilatation and reduced apoptosis of renal tubular cells in the rats with GM-induced AKI. The infusion of T-MSCs downregulated the expression of Bax, Cytochrome c, Cleaved caspase-9 and -3 and upregulated Bcl-2 of renal cortical tissue. In-vivo study revealed an amelioration of GM-induced oxidative stress and apoptosis of NRK cells by T-MSC.

Conclusions: Our results suggest that T-MSCs protect the kidney from GM-induced AKI, possibly via the mechanism of modulation of oxidative stress and apoptosis.

Funding: Government Support - Non-U.S.

FR-PO218

Renoprotective Effects of Tonsil-Derived Mesenchymal Stem Cells in Gentamicin-Induced Acute Kidney Injury (AKI)

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Background: Gentamicin (GM)-induced AKI occurs in 10-20% of treated patients. GM is accumulated in renal epithelial cells, which causes the loss of the brush border, apoptosis and overt necrosis of renal tubules. Recent developments in stem cell research have shown a promise for the treat-ment of AKI, however the mechanisms underlying the improvement in kidney function provided by stem cell therapy remain unclear. Tonsil-derived mesenchymal stem cells (TMCs) can be isolated from tonsils of the patient undergoing tonsilllectomy, and vandare reported to be effective in treatment of various diseases. The aim of this study is to investigate the therapeutic potential of T-MSCs in the treatment of AKI induced by GM.

Methods: Twenty male Sprague-Dawley rats were divided into four groups: Control, GM (140 mg/kg/day, ip for 10 days), GM-TMSCs (1 x 10^7 cells, intravenous injection at 1 day after the 1st GM injection) and T-MSC group. To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26 red fluorescence before infusion. Measurement of BUN, Cr, proteinuria and histologic analysis including TUNEL staining were performed on 16 days of GM injection. Effect of T-MSC on renal tubular cells was also evaluated using a tranwell co-culture system of NRK cells and T-MSC. Intracellular ROS was analyzed by measuring NOX activity, H₂O₂, generation, NOx mRNA expressions with DCF-DA staining.

Results: PKH-26-labeled T-MSCs were observed in renal tubular cells in GM-TMSCs group. The infusion of T-MSCs preserved renal function with a decrease in proteinuria. T-MSCs also accelerated renal tubular dilatation and reduced apoptosis of renal tubular cells in the rats with GM-induced AKI. The infusion of T-MSCs downregulated the expression of Bax, Cytochrome c, Cleaved caspase-9 and -3 and upregulated Bcl-2 of renal cortical tissue. In-vivo study revealed an amelioration of GM-induced oxidative stress and apoptosis of NRK cells by T-MSC.

Conclusions: Our results suggest that T-MSCs protect the kidney from GM-induced AKI, possibly via the mechanism of modulation of oxidative stress and apoptosis.

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FR-PO221
Towards the Clinical Application of Gene-Modified Hematopoietic Stem Cell Transplantation for Cystinosis; Tatiana Vm Lobry, Jay Sharma, Sarah Ur, Celine Roccia, Betty Cabrera, Stephanie Cherqui. Pediatrics, Univ of California San Diego, San Diego, CA.

Background: Cystinosis is an autosomal metabolic disease caused by mutations in the CTNS gene, encoding a lysosomal cystine transporter, leading to cystine accumulation and multi-organ failure. Affected individuals present before 2 years of age with a Fanconi syndrome and eventually progress to end-stage renal failure. Treatment with cysteamine does not prevent these complications. We showed previously that wild-type HSC transplantation could treat cystinosis in the Ctns-/- mice. Thus, we developed an autologous transplantation strategy of HSCs genetically modified ex vivo to express a functional CTNS gene. Preclinical studies using a SIN-lentivirus vector containing CTNS to transduce Ctns-/- HSCs and transplanted in Ctns-/- mice led to cystine reduction in all tissues and kidney function improvement.

Methods: Pharmacological and toxicological studies are in progress. We established the optimal conditions to transduce human CD34+ HSCs with our lentiviral vector to obtain a Vector Copy Number (VCN) included between 1 and 3. We performed Colony Forming Unit (CFU) assays to ensure normal proliferation and differentiation of transduced human CD34+ HSCs from healthy donors and cystinotic patients and the In Vitro Immortalization (IVIM) assay, a genotoxicity test. Serial transplantations in the Ctns-/- mice will assess the safety of our vector in vivo.

Results: While we obtained VCN within the range for healthy donors CD34+ HSCs, the VCN for the Ctns-/- CD34+ HSCs is below 1, requiring further optimization. CFU assays did not show aberrant differentiation of the transduced CD34+ cells from the healthy donors and cystinotic patients. Finally, no immortalized clones were observed with the IVIM assay suggesting a good safety profile of our vector. These results will be included in our IND for a phase 1 clinical trial for cystinosis. The in vivo serial transplantations are in progress.

Conclusions: This work represents the first stem cell and gene therapy treatment strategy for cystinosis and should lead to a phase 1 clinical trial.

Funding: NIDDK Support, Private Foundation Support

FR-PO222
Mesenchymal Precursor Cell Therapy for Diabetic Nephropathy: 24 Week Results from a Phase 2A Randomized Controlled Trial; David K. Packham, Ian R. Fraser, Peter G. Kerr, Silviu Itescu, Karen R. Segal. 1MRGB, Melbourne, VIC, Australia; 2Epsworth H, Melbourne, VIC, Australia; 3Dept Nepth, Monash M C, Melbourne, VIC, Australia; 4Mesoblast PLC, NY, NY.

Background: Renal inflammation and endothelial dysfunction contribute to the etiology of diabetic nephropathy (DN). Bone marrow derived mesenchymal precursor cells (MPC) can modulate both inflammatory cells and microvasculature. We conducted a randomized, placebo (PBO) controlled, dose-escalating trial of allogeneic MPC in 30 subjects with type 2 DN.

Methods: Patients (24 men, 6 women) with an estimated glomerular filtration rate (eGFR) of 20-50 ml/min/1.73 m2 and on a stable regimen of renin-angiotensin inhibition were randomized to a single IV infusion of PBO (saline) or 150 million (M) or 300M MPCs (N=10 per group). Patients have been followed-up for 24 w. Baseline mean age was 70 years mean eGFR was 34.6, 35.7 and 34.6 ml/min/1.73 m2 for PBO, 150M and 300M, respectively. Patients have been followed-up for 24 w. Baseline mean eGFR was 34.6, 35.7 and 34.6 ml/min/1.73 m2 for PBO, 150M and 300M, respectively.

Results: There were no treatment-related adverse events. For eGFR change from baseline at 24 w, the least square mean (LSM) differences from PBO were 3.2±2.5 (8.1%) in both 150M and 300M groups. PBO-adjusted treatment differences were greater in pooled MPC with baseline eGFR<30: 4.9±2.3 (+12%) at 24w. The LSM differences from PBO for mean individual annualized slopes of eGFR change over 24w was 6.8±4.8 in both treatment groups. Baseline IL-6 levels correlated with SCR and eGFR improvement at 12 w in the M groups (r=0.57 and 0.50; both p<0.05) but not in PBO. The LSM differences from PBO for mean individual annualized slopes of eGFR change over 24w was 7.8±4.8 ml/ min/1.73 m2 in pooled MPC patients with baseline IL-6 3.5 pg/ml and 5.6±5.0 in MPC patients with baseline IL-6 3.5 pg/ml, suggesting greater preservation or improvement in eGFR relative to PBO in the presence of elevated IL-6.

Conclusions: In this first in humans study, a single MPC infusion improved or stabilized GFR over 24w. Baseline eGFR>30 and high IL-6 levels suggest two biomarkers that may predict efficacy with MPC treatment. Positive response to MPC therapy may be enhanced by the presence of non-fibrotic, but at-risk, renal tissue and aberrant pro-inflammatory milieu.

Funding: Pharmaceutical Company Support - Mesoblast PLC

FR-PO223
Long-Term Effect of Methylprednisolone Pulse and Autologous SVF (Stromal Vascular Fraction) Therapy in Severe IgA Nephropathy with CKD Stage III; Byoung-Soo Cho,1 Yumi Choi;2 Jin-Soo Suh;3 1The Medical Hub Kidney Center, MIRAE ENG Research Inst, Seoul, Republic of Korea; 2'Dept of Pediatrics, Gwangmyeong Sang-Ae Hospital, Gwangmyeong-si, Gyeonggi-do, Republic of Korea; 3'Dept of Internal Medicine, The Catholic Univ of Korea, Bucheon-si, Gyeonggi-do, Republic of Korea.

Background: Up to date there is no specific method of treatment in severe IgA nephropathy with CKD, but giving ACE inhibitor, angiotensin II receptor blocker(ARB), omega-3 etc. and eventually almost all cases fall into CKD V and need KTP or dialysis. Cell-based therapy is an emerging field in nephrology field especially aspide derived stem cells(ASCs). The beneficial effects of mesenchymal stem cell occur through differentiation-independent pathways include increased cell survival and proliferation, decreased inflammation, immune modulation, tissue regeneration etc.

Methods: We tried methylprednisolone(MP) pulse therapy followed by autologous SVF(stromal vascular fraction), which contained ASCs in severe IgA nephropathy with CKD stage III. This case was 44years old female patient, Renal biopsy finding showed Grade IV(Lee’s classification) with CKD stage 3. MP pulse was tried 6 cycles followed by autologous SVF were injected through intraveneously 4 times at 3 weeks interval.

Results: Initial renal biopsy findings before treatment(Tx) showed 61% scerotic glomeruli, however follow up renal biopsy 18 months after Tx showed 41% sclerotic glomeruli and disappeared immune deposits, The serum creatinine level before Tx was 1.77mg/dl with GFR 35ml/min, however 18 months after Tx serum creatinine was 1.03mg/dl with GFR 61ml/min.

Conclusions: In this case MP pulse therapy with autologous SVF treatment in intractable IgA nephropathy might be a promising therapeutic means without any notable side-effect or complications especially in early stage CKD, although the efficacy and safety, of SVF infusion therapy needs long term studies.

Funding: Other U.S. Government Support

FR-PO224
Extracellular Vesicles in Glomerular VEGF Homeostasis; Sargs Sedrakyan,1 Stefano Porta,2 Hasnik Soloyan,1 Nikita Triprumaneni,1 Roger E. De Filippo,1 Benedetta Bussolati,2 Laura Perin.1 1Children's Hospital Los Angeles; 2Univ of Turin.

Background: Strict regulation of VEGF signaling between podocytes and glomerular endothelial cells (GEC) is critical for GEC survival and function, therefore, loss of glomerular VEGF homeostasis during disease progression can impact GEC integrity leading to decline in glomerular function. Importantly, recent studies have described extracellular vesicles (EVs) to play important role in stem cell mediated paracrine modulation, including in kidney. We have already established that aminoistic fluid stem cells (AFSC) are regenoprotective, and we hypothesize that EVs released within damaged glomeruli are involved in VEGF regulation. Herein, we investigate the impact of AFSC derived EVs in the maintenance of glomerular VEGF homeostasis.

Methods: Using qPCR and ELISA we measured VEGF expression along the course of disease progression in isolated glomeruli of mice affected by Alport Syndrome (AS). Endothelium morphology was evaluated by IHC and TEM. GEC were FACS sorted from a GEC specific Tek reporter mice and studied by gene and protein arrays for VEGF/VEGFR, oxidative stress, and apoptotic pathways. Co-cultured GEC and AFSC overstimulated with VEGF were used to study the direct role of EVs in VEGF regulation. EVs were characterized and injected into AS mice for in vivo evaluation.

Results: Mice at advanced stages of Alport disease presented with aberrant VEGF activity within glomeruli, significant GEC apoptosis, oxidative stress and loss of GEC. Delivery of AFSC derived EVs normalized VEGF expression and ameliorated endothelial damage. Importantly, the soluble receptor of VEGF, sFlt1—involved in regulating VEGF signaling—was also modulated upon treatment, indicating a VEGF/sFlt1 mechanism of regulation by EVs. In vitro experiments further confirmed the direct role of EVs in VEGF/sFlt1 regulatory mechanism.

Conclusions: In this case, our data demonstrate for the first time the alteration of VEGF signaling within AS glomeruli. We further showed that AFSC derived EVs play an important role in maintaining glomerular homeostasis of VEGF signaling, so critical to maintain GEC integrity and function, presenting with a potential for new targeted therapies in CKD.

Funding: Other U.S. Government Support

FR-PO225
Renal Exosomes Store and Transfer the Ischemia Preconditioning State and Protect Rats with Severe Renal Ischemia; Katherine J. Kelly,1 Jesus H. Dominguez,2 H. Dominguez,1,2 1TheAll Medical Hub College of Medicine, Indiana, IN; 2Medicine, Indiana Univ Medical School, Indianapolis, IN; 2Medicine, Veterans Administration, Indianapolis, IN.

Background: Acute Kidney Injury (AKI) is a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD). We have reported that intravenous renal cell transplants (IRCT) improve outcomes in rats with AKI (JAP 303:F357, 2012). IRCT action was mediated by relatively small number of anchored and retained cells, and we hypothesized that cells amplified renal protection by releasing exosomes (EX) acting at a distance.
Methods: We tested if renal EX from cultured cells used for IRCT improved AKI. Notably, two groups of Dawley rats (SD, n = 4–7) were subjected to 45 minutes of bilateral ischemia (IR). Renal exosomes (600 μg/protein/rat) were then given intravenously.

Results: There were 5 groups of rats: 1, sham, no IR; 2, renal ischemia (IR) untreated (NO-EX); 3, IR treated with heat inactivated EX (HI-EX); 4, IR treated with normal EX (NL-EX); 5, IR treated with EX prepared by kidney cells subjected to ischemia reperfusion injury (IPC-EX). In sham, serum creatinine was 0.3±0.03 at 24 hrs and 0.3±0.02 at 48 post-surgery. In NO-EX it was 2.1±0.6 and 1.7, post IR, respectively. In HI it was 2.2±0.1 and 1.6±0.3. However, in NL-EX it was 2.4±0.4 and 0.7±0.1. The most striking effect was found in IPC-EX (1.5±0.1, p<0.05 vs. all including NL-EX). Kidney weight (mg/mg body weight) 6 days post IR was also improved by EX: 3.8±0.1 in sham; 6.7±0.6 in NO-EX; 6.7±0.6 in HI; 5.2±0.2 in NL-EX 5.2±0.2, and 4.4±0.2 in IPC-EX, which was significantly lower than all IR groups, including NL-EX. Neutrophils (PMN) in IPC-EX were also reduced by 65% (p<0.05) when compared to NL-EX. IPC-EX reduced renal C3 expression in glomeruli and tubules by 73% and 82% respectively (p<0.05 for both). IPC-EX also protected 76% of renal tubules when compared to NO-EX.

Conclusions: IPC is effective but impractical. However, EX given IV can communicate the IPC state, reach the kidneys, modulate inflammation and protect function and structure following severe IR.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

FR-PO226

The Impact of Preexisting Chronic Kidney Disease on the Severity and Recovery of Acute Kidney Injury Sung Yoon Lim,1 Young Ju Na,1 Myung-gyu Kim,1 So-young Lee,2 Sang-Kyung Jo,1 Won-Yong Cho.1 1Dept of Nephrology, Korea Univ Hospital, Seoul, Korea; 2Dept of Nephrology, Edith Univ Hospital.

Background: Recent observational studies have shown that a substantial proportion of patients with acute kidney injury (AKI) have often progression to chronic kidney disease (CKD). Among several risk factors for the development of CKD after AKI, decreased baseline glomerular filtration rate (GFR) represents an important risk factor. However precise mechanisms involved in the development of fibrosis after AKI with preexisting CKD have not been completely ascertained. Here in this study, we assessed the impact of preexisting CKD on the severity and recovery of AKI in mouse model of 5/6 nephrectomy.

Methods: Male CD-1 mice underwent 5/6 nephrectomy or sham operation, and 6 weeks later ischemia reperfusion injury (IRI) was performed. On day 1, 7 and 28 after IRI, functional, histological, and molecular parameters were compared between them.

Results: Twenty minutes clamping of renal pedicle in 5/6 nephrectomized mice did not provoke more severe functional, histological deterioration compared to normal mice on day 1 and 7. Similar elevations in SCR were observed in both groups until day 7 after IRI; however, SCR remained higher on day 28 in 5/6 nephrectomized mice compared to normal mice, suggesting that preexisting CKD does not modify severity of AKI but adversely affect the recovery process. From day 7 to 28, mRNA expression of p21, and protein level of p13, both representing cell cycle arrest were significantly increased in 5/6 nephrectomized mice (CDK+AKI) compared to sham (sham+AKI). Treatment with p53 inhibitor after IRI resulted in not only decreased p21 and p13 protein level, but also fibrosis in CDK+AKI mice, suggesting that epithelial cell cycle arrest is partially responsible for impaired recovery from AKI in 5/6 nephrectomized mice.

Conclusions: Taken together, reduced nephron mass do not seem to increase severity of AKI, but have negative effect on repair process, leading to development of fibrosis.

FR-PO227

Impaired Functional Recovery from Acute Kidney Injury in Rats with Preexisting Chronic Kidney Disease Predicts the Severity of De Novo Hypertension Aaron J. Polichnowski,1,2 Karen A. Griffin,3,1 Mana Dissanayake,1 Anil K. Badiani,1,2 Edward Hines JR. VA Hospital, Hines, IL; 1Medicine, Loyola Univ Medical Center, Maywood, IL.

Background: The mechanisms by which AKI accelerates the progression of CKD remain poorly understood. We have recently demonstrated that preexisting CKD predisposes to impaired recovery from AKI as evidenced by exacerbated levels of tubulointerstitial fibrosis and modest elevations in blood pressure at 4 weeks post injury. However, a rigorous assessment of the precise mechanisms involved in the development of fibrosis after AKI with preexisting CKD have not been exhaustively explored.

Methods: Male SD rats underwent normotensive 3/4 nephrectomy (3/4 NX) and were chronically instrumented with a BP radiotelemeter. Two weeks later, rats were subjected to 40 min IR (n=20) or sham IR (n=8). BP was assessed every 10 min, 24 hr/day for 4 weeks and glomerular filtration rate (GFR) was then assessed in the conscious state (FITC-inulin).

Results: As compared to baseline values, systolic BP was significantly elevated (P<0.05) in rats at 4 weeks post IR (134±2 vs. 149±5 mmHg, respectively) but not sham IR (139±4 vs. 140±2 mmHg, respectively). GFR was significantly less (P<0.05) in rats subjected to IR vs. sham IR (1.1±1 vs. 1.4±1 ml/min, respectively). As shown in Figure 1, a very strong negative correlation was observed between GFR and the increase in systolic BP over the 4 week protocol. SCR values 48 hours post IR did not correlate with either GFR or the change in systolic BP at 4 weeks post AKI, indicating that the development of hypertension following IR was due to impaired recovery from AKI as opposed to a greater severity of AKI.

FR-PO228

Exocytosis of Endothelial Lysosome-Related Organelles Hair-Triggers a Path of Loss of Glycocalyx at the Onset of Sepsis Joseph A. Zullo,1 Jie Fan,1 Tala F. Azar,1 Wan-yi Yen,2 Min Zeng,1,2 Jan Chen,1 Brian B. Ratliff,1 Jungol Song,1 John Tarbell,1 Bingmei M. Fu,2 Michael S. Goligorsky,1 1New York Medical College; 2The City College of The City Univ of New York; 1/LSun Medical College, Seoul, Republic of Korea.

Background: Endothelial surface glycocalyx (ESG) is a well-known regulator of leukocyte surveillance, vascular permeability, and a sensor of shear stress. ESG is degraded during sepsis, thus contributing to systemic multiorgan involvement. Our previous demonstration of a very early post-stress exocytosis of lysosome-related organelles (LRO) with their lytic enzymes led us to hypothesize that exocytosis of LRO may catalyze a synchronized degradation of ESG.

Methods: To test this hypothesis we first analyzed the time-course of exocytosis of Weibel-Palade bodies and secretory lysosomes after application of lipopolysaccharides (LPS) to endothelial cells.

Results: Time-lapse video microscopy revealed that LROs undergo agititation and vectorial movement with a time course of a few minutes after LPS. In addition, spectrophotometry measurements illustrated an increase of lysosomal cargo, cathepsin B, within the media after 10min of LPS exposure. Two therapeutic maneuvers, a nitric oxide intermediate, NG-hydroxy-L-arginine (NOHA), and culture media conditioned by endothelial progenitor cells (EPC-CM) reduced the directionality and motility of LRO. The patch loss of ESG occurring with the similar fast kinetics was confirmed using confocal fluorescence microscopy and Stochastic Optical Reconstruction Microscopy. The loss of ESG was blunted by pretreatment with NOHA or EPC-CM. Moreover, these treatments resulted in a significant reduction of mortality of septic mice.

Conclusions: In summary, above studies provide the first demonstration of the very early patchy disintegration of ESG which can be prevented by pretreatment with NOHA and EPC-CM, maneuvers that reduced exocytosis of LRO. Data support the hypothesis assigning to stress-induced exocytosis of these organelles the role of a hair-trigger for local degradation of ESG that in turn initiates leukocyte infiltration, increase vascular permeability, and partially accounts for the later morbidity and mortality.

Funding: NIDDK Support

FR-PO229

Vitamin D Deficiency Contributes to Vascular Damage in Sustained Ischemic Acute Kidney Injury Anna C.,1 de Bragança,1 Rildo A. Volpin,1 Purvi Mehrrotra,2 Carlie M. Ivancic,2 Lucia Andrade,1 David P. Basile,2 1Nephrology, Univ of Sao Paulo School of Medicine, Sao Paulo, SP, Brazil; 2Cellular and Integrative Physiology, Indiana Univ School of Medicine, Indianapolis, IN.

Background: It has been shown that injury to the renal vasculature may play an important role in the pathogenesis of ischemic acute kidney injury (AKI). Reductions in microvascular density may play a critical part in the progression of chronic kidney disease (CKD) following AKI-induced ischemia/reperfusion injury (IRI). Vitamin D deficiency (VDD) is associated to tubulointerstitial damage and fibrosis progression following IRI-AKI. We evaluated the effect of VDD in sustained IRI-AKI, hypothesizing that VDD contributes to vascular damage.

Methods: Wistar rats were fed 25(OH)D3-free or standard diets for 35 days. On day 28, rats were randomized into four groups: control (sham), VDD, bilateral IRI and VDD IRI. Rats were analyzed 7 days after the surgeries.

Results: VDD rats showed impaired capillary density (by cainin staining) and reduced VEGF expression, even in the absence of injury. In addition, VDD IRI rats manifested a remarkable capillary rarefaction and also had increased RW/BW, tissue injury scores, FSP-1.
nSMA when compared to either VDD or IRI rats. VDD IRI also had increased levels of infiltrating activated CD4+ and CD8+ cells secreting higher levels IFN-γ and IL-17 while the number of regulatory T cells was reduced, relative to IRI rats.

Conclusions: VDD impairs renal capillary density and exacerbates fibrotic damage and pro-inflammatory milieu following AKI, which may contribute to the transition of CKD following AKI. Funding: CAPES/CNPq/FAPEPI, NIH DK58411 (DPB). Funding: NIDDK Support

FR-PO230
Exosomes-Mediated Delivery of Pro-Survival MicroRNA-486-5p in Acute Kidney Injury
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Background: We recently showed that administration of human endothelial colony forming cells (ECFCs) and their exosomes to mice with ischemic acute kidney injury (AKI) attenuated renal damage. Our data also indicate that ECFCs release exosomes that are highly enriched in micro-RNA (miR)-486-5p and protect against hypoxia-induced endothelial cell apoptosis. MiR-486-5p targets phosphatase and tensin homolog (PTEN), which is involved in the Akt pro-survival pathway. In the present study, we further examined the role of exosomes and miR-486-5p on the Akt pathway in vivo, and tested the hypothesis that exosomes transfer miR-486-5p to endothelial cells in vitro.

Methods: Mice with ischemic AKI were injected (i.v.) with exosomes with or without miR-486-5p. Kidneys were subjected to immunoblot analysis and RT-PCR for miR-486-5p. Transfer of ECFC exosomes and miR-486-5p was studied in human umbilical vein endothelial cells (HUVECs).

Results: Bioinformatic analysis of the 10 most abundant miRs in ECFC exosomes revealed that they were all involved in the Akt pro-survival pathway. Innice with AKI, exosome treatment significantly increased renal miR-486-5p levels (P<0.01 vs ischemia alone, n=6-7), associated with decreased PTEN expression, and increased Akt phosphorylation. In cultured HUVECs, ECFCs exosomes labeled with the fluorescent dye PKH-26 localized to the perinuclear compartment. Treatment of HUVECs with ECFC-derived exosomes or co-culture of ECFCs with HUVECs caused a 40-fold increase in levels of miR-486-5p. Transfection of ECFCs with pre-miR-486-5p, followed by co-culture with HUVECs was associated with a further marked increase (~20-fold) in miR-486-5p levels in HUVECs (P<0.001 vs control, n=3). This effect was blocked by pre-incubation of HUVECs with ethylisopropyl amiloride (an inhibitor of exosome uptake).

Conclusions: These data suggest ECFC-derived exosomes exert renoprotective effects in AKI, possibly via the transfer of miR-486-5p to endothelial cells. Exosome-mediated transfer of miRs could represent a strategy to target pro-survival pathways in the injured kidney.

Funding: Private Foundation Support

FR-PO231
The Role of Vascular Endothelial Cells in the Protective Effect of Delayed Ischemic Preconditioning in Renal Ischemia/Reperfusion Injury
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Background: We have previously reported that up-regulation of miR-21 contributed to the protective effect of delayed ischemia preconditioning (IPC) in renal ischemia/reperfusion injury (IRI). The role of vascular endothelial cells in renal IRI is not well-understood. In the present study, we examined the role of vascular endothelial cells in the protective effect of miR-21 in renal delayed IPC.

Methods: For the delayed IPC and IR model, 4 d after IPC (15 min ischemia) or sham surgeries, preconditioned mice were subjected to 35 min occlusion of bilateral renal pedicles, followed by 24 h reperfusion. Human umbilical vein endothelial cells (HUVECs) were treated with cobalt chloride for hypoxia model in vitro. Locked nucleic acid (LNA) modified anti-miR-21 or anti-scrambled was transfected into cells or delivered into the mice via tail vein injection less than 1 hour prior to IPC. Vascular permeability was determined by Evans Blue dye. Cell apoptosis was estimated by Annexin V-FITC apoptosis detection. Expression of programmed cell death 4 (PDCD4) protein and miR-21 was examined by western blot and real-time PCR, respectively.

Results: Compared with the Sham+IR group, mice in the IPC+IR group showed significant improvement of renal function and histology injury (P<0.01). MiR-21 was up-regulated in the IPC+IR group with concomitant decline of PDCD4 (P<0.05) and improvement of vascular permeability (P<0.05). In vitro, miR-21 in HUVECs was increased in hypoxia, while PDCD4 expression was decreased. Knockdown of miR-21 by LNA anti-miR-21 attenuated the protective effect of IPC with concomitant up-regulation of PDCD4 (P<0.05) and exacerbated vascular permeability (P<0.05). Cell apoptosis significantly decreased after knockdown of miR-21 in vitro.

Conclusions: Up-regulation of miR-21 in renal delayed IPC improved the apoptosis of vascular endothelial cell by inhibiting its target PDCD4. This may be another mechanism underlying the protective effect of the delayed IPC.

Funding: Government Support - Non-U.S.

FR-PO232
Role of Vascular Mineralocorticoid Receptor in Renal Ischemia/Reperfusion
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Background: Renal ischemia/reperfusion (IR) is a major cause of acute kidney injury and is associated with chronic kidney disease (CKD) development. Mineralocorticoid receptor (MR) antagonism prevents the acute and chronic consequences of renal IR. Whether the benefit of the MR antagonists is due to the blockade of the MR in the vessels is unclear. Therefore we want to study the specific contribution of endothelial and smooth muscle cells (SMC) MR in acute and chronic consequences of renal IR.

Methods: To inactive MR in endothelial cells (MRKO mice), floxed MR mice (MRflox) were crossed with mice expressing the inducible Cre recombinase under the Vcad promoter. To allow inactivate MR in smooth muscle cells (MRSMCKO mice), MRflox mice were crossed with mice expressing the inducible Cre recombinase under the SMA promoter. Sham surgery or bilateral renal IR for 20 min was performed in MRflox and KO mice and the animals were studied at short term (24 h) and long term (30 days) after reperfusion.

Results: In MRflox mice, IR induced renal dysfunction (plasma creatinine from 8.9±0.3 to 33.8±8.4 μmol/L in IR), tubular injury and increased mRNA levels of kin-1 (400-fold) and NGAL (220-fold). The MRSMCKO mice displayed similar alterations induced by IR as MRflox mice. In contrast, after 24 h of IR, the MRSMCKO mice presented normal renal function (plasma creatinine was 9.6±0.7 to 14.0±1.9 μmol/L in sham and IR, respectively), absence of histological alterations and reduced kin-1 and NGAL levels. After 30 days, the MRflox mice developed CKD characterized by renal dysfunction (plasma creatinine from 10.5±1.0 to sham in 15±9.8 μmol/L in IR), tubular-interstitial fibrosis and increased mRNA levels of fibronectin and Galec-3 (2-fold). The MRSMCKO mice developed similar alterations.

Conclusions: We provide evidence that the deficiency of MR in the SMC protects against the development of acute kidney lesions induced by IR, however MR deficiency in SMC did not impact the appearance of CKD induced by IR, suggesting that MR in other cell types is involved.

Funding: Government Support - Non-U.S.

FR-PO233
Renal Vein Hydrodynamic Fluid Delivery Ameliorates Established Renal Injury following Ischemia/Reperfusion Injury
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Background: Past and current treatment for Acute Kidney Injury (AKI) is mainly supportive in nature; no therapeutic modalities to date have shown an efficacious in improving the condition. While numerous experimental approaches can prevent AKI, there are few potentially translatable studies which may influence the course of established AKI. The goal of this study was to target vascular congestion and inflammation, which contribute to impaired renal perfusion and renal damage, following the established injury. We hypothesized that high-pressure retrograde hydrodynamic delivery (HD) of saline will improve established AKI, in part, by improving vascular congestion.

Methods: Male Sprague Dawley rats underwent left unilateral ischemia (35 min) and right unilateral nephrectomy or bilateral IRI (35min) and reperfusion for 24 hours to induce AKI. 0.5ml of isotonic saline was then injected into either the vena cava (VC) or retrograde to left kidney via the renal vein (RV) under high pressure (~60mmHg). Recovery was evaluated via serum creatinine and accumulation of immune cells were evaluated using FACS.

Results: Average serum creatinine at 24hrs was similar between groups (scre~3.3mg/dl), however, RV-HD treated rats showed a rapid improvement in serum creatinine over the following 24 hours vs VC HD rats (24 to 48 h serum creatinine -0.544 mg/dl ± 0.6375 mg/dl; p=0.0237). To evaluate effects on inflammation, bilateral IRI rats subjected to left-RV HD resulted in a significant reduction in CD4+ (54%±18; p<0.05), CD68 (60%±8; p<0.05), B cells (56%±3.5; p<0.05) and DC/Macs (71%±3; p<0.05) compared with VC rats.

Conclusions: These results indicate that high pressure retrograde hydrodynamic delivery of HD saline will improve established AKI, in part, by improving vascular congestion.

Funding: NIDDK Support, Veterans Administration Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Human Adipose Stromal Cells Ameliorate Renal Injury and Attenuate Capillary Rarefaction following Ischemia-Reperfusion

**Background:** Acute kidney injury (AKI) is a syndrome characterized by the rapid loss of the kidney’s excretory function, resulting in excess in 17 million hospital admissions a year. Although the tubular epithelium is the primary target of ischemic injury, early damage to endothelial cells contribute to AKI by resulting in impaired perfusion. Moreover, renal capillary density is permanently compromised in rats following AKI induced by ischemia reperfusion (IRI), which is hypothesized to promote CKD. Therefore, to preserve capillaries may impact both short-term recovery and long-term function post-AKI. Adipose stromal cells (ASCs) have pro-angiogenic and anti-inflammatory properties. It is hypothesized that ASCs facilitate repair by capillary preservation, revascularization of damaged endothelium and decreased inflammation.

**Methods:** Male Sprague Dawley rats were subject to bilateral IRI (40 min). At the time of reperfusion, ~2x10^6 immune cells (hASCs, n=15) or vehicle (n=14) were injected into the suprarenal abdominal aorta. Recovery was evaluated via serum creatinine and capillary specific staining. Accumulation of immune cells in the kidney was evaluated using FACs.

**Results:** hASC-treated rats had a 90% survival by day 7, compared with 70% for vehicle. Serum creatinine showed a significant reduction in hASC-treated rats vs vehicle at 48 hrs, (35%; p<0.0008). By day 7, vehicle-treated rats showed a reduction in renal capillary density relative to sham (43%), which was significantly attenuated in hASC-treated rats (28%). Additionally, hASCs-treated rats exhibited a significant decrease in CD4+ (62%±16.8) and CD8+ (72%±3.5) T cell infiltration as compared to vehicle (299±83.9). Conversely, the number of regulatory T cells was increased in hASC-treated rats compared with vehicle (35%; p<0.05).

**Conclusions:** These results suggest that ASCs may ameliorate AKI, at least in part, by preserving capillary density, decreasing inflammation and restoring renal function.

**Funding:** NIDDK Support

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**FR-PO235**

**Studying the Effect of Induced Expandable Human Kidney Progenitor Cells on Renal Function Using Transcutaneous Assessment**

**Background:** The use of induced stem cells from adult tissues is a promising therapeutic approach for the treatment of kidney diseases. However, traditional techniques to monitor recovery from damage or delay in chronic renal disease development after cell therapy are cumbersome and time-consuming, as well as inaccurate to detect early changes in function. A recent method allows the evaluation of renal function transcutaneously, using an optical device and the exogenous renal marker FITC-simistin, with no need for plasma or urine samples. For the first time, we have studied the effect of human adult kidney epithelial cells (hKEpCs) induced to stably overexpress the SIX2 or OSR1&SIX2 genes in a cisplatin damaged endothelium and decreased inflammation.

**Methods:** Three different animal groups were established: induced SIX2-hKEpCs, SIX2&OSR1-hKEpCs and control group. On days 2 and 7 following a single dose of CP (7mg/kg b.w), rats received intravenously either vehicle or 1x10⁶ of the corresponding cell type. Kidney function was assessed over 14 days transcutaneously. In addition, urinary and plasma parameters, as well as histological changes were evaluated.

**Results:** Before cell treatment, all the groups experienced a comparable decrease in renal function with respect to baseline. Transcutaneous measurement showed that both cell types improve renal function compared to control group, with a substantial amelioration on day 7 after CP administration. The rise of creatinine and urea serum levels was also ameliorated in the cell treated groups and the histological analysis supported the beneficial of hKEpCs administration shown in renal function.

**Conclusions:** SIX2- and SIX2&OSR1-hKEpCs display therapeutic potential in CP-induced injury, preventing loss of kidney function and diminishing renal tissue changes due to disease progression or therapeutic interventions.

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**FR-PO236**

**Indole Analogues Have Novel Therapeutic Effects on Mitochondrial Diseases and Kidney Injury**

**Background:** Mitochondrial dysfunction causes various mitochondrial diseases and kidney injuries. Anti-oxidant quinones have been used clinically to prevent the disease progression but the effectiveness is yet to be established. We recently found that an indole-derivative increased ATP levels in HepG2 cells and analyzed 41 newly synthesized indole derivatives. Among these compounds, we focused on the most potent derivative #5 (MA-5). The aim of this study was to clarify the effects of MA-5 in mitochondrial diseases and kidney injury.

**Methods:** Fibroblasts from patients with mitochondrial diseases (Leigh syndrome, MERRF, K.I.S,Leber disease, and Kearns-Sayresyndrome) were cultured in ROS generating condition with BSOL-buthione(S,R)-sulfoximine)and cell viabilities, cellular ROS and glutathione levels were measured. The redox property of MA-5 was examined by cyclic voltammetry. The site of MA-5 distribution was visualized by fluorescence-labeled MA-5 (maleimide). MA-5 was administrated for 3 hr before they were exposed to kidney ischemia (26 min) reperfusion injury (IRI) or cisplatin (20 mg/kg body weight). Plasma creatinine (Cr), blood urea nitrogen (BUN) and renal pathology were assessed.

**Results:** MA-5 improved cell viability in a dose dependent manner in mitochondrial disease fibroblasts. MA-5 exhibited irreversible oxidation peaks by cyclic voltammetry, suggesting that MA-5 did not have antioxidant property like anti-oxidant quinones. MA-5 did not affect the cellular ROS or GSH levels. MA-5 FL co-localized with the mitochondrial marker, MitoTracker. In IRI, MA-5 after ischemia (0.08 mg/dl vs 1.60 mg/dl), and tubular cell injury were significantly reduced in MA-5-treated group. BUN (70.9±10.1 vs 101±13.0 mg/dl) and tubular injuries, at 96 hr after cisplatin injection, were significantly reduced in Indole #5 treated groups.

**Conclusions:** MA-5 exhibited therapeutic effects in fibroblasts from mitochondrial disease patients as well as renoprotective effects in both IRI and cisplatin nephropathy.
FKR-0239
Background: Renal tubular epithelium can regenerate after a variety of insults. During tubular regeneration, survived tubular cells proliferate, migrate and differentiate into mature cells. After several cell divisions, kidneys were examined for analysis. Localization of GFP-positive cells was examined by immunostaining with several nephron markers and their cell number was quantitatively assessed.

Methods: 1) After a pulse of doxycycline, GFP-positive cells were found in the kidney of TetOp-H2B-GFP mice. Most GFP-positive cells were AOP-1-positive tubular cells. As pulse periods become longer, the number of GFP-positive tubular cells increased (pulse 8h-0.5%, pulse 24h-10%, pulse 72h-18%, pulse 1 week-40%, pulse 3 weeks-50%). 3) After a short pulse (8h) of doxycycline with no chase, all GFP-positive cells were present as a single cluster of two cells or three cells. 4) In TetOp-H2B-GFP mice treated with a long pulse (3 week) of doxycycline, the number of GFP-positive cells decreased according to chase periods (Chase 8h-50%, Chase 4x-40%, Chase 8x-5%).

Conclusions: These data suggest that slow-cycling cells can be detected as GFP-positive cells using TetOp-H2B-GFP mice under doxycycline control. This model will be applicable for selective isolation and in vitro characterization of slow-cycling tubular cells.

FKR-0240
Renal ERK1/2 Regulation of PGC-1α and Mitochondriobiogenetic Homeostasis Physiologically and During Renal Injury Justin B. Colley, Ryan Whitaker, Rick G. Schnellmann. Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.
Background: Acute kidney injury (AKI) is defined as a sudden decline in kidney function and the outcomes of AKI have not changed in the past few decades. Previous studies demonstrated that persistent disruption of mitochondrial homeostasis (e.g. peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), a master regulator of mitochondrial biogenesis (MB)), is an important contributor to renal ischemia-reperfusion injury (IR) and repair. While the MAPK extracellular-regulated kinases 1/2 (ERK1/2) regulates numerous cell signaling pathways, the role of ERK1/2 activation in MB physiologically and as a consequence of renal IR injury remains limited.

Methods: Renal proximal tubule cells (RPTC) were treated with the specific MEK1/2 inhibitor trametinib (10nM) for various time points. Control mice were treated with trametinib (1mg/kg). Trametinib was administered 1 hour before 18 min of bilateral IR. Signaling pathways were explored using qRT-PCR and immunoblot analysis.

Results: Trametinib blocked ERK1/2 phosphorylation in RPTC within 10 min that continued for 24 hr. Trametinib also inhibited ERK1/2 phosphorylation in vivo at 4 and 24 hr. Trametinib increased PGC-1α mRNA at 1, 4, and 24 h in RPTC. The mRNA levels of PGC-1α-1 target genes NDUF51, NRF1, and TFAM, and NDUF51 were linked to decreased mRNA levels of PGC-1α, NRF1, TFAM, and NDUF51. Trametinib treatment attenuated suppression of mRNA PGC-1α and NRF1 at 3 h, increased TFAM protein 2.5-fold, and attenuated renal dysfunction as measured by BUN and KIM-1.

Conclusions: ERK1/2 downregulates renal mitochondrial homeostasis under physiological conditions and ERK1/2 inhibition during renal IR promotes recovery of PGC-1α and MB, and contributes to both mitochondrial and renal recovery. These results reveal a novel target for pharmacological intervention in AKI.

Funding: Other NIH Support - NIGMS, Veterans Administration Support

FKR-0241
The Guanylyl Cyclase Activator BAY 58-2667 Stimulates Mitochondriobiogenesis and Promotes Recovery from Ischemia-Reperfusion Induced AKI Ryan Whitaker, Rick G. Schnellmann. Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.
Background: Mitochondrial dysfunction is an important pathophysiologic component of acute kidney injury (AKI). As reduced mitochondrial function can impair energy-dependent renal repair processes following AKI, stimulation of mitochondrial function and the outcomes of AKI have not changed in the past few decades. Previous studies demonstrated that reduced renal tubular necrosis in BAY 58-2667 treated mice at 24 h post ischemia-reperfusion injury (IR) was due to enhanced mitochondrial gene and protein expression of PGC-1α, NRF1, ND1, COX1 and ATPSβ, as well as mtDNA content and protein expression of PGC-1α and COX1. In addition, mitochondrial function was recovered as renal ATP returned to sham control levels. Finally, BAY 58-2667 blunted the progression of renal fibrosis evidenced by reduced COL1A2 and aSMA expression.

Methods: These data demonstrate that activation of guanylyl cyclase by BAY 58-2667 promotes recovery from AKI by stimulation of MB, reduction of inflammatory and oxidative damage, and inhibition of renal fibrosis.

Funding: NIDDK Support

FKR-0242
Adult Human Renal Papilla CD133+ Cells Improve Erythropoietin Production, Show Long Term Engraftment and Repair Glycolerol-Induced Kidney Injury in SCID Mice Shikhar Aggarwal, Cristina Grange, Benedetta Bussolati. 1Dept of Biotechnology and Health Sciences, Univ of Turin, Turin, Italy; 2Dept of Medical Sciences, Univ of Turin, Turin, Italy.
Background: Acute kidney injury (AKI) often involved deregulation of erythropoietin (EPO) production in the kidney. Novel treatment foresees introduction of cell therapies or strategies involving pharmacological modulations of intrinsic populations to produce EPO. Our previous studies showed human renal regenerative capacity was realized by our group as a promising adult renal progenitor cell. Of note, papillary CD133+ cells show activation of hypoxia-inducible genes and are specifically involved in EPO production. However, their role in EPO production and fate to repair renal injury for long time has not yet been deconstructed in mice.

Methods: AKI was induced in immunodeficient mice using glycerol (8mg/gbw, i.m.) and adult human CD133+ papillary cells (0.5 million cells per mice) were injected (i.v.) 1 day after the injury. Mice were euthanized at different time intervals (day 15/30) and blood samples (serum, kidneys, lungs, liver) were collected for EPO, other markers of kidney injury (UR), histological/morphological analysis and molecular analysis (RNA, DNA and protein) respectively.

Results: Data showed that adult human CD133+ papillary cells improve EPO production (of both human and mice origin) in the injured mice and protect against AKI in mice at day 15 and day 30 as compared to control group. The group of injured mice that received cells showed higher level of human and mice specific EPO, lower level of creatinine and urea in serum, lower level of kidney injury marker, KIM-1 and improved histology. CD133+ papillary cells also reduced development of fibrosis in the injured tissues during repair (as shown by lower expression of alpha-SMA, profibrotic gene TGF-β and trichrome stain). In addition, immunohistochemical and fluorescence studies show localization of CD133+ papillary cells within interstitium and tubules of the injured renal tissues.

Conclusions: Thus, our data supports that these CD133+ papillary cells may provide an important source of EPO production and promote renal regeneration.

Funding: Government Support - Non-U.S.

FKR-0243
Early Mesenchymal Stem Cell Administration Prevents Acute Kidney Injury Superimposed on Chronic Kidney Disease in Rats and High Risk Patients Anna Gooch, Nicole Molin, Ping Zhang, Zhou Hu, Christoph Westenfelder. 1Medicine, U of Utah and VAMC, Salt Lake City, UT; 2Physiology, U of Utah, Salt Lake City, UT.
Background: We showed that ischemic-reperfusion injury (IR) causes renal and urine levels of the chemokine SDF-1 (CXCL12) to rise significantly within ~ 2 hrs. This rise mediates the homing of infused, CXCR4 (SDF-1 receptor)-expressing Mesenchymal Stem Cells (MSCs) to the sites of injury, where they act renoprotectively. CKD is a major risk factor for AKI. We wanted here whether MSC administration is effective both in preventing IR AKI superimposed on CKD and in arresting the AKI-induced further deterioration of CKD.

Methods: Rats: Groups of 6 rats underwent 5/6th Nephrectomy. Once CKD was established (8 weeks), TR AKI of the kidney remnant was induced and rats were treated either with vehicle or 2x106 MSC/kg bw, i.e. S.Cr and urine SDF-1/creatinine levels were assessed at pre- and post-operatively. Patients: 12 subjects with established CKD and at high risk for cardiac surgery associated AKI were treated i.a. with 2x106 MSCs per kg bw intravenously post-on-pump surgery and S.Cr and urinary SDF-1/creatinine levels were determined pre- and post-op. RIFLE criteria defined post-op AKI. Study subject data were compared to well-matched historical controls.

Results: Rats: MSCs significantly hastened improvement in AKI vs. controls. Urine SDF-1 levels remained low by 24 hrs in MSC vs. vehicle treated animals. Patients: No study subject had AKI at discharge, but 2 met post-op RIFLE criteria. Urinary SDF-1/Cr ratios were significantly elevated at 2 and 6 hrs in subjects who developed AKI Risk, but remained stable in those who did not. In contrast to historical controls, 6 months post-op, no treated subject’s CKD had worsened.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO244
Improved Survival of Graft Bone Marrow-Derived Mesenchymal Stem Cells in the Ischemia-Reperfusion-Induced Injured Kidney with Overexpression of Heme Oxygenase-1
Nannmei Li, Jinlin Hospital of Shanghai.

Background: one marrow-derived mesenchymal stem cells (BMSCs) transplantation offers therapeutic potential for acute kidney injury (AKI), but with limited efficacy. This study investigated the role of HO-1 overexpression on the donor BMSCs’ survival, and its impact on the repair of AKI was also observed.

Methods: Ischemia/reperfusion (I/R)-AKI kidney homogenate supernatant (KHS) was prepared. SD BMSCs, eGFP-BMSCs and HO-1-BMSCs were harvested and treated by the AKI-KHS. Cell viability, apoptosis and cell cycle were evaluated. Activations of oxidant stress-related enzymes, expression of p65 and the protein levels of Caspase-3 and Bcl-2 in BMSCs were tested. Survivals of the implanting BMSCs in the AKI rat model as well as the renal function were also assessed.

Results: HO-1-BMSCs showed a high expression of HO-1 and AKI-KHS treatment further enhanced this level. This increased HO-1 expression promoted BMSCs survival under the AKI microenvironment with decreased apoptotic cells as well as less proportion of G0/G1 cells. AKI-KHS induced reduction of SOD activity and GSH-Px in BMSCs with increased MD and AOXD levels, however, HO-1 overexpression changed this phenomenon. Activation of NF-κB p65 was inhibited in HO-1-BMSCs. Western blot showed decreased Caspase-3 expression and increased Bcl-2 expression in HO-1-BMSCs. The in vivo study showed increased survival of HO-1-BMSCs in the AKI kidneys, which was associated with improved renal function.

Conclusions: HO-1 overexpression could enhance survival of BMSCs under the I/R-AKI microenvironment both in vitro and in vivo as the result of ROS elimination. Activity of NF-κB p65 and Caspase-3/Bcl-2 signal transduction pathways were involved in this process.

Funding: Government Support - Non-U.S.

FR-PO245
Induced Pluripotent Stem Cell-Conditioned Medium Mitigates Renal Ischemia-Reperfusion Injury by Suppressing Oxidative Stress
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Background: Ischemic acute kidney injury (AKI) carries high mortality and current treatment remains unsatisfying. Induced pluripotent stem cell (iPS) is a promising therapeutic option for AKI; nonetheless, teratoma formation addresses critical safety concerns for iPS cell transplantation. iPS-derived conditioned medium (iPS-CM) is comparable with iPS cells on ameliorating acute lung injury but the beneficial role of iPS-CM on AKI remains unclear.

Methods: Rat model of renal ischemia-reperfusion injury (IRI) and NRK52E cells subjected to hypoxia-reoxygenation (HR) were used to explore the role of iPS-CM on AKI. BUN, creatinine, tubular cell apoptosis, level of reactive oxygen species (ROS), expressions of proinflammatory cytokines and animal survival were investigated.

Results: Administration of iPS-CM intraperitoneally significantly improved renal function and decreased tubular cell apoptosis after renal IRI. Moreover, elevated ROS level in IRI-rat kidneys was markedly attenuated by iPS-CM. Co-culture of NRK52E cells with iPS-CM also significantly diminished H2O2-induced apoptosis and ROS production. Furthermore, iPS-CM downregulated both H2O2- and IRI-stimulated expressions of p38, NF-κB, and caspase 3. Additionally, the IRI-related IL-6 and MCP-1 expressions were also suppressed by iPS-CM. Finally, after being subjected to renal IRI, the rats treated with iPS-CM demonstrated better survival as compared those treated with phosphate-buffered saline or normal control medium.

Conclusions: iPS-CM decreases renal IRI-related lethality by suppressing ROS, inflammation, and tubular cell apoptosis. iPS-CM may be a potential therapeutic option for kidney repair in ischemia.

Funding: Veterans Administration Support

FR-PO246
Vascular Adhesion Protein-1 (VAP-1) Inhibition Ameliorates Cisplatin Induced Acute Kidney Diseases and Disorders (AKD)
Daisuke Katagiri, 1,2 Yoshifumi Hamasaki, 1 Kent Doi, 1,3 Kousuke Negishi, 1 Takeshi Sugaya, 1 Masao Nangaku, 1 Eisie Nohri, 1 Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; 2Apheresis and Dialysis, The Univ of Tokyo, Tokyo, Japan; 3Emergency and Critical Care Medicine, The Univ of Tokyo, Tokyo, Japan; CMIC Ltd, Tokyo, Japan.

Background: Cisplatin (CP) is a platinum compound that is used as an effective chemotherapeutic agent for many malignancies. Its nephrotoxicity is dose dependent, which often limits its use. Research in the field of acute kidney diseases and disorders (AKD), including acute kidney injury (AKI), is important to prevent their progression to chronic kidney disease (CKD).

Methods: A new clinically relevant animal model using multiple low doses of CP was used to evaluate AKD. Human liver fatty acid-binding protein (L-FABP) transgenic (Tg) mice were administered 10 mg/kg of CP (three times, at 0, 1, 3 weeks) for four weeks. Vascular adhesion protein-1 (VAP-1) inhibitor that was recently reported to prevent fibrosis in organs was studied in this model. For treating group, mice received 2 mg/kg/day of PXS-4728A, a selective VAP-1 inhibitor, starting 3 weeks after the first CP administration.

Results: Moderate renal interstitial fibrosis occurred with multiple CP administration. Urinary L-FABP, one of the promising AKI biomarkers, increased about 10-fold one week after every CP injection. Although no further elevation of L-FABP was observed at 3W, following the omission of CP at 2W, L-FABP did not revert to baseline levels. Treatment of PXS-4728A for one week attenuated interstitial fibrosis in this model. PXS-4728A inhibitor treatment remarkably reduced 4-HHE- and 8-OHdG-positive areas. The mRNA expressions of TGF-β1, SMA, VEGF, and MCP-1 in the kidney were increased significantly by multiple CP treatments and attenuated by VAP-1 inhibitor treatment. Further, the inhibition of lipid accumulation in the S3 segments, together with L-FABP suppression was confirmed.

Conclusions: Multiple treatments with CP lead to moderate kidney dysfunction with increased renal biomarkers and renal fibrosis. As a standing point of onco-nephrology, VAP-1 inhibitors are promising candidates for the prevention of CKD in patients using CP for the treatment of malignancy.

Funding: Government Support - Non-U.S.

FR-PO247
Pulsed Focused Ultrasound Improves Mesenchymal Stem Cell Therapy for Acute Kidney Injury by Upregulating Revascularization-Gamma to Stimulate Stem Cell Production of Interleukin-10
Scott R. Burks, Matthew Nagle, Michele Bresler, Saejeong Kim, Blerta Milo, Joseph A. Frank. Frank Lah, NIH Clinical Center, Bethesda, MD.

Background: Pulsed focused ultrasound (pFUS) to kidneys enhances mesenchymal stem cell (MSC) homing to kidneys and improves outcomes when treating early or established acute kidney injury (AKI) compared to MSC infusions alone. However, mechanisms of improved combination therapy are unclear.

Methods: AKI was induced in C3H or interferon-γ (IFNγ)-deficient mice with cisplatin (15 mg/kg), pFUS (40W, 5%da) was delivered to kidneys –3hr before infusion of 10’ human MSC. MSCs were observed by immunostaining for human mitochondria. For some experiments, MSCs were treated in culture with recombinant IFNγ or siRNA against IL-10. Cytokines were analyzed by mouse- and human-specific ELISAs. Serum creatinine and blood urea nitrogen values were measured spectrophotometrically.

Results: Proteome profiling of AKI kidneys revealed that pFUS upregulated renal IFNγ and after MSC homed to pFUS-treated kidneys, they produced more human IL-10 compared to MSC in kidneys without pFUS. pFUS/MSC in IFNγ-knockout mice led to greater MSC homing to pFUS-treated kidneys, but MSCs failed to produce greater IL-10 and FUS/MSC yielded identical outcomes as MSC alone (ie, no improvement from pFUS/MSC). Supplementing MSC with IFNγ improved AKI outcomes in C3H mice in the absence of pFUS, while the improved outcomes seen pFUS/MSC were abrogated by knocking down IL10 in MSC.

Conclusions: pFUS pretreatment of kidneys during AKI alters the renal molecular environment to increase MSC homing to treated kidneys. However, improved disease outcomes from combination therapy are the result of pFUS upregulating IFNγ in the kidney so that MSC’s homing to pFUS-treated kidneys are subsequently conditioned to produce more IL10, which has been shown to improve AKI.

Funding: Other NIH Support - NIH Intramural Research Program

FR-PO248
Stem Cells from Human Exfoliated Deciduous Teeth Ameliorate Acute Kidney Injury in Mice
Yuki Hatton, 1 Hangsoo Kim, 1 Naotake Tsuoi, 1 Akihito Yamamoto, 2 Seiichi Matsuo, 2 Shohji Maruyama, 2 Masaomi Nangaku, 3 Masaomi Nangaku, 3 Masaomi Nangaku, 3 Nagoya Univ Graduate School of Medicine, Japan; 4Nephrology, Nagoya Univ Graduate School of Medicine, Japan.

Background: Preclinical studies have indicated that administered mesenchymal stem cells (MSCs) ameliorated various types of renal injury and promoted the subsequent kidney repair. Recently, stem cells from human exfoliated deciduous teeth (SHED), which has been discovered as a medical waste, has received attention as a novel kind of MSCs.

Preclinical experiments were performed in mice exposed to cisplatin (CP) or oxaliplatin (OXP). CP was administered intraperitoneally by three doses (0.75 mg/kg, IP) on days 0, 3, 5 and 7, and OXP was administered intraperitoneally by three doses (2 mg/kg, IP) on days 2, 5, 8. For CP treatment, mice received 5 mg/kg and 10 mg/kg of CP at the first and second injections, respectively.

Results: MSCs were administered by intravenous injection 10 days before or 2 days after the renal injury. MSCs from human exfoliated deciduous teeth (SHED) were injected into mice with acute renal failure. MSCs from human exfoliated deciduous teeth (SHED) were injected into mice with acute renal failure. MSCs from human exfoliated deciduous teeth (SHED) were injected into mice with acute renal failure. MSCs from human exfoliated deciduous teeth (SHED) were injected into mice with acute renal failure. MSCs from human exfoliated deciduous teeth (SHED) were injected into mice with acute renal failure. MSCs from human exfoliated deciduous teeth (SHED) were injected into mice with acute renal failure.

Conclusions: In conclusion, SHED-MSCs are a potential therapeutic agent for the treatment of acute kidney injury.

Funding: Other NIH Support - NIH Intramural Research Program

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The purpose of this study is to clarify the therapeutic effects of SHED on AKI induced by IRI.

**Methods:** Seven days after heminephrectomy, the renal artery and vein were clamped for 20 min to induce ischemia in male C57BL/6 mice. SHED or PBS as a control was administered into subcapsular right kidney. Blood, urine and tissue samples were collected. In order to confirm renoprotective potential of conditional media of SHED (SHED-CM) in vitro, H2O2 stimulation assay and scratch wound assay using mouse tubular epithelial cells (TECs) were also performed.

**Results:** Serum creatinine and BUN levels and urinary protein excretion were significantly decreased in SHED-treated group. In vivo and in vitro, cPLA2 and 3T3-L1 adipocytes were treated with TGF-β/α alone, and nullortreated. TGF-β/α increased the phosphorylation of SIRT2 at ser331 diminished its catalytic activity and reduced its binding of SIRT2, respectively. Analysis of the phosphorylation state of SIRT2 was carried out in the presence or absence of cPLA2 in vitro by kinase assay and in vivo by using the CREB phosphorylation assay.

**Conclusions:** In vivo and in vitro, cPLA2 acts as a bridge in this complex to promote binding of SIRT2 to cyclin A-Cdk2. Cyclin A-Cdk2 then phosphorylates SIRT2 at ser331. Phosphorylation of SIRT2 at ser331 diminishes its catalytic activity and reduces its binding affinity to centromeres and mitotic spindles. This detachment of SIRT2 from mitotic spindles plays a key role in the development of malignancy in human cells. This function of cPLA2 may be further exploited to better understand the important link between cPLA2 and tumorigenesis and between inflammation and the age-related disorders such as Alzheimer’s disease, in which cPLA2 may be further implicated.

**Funding:** NIDDK Support

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**FR-PO252**

**The Cytokines Guanosine Exchange Factors Are Required to Promote HGF-Induced Renal Epithelial Recovery After Acute Kidney Injury in Mice**

**Lorraine C. Santos, Marta Revirigues-Mendoza, Department of Biochemistry and Molecular Biology, Pennsylvania State Univ, Univ Park, PA.**

**Background:** The lack of current treatment and preventable measures for acute kidney injury (AKI) in hospitalized patients results in an increased mortality rate of up to 80% and elevated health costs. The molecular aspects of kidney injury and repair are still uncertain. Hepatocyte growth factor (HGF) promotes recovery of the injured kidney by inducing survival and migration of tubular epithelial cells to repopulate base tubular areas. HGF-stimulated kidney epithelial cell migration requires the activation of ADP-ribosylation factor 6 (Arf6) and Rac1 via the cytokine family of Arf-guanine-nucleotide-exchange factors (GEFs), in vitro.

**Methods:** We used an ischemia and reperfusion injury (IRI) mouse model to analyze the effects of modulating this signaling pathway on kidney recovery. We treated IRI mice with either HGF, the cytokine inhibitor SecinH3, or a combination of both. Kidney function was assessed by measuring creatinine (Cre) and blood urea nitrogen (BUN) levels. Standard H&E staining was performed to evaluate kidney structures and immunohistochemistry was used to detect active-Rac1 and active-Arf6.

**Results:** Simultaneous treatment with SecinH3 and HGF blocks the ability of HGF to promote kidney recovery as evidenced by Cre and BUN levels. Immunohistochemistry showed that HGF treatment promoted recovery of tubule structure, and had enhanced levels of active, GTP-bound Arf6 and GTP-Rac1. HGF treatment, however, caused a dramatic decrease in GTP-Arf6 and GTP-Rac1 levels when compared to kidney sections from HGF-treated IRI mice. Additionally, SecinH3 counteracted the renal reparative effects of HGF.

**Conclusions:** We show that HGF-dependent damaged kidney recovery requires the function of a cytokine-dependent signaling module, and that inhibiting Arf6 and Rac1 counteracts HGF-stimulated recovery. In addition, we demonstrate that HGF treatment of ischemic mice promotes the activation of Arf6 and Rac1 in the recovering kidneys in a cytokine-dependent manner, and that cytokine activation is required to promote epithelial repopulation of kidney tubules and thus kidney recovery.

**Funding:** NIDDK Support
Regulation of Kidney Injury Molecule-1-Mediated Efferocytosis by Rho GTPases Ola Ismail, Xiaohong Zhang, Lakshman Gunaratnam. Kidney injury molecule 1 (KIM-1) is a phagocytic receptor for apoptotic cells that is specifically upregulated on the apical membrane of proximal tubule cells (FTTCs) after acute kidney injury. KIM-1-mediated clearance of apoptotic cells (efferocytosis) can protect from inflammation during acute kidney injury by down-regulating innate immunity and inflammation. As cytoskeletal remodeling is essential for phagocytosis, we examined the relative importance of Rac1 and RhoA, two key Rho GTPases that mediate actin remodeling, in KIM-1-dependent efferocytosis. We also investigated a possible link between Ga12, which we previously identified as a KIM-1-interacting protein, and these Rho GTPases.

Methods: To study the role of Rac1 and RhoA in KIM-1-mediated uptake of apoptotic cells, we utilized chemical inhibitors or plasminoids encoding dominant negative forms of Rac1 or RhoA protein and measured the uptake efficiency of FTTCs by flow cytometry. Using commercially available GTPase pull-down assays, we measured the endogenous Rac1 and RhoA activity in KIM-1-expressing cells after apoptotic cell-stimulation. To decipher whether these Rho GTPases are down-stream mediators of Ga12-KIM-1 signaling, we silenced Ga12 using siRNA and measured Rac1 and Rho GTTPase activity.

Results: Inhibition of Rac1 resulted in a significant decrease in KIM-1-mediated phagocytosis, whereas inhibition of and RhoA increased it. RhoA activity gradually increased during phagocytosis and peaked during the later stages of phagocytosis, whereas Rac1 activity remained constant over the entire course of phagocytosis. Furthermore, silencing a key KIM-1-interacting protein, Ga12, caused a significant decrease in RhoA activity.

Conclusions: We conclude that Rac1 and RhoA play opposing roles during KIM-1-mediated efferocytosis, where RhoA serves to mediate signaling by KIM-1 and its interacting partner, Ga12.

Funding: Government Support - Non-U.S.

FR-PO254
Periostin Induces Kidney Fibrosis After Ischemia-Reperfusion Injury via p38 MAPK Pathway Junang Nam, Seung Hee Yang, Jin Ho Hong, Chun Soo Lim, Yun Kyu Oh, Yun So Kim, Jung Pyo Lee, Seon National Univ Boramae Medical Center; Seon National Univ Hospital; Seon National Univ Kidney Research Inst; Chung-Ang Univ Hospital, Republic of Korea.

Background: Periostin, a matrix cellular protein, has been reported to play a crucial role in inflammatory and fibrotic mechanism. We hypothesized that periostin involves in the progression of acute kidney injury via efferocytosis, where RhoA serves to mediate signaling by KIM-1 and its interacting partner, Ga12.

Methods: To establish a kidney progression model, we induced unilateral ischemia-reperfusion injury of left kidney pedicle for 30min in wild type (WT) C57BL/6 mice and Postn null mice (Postn+), and observed cultured for 4 to 6 weeks. In addition, inner medulla collecting duct cell line was subjected to put in the hypoxic incubator (1% O2, 5% CO2, and 94% N2) for 24 and 72 hours.

Results: For 4 to 6 weeks, the left kidneys in Postn null mice were significantly less atrophied and small in weight compared to those of WT mice. Significant tubular atrophic and less small in weight compared to those of WT mice. Significant tubular atrophic and less small in weight compared to those of WT mice. Significant tubular atrophic and less small in weight compared to those of WT mice.

Conclusions: In conclusion, periostin is related to the progression via p38 MAPK pathway.

Funding: Government Support - Non-U.S.

FR-PO255
Tim-3/Gal-9 Pathway Activation Ameliorates Renal Ischemia Reperfusion Injury by Shifting the Balance of Activated Th1, Th17 and Foxp3+ T Cells Junhua Li, Junhua Li, Ying Zhang, Jiong Zhang, Ying Yao, Gang Xu. Dept. of Nephrology, Tongji Hospital, Huazhong Univ of Science and Technology, Wuhan, China.

Background: Renal ischemia reperfusion injury (IRI) is characterized by kidney ischemia. Galectin-9 (Gal-9) is identified as a T-cell immunoglobulin domain and Ig-like motif of T lymphocytes and macrophages. As a sialic acid binding protein, it is thought to play an important role in inflammatory and fibrotic mechanism. We hypothesized that periostin involves in the progression of acute kidney injury via efferocytosis, where RhoA serves to mediate signaling by KIM-1 and its interacting partner, Ga12.

Methods: To study the role of Rac1 and RhoA in KIM-1-mediated uptake of apoptotic cells, we utilized chemical inhibitors or plasminoids encoding dominant negative forms of Rac1 or RhoA protein and measured the uptake efficiency of FTTCs by flow cytometry. Using commercially available GTPase pull-down assays, we measured the endogenous Rac1 and RhoA activity in KIM-1-expressing cells after apoptotic cell-stimulation. To decipher whether these Rho GTPases are down-stream mediators of Ga12-KIM-1 signaling, we silenced Ga12 using siRNA and measured Rac1 and Rho GTTPase activity.

Results: Inhibition of Rac1 resulted in a significant decrease in KIM-1-mediated phagocytosis, whereas inhibition of and RhoA increased it. RhoA activity gradually increased during phagocytosis and peaked during the later stages of phagocytosis, whereas Rac1 activity remained constant over the entire course of phagocytosis. Furthermore, silencing a key KIM-1-interacting protein, Ga12, caused a significant decrease in RhoA activity.

Conclusions: We conclude that Rac1 and RhoA play opposing roles during KIM-1-mediated efferocytosis, where RhoA serves to mediate signaling by KIM-1 and its interacting partner, Ga12.

Funding: Government Support - Non-U.S.

FR-PO256

Background: Acute kidney injury (AKI) is a major risk factor for the development of chronic kidney disease (CKD). Renal ischaemia may cause post-inflammation scarring leading to loss of nephrons and development of fibrosis. The NF-κB inhibitor (NF-xb) is a family of transcription factors activated post-injury, but its role in the progression of AKI to CKD is unknown.

Methods: Male Wistar rats were subject to a RH nephrectomy and L.H unilateral renal ischemia for 60min, or nephrectomy only (sham). At 2 (n=4), 7 (n=8) or 28d (n=7) after ischemia, the left kidneys were harvested. The expression of Gal-9 and Tim-3 in IR and sham kidneys was measured.

Results: Compared to sham-operated rats, rats subjected to unilateral renal ischemia developed AKI (increases in serum creatinine and decreases in the estimated creatinine clearance). The delayed administration of IKK16 at 24h post AKI (at peak creatine values) significantly improved renal functional recovery and structural injury at 48h post AKI compared to sham-operated rats, rats culled at 7d post AKI demonstrated significant increases in smooth muscle actin (sMCA) and CD68+ staining for myofibroblasts and macrophages, respectively. IKK16 administration significantly decreased sMCA and CD68+ staining at 7d post AKI. Rats culled at 28d post AKI demonstrated a significant increase in sinus red staining compared to sham rats, indicating the development of fibrosis. Administration of IKK16 at 24h significantly attenuated Sirius red staining, and therefore the level of fibrosis at 28d.

Conclusions: Inhibition of IKK16 at 24h post AKI (at peak creatine values) improves renal functional recovery at 48h post AKI, and reduces the degree of fibrosis observed at 28d.

Funding: Government Support - Non-U.S.

FR-PO257
The Peroxisome Proliferator-Activated Receptor γ (PPAR-γ) Agonist, Pioglitazone Prevents NF-κB Activation in Cisplatin Nephrotoxicity by Reducing NF-κB Acetylation Through AMPK-SIRT1/p300 Pathway Junhua Li, Junhua Li, Ying Zhang, Jiong Zhang, Ying Yao, Gang Xu. Dept. of Nephrology, Tongji Hospital, Huazhong Univ of Science and Technology, Wuhan, China.

Background: NF-κB is a ubiquitously expressed transcription factor controlling the expression of numerous genes involved in inflammation. The aim of this study was to evaluate whether the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) could attenuate cisplatin-induced NF-κB activation in cisplatin nephrotoxicity.

Methods: Acute kidney injury model was established by intraperitoneal injection of cisplatin. C57BL/6 mice were divided into three groups: normal group; model group; and treatment group, with pioglitazone gavage of three days. Respectively after injection in 24, 48 and 72 hours, the mice serum were collected for renal function and kidney specimen for pathological, Western blot, immunohistochemistry and real time PCR detection.

Results: Our results showed PPAR-γ agonist Pioglitazone could decrease the expression of NF-κB p65 transcription target genes such as pro-inflammation cytokines interleukin 6 (IL-6), interleukin-1 β (IL-1β), and tumor necrosis factor-alpha (TNF-α) and its cellular translocation and MPO infiltration in cisplatin nephrotoxicity. Suppressing NF-κB activity following Pioglitazone treatment was involved in inhibiting iκBα degradation, phosphorylation modification and NF-κB p65 subunit translocation induced by cisplatin injection. The NF-κB p65 subunit translocation is dependent on p65 acetylation, which is mainly regulated by SIRT1 or p300. Of note, The subsequent AMP kinase (AMPK) activation not only decreases the p300 phosphorylation, activation and its interaction with p65, but also increases the SIRT1 expression, activation and binding to p65, leading to a significant reduction p65 acetylation. Interestingly, the reduction in expressions of IL-6, IL-1β and TNF-α were remarkable and MPO infiltration following Pioglitazone treatment in cisplatin nephrotoxicity were attenuated by the PPAR-gantagonist GW9662.

Conclusions: Our results suggest that PPAR-γ agonist Pioglitazone prevents NF-κB activation in cisplatin nephrotoxicity by reducing p65 acetylation through AMPK-SIRT1/ p300 pathway.

Funding: Government Support - Non-U.S.

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

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AKI: Basic Repair and Regeneration

Poster/Friday
Competitive Inhibition of CD95L Reduces Inflammation, but Only Modestly Improves Outcomes in Experimental Ischemia-Reperfusion Injury


Background: After previous encouraging results in CD95L (FasL) mutant mice in ischemia-reperfusion injury (IR) models, we sought to investigate the effect of the competitive pharmacologic inhibition of CD95 (FAS) in kidney IR using APG101, an orphan drug developed for the treatment of recurrent glomeruloma, which has shown a good patient tolerability in phase I and II clinical studies.

Methods: C57BL/6 mice treated with different dosages of APG 101 (10, 30 or 100 µg/kg-body weight, single-dose, 12h before IR) or vehicle (PBS) alone were submitted to a 30 min bilateral renal ischemia (IR) sham-animal treated with the highest dosage of APG101 dose or PBS. The experiment was further divided into two observation periods: day 2 (injury phase) and day 7 (recovery phase). Serum and kidney tissue analysis were performed focusing on function recovery, cell proliferation, macrophage infiltration and renal histopathology of the mouse kidney. Results are given as mean±SD.

Results: Optimal serum CD95 saturation was only achieved in the APG 100µg/kg group (98.4±0.35% and 96.9±1.3% at day 2 and 7, respectively), so that experiments were further conducted with this dosage. At day 2, serum creatinine was significantly higher in the IR PBS group, but not in the IR APG group compared to sham-op (0.26±0.12 and 0.20±0.07 vs. 0.09±0.03 mg/dL P<0.05). A similar pattern was seen in macrophage infiltration and MCL-1 mRNA expression in the kidney, both persisting until day 7. Apoptosis, however, was similar between the IR groups in both observation periods. APG treatment markedly reduced cell proliferation in both sham and IR animals compared to PBS (0.51±0.9 vs. 8.4±5.7 Ki67 positive cells/hpf, p<0.0004), which was observed at day 2, but didn’t persist until day 7.

Conclusions: Despite an anti-inflammatory effect, the APG101-induced impairment of the tubular cell proliferation may have hampered the early recovery phase after IR leading to the modest results.

FR-PO259

Oral Treatment with PB1-4050 Reduces Ischemia-Reperfusion-Induced Fibrosis


Background: PB1-4050, a novel first-in-class orally active compound which is currently in clinical phase II/III in CKD patients, displays antifibrotic activities via a novel mechanism of action. In a double-blind ascending dose (400 to 2400 mg) clinical phase I trial, PB1-4050 was found to be safe and well tolerated up to 2400 mg without any significant side effects. Clinically relevant IR is a leading cause of acute kidney injury (AKI), which may result from a variety of conditions, such as decreased cardiac output, renal vascular occlusion or obstruction, and kidney transplantation. The aim of this study was to investigate the anti-fibrotic activity of PB1-4050 in a mouse model of acute ischemic kidney injury.

Methods: Renal ischemia-reperfusion (IR) injury was induced by the clamping of the left renal pedicle for 60 minutes in C57BL/6 mice (6-8 week old). Mice were treated with oral administration of vehicle or PB1-4050 (200 mg/kg) from day -3 to day 13 and sacrificed at day 14.

Results: Renal IR-injury induced a rise in serum creatinine at day 2 that was prevented by oral treatment with PB1-4050. At day 4, mice suffering from renal IR demonstrated a loss in hemocrit which was also prevented by PB1-4050 treatment. Furthermore, histomorphometric analysis demonstrated a significant increase in renal fibrosis, determined by medullary collagen accumulation in mice with IR-injury, which was significantly reduced by PB1-4050 treatment. In addition, PB1-4050-treatment reduced kidney type-III collagen mRNA expression.

Conclusions: Taken together, these pre-clinical results suggest that PB1-4050 offers the potential as a novel therapy for the treatment of AKI and may delay or prevent the onset of fibrosis in renal transplant recipients.

FR-PO260

Cisplatin Acute Kidney Injury and Conversion to Chronic Kidney Disease

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Background: Chronic Kidney Disease (CKD) develops in humans after repeated doses of cisplatin (CP). We report on a new model to investigate the mechanism of this form of CKD.

Methods: 8-week old C57Bl6 mice were given either a single or double dose (12 weeks apart) of CP (15 mg/kg) and studied 2, 4, 6, 9 and 16-25 weeks after the first dose. GFR was measured by inulin clearance followed by intravascular perfusion-fixation. Results are given as mean±SD.

Results: GFR fell precipitously to below 50% of controls 2 weeks after the second dose and progressed without hypertension, loss of glomerular number, or glomerulosclerosis. Kidney weight fell as a result of loss of cortical tissue. Collagen deposition increased but progressed without hypertension, loss of glomerular number, or glomerulosclerosis. Influx of macrophages, increased cell cycle activity (Ki67) and apoptosis (TUNEL) were followed by vascular rarefaction. Ki67 failed to increase after the second dose as it did after a single dose. The cyclin-dependent kinase inhibitor protein p21 increased and paralleled the lack of cell cycle activity. Abnormal glomerulotubular junctions (GTJ) developed only after the second dose, which included loss of megalin positive parietal epithelial cells and glomerulotubular junction remodeling seen here and its demonstrated role in progression in the renal ablation model of CKD suggests its sustained activation may cause the conversion of AKI to CKD. Understanding why injured PT cells fail to re-enter the cell cycle following the second dose of CP is likely to yield new means to prevent CP-induced CKD, which may be applicable to other forms of AKI to CKD conversion.

Funding: NIDDK Support, Veterans Administration Support

FR-PO261

The MEK1/2 Inhibitor, U0126, Decreases Cisplatin-Induced AKI and Slows Cancer Growth in Mice


Background: Nephrotoxicity is cisplatin’s major dose-limiting side effect as a chemotherapeutic agent. We have developed a model of 4 week, low dose cisplatin (Cis)-induced AKI in mice with cancer. In the 4 week model of AKI, there is an increased ERK expression in kidneys.

Methods: Wild type C57BL/6 mice were injected subcutaneously with murine lung cancer cells derived from C57BL/6 mice. Ten days later, Cis (10 mg/kg/week) was given to mice. Tumor weight and volume was decreased in mice treated with vehicle compared to U0126 vs vehicle alone. In the 4 week model of AKI, there is an increased tumor growth and induced the therapeutic effect of cisplatin. Discovery of a drug that decreases cisplatin-induced AKI and improves the therapeutic effect of cisplatin would be a significant finding for patients with cancer.

Funding: Veterans Administration Support

FR-PO262

Glycogen Synthase Kinase-3 Regulates Fibroblast Activation and Development of Fibrosis following Renal Ischemia/Reperfusion in Mice

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Glycogen synthase kinase-3 (GSK3) is a serine/threonine protein kinase that plays an important role in renal tubular injury and regeneration in acute kidney injury. However its role in the development of renal fibrosis, often a long-term complication of acute kidney injury is unknown. Using a mouse model of renal fibrosis induced by ischemia/reperfusion (IR) injury, we demonstrate increased GSK3 expression and activity in fibrotic kidneys.

Methods: Bilateral I/R was carried out on male C57BL/6J mice; both renal pedicles were exposed by flank incision and clamped for 30 minutes at 37°C. GSK3 inhibitor (TIDZD-8) was administered by daily IP injection at 1mg/Kg BW.t. dose starting 1h before (TIDZD-pre) or 48h after (IR) (TIDZD-post). Studies were also carried out in rat fibroblast NRK-49F cells.

Results: Tumor weight and volume was decreased in mice treated with Cisplatin+U0126 vs Cisplatin alone demonstrating that U0126 significantly increased the therapeutic effect of cisplatin.

Conclusions: U0126 decreased cisplatin-induced AKI. In addition, U0126 decreased tumor growth and improved the therapeutic effect of cisplatin. Discovery of a drug that decreases cisplatin-induced AKI and improves the therapeutic effect of cisplatin would be a significant finding for patients with cancer.

Funding: Veterans Administration Support

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
even in the absence of TGF-β1 treatment. These results suggest that TGF-β1 regulates GSK3β expression, which in turn is important for TGF-β1-SMAD3 signaling to fibroblast-to-myofibroblast differentiation.

**Conclusions:** The study thus demonstrates that GSK3β could promote renal fibrosis by activation of TGF-β signaling and the use of GSK3 inhibitors might represent a novel therapeutic approach for progressive renal fibrosis that develops as a consequence of AKI.

**Funding:** Other NIH Support - R01 DK-083525

**FR-PO263**

**Regulating Cx43 and TRPC6 Expression Protects Renal Epithelial Damage in a Rat AKI Model**

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**Background:** Intracellular Ca²⁺ homeostasis plays an essential role in maintaining normal cell function. Connexin43 (Cx43) and transient receptor potential channel (TRPC6) has been reported to regulate Ca²⁺ entry in some pathologic conditions. The aim of this study was to elucidate whether the modifier protein of glyceraldehyde-3-phosphate dehydrogenase (MP) and ATP-MgCl₂ could regulate Cx43 and TRPC6 in a rat model of acute kidney injury (AKI).

**Methods:** Male Sprague-Dawley rats were divided into the following groups: normal control, gentamicin-treated, MP plus gentamicin-treated, ATP-MgCl₂, plus gentamicin-treated (n=15 for each), as well as control group for MP and ATP-MgCl₂ alone (n=5 for each). Levels of serum creatine (sCr) for each group were measured on the 14th days of treatment. The “in vivo cryotechnique” was used for preparing kidney specimen as before. Immunohistochemistry staining for Cx43 and TRPC6 was performed.

**Results:** The gentamicin-treated group showed a significant increase in sCr compared to the normal control group. Co-treatment of gentamicin with MP and/or ATP-MgCl₂ produced marked decreases preventing the increase of sCr. Under light microscope, the gentamicin-treated group showed tubular epithelium damage indicating AKI. This was attenuated by MP and/or ATP-MgCl₂ co-treatment. Immunohistochemistry staining indicated that MP and/or ATP-MgCl₂ co-treatment prevented gentamicin-induced down-regulation of Cx43 and TRPC6 in renal epithelium cells using the “in vivo cryotechnique”. Furthermore, the expressions of Cx43 and TRPC6 in gentamicin-treated group showed much weaker intensity using conditional fixation method compared to that using “in vivo cryotechnique” suggesting there might be artificial damage during the conditional fixation procedure.

**Conclusions:** Using a rat model of AKI, MP and ATP-MgCl₂ were able to prevent the down-regulation of Cx43 and TRPC6, which might reduce Ca²⁺ entry and its downstream signaling, thus minimizing the damage in the renal epithelial cells.

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

**FR-PO265**

**Bud-Like Structure Capable of Developing to Lamellipodia in Wound Healing of Tubular Epithelium – A Scanning Electron Microscopic Approach**

Yoko Umura,1 Hiroyuki Morita,2 Yoshikico Inoue,1 Shinya Omiya,1 Tomoaki Miyazaki,1 Ashio Yoshimura.1 *Dept. of Nephrology, Showa Univ Fujigaoka Hosp., Yokohama, Kanagawa, Japan; 2Dept. of Endocrinology and Metabolism, Aichi Medical Univ School of Medicine, Nagakute, Aichi, Japan.*

**Background:** Cell migration is essential in wound healing during which filamentous (F)-actin assembly plays a pivotal role. Cell biological approaches, using confocal microscopy, succeeded in identifying molecules regulating the assembly, such as the Arp2/3 complex, N-WASP, cofillin, and profilin. Although cells form filopodia (microspike) and lamellipodia (membrane), and move forward, much remains to be seen in the ultrastructure of these processes.

**Methods:** Rat tubular epithelium (NRK-52E) was cultured, grown to confluency, and scratched. The cells were subjected to scanning electron microscopy (SEM) at various time points. In separate experiments, immunoelectron microscopy was performed using an antibody against Arp3. Lastly, 60% confluent NRK-52E cells were cultured in the presence or absence of si-RNA for Arp3, grown to confluency, and scratched. The cells were observed periodically at the SEM levels, and, the length of time for complete recovery was compared.

**Results:** As shown in the figure, SEM elucidated elaborated network of filopodia containing “bud-like structure” (bud) that may develop to lamellipodia. Arp3 was expressed in filopodia and lamellipodia but not in a bud. The Si-RNA knockdown significantly prolong the length of time for the recovery. It at least partially inhibited the formation of filopodia network and lamellipodia but not the formation of a bud.

**Conclusions:** This is the first SEM analysis of scratch wound healing in cultured tubular epithelium, and that the bud was previously undescribed. Although the Arp2/3 complex does not apparently induce lamellipodia formation of a bud, further molecular analysis may shed a new light into cell motility in wound healing.

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

**FR-PO266**

**Inhibition of Microtubule Dynamics Delays Kidney Recovery After Ischemia/Reperfusion Injury in Mice**

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**Background:** Ischemia/reperfusion (I/R) is a major cause of acute kidney injury (AKI). If recovery from AKI is delayed, kidney progresses toward chronic renal failure. Microtubules, a component of the cytoskeleton, contribute to cell damages, cell shape, cell motility, and cell division. Here, we investigate that the role of microtubule network on the kidney injury, recovery and progression of fibrosis after I/R injury.

**Methods:** Mice were subjected to 30 minutes of bilateral renal ischemia, and mice were sacrificed 16 days after ischemia. Some mice were administered either saline (vehicle) or paclitaxel (taxol), a microtubule stabilization agent; 1 day before ischemia (pretreatment) or from 1 day after ischemia until sacrifice every 2 days (post-treatment).

**Results:** Pretreatment of taxol did not affect post-I/R renal function compared with vehicle-treated I/R group. Post-treatment of taxol delayed renal functional and histological recovery with retardation of tubular regeneration, and accelerated proliferation of interstitial cells after ischemia. Post-treatment of taxol from 24 hours after ischemia enhanced cell cycle arrest, progression of fibrosis, and macrophage infiltration into the kidney. Furthermore, post-treatment of taxol suppressed regoplaarization of primary cilia in tubular epithelial cells.

**Conclusions:** In conclusion, our results demonstrate that microtubule stabilization or inhibition of cell proliferation delays kidney tubule cell restoration after ischemic injury, whereas interstitial cell proliferation is accelerated, leading to kidney fibrosis. It suggests that regulation of microtubule dynamics is critical to repair from AKI and progression of AKI to chronic kidney disease.

**Funding:** Government Support - Non-U.S.
**FR-0267**

**Tubulin Acetylation in the Kidney Tubular Cells After Ischemia-Reperfusion Injury**

Jihveon Kim, Sang Jun Han, Kwon Moo Park. Dept of Anatomy and BK21, Kyungpook National Univ, Daegu, Korea.

**Background:** Acetylation of tubulin is known to play an important role in the stabilization of microtubules. Kidney ischemia/reperfusion (I/R) is a major cause of acute renal failure. I/R causes damage to the cytoskeleton in the tubular epithelial cells. Acetylation of α-tubulin can directly affect the function of tubulo-interstitial cells after I/R injury using western blotting and immunohistochemical staining. Mice were subjected to either 30 min of ischemia or sham-operation. Kidneys were harvested at various times after ischemia.

Acetylation of α-tubulin expression dramatically decreased 24 hours after ischemia and then gradually increased over time. However, total α-tubulin expression was not significantly changed after I/R. In normal kidney, immune-reactivities of kidney epithelial cell to acetylated α-tubulin antibody were different in tubules; the orders were the collecting duct, distal tubules and the proximal tubule. Twenty-four hours after ischemia, acetylated α-tubulin expression increased in the proximal tubule and the distal tubule with strong expression in the nuclei of the tubular cells. In the glomerulus, acetylated α-tubulin was also observed and the expression was very strong in the podocyte and Bowman’s capsule. Twenty-four hours after ischemia, acetylated α-tubulin expression in the proximal tubule was lower than that of normal cells. Nine days after ischemia, acetylated α-tubulin expression in the podocyte and interstitial cell increased. Expression of α-tubulin acetytransferase-1 (αTAT1), an enzyme involved in acetylation of α-tubulin, continuously decreased after ischemia. Histone deacetylase 6 (HDAC6), an enzyme involved in deacetylation of tubulin, also decreased after ischemia.

**Conclusions:** Ischemia/reperfusion reduced tubulin acetylation in renal tubular cells, suggesting that I/R-induced decrease of tubulin acetylation is associated with reduction of stability of microtubule in cells.

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

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**FR-0268**

**Hypertension Aggravates Acute Kidney Injury (AKI) and Accelerates Progression to Chronic Kidney Disease (CKD)**

Robert Grote, 1 Anja Thorenz, 1 Falka Gueler, 1 Katja Hupeer, 2 Song Hong, 1 Hermann G. Haller, Jan H. Braesen. 4

**Background:** Acute kidney injury (AKI) results from ischemia/reperfusion (I/R) and toxic injury in the kidney. AKI is often associated with cardiovascular complications. The aim of this study was to investigate the link between hypertension and AKI in a mouse model of AKI. The results showed that hypertension significantly aggravated AKI and accelerated the progression to chronic kidney disease.

**Methods:** Male Sprague-Dawley rats were divided into four groups: control, hypertensive, AKI, and hypertensive AKI. The hypertensive group received bilateral renal artery stenosis (BRS) for 12 weeks, while the AKI group was treated with furosemide for 24 hours. The hypertensive AKI group received both BRS and furosemide. Renal function was assessed by measuring urinary creatinine and blood pressure was measured by tail cuff method.

**Results:** The hypertensive AKI group had significantly higher blood pressure and lower renal function compared to the other groups. The histological analysis showed more severe tubular and interstitial injury in the hypertensive AKI group compared to the other groups.

**Conclusions:** Hypertension significantly aggravates AKI and accelerates the progression to chronic kidney disease. These findings highlight the importance of managing hypertension in patients with AKI to prevent the development of chronic kidney disease.

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

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**FR-0269**

**Pericyte MyD88 Controls Inflammatory and Fibrotic Responses to Kidney Injury**

Irina Alexandra Lea, 1 Ivan G. Gomez, 1 Bryce Gordon Johnson, 1 William A. Altermeier, 1 Jeremy Stuart Duffield. 1

**Background:** Pericytes, a type of smooth muscle cell, play a crucial role in regulating blood vessel tone and microenvironment. However, the role of pericytes in kidney injury is not fully understood. The aim of this study was to investigate the role of pericytes in kidney injury.

**Methods:** Male C57BL/6 mice were subjected to unilateral ischemia reperfusion (UIR) injury. Pericyte-specific MyD88 knockout mice and wild-type littermates were compared.

**Results:** Pericyte-specific MyD88 knockout mice had significantly worse renal function and tubulointerstitial injury compared to wild-type littermates.

**Conclusions:** Pericyte MyD88 plays a critical role in regulating inflammatory and fibrotic responses to kidney injury.

**Funding:** Government Support - Non-U.S.
Background: Ischemia reperfusion injury (IRI) of the kidney leads to acute kidney injury (AKI) and frequently precipitates the development of tubulointerstitial fibrosis. Bone morphogenic protein (BMP) signaling has been implicated in the pathogenesis and progression of the disease, but its tubular-specific role is unclear.

Methods: We induced IRI in mice by clamping the left renal pedicle for 25 minutes. The severity of IRI was determined by histology scoring, elevated mRNA expression of renal injury markers NGAL and KIM-1 and increased urinary NGAL (uNGAL) excretion 24h post-ischemia. Activation of canonical BMP signaling was detected by nuclear pSmad1/5/8 immunostaining and Western blotting. To achieve a doxycycline-dependent Cre-mediated inactivation of BMP receptor 1a (Bmpr1a) in renal tubules, we generated Pax5rtTA.LC1.Bmpr1a Δ/Δ mice (Bmpr1a Δ/Δ mice).

Results: Canonical BMP activity, as revealed by pSmad1/5/8, was widely detected in healthy wild-type (wt) mouse kidney tubules. IRI caused a sustained injury in wt kidneys as shown by elevated NGAL and KIM-1 expression and increased uNGAL excretion. In parallel, we observed a transient decrease of pSmad1/5/8 with minimal activity at 48 hours and a subsequent re-activation at 7 days post-ischemia. Bmpr1a Δ/Δ mice displayed normal renal tissue morphology and renal functions at baseline. Following IRI, Bmpr1a Δ/Δ mice exhibited improved initial injury similar to controls, but at 7 days post-ischemia, the expression of collagen IV and TGF-β1 were significantly up-regulated in Bmpr1a Δ/Δ kidneys compared to controls. Unlike controls, Bmpr1a Δ/Δ mice failed to reactive tubular pSmad1/5/8 activity at 7 days after injury. 21 days following IRI, Bmpr1a Δ/Δ kidneys displayed an increased percentage of tubulointerstitial fibrosis compared to controls.

Conclusions: Tubular Bmpr1a-dependent Smad1/5/8 signaling is transiently decreased after renal IRI and its reactivation limits the progression of tubulointerstitial fibrosis.

FR-P0273
PNUTS (Phosphatase 1 Nuclear-Targeting Subunit) is Down-Regulated in Acute Kidney Injury and by Aging, and Regulates Cell Cycle, Fibrosis, DNA Damage of Renal Tubular Cells

Background: PNUTS (phosphatase 1 nuclear-targeting subunit, also known as PPP1R10) has recently reported to be regulated in cardiac aging and play roles in DNA damage. Aging and fibrosis play crucial roles in AKI to CKD transition, however the precise mechanism is not known. Because the biological role of PNUTS in aged kidney, fibrosis, and cell cycle in AKI is poorly understood, we studied the regulation and the functional roles of PNUTS in AKI and aging.

Methods: We used an in vivo mice aristolochic acid (AA)-induced AKI model and cultured renal tubular cells (NRK-52E cells). To assess aging effects, we evaluated PNUTS expression, renal function, and renal fibrosis in AA-induced AKI model in different aged mice (20-, 50- and 90-week-old). To elucidate the function of PNUTS, cell cycle regulation (by FACs), DNA damage (by gammaH2AX expression), and fibrosis (by CTGF expression) were examined in NRK-52E cells transfected with siRNA for PNUTS or PNUTS expression vector.

Results: In mice with AA-induced AKI, protein and mRNA expression of PNUTS were reduced compared with control mice. Moreover, PNUTS expression were decreased in accordance to aging. Reduction of renal function and renal fibrosis were more apparent in aged AKI mice. Immunohistochemical examination revealed the reduced expression of PNUTS in the proximal tubular cells in AA-induced AKI. PNUTS mRNA and protein expression showed a dose-dependent reduction by H2O2 in NRK-52E cells. Overexpression of PNUTS reduced H2O2-induced caspase3 activity and apoptotic (TUNEL positive) cell number. Transfection of siPNUTS significantly increased G2/M phase cell cycles, CTGF expression, and DNA damage.

Conclusions: These results indicate that PNUTS expression was reduced in AA-induced AKI and in aged mice. Expression of PNUTS was partially regulated by oxidative stress. PNUTS regulates cell cycle, CTGF expression, DNA damage, and apoptosis in NRK-52E cells. These results suggest that regulation of PNUTS may play a key role in the pathophysiology of AKI and age-related renal damage.

FR-P0274
Class Ia HDAC Inhibitors Restore BMP-7 Expression and Inhibit the Pathogenesis of Renal Fibrosis following Chronic Renal Injury

Background: BMP-7 is a potent anti-fibrotic cytokine that is also required for the repair of renal injuries. However, chronic renal injury leads to the loss of BMP-7 and fibrotic response. We investigate molecular mechanisms that lead to the loss of BMP-7 expression and examine potential therapeutic strategies for stimulating the innate reparative mechanisms of the kidney.

Methods: BMP-7 expression was studied in vitro in normal and diseased kidney (IMCD cells and in vivo in rats, dogs, and in patients of unilateral ureteral obstruction, UUO). The therapeutic effects of broad spectrum histone deacetylase (HDAC) inhibition with Trichostatin A (TSA) and Class Ia HDAC inhibition with MS-275 were evaluated by assessing renal pathology.

Results: MS-275 results in an 83.1% decrease in BMP-7 mRNA expression that is paralleled by a 63.0% decrease in the acetylation of histone proteins in the proximal Bmp7 promoter, a process that results in gene repression. These changes are HDAC-dependent and blocked by treatment with TSA. An in vitro pharmacological screen in IMCD cells revealed that MS-275 stimulates BMP-7 expression, while inhibitors of other HDAC isoforms have no effects. These results were confirmed by using siRNA-mediated genetic ablation to demonstrate specificity and chromatin immunoprecipitation to show binding of the Class Ia HDAC proteins HDAC1 and HDAC2 to the Bmp7 promoter. MS-275 also stimulates TGF-β-dependent pro-fibrotic genes of BMP-7 in vitro by suppressing the expression of the TGF-β-dependent pro-fibrotic genes COL1α1 and asdBα by 68.2% and 97.6%, respectively.

Conclusions: These findings demonstrate that HDAC1 and HDAC2 are responsible for the loss of BMP-7 expression and its renal protective functions in the injured kidney. Furthermore, our study suggests that Class I HDAC inhibitors have a tremendous therapeutic potential for stimulating kidney repair and inhibiting disease progression following chronic renal injury.

Funding: NIDDK Support, Private Foundation Support

FR-P0275
Gli2 in Perivascular MSC Is Required for Kidney Fibrosis and Can Be Targeted Pharmacologically

Background: We recently demonstrated that perivascular mesenchymal stem cell (MSC)-like cells are defined by expression of Gli2 and are critical myofibroblast precursors. We now investigate the role of Gli transcriptional activators in myofibroblast progenitors during kidney fibrosis and value as therapeutic targets.

Methods: We utilized mouse genetics, drug binding, RNAi and retroviral overexpression to dissect the roles of Gli1 vs. Gli2 in myofibroblast activation and fibrosis. We pharmacologically targeted Gli proteins with Darniparsin, an arsenville, and GANT61, a small molecule Gli inhibitor. We evaluated them in two separate mouse CKD models. We measured hedgehog pathway activity and expression of Gli in human kidney fibrosis specimen.

Results: In vitro knockdown of Gli1 had no appreciable effect whereas knockdown of Gli2 induced a G0/G1 cell cycle arrest of murine fibroblasts. Conversely, Gli2 overexpression rescued this cell-cycle effect and drove proliferation. In vivo, knockout of Gli1 showed no effect on fibrosis severity after UUO whereas either conditional knockout of Gli2 or overexpression of the Gli3 repressor in Gli1+ mice pericytes ameliorated fibrosis and induced a G1/G0 cell cycle arrest specifically in myofibroblasts, consistent with our in vitro results. We show that darniparsin directly binds to Gli2, lowers Gli2 protein levels and induces a G0/G1 cell cycle arrest. This effect of darniparsin absolutely requires Gli2, and Gli2 overexpression rescued the cell cycle defect. When administered in a therapeutic dosing strategy after UUO or IRI, darniparsin potently reduced Gli1 and Gli2 expression, fibroblast-specific protein 1-like 1 (Fsp1-like 1) expression, Gli1-dependent TGF-β-dependent pro-fibrotic genes (SMA, TGF-β, CTGF, COL1α1), structurally unrelated to darniparsin, showed the exact same effects. In human kidneys with fibrosis there is strong upregulation of Gli1 and Gli2 mRNA, suggesting this pathway is conserved in humans.

Conclusions: Gli2 is a critical driver of myofibroblast proliferation and a novel therapeutic target in kidney fibrosis.

Funding: NIDDK Support

FR-P0276
Klotho Influences the Fate of Fibrosis in Cardio-Renal Protection

Background: Soluble Klotho is an endogenous hormone produced predominantly by extracellular domain shedding of membrane Klotho in the kidney. Although Klotho is not thought to provide cardio-renal protection through its regulation of ion transport and growth factor signaling, specific cellular localization and function of Klotho in the normal and diseased kidney are not clearly defined.

Methods: We evaluated Klotho expression and localization in human and mouse kidney via immunohistofluorescence (ISH), immunohistochemistry (IHC) or RNAseq. Cardio-renal protective effects of soluble human Klotho administration were studied in mouse unilateral ureteral obstruction (UUO; 5 day) and isoproterenol-induced cardiac hypertrophy (ISO, 5 mg/g/l x 10 days) models.

Results: In normal adult human kidney (fresh nephrectomy and autopsy, n=9), Klotho was highly expressed in distal tubules (DT) and in both cortical and outer medulla collecting ducts (CD). Proximal tubule and podocyte expression was low but detectable. Following UUO, renal Klotho mRNA was decreased 61% and protein content was reduced greatly in the remaining renal vs sham kidney. Klotho treatment (10 μg/kg, QD, IP) attenuated UUO-induced tubulointerstitial fibrosis (picrosirius red stain, n=10) by 67% (*p<.05) and...
biomarker mRNA (40.4%±6.2%; 25.1±5.5%; 16.0±3.7%) vs Vehicle control. In the ISO model, IRX-injected mice showed significantly increased cardiac hypertrophy (HW/BW; n=6): 5.4±1.0 (p≤0.01) in Klotho- vs 5.8±0.8 in Vehicle control.

Conclusions: Klotho is highly expressed in normal human and mouse distal nephron. Klotho mRNA and protein are reduced in preclinical models of cardiac and renal disease. Development of a combinatorial Klotho antagonist severity of pathology and biomarker expression in the UUO model of renal fibrosis and ISO-induced cardiac hypertrophy. Klotho pharmacotherapy has the potential to prevent CKD progression as well as the progression of extra-renal Klotho-dependent diseases.

**FR-P0277**

**Kidney Interstitial Cell Derived Tenascin C Plays an Important Role in Promoting Injury-Repairing of the Kidney by Stimulating Cell Proliferation**

Min Zhang, Qionghong Xie, Xiaoyi Mao, Da Shang, Chuanming Hao. *Div of Nephrology, Huashan Hospital, Shanghai, China.*

**Background:** Tenascin-C (TNC) is a glycoprotein expressed in extracellular matrix during development and injury repairing. This study explored the role of TNC in acute kidney injury (AKI).

**Methods:** A TNC promoter driven inducible CreERT2 knock-in mouse with EGFP reporter (IRE6-EGFP) as generated (TNC-CreERT2;EGFP). AKI was induced by 40 minutes of ischemia followed by reperfusion in unilateral nephrectomized mice (UN+UiR). Cell lineage tracing was conducted in TNC-CreERT2;R26-tdTomato mice to examine the origin of TNC expressing cells. The effect of TNC on cell proliferation was examined using a cell count kit in cultured HK2 cells. TNC expression was also examined in human biopsies with IRB approval.

**Results:** In normal kidney, TNC was restricted in renal papilla in both mice and human. Following IR, TNC was markedly induced in renal cortex, particularly in injured areas. TNC reporter showed that induced TNC expression is localized in interstitial cells, but not tubular epithelial cells. TNC induction was also shown in human biopsies with IRB approval.

**Conclusions:** TNC is induced in renal interstitial cells after IR-induced AKI, protecting the kidney from injury. The protective effect of TNC on AKI may be associated with promoting renal recovery by stimulating epithelial cell proliferation.

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

**FR-P0278**

**TAZ and YAP Are Mechanoregulators of TGF-β Smad Signaling and Renal Fibrogenesis**


**Background:** Fibrosis is a final common injury pathway responsible for the progression of most forms of CKD, for which no specific treatments exist. Driven largely by TGF-β signalling, fibroblast-myofibroblast transition is crucial for fibrogenesis. While it is known that fibroblast activation is mechanosensitive, with soft matrix akin to a healthy kidney, fibrogenesis of most forms of CKD, for which no specific treatments exist. Driven largely by TGF-β signalling, fibroblast-myofibroblast transition is crucial for fibrogenesis. Here, our aim was to examine how stiffness regulates TGF-β signalling via TAZ/YAP, and to test if TAZ/ YAP inhibition can attenuate renal fibrosis.

**Methods:** The effects of matrix stiffness on TAZ/YAP localization and TGF-β-Smad signalling were examined in rat renal fibroblasts (NRK49Fs) cultured on soft (2 kPa) and stiff (100 kPa) gels. To test the effect of TAZ/YAP inhibition, NRK49F cells and mice were treated with verteporfin (VP), a drug used as a masacural degeneration treatment with retinal disease in animal models.

**Results:** In NRK49F cells, stiff matrix resulted in nuclear TAZ/YAP localization and enhanced TGF-β signalling. On growth on soft matrix, contrast, reduced TAZ/ YAP nuclear localization, and impaired TGF-β-induced Smad2/3 nuclear accumulation and transcriptional activity. Verteporfin treatment of TAZ/YAP-overexpressing cells resulted in a dramatic loss of TAZ/YAP localization, leading to a significant inhibition of TGF-β-Smad signaling. VP-induced TAZ/YAP loss also enhanced prostatesmal Smad2/3 degradation following TGF-β stimulation. *In vivo*, VP similarly reduced renal TAZ/YAP and Smad2/3 levels in UUO mice, leading to diminished myofibroblast accumulation and interstitial collagen deposition.

**Conclusions:** Our data suggest that fibrogenesis is regulated by a novel mechanism through stiffness that, through control of the mechanosensory proteins TAZ and YAP, regulates TGF-β-Smad signaling. Furthermore, we speculate verteporfin as a potential anti-fibrotic treatment that interferes with this pro-fibroblast-mechanochemical synergy.

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

**FR-P0279**

**Targeted Deletion of Numb from Proximal Tubules Attenuates Interstitial Fibrosis by Mitigating G2/M Arrest**

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**Background:** Progressive tubulointerstitial fibrosis (TIF) is the final common pathway leading to end stage renal disease. Tubular epithelial cells (TECs) have a crucial role in the pathogenesis of TIF. Numb is a multifunctional protein involved in diverse cellular processes. However, little is known about the physiologic and pathologic role of Numb in kidney.

**Methods:** We examined the expression and distribution of Numb in normal adult mouse kidney as well as in mouse model of renal fibrosis induced by unilateral ureteral obstruction (UUO). Here we report for Numb’s role in renal fibrosis, we generated a conditional knockout mouse model in which Numb is selectively ablated from proximal tubules (PEPCK-Numb-KO). To confirm the role of Numb in regulating cell cycle, Numb was overexpressed in NRC2 cells by infecting with a Numb adenovirus (Ad-Numb) and endogenous Numb was knocked down by siRNA in HK-2 cells before aristolochic acid (AA) treatment. To examine the role of p53 in Numb-induced G2/M arrest, Ad-Numb infected HK-2 cells were incubated with pifithrin-α, a p53 inhibitor.

**Results:** Numb is expressed in renal tubules and glomeruli. The expression of Numb in renal tubules was significantly increased after UUO. After UUO, PEPCK-Numb-KO mice exhibited significantly attenuated TIF. Ectopic expression of Numb increased the fraction of cells in G2/M stage and upregulated the expression of TGF-β1 and CTGF in NRC2 cells. Knocking down endogenous Numb attenuated AA-induced G2/M arrest and profibrotic cytokines production. Furthermore, G2/M arrest and expression of profibrotic cytokines were significantly reduced in PEPCK-Numb-KO mice after UUO. Inhibiting p53 activity dramatically mitigated Numb-induced G2/M arrest and profibrotic cytokines production.

**Conclusions:** In summary, our studies demonstrate that Numb has a profound effect on promoting G2/M arrest of TECs through stabilizing p53 protein. Depletion of Numb markedly attenuates G2/M arrest of proximal tubules which in turn reduces TIF. Collectively, these data indicate that targeting Numb might be a novel therapeutic approach for the treatment of fibrotic kidney diseases.

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

**FR-P0280**

**Identification of a New Aldosterone Synthase Inhibitor with Anti-Fibrotic Activity in Animal Models**


**Background:** The renin-angiotensin-aldosterone system (RAAS) plays a critical role in renal physiology. Inhibitors of ACE and ARBs are currently the mainstay in the treatment and management of the chronic kidney disease (CKD). Despite initial success in reducing aldosterone, concentrations return to pretreatment levels in 30-40% of patients. This “aldosterone escape” significantly limits the therapeutic effectiveness. Through mineralocorticoid receptor dependent and independent processes, aldosterone is thought to directly accelerate renal damage by sustaining inflammation and fibrosis. An attractive approach to deal with aldosterone escape is to inhibit aldosterone synthase (AS), the enzyme responsible for aldosterone production (encoded by the CYP11B2 gene).

**Methods:** We have identified a promising series of potent and selective small molecule inhibitors of AS. Lead compound ANG3586 has 7 nM potency against AS and excellent selectivity against other P450 enzymes. It is orally bioavailable in rodents and appears to be well tolerated. ANG3586 was tested in the rat remnant kidney model (25 mg/kg, po, bid) and the mouse unilateral ureteral obstruction (UUO) model (25 mg/kg, po, bid, ten days). In vivo, rats treated with vehicle or ANG3586. The elevated blood pressure in 5/6 nephrectomized animals was reduced to normal by compound treatment. ANG3586 also markedly reduced kidney collagen content and improved renal histology. Renal function, as determined by urine BUN and creatinine levels, urine albumin to creatinine ratio and urine NGAL, was found to be markedly improved. In the mouse UUO model, ANG3586 reduced the increase in kidney weight, kidney collagen and alpha-smooth muscle actin staining. Since UO does not result in distinctly increased blood pressure, the anti-fibrotic activity appears independent of blood pressure lowering activity of ANG3586.

**Conclusions:** Taken together, ANG3586 shows promise as a potential novel anti- fibrotic agent.

**Funding:** NIDDK Support

**FR-P0281**

**Tubulointerstitial Fibrosis Increases Peritubular Capillary Permeability and Induces Subsequent Hypoxia**

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**Background:** We previously showed that folic acid-induced tubulointerstitial injury significantly increased peritubular capillary permeability. In this study, we investigated whether the administration of folic acid induces the expression of peritubular capillaries and oxygen supply changes contribute to this cross-talk of tubular to glomerular injury.

**Methods:** We identified L-carcinofaiceae, which have carcinoeaease collagen in the collagen I promoter, were mated with Neph25 mice, which express human CD25 receptor on podocytes, and develop glomerulocarcinoma when immunotoxic in mice. Treated were fed with folic acid (FA, 240mg/kg BW, i.p.). At day 42,
mice were sacrificed to assess interstitial fibrosis, peritubular capillary number (CD31 positive), and collagen I were increased in FA compared to VEH (picrosirius red area, FA 14.5 ±1.6 vs. VEH 31.6±5.1×10⁴, p < 0.05). Interstitial pathological changes were assessed in tissue sections stained with Collagen I and Masson's trichrome. The expression of Col1A1 and Collagen I were examined by Western blot and qPCR. Renal expression fibrotic factors, including renal fibrosis. Excess deposition of extracellular matrix (ECM) components including collagen is the eponymous lesion of renal fibrosis. Results: Wild-type C57BL/6 mice, at the age of 6-9 weeks, were fed with either standard rodent chow or HM diet. After 2 weeks on the diet, mice were sacrificed. Kidney sections were stained with antibodies against CD31 or Collagen I and Masson's trichrome. The expression of Col1A1 and Collagen I were examined by Western blot and qPCR. Renal pathological changes were assessed in tissue sections stained with Collagen I and Masson's staining. OCC-2 cells were transduced with pCol-GL3 reporter plasmid, pRL null together with siG9a or Flag-tagged G9a to examine the promoter activity of COL1A1. The level on G9a and H3K9me2 on the promoter of COL1A1 was assessed by CHIP assay. Conclusions: We demonstrated that elevated concentration of Hcy induced the expression of collagen type I in cultured HK-2 cells as well as in kidney tissue of Hcy mice. Meanwhile, Hcy inhibited the expression of histone methyltransferase G9a. Mechanistically, silencing endogenous G9a by siRNA enhanced the promoter activity of COL1A1 in HK-2 cells. Conversely, overexpression G9a inhibited the promoter activity of COL1A1. CHIP assay demonstrated that G9a binds to the promoter-less restrictive silencer element (NRESE) on the promoter of COL1A1. The level on G9a and H3K9me2 on the promoter of COL1A1, led to upregulation of COL1A1. These results show that homocysteine induces collagen I expression by downregulating histone methyltransferase G9a and provide a novel mechanism on explaining how Hcy promotes ECM production. Funding: Government Support - Non-U.S.

FR-PO283

The Podocyte Adhesive Exhibits Matrix Ligand Specificity with Implications for Glomerular Disease

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Background: Adhesion at both the podocyte slit diaphragm and podocyte-extracellular matrix (ECM) interface is essential glomerular filtration barrier integrity. These structures converge onto many of the same signalling pathways, including those controlling the actin cytoskeleton. Podocytes adhere to laminin-521 in the glomerular basement membrane via integrin α3β1 and evidence suggests that attachment to collagen IV is upregulated in disease states. Whether changes in ECM ligand alter podocyte adhesion signalling remains unclear.

Methods: We analysed podocyte morphology following engagement of either laminin-521 or type IV collagen (α1α1α2) and isolated basolateral adhesion complexes for MS was generated. These cell phenotypes were enhanced with overexpression of the key slit diaphragm protein nephrin. The composition of isolated adhesion complexes was determined by ECM ligand and nephrin expression status. MS and protein interaction network mapping highlighted PKCs as a key signalling node in laminin adhesion complexes. Analysis of nephrin-nephrin complexes highlighted significant overlap with ECM adhesion signalling, suggesting crosstalk mechanisms.

Conclusions: In human podocytes we discovered that both ECM ligand and overexpression of nephrin influences morphology, adhesion complex composition and intracellular signalling. Enhanced understanding about the pathways that control podocyte adhesive responses may ultimately inform therapeutic strategies to correct or repair glomerular barrier function. Funding: Private Foundation Support

FR-PO284

Low-Density Lipoprotein Receptor-Related Protein 5 Drives Tubulointerstitial Fibrosis via Regulation of TGF-β Signaling

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Background: Low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor of the canonical Wnt/b-catadin pathway, was recently reported to drive idopathic pulmonary fibrosis through activating β-catenin. In this study, we examined the potential role of LRP5 in the regulation of TGF-β signaling in tubulointerstitial fibrosis.

Methods: LRP5-deficient (Lrp5−−) mice and age-matched wild-type (WT) mice were subjected to unilateral ureteral obstruction (UUO). Renal expression fibrotic factors, including α-SMA, CTGF, collagens and fibronectin, was quantified by picro-sirus red staining, western blot analysis and immunostaining. Primary tubular epithelial cells (PTECs) were cultured from Lrp5−− mice and WT mice. Co-Immuno precipitation was performed in a human proximal tubular epithelial cell line (HKC-8) over-expressing LRP5 and TGF-β receptors. Results: Lrp5−− mice with UUO showed ameliorated collagen I fibrosis and alleviated TGF-β signaling compared with WT mice with UUO. However, activation of the Wnt-β-catenin signaling was not different between Lrp5−− mice and WT mice, indicating that attenuated tubulointerstitial fibrosis in Lrp5−− mice was not due to mitigated activation of the fibrotic Wnt-β-catenin pathway. Instead, LRP5+/+ kidneys displayed alleviated TGF-β signaling in comparison to that in WT/WW kidneys. Overexpression of LRP5 in HKC-8 resulted in enhanced TGF-β signaling including enhanced TGF-β driven transcriptional activity and elevated expression of fibrosis markers regulated by TGF-β signaling. Knock-down of LRP5 in HKC-8 cells diminished the activation of the TGF-β signaling pathway. Meanwhile, LRP5−−/− PTECs were subjected to UNO. In addition, immunoprecipitation assay demonstrated physical association between LRP5 and TGF-β receptor 1, suggesting that LRP5 might act as a co-receptor of the TGF-β signaling pathway in the regulation of tubulointerstitial fibrogenic process. Conclusions: LRP5 promotes tubulointerstitial fibrosis via regulation of the TGF-β signaling. This activity is independent of its role in the Wnt/β-catenin pathway. Funding: Other NIH Support - GM104934

FR-PO285

Loss of Endothelial Nitric Oxide Oxides Sma3 Linker Phosphorylation and Precedes Insulin Resistance in High-Fat Diet Induced Obesity

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Background: Deficiency of endothelial nitric oxide synthase (NOS3/enOS) confers susceptibility to diet-induced obesity and it’s complications. enOS-derived nitric oxide (NO) acts as a potent vasodilator, enhances insulin sensitivity and also inhibits inflammation. TGF-β/Smad signaling plays an important role in regulating glucose and energy homeostasis. Sma3 deficient mice are protected from diet-induced obesity and obesity-related kidney injury. This study investigated whether the loss of endothelial-derived NO promotes Sma3 activation, which precedes insulin resistance in high-fat diet (HFD) induced obesity.

Methods: C57BL6/J wild type, eNOS deficient (eNOS−/−) with C57BL6/J background mice were given HFD or normal diet (ND) treatment for 1, 3, 7 days and 4, 8 or 16 weeks. Results: Within 7 days of HFD treatment in WT mice, Western blotting showed a marked decrease in total eNOS level but it’s complications. NO derived NO promotes Smad3 activation, which precedes insulin resistance in high-fat diet (HFD) induced obesity.

Conclusions: Lrp5−−/− mice was not due to mitigated activation of the fibrotic Wnt-β-catenin pathway. Instead, LRP5+/+ kidneys displayed alleviated TGF-β signaling in comparison to that in WT/WW kidneys. Overexpression of LRP5 in HKC-8 resulted in enhanced TGF-β signaling including enhanced TGF-β driven transcriptional activity and elevated expression of fibrosis markers regulated by TGF-β signaling. Knock-down of LRP5 in HKC-8 cells diminished the activation of the TGF-β signaling pathway. Meanwhile, LRP5−−/− PTECs were subjected to UNO. In addition, immunoprecipitation assay demonstrated physical association between LRP5 and TGF-β receptor 1, suggesting that LRP5 might act as a co-receptor of the TGF-β signaling pathway in the regulation of tubulointerstitial fibrogenic process. Conclusions: LRP5 promotes tubulointerstitial fibrosis via regulation of the TGF-β signaling. This activity is independent of its role in the Wnt-β-catenin pathway. Funding: Other NIH Support - GM104934

FR-PO285

Low-Density Lipoprotein Receptor-Related Protein 5 Drives Tubulointerstitial Fibrosis via Regulation of TGF-β Signaling

Xueming He, Rui Cheng, Jian-xing Ma. Dept of Physiology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background: Low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor of the canonical Wnt-β-catenin pathway, was recently reported to drive idopathic pulmonary fibrosis through activating β-catenin. In this study, we examined the potential role of LRP5 in the regulation of TGF-β signaling in tubulointerstitial fibrosis.

Methods: LRP5-deficient (Lrp5−−) mice and age-matched wild-type (WT) mice were subjected to unilateral ureteral obstruction (UUO). Renal expression fibrotic factors, including α-SMA, CTGF, collagens and fibronectin, was quantified by picro-sirus red staining, western blot analysis and immunostaining. Primary tubular epithelial cells (PTECs) were cultured from Lrp5−− mice and WT mice. Co-Immuno precipitation was performed in a human proximal tubular epithelial cell line (HKC-8) over-expressing LRP5 and TGF-β receptors. Results: Lrp5−− mice with UUO showed ameliorated collagen I fibrosis and alleviated TGF-β signaling compared with WT mice with UUO. However, activation of the Wnt-β-catenin signaling was not different between Lrp5−− mice and WT mice, indicating that attenuated tubulointerstitial fibrosis in Lrp5−− mice was not due to mitigated activation of the fibrotic Wnt-β-catenin pathway. Instead, LRP5+/+ kidneys displayed alleviated TGF-β signaling in comparison to that in WT/WW kidneys. Overexpression of LRP5 in HKC-8 resulted in enhanced TGF-β signaling including enhanced TGF-β driven transcriptional activity and elevated expression of fibrosis markers regulated by TGF-β signaling. Knock-down of LRP5 in HKC-8 cells diminished the activation of the TGF-β signaling pathway. Meanwhile, LRP5−−/− PTECs were subjected to UNO. In addition, immunoprecipitation assay demonstrated physical association between LRP5 and TGF-β receptor 1, suggesting that LRP5 might act as a co-receptor of the TGF-β signaling pathway in the regulation of tubulointerstitial fibrogenic process. Conclusions: LRP5 promotes tubulointerstitial fibrosis via regulation of the TGF-β signaling. This activity is independent of its role in the Wnt-β-catenin pathway. Funding: Other NIH Support - GM104934
**FR-PO286**

HIF1α and HIF2α Both Mediate Glomerulosclerosis but Differentially Regulate the COL1A2 Promoter  

**Promoter** Bethany Baumann, Tomoko Hayashida, Xiaoyan Liang, H. William Schnaper. Northwestern Univ, Chicago, IL.

**Background:** TGFβ increases HIF1α and HIF2α levels in normoxia and both HIFs contribute to TGFβ induction of type I collagen in vitro, suggesting a potential role for HIFs in renal disease regardless of oxygen tension. Here, we studied the role of HIFs in mouse glomerulosclerosis (GS).

**Methods:** HIF1α-/- or +/+; bactin-Cre;ERT2, NEP52 mice express human Tac on podocytes. LM2B, a toxin/anti-Tac chimera, binds to Tac, ablatting podocytes to cause GS. Systemic Cre recombination was induced by tamoxifen at 4 weeks of age and LM2B injected after 9 weeks. Mice were sacrificed 4 weeks later HIF2α-/- or +/+ mice were generated on a 129 background and bred with PDKGFRβ-Cre mice to delete HIF2α from pericytes and mesangial cells. GS was induced by Adriamycin injection at 8 weeks of age. Mice were sacrificed 2 weeks later. Disease progression was analyzed by histology, scoring 50-100 glomerular/animal on a fibrosis scale of 0-4, and by qPCR for COL1A2 mRNA with laser-captured glomeruli. In vitro studies investigating a mechanism by which HIFs regulate COL1A2 promoter were also performed.

**Results:** HIF1α: Histologically, control mice scored 0.46 (+/- 0.12), diseased WT mice 3.13 (+/- 0.19), and diseased HIF1αKO mice 1.42 (+/- 0.28). Glomerular COL1A2 mRNA with LM2B injection was increased 3.4x over the healthy controls in WT, but only 1.9x with HIF1α KO. In vitro, TGFβ induced COL1A2 promoter activity by 2.4x, which was abrogated when a hypoxia response element (HRE) 335 bp 5′ to the transcription start site was mutated. By DNA precipitation assay, HIF1α binding to a -335 COL1A2 HRE probe was detected after TGFβ treatment. Interestingly, Smad3 also bound the -335 COL1A2 HRE probe in both TGFβ-treated cell lysate and whole kidney lysate from WT HIF1α NEP52 mice with GS. HIF2α; PDKGFRβ-Cre mice showed less GS than HIF2α-/- mice by histology. In vitro, HIF2α enhanced COL1A2 promoter activity independently of the -335 HRE. Instead, HIF2α increased the transcriptional activity of Smad3.

**Conclusions:** Both HIF1α and -2a contribute to the development of GS in mice. Out in vitro studies strongly suggest that HIF1α and -2a each enhance TGFβ-mediated fibrogenesis, but through distinct mechanisms.

**Funding:** NIDDK Support

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**FR-PO287**

MiR302a-3p Modulates Renal Epithelial-Mesenchymal Transition in DKD by Targeting ZEB1  

**Authors** Xiaoyan Liang, H. William Schnaper. Dept of Nephrology, Xiangya Hospital, Central South Univ, Kidney Inst, Changsha, Hunan, China.

**Background:** Recent study found that miRNAs are involved in diabetic kidney disease (DKD). The objective of this study is to determine the role of miR302a-3p in the process of renal epithelial-mesenchymal transition (EMT) in DKD.

**Methods:** The levels of miR302a-3p in the plasma of DKD patients were detected by realtime PCR and the relationship of miR302a-3p and UAE or eGFR were analyzed. Secondly, miR302a-3p expression was determined in HK-2 cells treated with high glucose for different time. And then miR302a-3p mimics and inhibitor were transfectated to HK-2 cells following exposure to high glucose and low glucose respectively. The expressions of ZO-1, vimentin and ZEB-1 were determined by realtime PCR and western blot.

**Results:** The expression of circulating miR302a-3p was significantly increased in the diabetes mellitus group (DM, n=22) compared with control (healthy persons, n=30) and then decreased in the early stage of diabetic nephropathy group (DNG, n=20). Furthermore, its expression in clinical diabetic nephropathy group (DNC, n=18) was decreased significantly compared with DM group. Circulating miR302a-3p expression had negative relevance with UAE and eGFR (p<0.0001). In contrast, plasma levels of Pro-C6, a biomarker of collagen Type III and VI turnover were strongly correlated with eGFR (p<0.0001). In advanced disease stages compared to early and mild stages. Plasma levels of Pro-C6, a marker for collagen type III degradation, were strongly correlated with eGFR (r=0.62, P=0.0001), with lower levels in advanced disease stages compared to early and mild stages. Plasma levels of Pro-C6, a marker for collagen type VI degradation, significantly increased with disease progression and strongly correlated with eGFR (p<0.0001). In contrast, plasma C3M and urinary Pro-C6 levels showed no correlation with renal function.

**Conclusions:** We identified two biomarkers of tissue turnover associated with ECM remodeling and subsequent fibrosis in the transplanted kidney leading to loss of renal function. As such they have great potential as early diagnostic markers for kidney allograft failure.

**Funding:** Other NIH Support - National Natural Science Funds of China (Grant No.81100515)

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**FR-PO288**

**Kruppel-Like Factor 15 Works as an Early Anti-Fibrotic Transcriptional Regulator in Angiotensin II-Induced Renal Fibrosis via Down-Regulation of Connective Tissue Growth Factor**  

**Authors** Xiaonan Cui, Xiangchen Gu, Xiang Gao, Changlin Mei, 1 Kidney Inst of PLA, Dept of Medicine, Changzheng Hospital, Second Military Medical Univ, Shanghai, China; 2Kidney Inst of PLA, Dept of Medicine, Changzheng Hospital, Second Military Medical Univ, Shanghai, China; 3Kidney Inst of PLA, Dept of Medicine, Changzheng Hospital, Second Military Medical Univ, Shanghai, China.

**Background:** Angiotensin II (Ang II) has been regarded as an important profibrogenic cytokine in renal fibrosis. One of the main targets of Ang II in renal fibrosis is CTGF. Krüppel-like factor 15 (KLF15) is recognized as an important negative transcription factor in renal fibrosis. This study is aimed to detect the possible role and mechanism of KLF15 in renal fibrosis induced by Ang II.

**Methods:** Firstly, mice were randomized into control group, Ang II group, Ang II+losartan group, the renal fibrosis levels and KLF15 were measured by Real-Time PCR and IMF methods respectively at 4 weeks or 6 weeks. Then NRK-49F were stimulated with Ang II and (or) infected with Ad-GFP-KLF15, and the expressions of KLF15, COL1A2, and extracellular matrix were detected by Real-Time PCR and Western Blot. CoIP and ChIP assay were also performed to investigate the relationship among coactivator P/CAF, transcription regulator KLF15, and CTGF promoter.

**Results:** The mRNA model of Ang II-induced renal fibrosis demonstrated a significant decrease in renal KLF15 expression at 4 weeks and progressive renal fibrosis at 6 weeks. Losartan effectively prevented the decrease in KLF15 expressions induced by Angiotensin II. Stimulated with Ang II, NRK-49F exhibited significant decreases in KLF15, accompanied by increased increase in CTGF and extracellular matrix. Losartan prevented the decrease in Ang II induced KLF15. Furthermore, overexpression of KLF15 inhibited Ang II induced CTGF in NRK-49F. CoIP and ChIP demonstrated KLF15 could directly bind to P/CAF, and repressed its recruitment to CTGF promoter.

**Conclusions:** These results unveiled that Ang II could downregulate KLF15 via AT1 receptor. Transcription regulator KLF15 is likely to inhibit Ang II induced CTGF by repressing coactivator P/CAF’s recruitment to CTGF promoter.

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

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**FR-PO289**

Biomarkers of Collagen Type III and VI Turnover Can Identify Renal Allograft Failure in Kidney Transplant Recipients  

**Authors** Federica Genovese,1 Signe Holm Nielsen,1,2 Daniel Guldager Kring Rasmussen,1,2 Morten Asser Karsdal,1,3 Stephen J.L. Bakker,1 Peter Olinga,1 Elisabeth G.D. Stribos,1 Henricus A.M. Matthews.1,2 Fibrosis Biology and Biomarkers, Nordic Bioscient, Herlev, Denmark; 3Kidney Inst of PLA, Dept of Medicine, Changzheng Hospital, Second Military Medical Univ, Shanghai, China; 4Southern Denmark Univ, Odense, Denmark; 5Univ of Groningen, Groningen, Netherlands.

**Background:** Chronic allograft loss poses a major problem in improving long-term survival in renal transplant recipients (RTR). Intestinal fibrosis and tubular atrophy are already present in 40% of kidney allografts 3-6 months after transplantation. Extracellular matrix (ECM) turnover levels, reflecting the onset of fibrosis, can be early and superior markers to detect early fibrosis in RTR. We evaluated a non-invasive tool measuring the plasma and urinary biomarker profile related to ECM turnover.

**Methods:** 78 patients attending the University Medical Center Groningen during one week for a routine check-up after kidney transplantation were enrolled in the study. Plasma and/or 24-hour urine samples were collected from 75 and 42 RTR, respectively. Afterwards, markers of collagen remodeling were determined by competitive ELISAs.

**Results:** There was no correlation between age or time after transplant and glomerular filtration rate (eGFR) in this population. Urinary levels of C3M, a marker for collagen type III degradation, were strongly correlated with eGFR (r=0.62, P=0.0001), with lower levels in advanced disease stages compared to early and mild stages. Plasma levels of Pro-C6, a marker for collagen type VI fibrosis, significantly increased with disease progression and strongly correlated with eGFR (r=0.62, P=0.0001). In contrast, plasma C3M and urinary Pro-C6 levels showed no correlation with renal function.

**Conclusions:** We identified two biomarkers of tissue turnover associated with ECM remodeling and subsequent fibrosis in the transplanted kidney leading to loss of renal function. As such they have great potential as early diagnostic markers for kidney allograft failure.

**Funding:** None

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**FR-PO290**

Hyaluronidase-2 Dependent Regulation of CD44 Variant Expression in Anti-fibrotic versus Pro-Fibrotic Cells  

**Authors** Soma Meran, Adam Midgley, Robert Steadman, Aled O. Philips. Nephrology, Cardiff Univ, Cardiff, United Kingdom.

**Background:** Hyaluronan (HA) is a GAG with increased expression in progressive renal disease, and its expression correlates with poor renal outcomes. The HA receptor (CD44) is a transmembrane protein that plays a role in the adhesion of cells and the regulation of extracellular matrix expression, thus playing an important role in the maintenance of tissue homeostasis. We have previously identified CD44v7 as a key mediator in the reversal of myofibroblast phenotype, but its mechanism is unknown. Here we investigate whether HA2 plays a regulatory role in alternative splicing of CD44v7/8 variant isoforms.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: Fibroblasts & renal epithelial cells were incubated with TGFβ1 to induce myofibroblast differentiation, and compared to cells incubated with a TGFβ1 & BMP2 to induce myofibroblast reversal. QPCR, confocal microscopy, ChIP, siRNA & plasmid overexpression were used to assess Hyal2 effects.

Results: Hyal2 was upregulated by both profibrotic (TGFβ1) & anti-fibrotic (BMP7) cellular treatments. However in profibrotic cells, Hyal2 was cytoplasmic, whereas in anti-fibrotic cells Hyal2 translocated to the nucleus. In profibrotic cells Hyal2 did not associate with CD44. In contrast in anti-fibrotic cells Hyal2 associated with CD44s at the nucleus, whilst CD44s/7-8 located to the cell surface. In anti-fibrotic cells Hyal2 nuclear translocation was increased CD44s/7-8 mRNA & protein expression. CD44s/7-8 was subsequently necessary for HA internalization and consequent reversal of myofibroblast phenotype. ChIP demonstrated association between Hyal2 and introns flanking the CD44s-7-8 exon nucleotide sequence similar to a2G splice facilitator. Moreover, Hyal2 inhibits endocytosed BMP7 directed activation of splice regulators SL2E & SRSF5.

Conclusions: Hyal displays nonenzymatic activity & translocates to the nucleus regulating expression of CD44s-7-8 splice variant, which is crucial for reversing myofibroblast phenotype. Hence Hyal is a novel splice regulator and a critical regulator in reversal of myofibroblast phenotype & fibrosis prevention.

FR-PO291 FGF Signaling Contributors to Podocyte Injury in Murine HIV-Associated Nephrupathy Koji Okamoto, Eisei Norii, Jeffrey B. Kopp. 1 Kidney Section, NIDDK, NIH, Bethesda, MD. 1 Dept of Nephrology, Endocrinology, Hemodialysis & Apheresis, Univ Hospital, The Univ of Tokyo, Tokyo, Japan.

Background: We reported that fibroblast growth factor receptor (FGFR), its ligand fibroblast growth factor 2 (FGF2), and their amplifying co-factor glypicans 5 (GPC5) play important roles in idiopathic nephritic syndrome and diabetic nephropathy (Okamoto, Nature Genetics, 2011). We have investigated the role of the FGF2 signal pathway in HIV-associated nephropathy (HIVAN).

Methods: FGF2 ligands and FGF expression were studied in a mouse podocyte cell line and HIVAN transgenic mice, both of which express the HIV accessory protein Vpr in the presence of doxycycline. To study FGF2 trapping in glomeruli, biotinylated FGF2 was administered intravenously and detected with fluorescent streptavidin. Vpr mice and control mice received FGF2 (5 mg/animal/weekly for 4 weeks) or FGF antagonist (PD173074,50 mg/animal/bi-weekly for 4 weeks).

Results: In cultured mouse podocytes FGF3 mRNA was increased 11-fold after Vpr induction. In Vpr mice compared with control mice, renal cortex FGF2 content was increased 3-fold, as assessed by ELISA. Intra-glomerular protein expression of FGF3 and GPC5 were increased detected by immunofluorescent staining. These results suggest that Vpr mouse glomeruli might have increased FGF2 binding capacity and so we tested the binding capacity of FGF2 in vivo. One hour after intravenous administration of biotinylated FGF2, more bioactive signal remained in glomeruli of Vpr mice compared with control mice (60% increase). Urine albumin/creatinine ratios (g/g) were significantly increased in FGF2-treated Vpr mice compared to untreated Vpr mice on day 14 (0.50±0.19 vs 2.3±0.6), day 21 (1.7±0.16 vs 18.7±5.1) and day 28 (1.87±0.44 vs 21.8±9.9). Further, the FGF antagonist diminished albuminuria in Vpr mice at day 21 (0.47±0.16 vs 1.7±0.16 g/g) and at day 28 (0.36±0.41 vs 1.87±0.44 g/g).

Conclusions: In a HIVAN mouse model, podocyte FGF2 expression increased protein expression of FGF2, FGF receptors and GPC5. Administration of FGF2 increased renal cortex FGF2 content was subsequently necessary for HA internalization and consequent reversal of myofibroblast phenotype & fibrosis prevention.

FR-PO293 Increased Expression of Complement C1 from Pericyte/Myofibroblasts Contributes to Renal Fibrosis via Activation of Wnt/β Catenin Signaling Sandhya Xavier, 1 Susan G. Landes, 1 Amandeep Bajwa, 1 Jing Yu, 2 Jeremy Stuart Duffield, 1 Didier Portilla. 1 Dept of Medicine and Center for Immunity, Inflammation and Regenerative Medicine, Univ of Virginia, VA; 2 Univ of Virginia; 2Blegen Ide.

Background: Pericytes/fibroblasts are progenitors of scar-forming cells known as myofibroblasts. We have characterized the inflammatory nature of pericytes/fibroblasts isolated from UUO mice. We have also shown that Wnt/β-catenin signaling is activated during kidney fibrosis. Role of complement C1 on pericyte function or in Wnt activation remains unknown.

Methods: We used the unilateral ureteral obstruction (UOO) and folic acid nephropathy models. Pericytes were isolated using magnetic beads containing anti-PDGFRB Receptor ab. Expression of C1 complex was examined by western blotting, immunofluorescence, and realtime-PCR in tissue and in cell lysates and supernatants obtained from pericytes cultured from sham, day3 and day10 UUO mice kidneys. To phosphatase reporter assays were used to study Wnt signaling.

Results: Expression of C1q chains a,b,c, as well as subunits C1r and C1s were increased during fibrosis along with increased expression of TGF-β, n-SMA and Wnt target genes wisp1 and 2. Immunostain showed C1q localization in the interstitial compartment of UOO but not in sham mice consistent with PCR and western blot data. In cultured pericytes, C1 complex component C1q protein was increased in culture supernatants of Day3 and Day10 but not in shamms. Expression of C1q proteins was absent in supernatants of UUO pericytes isolated from C1QKO mice. To phosphatase reporter assays for Wnt signaling showed that pericytes from UUO kidneys had pronounced activation of the reporter following Wnt3a treatment as compared to shams, and this effect was blunted in pericytes isolated from C1QKO mice.

Conclusions: We demonstrate both in vivo and in vitro that increased expression of the C1 complex occurs in response to kidney injury along with activation of Wnt signaling. Our in vitro and in vivo data, showing that inhibition of C1 complex using C1INH prevents renal fibrosis, we conclude that its inhibition in pericytes/fibroblasts leads to inhibition of Wnt activation and reduced renal fibrosis.

Funding: NIDDK Support, Veterans Administration Support

FR-PO294 The Role and Association of Inflammatory and Apoptotic Caspases in Tubulointerstitial Fibrosis Chun Zhang, You Ke, Hua Su. Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.

Background: Caspases are a family of cysteine proteases with pivotal functions in apoptotic and inflammatory signaling. According to their difference of structures and functions, two distinct types of Caspases protein in tubulointerstitial fibrosis (TIF) are not well characterized.

Methods: Unilateral Ureteral Obstruction (UUO) animal model was constructed on wild-type(WT) and caspase-1 knockout (KO) mice. In vitro study, the cultured tubular epithelial cell line NRK-52E (TECs) was employed and the expression of caspase-1 and caspase-3 was modulated by transfection of Lentiviral shRNA.

Results: In current study, we found both Caspase-1 and Caspase-7 protein levels were elevated in UUO WT mice. While in UUO mice with Caspase-1 KO background the increased Caspase-7 was suppressed significantly along with the minimized extracellular matrix accumulation which was demonstrated by western blot, immunohistochemistry and Masson’ trichrome staining. In vitro TGF-β1 simulation promoted the expression of Caspase-1 and Caspase-7 simultaneously in TECs. Notably, genetic deletion of either Caspase-1 or Caspase-7 could abrogate TGF-β1 driven TECs’ transdifferentiation and apoptosis. In addition, knocking down Caspase-1 or Caspase-7 upregulation in TGF-β1 treated TECs was consistent with in vivo study. However genetic deletion of Caspase-7 did not influence Caspase-1’s abundance.

Conclusions: Our observation firstly links inflammatory and apoptotic Caspases together in TIF and further elucidates Caspase-1 activation is an upstream event of apoptotic Caspase-7 induction during TIF and TECs’ transdifferentiation and apoptosis.

Funding: Government Support - Non-U.S.

FR-PO295 MAD2B-Sno-Smad3 Signaling Pathway Is Implicated in Fibroblast Activation and Tubulointerstitial Fibrosis Chun Zhang, Hui Zhang, Hua Su. Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.

Background: Mitotic arrest deficient protein MAD2B, an anaphase-promoting complex (APC)/cyclosome inhibitor, is indispensable for mitotic checkpoint control. Previously we found MAD2B was expressed in glomerular and tubulointerstitial compartment. In addition our data indicated MAD2B was involved in podocyte injury triggered by high glucose. But its role in renal fibrosis remains elusive.

Methods: The object of this study included patients with renal tubulointerstitial fibrosis (TIF) (secondary glomerulonephritis and interstitial nephritis were excluded) , Unilateral Ureteral Obstruction(UUO) mice and in vitro cultured tubular epithelial cell line (NRK-52E) and renal fibroblast cell line (NRK-49F). In vivo gene silencing of MAD2B was carried out by intrarenal Lentiviral gene delivery.

Results: We used the unilateral ureteral obstruction (UOO) and folic acid nephropathy models. Pericytes were isolated using magnetic beads containing anti-PDGFRB Receptor ab. Expression of C1 complex was examined by western blotting, immunofluorescence, and realtime-PCR in tissue and in cell lysates and supernatants obtained from pericytes cultured from sham, day3 and day10 UUO mice kidneys. To phosphatase reporter assays were used to study Wnt signaling.

Conclusions: Expression of C1q chains a,b,c, as well as subunits C1r and C1s were increased during fibrosis along with increased expression of TGF-β, n-SMA and Wnt target genes wisp1 and 2. Immunostain showed C1q localization in the interstitial compartment of UOO but not in sham mice consistent with PCR and western blot data. In cultured pericytes, C1 complex component C1q protein was increased in culture supernatants of Day3 and Day10 but not in shamms. Expression of C1q proteins was absent in supernatants of UUO pericytes isolated from C1QKO mice. To phosphatase reporter assays for Wnt signaling showed that pericytes from UUO kidneys had pronounced activation of the reporter following Wnt3a treatment as compared to shams, and this effect was blunted in pericytes isolated from C1QKO mice.

Conclusions: We demonstrate both in vivo and in vitro that increased expression of the C1 complex occurs in response to kidney injury along with activation of Wnt signaling. Our in vitro and in vivo data, showing that inhibition of C1 complex using C1INH prevents renal fibrosis, we conclude that its inhibition in pericytes/fibroblasts leads to inhibition of Wnt activation and reduced renal fibrosis.

Funding: NIDDK Support, Veterans Administration Support

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

422A
**Results:** By immunohistochemistry and western blot, it showed the expression of MAP2, a neuron-specific protein, in TIF patients and this was reduced in control type II neurons. Next we assessed the protein expression of the types of cells contributing to the elevated MADDAB abundance. It is well-known that TECs and fibroblast are the main culprits in TIF. Our data suggested that the overexpression of the TIF MADDAB may be due to the increased number of TECs. Conversely, the expression of the TIF MADDAB was reduced in control type II neurons. Furthermore, TGF-P1 induced fibroblast activation can be abrogated by MADDAB genetic deletion. Intriguingly, SmoN, a repressor of Smad3, was decreased in NRK-49F cells treated with TGF-C which could be alleviated by MADDAB knocking down. Consistently, in UUO mice the expression of SmoN was significantly decreased in the renal cortex accompanying with enhanced expression of Smad3. And locally genetic deletion of MADDAB by Lentiviral transfection preserved SmoN’s abundance and consequently suppressed SmoN signaling which finally dampened the fibroblast activation and ECM accumulation in UUO mice.

**Conclusions:** Our observation proposes that MADDAB participates in fibroblast activation and tubulointerstitial fibrosis by repressing SmoN and subsequently activating SmoN signaling pathway. Regulation of MADDAB-SmoN pathway may be a promising therapy for tubulointerstitial fibrosis. However, the regulatory mechanisms between MADDAB and SmoN still need further investigation.

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

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**FR-PO298**

**Losartan Reduces Renal Fibrogenesis by Up-Regulating Klotho in Uremic Rats**

**Edgar Maciquizin,** Josse Carla Paterno, Gabriel H. Pokorny, Mariana S. Perez, Nestor Schor, Miriam A. Bolim. *Nephrology, UNIFESP, Sao Paulo, Brazil.*

**Background:** Klotho is a transmembrane protein expressed mainly in the kidney. Soluble Klotho (sKlotho) is released into the serum and exerts its function as an endocrine factor with diverse functions through mechanisms involving Wnt and TGFβ1 signaling. Renal fibrosis is the end stage of the progressive chronic kidney disease (CKD) and renal klotho is markedly decreased in CKD patients. Renin angiotensin system (RAS) blockade is a relevant therapy to reduce CKD progression and the beneficial effects go further to the antihypertensive effect. The aim of this study was to investigate a possible link between RAS and Klotho by evaluating the effects of losartan on Klotho/Wnt signaling in 5/6 nephrectomy model of CKD in rats.

**Methods:** Adult male Wistar rats were underwent 5/6 nephrectomy (Nx). The Nx animals were separated into three groups: control, with no treatment (Nx), treated with losartan (LOS; 25 mg/kg/day, p.o.) or propranolol (PROP; 25mg/kg/day, p.o.). Results were compared with SHAM group. Blood pressure was measured by tail-cuff plethysmography. After 8 weeks, animals were sacrificed and the remnant kidney was removed to determine the renal expression of collagen, fibronectin, epithelial-to-mesenchymal transition (EMT) markers (FSP1 and α-SMA) and Klotho signaling (Klotho, Wnts and GSK3β) by real time PCR.

**Results:** Nx rats presented hypertension that was blunted by both losartan and propranolol. The expression levels of collagen and fibronectin were increased in Nx group which was reverted only in LOS group. The presence of the EMT markers, FSP1 and α-SMA, was observed in Nx group which was decreased with losartan treatment. Klotho was reduced in Nx animals and LOS but not propranolol significantly increased klotho expression. Nx animals showed upregulation of GSK3β, Wnt1 and Wnt3. LOS treatment prevented the increase in Wnt1 and GSK3β but not Wnt3.

**Conclusions:** These data suggest that the beneficial effect of losartan on renal fibrosis is independent of blood pressure reduction and may be, at least in part, due to upregulation of Klotho/Wnt signaling. Losartan induced no change in klotho expression. The interaction between the RAS and Klotho can inactivate the Wnt pathway.

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

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**FR-PO297**

**PBI-4050 Inhibits the Development of Renal Fibrosis in a Model of Tubulointerstitial Fibrosis**

**Ming-Zhi Zhang,** Lyne Gagnon, Raymond C. Harris. *1 Medicine, Vanderbilt Univ, Nashville, TN; 2ProMetic Biosciences, Laval, QC, Canada.*

**Background:** Kidney fibrosis occurs in chronic kidney diseases and leads to gradual loss of kidney function. Although the etiology of kidney fibrosis is multifactorial, there is increasing evidence linking chronic inflammation to kidney fibrosis. PBI-4050, a novel first-in-class orally active low molecular weight compound currently in phase II clinical trials, is an anti-fibrotic and anti-inflammatory drug that suppresses TGF-β1 signaling. Activation of epidermal growth factor receptor (EGFR) contributes to the development of renal fibrosis, and homologous transgenic mice with overexpression of an EGFR ligand, human hepatocyte-binding EGF (HB-EGF), in renal proximal tubule develop spontaneous tubulointerstitial fibrosis by 3–4 weeks of age. We examined whether PBI-4050 could prevent the development of renal fibrosis in homologous HB-EGF mice.

**Methods:** Homozygous HB-EGF mice on a C57BL/6 background were treated with PBI-4050 (200 mg/kg/day) by daily gavage gavage from 4 to 14 weeks of age. Serum and tissue were collected and homogenized. HB-EGF mouse kidney, ERK was activated in both proximal tubule epithelial cells (PTEC) and their surrounding interstitial cells. PBI-4050 treatment led to marked decreases in ERK activity in proximal tubule epithelial cells and interstitial cells, suggesting that PBI-4050 inhibits not only the EGFR-mediated ERK activation in PTEC, but also subsequent ERK activation in the interstitial cells, leading to inhibition of the development of renal fibrosis. PBI-4050 treatment significantly reduced the development of renal interstitial fibrosis. PBI-4050 caused marked decreases in renal macrophage infiltration (F4/80 staining) as well as neutrophil and eosinophil infiltration (MPO staining). In addition, PBI-4050 treatment reduced the expression levels of the pro-fibrotic and fibrogenic components including CTGF and TGF-β1, α-SMA (a marker of myofibroblasts), fibronectin, collagen I and collagen IV.

**Conclusions:** These studies suggest that PBI-4050 significantly inhibits the development of renal fibrosis in homozygous HB-EGF mice through multiple mechanisms, including through anti-inflammatory effects.

**Funding:** NIDDK Support, Pharmaceutical Company Support - ProMetic Biosciences
Results: In vitro treatment of TGF-β1-activated fibroblasts with EPC extract produced antifibrotic effects, but did not influence expression of endothelial markers. In two distinct models of renal fibrosis, unilateral ureteral obstruction (UUO) and chronic phase of folic acid-induced nephropathy (FAN), subcapsular injection of EPC extract to the kidney prevented and reversed accumulation of α-SMA-positive myofibroblasts and reduced expression of extracellular matrix proteins. Expression of cytokine TNF-α decreased and was enriched in LIF and VEGF. Only LIF was capable of inducing fibroblast-to-myofibroblast transition of TGF-β1-activated fibroblasts. In vivo subcapsular administration of LIF reduced the number of myofibroblasts, improved the density of peritubular capillaries, but did not affect the degree of interstitial fibrosis. Effects of LIF, as well as Hyper-IL-6, in the presence of TGF-β1 were mediated via gap-junction pathway resulting in induction of p53 and p21 and associated with open chromatin conformation.

Conclusions: EPC extract does not reverse endothelial-mesenchymal transition, but it prevents and reverses fibroblast-to-myofibroblast transition and renal fibrosis. The component of EPC extract, LIF, is capable of preventing development of the contractile phenotype of activated fibroblasts, but does not eliminate TGF-β1-induced collagen synthesis in cultured fibroblasts and models of renal fibrosis. LIF component of EPC extract is a participant of its antifibrotic effect, but not the sole one, as other yet undisclosed factors contribute to the antifibrotic effect of the extract.

Funding: NIDDK Support

FR-PO301 Mitochondrial Metabolic Switch to Glycolysis in Proximal Tubular Epithelial Cell in Fibrotic Kidneys Lei Jiang, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ; Nanjing, Jiangsu, China.

Background: Renal proximal tubule is susceptible to hypoxic injury since its reliance on aerobic oxidative metabolism. Mitochondrial dysfunction contributes to progression of chronic renal disease. However, the profile of the energy metabolism of renal tubule in different phases of fibrosis is uncertain, and the relationship between the change of energy metabolism and tubular epithelial cell damage is unclear.

Methods: Gene expression profiles related to energy metabolism of the proximal epithelial cell in fibrotic kidneys were analyzed. 2-Dexoyglucose (2-DG) was given to CD1 mice under UUO intraperitoneally. Primary tubular epithelial cells (PTC) cultured from normal CD-1 mice renal cortex was used. 2-DG (inhibitor of glycolysis), bromopyruvic acid (inhibitor of hexokinase), dichloroacetate acid (inhibitor of glycolysis), olignomic (inhibitor of oxidative phosphorylation), etomoxir (inhibitor of fatty acid oxidation), DON (inhibitor of glutaminase metabolism), PDZK1 RNAi or HEK1 siRNA was used in PTC with or without TGF-β1 stimulation. The oxygen consumption rate (OCR) and extracellular acidification rate (ECR) were detected by Seahorse Metabolic Analyzer.

Results: 1. Glycolysis was upregulated in the proximal tubule epithelium in fibrotic kidney. 2. Genes related to glycolysis were upregulated, however, genes related to oxidative phosphorylation, fatty acid metabolism and glutaminase metabolism were downregulated. The key limiting enzymes for glycolysis were upregulated in the fibrotic kidney. 3. 2-DG could block the renal fibrosis under UUO. 4. OCR was decreased under TGF-β1 stimulation in PTC, however, ECAR was increased after TGF-β1 stimulation. 5. Inhibiting oxidative phosphorylation, fatty acid oxidation or glutaminase metabolism could increase the lactate production in PTC. Lactate could directly induce PTC damage. 6. Inhibiting glycolysis could ameliorate the damage of PTC under TGF-β1 incubation.

Conclusions: The mitochondrial metabolism including oxidative phosphorylation, fatty acid oxidation and glutaminase metabolism is defective in proximal tubular epithelial cell in the fibrotic kidney. The metabolism switch is to glycolysis, and the glycolytic product lactate further aggravates the injury.

Funding: Government Support - Non-U.S.

FR-PO302 The Effects of CCN3/NOV on the Formation of Extracellular Matrix in Human Mesangial Cells Haifei Liu, Long Chen, Hong Liu, Bi-Cheng Liu. Dept of Nephrology, Zhong Da Hospital, Southeast Univ, Nanjing, Jiangsu, China.

Background: Glomerulosclerosis is characterized by mesangial cells proliferation and accumulation of extracellular matrix (ECM) in glomeruli. Mesangial cells actively participate in a variety of damage factors, leading to ECM deposition. ECM accumulation is the net result of the balance between synthesis and degradation. CCN3, a matricellular protein of the CYR61-CTGF-NOV (CCN) family, associates specifically with ECM. A recent study found that treatment with the matricellular protein CCN3 can block and/or reverse fibrosis development in obesity with diabetic nephropathy. However, whether CCN3 can alleviate the formation of glomerulosclerosis by inhibiting the production of ECM and/or promoting the degradation of ECM is still unknown. This study aims to explore the potential role of CCN3 in ECM accumulation of mesangial cells induced by TGF-β1.

Methods: Human mesangial cells lines were stimulated with TGF-β1 (2ng/ml) and CCN3 for different concentration (5, 50, 500 ng/ml) virtually blocked this TGF-β1 induced effect on them (P < 0.05). On the other hands, TGF-β1 downregulated MMP-2 and MMP-9 at mRNA and protein levels, whereas a 1-hour pretreatment of the cells with CCN3 for different concentration (5, 50, 500 ng/ml) enhanced the expression of MMP-2 and MMP-9 (P < 0.05).

Conclusions: This study identifies that CCN3 as a new actor alleviates the formation of glomerulosclerosis by inhibiting the production of ECM and promoting the degradation of ECM.

Funding: Government Support - Non-U.S.

FR-PO303 Spleen Tyrosine Kinase (Syk) Inhibition Suppresses Renal Fibrosis Through Anti-Inflammatory Effects and Down-Regulation MAPK-p38 Pathway Kuan-hsing Chen, Hsiang-Hao Hsu, Cheng-chieh Hung. Nephrology, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

Background: Spleen tyrosine kinase (Syk) is a 72-kDa, a member of the Src family of non-receptor tyrosine. The central role of Syk in signaling processes is known to be involved in adaptive immunity, but also in autoinflammatory and allergic disease. However, the possible role of the anti-fibrogenic properties in renal interstitial fibrosis had not been explored.

Methods: In vitro study: Cultured rat renal interstitial fibroblasts (NRK-49F) were stimulated with recombinant human TGF-β1 (1ng/ml) for different periods before harvesting. Alternatively, NRK-49F cells were pre-incubated with Syk inhibitor for 30 mins before TGF-β1 treatment. Total RNA was extracted for RT-PCR and total lyses were extracted for Western Blot analysis. In vivo study: UUO mice renal cortex was used. 2-DG (inhibitor of glycolysis), bromopyruvic acid (inhibitor of glutaminase metabolism), PDZK1 RNAi or HEK1 siRNA was used in PTC with or without TGF-β1 stimulation. The oxygen consumption rate (OCR) and extracellular acidification rate (ECR) were detected by Seahorse Metabolic Analyzer.

Results: Our results demonstrated that the inhibition of Syk in NRK49F cells inhibited the stimulation effect of TGF-β1 leading to fibroblast transition to the myofibroblast phenotype (upregulation of α-SMA) and extracellular matrix proteins accumulation, collagen type I, type IV. In addition, in UUO model, Syk inhibitor attenuated the tubulo-interstitial fibrosis and expression of α-SMA, collagen I and fibronectin in UUO kidney. The anti-fibrosis of Syk inhibitor in UUO model may be related to anti-inflammatory effects (down-regulate inflammatory cytokines and reduce macrophage infiltration). Moreover, the effects of Syk inhibition in inhibition of kidney myofibroblast activation by TGF-β1 were associated with down-regulation of MAPK-p38 pathway.

Conclusions: In conclusion, we demonstrated that Syk inhibitor ameliorates TGF-β1 induced kidney myofibroblast activation and also reduces the tubulointerstitial fibrosis in UUO mice. The mechanisms may be related to anti-inflammatory effects and down-regulate MAPK-p38 pathway.

Funding: Government Support - Non-U.S.
FR-PO305

BMP-7 Inhibits Renal Akt Signaling Debra F. Higgins, Catherine Godson, School of Medicine, Conway Inst, Univ College Dublin, Dublin, Ireland.

Background: Bone morphogenetic protein-7 (BMP-7), a member of the TGFβ superfamily, counteracts pro-fibrotic TGFB, and protects from fibrosis in acute and chronic renal injury models.

Methods: Using the chronic renal fibrosis model, unilateral ureteral obstruction (UUO), mice were treated with recombinant BMP-7 on signaling pathways involved in hypoxia and TGFβ-induced fibrosis. Mice undergoing UUO were treated with either vehicle or rBMP-7 (300ng/kg i.p.), kidneys were harvested on day 8 post-obstruction and analysed for markers of renal fibrosis and activation of SMAD, MAPK, and PI3K signaling.

Results: In response to UUO, SMAD1/5/8 activity was lost in vehicle-treated kidneys, yet maintained in BMP-7-treated kidneys. Collagen accumulation was significantly increased in obstructed kidneys of vehicle-treated animals compared with contralateral and this response was not observed in BMP-7-treated obstructed kidneys. Immunohistochemical analysis of type I, III, and IV collagen revealed that accumulation of type I collagen was significantly impaired in BMP-7-treated obstructed kidneys. Activation of SMAD2, SMAD3, ERK, p38 and Akt signaling pathways occurred during fibrogenesis and BMP-7 significantly attenuated SMAD3 and Akt signaling in vivo. In the kidney, inner medullary collecting duct and tubular epithelial cells are responsive to BMP-7. Analysis in mouse inner medullary collecting duct (mIMCD) and human tubular epithelial (HK-2) cells stimulated with either TGFβ or hypoxia (1% oxygen) to induce Akt activation provided further evidence that BMP-7 could specifically inhibit PI3K / Akt signaling.

Conclusions: These data demonstrate an important mechanism by which BMP-7 orchestrates renal protection through Akt inhibition and strengthens the argument for use of Akt inhibitors as anti-fibrotic therapeutics.

Funding: Pharmaceutical Company Support - Hoffmann La Roche, Government Support - Non-U.S.

FR-PO306

Prevention of Renal Interstitial Fibrosis by Simultaneous Deletion of Bax and Bak Hee-Seong Jung, 1 Babu J. Padanilam, 1, 2 Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE; 1Internal Medicine, Section of Nephrology, Univ of Nebraska Medical Center, Omaha, NE.

Background: Proximal tubular injury and apoptosis are key mediators of development of kidney fibrosis, a hallmark of chronic kidney disease. However, the molecular mechanism by which tubular apoptotic cell death leads to kidney fibrosis is poorly understood.

Methods: Here we tested the roles of Bax and Bak, two crucial proteins involved in intrinsic apoptotic cell death, in progression of kidney fibrosis. Mice with proximal tubule-specific Bax deletion, systemic deletion of Bak and dual deletion of Bax and Bak were subjected to unilateral ureteral obstruction (UUO).

Results: Dual deficiency of Bax and Bak inhibited tubular apoptosis and atrophy. Consistent with decreased tubular injury, dual ablation of Bax and Bak suppressed UUO-induced inflammation and kidney fibrosis with decreased tubular cell cycle arrest, expression of fibrogenic and inflammatory cytokines, and oxidative stress in the kidney. Bax or Bak deficiency was insufficient to prevent apoptosis and all other aforementioned malevolent effects, suggesting compensatory mediation by each in the other respective signaling pathways.

Conclusions: These data suggest that dual ablation of Bax and Bak in the kidney is required to prevent UUO-induced tubular apoptosis and the consequent kidney inflammation and fibrosis.

Funding: NIDDK Support

FR-PO307

Investigating the Role of Cilia in Regulating Fibrosis in the Kidney and Liver Using PKD Mouse Models Kurt Zimmerman, Cheng 'Jack' Song, Bradley K. Yoder, Cell, Developmental, and Integrative Biology, UAB, Birmingham, AL.

Background: Cystic kidney disorders are frequently caused by mutations in cilia associated proteins (intratubular lag transport, IFT) or ciliary signaling proteins (polycystin-1 or polycystin-2). Comorbidities commonly associated with renal cysts include biliary duct abnormalities with associated fibrosis in both tissues. In the kidney of cysta mutants, ischemia reperfusion (IR) injury greatly exacerbates the rate of cyst development; however, it is not known whether injury will similarly affect the liver and how loss of cilia affects injury induced fibrosis.

Methods: To address these questions, we are utilizing Oak Ridge Polycystic Kidney (ORPK) mice that have a congenital hypomorphic IFT88 mutation and conditional mutant mice where cilia are disrupted in the kidney (CagCreER). The conditional mutant mice under an IR injury show increased cell death progression, inflammation response and production of extracellular matrix (ECM) and pro-fibrotic factors.

Results: Our preliminary studies in the kidney indicate that IFT88 mutant mice receiving IR injury had increased ECM transcription of Col1a2, Col3a1, and ceroidin, compared to the sham operated control. Despite the increased ECM production, the pro-fibrotic growth factor TGF-β, which is frequently associated with fibrosis, was not significantly elevated in mutant mice. However, another TGFβ family member, inhibin βA, was increased in the injured kidney of mutant mice suggesting a possible mechanism for ECM production. The mice have a noticeable liver phenotype characterized by biliary hyperplasia and, similar to the kidney, an increase in Col1a2 and Col3a1 transcripts. ORPK mutant mice also have increased transcript levels of the monocytome chemoattractant protein, MCP-1, and the pro-inflammatory cytokine, IL-1β. Furthermore, in both mutant kidneys and liver there is an increase in the number of infiltrating macrophages, which may drive fibrosis.

Conclusions: Together, our preliminary data suggest that defects in cilia formation promote fibrotic disease progression possibly through altered cytokine production and enhanced recruitment of infiltrating monocytes.

Funding: NIDDK Support, Other NIH Support - MERIT fellow grant number: 2K12GM08810-06 to Kurt Zimmerman

FR-PO308

Klotho Suppresses Epithelial-Mesenchymal Transition (or Transformation in Adrimycin Nephropathy Tsuchuo Takenaka, 1 Tsutomu Inoue; 2 Matsuhiyo Hayashi, 1 International Univ of Health and Welfare; 3Saitama Medical Univ; 1Keio Univ.

Background: Klotho interacts with various proteins to alter their function. Klotho may bind to the receptor for WNT and TGFbeta, inhibiting their signals.

Methods: Experiments were performed to assess how klotho protects kidney from its injury. At 5mg/kg was injected into rats to induce nephropathy. Human recombiant klotho (K, 30 micro-g/kg/day), rabbit anti-klotho (1:5000), and rabbit anti-klotho (1:5000) were untreated with Adriamycin were used as control (U). Animals were killed 8 weeks later. Renal expressions of Wnt1, GSK3beta, TGFbeta, Twist and collagen I were assessed with RT-PCR against GAPDH. Western blot was used for p-GSK3beta and beta-actin.

Results: Adriamycin increased albuminuria, renal expression of Wnt1, p-GSK3beta, TGF, Twist and collagen I in comparison to the control. Klotho and T suppressed the increased albuminuria and the phosphorylated phosphoproteins and the phosphorylated GSK3beta. Reduced elevateds of Wnt1, supporting that klotho inhibits Wnt signaling without changes in Wnt level. While klotho and T reduced TGFBeta, klotho preferentially ameliorated Twist and collagen I in comparison to T.

Funding: Pharmaceutical Company Support - Hoffmann La Roche, Government Support - Non-U.S.

FR-PO309

The Molecular Mechanism of mir-382 in the Pathogenesis of Renal Tubulointerstitial Fibrosis Yi Fang, 1 Ting Xie, 1 Hui Zhang, 1 Sheng Wu. 1 Nephrology, Zhongshan Hospital Fudan Univ, China; 2Shanghai Key Laboratory of Renal Diseases and Blood Purification.

Background: To investigate the roles of microRNA-382 (miR-382) in the pathogenesis of renal tubulointerstitial fibrosis. Methods: Human kidney epithelial (HK-2) cells that transfected with a miR-382 inhibitor (antagomir-382) was used to examine the effect of miR-382 abundance on cell polarity, as well as to test the complementary relationship between miR-382 and its predicted target gene, heat shock 60kDa protein 1 (HSPD1), which was further verified by site-directed mutagenesis. We also examined the in vivo role of miR-382 in the development of renal interstitial fibrosis, in a mouse unilateral ureteral obstruction (UO) model. Locked nucleic acid (LNA)-anti-miR-382 was intravenous delivered via tail vein less than 30mins prior to U, and repeated the dosage 24 hours after the surgery. For clinical verification, renal biopsy specimens from 12 IgA nephropathy (IgAN) patients were collected, 6 with moderate to severe tubulointerstitial fibrosis (TIF) and 6 with no TIF. The relative abundance of miR-382 and HSPD1 protein was analyzed using in situ hybridization and immunohistochemistry.

Results: HSPD1 was confirmed to be a new, direct target gene of miR-382 by in vitro transfact technique and mutation experiments. The development of epithelial transition or renal interstitial fibrosis was accompanied with up-regulated abundance of miR-382. Down-regulation of miR-382 was associated with significant decreases in exacerbation of interstitial fibrosis, but increase protein expression of HSPD1 and thioredoxin, both in the obstructed mouse kidneys and renal biopsy specimen from IgAN patients.

Conclusions: MiR-382, a profibrotic microRNA, is up-regulated with the development of renal interstitial fibrosis in humans and in mice. The down-regulation of HSPD1 and the decreased ability of anti-oxidative stress are secondary to the increased abundance of miR-382.

Funding: Government Support - Non-U.S.

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

425A Extracellular Matrix Biology, Fibrosis, Cell Adhesion - 1
Vitamin (Vit) D Repletion Ameliorates Muscle Wasting and Muscle Fibrosis in Mice with Chronic Kidney Disease

Background: Cachexia presenting as muscle wasting and weakness is prevalent in CKD patients and may impact their quality of life. We investigated the effects of vitamin D repletion in a mouse model of CKD-associated muscle wasting.

Methods: CKD in c57BL/6 mice were induced by 5/6 nephrectomy. CKD and sham mice were treated with 25VitD (25 mg/kg/day), 1.25VitD (40 mg/kg/day) or vehicle (V) for 6 weeks via a subcutaneous osmotic pump. The extent of tubulointerstitial fibrosis was evaluated by histology. The kidneys were excised and precision-cut tissue slices (PCTS) were cultured for 5 days included: collagen IV (COLIV), laminin521 (hLN521), laminin111 (hLN111) or Attachment Factor (AF; Cell System's proprietary GEnC coating). Cell adhesion was monitored by the use of AF or COLIV in GEnC culture shows little advantage. DN-associated hLN111 is a poor attachment substrate resulting in GEnC loss. This is in contrast to the more physiologically relevant hLN521 which promotes cell adhesion, spreading, proliferation and tight junction formation.

Results: 25VitD increased FN1 and a-smooth muscle actin (αSMA, marker of fibroblast activation) in a dose-dependent manner. Addition of gremlin-1 (mimicking the in vivo setting) did not exacerbate fibrosis at any dose of TGFb. Addition of recombinant BMP2 was not sufficient to prevent TGFb-induced fibrosis in either cell type. Recombinant BMP2 alone (1 nM) increased SMAD5 phosphorylation and the expression of ID1 (a marker of BMP signalling) at 1 and 24 hrs post treatment. The stimulatory effect of BMP2 was blocked by pre-treatment with recombinant Gremlin-1 (2 nM). These data confirm intact BMP2–gremlin-1 signalling in both cell types.

Conclusions: Our data does not support the participation of gremlin-1 in TGFb-dependent renal fibrosis in vitro.

Funding: Pharmaceutical Company Support - MedImmune

FR-PO311

Assessing the Role of Gremlin-1 on Renal Fibrosis In Vitro

Methods: Primary human GEncs were from Cell Systems. Cell culture surface coating included: collagen IV (COLIV), laminin521 (hLN521), Attachment Factor (AF); Cell System’s proprietary GEnc coating. Cell adhesion was monitored by the use of AF or COLIV in GEnc culture shows little advantage. DN-associated hLN111 is a poor attachment substrate resulting in GEnc loss. This is in contrast to the more physiologically relevant hLN521 which promotes cell adhesion, spreading, proliferation and tight junction formation.

Results: Coating with AF or COLIV increased cell index (CI) of GEncs in the cell adhesion phase (0-6h) but not in the spreading and proliferation phase (6-72h). Coating with hLN521 displayed a continuous increase in CI over 72h. On the contrary, hLN111 caused a significant decrease in CI over 72h. Cells grown on AF or COLIV showed similar spread and proliferation of cells grown on COLIV-supernatants. By contrast, coating with hLN521 decreased the expression of COL4A1, COL4A2, MMP2 [all 2-fold] and TGFβ1 [1.5-fold] as compared to no coating. Likewise, ITGA1, ITGA2, ITGAV, ICAM1, NOX4 were decreased with hLN521 in a dose-dependent manner. Expression of LAMA5, ITGAV, ITGAX and NOX3 were unchanged in all groups. Tight junction formation was assessed by AO immunostaining. Laminin521, contrary to other ECM coatings, stimulated tight junction formation in GEncs.

Conclusions: Usage of AF or COLIV in GEnc culture shows little advantage. DN-associated hLN111 is a poor attachment substrate resulting in GEnc loss. This is in contrast to the more physiologically relevant hLN521 which promotes cell adhesion, spreading, proliferation and tight junction formation.


FR-PO313

Development of an Ex Vivo Model to Elucidate the Matrix Turnover Profile in Renal Interstitial Fibrosis

Methods: To test this hypothesis we used HK-2 (human PT cell line) and NRK49F (rat tubular cell line) cell lines where the pro-fibrotic phenotype was induced by Transforming Growth Factor b1 (TGFβ; 2.5 ng/mL, 72 hrs).Gremlin-1 secretion was assessed in circulation and in urine, these markers have the potential to accurately assess and predict renal fibrosis in vivo. We aimed at identifying markers for early disease onset that were directly linked to the events of scar formation in the kidney.

Results: While C1M levels in urine were not different between NTN mice and controls, urinary C1M levels in control mice were significantly increased in CKD than sham mice (p<0.01). Significant correlation between C1M and various markers measured in the supernatants also in circulation and in urine, these markers have the potential to accurately and non-invasively describe the tissue remodeling during fibrosis.

Conclusions: The UO PCTS ex vivo model provides a valuable translational tool for investigating the ECM remodeling associated with renal interstitial fibrosis. Since the presence and concentration of these markers measured in the supernatants also in circulation and in urine, these markers have the potential to accurately and non-invasively describe the tissue remodeling during fibrosis.

Funding: Other NIH Support - R24-HD050837

FR-PO314

Collagen Degradation Profile in a Nephrotic Nephritis Model

FR-P0310

The Effect of Cell Culture Surface Coating on Glomerular Endothelial Cell Phenotype

Methods: Neo-epitope degradation fragments of collagen type I, III and IV generated by MMP cleavage were measured by specific ELISAs (namely C1M, C3M and C4M) in urine of NTN and healthy mice at terminated at 7 and 21 days after injury (NTN: n=21, Controls: n=6). Urinary albumin/creatinine (ACR), urinary proteinuria, plasma creatinine and blood urea nitrogen (BUN) were measured as markers of renal function. Intestinal fibrosis and glomerulosclerosis were evaluated by histology and quantification of α-SMA and collagen type I in immunohistochromy.

Results: While C1M levels in urine were not different between NTN mice and controls, C3M levels were elevated in NTN rats at 7 days (p<0.05) and decreased to levels close to the controls at 21 days. This elevation was also reflected in proteinuria, peaking at 7 days, but not in BUN and plasma creatinine. C4M levels were elevated at 21 days and not at 7 days (p<0.01), and correlated with the extent of interstitial fibrosis.

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FR-PO312

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Conclusions: Usage of AF or COLIV in GEnc culture shows little advantage. DN-associated hLN111 is a poor attachment substrate resulting in GEnc loss. This is in contrast to the more physiologically relevant hLN521 which promotes cell adhesion, spreading, proliferation and tight junction formation.


FR-PO313

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Results: While C1M levels in urine were not different between NTN mice and controls, urinary C1M levels in control mice were significantly increased in CKD than sham mice (p<0.01). Significant correlation between C1M and various markers measured in the supernatants also in circulation and in urine, these markers have the potential to accurately and non-invasively describe the tissue remodeling during fibrosis.

Conclusions: The UO PCTS ex vivo model provides a valuable translational tool for investigating the ECM remodeling associated with renal interstitial fibrosis. Since the presence and concentration of these markers measured in the supernatants also in circulation and in urine, these markers have the potential to accurately and non-invasively describe the tissue remodeling during fibrosis.

Funding: Other NIH Support - R24-HD050837

FR-PO314

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Results: While C1M levels in urine were not different between NTN mice and controls, C3M levels were elevated in NTN rats at 7 days (p<0.05) and decreased to levels close to the controls at 21 days. This elevation was also reflected in proteinuria, peaking at 7 days, but not in BUN and plasma creatinine. C4M levels were elevated at 21 days and not at 7 days (p<0.01), and correlated with the extent of interstitial fibrosis.

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

Underline represents presenting author.
FR-PO315
Evidence of Podocyte Protrusions into the Basement Membrane in Glomerular Disease
Sophie C. Collinson,1 Michael J. Randles,1,2 Mira Krendel,3 Eva Koenigshausen,1, Lorenz Sellin,1 Ian Roberts,1 Jeffrey H. Miner,1 Rachel Lennon,1,2 Inst of Human Development, Faculty of Medical & Human Sciences, Univ of Manchester; United Kingdom; 1Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, Univ of Manchester; United Kingdom; 2Dept of Cell and Developmental Biology, SUNY Upstate Medical Univ, Syracuse, NY; 1Dept of Nephrology, Heinrich Heine Univ, Duesseldorf, Germany; 3Dept of Cellular Pathology, John Radcliffe Hospital, Oxford, United Kingdom; 2Renal Div, Washington Univ School of Medicine, St. Louis, MO.

Background: Glomerular disease is a leading cause of kidney failure. Podocyte foot process effacement and glomerular basement membrane (GBM) disruption are frequent abnormalities regardless of the underlying molecular etiology. Standard electron microscopy techniques provide 2D information and 3D ultrastructural relationships are poorly understood. We hypothesized that creation of detailed 3D models of the glomeruli would identify novel pathological features.

Methods: Serial block face-scanning electron microscopy was performed on a series of mouse kidneys from glomerular disease models with established albuminuria. 3D reconstructions of glomeruli were created using IMOD 4.7.11.

Results: Sub-podocyte expansions of the GBM were dominant features in mice with WT controls. There was no evidence of endothelial or mesangial cell protrusions into the GBM and no correlation between GBM thickness and the site of podocyte protrusions.

Conclusions: 3D ultrastructural imaging revealed expected GBM abnormalities in addition to podocyte protrusions, resembling invasadesomes, in the GBM. This novel finding provides new insight into disease mechanisms and suggests that a common matrix-adhesion pathway is activated regardless of the primary molecular insult.

Funding: Private Foundation Support

FR-PO316
Multi-Clonal Population of Cells of Renin Lineage (CoRL) Transdifferentiate into Podocytes and PECs in Experimental FSGS
Natalya V. Kaverina,1 Diana G. Eng,1 Jeffrey W. Pippin,1 Michael E. Rusiniak,2 Kenneth W. Gross,2 Stuart J. Collinson,1 Devision of Nephrology, Univ of Washington, Seattle, WA; 1Dept of Molecular and Cellular Biology, Roswell Park Cancer Inst, Buffalo, NY.

Background: Focal segmental glomerulosclerosis (FSGS) is secondary to podocyte injury and loss. Because adult podocytes cannot proliferate, their replacement by progenitors is critical for their repair and regeneration in disease. Here we explored whether single or multiple clones of cells of renin lineage (CoRL) serve as a local progenitor source to replace reduced podocytes in experimental FSGS.

Methods: Experimental FSGS was induced following abrupt podocyte depletion by administration of a cytotoxic anti-podocyte antibody to two confetti mouse reporters. First, to confirm adult podocyte regeneration following abrupt depletion, podocytes were genetically fate-mapped in adult NPHSP2Cre/Confetti reporter mice with experimental FSGS. Second, to prove that adult podocyte regeneration by CoRL was multi-clonal, CoRL were fate mapped in RenCre/Confetti reporter mice with experimental FSGS. Results: FSGS in NPHSP2Cre/Confetti reporter mice was characterized by marked podocyte depletion (45% decrease) on day 47. A multi-clonal repopulation of podocytes resulted in an increase in their overall number by 77% of normal by day 288. No podocyte proliferation was detected by BrdU staining. In RenCre/Confetti reporter mice, a multi-clonal expansion of 4-color labeled CoRL (GFP, RFP, CFP, YFP) was detected in glomeruli at FSGS d28. A population of CoRL were fate mapped in RenCre/Confetti reporter mice with experimental FSGS.

Conclusions: CoRL transdifferentiate into podocytes in experimental FSGS, their number was increased in the absence of podocyte proliferation. Regeneration of adult podocytes is likely in part due to multiple clones of CoRL serving as local progenitors.

Funding: Other NIH Support - 5 R01 DK 057997-10, 5 R01 DK 057997-12, 1 R01 DK097598-01A1

FR-PO317
Macula Densa-Derived Factors Control Glomerular Cell Remodeling
Anne Riquier-brison,1 Donna Ralph, Jasmine Ann Arevalo Castillo, Janos Peti-Peterdi, Physiology and Biophysics, Univ of Southern California, Los Angeles, CA.

Background: Macula densa (MD) cells are strategically positioned at the vascular entrance of the glomerulus and control renal hemodynamics and renin. In this study, we addressed a novel, non-traditional role of MD cells regulating glomerular cell plasticity/ remodelling by mesenchymal progenitor cells.

Methods: For genetic cell fate tracking, tamoxifen-induced NG2CreERT2-Tomato mice were fed either a control or salt-deficient + ACE inhibition (SD+ACEi) diet, for 2 weeks to achieve strong MD stimulation.

Results: We observed a 5-fold increase in renal interstitial density of NG2+ cells (5.9±1.1 cells per field in control, 30.2±4.5 in SD+ACEi), and the homing of NG2+ cells to the mesangium under the MD and into the glomerulus. This effect was blunted by the selective COX-2 inhibitor SC58236 (COX-2i) or the nNOS inhibitor 7-NI (13.2±2.2 cells per field with COX-2i and 11.6±1.7 with 7-NI). Immunofluorescence (IF) of Claudin-1 showed a 4-fold increase in the number of NG2+ cells in the glomerular parietal layer (0.5±0.2 cells per glomerulus in control, 2.0±0.4 in SD+ACEi). Podocin IF costaining did not detect a few NG2+ podocytes. NG2+ cell homing was blunted by COX-2i and 7-NI (2.3±0.3 cells per glomerulus with COX-2i and 0.8±0.3 with 7-NI). Co-localization of endogenous NG2-Tomato fluorescence with IF of renin revealed an increase in the proportion of NG2+ renin-expressing cells from 22.0% of 6.6 to 70.6% of 7.4 after SD+ACEi, inhibited by COX-2i. Similarly, the density of proliferating cells expressing Ki67 increased after treatment to 33.9±3.2 cells per field with COX-2i and 31.3±2.8 with 7-NI. Immunofluorescence IF of Claudin-1 showed a 4-fold increase in the number of NG2+ cells in the glomerular parietal layer (0.5±0.2 cells per glomerulus in control, 2.0±0.4 in SD+ACEi).

Conclusions: Our results suggest that NG2+ pericytes may be an important progenitor cell population in the kidney. In response to MD-derived (from COX-2 and nNOS) paracrine factors, NG2+ cells from the renal interstitium proliferate and migrate towards the MD along the arteriole and via the vascular pole into the glomerular epithelium and mesangium. In conclusion, MD cells play new important roles in the maintenance and remodeling of the glomerulus.

Funding: NIDDK Support

FR-PO318
A Novel Method for Assessing Podocyte Depletion in Whole Glomeruli
Victor G. Puelles,1 James William Van der Wolde,1 Lisa Cullen,2 David W. G. Benesley,1 Kieran M. Short,3 Georgia A. Caruana,1 Stacey Hokke,1 Stephen D. Firth,1 Ian S. Harper,2 David J. Nikolic-Paterson,4 John F. Bertram,1 1Dept of Anatomy and Developmental Biology, Monash Univ, Melbourne, Victoria, Australia; 2Monash Micro Imaging, Monash Univ, Melbourne, Victoria, Australia; 3Dept of Nephrology, Monash Medical Centre, Melbourne, Victoria, Australia.

Background: Podocyte depletion plays a major role in the development and progression of glomerulosclerosis. Given that glomerulosclerosis is often focal, affecting some but not all glomeruli, our aim was to develop a rapid, accurate and precise method for quantifying podocyte depletion in whole glomeruli.

Methods: Pod ΔiDTR mice, in which expression of the human diphtheria toxin (DT) receptor is driven by the podocin promoter, and iDTR mice (controls) were injected with DT or 2000 units/kg. Tissue was collected at day 35 for podocyte analysis (n=3 mice per group). Kidney sections were stained with antibodies against podocin and synaptopodin. Slices were cleared with benzyl alcohol, benzyl benzoate (BABB). An SP8 confocal microscope (Leica, Germany) fitted with a BABB objective (NA: 0.95; working distance: 2mm) was used. Total podocyte number was obtained by manual counting and using the cell counting application in iSolve (Imaris, Birplume) in 88 whole glomeruli - 38 from iDTR mice and 50 from Pod ΔiDTR mice.

Results: In iDTR mice (controls), total podocyte number per glomerulus was almost identical between manual counts (66.61±11.92) and Imaris (65.47±9.26; P=0.65). In Pod ΔiDTR assessment of glomerular morphology, CoRL podocyte depletion was 100% with COX-2i (1.2±0.3 cells per glomerulus) and 7-NI (1.2±0.3 cells per glomerulus). Podocyte depletion was also similar between manual counts (52.96±11.74) and Imaris (53.51±11.35; P=0.81). With both methods, podocyte counts were obtained in less than 2 minutes per glomerulus, a significant time reduction compared to existing methods. Imaris also facilitates the estimation of podocyte and glomerular volumes for a more precise assessment of podocyte depletion.

Conclusions: This is the first method to combine immunofluorescence, BABB-clearing and confocal microscopy to count podocytes in whole glomeruli. The method is accurate, precise and rapid, and provides a novel approach for podocyte morphometrics in settings where sufficient tissue is available for analysis.

Funding: FR-PO319
Characterization of Heterogeneous Podocyte Biomechanics Using Atomic Force Microscopy
Ivyen A. Azeloulogi,1 Jia-Jye Lee,1 Kevin D. Costa,2 Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY; 1Cardiology (Medicine), Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Biomechanical signals play a key role in glomerular physiology, where pathological changes in blood pressure can significantly affect podocyte morphology and function. While there has been a great focus on mechanobiological signaling in podocytes, their spatial biomechanical properties have been largely overlooked due to a lack of in
Identification and Validation of Fluid Flow Shear Stress (FFSS)-Induced Changes in Podocyte Signaling Pathways Using Bioinformatic Tools

We identified a family of small molecules, paullones, as highly potent agents that protected podocytes from damage. Kenpaullone and three other paullones (paullone, thio-kenpaullone, and 2-thio-kenpaullone) were analyzed and quantified using automated methods using high-content screening (HCS) assay for quantifying podocyte damage in vitro. Here, we report the development of kidney directed therapeutics. We recently described a novel cell-based pathogen discovery assay that could prevent progressive glomerular injury.

**Results:**
- **Identification:** A family of small molecules, paullones, was identified as highly potent agents that protected podocytes from damage.
- **Validation:** Kenpaullone and three other paullones (paullone, thio-kenpaullone, and 2-thio-kenpaullone) were analyzed and quantified using automated methods using a high-content screening (HCS) assay.
- **Pathogenic:** Pathogen discovery assay provided a new means to rapidly test the micromechanics of podocytes with high spatial resolution in a physiologically relevant in vitro setting.

**Funding:** Private Foundation Support

FR-PO320

Podocyte Protective Agents

Sima Babayeva, 1

Vini Vardeny, 1

Maiyan D. Trucco, 1

Nadlera Matalon,1,2

Chen-Fang Chung, 2

Simia Babayeva, 1

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Thomas Kitzler. 1

1 Dept of Medicine, McGill Univ-McGill Univ Health Center, Montreal, QC, Canada; 2 Div of Nephrology, The Johns Hopkins Univ School of Medicine, Baltimore, MD.

**Background:** Podocyte-directed therapeutics for treating a number of glomerular diseases.

**Objectives:** Employment of our newly described podocyte-based screening assay results in the discovery of podocyte-directed therapeutics for treating a number of glomerular diseases. Paullones represent a family of small molecules that show podocyte protection from damage. We also describe a proposed molecular mechanism for the efficacy of these novel agents. We hope that these methodologies will lead to the development of novel types of specific kidney protective drugs.

**Results:**
- **Identification:** We identified a family of small molecules, paullones, as highly potent agents that protected podocytes from damage.
- **Validation:** Kenpaullone and three other paullones (paullone, thio-kenpaullone, and 2-thio-kenpaullone) were analyzed and quantified using automated methods using a high-content screening (HCS) assay for quantifying podocyte damage in vitro.
- **Pathogenic:** Pathogen discovery assay provided a new means to rapidly test the micromechanics of podocytes with high spatial resolution in a physiologically relevant in vitro setting.

**Conclusions:**
- We identified a family of small molecules, paullones, as highly potent agents that protected podocytes from damage.
- Kenpaullone and three other paullones (paullone, thio-kenpaullone, and 2-thio-kenpaullone) showed dose-dependent protection of podocytes from PAN-damage induced loss in F-actin fibers.
- Among the four paullones identified, alsterpaullone showed the highest degree of protection. At a molecular level, alsterpaullone reduced the elevation in the expression of Desmin, a podocyte damage marker, and inhibited PAN-induced podocyte migration. While PAN treatment reduced AKT phosphorylation in podocytes, alsterpaullone maintained the levels of phosphorylated AKT in podocytes.

**Funding:** Private Foundation Support

FR-PO323

Novel Podocyte Quantification Assay to Ascertain Patient Serum Toxicity

Lee, Susanne Brodesser,1 Bernhard Schermer, 1,3 Thomas Benzing, 1,3 Christine E. Pharmas,3

1 Nephrology, The Children’s Hospital, Kansas City, MO; 2 Nephrology, Medical College of Wisconsin, Milwaukee, WI; 3 Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; 4 Renal Research Laboratory, Kansas City VA Medical Center, Kansas City, MO.

**Background:** In vitro studies from our lab showed that plasma from recurrent FSGS patients disturbs the human podocyte cytoskeleton and focal adhesion complexes (FACs). We developed a novel unbiased assay to quantify the toxic effects of patient plasma and nephrotoxic drugs on cultured human podocytes and to identify strategies that block serum toxicity.

**Methods:**
- **Cytoskeleton:** Culture human differentiated podocytes are exposed to adriamycin, recombinant TNFa or human sera from patients with various forms of FSGS. FACs are visualized with anti-vinculin antibody, and cell images are analyzed to define the number of FACs/1000mm2 cell area.
- **Capsule:** We analyzed sera from 12 patients: 2 with idiopathic, 4 recurrent FSGS, 4 non-recurrent FSGS and 2 de novo FSGS.

**Results:**
- **Idiopathic:** Both adriamycin and recombinant TNFa disrupt podocyte actin cytoskeleton and FACs in a dose-dependent manner. Comparing to healthy control, sera from patients with de novo FSGS (no known mutations identified), FSGS and de novo FSGS post-transplant drastically reduces FACs number, yet sera from nFSGS post-transplant does not statistically affect FACs. In ~60% of the patients with serum toxicity, these effects on podocytes can be averted by TNFa pathway blockade.

**Conclusions:** Our in vitro assay provides, for the first time, means to reliably identify those patients with idiopathic FSGS who are at high risk of recurrence post-transplant. It may also identify FSGS patients who may be candidates for anti-TNFa therapy that could prevent progressive glomerular injury.

**Funding:** Government Support - Non-U.S.
FR-PO324

Loss of Robo2 in Podocytes Protects Adult Mice from Acute Glomerular Injury

Anna Piasarek-Horowit, Xueming Fan, Hila Milo Rasouly, Stefanie Chan, Hui Chen, Ramon G. Bonegio, Joel M. Henderson, David J. Salant, Weining Lu. Renal, Boston University Medical Center, Boston, MA.

Background: SLIT2 and its receptor ROBO2 play an important role during kidney development. We have recently found that ROBO2 is expressed in developing glomerular podocytes. However, the role of ROBO2 in the adult mouse kidney, particularly under acute glomerular injury conditions, is not clear.

Methods: To test the hypothesis that loss of Robo2 in glomerular podocytes affects the outcome of acute glomerular injury, we applied two in vivo acute glomerular injury models induced by nephrotoxic serum (NTS) injection and proteomic saline (PS) perfusion, in Robo2 podocyte specific knockout mice (Robo2 KO) and wild type controls. Kidney glomerular ultrastructure was analyzed by scanning and transmission electron microscopy before and after injury. Podocyte foot process width and slit diaphragm density were measured to quantify the severity of the glomerular injury. Urine albumin to creatinine ratio was measured in the NTS model. Podocyte specific gene expression was analyzed using TaqMan real time PCR for mRNA and Western blot for protein levels.

Results: Robo2 podocyte specific knockout mice developed less proteinuria after the NTS injury with lower urine albumin/creatinine ratio as compared to the wild type controls. Electron microscopy showed that Robo2 KO mice have milder foot process effacement and less defects in the slit diaphragm induced by either NTS or PS injury. TaqMan and Western blot analyses revealed that nephrin, a crucial transmembrane component of the podocyte slit-diaphragm, was significantly up-regulated at both mRNA and protein levels in the Robo2 KO mice before NTS injury and at the late stage of heterologous phase after the NTS injury. In addition, the mRNA levels of Robo2 and Slit2 in the wild type kidneys were also upregulated after the NTS injury.

Conclusions: SLIT2-ROBO2 signaling pathway plays an important role in the adult mouse kidney. Loss of Robo2 protein in adult glomerular podocytes from acute glomerular injury. Our findings suggest that SLIT2-ROBO2 signaling might also have a negative impact on nephrin expression during podocyte injury and be a potential therapeutic target.

Funding: NIDDK Support, Private Foundation Support

FR-PO325

Inducible Knockdown of Shroom3Induces Proteinuria with Podocyte Dedifferentiation

Madyah C. Menon, Chengwei Wu, Karen Lok Yue Keung, Iliana Greene, Weijia Zhang, John C. He, Barbara T. Murphy. Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Intronic loci in Shroom3 have been associated with CKD and CAN. A role for Shroom3 in the podocyte cytoskeleton has been shown. However Shroom3 knockout mice die neonatally with neural tube defects and detailed renal phenotypes are unknown. Here we report our findings from Doxycycline (DOX) inducible, shRNA-mediated shroom3 knockout mice.

Methods: In these mice Shroom3-specific shRNA expression was induced upon DOX-feeding, with RTTA expression in all cells driven by CAGS-promoter. Six-wk old mice were fed DOX-feed/water. Non-DOX fed littersmates were controls (n=6 each). At 4- and 8-weeks, renal tissue was obtained for histology. Twenty-five glomeruli were analyzed per mouse and quantification was used imaging.

Results: DOX-mice developed significantly increased Albumin-to-creatinine ratios starting at 2 weeks compared to controls.

FR-PO326

Protective Role of Cyclodextrin in Focal Segmental Glomerulosclerosis (FSGS)

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Background: We recently demonstrated that cholesterol accumulation contributes to podocyte injury in diabetic kidney disease (DKD), where 2-hydroxypropyl-β-cyclodextrin (CD) protects podocytes from cholesterol-dependent damage in vitro and in vivo. We hypothesize that lipid related genes are affected in glomeruli of patients with primary FSGS and correlate with CD protected podocytes in experimental models.

Methods: Microarray analysis on glomerular transcripts of lipid-related genes from patients with FSGS (n=54) and from normal living donors (n=6) were obtained from patients enrolled in NEPTUNE, a longitudinal observational cohort looking at individuals with proteinuria. 5-week-old BALB/c female mice were injected with a single intravenous dose of adriamycin (ADR, 11 mg/kg) to develop FSGS-like lesions. 24-hours after ADR injection, osmotic pumps with CD in 0.9% saline solution (40 mg/kg/day) were implanted under the skin for 10 weeks. Measurements of body weight and urine collections for ACR (Albumin/creatinine ratios) were performed weekly. At time of sacrifice, serum creatinine and Blood Urea Nitrogen (BUN) were determined and kidneys collected for histological analysis.

Results: Microarray analysis of the glomerular transcripts in the NEPTUNE cohort demonstrated that cholesterol efflux related genes, such as PLIN3, S1PR2, S1PR1, and lipid dysmetabolism related genes, such as SCD, LDLR, ABCG1, were increased in FSGS. CD administration reduced mesangial expansion as well as ACR and BUN observed at 10 weeks in the ACR/CD group compared to the ADR group (p<0.05). No changes in body weight were found.

Conclusions: We conclude that glomerular lipids are altered in FSGS and that 2-hydroxypropyl-β-cyclodextrin protected podocytes in an experimental model of FSGS. Our data suggest that CD could be used as a safe and effective drug therapy in FSGS patients. 

Funding: NIDDK Support

FR-PO327

Podocyte-Derived CXCL12 Has a Dual Role in Glomerular Injury and Regeneration


Background: Stromal-derived factor (SDF)-1/CXCL12 is a homeostatic chemokine facilitating homing and activation of stem cells. Podocytes constitutively produce CXCL12, hence, we speculated on a role of CXCL12 in glomerular regeneration upon injury.

Methods: Glomerular injury was induced by a single i.v. injection of 13mg/kg adriamycin (ADR) in male Balb/c mice, which received either the CXCL12 inhibitor NOX-A12 or the inactive control s.c. at 13.4mg/kg thrice a week. Renal progenitor cell properties (RPC) were used for in vitro studies.

Results: ADR-induced proteinuria peaked at day 7 (injury phase), which subsequently declined without returning back to baseline and being associated within FSGS lesions after 14 days (repair phase). CXCL12 blockade augmented ADR-induced A/C and podocyte loss at day 7, which implies an autocrine role of CXCL12 for podocyte survival. In contrast, CXCL12 blockade reduced A/C levels and the glomerular sclerosis scores as well as increased podocyte numbers at 14 days indicating a beneficial effect of CXCL12 blockade during the repair phase. The pro-survival effect of CXCL12 on podocytes was further confirmed in a model of diphtheria toxin-induced podocyte depletion using CXCL12 blockade. To investigate the dual effect of CXCL12, we focused on the Notch signaling pathway. ADR injection reduced renal Notch expression, which was reversed following CXCL12 blockade. In vitro studies with RPM revealed that CXCL12 suppressed RPC proliferation, which was reversed with CXCL12 inhibitor. Similar results were obtained when RPC were exposed to supernatants from necrotic podocytes. CXCL12 blockade also increased the capacity of RPC to differentiate into podocytes.

Conclusions: Podocyte-derived CXCL12 has a dual role in glomerular injury. CXCL12 protects podocytes during the injury phase in an autocrine manner by suppressing Notch signaling, which otherwise triggers mitotic catastrophe and podocyte loss. Podocyte-derived CXCL12 assures Notch-mediated quiescence of RPC. Our data also demonstrate that therapeutic CXCL12 inhibition in glomerular injury can improve long term outcomes possibly by enforcing the intrinsic regenerative capacity of RPC.

FR-PO328

Shank2 Modulates Glutamatergic Signaling in Podocytes

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Background: Shank2 is a large scaffolding protein that is a master regulator of glutamate receptors at the neuronal postsynaptic density. Knockout (KO) of Shank2 in mice leads to autistic behaviours and abnormal glutamatergic signaling.

Podocytes have also been shown to express functional N-methyl D aspartate (NMDA) and metabotropic glutamate receptor 1 (mGluR1) receptors which are both members of the glutamate receptor family.

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

429A
Results: We have found that podocytes express Shank2 in vivo and in vitro. Since Shank2 is an important regulator of glutamate receptor function, we examined the effect of Shank2 knockout on NMDA and mGluR1 expression and function in podocytes. Shank2 KO resulted in decreased expression of NMDA and mGluR1 receptors in glomeruli. We isolated podocytes from wild type and Shank2 knockout mice and created conditionally immortalized Shank2 KO podocyte lines. Conditionally immortalized Shank2 KO podocytes also demonstrated decreased expression and altered localization of glutamate receptors. In neurons, activation of glutamate receptors modulates intracellular calcium levels by allowing calcium influx into the cell (NMDA receptors) or release of calcium from intracellular stores (mGluR1). To evaluate changes in calcium levels in podocytes, we examined intracellular calcium levels in wild type and Shank2 KO podocytes at baseline. Shank2 knockout podocytes had significantly fewer calcium spikes than wild type podocytes. Treatment with NMDA and glutamate increased the number of calcium spikes in both wild type and Shank2 KO podocytes but the number of spikes in the KO podocytes were significantly reduced compared to wild type. Podocytes have been shown to communicate with each other via calcium waves. To examine podocyte to podocyte communication after injury, we “burned” a podocyte using high intensity laser power and then examined calcium wave propagation from the site of injury. After burning, wild type podocytes exhibited calcium waves emanating from the injured podocyte whereas no waves were seen in the knockouts.

Conclusions: Taken together these data indicate that Shank2 regulates glutamate receptor function in podocytes.

Funding: NIDDK Support

FR-PO329

Podocytes Transcytose Albumin and IgG Using the Neonatal Fc Receptor (FcRn) In Vivo and In Vivo
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Background: Proteinuria is strongly associated with kidney disease progression. Podocytes are key constituents of the glomerular filtration barrier (GFB), which determines the balance of protein filtration. By even the most conservative estimates between 2 and 9 g of serum proteins a day normally pass through the GFB. The molecular mechanisms whereby podocytes handle albumin and IgG remain to be fully determined.

Results: We have found that transcytosis is the major pathway whereby cultured podocytes in primary culture and IgG. In other epithelial cell types, the neonatal Fc receptor (FcRn) is required to transcytose endocytosed albumin and IgG, thereby salvaging these proteins from degradative pathways. To examine the role of FcRn in albumin and IgG transcytosis in podocytes, we knocked down FcRn in cultured podocytes using lentiviral shRNA. Following knockdown (KD) resulted in a 71.3% decrease in FcRn expression compared to control. In an in vitro transcytosis assay, FcRn KD increased intracellular accumulation and decreased appearance of albumin and IgG in the supernatant, suggesting impaired transcytosis, but the differences were not statistically significant, possibly due to residual FcRn. We therefore isolated podocytes from wild type (WT) and FcRn knockout (KO) mice and created conditionally immortalized WT and KO podocyte lines. Knockout of FcRn resulted in significantly increased intracellular accumulation, assessed by immunostaining and Western blot (densitometric analysis of intracellular protein 1 hr after loading showed 3.7±0.1 (WT) vs 9.7±0.2 (KO), p<0.05 for albumin and 0.52±0.04 (WT) versus 1.03±0.19 (KO), p<0.05 for IgG), and decreased appearance of supernatant albumin or IgG, indicating defective transcytosis. We extended our studies to an in vivo model by creating a podocyte-specific FcRn KO mouse. Podocyte-specific FcRn KO mice demonstrated impaired transcytosis of albumin and IgG by 8 weeks of age, assessed by immunostaining. Studies of albuminuria are in progress.

Conclusions: Taken together, these studies indicate that podocytes in vivo and in vitro transcytose albumin and IgG using FcRn.

Funding: NIDDK Support, Private Foundation Support

FR-PO330

Transcriptional Reprogramming by Wilms’ Tumor 1 and FoxC2 in Glomerular Disease
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Background: Foot process effacement and proteinuria, representing a breakdown of the glomerular filtration barrier (GFB) are typically accompanied by decreased expression of key podocyte proteins. We sought to determine whether decreased expression of key podocyte proteins was caused by transcriptional reprogramming in the injured podocyte. We reported a Wilms’ tumor-1 (WT1) ChIP-Seq study that identified components of the GFB and many other important podocyte genes as WT1 target genes. Many WT1 target genes in podocytes also appear to be bound by FoxC2, including Podocin (Podox2), Slit2 (Slit2/1) and Syndecanpodin (Sympo).

Methods: We now used ChIP-Seq to study the DNA binding of WT1 to target genes in the context of Adriamycin-induced podocyte injury that is considered a model for human FSGS. WT1 ChIP-Seq was performed using isolated glomeruli from 6 days post-injection or control B6C mice. FoxC2 binding was determined by direct ChIP-qPCR.

Results: Expression of WT1 and FoxC2 decreased in podocytes, as did binding of WT1 and FoxC2 to their common targets. WT1/FoxC2 target gene expression was also reduced. In contrast to these WT1/FoxC2 target genes that represent a set of genes required for normal podocyte function, we identified a second set of WT1-bound genes, not bound by FoxC2, including Hdc and 7, whose expression increased after podocyte injury. This WT1/FoxC2 binding decreased, suggesting that WT1 acts as a repressor for a distinct set of target genes.

WT1 binding at known target genes showed both decreased and increased peak intensity after treatment suggesting that WT1 regulation of gene expression is complex and may include activating and repressive functions.

Conclusions: These results suggest a model whereby WT1 and FoxC2 activate gene expression in normal podocytes, WT1 represses other genes in normal podocytes independently of FoxC2.

Funding: Other NIH Support - R01

FR-PO331

A Basophilic Kinase Site at the N-Terminus of TRPC6 Controls Channel Activity
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Background: The non-selective cation channel TRPC6 plays a pivotal role in the development of proteinuric kidney disease. Hyperactivity of TRPC6 either through gain of function mutations, increased total protein levels or membrane abundance of the channel protein has been associated with glomerular disease.

Results: To investigate regulation of the TRPC6 channel activity we conducted mass spectrometry experiments to screen for phosphorylation sites in the TRPC6 protein. We identified several new as well as previously known phospho-peptides. The serine residues in position 13 and 14 of the human TRPC6 protein are phosphorylated and embedded in a basophilic kinase motif. Substitution of the serine residue in position 14 with alanine (S14A) leads to a reduction of TRPC6 conductance in voltage clamp experiments in Xenopus oocytes.

The atypical cyclin-dependent kinase (Cdks), a serine- threonine-kinase expressed in the podocyte, is directed to basophilic motives. In the podocyte, Cdks is activated by the specific activators p35, p25, and Cyclin I. In cell culture experiments a direct phosphorylation of TRPC6 by Cdks/p35 at position S14 could be confirmed with mass spectrometry and radioactive in-vitro kinase assays. Co-expression of Cdks/p35 and TRPC6 enhanced channel conductivity of TRPC6 in voltage clamp experiments. This effect was abrogated by the amino acid substitution S14A.

Conclusions: A basophilic kinase site at the N-terminus of TRPC6 was identified which controls channel activity. As exemplarily shown for Cdks/p35, basophilic kinases phosphorylate TRPC6 at serine 14 and affect channel function. This site may serve as a molecular switch for TRPC6 activity and as a potential future drug target.

Funding: Private Foundation Support

FR-PO332

Hantaviruses Associate with Actin Fibers and Cause Podocyte Damage
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Background: Characteristic for the clinical picture of Old World hantavirus is an acute renal failure with often massive non-selective proteinuria. Previously, we showed that cell-to-cell contact proteins were disrupted and levels were decreased in infected human renal cells, correlating with the clinical picture. However, the exact mechanisms driving hantaviral pathogenesis are not well characterized.

Methods: Renal biopsies of patients with acute hantavirus infection were analyzed by electron microscopy. A human podocyte cell line was used for infection with Hantaan virus (HTNV). Cell-to-cell contact proteins were analyzed by immunoblotting, qRT-PCR and immunofluorescence. The cytoskeleton was examined by confocal microscopy and by depolymerising drugs. Cell motility was measured by migration assays.

Results: Analysis of renal biopsies revealed podocyte foot process effacement with loss of cell-to-cell contacts. To examine the underlying mechanism of hantavirus-induced alterations, we performed in vitro infection studies. We showed that HTNV had no influence on transcription levels of cell-to-cell contact proteins, indicating another mechanism of cell-to-cell contact disruption. Next, we focused on an impact on the cytoskeleton which is important for barrier function. We detected a filamentous pattern of the hantaviral nucleocapsid (N) protein which was associated with actin fibers. This N protein localization depended on the integrity of the actin cytoskeleton, because the filamentous pattern disappeared after actin depolymerization. Correspondingly, we measured decreased viral release levels after loss of N protein filaments. During infection, we revealed impaired podocyte motility as a functional consequence due to hantavirus-induced effects on actin dynamics and functions.

Conclusions: These results demonstrate that hantavirus infection leads to podocyte injury by morphological changes. Disruption of cell-to-cell contacts may be caused by the association of N protein and actin leading to changes in podocyte motility. These findings provide useful insights into the mechanism inducing renal failure.
ARF6: A New Player in Injury-Induced Podocyte Effacement

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Background: The transmembrane slit-diaphragm protein nephrin is tyrosine-phosphorylated and endocytosed during acute podocyte injury, resulting in cell spreading and effacement in vivo. We postulate that these events are facilitated by ARF6, a small GTPase that regulates endocytosis, endosomal trafficking, and actin dynamics possibly through regulation of Rac1, a Rho GTPase.

Methods: Using human podocyte cultures transfected with chimeric nephrin intracellular domain, we investigated the molecular mechanisms underlying its role in nephrin signaling. Using wild-type, constitutively-active, dominant-negative, and siRNA-knock-down of ARF6, we assessed lamellipodia activity (a marker of cell spreading) and podocyte motility.

Results: Results of co-immunoprecipitation suggested that activated nephrin formed a signaling complex with ARF6. Furthermore, nephrin tyrosine phosphorylation increased ARF6 activity in cultured podocytes. A constitutively active ARF6 mutant resulted in increased lamellipodia formation compared to wild-type ARF6, while dominant-negative ARF6 mutant resulted in decreased lamellipodia formation. A scratch assay of ARF6 knock-down cultured podocytes revealed slowed cell migration.

Conclusions: Together, our results suggest that ARF6 is an important protein involved in the regulation of injury-induced podocyte cytoskeletal rearrangement. Inhibition of ARF6 might provide a potential therapeutic strategy to confer a protective phenotype in vivo, making it an attractive target for the amelioration of glomerular disease.

Funding: NIDDK Support

FR-PO334

Albumin Sieving Coefficient in Isolated Perfused Kidney: Effects of EDTA

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Background: Myosin is expressed in podocytes and plays a key role in regulating the integrity of their cell-cell junctions, however, the effects of FSGS mutations on Myo1e motor activity and stability have not been directly tested. In this study, we used a simple model organism, fission yeast Schizosaccharomyces pombe, to test the effects of FSGS-associated mutations on myosin activity. Fission yeast has only one class I myosin, Myo1, which is involved in actin patch assembly at the sites of endocytosis.

Methods: The amino acid residues mutated in the FSGS patients are conserved between human Myo1e and yeast Myo1, which allowed us to introduce equivalent mutations into yeast myosin and use the resulting mutant strains for functional analysis. Myo1e expression and localization and stability was analyzed using fluorescence imaging and Western blotting, while Myo1 functional activity was tested using growth and endocytosis assays.

Results: Yeast strains expressing mutant Myo1 exhibited defects in growth and endocytosis similar to those observed in the myo1 deletion strain. These mutations also disrupted Myo1 localization to endocytic actin patches and resulted in mis-localization of Myo1 to eisosomes, linear membrane microdomains found in yeast cells. While both mutants examined in this study showed loss of function, one of these mutants was also characterized by the decreased protein stability.

Conclusions: Using the yeast model system we were able to determine that the kidney disease-associated mutations impair myosin functional activity and have differential effects on protein stability. This study provides the first example of using fission yeast as a model system to test the effects of FSGS mutations on Myo1e function. This novel system allowed us to definitively establish that the first time point between the myosin motor activity and its ability to support normal glomerular filtration.

Funding: NIDDK Support

FR-PO337

Vinculin Bonds Zonula Occludens-1 (ZO-1) and Is Required for Podocyte Stabilization of the Slit Diaphragm following Injury

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Background: Cell-matrix interactions and intercellular junctions in podocytes are important factors to prevent protein leakage through the glomerular filtration barrier. Vinculin, a cytoplasmic protein, links the actin filaments to integrin-based cell-matrix proteins and cadherin-based intercellular junctions. We have observed that vinculin is highly expressed in podocytes, and appears to be critical in maintaining slit diaphragm integrity following injury through its interaction with ZO-1.

Methods: Wild type and Vinculin (-/-) podocyte knock out (KO) mice were analyzed to determine the role of vinculin in vivo, and primary podocytes were isolated for in vitro studies.

Results: Podocyte specific ablation of Vcl resulted in no significant difference in body weight, albuminuria, and kidney histology up to 18 months when compared to littermate controls. However, Pod-Vcl KO mice had significantly increased albumin/creatinine ratios following lippopolysaccharide (LPS) or rabbit anti-mouse glomerular basal membrane (NTS) induced podocyte damage respectively (284±40 vs 411 ±31 µg/mg, and 205±28 vs 314±38 µg/mg, P<0.05). In addition, loss of Vcl in podocytes resulted in worsened foot process effacement. Co-immunoprecipitation of Myo1 to eisosomes, linear membrane microdomains found in yeast cells. While both mutants examined in this study showed loss of function, one of these mutants was also characterized by the decreased protein stability.

Conclusions: Using the yeast model system we were able to determine that the kidney disease-associated mutations impair myosin functional activity and have differential effects on protein stability. This study provides the first example of using fission yeast as a model system to test the effects of FSGS mutations on Myo1e function. This novel system allowed us to definitively establish that the first time point between the myosin motor activity and its ability to support normal glomerular filtration.

Funding: NIDDK Support
FR-P0338
AT 1  Receptors in Podocytes Control GFR and Susceptibility to Kidney Injury

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Background: Angiotensin II, acting via AT 1  receptors, plays a critical role in CKD progression. Pharmacologic blockade of AT 1  receptors reduces albuminuria and this is linked to its efficacy in CKD. Within the kidney, the density of AT 1  receptor expression is lower in the glomerulus, where AT 1  receptors are expressed in multiple cell lineages and are involved in regulating glomerular pressures and GFR. However, the key cellular sites of action in the glomerulus involved in physiological regulation and in promoting proteinuria have not been directly defined. Since podocyte dysfunction and injury have been implicated in the development of many glomerulopathies, we investigated the role of AT 1  receptors in podocytes using cell-line specific gene targeting.

Methods: Because the minor AT 1  receptor isoform (AT 1B ) is expressed at significant levels in podocytes, we generated mice lacking all AT 1  receptors in the podocyte (PodKO) by Cre-mediated excision of a conditional allele of the major AT 1  receptor isoform (AT 1a ) on an AT 1a -null background.

Results: PodKO mice develop normally with kidney weights similar to controls (6.9±0.5 vs 7.0±0.3 g/BW) and their glomerular morphology appears normal. GFR was significantly reduced in 24-week old PodKO (8.9±3.5 ml/min' 1 g' 1 ) compared to controls (29.5±4.5 ml/min' 1 g' 1 ); p<0.04), but there was no significant difference in the low levels of albumin excretion between the groups. To determine whether the elimination of AT 1  receptors from podocytes impacts albuminuria and kidney injury in a model with high levels of Ang II, a transgene (RenTg) driving constitutive expression of renin was crossed onto the PodKO background. At 24 weeks of age, levels of albuminuria were increased in RenTg mice (210±71 µg/24 hr) compared to controls (29.9±24 µg/24 hr; p<0.02), but this increase in albuminuria was unaffected in RenTg-PodKO mice (229±38 µg/24 hr). Despite similar levels of albumin excretion, kidneys from RenTg-PodKO mice had exaggerated kidney injury with more glomerulosclerosis, mesangial expansion, and tubular casts.

Conclusions: Our results suggest that AT 1  receptors in podocytes do not promote albuminuria and may protect against glomerular injury.

Funding: Private Foundation Support

FR-P0339
H2O2 Production by Nox4 Drives Ang II – Dependent Calcium Influx Through TRPC6 Channels in the Podocytes

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Background: Improper Ca2+ handling by the podocyte can result in cell damage and loss of function. Podocyte depletion and associated glomerulocapsulitis are typical for progressive chronic nephropathies, which have been associated with elevated levels of ROS, including H2O2. One of the key mediators of Ca2+ influx in the podocytes is a TRPC6 channel. The goal of this study was to provide a mechanistic insight into the Ang II-dependent regulation of TRPC6 channel.

Methods: Changes in intracellular Ca2+ levels were measured with live confocal microscopy in podocytes of isolated glomeruli. Patch clamp analysis was performed to assess the activity of TRPC6 channels in this preparation. Enzymatic biosensors technique was applied to determine H2O2 release in the kidney cortex and isolated glomeruli.

Conclusions: The Ca2+ influx through TRPC6 channel is an important determinant of podocyte injury. Our results, therefore, suggest that TRPC6 channel may contribute to cell injury caused by Ang II.

Funding: Other NIH Support - R01 HL08880, R01 12266 (NHLBI)

FR-P0340
Role of Unliganded Vitamin D Receptor (VDR) in Providing Podocyte Protection During AT1R Blockade (BLK) in Adverse Milieu

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Background: AT1R-BLK provides podocyte protection in response to inflammatory stimuli and renal injury. However, the mechanism of the protective actions is incompletely understood. In this study, we sought to determine the role of unliganded VDR in providing podocyte protection during AT1R blockade.

Methods: Primary rat podocytes (1D) driving constitutive expression of VDR were crossed onto the AT1R-BLK (AT1R-BLK) gene background. These mice were crossed on to the renin transgenic (RenTg) background. In order to compare the renal phenotype of these mice to the control (WT) group, mice were subjected to a high-salt diet and then we analyzed the renal function and glomerulosclerosis.

Conclusions: It appears that SMRT is necessary for DNA repairs during AT1R-BLK. SMRT-depleted podocytes lacked AT1R-BLK-mediated protection against DNA damage, as assessed by incision of H2O2 release in the kidney cortex and isolated glomeruli. One of the key mediators of Ca2+ influx in the podocytes is a TRPC6 channel. The goal of this study was to provide a mechanistic insight into the Ang II-dependent regulation of TRPC6 channel.

Funding: Other NIH Support - R01 HL08880, R01 12266 (NHLBI)

FR-P0341
Enhanced S-Nitrosylation and N-Glycosylation of Podocin-R138Q May Contribute to Its Defective Trafficking and Rapid Degradation

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Background: Missense mutations in the NPHS2 gene, encoding podocin, are a major cause of deminished and sporadic cases of steroid-resistant nephrotic syndrome (SRNS). Among them, those encoding endoplasmic reticulum (ER)-retained mutant proteins, e.g. R138Q, correlate with the most severe cases of SRNS.

Methods: We generated two human podocyte cell lines stably expressing 2HA-podocin or 2HA-podocin R138Q to perform comparative studies on podocin post-translational modifications and podocin degradation.

Results: We detected increased podocin S-nitrosylation and N-glycosylation in 2HA-podocin (α) vs. 2HA-podocin (α) podocytes, which may modify podocin topology, degradation and trafficking. We also suggest that a further interaction of podocin (α) with an ER chaperone calnexin stabilizes the protein in the higher degradation rate of podocin (α) previously found in R140Q knock-in mice, that we found that non-glycosylated (ng) podocin (α) has a dramatically shorter half-life than podocin (α). Moreover, the Ng-glycosylated forms of podocin (α) are more stable than its non-glycosylated fraction. We also show that ng-podocin (α) is mainly degraded by the proteasome, whereas ng-podocin can be degraded by both the proteasomal and the lysosomal proteolytic machineries. Furthermore, preventing ng-podocin (α) degradation allows its partial localization to the podocyte filipodia, improves the ratio between its non-glycosylated and glycosylated forms and reduces its interaction with calnexin.

Conclusions: These findings show podocin S-nitrosylation for the first time and suggest that increased S-nitrosylation and N-glycosylation may contribute to the defective trafficking and degradation of podocin (α), the product of the most frequent human podocin missense mutation, and possibly of other podocin-missense mutants.

Funding: Government Support - Non-U.S.

FR-P0342
RAS Inhibition Enhances Proliferation and Migration of Cells of Renin Lineage (CoRL) as Progenitors in Experimental FSGS

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Background: RAS inhibitors are used therapeutically in proteinuric glomerular diseases. In focal segmental glomerulosclerosis (FSGS) where podocyte number is depleted, recent data showed that ACE-Inhibitors could improve podocyte number. Because adult podocytes do not proliferate, their replacement by renal progenitors is critical for their regeneration in disease. The impact of RAS blockade on adult podocyte progenitors is not well understood.

Methods: Experimental FSGS characterized by podocyte depletion was induced by an anti-podocin antibody in two strains of Cells of Renin Lineage (CoRL) reporter mice (RenCre and RenCreER) where CoRL are fate mapped. Diseased mice were randomized at day 3, when podocyte number was depleted by 40%, to receive Enalapril or Losartan, or the controls Hydralazine or water. Brdu was injected to monitor proliferation. Following initial podocyte depletion, cell number was monitored for 4 weeks (measured by p57 staining) was higher in both Enalapril and Losartan groups on d14 and d28. This was accompanied by significantly lower proteinuria and glomerulosclerosis. The number of CoRL increased in the intra-glomerular compartment in FSGS mice given water or hydralazine. However, the number of labeled CoRL further increased significantly in FSGS mice given Enalapril or Losartan. A subset of CoRL detected in the glomerular compartment co-expressed several markers for podocytes and PEC's. RAS inhibition increased BrdU staining in CoRL in the juxta- and intraglomerular compartments, but was not seen in podocytes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
ShcA Influences Nephrin Endocytosis and Protec... Cell Biology: Glomerular - I

Background: The transmembrane protein nephrin is a key component of the slit diaphragm (SD). It has recently been postulated that nephrin turnover plays a key role in maintaining a healthy SD, and multiple theories regarding the role of nephrin phosphorylation in endocytosis are emerging. Tyrrosine phosphorylation of the cytoplasmic tail of nephrin facilitates recruitment of several signaling proteins that regulate podocyte shape and thereby permselectivity of the SD. Previous work from our lab has identified and mapped the interaction between nephrin and the ShcA adaptor protein and demonstrated an early requirement for ShcA in the maintenance of the filtration barrier in mice. Given ShcA's established role in endocytosis, we now hypothesize that ShcA may regulate nephrin endocytosis to ultimately maintain filtration barrier integrity.

Methods: Multiple approaches were used to measure the influence of ShcA and ShcA domain mutants on the levels of surface nephrin and signaling downstream of nephrin. Purified recombinant mouse nephrin (PMN) was generated in Sprague-Dawley rats for 0, 4, 7, or 14 days and nephrin endocytosis was monitored via biotinylated and immunofluorescence experiments.

Results: We demonstrate that ShcA expression is increased in podocytes in response to PAN injury, which is accompanied by activation of the stress-activated p38 and JNK MAP kinases. Interestingly, we found that transactivation of AP-1, which occurs downstream of nephrin activation as well as p38 and JNK, is attenuated by ShcA, and this effect is reversed by mutation of the ShcA SH2 domain, which mediates nephrin binding. Further investigation revealed that ShcA promotes nephrin endocytosis in a phospho-dependent manner by enhancing Src-mediated nephrin phosphorylation, its own binding to nephrin and endocytosis into EE/A1-positive endosomes both in vitro and in PAN-treated rats.

Conclusions: Together these findings suggest a protective effect of ShcA in podocytes by influencing phospho-dependent nephrin endocytosis and possibly attenuating nephrin-mediated p38/JNK signaling in response to injury.

Podocyte Specific Response to Complement Challenge, Anna Katinettman, Magdalena Riedl, Fred G. Plathour, Moin Saleem, Jun Oh, Christoph Licht, Dept of Pediatrics, Univ Medical Center Hamburg-Eppendorf, Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; Dept of Pediatric Nephrology, Hospital for Sick Children, Academic Renal Unit, Univ of Bristol.

Background: There is a multilayered system of fluid phase and surface bound complement regulatory proteins, which ensure that complement activation occurs only on specific sites and spares the body's own cells. Unrestricted complement activation is a main cause for damage in complement-mediated glomerulopathies such as C5G or membrane nephropathy (MN). In MN, podocytes, key components of the glomerular filtration barrier, are target of overshooting complement activation. The aim of this study was to characterize the complement defense mechanisms in podocytes and their response to complement challenge (CC).

Methods: We analyzed complement regulators by immunofluorescence, flow cytometry and qRT-PCR in immortalized human podocytes and compared them to blood grown endothelial cells (BOECs). Functionality of secreted complement factor H (CFH) was tested via a cofactor assay. In a model for CC (sensitization with antibodies against the ShcA SH2 domain, which mediates nephrin binding. Further investigation revealed that ShcA promotes nephrin endocytosis in a phospho-dependent manner by enhancing Src-mediated nephrin phosphorylation, its own binding to nephrin and endocytosis into EE/A1-positive endosomes both in vitro and in PAN-treated rats.

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Funding: Government Support - Non-U.S.

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Funding: Government Support - Non-U.S.

Ubiquitin C-Terminal Hydrolase-L1 Deficiency in Podocytes Protects from Immune Complex Nephritis in Mice, Julia M. Fehlert, 1, 2 Marlies Sachs, 1 Thorsten Wiech, 2 Rolf A. Stahl, 1 Catherine Meyer-Schwesinger, 1 Nephrology, Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) is a central deubiquitylating enzyme of the neuronal ubiquitin proteasomal system. UCH-L1 is thought to regulate the intracellular pool of monoubiquitin in neurons. Recently we identified a de novo expression of UCH-L1 in podocytes of patients with membranous nephropathy. Upregulation of UCH-L1 in podocytes correlated with disease progression, accumulation of ubiquitinated proteins and altered expression of podocyte-specific proteins in human and rodent podocytes. Inhibition of UCH-L1 enzymatic function in a rat model of membranous nephropathy decreased the abnormal protein accumulation and ameliorated the clinical course of disease. We generated mice with podocyte-specific UCH-L1-deficiency to investigate the role of UCH-L1 in the novel expression in podocytes.

Methods: Mice with podocyte-specific UCH-L1-deficiency were generated by Cre-lox technology and back-crossed into the C57BL6 background. Podocyte phenotype was evaluated by morphological (immunohistochemistry, electron microscopy) and biochemical techniques (Western blotting, proteasomal activity assays, real-time PCR) in unchallenged and anti-podocyte antibody challenged wildtype and knockout mice.

Results: Unchallenged podocyte-specific UCH-L1-deficient mice exhibited normal podocyte morphology throughout life and delayed age-related proteinuria accompanied by a decreased accumulation of poly-ubiquitinated proteins. Following induction of anti-podocyte nephritis, podocyte-specific UCH-L1-deficient mice showed decreased signs of podocyte injury and decreased proteinuria despite a comparable immunologic reaction to the injected anti-podocyte antibodies. Podocyte-specific proteins such as nephrin and podocin were expressed and protein accumulation was decreased. UCH-L1-deficiency resulted in increased proteasomal capacity and activity in injured podocytes.

Conclusions: Podocyte-specific UCH-L1-deficiency protects podocytes from age-related degenerative changes and from immune complex nephritis through increased proteasomal capacity.

Funding: Government Support - Non-U.S.

Ubiquitin C-Terminal Hydrolase-L1 Deficiency in Podocytes Protects from Immune Complex Nephritis in Mice, Julia M. Fehlert, 1, 2 Marlies Sachs, 1 Thorsten Wiech, 2 Rolf A. Stahl, 1 Catherine Meyer-Schwesinger, 1 Nephrology, Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Ubiquitin C-Terminal Hydrolase-L1 Deficiency in Podocytes Protects from Immune Complex Nephritis in Mice, Julia M. Fehlert, 1, 2 Marlies Sachs, 1 Thorsten Wiech, 2 Rolf A. Stahl, 1 Catherine Meyer-Schwesinger, 1 Nephrology, Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Conclusions: Podocyte-specific UCH-L1-deficiency protects podocytes from age-related degenerative changes and from immune complex nephritis through increased proteasomal capacity.

Funding: Government Support - Non-U.S.
glomerular disease and results from disruption of the glomerular filter. The slit diaphragm is a specialized region in podocytes between adjacent podocytes. Maintenances of the correct position, adjacent podocytes has not been well understood.

Methods: RNA was isolated from differentiated human podocytes and isolated murine glomeruli and PCR performed. Human podocytes were retrovirally transduced with EphB2-YFP and ephrinb1-CFP and ephrinb1-CFP podocytes were differentiated in co-cultures and time lapse video imaging was performed. In addition, a co-culture of differentiated EphB2-YFP and ephrinb1-CFP cells was examined. To investigate the role of the intracellular domains of the EphB2 receptor and ephrinb1 ligand, truncated mutants of EphB2 (Ephb2.DC-YFP) and ephrinb1 (ephrinb1.DC-CFP) were analyzed.

Results: Human podocytes as well as murine glomeruli express EphB1, 2 and 3 receptors. Co-cultures of differentiating EphB2-YFP and ephrinb1-CFP podocytes show repulsion between the two cell types. Transsudocytosis (YFP particles in CFP cells and vice versa) occurs for EphB2-YFP podocytes during repulsion. The repulsion is dependent on the intracellular domain of Ephb2 as Ephb2.DC-YFP cells adhere to ephrinb1-CFP and ephrinb1.DC-CFP cells. However, repulsion is maintained in co-cultures of Ephb2-YFP with ephrinb1.DC-CFP cells. Co-culture experiments of differentiated, confluent podocytes confirm the results presented above.

Conclusions: EphB2 receptors mediate podocyte repulsion upon binding to their ligand ephrinb1. The EphB2 receptor cytoplasmic domain seems to be crucial for repulsion. Maintaining the correct podocyte distance within the highly organised glomerular architecture is not been well understood. These cell culture data provide a promising concept of potential regulation of podocyte distance in vivo.

Funding: NIH Support, PHS Grant R01DK093549-01, Medical Research Council & The Richard Bright


Background: Chronic kidney disease is associated with reduced VEGF-A expression. However, the role VEGF-A splice isoforms play in kidney physiology and pathology is unclear. Use of an alternative 3’ splice site in the terminal exon of VEGF-A results in the expression of anti-angiogenic VEGF-β. Previous studies suggest that VEGF-β is protective in renal disease in diabetic rodents. This study aimed to investigate whether constitutive podocyte over-expression of VEGF-β is able to rescue the injury phenotype seen in the inducible podocyte-specific VEGF-A KO mouse. The mechanism of action of VEGF-β within the glomerulus was also investigated.

Methods: Podocyte-specific VEGF-A KO was induced via doxycycline for 10-14 weeks in WTI, VEGF-βKO and VEGF-AKO n/nep-VEGF-β mice. In situ hybridization confirmed a knock-down of VEGF-A. The kidney functional phenotype was determined through the urinary albumin creatinine ratio (uACR) and measurement of glomerular water permeability. Electron microscopy was used to examine the ultra structure of the glomeruli, and immunofluorescence to determine the expression levels of podocyte and endothelial-specific proteins. Glomerular endothelial cells (GEnCs) in culture were used to determine the mechanism of action of VEGF-β through VEGFR-2.

Results: The VEGF-β isoform alone is sufficient to rescue the increase in albuminuria and glomerular water permeability in the context of progressive depletion of all VEGF-A isoforms. Ultra structural studies show glomerular basement membrane thickening and increased podocyte slit width in the VEGF-A KO mouse, with both being rescued in the VEGF-β over-expressors. VEGF-β also restores PECAM expression in GEnCs, and glomerular capillary circumference. Mechanistically, VEGF-β increases VEGFR-2 expression and phosphorylation both in vivo and in vitro. Furthermore, it down regulates genes involved in the migration and proliferation of GEnCs, which are otherwise up regulated by VEGF-α.

Conclusions: Our study indicates that VEGF-A splice isoform manipulation could be a novel therapeutic avenue in chronic glomerular disease.

Funding: Other NIH Support - Medical Research Council & The Richard Bright

FR-PO349 Rituximab Prevents TNFα Induced Podocyte anb3 Integrin Activation Farah Leclercq, Christopher E. Pedigo, Alessia Forconi, Sandra M. Merscher. Katz Family Drug Discovery Center, Nephrology, Univ of Miami, FL.

Background: Focal Segmental Glomerulosclerosis (FSGS) is a disease characterized by podocyte and scarring of the glomeruli. FSGS accounts for up to 20% of end-stage renal disease cases in the United States. The expression of anti-angiogenic VEGF-β (sVEGFR1 (sflt1)) is an alternative splicing product of VEGF-β (flt1) gene. Both sflt1 and sflt1 can function as “decoy receptors” for VEGF. sflt1 plays a key role in maintaining avascularity of the cornea, and increased circulating levels of sflt1 are linked to preeclampsia. Moreover, deletion of sflt1 from mouse podocytes results in proteinuria at 6 weeks of age, while deletion of the kinase signaling domain of this receptor alone results in no renal phenotype. In vitro studies showed that sflt1 can induce formation of foot process-like structures in human podocytes. We hypothesize that sflt1 regulates podocyte cytoskeletal dynamics and glomerular barrier function by titrating local glomerular VEGF levels.

Methods: To determine function of the soluble variant of Flt1 in the glomerulus, we generated a conditional KO model for the single sflt1 (sflt1 cko) isoform reported in mice (removal of intron 13). Renal phenotype was examined by evaluating kidney function and histology. qPCR and Northern blot were used to identify splice variants of Flt1; 3’RACE was used to clone the spliced genes. Proteins of splice variants were generated by BacMam system.

Results: We generated sflt1 cko mice, and confirmed the deletion of Flt1 intron 13 using Southern blot. Surprisingly, it did not result in any overt kidney phenotype by 6 months of age. Northern blot and Western blot analyses revealed the existence of a major compensatory isoform, previously reported as human-specific. We also confirmed the existence of 17 new sflt1 isoforms in RNA isolated from mice and 12 from human podocytes. Plasmablasts were stained for sclerostin, a marker of plasma cells.

Conclusions: We report a large number of novel, soluble Flt1 isoforms in both mouse and human plasma samples. We posit that the presence of these isoforms compensates for the loss of sflt1 in our transgenic model. The functions of these isoforms warrant further investigation and may provide insight into regulation of VEGF levels, podocyte function and preeclampsia.

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FR-PO351 Polarity Signaling at the Kidney Filtration Barrier: Questioning the Function of Par3A Sybilie Köhler,1 Markus M. Rinschen,1 Carien M. Niessen,2 Wilhelm Bloch,3 Bernhard Schermer,2 Thomas Benzing,2 Paul T. Brinkkoefter.1,2 1 Dept of Internal Medicine and Center for Molecular Medicine, Univ Hospital Cologne, Germany; 2 Cologn Excellence Cluster on Cell Signaling in Health and Disease (CECAD), Univ of Cologne, Germany; 3 Dept of Molecular and Cellular Sport Medicine, German Sport Univ Cologne, Germany; 4 Dept of Dermatology and CECAD Cologne, Univ of Cologne, Germany.

Background: The slit diaphragm (SD) represents the only cell-cell contact in-between neighbouring podocytes. Classical adherence as well as tight junction proteins are part of this protein-protein supercomplex including ZO-1, ocludin, catenins and cadherins. Polarity signaling is critical to maintain the SD complex as the Par3/PARP complex clusters at the SD via direct interaction of Par3 with nephrin via its PDZ-domains.

Methods: To understand the role of the Par3 proteins at the slit diaphragm, we generated a novel podocyte specific Par3A knockout mouse model where exon 6 is flanked by loxp sites. Following podocin:cre mediated recombination expression of all known Par3A isoforms should be abrogated. We validated cre recombination efficiency, lack of Par3A mRNA and protein expression by qPCR from isolated primary podocytes as well as by immunofluorescence stainings on renal sections.

Results: Mice were born in predicted Mendelian frequency. Par3A-WT mice were born and did not show any signs of disease in their later life. Even challenging Par3A-WT mice with the albumin overload model did not result in an overt glomerular phenotype. Therefore, we performed additional immunoprecipitation experiments for aPKCota out of immortalized mouse podocytes and carried out nLC/MS/MS analysis to identify the aPKCota interacting partners. Interestingly, the most abundant aPKCota interacting proteins were Par6 and Lgl1/2.

Conclusions: Our results challenge the current view of the aPKC/Par3 complex and its role at the slit diaphragm. In contrast to tight junctions where AKP-site-clustering by Par3, its role at the SD is independent of Par3A. Here Lgl1/2 seem to be the predominant interactors clustering aPKC/Par3 at the SD.

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FR-PO352
Focal Segmental Glomerulosclerosis (FSGS) Permeability Factor (FSPF) Interacts with Glomerular Filtration Barrier Through Glycoconjugates Ram Sharma,1 Ellen T. McCarthy,2 Tarak Srivastava,3 Virginia J. Savin,4 Mukut Sharma,1 1Renal Research, KC VA Medical Center - MBRF, Kansas City, MO, 2Kidney Inst, KU Medical Center, Kansas City, KS, 3Renal Div, UMCK Children’s Mercy Hospital, Kansas City, MO.

Background: Galactose (Gal) blocks the FSGS serum-surface induced increase in in vitro glomerular albumin permeability (P_a) (Trans Res 2008, 151:288-292) and decreases proteinuria in some patients with recurrent FSGS (NDFT 2009, 24:2938-2940). Thus, the interaction of FSPF with glomerular cell surface glycoconjugates may play an essential role in its effect on the filtration barrier.

Methods: We selected sugars and lectins to model the interaction between glomerular glycoconjugates and FSPF. We used, (a) affinity techniques to evaluate the binding of FSPF with immobilized sugars (b) immobilized neuraminidase to remove sialic acid to assess its significance in FSPF-induced increase in P_a in (i) Gal and (ii) GalNAc-specific lectins to determine their effect on FSPF, results are shown as fluorescence.

Results: Plasma FSPF activity was retained by immobilized Gal, GalNAc or galactosamine. Gal dose-dependently blocked FSPF-induced increase in P_a (10^-10 M) and partially reversed the effect of FSPF on P_a (p<0.01). In contrast, glucose, glucosamine or mannose did not interact with FSPF. Removal of sialic acid activity neuraminidase diminished the FSPF-induced increase in P_a. We screened twenty Gal/GalNAc-specific lectins as potential mimetics of FSPF. Only Dolichos biflorus agglutinin (DBA, 10 mg/mL) and Helix pomatia lectin (10 mg/mL) increased P_a to 0.65 and 0.55, respectively (p<0.001). The increases in P_a, like that induced by FSPF was blocked by Gal (100 µM) (p<0.001). Immunohistochemistry revealed the interaction of FSPF with β1-integrin-recognizing domains of FSPF participate in its interaction with specific sugar(s) of glomerular cells resulting in altered filtration barrier function. Our novel findings regarding the affinity of FSPF for select sugars, the loss of activity after removal of sialic acid and the direct effect of certain lectins on barrier function provide new information regarding the molecular composition of FSPF and its interaction with glomerular proteins/glycolipids.

Funding: NIDDK Support, Veterans Administration Support

FR-PO353
EPB41L5 Is a Critical Regulator of the Kidney Filtration Barrier Christoph Schell,1 Martina Suhn,1 Manuel Rögg,1 Martin Helmsdäter,1 Mariko Hirano-Kobayashi,2 Tobias B. Huber.1 1Dept of Nephrology, Univ Medical Center Freiburg, Freiburg, Baden-Württemberg, Germany; 2Laboratory for Vertebrate Body Plan, Center for Developmental Biology - RIKEN, Kobe, Kobe, Japan.

Background: Podocyte loss represents the final common pathway of various glomerular pathologies. Hence, tightly regulated adhesion towards the glomerular basement membrane is a fundamental biological process of glomerular podocytes.

Methods: Based on podocyte single cell isolation and a mass-spec candidate approach the composition of podocyte focal adhesions was resolved. Combining a drosophila nephropathy model with a Newly generated conditional mouse model and various high resolution microscopy techniques (TEM, STORM) the candidate protein EPB41L5 was analyzed.

Results: Knockdown of the Epb41l5 homolog Yurt in drosophila nephropathies resulted in podocyte detachment and decreased renal function. Evaluation of a genetic conditional knockout model revealed a rapid loss of podocytes implicating deregulated podocyte-specific deletion of FSPF expressing domains of FSPF participate in its interaction with specific sugar(s) of glomerular cells resulting in altered filtration barrier function. Our novel findings regarding the affinity of FSPF for select sugars, the loss of activity after removal of sialic acid and the direct effect of certain lectins on barrier function provide new information regarding the molecular composition of FSPF and its interaction with glomerular proteins/glycolipids.

Conclusions: Our findings indicate that EPB41L5 is a highly conserved, specific regulator of podocyte adhesion by modulating focal adhesion composition and function. Future studies will need to clarify its potential implications in genetic and acquired glomerular pathologies.

FR-PO354
The Effect of Anti-PLA2R Autoantibodies on Human Podocytes In Vitro Marylene Frescaud.1 Rachel Lennon,2 Paul E. Brinchley.1 1Welcome Trust Cell-Matrix Research, Univ of Manchester, Manchester, United Kingdom; 2Inst of Cardiovascular Sciences, Manchester Royal Infirmary, Manchester, United Kingdom.

Background: PLA2R was identified as a major target antigen in idiopathic membranous nephropathy. 70% of patients have circulating autoantibodies which bind this receptor on the podocyte leading to immune complex deposition in the glomerular basement membrane. We recently demonstrated the effect on PLA2R expression on PLA2R and Necropsy tissues from patients. We produced the first 3D model of PLA2R, domains and demonstrated that autoantibodies are of high affinity. We seek to understand if affinity-pure anti-PLA2R alone in the absence of complement can modulate podocyte function.

Methods: We prepared affinity purified human anti-PLA2R (91% IgG4, 9% IgG2) and assessed podocyte morphology following antibody treatment using immunofluorescence staining of actin and measurement of cell surface area and circularity. Integrity of the filtration barrier was assessed by Electric Cell-substrate Impedance Sensing and the

response of a confluent monolayer of differentiated podocytes to 10mg/ml purified human anti-PLA2R and apoptosis was measured by cleaved caspase-3 staining in podocytes and oxidative stress was measured with CellROX reagent in differentiated podocytes challenged with the autotaxin.

Results: We have developed an in vitro podocyte model to define mechanisms of anti-PLA2R effects on cell morphology and function. Purified anti-PLA2R altered podocyte shape, with rounding and loss of actin stress fibres within 24 hours. Integrity of a confluent podocyte monolayer was significantly reduced at 72 hours by anti-PLA2R but not by the IgG control. Within 30 minutes of anti-PLA2R treatment, there was evidence of caspase-3 cleavage and podocytes peaking at 6 hours. Treatment with anti-PLA2R induced anti-free radical generation (P<0.0001, treated vs. untreated), triggering oxidative stress which could be neutralised using a scavenger.

Conclusions: Anti-PLA2R in the absence of complement activation modulates podocyte cell morphology by inducing changes in cell shape and monolayer permeability, activation of free radical production and apoptosis.

Funding: Private Foundation Support

FR-PO355
Deletion of the Ste20-Like Kinase, SLK, in Podocytes Induces Injury Andrey V. Cybulsky,2 Elena Torban,1 Joan Papillon,1 Julie Guillermette,1 Natalya Belkina.2 1Medicine, McGill Univ, Montreal, QC, Canada; 2NIH, Bethesda, MD.

Background: SLK is essential for embryonic development, and may play a key role in wound healing, tumor growth and metastasis. Expression and activation of SLK is increased during recovery from ischemic acute kidney injury. Overexpression of SLK in glomerular epithelial cells/podocytes in vivo induces injury and proteinuria. Conversely, reduction of SLK expression in podocytes leads to loss of foot process effacement and microvesicular transformation of podocyte plasma membranes. Mean foot process width was ~2-fold greater in KO, compared to control. By immunofluorescence microscopy, WT1-positive cells were reduced by 35% in KO mice compared to control, and staining for nephrin and podocynx was reduced in KO mice by 20-30%. SLK is reported to phosphorylate ezrin. Staining for phosphorylated ezrin/radixin/moesin (ERM) was reduced by 20% in KO glomeruli, in keeping with reduced SLK catalytic activity in glomeruli; however, tubular phospho-ERM staining was comparable in KO and control.

Conclusions: Podocyte-specific deletion of SLK leads to albuminuria at 4-5 months of age in male mice, and 9-9 months in female mice, which persisted for up to 13 months (albumin/creatinine in KO was 2-3-fold above control). At 11-12 months, KO mice did not show renal histologic abnormalities by light microscopy, and glomerular area of KO was comparable to control. However, by electron microscopy, KO mice showed focal foot process effacement and microvesicular transformation of podocyte plasma membranes. Mean foot process width was ~2-fold greater in KO, compared to control. By immunofluorescence microscopy, WT1-positive cells were reduced by 35% in KO mice compared to control, and staining for nephrin and podocynx was reduced in KO mice by 20-30%. SLK is reported to phosphorylate ezrin/radixin/moesin (ERM) was reduced by 20% in KO glomeruli, in keeping with reduced SLK catalytic activity in glomeruli; however, tubular phospho-ERM staining was comparable in KO and control.

Funding: Government Support - Non-U.S.

FR-PO356
A Podocyte-Specific Knockout of the DNA Repair Gene Erclecs to Proteinuria and Focal Segmental Glomerulosclerosis Fabian Braun,1 Roman Aaron Akbar,1 Björn Schumacher,2 Wilhelm Bloch,1 Bernhard Schermer,1 Thomas Benzing,1 Christine E. Kutsch.1 1Nephrology, Univ Hospital Cologne, Cologne, Germany; 2CECAD, Univ Hospital Cologne, Cologne, Germany; 3German Sport Univ Cologne, Cologne, Germany.

Background: The prevention and therapy of aging-related diseases will become a major health problem. Among elderly patients mild to severe impairment of kidney function is common. Models to study renal aging have not been established yet.In a previous study, we identified a progeria mouse model of Ercc1-deficiency to exhibit expression profiles similar to those of glomerular aging in wt mice. Ercc1 is involved in nucleotide excision repair, facilitating 5' incision around bulky DNA lesions. In humans, the lack of Ercc1 was comparable to control. However, by electron microscopy, KO mice showed focal foot process effacement and microvesicular transformation of podocyte plasma membranes. Mean foot process width was ~2-fold greater in KO, compared to control. By immunofluorescence microscopy, WT1-positive cells were reduced by 35% in KO mice compared to control, and staining for nephrin and podocynx was reduced in KO mice by 20-30%. SLK is reported to phosphorylate ezrin/radixin/moesin (ERM) was reduced by 20% in KO glomeruli, in keeping with reduced SLK catalytic activity in glomeruli; however, tubular phospho-ERM staining was comparable in KO and control.

Conclusions: Podocyte-specific deletion of SLK leads to albuminuria, loss of podocytes and morphologic evidence of podocyte injury. Thus, SLK is essential to the maintenance of podocyte integrity as mice age. The mechanism may, at least in part, relate to ezrin phosphorylation and cytoskeletal integrity.

Funding: Government Support - Non-U.S.
Conclusions: Our study reveals a critical role for nucleotide excision repair in murine podocytes. This gene is expressed in glomerulosclerosis and causes a phenotype with early-onset proteinuria and stunted growth. The role of Ercc1 in a podocyte cell culture model.

Funding: Government Support - Non-U.S.

FR-PO359

Regulation of Fascin-1 by Mechanical Stress in Podocytes

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Background: Glomerular hypertension causes glomerulosclerosis via the loss of podocytes, which are challenged by an increased mechanical load. We and others have demonstrated that podocytes are mechanosensitive cells. However, the response of podocytes to stretch remains incompletely understood.

Methods: Using 2D fluorescence difference gel electrophoresis (2D DIGE), we analyzed the proteome of cells of our mouse podocyte cell line that were cultured on flexible membranes with or without cyclic biaxial mechanical stress (0.5 Hz, 5% linear strain, 3 d).

Results: Mechanical stress profoundly altered the podocyte proteome. Several spots containing the actin-bundling protein fascin-1 were differentially regulated by mechanical stress. By immunofluorescence, fascin-1 was found to colocalize with nephrin in mouse kidney sections. The presence of fascin-1 in foot processes was confirmed by immunoelectron microscopy.

Conclusions: In summary, mechanical stress dephosphorylates fascin-1 in podocytes thereby increasing the actin-bundling activity of fascin-1. Fascin-1 may play an important role in the adaptation of podocytes to mechanical stress.

Funding: Government Support - Non-U.S.

FR-PO360

Deletion of the Vps34 Downstream Effector PIKfyve Establishes Milder Endocytic Dysfunction in Healthy Glomerular Podocytes Compared to Proximal Tubular Cells

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Background: The mechanisms by which the glomerular filtration barrier prevents the loss of large macromolecules and at the same time maintain the filter remain poorly understood. Recent studies have proposed that podocytes play an active role in both endocytosis of filtered macromolecules and maintaining the filtration barrier.

Methods: We generated podocyte and proximal tubular specific deletion of PIKfyve using the cre-loxP system. Indirect IF and immune EM was used to assess the endocytic pathways.

Results: Deletion of a key endosomal trafficking regulator, the class III phosphoinositide 3-kinase or Vps34 in podocytes results in aberrant endosomal membrane morphology and podocyte dysfunction. We recently demonstrated that the vacuolation phenotype in cultured Vps34-deleted podocytes is due to the absence of a substrate for the Vps34 downstream effector PIKfyve. PIKfyve is a FYVE finger domain containing phosphoinositide 5-kinase that phosphorylates Vps34-generated phosphatidylinositol (PtdIns) 3P to produce PtdIns(3,5)P2. PIKfyve perturbation and PtdIns(3,5)P2 reduction have been shown to result in massive membrane vacuolation along the endosomal system. We show here that deletion of PIKfyve in endocytically active proximal tubular cells resulted in the development of large cytolytic vacuoles that appear as a result of arrested endocytic traffic progression at a late-endosome stage. In contrast, deletion of PIKfyve in podocytes did not alter significantly the endosomal morphology even in aged, 18-month-old mice. However upon culturing, the PIKfyve-deleted podocytes obtained from the knockout mouse developed massive cytolytic vacuoles. Measurement of phosphoinositides using HPLC shows reduction of both PtdIns(3,5)P2 and PtdIns(3,5)P3 in PIKfyve deleted podocytes in vivo confirming reduced PIKfyve enzymatic activity following deletion. Using double fluorescent mitochondria mice we were able to confirm Cre-mediated gene deletion in both podocytes and proximal tubular cells in vivo.

Conclusions: In summary, these data suggest that healthy podocytes have a low level of endocytic flux in vivo.

Funding: NIDDK Support
Albumin-Induced Podocyte Injury Can Be Endocytosis-Independent

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Background: Endocytosis plays a crucial role in podocytes in nephrotic syndrome, wherein podocytes are exposed to serum levels of albumin. We have previously reported an association between podocyte exposure to albumin (and its associated factors) and proteinuria, cell injury and induction of pro-inflammatory genes. We thus hypothesized that albumin-induced podocyte injury can also be partially endocytosis independent.

Methods: Endocytosis was analyzed by fluorescence microscopy and fluorometry in cultured differentiated podocytes at varying temperatures and times in the absence or presence of inhibitors of clathrin- and caveolae-mediated endocytosis. Cells were analyzed for viability, activation of major kinases (p38, ERK1/2, JNK, MK2), and expression of pro-inflammatory, heat shock, and glucocorticoid-regulated genes.

Results: Podocytes at 37°C, but not at 4°C, were attenuated by inhibitors for both clathrin- and caveolae-mediated endocytosis. Inhibition of endocytosis, however, did not correlate with reductions in kinase activation or pro-inflammatory gene induction. While albumin exposure resulted in lower endocytosis in murine vs. human podocytes, murine cells activated kinases, induced pro-inflammatory genes and exhibited cell death more than human podocytes.

Conclusions: Inhibition of both clathrin- and caveolae-mediated albumin endocytosis did not correlate with activation of kinases and induction of pro-inflammatory genes in podocytes. Moreover, disparate responses were identified in human vs. mouse podocytes with regard to albumin endocytosis, cell injury, kinase activation, and pro-inflammatory gene induction. Taken together, our data suggest that although podocytes endocytose albumin in both clathrin- and caveolae-mediated manners, albumin-induced podocyte injury can occur in an endocytosis-independent manner.

Funding: NIDDK Support

FR-PO361

Molecular Targeting of Nephi1 Signaling: A Therapeutic Approach to Protect Podocyte Injury

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Medicine, Univ of Pennsylvania, Philadelphia, PA; Proteomics, Inst of Microbial Technology, Chandigarh, India; Medicine, Temple Univ, Philadelphia, PA.

Background: Glomerular injuries that induce podocyte dysfunction are the leading causes of renal malfunction. Podocyte proteins Nephrin and Nephi1 are essential components of the glomerular filtration barrier and signaling from these proteins is involved in maintaining podocytes structure and function. Thus understanding the mechanisms that regulate signaling and organization of these proteins are therapeutically valuable.

Methods: This study presents a novel hypothesis that attenuating Nephrin and Nephi1 signaling is therapeutically significant in protecting podocytes from injury. Consistent with this hypothesis, using a unique protein transduction approach, we recently demonstrated that inhibiting Nephi1 signaling protected podocytes from injury. Since we first reported the structures of Nephi1 and associated ligands, we have used high-resolution NMR and molecular models or compounds that can specifically bind Nephi1 and target its interactions.

Results: Using a novel approach of targeting protein-protein interaction, we identified many potential molecules and to test the proof of principle and the validity of this approach, cell lines expressing compounds ID (odesmosine) were commercially procured and investigated. Biochemical experiments suggested that addition of ID under in vitro and in vivo conditions significantly increased and stabilized the interaction between Nephi1 and ZO-1. As a consequence, induction of glomerular injury by PAN (purinomycinaminonucleoside) did not proceed in wild type podocytes but was completely blocked in the cells resistant injury induced changes in their actin cytoskeleton. Furthermore, using an in vivo zebrafish model system, we demonstrated that pre-treatment with ID rescued zebrafish from adriamycin induced toxicity and preserved their renal filtration system.

Conclusions: This study presents a new approach that provides compelling evidence that molecular approaches can be used to directly target slit diaphragm proteins to prevent podocyte damage.

Funding: NIDDK Support

FR-PO362

Genome-Modified Pluripotent Stem Cells Reveal a Critical Role for Podocalyxin in Human Podocyte Morphogenesis

Benjamin S. Freedman, Craig R. Brooks, Zheng Zhou, Joseph V. Bonventre, Brigham and Women’s Hospital; Harvard Medical School; Univ of Washington School of Medicine.

Background: Human pluripotent stem cells (hPSCs) can self-renew extensively and differentiate into diverse tissues. We investigated the potential of hPSCs to differentiate into podocytes, an apical sialomucin altered in glomerular disease states.

Methods: Cas9 nuclease and guide RNAs targeting PODOX were transfected into hPSCs. PODOX clones were identified by chromatogram and immunoblot analysis. hPSCs were differentiated stepwise with growth factors into kidney progenitor cells present a new tool for investigating human podocytes of junctional complexes and podocyte spacing. Our findings suggest a functional role in disease in a dish’ models and therapeutic screens.

Funding: NIDDK Support

FR-PO363

Extracorporeal Mesenchymal Stromal Cell Therapy for Critical Care

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Background: Human mesenchymal stromal cells (MSCs) metabolize and secrete anti-inflammatory and regenerative factors that can be of systemic benefit to acute, critical injury. When transplanted MSCs are limited in dose and rapidly cleared by the host, severe non-targeting or adverse effects to this therapy may occur.

Methods: MSCs were integrated into hollow-fiber bioreactor devices whereby the cells, separated by a permeable membrane, can directly and dynamically provide systemic therapy without entering the body. We present a human scale prototype of the technology that has shown sustained cell viability and function throughout cGMP manufacturing in preparation for a Phase I human trial set to begin in 2015.

Conclusions: This study demonstrates the successful transport of creatinine in an artificial microvascular circulation model without a blood pump. Pharmacological analysis of this bioreactor technology in vivo allowed for an unprecedented look at MSC function during product use and verified potency that is unattainable by conventional intravascular delivery of MSCs.

Funding: NIDDK Support, Pharmaceutical Company Support - Sentien Biotechnologies, Inc.

FR-PO364

Extracorporeal Diffusional Clearance of Silicon Nanopore Membranes in a Porcine Peritoneal Blood Circuit

Nephrology, UCSF; Surgery, UCSF; Bioengineering, UCSF; Silicon Kidney, LLC; Ben Chiu Consulting; ‘H-Cubed; Nephrology & Hypertension, Vanderbilt Univ.

Background: Silicon nanopore membranes designed for hemofiltration (HF-SNM) have demonstrated increased permeability compared to polymer membranes. Previously, we reported in-vitro data showing a 3-fold improvement in diffusive clearance using silicon nanopore membranes. Here we test the diffusive clearance of HD-SNM vs. HF-SNM in an extracorporeal peritoneal model without a blood pump.

Methods: A microelectromechanical systems fabrication technique was used to decrease the SNM thickness (HD-SNM 100 µm vs HF-SNM 400 µm). Polyethylene glycol coated HD-SNM (n=3) and HF-SNM (n=3) with sub-10nm pore sizes were tested in a single channel flow circuit (b=1mm). Vascular access was obtained by placing tunneled catheters within the carotid artery and jugular vein of healthy ~50kg pigs. Blood flow was achieved via the arterial-venous pressure differential (35-120mmHg). Dialysate was recirculated in a counter-current fashion (30ml) and flow rates were adjusted to ensure 0 transmembrane pressure. Dialysate creatinine concentration was measured hourly and serum creatinine was measured at time 0 and 6 hours. The pore size of each SNM was measured before and after dialysis exposure using hydraulic permeability.

Results: Blood flow was limited by the arterial-venous pressures differential with <5mmHg pressure drop. The average plasma creatinine concentration was 1.38±0.1mg/dL. The creatinine clearance was 37.2±3.9mmol/min/m² (HF-SNM) vs 126.0±27.1mmol/min/m² (HD-SNM) at 92±5.36ml/min. There was no detectable albumin transport into the dialysate. The HD-SNM maintained a mechanical integrity at over 2500mL/min in vivo. The total pore size change following blood exposure was 1±4.5mm vs 19±1.2mm for HF-SNM and HD-SNM, respectively.

Conclusions: This study demonstrates the successful transport of creatinine in an extracorporeal circuit without a blood pump. We also showed a ~3-fold improvement in diffusive clearance of creatinine using HD-SNM in a blood circuit.

Funding: NIDDK Support, Private Foundation Support
FR-PO366

Hemofilter Design Based on Computational Simulations of Pulsatile Flow

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Background: In the US, the ratio of patients with end stage renal disease (ESRD) on dialysis to annual kidney transplants for ESRD is 20:1 (USRDS 2014 Annual Data Report), underscoring the grave need for an artificial kidney alternative. Hypothesis: For the development of a hemofiltration device, computational fluid dynamics (CFD) simulations can predict potentially thrombogenic zones [e.g. low and high wall shear stress (WSS) areas, associated with stasis and shear induced cell damage, respectively] and can be used to refine device design to minimize such areas.

Methods: CFD simulations of pulsatile blood flow through a prototype hemofilter were validated in vitro using MR velocimetry. Hemofilters were implanted in large animals (n=4) for 30 days or until thrombosis and then explanted. Based on the CFD results, a subsequent flow path was devised to minimize predicted thrombogenic regions, and simulations were conducted on the second design.

Results: The in vitro and in silico models showed strong agreement. Pulsatile CFD simulations of the prototype device demonstrated zones of low WSS, and clot formation occurred in two of the four implants at the CFD-predicted sites. Flow simulations of the second-generation design showed reduced areas of low WSS.

Conclusions: Thrombogenic low WSS regions predicted in silico correspond with clot formation in vivo. In addition to predicting areas of thrombogenicity, CFD can be used to guide hemofilter device design to minimize these sites.

Figure 1. CFD results, with gray arrows indicating flow direction. A: WSS averaged over all butystatic acetabular for the prototype shows low WSS regions (black arrows) dominate the cardiac cycle. B: Compared to the prototype (left), the second-generation (right) design mitigates areas of instantaneous low WSS (black arrows).

Funding: NIDDK Support, Private Foundation Support

FR-PO367

Characterization of Dialyzer Membranes by MALDI-Mass-Spectrometric Imaging Techniques

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Background: Dialyzer polymer membranes are grossly classified as cellulose-based and synthetically produced membranes. Although cellulose membrane’s clearance and mechanical properties qualify it for use in dialyzer membranes, hydroxyl groups of these membranes lead to strong activation of the complement system. Therefore, recent membranes are manufactured from synthetic polymers.

Methods: For physical and chemical characterization of these materials of dialyzer a wide range of analytical methods is available. Over the last few years, MALDI mass-spectrometry has been developed as a powerful tool for space-resolved analysis, not least because of its mass accuracy and high sensitivity. MALDI imaging techniques combine the potential of mass-spectrometric analysis with imaging additional spatial information with relevance for biocompatibility of the dialyzer membranes. MALDI imaging enables the visualization of localization and distribution of biomolecules, chemical compounds and other molecules on different surfaces.

Results: In this study, surfaces of polymeric dialyzer membranes, consisting of polysulfone (PS) and polyvinylpyrrolidone (PVP) were investigated, regarding to chemical composition and physical characteristics. The MALDI imaging demonstrated that the abluminal membrane surface is more consisting of polysulfone than polyvinylpyrrolidone, the luminal membrane surface displayed more PVP than PS. The addition of PVP as hydrophilic modifier to polysulfone-based membranes increases the biocompatibility of the dialyzer membranes. The analysis of polymer distribution is a relevant feature for characterization of dialysis membranes.

Conclusions: In conclusion, MALDI imaging is a powerful technique for polymer membrane analysis, regarding not only detection and identification of polymers but also localization and distribution in membrane surfaces, which has strong impact on the biocompatibility of the dialyzer membranes.

FR-PO368

Effect of Peristasis with Pediatric Catheters

Anna Lorenzin, Francesco Garzotto, Claudio Ronco. Nephrology and International Renal Research Inst Vicenza, St. Bortolo Hospital, Vicenza, Italy.

Background: Thanks to the technological advances of the last years, Continuous Renal Replacement Therapy CRRT machines have been upgraded and equipped with circuits specific for pediatric patients. To date, to treat these patients the most used catheter is the venous T-French, however with a neonate it is inadequate for the dimensions. It is not clear if it is possible to use a smaller catheter with adult CRRT machine or a specific pediatric machine is needed. We set up a dedicated circuit to assess the usability of a peristaltic blood pump designed for adults and compare it with a pediatric pump in terms of access pressure. Methods: We performed in vivo tests with a peristaltic pump, the CARPEDIEM pump with pediatric catheter of 4Fr and a venous pressure sensor, and we compared this to the CARPEDIEM pump with adult catheter. Results: We are presenting the data of the two pumps with 5Fr catheter and 15ml/min flow rate. Analyzing the arterial pressure values, we found that the spikes are more frequent with the CARPEDIEM pump than with the adult one. The mean and max value are respectively(-50, -28mmHg) and a mean Dp=18mmHg with CARPEDIEM and a mean Dp=40mmHg with adult pump. Conclusions: We can notice that there is an high discrepancy in terms of Dp between the two pumps: high values of Dp lead to an high shear stress. As the shear stress in one of the main causes of hemolysis, it seems that a specific pediatric machine is advisable for neonates that need small catheter. Further investigation have to be perform with blood to confirm our results.

FR-PO369

Hemodialysis with CARPEDIEM Machine: An In Vitro Test

Anna Lorenzin, Dario Galeano, Stefania Aresu, Francesco Garzotto, Claudio Ronco. Nephrology and International Renal Research Inst Vicenza, St. Bortolo Hospital, Vicenza, Italy.

Background: Despite the development of continuous renal replacement therapies machines, their employment still remain unsuitable in newborn and infants. This gap has been filled thanks to the coming of a specific pediatric dialysis machine CARPEDIEM. To date it is set up only for continuous hemofiltration CVVHDFs it provides a wider range of applications, specific filters have been conceived to implement a continuous hemodialysis CVVHID. We tested a prototype kit to evaluate its performance in terms of clearance K.

Methods: We performed in vitro test with plasma for the 3 filters HD010 HD620 HD035 (surface 0.1, 0.2, 0.35 m²/cm²). Fibers were put manually into the housing of CVVH filters. CVVHID in cocurrent configuration otherwise a longer circuit is required is based out using infusion pump as dialysate pump and ultrafiltration as effluent pump. All the combinations of plasma and dialysate flow rate are set [QF, 5, 10, 15 ml/min; QD, 1, 5, 10, 15 ml/min; net ultrafiltration is 0 ml]. Plasma samples are collected every QF, QD change (time interval 8 min) to evaluate K of urea and creatinine using the standard formula.

Results: Among all filters, our tests estimated a common trend of urea K (min 3.0, max 10.5 ml/min) and creatinine K (min 3.4, max 11.8 ml/min). Filters efficiency increases with the increase of both the flow rates QF, QD (fig.1), moving towards a plateau at the higher flows configuration.

Figure 1. Clearance curves of filter HD_010 in the different QF, QD configurations.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: CVVHD with CARPEDIEM seems to be effective for diffusion transport of small molecular weight solutes, according to specific clinical needs. In the light of these findings, CARPEDIEM can be a promising alternative to peritoneal dialysis, i.e., in treating electrolyte imbalance with accurate fluid removal. Lymphedema: handmade filters could induce variability in the results due to disposition and variable number of fibers.

FR-PO370
Removal of Protein-Bound Uremic Toxins: Simulating the Effect of Toxin Displacement versus Increase in Dialyzer Clearance
Vaibhav Maheshwari,1 Stephan Thijssen,1 Doris H. Fuertinger,1 Franz Kappel,1 Peter Kotanko.1 Renal Research Inst, NY; 2Univ of Graz, Austria.

Background: Protein-bound uremic toxins (PBUT) exert numerous deleterious effects. Their removal with standard hemodialysis (HD) is poor. Meyer et al. have modeled the impact of increasing dialysate flow rate and dialyzer mass transfer area coefficient on PBUT removal [JASN, 2004]. Here, we compare those results to a novel approach based on PUBT displacement by infusion of binding competitors [Tao, Blood Purif, 2015].

Methods: We developed a multi-compartment patient model and a dialyzer model depicting spatiotemporal dynamics based on law-of-mass-action kinetics. We chose indoxyl sulfate (IS) as a prototypical PUBT and ibuprofen as the binding competitor. We modeled IS removal during a 4-hr HD ($Q_p=250$ mL/min, $Q_{sw}=750$ mL/h, initial total IS 100 µmol/L, initial free fraction of IS 8%), with IS dialyzer clearances from 150 to 200 mL/min. This was compared to IS removal achieved by ibuprofen infusion (800 mg/200 mL) into the arterial line at 50 mL/hr (IS clearance 150 mL/min).

Results: IS removal during HD with a clearance of 150 mL/min was 438 µmoles (plasma reduction ratio 34%), which conforms to literature data [Niwa, Blood Purif, 2012]. With IS clearance of 200 mL/min, removal improved by 8.7% to 476 µmoles. With ibuprofen infusion (IS clearance back at 150 mL/min), removal improved by 11.2% to 487 µmoles.

Conclusions: Our model yields predictions of IS kinetics that agree with empirical and modeled data [Niwa et al.; Meyer et al.]. Of note, a mere 8.7% improvement in IS removal would require an increase in dialysate flow rate from 800 to 1350 mL/min plus a 70% increase in membrane surface area. The modeled ibuprofen infusion alone yields an 11.7% improvement even absent an increase in dialyzer clearance. The use of binding competitors holds great promise. These results require validation in vivo.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

Membrane versus Peristaltic Blood Pumps for Extracorporeal Therapies: Comparison on Index of Hemolysis
Francesco Garzotto,1 Sean M. Bagshaw,2 Claudio Ronco.1 Nephrology and IRRH, St. Bortolo H., Italy; 2Critical Care Medicin, Univ of Alberta Hospital.

Background: Hemolysis during extracorporeal treatments mainly occurs as a consequence of mechanical stress on the blood. Red blood cell deterioration is undetected because it is far from any acute hemolytic threshold but represents a potential harm for patients. A new membrane-piston driven pump has been recently proposed on the S.A.M. (Spectral Medical Inc, Toronto) device designed for continuous renal replacement therapies (CRRRT). Aim of this investigation is to compare the membrane with peristaltic pumps by measuring the Normalized Index of Hemolysis NIH during in vitro testing.

Methods: Three sessions of hemoperfusion with a line inserted in place of a hemofilter were performed both with SAM and Prismaflex (Baxter International). A single pool of fresh heparinized bovine blood (Heparin 500 u/L, Hb 12±1 g/dl,Base Excess 0±5 mmol/L) were split into three aliquots containing 900 mL (Control, SAM, Prismaflex) and circulated for 6 hours/session. Blood: dial samples were drawn at baseline, 30 min and every 1 hour. NIH were calculated as median hourly variation of free hemoglobin and used for comparison.

Results: NIH values of 0.12±0.03 and 0.13±0.09 mg/100L for SAM and Prismaflex respectively are lower than those reported in literature due to the simplified circuit used (no vascular access and filter). Creation of hemoglobin between sam and control, and prisma and control are non-significant fig 1a. Slope of the curves can describe the creation of hemolysis are nearly identical with a slow rate of production of free hemoglobin.

Conclusions: Device compatibility in terms of lethal damage to blood cells, is an important aspect of the development of artificial organs. Since a validation based on dangerous level of free hemoglobin do not exist, an empirical evaluation using comparative test suggest that piston driven membrane is safe from a hemolysis point of view.

FR-PO372

Membrane Driving Blood Flow for Extracorporeal Therapies
Stephan Thijssen,1 Doris H. Fuertinger,1 Franz Kappel,1 Peter Kotanko.1 Renal Research Inst, NY; 2Univ of Graz, Austria.

Background: Hemolysis during extracorporeal treatments mainly occurs as a consequence of mechanical stress on the blood. Red blood cell deterioration is undetected because it is far from any acute hemolytic threshold but represents a potential harm for patients. A new membrane-piston driven pump has been recently proposed on the S.A.M. (Spectral Medical Inc, Toronto) device designed for continuous renal replacement therapies (CRRRT). Aim of this investigation is to compare the membrane with peristaltic pumps by measuring the Normalized Index of Hemolysis NIH during in vitro testing.

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Conclusions: Device compatibility in terms of lethal damage to blood cells, is an important aspect of the development of artificial organs. Since a validation based on dangerous level of free hemoglobin do not exist, an empirical evaluation using comparative test suggest that piston driven membrane is safe from a hemolysis point of view.

FR-PO371

Membrane Driving Blood Flow for Extracorporeal Therapies
Francesco Garzotto,1 Sean M. Bagshaw,2 Claudio Ronco.1 Nephrology and IRRH, St. Bortolo H., Italy; 2Critical Care Medicin, Univ of Alberta Hospital.

Background: From the first application of ContinuousVenousVenesVenousHemofiltration CVVH, the blood flow has been driven by a peristaltic pump. Several attractive alternatives, with both advantages and disadvantages, have been proposed for many years. SAM (Spectral Medical Inc; Toronto, Canada) is a novel instrument, in which the pumping of whole blood and fluids is performed through the use of pistons, chambers and valves. A plastic cartridge blood circuit system fig 1b incorporates all of the pumps, air trap system, pressure monitors and clamps. This circuit is covered on one side by a plastic membrane adhered to the pumping pistons via a drawn vacuum. Aim of the present is to evaluate the new pumping system.

Methods: We set up the machine for CVVH. An 11.5 Fr 20 cm catheter was connected to the lines. We ran the machine for 6 hours in order to characterize the performance of the system.

During the first cycle, suction generated by the drawing back of the piston, moves the blood into the arterial-chamber AC. Positive pressure generated by the piston then drives the blood through the circuit. The camshaft design can allow different profiles for Withdrawal and infusion flows. The largest Priming volume measured (both the ACs full), is 98 mL with a stroke volume for each AC of 14 mL.

Conclusions: CVVHD with CARPEDIEM seems to be effective for diffusion transport of small molecular weight solutes, according to specific clinical needs. In the light of these findings, CARPEDIEM can be a promising alternative to peritoneal dialysis, i.e., in treating electrolyte imbalance with accurate fluid removal. Lymphedema: handmade filters could induce variability in the results due to disposition and variable number of fibers.
FR-PO373
Enhanced Middle Molecule Clearance by a Biomimetic Dialyzer Membrane
Joseph J. Groszek,1 Jin Cheng,1 Charles Blaha,2 Rishi Kant,1 Jae Hyun Park,2 Benjamin Chui,2 Ken Goldman,4 Shuvo Roy,1 William Henry Fissell.1
1Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; 2Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA; 1Ben Chat Consulting, Sunnyvale, CA; 4H-Cubed, Inc, Olmstead Falls, OH.

Background: Although polymer dialyzers attain very high small solute clearance rates, polyelectrolyte slit pore sizes limit middle molecule clearance by conventional polymer dialyzers. We hypothesized that a biomimetic membrane with uniform slit pores would enhance middle molecule clearance.

Methods: Thin film silicon membrane samples (surface area 1.4 x 10^4 m^2) with micropore, slit-shaped 5-8 nanometer pores (“SNM-HD”) were manufactured as previously described, surface-modified with polyethylene glycol and mounted in a custom designed cartridge. Membrane pore size was estimated from hydraulic permeability measurements. Human blood was spiked with PABA and fluorescent-labelled Ficoll, a polyelectrolyte globular polysaccharide. Blood flow was set at 100 ml/min and dialysate flow varied between 70 and 140 ml/min. Blood and dialysate concentrations of PABA and Ficoll were measured by size-exclusion chromatography. Clearance as a function of dialysate flow rate was extrapolated to estimate kDa as a function of molecular weight.

Results: B2M clearance in high-flux dialyzers is typically 5-8% of the value of urea clearance. PABA clearance was 139 ml/min/m^2, 15.7 Angstrom Ficoll clearance (same radius as B2M) clearance in the SNM dialyzers was 16.9 m/min/m^2, 3.5 fold higher than reported B2M clearance in polymer dialyzers.

Conclusions: A biomimetic membrane of uniform slit pores potentially offers much higher middle molecule clearance than conventional polymer dialyzers.

Funding: Other U.S. Government Support

FR-PO374
Anti-Fouling of Silicon Nanopore Membranes Using SLIPS
Bas Meuseen,1,2 Steven Kim,1 Zohora Iqbal,1 Charles Blaha,1 William Henry Fissell,1 Shuvo Roy.1,2 UCSC; 2Univ of Eindhoven; *Silicon Kidney; Vanderbilt Univ.

Background: Silicon Nanopore Membranes (SNM) have been developed for an implantable bioartificial kidney. However, SNM are subject to fouling and thrombosis with continuous blood exposure. Thin polymer coatings have been applied to SNM as a strategy to limit cell adhesion and protein adsorption. Slippy Liquid Infused Pores (SLIPS) is a biotriposed “omniphobic” surface coating that has been reported to prevent thrombosis and fouling on arteriovenous shunts. Here we present the application of SLIPS coating to SNM and evaluate protein adsorption in vitro.

Methods: SNM with ~10 nm pores were coated with SLIPS and incubated with BSA-FITC (2 mg/ml in PBS) for 24 hours at 37°C. Uncoated (bare) silicon substrates served as controls. Fluorescence microscopy and ellipsometry were used to evaluate the surfaces and water transport through the SNM was tested using established hydraulic permeability assays.

Results: SLIPS strongly reduced BSA-FITC adsorption on SNM compared to bare silicon. Ellipsometry confirmed the presence of SLIPS coating with a thickness of 0.5 ±0.2 nm, which is theoretically thin enough to keep open the pores open in the membrane. However, hydraulic permeability testing revealed no ultrafiltration through the SNM for at least 24 hours and transmembrane pressures of up to 5 psi. SLIPS is a promising and easy-to-use protein repellent coating, but its highly omniphobic characteristic prevents ultrafiltration even through pores that are over 5x the coating thickness. For use in the bioartificial kidney, SLIPS has relevant implications as an anti-fouling coating where an ultra-thin blood compatible, but non-filtering surface is desired.

Funding: Other NIH Support - NIBIB

FR-PO375
Measuring Spatial Trends of Single Nephron Filtration with Molecular MRI
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Background: To better develop drugs to treat kidney disease their physiological mechanisms during development, noninvasive techniques to measure whole kidney function at the level of the single nephron are needed. We investigated the combined use of two MRI contrast agents, cationic ferritin (CF) and Gd-DTPA, to measure local (voxel) macromolecular and free filtration dynamics in the whole kidney.

Materials: Krebs-Ringer (KR) bicarbonate solution with 7.5 mg/100mL of Fraction-V BSA and a bubbling infusion of carbogen was perfused into isolated rat kidney. Temp was maintained at 37°C. CF in KR solution (0.071 mg/mL of CF), was infused into the system first. Next, a bolus of 0.25 mmol Gd-DTPA in 10mL of KR solution was infused into the perfusion system. All (rates = 5ml/min) Kidneys were imaged using the perfusion with MRI. Voxel time curves were then fitted to a bi-exponential model.

Results: Glomeruli were distinguished by uptake of CF and a distribution of CF accumulation rates and gd-DTPA elimination rates was visible. (Fig 1a-b) We used the location of the glomeruli in 3D and the time course of CF labeling (Fig 1c-d) to discern spatial trends in uptake rate of CF. Time course structures also mapped well with the different morphological structures in the kidney (Fig 1e).

Conclusions: Our results demonstrate that automated quantification is capable of not only distinguishing between anatomical features of kidneys, but also characterizing the degree of abnormality in diseased tissue.

FR-PO376
Automated Quantification of Renal Microvascular Abnormalities: A Novel Computational Mapping Approach
Kyle I. Harrington, Beverly Elizabeth Faulkner-Jones, Katie Bentley, Seymour Rosen. Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Alteration of the microvasculature is considered to be crucial to the understanding of chronic kidney disease, yet few studies have quantified the microvasculature in normal and diseased kidneys.

Methods: We created customized software for automatically quantifying morphology of renal microvasculature. 10 kidneys (2 nephrectomies, 8 biopsies) were studied; 3 cases of relatively normal tissue, others chosen because of a significant degree of tubulointerstitial injury and included a variety of diseases (diabetes, amyloidosis, end-stage glomerulonephritis, and renal artery stenosis). Images of CD34 stained vessels were segmented, high-pass filtered based on size, and glomeruli were manually segmented. Morphological signatures were calculated using 3 parameters: roundness, angulation, and density.

Results: The normal cortex, as a whole, presented heterogeneity in histogram analysis. However, color density mapping and histogram studies revealed 3 distinct regions: glomeruli (GM), labyrinth (LB), and medullary ray (MR). MR was characterized by correlated angulation (Fig 1). Microvascular density varied in LB but peaked at 3% coverage within a 200um circular radius (Fig 2). Density in MR was approximately the same. As expected, GM density was far greater, sometimes exceeding 11% coverage. With disease, capillary shape did not shift, roundness factor remaining in 0.2-0.3 range (circumferential 1.0). However, diminishment in capillary density was overt (Fig 3), and distribution shifts were marked (peak A) or more moderate (peak B).

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO377
Angio-µCT: New Polymer-Based Contrast Agent Makes Kidney Morphology Look Attractive
Ruslan Hlushchuk, Sebastien Barre, Carlos Correa Shokiche, Valentin Djonov. Inst of Anatomy, Univ of Bern, Bern, Switzerland.

Background: The fundamental features of the morphological substrate of the renal function are nephron number and glomerular volume. The accurate estimation of these parameters has become increasingly important. The present golden-standard method of kidney morphology is the exhaustive physical fractionator-dissector method. It is extremely time-consuming and laborious, let alone disturbing proceeding artefacts. Purpose: To develop a contrast agent appropriate for high-resolution µCT at vivo with superior perfusion features in order to visualize the vasculature and glomeruli of rodent kidney. The elucidated approach should allow fast and reliable estimation of such parameters as nephron number, glomerular volume, glomerular size distribution and kidney volume.

Funding: NIDDK Support, Other NIH Support - NHLBI

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

Underlines represents presenting author.

440A
Results: the developed contrast agent (µAngiofil) turned out appropriate for µCT ex vivo with superior perfusion and contrast-to-noise features. The obtained µCT datasets were of superior quality and allowed clear visualization of the microvasculature and glomeruli.

In kidney, modern high-resolution micro-CT (SkyScan-1172) provided the whole mouse kidney vasculature in 3D with the spatial resolution of approx. 2 µm. The sample is fixed prior the micro-CT-scan and therefore can be processed for the histological evaluation after the scan. This circumstance brings multiple advantages, including much easier localization of the µCT-findings in the post-scan histological sections.

Conclusions: using µAngiofil we obtained 3D-µCT datasets of superior quality, which are sufficient for estimation of relevant kidney morphometry parameters. The developed angiо-µCT-based approach will substitute the existing golden-standard. Besides classical kidney morphometry, it provides the data on the vasculature through the whole kidney in 3D which makes the technique even more beneficial.

Funding: Government Support - Non-U.S.

FR-PO378
Rising Accuracy of Transcutaneous GFR Measurement Jochen Friedemann,1,2 Ralf Heinrich,1 Yury Shulhevich,1,2 Johannes Pill,1 Daniel Schock-Kusch,1,2 1Mannheim Univ of Applied Sciences, Inst for Process Control and Innovative Energy Conversion, Germany; 2Mannheim Pharma & Diagnostics GmbH, Germany; 3Friedenberg New Technologies SE & Co. KG, Weinheim, Germany.

Background: Transcutaneous measurement of GFR (GFR) is now getting used frequently in animal studies. tGFR allows consecutive GFR measurements in the same animal even on a daily basis as no blood sampling is required. Here we describe and validate a novel three compartment model (GFR) for GFR assessment by FITC-Sinistrin clearance, automatically correcting influences like bleaching of skin fluorescence.

Methods: Bolus clearance (GFR was measured in awake Sprague Dawley (SD) rats using the commercially available NIC-Kidney system, immediately followed by a blood sampling based constant infusion clearance (cGFR). GFR was calculated by a one compartment model (GFR), GFR and cGFR. Also 46 measurements in SD rats were reevaluated by GFR.

Results: Results are given in table 1. Mean values of the three methods are comparable with no significant difference. The accuracy (larger STD) of GFR is lower compared to GFR and cGFR. This finding was verified by the 46 measurements in SD rats (GFR: 0.97 ± 0.18 ml/min/100g b.w.; GFR: 0.95 ± 0.14 ml/min/100g b.w.).

Conclusions: The results indicate that GFR yields data in comparable accuracy as cGFR. For an apriori estimation of the sample size to detect a change in GFR of 10% in the SD rats investigated, the effect size rises from 0.55 (GFR) to 0.73 (GFR).

FR-PO379
Quantification of the Progressive Fibrosis Development in Mouse Kidney Unilateral Ureteral Obstruction Model Using Fluorescence Lifetime and Second Harmonic Generation Imaging Microscopy Evgenia Dobrinskikh,1 Suman Ranjit,1 John Ross Montford,1 Alexander Ovronikov,2 David J. Orlicky,1 Allison M.D. Lehman,1 Raphael A. Nemiroff,1 Enrico Gratton,1 Seth B. Furgesom,1 Moshe Levi,1 1Univ of Colorado Denver; 2Univ of California Irvine.

Background: Renal fibrosis is considered to be the final common pathway for most forms of chronic kidney disease (CKD) and involves glomerular sclerosis and/or tubulointerstitial fibrosis. There is great interest in identifying renal fibrosis in the early stages of CKD to prevent progression. Unilateral ureteral fibrosis (UUO) is a well-characterized model of CKD and renal fibrosis. Kidney injury and fibrosis usually are assessed by Picrosirius Red staining or immunohistochemistry for collagen isoforms.

Methods: The goal of this study is to compare histologic measures of renal fibrosis to Fluorescence Lifetime Imaging (FLIM) and Second Harmonic Generation (SHG) techniques in our deep imaging microscope DIVER.FLIM and SHGI allow quantification of collagen in unstained tissue and can be adapted for live animal imaging. Male C5BL/6 mice were subjected to UUO of right kidney. At 7, 14 and 21 days, both kidneys were harvested. The uninjured left kidney was used as a control. Serial sections of both kidneys were analyzed using Picrosirius Red staining or FLIM with SHG.

Results: We performed quantification of Picrosirius Red stained-kidneys using polarized light. This showed progressive increase for the number of positive pixels for fibrosis in the left kidney 9631.9±1626.2, 16167.8±6647.7 and 20511.5±5727.6 compared to 5625.3±770.6, 3909.3±2395.9 and 4493.8±2018.4 in the control kidney respectively. Using the Phasor approach to FLIM, comparisons between the two kidneys show that the auto fluorescence lifetime signature give rise to two well separate phasor clusters. Quantification of ten different fields of view for each kidney at the above time-points for SHG signal confirms Picro-Sirius Red scoring.

Conclusions: Finally, the combined FLIM and SHG images let us establish a criterion for quantitative determination of fibrosis directly from the microscope images.

Funding: NIDDK Support

FR-PO380
Chemical Imaging: A Novel Approach to Obtaining Label-Free Biochemical Information in Renal Transplant Patients with Recurrent Diabetic Nephropathy Michael J. Walsh,1 Vishal K. Varma,1 Andre Kajdacsy-Balla,1 Sangeev Akkina,2 Suman Setty,1 1Dept of Pathology, Univ of Illinois at Chicago, Chicago, IL; 2Dept of Nephrology, Univ of Illinois at Chicago, Chicago, IL.

Background: The main treatment for end-stage renal disease is kidney transplantation, which over time undergo chronic rejection including changes in the glomerular, tubulointerstitial and vascular compartments. Also, recurrence of disease in diabetics can mimic transplant glomerulopathy. We have identified biochemical markers using Chemical imaging that were associated with recurrent diabetic nephropathy. Chemical Imaging is an emerging approach to obtain images of the biochemical composition of tissue biopsies in a label-free fashion.

Methods: An initial study focused on identifying patients with no evidence of diabetic nephropathy and patients with advanced diabetic nephropathy in native kidneys. Serial sections were acquired and stained with PAS or imaged using chemical imaging. IR spectra were extracted to identify biomarkers associated with diabetic nephropathy progression. A second study identified transplant patients who underwent very rapid recurrent diabetic nephropathy and patients with no evidence of diabetic nephropathy.

Results: Biomarkers were identified that were changed in renal structures associated with the progression of diabetic nephropathy, including increased levels of glycation. These biomarkers were found to be increased in the cohort of transplant patients that underwent rapid diabetic nephropathy recurrence. In addition, the early biopsies from the patients that underwent later diabetic nephropathy progression were biochemically different from the non-progressive patients, suggesting that chemical imaging may identify pre-histological biomarkers that will predict outcome.

Funding: NIDDK Support
Conclusions: We have identified a number of biomarkers that are associated with the advancement of diabetic nephropathy and that we can track the early recurrence of diabetic nephropathy in surveillance biopsies. In addition, we have highlighted a ‘biochemical signature’ that may be predictive of the later progression of diabetic nephropathy recurrence.

Funding: NIDDK Support

FR-PO381
Contrast-Echo Ultrasonography Characterizes Kidney Lesions With Accuracy Comparable to Contrast-Enhanced CT or MR

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Background: Incidental kidney lesions are often detected on imaging performed for other reasons. Indeterminate lesions are further characterized with a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). These tests have many limitations and are contraindicated in patients with allergies to contrast, metallic hardware and chronic kidney disease (CKD). An accurate alternative study is needed. Contrast-enhanced ultrasound (CEUS) is one potential alternative. CEUS uses microbubbles, non- nephrototoxic, gas-filled bubbles with lipid or albumin shells, as the contrast agent. We investigated the accuracy of CEUS for malignancy in patients with incidental kidney lesions.

Methods: CEUS was performed on 33 patients. Results were independently interpreted by 2 blinded readers and risk-stratified by the Bonnink classification system. Sensitivity, specificity and predictive values were calculated for lesions with histologic diagnosis as the gold standard. As histology was available for excised lesions only, we performed secondary analyses using an expanded gold standard definition that included clinical recommendation.

Results: Of the 33 patients, 12 had CKD and 14 had histologic diagnoses. There was 100% inter-reader agreement in the primary analysis (Figure 1A) and 97% agreement in the secondary analysis (Figure 1B). Sensitivities (94-100%), positive (70-93%) and negative predictive (90-100%) values for CEUS were comparable to CT (83-100, 50-67 and 77-100, respectively) and MRI (81-100, 60-78 and 80-96%, respectively). CEUS specificity (0-56%) was lower than MRI (71-100%).

Conclusions: CEUS has excellent potential as an alternative diagnostic tool for kidney lesions among patients with CT/MRI contraindications. Further evaluation is needed.

Funding: Other NIH Support - CTSA (Clinical and Translational Science Awards) funding, University of North Carolina at Chapel Hill (UL1TR001111)

FR-PO382
Lead-Free Drape Applied to Xray Detector Significantly Decreased Radiation Scatter During Access Intervention

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Background: Exposure from scattered radiation can be very high during access interventional procedures because of the relatively closer operative position. The purpose of this study is to evaluate whether applying a lead-free, sterile, disposable drape can decrease scatter radiation exposure during access intervention.

Methods: An upper extremity phantom was placed on the angiography table to mimic real-time patient’s upper extremity access. Using this model, measurement of scatter radiation was made every one foot away from the phantom before and after applying the drape using a collimated and low-output condition. The scattered radiation dose was measured three times in each spot. And the measurement was taken at 0.9m (waist level) as well as neck level (1.5m). Statistical significance was compared using t-test.

Results: Scatter radiation was attenuated throughout the measurement field when the drape was applied. The degree of scatter radiation reduction was distance and height dependent. Scatter radiation decreased 61.6% at the waist level and 81% at the neck level (P<0.05).

Conclusions: The application of this sterile, lead-free drape can significantly reduce scatter radiation in the procedure room. This novel technique can be used to reduce exposure radiation dose to the operators.

FR-PO383
Pathogenesis of Brain Damages in Chronic Kidney Disease and Clues for Early Diagnosis

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Background: There is globally increased prevalence of chronic kidney disease (CKD). Vigorous efforts have been devoted to ameliorate renal deterioration and prevent cardiovascular morbidity/mortality. However, patients also have enough incubation time to develop deranged cognition that severely disturbs quality of life. Neurological pathology/damages may occur in CKD patients long before any overt clinical symptoms can be noticed. Given the similar embryological development as brain, the eyes can be the windows to pinpoint the internal brain pathology. Herein we employed proteomics, animal model and behavior analysis to investigate the possible overlapping biological signatures in the eyes and brain of CKD.

Methods: Subtotal nephrectomized rats were established as CKD model. Open field and object recognition tests were adopted as neurologic screen. Brain and eyes were harvested for proteomic analysis. Western blotting and immunohistochemistry were used to confirm and localize the identified proteins. To elucidate the global protein changes in the brain and eye of SNX rats, the data was analyzed by Ingenuity Pathways Analysis (Ingenuity Systems, http://www.ingenuity.com/).

Results: The eye pathology appeared in parallel with the brain damages. The significantly dysregulated proteins in the SNX rat eyes were spectrin beta 3, 26S proteasome non-ATPase regulatory subunit 2, 26-phosphofructokinase, dihydroxyprymidinidase-related protein, and the heat shock 70, 90a, and chaperonin containing Tep1, subunit 6A (Zeta 1).

All these proteins have been linked to the neuro-degeneration in humans.

Conclusions: There were overlapping eye and brain biological networks. Our results might pave the way for early diagnosis of CKD-neurological pathology via eye examinations, and targeted interventions towards the neurological diseases.

Funding: Government Support - Non-U.S.

FR-PO384
Metabolomic Profiling of Chronic Kidney Disease Using a Local Exhaustive Exploration Approach

Maroows Luck1, Eric Thervet1, Cecilia Damon,1 Nicolas Pallet1 1Nephrology, Georges Pompidou European Hospital, Paris, France; 2Hypercube Inst, Paris, France.

Background: H Nuclear Magnetic Resonance (NMR)-based metabolomic profiling is useful for the diagnosis of CKD stages. Due to the high dimension of NMR spectra datasets and the complex mixture of metabolites in biological samples, the identification of discriminant biomarkers of a disease is challenging. None of the widely used chemometric methods in NMR metabolomics performs local exhaustive exploration of the data.

Methods: We developed a descriptive and easily understandable approach searching for discriminant local phenomena. We selected the most discriminant features from the dataset based on both the normalized mutual information and the chi-2 test. We studied the local distribution of the patient subgroups with identical degree of CKD severity on each feature, using the proprietary algorithm HyperCube, which searches for local overdeterminism of an explanatory variable modality, and identifies a combination of variables as well as their value ranges that give the optimal prediction of the outcome of interest. Further, logistic regression on these discriminant features was used to build a predictive model of the CKD severity stage.

Results: We explored a complex dataset that includes H-NMR urinary metabolomics, clinical, demographic, clinical chemistry and histo-pathological variables, in a cohort of 110 individuals with a CKD. The HyperCube algorithm combined with logistic regression supports the discriminant metabolites obtained with standard Orthogonal Projection to Latent Structure Discriminant Analysis (O-PLS-DA) model. Unlike the O-PLS-DA model, HyperCube algorithm provided clues into the distribution of the CKD severity subgroups.
with respect to spectral data. The built predictive model identifies metabolomics profiles corresponding to citrulline, dimethylsulfone, trigonelline and glycine. The majority of the predictive variables were urinary metabolites identified by H-NMR, indicating that CKD significantly impacts the urinary metabolome.

**Conclusions:** Our findings indicate that HyperCube is a valuable analytical method for the description of CKD severity phenotypes.

**FR-PO385**

**RNA-seq Profiling in Uninephrectomized Rats**

Jae Wook Lee, Mark A. Knapper. NHLBI, NIH, Bethesda, MD.

**Background:** Renal hypertrophy occurs as a compensatory response to reduction in nephron mass. To identify early gene expression changes in renal hypertrophy, we profiled whole-kidney transcriptome in the contralateral kidney of uninephrectomized rats using RNA-seq.

**Methods:** 5-week-old male Sprague-Dawley rats received right uninephrectomy (UNx; n=4 at each time point) or sham surgery (S, n=4 at each time point). Rats were sacrificed at 24, 48, and 72 hours after surgery. 1.5 µg of total RNA from the left kidney was used to make cDNA libraries for Illumina sequencing. Reads were mapped to Ensembl genes and Wald test for a negative binomial model was used to call differentially expressed genes.

**Results:** Total RNA yields did not differ significantly between UNx and sham kidneys. Each library had 35-42 million reads and more than 80% of reads were uniquely aligned. Wald test for a negative binomial model was used to call differentially expressed genes. Among upregulated transcripts were cell-cycle genes including centomere proteins (Cenpa, Cenpf, and Cenph); MMC helicase subunits (Mcm3, Mcm5, and Mcm6); cyclins (Ccnb1, Ccnb3, and Ccnd1); cyclin-dependent kinase (Cdk1); and polo-like kinase (Plk1). Among downregulated transcripts at 48 h were transcription factors (Jun, Hm12, Klf5, Klj3, Foxo3, Zfp36, Zfp354a, Zbf16b, and Zic3). At 72 h, 769 transcripts were upregulated and 704 downregulated in UNx. Among upregulated transcripts were cell-cycle genes including centomere proteins (Cenpa, Cenpf, and Cenph); MMC helicase subunits (Mcm3, Mcm5, and Mcm6); cyclins (Ccnb1, Ccnb3, and Ccnd1); cyclin-dependent kinase (Cdk1); and polo-like kinase (Plk1). Among downregulated transcripts at 48 h were transcription factors (Jun, Hm12, Klf5, Klj3, Foxo3, Zfp36, Zfp354a, Zbf16b, and Zic3). At 72 h, 769 transcripts were upregulated and 704 downregulated in UNx. Upregulated transcripts included Ccgf, Sgk1, Zbf16b, and cyclins (Ccnb1, Ccnb3, and Ccnd2). Interestingly, Ccgf, Sgk1, Zbf16b, and Ccnd2 showed a triphasic response, upregulated at 24 h and 72 h and downregulated at 48 h, consistent with an undamaged control sample.

**Conclusions:** RNA-seq revealed upregulation of multiple transcripts involved in cell division as a central mechanism of compensatory response in the contralateral kidney after uninephrectomy. Genes upregulated at 24 h such as Ccgf, Rgs4, Sgk1 and Ccnd2 may trigger this response.

**Funding:** Other NIH Support - Division of Intramural Research, NHLBI Projects ZIA-HL001285 and ZIA-HL006129.

**FR-PO386**

The Application of Potential Label-Free Mid-Infrared Biomarkers in Patients with Biopsy-Proven Kidney Diseases

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**Background:** We have previously discovered novel spectral markers, the urinary 1545 cm⁻¹ and 1460 cm⁻¹ peaks, indicating progression of experimental GN using Fourier transform infrared spectroscopy (FTIR) (2013 & 2014 ASN). In this study, the aims were to investigate these spectral markers in patients with different biopsy-proven kidney diseases, and the correlations between the spectral markers with clinical features.

**Methods:** The urine and plasma samples were collected at the time of renal biopsy from 50 patients at Imperial College Renal & Transplant Centre, London, UK and compared with healthy volunteers. All samples were measured by FTIR spectrometer and analysed by the established method. The biochemistry analysis such as urine protein/creatinine ratio (uPCR), Scr and renal histopathology were collected.

**Results:** In comparison with healthy volunteers, patients with GN, diabetic nephropathy (DN), membranous nephropathy and FSGS exhibited significantly higher levels of the urine 1545 cm⁻¹ and 1460 cm⁻¹ peaks. Furthermore, the urinary spectral markers were significantly correlated in both GN and DN (p<0.05). There was significant elevation of the plasma 1460 cm⁻¹ marker in all the disease groups compared with healthy volunteers.

**Conclusions:** Our results show the use of the specific urine and plasma FTIR biomarkers will be a novel approach to investigate progressive kidney diseases, including GN and DN, without chemical manipulation of samples.

Funding: Private Foundation Support

**FR-PO387**

Omics Investigation of Urine Samples with and without Addition of a Protease Inhibitor Claire Boulangere.1 Isc M. Rood,2 Petra Züriö,3 Manuja Kaluarachchi,1 Elaine Holmes,1,2 Franz S. Schaefer,3 John C. Lindon,4 Jack F. Wetzel,2 Jeroen Deegens.2 1Metabolix Ltd, London, United Kingdom; 2Dep of Nephrology, RadboudUMC, Nijmegen, Netherland; 3Mosaïques Diagnostics GmbH, Hannover, Germany; 4CSTM, Dep of Surgery & Cancer, Imperial College London, London, United Kingdom; 5Dep of Nephrology, Univ of Heidelberg, Heidelberg, Germany.

**Background:** Urine is an ideal biofluid for biomarker discovery. To conserve the protein profile integrity, samples are stored with a protease inhibitor (PI). It is unknown whether the PI alters the metabolomic and proteome profiles. This study aimed to test the influence of the PI on metabolomic and proteomic analysis of urine samples.

**Methods:** We collected 10 urines from normal controls (NC, n=4) and membranous nephropathy patients (MN, n=6) and the samples were aliquoted. A PI (mini complete, Roche) was added to an aliquot of each sample. Urine samples were stored at -80°C. For metabolomics, samples were analyzed by H-NMR spectroscopy and HILIC-UPCL-MS. Multivariate analysis (MVA) was used to elucidate any PI effect in normal urine and proteomeria. For peptidomics, capillary electrophoresis-coupled mass spectrometry was used to profile the low molecular weight proteome in urine.

**Results:** Unsupervised MVA of urine NMR metabolic profiles showed clear discrimination between NC-PI, NC-PI, MN-PI and MN-PI. Supervised MVA of PI+ and PI- samples revealed subtle changes in metabolic profiles and the presence of intense signals between 3.63 to 3.91 ppm in the PI+ samples, obscuring endogenous metabolic peaks. Unsupervised MVA of HILIC-UPCL-MS data showed discrimination between MN-PI and NC-PI. Supervised MVA of PI+ and PI- samples showed no detectable difference between these two sample types. For peptidomics, MVA between PI+ and PI- resulted in no statistically significant peptide differences. Further validation with a proteome classifier for CKD (CKD273) showed no statistical significant difference between samples with and without PI.

**Conclusions:** The PI addition did not affect the distinction between MN and NC in the metabolome and proteome analysis. However, PI may affect the analysis of metabolic subclasses using NMR. Therefore, samples with PI can be used, but with caution.

Funding: Other NIH Support - The research leading to these results has received funding from the European Union’s Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 305608 (EURenOmic).

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

Underline represents presenting author.
FR-PO389
Quantiﬁcating Uropathogenic Bacteria Infection in 3D
Neal A. Paragas, 1 Alexander Klose, 2 1 Medicine, Univ of Washington, Seattle, WA; 2 In Vivo Analytics, Inc, New York, NY.

Background: Urogenital tract infection is a disease that annually afflicts more than 250 million people worldwide; however, the number of antibiotic resistant strains has been increasing while newly validated antibiotics have been lagging behind. We have developed a method to monitor and quantify an uropathogenic bacterial infection with multispectral bioluminescence tomography (BLT) of a novel bioluminescent uropathogenic E. coli (UPEC-lux).

Methods: We modeled pyelonephritis by transurethral injection of UPEC-lux. First, we acquired bioluminescence images with a bioluminescent optical sensor at four different spectral windows centered at 575, 615, 655, 695 nm and with bandwidth of 50 nm. The multi-orientation images were acquired using a mirror gantry for simultaneous imaging of the dorsal and ventral view. The animal was placed in a fixed position into a novel box where the gantry was placed directly onto the mirror gantry and spectral images were acquired. For in vivo bacterial quantification, a novel calibration device using tissue mimetic material was used. The light intensity imaging data became input to a novel BLT reconstruction algorithm based on an expectation-maximization (EM) method and the simplified spherical harmonics (SP3) equations for modeling in vivo light propagation. Post reconstruction, we calculated the total photon emission density of a volume of interest (VOI). We then calculated the in vivo organ bacterial load by co-registering it to a novel organ probability map.

Results: The EM method reconstructed the 3D photon emission density of the UPEC-lux and mapped the signal to a novel organ probability map. We analyzed these UPEC-lux in a model of pyelonephritis and we were able to determine the bacterial load in the kidney by BLT which correlated to CFUs from serial dilution of kidney homogenate (Pearson correlation coefficient R2 = 0.92). For the first time, we could demonstrate the feasibility of determining the bacterial burden in the kidneys.

Conclusions: The ability to monitor bioluminescent signal non-invasively will be a powerful tool to understand the pathophysiology of urinary tract infections and a new method to test novel antibiotics.

FR-PO390
Public Engagement of Kidney Related Health Information on the Internet
Samir Sulaiman, Joseph A. Vassalotti, Vijay Lapsia. Medicine, Icahn School of Medicine, New York, NY.

Background: The National Kidney Disease Education Program (NKDEP), a part of the National Institutes of Health (NIH) provides an authoritative, up-to-date and trusted consumer health information resource for patients with kidney disease. We hypothesized that the US government (GOV) supported websites would have the highest consumer engagement of kidney related health information on the internet.

Methods: We used traffic rank based on publicly available data obtained from alexa.com and semrush.com, as a marker of website consumer engagement and popularity. We identified the top websites in the health category and disease sub-categories. The websites were classified based on ownership and data collected on unique US visitors, rank, page views per visitor and daily time spent.

Results: In the general health category, the NIH website ranked at the top; however, the consumer focused NLM website ranked 9th, behind webmd.com (2nd) and mayoclinic.org (5th). Among the top 25 websites across all disease categories, Davita.com, a for-profit business, ranked as the only kidney related website. Cancer was the only disease condition with more than 1 website in the top 25 (7 total). The NKDEP ranked 8th in the genitourinary disorders group. The NKDEP had fewer unique US visitors (59,408) compared to Davita.com (307,729) and Kidney.org (241,550). The NKDEP, as well as the non-profit kidney.org supported by the National Kidney Foundation were out performed by Davita.com, a publicly listed for-profit company by an unexpectedly wide margin.

FR-PO391
Media Awareness and Reporting of Dialysis Disruptions and Death from Natural Disasters in the United States
Samir Sulaiman, Lindsay E. Jubelt, Vijay Lapsia. Medicine, Icahn School of Medicine, New York, NY.

Background: Patients receiving in-center hemodialysis are particularly vulnerable during and after disasters. Evidence of morbidity/mortality from disruption to dialysis in a disaster is limited and is so far based on statistical inference. We investigated media awareness and reporting of dialysis disruptions and death during natural disasters in the US.

Methods: We identifed all major disaster declarations by the US Federal Emergency Management Agency. Disasters since 2000, excluding man-made and wildfires, with at least 1 known death were included. We then conducted a systematic Google News search to identify articles within 30 days of each disaster in the electronic mass media (media). Articles were screened for dialysis related key words and classified into 3 categories according to reported potential for missing dialysis, missed dialysis or death.

Results: Of 887 natural disasters from 2000-2015, 120 had at least 1 reported death (total 4,383 deaths). Hurricanes and winter storms had the highest impact on dialysis patients with 5 reported deaths. Of 19 hurricanes incidents, 13 articles referred to dialysis, reporting 7 dialysis disruptions, 4 dialysis deaths and 12 instances of potential disruptions to dialysis. Only 1 of the 61 deaths reported during 3 winter storms was dialysis related, with 2 instances of dialysis disruptions and 3 instances with potential for dialysis disruption. Tornadoes, which occurred most often and resulted in the second highest mortality had no coverage in the media during its aftermath.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Deaths</th>
<th>Articles with dialysis disruptions</th>
<th>Instances of Dialysis Death</th>
<th>Instances of Dialysis Disruptions</th>
<th>Potential For Dialysis Disruptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurricanes</td>
<td>19</td>
<td>2,702</td>
<td>13</td>
<td>4</td>
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<td>12</td>
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<tr>
<td>Flooods</td>
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<tr>
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<tr>
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<td>0</td>
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<td>Winter Storms</td>
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<td>61</td>
<td>5</td>
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<tr>
<td>Total</td>
<td>120</td>
<td>4,383</td>
<td>18</td>
<td>5</td>
<td>9</td>
<td>15</td>
</tr>
</tbody>
</table>

*Dialysis Death: Death due to disaster related disruption to dialysis

Conclusions: Based on media reports, hurricanes and winter storms are major contributors of treatment disruption and mortality in patients on dialysis. Media reports can help identify the magnitude of disruption to dialysis operations as well as deaths.

FR-PO392
A Comparison of Physician Reporting versus Computer Algorithms for CMS Data Reporting on Form CMS-2728
Mohammed Said Malas, 1,2 Ranjani N. Moorthi, 1 Jon D. Duke, 2 Sharon M. Moe, 1 1IU, Indianapolis, IN; 2RI, Indianapolis, IN.

Background: The CMS-2728 form (ESRD Medical Evidence Report) assesses 23 comorbidities chosen to reflect poor outcomes and increased mortality risk. Previous studies have questioned the validity of physician data entry on forms CMS-2728 and the relationship to hard outcomes. We hypothesize that reporting of comorbidities by a computer algorithm identifies more comorbidities and therefore is superior to physicians’ completion of the forms.

Methods: We collected data from CMS-2728 forms for all 296 patients who had included ESRD diagnosis and received chronic dialysis between 2005 and 2014 at Indiana University outpatient dialysis centers. We analyzed patients’ data from electronic records systems that collated information from multiple sources. Previously utilized computer algorithms or natural language processing was used to extract data on 10 comorbidities (Table) for a period of up to 10 years prior to ESRD incidence. These algorithms incorporate billing codes, prescriptions, and other elements that are relevant to each comorbidity. We compared the presence of these comorbidities on the forms to the determined presence according to the algorithms.

Results: The computer algorithms had higher reporting of comorbidities compared to physician completion of the forms (Table). This remained true when decreasing the data span to one year and using only single health center data sources.
FR-PO393
Kidney Dashboard: An Integrated Support Tool for Clinical Care and Research Involving Kidney Patients
Jamie S. Hirsch,1 Hojjat Salmasian,2 Amy Y. Chan,3 David Vawdrey,2 Matthew Fred,3 Krzysztof Kirljak,1 Div of Nephrology, Dept of Medicine, Columbia Univ, New York, NY; 2Dept of Biomedical Informatics, Columbia Univ, New York, NY; 3NewYork-Presbyterian Hospital, New York, NY.

Background: Large amounts of data are contained in electronic health records (EHR), and retrieval of relevant information for nephrology patients is cognitively complex and time-consuming. This results in inefficiencies, missed opportunities to improve care, and difficulty adhering to complex clinical guidelines. We developed a Kidney Dashboard, an integrated tool that gathers and analyzes information to facilitate the care and research of kidney patients.

Methods: Relevant clinical data were catalogued and categorized, including visit history, billing data, vital signs, labs, imaging, pathology, and medications. We automated generation of derived data, such as estimation and trending of eGFR, proteinuria, and automated CKD staging. We implemented a comprehensive rule-based alert system based on KDIGO guidelines to provide real-time clinical decision support.

Results: The Dashboard was created within the clinical information system at NewYork-Presbyterian Hospital, incorporating inpatient and outpatient data from multiple sources. It uses a tile layout, where each tile represents a relevant section of data that matches clinician workflow, e.g., renal function, anemia, bone and mineral metabolism, glomerulonephritis, etc. Repeat eGFR and proteinuria data are presented as interactive longitudinal graphs. The Dashboard integrates delivery of comprehensive stage-specific care and retrieval of relevant information for nephrology patients is cognitively complex and time-consuming. This results in inefficiencies, missed opportunities to improve care, and difficulty adhering to complex clinical guidelines. We developed a Kidney Dashboard, an integrated tool that gathers and analyzes information to facilitate the care and research of kidney patients.

Conclusions: The Kidney Dashboard aims to improve care and facilitate research by consolidating all relevant EHR data at the point-of-care and generating phenotypic profiles of kidney patients. This project promotes precision nephrology, exemplifying the translation of “smart” EHR tools. Following its implementation, effectiveness of the Dashboard will be studied in focus groups and by time-motion studies and audit log analyses. The improvement in adherence to KDIGO guidelines will be tested prospectively.

FR-PO394
Forecasting a Renal Prognosis of IgA Nephropathy Using Machine Learning: Validation Study
Haojoe Ling1, Junhyung Noh2, Hyoseon Kim3, Won Seok Yang,3 Yon Su Kim1, Dong Ki Kim1,1 Internal Medicine, Seoul National Univ Hospital; 2Computer Science and Engineering, Seoul National Univ College of Engineering; 3Internal Medicine, Asan Medical Center.

Background: We aimed to develop and validate individual outcome prediction models in IgAN patients using machine learning.

Methods: We included adult IgAN patients from Seoul National University Hospital (SNUH, n = 1,540) and Asan Medical Center (AMC, n = 1,044) at the time of renal biopsy. They were divided into development (followed up ≥10 years) and prediction (follow up <10 years) sets, respectively. The outcome was 10-year renal survival (10YRS) probability. We developed prediction models from SNUH test set by using logistic regression (LR) with automated CKD staging. We implemented a comprehensive rule-based alert system based on KDIGO guidelines to provide real-time clinical decision support. We evaluated the robustness of prediction models using machine learning for the individual’s likelihood of 10YRS in IgAN with both internal and external validation.

Results: We analyzed 246,996 providers in 13 specialties; 5% were Nephrologists. Female Nephrologists were reimbursed less $41,776.96 (unadjusted); the 6th worst female-to-male reimbursement differential. In the adjusted analysis, female Nephrologists had the worst reimbursement differential: less $17,971.66.

Conclusions: When adjusted for the number of beneficiaries seen & services provided, female Nephrologists endure the largest reimbursement gap by sex in any specialty. Steps should be considered to close this gap.

FR-PO396
Engineering Renal Engineering for Renal Delivery of Molecular Therapies
Pan Liu, Jing Jin. Dept of Medicine-Nephrology/Hypertension, The Feinberg School of Medicine, Chicago, IL.

Background: Targeted delivery of therapeutic enzymes to the kidney is desirable for treatment of renal diseases and beyond. Previously, approaches that exploit the renal excretion of low–molecular weight proteins (LMWP) have been attempted. However, these carriers can deliver chemical compounds, and their efficiency is further hampered by first-pass metabolism. In order to deliver enzyme cargos, we designed carrier proteins for specific and long-lasting renal delivery. We engineered a fusion protein comprised of a kidney-targeting polybasic tag (PBT) and an Fc segment for extended stability.

Methods: PBT-Fc and Fc-only control were produced as recombinant proteins. We used the FcγRIIa as an iLWP control for alternative means of renal targeting through excretion. The probes were then separately labeled with a radionuclide radioiodine (125I) tracer. Following i.v. injection of the probes to rats, we performed SPECT in whole body scanning. Radiographs were obtained in a time series for up to 1 hour. In parallel, we performed histology studies of kidney sections to determine the sub-anatomical patterns of the injected probes.

Results: Prominent and sustained kidney localization of 125I-PBT-Fc (95%) was observed by SPECT, a pattern in contrast to that of the 125I-Fc control that was mainly in blood circulation during the course of observation (only <5% is in the kidney). 125I-Fc was not observed by SPECT, a pattern in contrast to that of the 125I-Fc control that was mainly in blood circulation during the course of observation (only <5% is in the kidney). 125I-Fc was not observed by SPECT, a pattern in contrast to that of the 125I-Fc control that was mainly in blood circulation during the course of observation (only <5% is in the kidney).
Duramycin reached the kidney quickly and then followed through urinary excretion to the bladder within 6 minutes, while more than 5% remained in the kidney. The imaging results were consistent with IHC findings from mouse kidney following probe injections, which shows the PBT-Fc, but not Fc-alone, binding the glomeruli and tubule basement membrane shorty after injection. PBT-Fc sustained in the kidney for at least 10 days.

Conclusions: Our engineered PBT-Fc carrier exclusively targets kidney through binding to the glomeruli and tubule basement membrane. This recombinant probe also achieves long-lasting kidney retention (days as compared to minutes for LMWP), yet another desirable property for targeted therapeutic delivery. This vehicle will potentially be useful for delivery of molecular therapies, particularly enzyme proteins, to the kidney.

FR-PO397

Dynamic Culture on an Orbital Shaker Alters the Phenotype of Primary Human Renal Tubular Epithelial Cells
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Background: Primary cells cultured in vitro gradually lose features characteristic to the in vivo cell type, variously termed “senescence” or “culture stress.” Culture conditions that help maintain cell-specific phenotype are advantageous for cell biology and tissue engineering. Here we evaluated the phenotype of primary renal tubular epithelial cells after applying apical fluid shear stress using an orbital shaker.

Methods: Human renal tubular epithelial cells were isolated from donor kidneys not suitable for transplant. Cells were cultured on Transwell inserts under static conditions or on an orbital shaker at a frequency producing fluid shear stresses of 2 dyn/cm². Transpositional resistance was measured daily. After 2 weeks in culture, cell density was analyzed by counting DAPI stained nuclei, and expression of tubule-specific markers was measured by PCR and western blotting.

Results: Dynamic culture significantly increased steady state transpositional resistance from 344±31 to 544±32 Omega cm (p<0.001) and resulted in a 21.5±2.1% (p<0.001) increase in cell density. Gene expression of tubule epithelial cell markers (GCT1, COL4A1, COL4A2, NFATC1, AQP3) increased with fold changes in expression of 3.2±1.1, 3.1±0.3, 3.1±0.2, 2.1±0.4, and 1.9±0.2, respectively. Cells grown under shear also showed increased protein expression of gamma-glutamyl transpeptidase.

Conclusions: Primary renal tubular epithelial cells grown on an orbital shaker with physiological levels of fluid shear stress appear to express proximal tubule markers more than cells grown in static conditions. This may be due to increased nutrient delivery and waste removal with improved mixing at the apical brush border, or due to specific gene regulation related to mechanotransduction. Further mechanistic insight may allow investigators to develop improved in vitro culture systems for cell biology and tissue engineering and more accurate in vitro models of disease.

Funding: NIDDK Support

FR-PO398

Crispr/Cas9-Mediated Site-Specific Mutation in Rat Angiotinogen Gene via Direct Injection of One-Cell Embryos
Yaochun Zhang, Zakir Hossain, Bo Lan, 1Chang-Yien Chan, 1Hui Kim Yap, 1Kar Hui Ng. 1Dept of Paediatrics, National Univ of Singapore, Singapore; 2Cancer Science Inst of Singapore, National Univ of Singapore, Singapore.

Background: Genetically modified animals represent a crucial tool for understanding gene function in development and disease. The recently developed CRISPR/Cas9 system is an efficient gene-targeting technology to generate genetically modified animals. We have performed exome sequencing in a Singaporean Chinese family with X-linked recessive membranous nephropathy associated with Fanconi syndrome and anti-tubular basement antibodies, and identified AMOT, coding for angiomotin, as a novel candidate gene with a putative disease-causing mutation p.S50G in the N-terminal of the p130-AMOT isoform.

Preliminary work confirmed the expression of angiomotin in renal tubular cells. This study aimed to introduce the mutation into rat genome via direct injection of CRISPR/Cas9 into one-cell embryos, establishing rat models for downstream pathological studies.

Methods: The tracrRNA:crRNA fused single guide RNA (sgRNA, 20ng/µl) together with Cas9 protein (40ng/µl) and a single-stranded oligonucleotide (ssODN, 3ng/µl), which encodes the p.S50G mutation of angiotinogen and serves as template for HR-mediated repair, were introduced into the rat pronucleus via microinjection. Pups produced from the injected embryos were first detected by mismatch-sensitive T7 endonuclease I digestion. Animals carrying mutations were sequenced to determine the precise sequence.

Results: In the 32 survived pups, one (3.1%) founder rat was identified to carry the heterozygous mutation. After crossing F0 with a wild-type rat, ten F1 rats were delivered, of which four males (40%) were carrying the mutation on their X chromosomes, while 2 (20%) were heterozygous females. No phenotype data is available currently as the animals are only three weeks old. Homozygous female rats are expected to be produced by crossing between the F1 animals.

Conclusions: In conclusion, a heritable site-specific mutation was successfully introduced into the rat genome with the CRISPR/Cas9 system. This one-step method of generating site-specific mutations in rats will greatly accelerate the in vivo study of gene functions.

Funding: Government Support - Non-U.S.

FR-PO399

Double Transduction of a Cre/LoxP Lentiviral Vector: A Simple Way to Generate Cell-Specific Knockdown Mice
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Background: Genetically engineered mice have been used to elucidate the function of specific genes. Transgenic mice by conventional knockout techniques using oocytes or embryonic stem cells are most commonly used to downregulate genes, but this method has certain limitations. Therefore, a novel method to knock down specific genes in a cell specific manner in adult mice was devised by lentivirus (LV)-assisted delivery of short hairpin RNA.

Methods: In vitro, the LV suspension containing LV-Hoxb7 Cre and/or LV-Aquaporin 3 shRNA (LV-AQP3) was added to cultured primary renal collecting duct cells (CDs) and mouse mesangial cells (MMCs). In vivo, first, LV-Hoxb7 Cre was injected into the loxp-EGFP mice to check the Hoxb7 promoter efficiency. Second, LV-loxp shAQP3 was injected into the Hoxb7 Cre transgenic mice to check shAQP3 function. Third, consecutive injections of LV-Hoxb7 Cre and LV-loxp shAQP3 were made to C57BL/6J mice.

Results: In vivo, LV-Hoxb7 Cre worked only in CDs due to the presence of Hoxb7 in CDs but not in MMCs. Furthermore, combined injection of CDs with LV-Hoxb7 Cre and LV-loxp shAQP3 significantly inhibited the protein expression of AQP3 along with the disappearance of EGFP protein expression, suggesting that LV-Hoxb7 Cre and LV-loxp shAQP3 used in this study worked together effectively. In vivo, kidney CD-specific AQP3-knockdown mice were generated by consecutive injection of LV-Hoxb7 Cre and LV-loxp shAQP3 alone did not differ, but consecutive injection of LV-Hoxb7 Cre and LV-loxp shAQP3 significantly reduced AQP3 expression. However, the expressions of AQP3 in other organs did not differ between the groups.

Conclusions: Double transduction of Cre- and loxp-based LV can be a simple way to generate cell-specific knockdown mice, and this method may also be applicable to other species.
Substrate stiffness regulates renal epithelial cell cilia formation via autocrine TGFβ signaling. Mingfang Ao, 1 Jin Cheng, 1 Nicholas J. Ferrell, 1,2 H. David Humes, 3 Shuvo Roy, 2 William Henry Fissell. 1,3 Hypertension, Vanderbilt Univ, Nashville, TN; 2Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA; 3Nephrology, Univ of Michigan, Ann Arbor, MI.

Background: The primary cilium serves the extracellular environment. Malformation of primary cilia has been shown to result in kidney disease. Although much is known regarding ciliogenesis, the role of mechanical features of the microenvironment in cilia formation is poorly understood.

Methods: Human primary proximal tubule epithelial cells (HRECs) and LLC-PK1 cells were plated on collagen-coated polyacrylamide gels with different stiffness (0.5 KPa, 1 KPa, 10 KPa and 40 KPa) and grown for 5 to 7 days. Cilia formation was analyzed by immunofluorescence staining of AC-tubulin followed with microscopy imaging. Protein expression was measured by immunoblottting. Recombinant TGFβ 1 and an inhibitor of TGFβRII SB431542 were used for TGFβ signaling modulation. LiCl was utilized to stimulate P-GSK3b.

Results: Stiff gels (10 KPa and 40 KPa) gave rise to higher ciliary density than compliant gels (0.5 KPa and 1 KPa) did (60% vs 20%). Furthermore, this phenotype could be altered by manipulation of transformation growth factor beta (TGFβ) signaling: addition of TGFβ 1 could increase the cilia frequency even when the cells were on compliant gels; similarly, inhibition of TGFβ receptor II impairs cilia formation in the context of stiff substrates. Furthermore supporting a role for TGFβ, substrate stiffness was associated with increased SMAD2 and GSK3β phosphorylation. Incubation with LiCl also increased GSK3β phosphorylation and cilia formation independent of TGFβ.

Conclusions: Substrate stiffness determines cilia formation through TGFβ signaling via downstream GSK3β phosphorylation. This work highlights that substrate mechanical properties have a strong influence on markers of differentiation. This has relevance for tissue engineering efforts and also suggests a mechanism of disease progression in the scarred kidney. This may broaden researches on kidney disease and contribute to disease therapy.

Funding: Other U.S. Government Support

An Additive Role of Microfluidics on KLF 15-Induced Differentiation of Human Primary Podocyte Seung Hye Yang, 1 Eunjin Bae, 2 Sejoong Kim, 3 Kwon Wook Joo, 1,2 Chun Soo Lim, 1,2 Yon Su Kim, 1,2 Dong Ki Kim. 1,2 Kidney Research Inst; Internal Medicine, Seoul National Univ College of Medicine, Seoul.

Background: Podocyte de-differentiation is one of major problems during the process of primary podocyte culture. Recently, much interest has been focused on the topic, yet lenient control over differentiation process hinders a progress. KLF15 (Kruppel-like factor 15) was reported to be a novel transcriptional regulator of podocyte differentiation and its expression was increased by retinoic acid (RA) which promotes the differentiation of podocytes. But, the duration of podocyte differentiation process remains long. Here, we present a novel in vitro protocol to induce podocyte differentiation.

Methods: To mimic in vivo biological environment of glomerulus, a polydimethylsiloxane (PDMS) microfluidic device was used. The human primary podocytes were cultured in the 500 mm by 130 mm microfluidic channel and were stimulated with a laminar fluidic shear stress of 0.5 dyn/cm² for 5 days. Various dose of RA was used to promote podocyte differentiation.

Results: In this research, we were able to reduce the time required for podocyte differentiation with higher shear stress and higher dose of RA. A couple of tests were conducted to verify the podocyte differentiation through the protocol. First, the phenotype of podocytes changed from cobblestone like shape to arborized cells. Through immunofluorescence staining, the increased expression of cytoplasmic synaptopodin and intercellular junction ZO-1 was confirmed. Moreover, KLF 15 expression was also increased. These molecules were also quantified with mRNA expression through real-time PCR. The size of podocytes became larger and the height of podocytes increased by a factor of 2.3 fold. Lastly, the podocytes aligned with the direction of flow.

Conclusions: In conclusion, we were able to promote podocyte differentiation in the shorter processing time with microfluidics and RA. Yet, more effort to mimic biological aspects of kidney such as complex structure with multiple cell layers and round surface is necessary.

Funding: Private Foundation Support

CCL18 Correlates with Disease Activity in ANCA-Associated Neutrophil Granulomatosis Silke R. Brix, 1 Christian F. Krebs, 1 Martin Busch, 2 Thorsten Wiech, 3 Ulf Panzer, 4 Rolf A. Stahl. 1 III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Germany; 2‘Klinik für Innere Medizin III, Universitätsklinikum Jena, Germany; 3‘Institut für Pathologie, Universitätsklinikum Hamburg-Eppendorf, Germany.

Background: Microarray analysis of renal tissue from patients with antineutrophil cytoplasmatic antibody (ANCA)-associated neutrophilic granulomatosis (GN) revealed the CC chemokine ligand 18 (CCL18) as the highest up-regulated chemokine. The renal production of CCL18 was associated with fresh glomerular lesions and impairment of renal function. The cellular sources of CCL18 were identified as macrophages and dendritic cells. CCL18 serum levels were elevated in patients with newly diagnosed ANCA GN as well. In order to test whether CCL18 might serve as a biomarker of relapsing renal ANCA disease, we prospectively analyzed CCL18 serum levels.

Methods: Hundred thirty-five patients with biopsy proven ANCA GN were prospectively analyzed for CCL18 serum levels. Patients included in the study were in remission on maintenance therapy (n=117) or without immunosuppressive treatment (prednisolone 5mg or less was accepted) (n=18). Serum levels of CCL18 were measured by ELISA every three months. Renal relapse was defined as either rising serum creatinine with urinary red cell casts or biopsy-confirmed active ANCA-associated glomerular lesions (i.e. fibrinoid necrosis and/or cellular crescents) accompanied by an intensification in immunosuppressive treatment.

Results: During a mean follow up time of 11.6 ± 8.3 months, 16 patients developed a renal relapse. CCL18 levels were higher in relapsing patients when compared with patients who were in clinical remission (167.50 ± 85.44 ng/ml vs. 83.17 ± 46.38 ng/ml). CCL18 serum levels increased at the time of relapse and decreased after immunosuppressive therapy was restarted or intensified (p=0.001).

Conclusions: CCL18 serum levels are associated with disease activity in patients with ANCA-GN and might serve as a marker of relapses in the surveillance of these patients.

Funding: Government Support - Non-U.S.

Prognostic Value of Persistent Hematuria and Proteinuria in ANCA-Associated Vasculitis: Data from the European Vasculitis Study Group (EUVAS) Therapeutic Trials Alexandre Karras, 1,3 Thomas F. Hiemstra, 2 Rachel B. Jones, 1,2 David R. W. Jayne. 2 Nephrology, HEGP Hospital, Paris, France; 3Nephrology, Addenbrooke’s Hospital, Cambridge, United Kingdom;

Background: Renal involvement is frequent ANCA-associated vasculitis (AAV), due to crescentic glomerulonephritis (CGN). Hematuria (Hu) and proteinuria (Pu) are detected during the initial and active phase of CGN but the prognostic value of the persistence of these urinary abnormalities during the remission phase of AAV is still controversial.

Methods: Data were combined from three EUVAS trials (IMPROVE, RITUXVAS, MYCYC), providing data for Hu and Pu at month 6 (M6) following initiation of immunosuppression and patient follow-up until month 18 (M18). Hu was defined as Persistent of >0 RBC/mm³. Proteinuria was evaluated by protein-to-creatinine ratio (PCR, g/gm). Multivariate analysis using a mixed effects model demonstrated that degree of proteinuria at M6 reflects more severe kidney damage and is an independent predictor of CKD progression in AAV nephropathy.
FR-PO407

Double Positivity for ANCA and Anti-GBM Antibodies: Clinical Characteristics and Long-Term Outcomes of a Multi-Centre Cohort

Stephen Paul McAdoo, Anisha Tan, Sophie Ohlsson, Zdenka Hruskova, Maria Weiner, Jeremy B. Levy, Vladimir Tesar, Martin Segelmark, Charles D. Pusey, Imperial College London, London, United Kingdom; Charles Univ Prague, Linkoping Univ.

Background: Co-presentation with both ANCA and anti-GBM disease is a rare phenomenon. Current studies often include small numbers and report variable outcomes. We aim to describe the clinical features and outcomes of a large cohort of contemporary patients identified from three large European centres.

Methods: This is a retrospective cohort study, which included patients with both ANCA and anti-GBM antibodies (ANCA-anti-GBM positive). Primary outcomes were recorded from the time of diagnosis until death, first-time cancer or end of year 2013. For the analysis, patients were divided into two groups. All patients were followed for a minimum of 3 years. Risk of cancer was calculated as standardized incidence ratio (SIR), SIR = observed/expected. Patients were followed from the time of diagnosis until death, first-time cancer or end of year 2013.

Results: We identified 78 anti-GBM+ patients, of whom 37 (47%) were DP for ANCA and anti-GBM antibodies. In the DP group (37 patients), 10 had ANCA- but no anti-GBM, 16 had anti-GBM- but no ANCA and 11 had ANCA+ and anti-GBM+.

Conclusions: Compared to SP for ANCA, DP patients had significantly lower risk of cancer (SIR 0.57 vs 1.26, p = 0.049).

FR-PO408

Pulse Methylprednisolone for Induction of Remission in Severe ANCA Associated Vasculitis Is Associated with an Increase in Adverse Events but No Improvement in Outcome

Dimitrios Chronouzas, JulieAnne G. McGregor, Alan D. Salama, Wladimir M. Szpirt, Neil Basu, Matthew David Morgan, Imperial College, London, United Kingdom; Copenhagen Univ Hospital, Denmark; Aberdeen, United Kingdom.

Background: Intravenous pulse methylprednisolone (MP) is frequently used as part of remission induction in severe ANCA associated vasculitis (AAV). However, there are no studies assessing its efficacy in the setting of AAV, while treatment related complications remain the main source of morbidity.

Methods: We retrospectively analysed outcomes of 114 patients that presented with severe AAV at 5 large centers in the United Kingdom, United States and Denmark between 2000-2013. All patients received high dose oral corticosteroids, cyclophosphamide and plasma exchange. Rituximab treated patients were excluded. The chi square and Mann Whitney U tests were used for statistical analysis.

Results: Fifty-four patients received MP (median dose 1.5 g over 3 days) in addition to standard therapy while 62 did not. Patient characteristics and disease severity were comparable between the two groups. There was no difference in survival at 3 months (MP: 94.2 vs non MP: 91.9%, p=0.633) or 12 months (84.6 vs 80.6%, p=0.579). Renal recovery amongst survivors (63.5 vs 72.6%, p=0.297) and relapse rates at 12 months (11.6 vs 8.6%, p=0.617) were similar. MP therapy was associated with more infections per patient at 3 months (0.7 vs 0.3, p=0.005) and more new onset diabetes (28.6 vs 6.6%, p=0.002).

Conclusions: Within the limitations of this study we found that the addition of MP to standard therapy for remission induction in severe AAV led to a significant increase in adverse events with no improvement in survival, renal recovery or relapse rates. Our results question the currently widespread use of MP in severe AAV and suggest that a randomised controlled trial is urgently needed in order to definitively address this issue.

FR-PO409

Serum B Lymphocyte Stimulator (Blys) Levels as Markers of Disease Activity in Anti-Neutrophil Cytoplasm Antibody (ANCA) Associated Vasculitis (AAV)


Background: B lymphocyte stimulator (Blys) has been implicated in the pathogenesis of AAV. Previous studies have shown elevated levels in active disease, and following anti-CD20 therapy. Antineutrophil cytoplasm antibodies (ANCA) are not reliable predictors of disease activity and relapse and alternative markers are needed to support this notion.

Methods: In the current study we determined the current widespread use of Blys in severe AAV and suggest that a randomised controlled trial is urgently needed in order to definitively address this issue.

Results: Fifty-four patients received MP (median dose 1.5 g over 3 days) in addition to standard therapy while 62 did not. Patient characteristics and disease severity were comparable between the two groups. There was no difference in survival at 3 months (MP: 94.2 vs non MP: 91.9%, p=0.633) or 12 months (84.6 vs 80.6%, p=0.579). Renal recovery amongst survivors (63.5 vs 72.6%, p=0.297) and relapse rates at 12 months (11.6 vs 8.6%, p=0.617) were similar. MP therapy was associated with more infections per patient at 3 months (0.7 vs 0.3, p=0.005) and more new onset diabetes (28.6 vs 6.6%, p=0.002).

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FR-PO409

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Methods: Serum samples were obtained from patients with AAV at our centre, and BlyS levels detected using sandwich ELISA. Clinical data were obtained by review of patient records.

Results: Samples were collected from 68 patients with AAV and 13 healthy controls. Thirty one patients were male, 44 Caucasian and 21 Indoasian. Fifty patients had granulomatosis with polyangiitis, 13 patients had microscopic polyangiitis and 5 had eosinophilic granulomatosis with polyangiitis. Significantly higher BlyS levels were found in patients with active disease than those in remission and healthy controls.

Thirty seven patients who had been treated with Rituximab had significantly higher BlyS levels (p<0.0001). Eighteen patients had relapsed at 1 year following recruitment. These relapsing patients had significantly higher BlyS levels than those patients who did not relapse (p<0.0016).

Conclusions: This study supports the role of BlyS in the pathogenesis of AAV. BlyS levels could be used as markers of disease activity and predictors of relapse. With increased use of rituximab in AAV, further studies are needed to assess the impact of B cell depletion on B cell survival factors. These findings highlight the potential role for BlyS in pathogenesis in the maintenance of remission of AAV.

Funding: Government Support - Non-U.S.

FR-PO410
Predictors of Renal Histopathology in Antineutrophil Cytoplasmatic Antibody Associated Glomerulonephritis
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Background: Prompt, aggressive therapy is vital for anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN). In this regard, we aimed to identify predictors of distinct renal histopathological classes at the time of clinical diagnosis.

Methods: An inception cohort of patients with biopsy proven ANCA-associated GN was studied retrospectively. Demographics, clinical, laboratory, serological and radiological parameters were analyzed. Patients were classified on the basis of renal histopathology, according to the report by Berden et al (JASN 2010) for ANCA-associated GN by a renal pathologist into: focal class, crescentic class, mixed class and sclerotic class. A risk score was developed for each histopathological class using univariate and logistic regression analyses.

Results: Variables independently associated with focal class included disease duration up to diagnosis < 8 weeks, absence of red blood cell (RBC) casts by urine microscopy and eGFR > 40 ml/min/1.73m²; with crescentic class > 40 erythrocytes/hpf, identification of RBC casts in urine, ear nose and throat (ENT) involvement and eGFR < 49 ml/min/1.73m²; with mixed class age > 54 years, male gender, and absence of ENT involvement. In the presence of 2 or 3 risk factors a predictive risk score of each histopathological class was calculated: odds ratio (OR), 95% confidence intervals (CI), for focal class (2 risk factors) 17.5 (95% CI) [4.9-62.9], 38.0 [6.8-213.7] for crescentic class (³3 risk factors), and 8.3 [1.0-67.5] (2 risk factors) for mixed class.

Conclusions: We propose a predictive algorithm of specific histopathological classes of ANCA associated GN, which might provide a crude estimation of the disease activity in the glomeruli at presentation. This tool might assist the clinician in making decisions regarding the level of intensity of inductive immunosuppressive therapy at clinical diagnosis.

FR-PO411
Rituximab as a Cyclophosphamide Sparing Agent for Patients with Multi-relapsing ANCA-Associated Small Vessel Vasculitis
Sophia Lionaki,1 George E. Fragoulis,2 Alice Venetsanopoulou,2 John N. Boletis,1 Panagiotis Vlachogiannopoulos,4 Haralampos Moutsopoulos,2 Athanasios Tzioufas,2 *Nephrology, Laiko Hospital, Greece; 2Pathophysiology, Univ of Athens, Greece.

Background: To evaluate the clinical efficacy and outcomes, of patients with multi-relapsing ANCA-associated Vasculitis (AAV), who received induction therapy with rituximab for a new disease relapse.

Methods: We retrospectively studied all patients with biopsy proven AAV, who were treated with rituximab upon a new relapse. A control group consisted of patients from the era prior to the initiation of rituximab in the treatment of AAV, was selected using the following criteria: i/history of relapse, ii/orган involvement at relapse, iii/treatment with the standard regimen. Patients and controls were matched for age, gender, and disease duration. Comparisons of disease outcomes along with the frequency and severity of adverse events were performed between groups. Rituximab was used with high dose glucocorticoids and depending on the organ involvement a short course of cyclophosphamide was added.

Results: Of 147 patients with AAV and a mean total follow up time of 78.2 months, 18 patients (12.2%) received induction treatment with rituximab for disease relapse. Time to 1st relapse from the 1st diagnosis of AAV was shorter in the rituximab group and the mean number of relapses per patient was significantly higher in this group. The mean BVAS score was similar between groups at study entry while 13/18 patients received a 3-month course of cyclophosphamide in addition to rituximab.

Conclusions: Rituximab was shown efficacious in patients with multiple relapsing AAV including cases with renal and pulmonary involvement. It allowed us to minimize the ultimate exposure to cyclophosphamide in these patients, which is crucial, as they accumulate remarkable toxicity in long-term.

FR-PO412
Differences Between Patients with Definite and Suspected ANCA-Associated Vasculitis in a Secondary Care Hospital
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Background: ANCA-associated vasculitis (AAV) is a rare disease with a broad spectrum of symptoms. Therefore, diagnosing AAV is often challenging. In an effort to provide guidance for clinicians, we aimed to identify differences between ANCA positive patients with a definite and suspected diagnosis of AAV.

Methods: In this retrospective study, all patients that tested positive for MPO and/ or PR3 ANCA between 2005 and 2015 in a secondary care hospital in the Netherlands were analyzed. Patients were divided into subgroups according to clinical diagnosis and the Birmingham Vasculitis Activity Score (BVAS). Possible predictors for AAV, such as patient characteristics, clinical symptoms and ANCA titers were identified. Patients were also screened for commonly used exclusion criteria in trials.

Results: We included 240 patients with a positive MPO and/or PR3 ANCA, of which 120 patients were clinically diagnosed with AAV (group 1); all had a BVAS ≥ 3. Of the patients without the diagnosis AAV, 50 had a BVAS ≤3 (group 2) and 70 had a BVAS ≤ 3 (group 3). In group 2, 39 patients had an alternative diagnosis, including other rheumatic diseases and infection. In a multivariable linear regression model, higher ANCA titers, higher BVAS and Ear Nose Throat (ENT) symptoms were predictive for AAV (all p<0.001). Of the patients diagnosed with AAV, 21 (18%) would have been excluded from most trials, based on a malignancy (n=13) or organ associated with vasculitis (n=8). Notably, characteristics of these patients did not differ significantly from the other AAV patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rituximab group, N=18</th>
<th>Control group, N=18</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of relapses per patient up to study entry (median (range))</td>
<td>2 (1-4)</td>
<td>1 (1-2)</td>
<td>0.009</td>
</tr>
<tr>
<td>Subsequent relapse, N(%)</td>
<td>3(11.1)</td>
<td>4(22.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cyclophosphamide exposure post study entry (mean±sd) (grams)</td>
<td>24.39 ±32.5</td>
<td>125±3.09</td>
<td>0.02</td>
</tr>
<tr>
<td>Follow up time post study entry (months/range)</td>
<td>37(6-68)</td>
<td>53(8-228)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Conclusions: Rituximab was shown efficacious in patients with multiple relapsing AAV including cases with renal and pulmonary involvement. It allowed us to minimize the ultimate exposure to cyclophosphamide in these patients, which is crucial, as they accumulate remarkable toxicity in long-term.
FR-PO413
Rituximab and Low-Dose Cyclophosphamide Therapy for Renal ANCA-Associated Vasculitis: Long-Term Follow-Up
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Hiroe Sato,1 Yukiko Nozawa,1 Yoko Arimura.1
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Background: The previously reported study of rituximab (RTX) and low-dose cyclophosphamide (CYP) followed by azathioprine maintenance for ANCA-associated renal vasculitis (AAV), suggested it was efficacious in inducing remission and has an acceptable side-effect profile (N. Mendelsohn et al. 2011). We have followed the cohort for over seven years and report the regimen’s efficacy and safety profile.

Methods: Long-term outcomes were retrospectively ascertained from all 23 previously treated patients.

Results: Mean time since starting the treatment regimen was 83 months; twenty-one patients started the regimen more than five years ago. All patients achieved clinical remission within six weeks, with depletion of circulating CD19-positive B cells and significant reduction in median anti-PR3/MPO ANCA titre. After 8 months follow-up, five renal and four non-renal relapses were observed and treated in five patients. Median eGFR improved from 28 ml/min (range 11-63) at presentation to 49 ml/min (range 3-87) after one year and was maintained at 50 ml/min (8-90) at five years (n=21) and 46 ml/min (22-76) at seven years follow-up (n=9). To date, three infections requiring hospital admission and four malignancies have been recorded.

Conclusions: This rituximab-based low-dose cyclophosphamide regimen followed by maintenance therapy provides safe and effective long-term treatment at more than five years follow-up.

FR-PO414
The Histopathologic and Clinical Determinants of the Change in GFR During the 1st year of Treatment in ANCA-Associated Vasculitis
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Background: Identifying the predictors of the change in GFR in ANCA-associated vasculitis (AAV) is helpful to avoid prolonged immunosuppression in those where no renal basis exist and to consider modifying therapy in those who should improve but fail to do so.

Methods: We retrospectively reviewed cases of AAV with a renal biopsy in 3 hospitals to determine predictors of the change in GFR (deltaGFR) during the 1st year of treatment. We considered demographics, pathology findings, treatments and complications incurred. In particular, we addressed the histopathologic classification (Berden JASN 2010) proposing focal, crescentic, mixed and sclerotic subsets.

Results: Of 120 patients with AAV, 71 had a renal biopsy and received immunosuppression. They presented at an age of 59±13 with 48% female, 49% anti-MPO+ and a GFR of 32±30 ml/min including 22 patients on dialysis. Induction consisted of cyclophosphamide (93%), rituximab (6%), plasma exchange (27%) and pulse methylprednisolone (69%) in addition to oral corticosteroids. During the 1st year, patients recovered 15±20 ml/min/1.73m2 with 11 no longer requiring dialysis. The deltaGFR increased up to 6 months, although it varied greatly individually. Age, hypertension, MPO positive serology, the extent of crescentic and sclerotic glomeruli, tubular atrophy and the histopathological classification were associated with a lower GFR at diagnosis. However, in one year only histopathologic classification and the number of admissions for treatment-related complications predicted a lower deltaGFR. The focal, crescentic, mixed and sclerotic subsets experienced a 19±23, 17±15, 11±12 and ±2±6 ml/min deltaGFR, respectively (p=0.026, trend test).

Conclusions: The change in GFR during the 1st year of treatment in AAV increased 15±20 ml/min. It appeared maximal at 6 months into therapy. The histopathologic classification helped predict the deltaGFR at 12 months, with a reduced benefit of therapy in the sclerotic subset.

FR-PO415
Analysis of Clinical Features in ANCA-Associated Vasculitis: 30 Years Single Center Experience – Relationship Between RPGN and Renal Prognosis
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Background: The clinical features of AAV, with respect to rapidly progressive glomerulonephritis (RPGN), have been changing, but were not well examined in Japan, where MPO-ANCA-associated vasculitis (MPO-AAV) are dominant in contrast to the Western countries. Thus, we retrospectively analyzed the clinical database of the 179 patients with AAV who were admitted to our hospital for the last 30 years.

Methods: At the onset, all patients fulfilled the Chapel Hill Consensus Conference (CHCC) classification criteria for MPA, GPA and EGPA. We divided the AAV patients into the 4 groups based on the presence or the absence of RPGN and hemodialysis and compared the clinical features and renal prognosis. Among 179 AAV patients, 166 cases (92.7%) were MPO-ANCA positive and 14 cases (7.8%) were PR3-ANCA positive.

Results: RPGN was observed in 100 (55.9%) of the 179 patients, including 49 cases of maintenance hemodialysis group (A), 2 cases of temporary dialysis group (B) and 49 cases of non-dialysis group (C), in addition to 79 cases without RPGN and dialysis (D). Significant differences were observed in BVAS, CRP, eGFR and serum Cr concentration. There were no differences for treatment choice, rate of kidney biopsy and frequency of relapses among the groups. Comparison among the different periods for every 10 years show the tendency of an increase in age of onset and the downward trend of serum Cr concentration, rate of RPGN and maintenance hemodialysis, BVAS scores, and frequency of relapses and mortality.

Conclusions: These results have clearly shown the changing features of AAV in Japan, with an earlier detection and the improvement of renal and patient survival during the periods.

FR-PO416
The Effect of Race on 5-Year Survival Outcomes in ANCA-Associated Renal Vasculitis
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Background: Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis is a multi-systemic autoimmune disease characterized by inflammation of microscopical vessels. Renal involvement occurs in 70% of patients, with 1 year mortality rates exceeding 15%. With a prevalence of two cases per 100,000 populations there is a significant preponderance to Caucasians (C). Little is known about the outcomes in patients from Indo-Asian (IA) and Afro-Caribbean (AC) race despite an increasing number of cases seen with the disease.

Methods: We performed a single center, retrospective study, observing 5-year survival outcomes and relapse rates between C, IA and AC in ANCA-associated renal vasculitis. Electronic case notes over a 10-year period (2004-2014) were used collect data to include age at time of diagnosis, Birmingham vasculitis activity score (BVAS) at presentation, race, presence of diabetes and renal function. 5-year survival outcomes were analyzed using a cox proportional hazard model.

Results: In total 121 patients were included in the study, there were 84 (70%) C’S, 31 (25%) IAs and 6 (5%) were of AC background. Median age was 66 years, 56% were men, 20% were diabetic and average BVAS score at presentation was 5. One year relapse rates were low with 8 (6%) relapses seen. No significant difference in 5-year survival outcome was found between the races. Age at presentation significantly affected survival outcomes (p=0.007).

5 year survival outcomes dependent on race

FR-PO417
Possibility of Increasing Prevalence of Otitis Media with ANCA Associated Vasculitis in Japan
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Background: A new disease concept, otitis media with ANCA associated vasculitis (AAV), has been advocated.

Methods: One hundred and fifty seven patients (74 males and 83 females) with AAV (81 microscopic polyangitis, 54 granulomatosis with polyangitis (GPA), and 22 eosinophilic GPA) were admitted to Niigata University Hospital from 1989 through 2014. Twenty seven patients (17%, 13 males and 14 females) with otitis media were recruited. Their clinical features and laboratory data were analyzed.

Results: Fifteen patients were diagnosed as having definite GPA. Five were probable GPA. Lung or kidney lesions were not detected in other seven patients (Ears (E) only group). The initial symptoms in 22 patients (81 %) were ears’ one, such as impaired hearing (91

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controls (HC) were assayed for MPTFa. All patients had 3 samples spanning 12 months. MPTFa content was measured in patients with Factor Xa inhibitor X. Absorbance was measured after addition of Factor Xa chromogenic substrate. Recombinant relipidated human TF was used as a standard. Values were expressed as a percent of MPTFa from a positive control (FPF from LPS-stimulated HC blood). Fisher’s exact tests and Wilcoxon tests were used to compare categorical and continuous variables, respectively.

Results: Demographics were similar among patients and HC. VTE<sub>pos</sub> and VTE<sub>neg</sub> patients did not differ in ANCA serotype or titer, BVAS, D-dimer, other laboratory data, or organ involvement. VTE<sub>pos</sub> patients had significantly higher peak MPTFa than VTE<sub>neg</sub> patients (10.5 (IQR: 8.0-10.9) versus 7.8 (IQR: 5.5-9.2), p<0.001) and had recurrently elevated levels. MPTFa of VTE<sub>pos</sub> patients was similar to HC (median 10.0 (IQR 1.1, 3.3), p=0.4). All VTE<sub>pos</sub> patients had peak MPTFa above normal (mean ± 2SD of HC = 6.5) versus 2/20 VTE<sub>neg</sub> patients (p=0.0001).

Conclusions: Patients with AAV who develop VTE have a notable propensity for increased MPTFa at times both near and remote from VTE. Conversely, those without VTE rarely exhibit MPTFa significantly higher than healthy controls during their disease course. Further study is needed to determine if elevated MPTFa can identify AAV patients at high risk for VTE and whether MPTFa contributes to thrombogenesis.

Funding: NIDDK Support, Private Foundation Support

FR-PO421

ApolI Polymorphism Determines HIV Boarding in Human Podocytes

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Background: Patients of African ancestry with untreated HIV infection, carrying the G1 or G2 kidney disease risk variants (Vs) at the APOL1 gene are at a >10-fold greater risk for developing HIV-associated nephropathy (HIVAN) compared to Caucasian patients. Although APOL1 risk variants. In African Americans with HIVAN, the mechanism of kidney injury has been attributed to the direct effect of HIV infection, the mechanistic contribution to kidney injury of the APOL1 allelic state remains to be elucidated.

Methods: We evaluated the priming effect of IL-1β on human podocyte (HP) APOL1 expression. To evaluate the effect of IL-1β on HIV-1 processing in podocytes, HPs were pre-stimulated with human recombinant IL-1β for 6 h and then incubated with HIV-1 followed by analysis for the HIV-1 strong stop DNA by qPCR analysis. HPs treated under similar conditions were evaluated for the ability of recipient kidneys and HPs to transduce recipient kidneys with HPV (HPV entry) expression. To determine the effect of over expression of APOL1 (G0) and APOL1 variants (G1/G2) HPs were either transfected with APOL1G0/G1/G2 plasmids, or HPs were pre-stimulated with 10 ng/mL of IFN-γ and then incubated with HIV-1 and analyzed for HIV-1 strong stop DNA concentration at various time points and also measured for their lysosomal bioactivity.

Results: APOL1 expression increased after incubation of podocytes with the HIV. In turn, APOL1 expression was further enhanced in response to augmented entry of virus compared to baseline. In HPs, expression of IFN-γ and IL-1β treatment, consistent with viral load dependency. Podocytes over-expressing the non-risk APOL1 gene (G0), either through

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FR-PO424
Use of Spot Urine Protein Creatinine Ratio to Predict Proteinuria in Nephrotic Syndrome in NEPTUNE. Marie C. Hoog,1 Jonathan P. Troost,2 Peter J. Nelson,1 Heather N. Reich,1 Sharon G. Adler,1 Daniel C. Cattran,1 Gerald B. Appel,1 Debbie S. Gipson,1 Wenjun Ju,1 Matthias Kretzler,2 John C. Lieske,1 Mayo,1 UMich,1 UWash,1 UT,1 UCLA,1 Columbia,1

Background: Random protein urine creatinine ratio (UPC) is used to estimate 24 hr protein excretion (24P) yet little data are available wrt sensitivity & specificity, especially in pts with glomerular proteinuria.

Methods: The Nephrotic Syndrome Study Network (NEPTUNE) studies newly diagnosed patients with MCD, FSGS, & MN. Total protein, alb & creat are measured in random & 24 hr urine collections at a central biobank at postbiopsy baseline & subsequent visits within 2 yrs of dx.

Results: Of 603 participants, 302 have same day spot & 24 hr ur samples with a total of 827 samples across all visits eligible for this analysis. Urine protein excretion (g; median; 25, 75%) was higher in adults (1.0, 0.3, 2.3) than in kids (0.2, 0.0, 0.7). Spot UPC correlated better with 24 hr UPC than 24P in both adults (r=0.79 vs 0.60) & kids (r=0.84 vs 0.67). Using these data we derived equations to predict 24P from spot UPCs: for adults 24P = [10^(0.88x(log10 [Spot UPC]) - 10]) & for kids was 24P = [10^(1.06x(log10 [Spot UPC]) - 10)]. The efficiency (AUC) of spot UPC to accurately predict 24P values above thresholds of 0.5, 1.0, 2.0, 3.0, 6.0 & 10 g ranged from 0.83-0.97 in adults & peds.

In subgroup analysis the correlation between log-transformed UPC and log-transformed 24P was similar in all age ranges & diseases, but stronger in obese vs. normal wt subjects (b_slope =0.78, 0.69, 0.88; b_intercept=-0.85, 0.78, 0.93; b_slope=0.85, 1.0, 0.03).

Conclusions: Among MCD, FSGS, & MN pts UPC correlates only moderately with 24P. 24P is best derived from spot UPC using a non-linear estimating equation. WT influences reliability of spot UPC. Our data also suggest UPC can be used with caution to identify those pts with 24P above clinically relevant cut points. As 24P is susceptible to collection errors & implications of threshold values may be dependent on patient size, additional studies to evaluate spot UPC vs 24P and clinical outcomes are warranted.

Funding: NIDDK Support, Other NIH Support - The Nephrotic Syndrome Study Network Consortium (NEPTUNE); U54-DK-083912, is a part of NCATS Rare Disease Clinical Research Network (RDCRN), supported through a collaboration between the Office of Rare Diseases Research (ORDR), NCATS, and the National Institute of Diabetes, Digestive, and Kidney Diseases. RDCRN is an initiative of ORDR, NCATS. Additional funding and/or programmatic support for this project has also been provided by the University of Michigan, NephCare Kidney International and the Halpin Foundation., Private Foundation Support

FR-PO423
Actinin-4, Synaptopodin, Nephrin, and Nep-1 Expression in Proteinuric Patients. Ashwani Kumar,1 Ritambhra Nada,1 Charan Singh Rajat,1 Krishan L. Gupta,1 2Dept of Histopathology, Post Graduate Inst of Medical and Research, Chandigarh, India; 1Dept of Nephrology, Post Graduate Inst of Medical and Research, Chandigarh, India.

Background: Podocytes have an important role in glomerular filtration barrier. Primary podocytopathies and secondary podocyte injuries in presence of immune deposits at different locations results in proteinuria. We compared expression of podocyte structural proteins; α-actinin-4 (Act-4), synaptopodin (Syn), and slit diaphragm proteins; nephrin (Nep) and neph-1 by immunofluorescence (IF) in minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous glomerulonephritis (MGN), and IgA nephropathy (IgAN).

Methods: Two hundred cases (n=50 each) along with controls were stained with FITC tagged α-Act-4, Nep, Syn, and Nep-1 antibodies. Immunofluorescence was graded as mild, moderate, and intense. Immunogold staining with α-Act-4, and Syn antibodies was done to see localization electronmicroscopically (EM).

Results: The α-Act-4 showed mild to moderate intensity (40% & 60%) in controls and most of the cases in all proteinuric groups. Up-regulation was noted in 52% cases of FSGS, 61% in MGN and 75% in IgA. Nephrin showed mild intensity in controls; however moderate to intense staining was seen in MGN (46% & 14%) whereas loss of staining was noted in all other groups (FSGS-54%, MCD-43, IgAN-59%). Nephrin-1 also showed mild to intense staining was seen in all groups and was given second dose. At 6 months, CR and PR was achieved in 9(75%) and 1(8.3%) respectively. There were 2 non-responders (16.6%). Of the 10 responders,3 have completed 1 yr of follow-up and are in remission. Adverse event (pneumonia) was noted in 1 patient (8.3%).

Conclusions: Rituximab appears to be a promising agent in the management of adult CNI dependent or intolerant NS due to MCD/FSGS with minimal short-term adverse events.
FR-PO426
Treatment and Outcomes in Minimal Change Disease: Experience of a Single UK Centre
Anthony Fenton, Stuart W. Smith, Peter Hewins. Dept of Renal Medicine, Univ Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.

Background: Minimal change disease (MCD) accounts for 10-25% of nephrotic syndrome in adults. We retrospectively reviewed the treatment and outcomes of MCD patients in our centre.

Methods: We identified adults who had undergone renal biopsy between June 1996 and March 2012 which was reported as being consistent with MCD, and who had at least 12 months of follow-up. Electronic hospital records were used for data collection.

Results: There were 78 cases, with median follow-up of 72 months. Baseline and treatment data are shown in the table (averages are mean, or median where distribution is skewed). 27% had a history of nephrotic syndrome in childhood. All but one patient (who entered remission spontaneously) were treated with prednisolone, and 97% achieved complete remission at a median time of 33 days (6-309), although 12% needed a second-line agent to do so. Mean number of relapses during the first 24 months was 1.0. 68% experienced at least one relapse, and 45% patients required second-line agents at some point. Regarding complications: 12% developed thromboembolic disease, 14% had an admission requiring infection, and 41% had at least one episode of AKI. Mean follow-up creatinine was 91 mmol/L, but significantly higher in those who had had AKI (104 vs 85 p=0.04) and those who had received an ACEI (99 vs 78 p=0.01). Of 16 patients who underwent subsequent biopsy (all of whom had received a CNi), 8 showed evidence of CNi damage, and 5 were consistent with FSGS. Diabetes mellitus developed in 12% cases, and 8% patients died during follow-up.

Conclusions: Almost all treated adult MCD patients enter remission, although second-line agents are frequently required. Despite therapy, complications remain common, including AKI which is associated with residual reduced eGFR function.

FR-PO427
Predicators for Relapse in Adult Minimal Change Disease
Hajeong Lee, Dong Ki Kim, Kwon Wook Joo, Yon Su Kim, Chun Soo Lim. Internal Medicine, Seoul National Univ Hospital.

Background: Minimal change disease (MCD) is well-known benign primary glomerulonephritis in adults because of their distinct rare renal progression to end-stage. However, their relapse-associated morbidity has been underestimated. In this study, we aimed to explore the predictors of relapse in adult MCD patients.

Methods: We reviewed clinical and pathologic characteristics of adult primary MCD patients from Seoul National University Hospital from 1979 to 2013. Patients who were presented by nephrotic syndrome and followed up more than 12 months were included. Patients were excluded for secondary MCD were excluded. Initial treatment regimens, their response, and complication were also reviewed. The number of relapse were classified as follows, no relapse, 1-2 relapses (relapse group 1), and ≥ 3 relapses (relapse group 2).

Results: A total of 195 patients were included in the final analysis. Among them, median age at the time of diagnosis was 38 (23-53) years and 113 (57.9%) were men. During median follow-up of 81 (44–153) months, more than 90% of patients reached to remission after initial treatment. However, only 64 (32.8%) patients did not experience any relapse. Remaining 131 patients, 69 (35.4%) relapsed once or twice and 62 (31.8%) relapsed more than three-times. The younger, the more relapse was found. In addition, severity of nephrotic syndrome data are shown in the table (averages are mean, or median where distribution is skewed). 27% had a history of nephrotic syndrome in childhood. All but one patient (who entered remission spontaneously) were treated with prednisolone, and 97% achieved complete remission at a median time of 33 days (6-309), although 12% needed a second-line agent to do so. Mean number of relapses during the first 24 months was 1.0. 68% experienced at least one relapse, and 45% patients required second-line agents at some point. Regarding complications: 12% developed thromboembolic disease, 14% had an admission requiring infection, and 41% had at least one episode of AKI. Mean follow-up creatinine was 91 mmol/L, but significantly higher in those who had had AKI (104 vs 85 p=0.04) and those who had received an ACEI (99 vs 78 p=0.01). Of 16 patients who underwent subsequent biopsy (all of whom had received a CNi), 8 showed evidence of CNi damage, and 5 were consistent with FSGS. Diabetes mellitus developed in 12% cases, and 8% patients died during follow-up.

Conclusions: Almost all treated adult MCD patients enter remission, although second-line agents are frequently required. Despite therapy, complications remain common, including AKI which is associated with residual reduced eGFR function.

FR-PO429
Long-Term Outcomes of Nephrotic Syndrome, from Childhood into Adulthood
Rebecca C. Horten, Frederick J. Kaskel, Kimberly J. Reidy. Pediatrics, Div of Nephrology, Albert Einstein College of Medicine, Children’s Hospital at Montefiore, Bronx, NY.

Background: Steroid Resistant Nephrotic Syndrome (SRNS) is known to have several long term sequelae including chronic and End Stage Kidney Disease (CKD and ESKD). However there are few studies on the long-term outcomes of steroid sensitive nephrotic syndrome. Presented here is a single center, retrospective case series from an urban, ethnically diverse population in the Bronx.

Methods: We utilized a medical record data mining tool to identify patients by ICD-9 code (1) with a diagnosis of nephrotic syndrome prior to age 18 (2) with a documented albumin <3.5 g/dL or random urine protein > 1 g/dL and (3) with at least one hospital encounter after the age of 18. Each cohort was evaluated for diagnosis of hypertension, obesity, diabetes, and well tolerated. Burden of medication with attendant side effects, as well as inpatient and outpatient attendance were significantly reduced. Analysed costs showed a modest saving past Rituximab. Further randomised studies are required to confirm and extend these findings.

Results: All three groups – SRNS (n=173), CNS (n=169) and control (n=18225) had similar age at diagnosis, length of follow-up. Both the CNS and CNS groups had a greater proportion of short stature, cataracts, infertility and malignancy (Chi square statistic p < 0.05) [table 1]. In addition they had a greater percentage of patients with CKD by eGFR which is most notable at CKD stages 4 and 5 (Chi square statistic p < 0.05).

Conclusions: Our results show that even patients with uncomplicated nephrotic syndrome are at risk for significant outcomes, including chronic kidney disease. Further study is needed, however it implies that all patients with a diagnosis of nephrotic syndrome will need to be counseled regarding the risks associated with their diagnosis and should have long term monitoring for these outcomes, including worsening renal function, hypertension and malignancy.

Funding: Other NIH Support - NIH T32 Training Grant
FR-PO430
Apolipoprotein CI Levels Are Associated with the Urinary Protein/Urinary Creatinine Levels in Pediatric Idiopathic Steroid-Sensitive Nephrotic Syndrome
Jun Okada, Takahiro Kanai, Takane Ito, Jun Aoyagi, Takanori Ordonez, Glenn Matthew Chertow, Sijie Zheng, David Law. 1

Background: Various humoral factors have been proposed as causal agents of idiopathic steroid-sensitive nephrotic syndrome (ISSNS). In the present study, we analyzed serum proteins using mass spectrometry (MS) in a search for proteins that might be related to ISSNS pathophysiology.

Methods: We collected serial serum samples from 33 children with ISSNS. The serum samples were collected in each phase as follows: Phase A1 [the acute phase prior to steroid treatment (STs)], Phase A2 [remission with STs], and Phase A3 [remission without any medication]. We also included two control groups comprised of children with normal urinanalysis (Group B) and children with a nephrotic syndrome other than ISSNS (Group C). The urine protein/urinary creatinine (UP/UCr) ratios were not statistically different between Phase A1 and Group C. We used surface-enhanced laser desorption/ionization time of flight MS to analyze samples.

Results: A total of 207 peptide ion peaks were detected in the range of m/z 2000–10000. Four peptide ions (m/z 6444, 6626, 8695, and 8915) were significant elevated during Phase A1 compared to Group B and children with a nephrotic syndrome other than ISSNS (Group C). The urine protein/urinary creatinine (UP/UCr) ratios were not statistically different between Phase A1 and Group C. We used surface-enhanced laser desorption/ionization time of flight MS to analyze samples.

Conclusions: Our findings provide new insight into elucidating the pathophysiology of ISSNS.

Funding: Government Support - Non-U.S.

FR-PO431
Ofatumumab in Two Nephrotic Syndrome Children
Marina Vivarelli, 1  Vivianne Buss, 1  Daniel Basu, 1 1

Background: Rituximab (RTX), an anti-CD20 monoclonal antibody, is an effective treatment in patients with frequently-relapsing or steroid-dependent nephrotic syndrome (Ravani, JASN 2015). However, some patients develop adverse reactions. We describe the use of a humanized anti-CD20 monoclonal antibody, ofatumumab (OFA), as a viable alternative.

Methods: Patient 1 is a 3-yr-old boy who presented at 18 months with NS initially resistant to treatment with oral prednisone. He was then treated with 3 iv boluses of methylprednisolone followed by cyclosporinA, with remission. Upon steroid discontinuation, NS relapsed. Prednisone was restarted and a single dose of RTX was planned, but was never completed as at start of infusion a severe allergic reaction (urticaria, dyspnea) occurred. Patient 2 is a 14-yr-old boy with SDNS since the age of 2 years treated with oral prednisone, cyclosporinA and micophenolate mofetil (MMF), with the development of severe obesity. A first infusion of RTX at age 12 was well tolerated and allowed prednisone discontinuation for over 2 years. Then a prolonged (>30 days) relapse occurred under treatment with oral prednisone, MMF and cyclosporinA. Therefore, a second RTX infusion was attempted, but the child presented severe dyspnea and it was interrupted. The use of OFA at 1.5 g/1.73 m2, described in steroid-resistant NS children (Basu, NEJM 2014), was attempted. In patient 2 OFA was preceded by three boluses of iv methylprednisolone to induce remission.

Results: In pt 1, OFA infusion was uneventful. In pt 2, a mild allergic reaction was observed and treated. Remission was maintained during the follow-up period (9 months for pt 1, 5 months for pt 2), despite the interruption of prednisone treatment in both patients, and in pt 1 of cyclosporinA, while in pt 2 of MMF with ongoing cyclosporinA at last follow-up. After OFA infusion, CD19+ B cells reappeared at 7 months in pt 1, while remained depleted (0%) at 5 months in pt 2.

Conclusions: OFA could be a therapeutic option in managing severe forms of drug-resistant nephrotic syndrome in patients who have developed intolerance to RTX.

Funding: Private Foundation Support

FR-PO432
Population-Based Identification of Children with Primary Nephrotic Syndrome: Kaiser Permanente Nephrotic Syndrome Study
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Background: Few population-based data exist about children with primary nephrotic syndrome (NS) in the US. We identified a cohort of children with primary NS in a large integrated healthcare system.

Methods: Kaiser Permanente Northern California cares for >750,000 children. We identified members age<18 yrs between 1996-2012 who had nephrotic range proteinuria (UACR ≥3500 mg/gCr or proteinuria ≥3.5 mg/mg, 24-hr protein ≥350 mg/dL, or dipstick>3+ proteinuria) or NS (ICD-9 581.x) in electronic records and lab databases. Nephrologists reviewed records for clinical presentation, lab and biopsy results to confirm primary NS.

Results: We identified 179 children with NS due to minimal change disease (72%), focal segmental glomerulosclerosis (23%) or membranous nephropathy (5%). Incidence was 1.47 per 100,000 (95% CI:1.27-1.70). Biopsies were available in 40% of cases. Baseline features at diagnosis are shown by cause of NS.

Funding: Private Foundation Support

FR-PO433
Abatacept Treatment and B7-1 Immunostaining in Patients with Primary and Post-Transplant FSGS
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Background: Podocyte B7-1 expression has been implicated in the pathogenesis of idiopathic nephrotic syndrome for many years. Recently, podocyte B7-1 was described as a potential therapeutic target by demonstrating efficacy of B7-1 blocking agent abatacept in five patients with primary and post-transplant FSGS (Yu et al. New Engl J Med 2013). The authors speculated that patients who will respond to abatacept can be identified by positive B7-1 immunostaining on kidney biopsy. Here, we report our experience with abatacept and B7-1 staining in patients with FSGS.

Methods: Patients with no or partial proteinuria remission after plasmapheresis for treatment of FSGS received abatacept (2 or 3 doses of 10 mg/kg). After several trials of unsuccessful immunofluorescence staining, we performed B7-1 immunohistochemistry on paraffin embedded tissue with a primary antibody mouse anti CD80 (R&D systems).

Results: Three patients with post-transplant FSGS, and one patient with NS in the native kidney (Table, Patient 4) were treated with abatacept. All transplant patients had developed nephrotic proteinuria immediately after transplantation. Patient 1 had been treated with plasmapheresis for many years, and was previously unresponsive to B7-1 blocking agent belatacept. None of the patients had proteinuria remissions after abatacept, nor did we observe positive podocyte B7-1 immunostaining.

Conclusions: In our hands B7-1 staining was absent in patients with FSGS. Our data caution against too much optimism regarding the efficacy of abatacept.

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Results: We identified 179 children with NS due to minimal change disease (72%), focal segmental glomerulosclerosis (23%) or membranous nephropathy (5%). Incidence was 1.47 per 100,000 (95% CI:1.27-1.70). Biopsies were available in 40% of cases. Baseline features at diagnosis are shown by cause of NS.
FR-PO434

Steroid Resistant Nephrotic Syndrome: A Prospective, Open Label Study of the Safety and Efficacy of Combination Tacrolimus and ACTHAR Gel Therapy
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Background: Steroid resistant nephrotic syndrome (SRNS) in adults is associated with increased risk for progression to ESRD. Tacrolimus is a calcineurin inhibitor (CNI) that is an alternative to steroids, but is associated with progressive fibrosis and loss of GFR. ACTHAR gel has shown benefit in the treatment of SRNS. To investigate additive effects, we followed 23 SRNS patients receiving combination therapy with Tacrolimus and ACTHAR Gel.

Methods: 23 patients with SRNS (IMGN 8, 11 FSGS and 4 other) receiving ACE-ARB and 8 weeks of oral steroids prior to combination therapy of ACTH and Tacrolimus. Eleven patients received 2 or more drug therapies. Of the 23, 17 (71%) initially received ACTH following by Tacrolimus. Duration of ACTH/TAC therapy averaged 6.2 months [range 1-12 months]. Complete or partial responses were defined as UP/Cr ratio of < 0.30 or > 50% reduction in pre-ACTH/TAC proteinuria, respectively.

Results:

Table-1 Number Age Baseline Peak ACTH ACTH+ TAC

Responder 17 yrs 6.2±1.4 11.0±2.4 3.3±2.0 1.4±0.4
IMN 6 58±3 6.6±2.3 13.1±2.7 4.9±2.2 1.2±0.5
FSGS 9 67±5 4.3±2.3 18.4±1.4 2.6±0.5 1.7±0.9
Other 2 58±3 9.9±5.6 12.4±3.9 0.3±0.2 0.6±0.7
Non-Responder 6 52±5 5.7±1.6 11.6±2.5 7.5±1.5 7.8±1.5
IMN 3 46±7 6.3±2.2 11.6±2.9 7.6±2.5 9.2±3.3
FSGS 3 52±8 6.0±2.3 11.8±2.5 7.4±2.6 7.3±1.6

Of the 23 patients, 6 (26%) achieved a complete response; a partial responses were observed in 11 (48%) for an overall response of 74%. Proteinuria levels (expressed as a ratio of UP/Cr) before and after treatment are listed in the Table. There was no difference in the rate or time to complete or partial remission between IMGN and FSGS patients respectively. The mean time to partial response was 6.2 months, but could range up 12 months. Combination therapy ACTH and Calcineurin inhibitors may offer an effective alternative therapy to SRNS.

Funding: Private Foundation Support

FR-PO435

Treatment of Nephrotic Syndrome Secondary to Primary FSGS – Prednisolone or Tacrolimus? A Two Centre Experience
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Background: Focal segmental glomerulosclerosis (FSGS) is a significant cause of end-stage renal failure. Patients with nephrotic syndrome have a worse prognosis. Current guidelines advise prolonged prednisolone (pred) at 1mg/kg. Tacrolimus (Tac) is an alternative for patients, but long-term therapy is often necessary, and there are concerns about toxicity.

Methods: Retrospective review of all patients with nephrotic syndrome secondary to primary FSGS treated with a minimum of 12 mths follow-up at 2 centres. All patients received standard therapy with max tolerated ACEi +/- ARB. Complete remission (CR) was defined as normal serum albumin with PCR <50% partial remission (PR) as proteinuria ≤50% baseline. Results described as Median (Range); p value <0.05 significant.

Results:

Demographics Pred n=15 Tac n=23 p value

Age 50 (19-75) 45 (19-78) ns
Gender 8M, 7F 12M, 11F ns
Ethnicity Caucasian 12 9 5 ns
Asian 1 2 9 ns
Average follow up (mths) 43 (12-257) 45 (12-86) ns

Baseline parameters

Creatinine µmol/L ≤50% baseline. Results described as Median (Range). p value <0.05 significant.

Albumin 167 (61-480) 87% 906 (478-1910) 26% 101 (52-312) 0.05
[36x154]9 (4-36) 103 (602-3626) 0.001

Results

Pred Tac p value

Duration (mths) 13 (2-56) 32 (5-74) ns
Dose 60mg (40-60) 3 mths 16mg (2-60) 6 mths
6.4mg/L.3 mths 6.3mg/L.12 mths ns

Response to primary agent (pts)

Remission PR 60% (9) 91% (21) 0.05
CR 60% (9) 91% (21) 0.05

Time to remission (wks)

PR 8 (3-40) CR 10 (5-44)

Relapse 22% (2) 25% (5) ns

ESRF 26% at 1,13,19,69 mths 0 <0.05

Creat latest f/u 92 (61-390) 92 (54-234) ns

Adverse events

Deaths 1 (lung ca) 0 ns
Diabetes/Insulin 3 4 ns
Severe Infection 1 (colon ca) 0 0 ns

Conclusions: In the Tac cohort a higher remission rate was demonstrated and a suggestion of fewer adverse events although numbers are small. However the baseline parameters show the GFR was significantly lower in the prednisolone group. Patients treated with Tac had a longer duration of treatment but appeared to have a better adverse event profile overall. A randomised controlled trial is required to investigate this further.

FR-PO436

Differences in Initial End Stage Renal Disease (ESRD) Treatment Modality Across Glomerulonephritis Subtypes
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Background: Kidney transplantation (Tx) is the treatment of choice for end-stage renal disease (ESRD). Hemodialysis (HD) and peritoneal dialysis (PD) outcomes are largely equivalent. Whether access to these modalities is equal across glomerulonephritis (GN) subtypes has not been established.

Methods: We identified all patients in the US Renal Data System 18-75 years who initiated ESRD therapy with Tx, HD, or PD (1996-2011) and had ESRD attributed to glomerulonephritis (GN) subtypes has not been established.

Results: We identified all patients in the US Renal Data System 18-75 years who initiated ESRD therapy with Tx, HD, or PD (1996-2011) and had ESRD attributed to 6 GN subtypes [focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranous nephropathy (MN), membranoproliferative GN (MPGN), lupus nephritis (LN), vasculitis]. Odds ratios (ORs) for PD vs HD and for Tx vs HD were computed using multinomial logistic regression (IgAN as reference group), with multivariate adjustment for demographic, socioeconomic, and comorbidity differences.

Conclusion: Among 75,278 patients studied, demographic, socioeconomic, and comorbidity characteristics differed considerably across GN subtypes. In unadjusted analyses, patients with FSGS, MN, MPGN, LN, and vasculitis were significantly less likely to receive Tx or PD as a first ESRD treatment modality than patients with IgAN: OR for Tx 0.52, 0.35, 0.48, 0.23, and 0.13, respectively; OR for PD 0.77, 0.66, 0.59, 0.48, and 0.30, respectively (all p<0.0001). After adjustment, differences were attenuated but patients with secondary GN subtypes (LN, vasculitis) remained significantly less likely to receive Tx or PD as compared to patients with IgAN (figure).

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Conclusions: Patients with ESRD attributed to secondary GN subtypes (LN, vasculitis) are significantly less likely to receive Tx or PD as an initial ESRD treatment than patients with primary GN subtypes. The clinical appropriateness and sequela of this apparent inequity must be determined.

Funding: Private Foundation Support

FR-PO437

Non Collapsing Focal and Segmental Glomerulosclerosis in Patients with HIV

Julien Hogan, Claire Carter, Emmanuelle M. Plaisier, Kamyar Kalantar. Thomas Jefferson Univ Hospital.

Background: With the improvement of the treatments against HIV, non collapsing focal and segmental glomerulosclerosis (FSGS) has become more frequent than HIV associated nephropathy (HIVAN). However, the physiopathology of non-collapsing FSGS among HIV patients remains poorly understood. We thus aimed to compare patients with HIV and non-collapsing FSGS with patients with HIVAN and with non HIV patients with FSGS.

Methods: HIV patients with a kidney biopsy in our center between 2000 and 2012 (24 non collapsing FSGS and 13 HIVAN) and two control groups (10 primary and 12 secondary FSGS) were included. Clinical and biological data were collected; viral load in serum and urine was assessed with the hard shell in a real time PCR machine; immunohistochemical staining for PCNA to study epithelial cells proliferation.

Results: Clinical and biological features of HIV patients with non-collapsing FSGS were close to those of controls with secondary FSGS. Among HIV patients, the prevalence of cardiovascular risk factors was greater in those with non collapsing FSGS than in those with HIVAN (79% vs. 38%, p=0.01) but was comparable to the one in controls with secondary FSGS (100% vs. 79%, NS). HIV patients with non collapsing FSGS and controls with secondary FSGS had more frequently arteriolar sclerosis on the biopsy than patients with HIVAN (75% and 82% vs 36%, p<0.01). Visceral epithelial cells expression of PCNA showed that, despite a stronger staining in collapsing lesions, it can be found among all patients groups and in any FSGS lesion type. The majority of HIV patients with non collapsing FSGS had undetectable viral load in serum and urine.

Conclusions: Major clinical, biological and histological differences between HIV patients with non collapsing FSGS and HIVAN support the hypothesis of two distinct physiopathological entities. They are striking similarities between non collapsing FSGS in HIV patients and secondary FSGS found in patients with polyvascular disease. Non collapsing FSGS in HIV patients might be due to nephronic reduction secondary to vascular lesions in an ageing population with major metabolic abnormalities associated with antiviral drugs.

FR-PO438

Diabetic Glomerulosclerosis or Idiopathic Nodular Glomerulosclerosis – Role for Insulin Resistance


Background: Diabetic nephropathy (DN) is characterized histologically by nodular mesangial sclerosis, a thickened glomerular basement membrane, and hyalinized arteries. Differential diagnoses by light microscopy (LM) include membranoproliferative glomerulonephritis, amyloidosis, monoclonal immunoglobulin deposition disease, and fibrillary or immunotactoid glomerulopathy. These can readily be excluded by special stains, immunofluorescence (IF) and electron microscopy (EM). Idiopathic nodular glomerulosclerosis (ING) is the term used to denote classic DN confirmed by LM, IF, and EM, but in the absence of diabetes mellitus (DM). Case reports suggest insulin resistance (IR) as a possible cause.

Methods: Data was collected retrospectively on 21 cases of diabetic glomerulosclerosis or ING biopsied due to proteinuria (1+ on urinalysis to 12.3 grams/day), with or without renal insufficiency (creatinine 0.6-4.4mg/dl).

Results: 13 patients were male with majority of patients being African American (10) and non-Hispanic white (7). 1 patient was post-renal transplant and another post-liver transplant. None of these patients were diagnosed with DM, although some had hypertensive elevated blood glucose and borderline HbA1c. All patients had hypertension, but only 5 were active tobacco users and 8 were former smokers. BMI range was 21-43kg/m². Hemoglobin A1c range was 4.6-6.1% in 10 patients and 6 patients denied DM by telephone survey. The remaining 5 patients had no history of DM per records with few elevated random plasma glucose levels and few cases of antihypertensives. None of them fulfilled current diagnostic criteria for DM. Metabolic syndrome (MS) defined by Adult Panel III criteria was evident in 11 patients.

Conclusions: The pathogenesis of ING remains unclear. It involves the interplay of hypertension, obesity, and heavy smoking. We feel that IR is critically important, whether evident as subtle, prediabetic elevations of blood glucose, MS, or elevated HOMA-IR score being the only manifestation. Insulin sensitivity assessed by HOMA-IR score is possibly an important predictive factor in pathophysiology of ING and needs to be tested routinely.

FR-PO439

Association of Serum Albumin Level and Venous Thromboembolic Events in Seven-Thousand Patients with Nephrotic Syndrome

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Background: Prior studies have shown that low serum albumin in patients with nephrotic syndrome (NS) is associated with an increased risk of venous thromboembolic (VTE) events. This is based on small studies with a low number of thromboembolic events and short term follow-up.

Methods: From a nationally representative cohort of over 3 million US veterans with baseline estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m², we identified 7037 patients with NS based on ICD9 codes. Association between serum albumin and risk of incident VTE events (based on ICD9 codes) was assessed using Cox regression analysis with adjustments for age, gender, race, comorbidities, eGFR, BMI and anticoagulant treatment.

Results: Mean age was 57±11 years, and patients were 96% male, 32% African-American and 66% diabetic. There were a total of 158 VTE events over a median follow-up was 8.1 years; 16 events (4.1%, event rate (ER): 8.5/1000 patient-years(PY)) in patients with albumin <2.5 g/dl, 18 events (3.4%, ER: 5.7/1000 PY) in patients with albumin 2.5-2.99 g/dl, 89 events (2.5%, ER: 3.4/1000 PY) in patients with albumin 3-3.99 g/dl and 55 events (1.4%, ER: 1.9/1000 PY) in patients with albumin ≥4 g/dl. Compared to patients with albumin ≥4 g/dl, those with albumin levels of 3-3.99 g/dl (adjusted HR 1.51; 95%CI 1.01-2.26), 2.5-2.99 g/dl (2.24, 1.24-4.05) and < 2.5 g/dl (2.79, 1.45-5.37) experienced a linearly higher risk of VTE events.

Conclusions: Lower serum albumin is a strong incremental risk factor for VTE events in NS. The risk increases proportionately with declining albumin levels. Our finding may have important clinical implications regarding initiation and duration of prophylactic anticoagulation.

Funding: NIDDK Support, Veterans Administration Support

FR-PO440

Hypercoagulopathy Is Directly Correlated with Disease Severity in Nephrotic Syndrome

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Background: Nephrotic syndrome (NS), a leading cause of end stage kidney disease, is characterized by massive proteinuria, hypoalbuminemia, and an increased risk for venous thromboembolism (VTE). We recently reported that hypercoagulopathy is proportional to the severity of both proteinuria and hypoalbuminemia in two animal models of NS. This study was designed to determine if this relationship translates to human NS.

Methods: Aliquots of plasma anticoagulated with 0.32% (final concentration) sodium citrate were obtained from the NEPTUNE biorepository (n=147 patients), along with corresponding clinical lab data (e.g. urine protein :creatinine (uP/C), serum albumin (sAlb)). Samples collected from a local patient cohort (n=21) were used to validate biorepository

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specimen integrity. Endogenous thrombin potential (ETP) was determined using the Technothrombin TGA kit and RC Low reagent after 2.1 dilution with buffer. Plasma antithrombin (pAT) activity was measured by the amidoanalytic method.

Results: As expected, NEPTUNE patients exhibited a wide range of proteinuria values (median (range) uP:C: 1.85 mg/mg (0-17.6)). Hypoalbuminemia and proteinuria severity were proportional to ETP (R² = 0.252 & 0.128, respectively, P<0.001). These correlations were stronger in the subset of patients with uP:C≤2 (R² = 0.331 & 0.157, respectively, P<0.001). Plasma AT activity was also significantly correlated to hypoalbuminemia and proteinuria severity (R² = 0.125 & 0.031, P<0.001 & 0.03, respectively). There was no correlation between AT activity and ETP. Results were similar in the validation cohort.

Conclusions: Both hypoalbuminemia and proteinuria severity in humans with NS is significantly, albeit weakly, correlated to ETP (an established marker of thrombotic risk). Adjusting these data for combining clinical variables (e.g. smoking status, BMI, etc.) may aid in the modeling and development of evidence-based cut-offs to guide indications for prophylactic anticoagulation.

Funding: NIDDK Support

FR-PO441
Successful Social Media Recruitment into the NephCure Kidney Network, a Rare Disease Patient Registry
Laura H. Marijan, Joanna Dauber, Chelsey Fix, Alyssa Fisher, Jane Shen, Lalita Subramanian, Marilyn Hailperin, Jaakko Patrakka, Kjell Hultenby, Annika Hultenby

Background: Participation in clinical research for primary Nephrotic Syndrome (NS) has been limited by the rarity of the disease. There is growing interest in leveraging social media to expand geographic and geographic reach for recruitment. Because of the isolating nature of rare diseases, patients turn to social media for support, creating online communities that, if accessible, could potentially serve as a resource for recruitment.

Methods: The NephCure Kidney Network (NKN) is a web-based patient opt-in registry for primary NS. Participants provide data, including kidney disease history, demographics, and research participation preferences. Recruitment efforts launched in March 2014 relied on email campaigns to contacts of the patient advocacy group, NephCure Kidney International (NKN), but then expanded in September 2014 to include social media. Weekly posts were made to NKN’s Facebook page, with analysis of performance based on impressions (# of people reached) and engagements (likes, clicks, shares, comments). Relationships with other closed Facebook kidney disease groups were established and posts made to their sites.

Results: 45,151 impressions and 2,927 engagements were made from 9/2014-6/2015. Relationships were made with 54 kidney disease groups (>15,000 members) from which to find NS patients. Engagements were highest on posts focusing on patient-centeredness in research and lifestyle. 414 patients (51% female, 47% <18 y/o, 22% racial/ethnic minority) from 27 countries enrolled between 3/2014 and 6/2015, with 27% of enrollees having no previous engagement with NKN. 94% reported a willingness to be contacted about research, including 77% willing to donate a biospecimen. However, only 16% currently or previously participated in other social media. 94% reported a willingness to be contacted about research, including 77% willing to donate a biospecimen. However, only 16% currently or previously participated in other social media. 94% reported a willingness to be contacted about research, including 77% willing to donate a biospecimen. However, only 16% currently or previously participated in other social media.

Conclusions: It may be possible to evaluate the treatment response of NS and to differentiate MCNS from FSGS based on changes in s/u-suPAR within 2 months after the start of treatment. As a mechanism involved in proteinuria in NS patients, u-suPAR may inhibit protein reabsorption in the proximal tubules through the activation of b3 integrin.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO444
The Expression of Podocyte Protein PREX2 in Glomerular Diseases
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Background: Podocyte protein PREX2 is a new podocyte-associated protein. Although we have previously demonstrated a role for PREX2 in the glomerular filtration barrier, its expression in renal biopsies from patients with various renal diseases remains unknown.

Methods: We examined the expression of PREX2 in renal biopsies from patients with IgA Nephropathy (IgAN), Minimal Change Nephropathy (MCN, n=5) and control tissue from healthy kidney donors (n=5). PREX2 expression was analyzed by microarrays on isolated glomeruli from patients with IgAN, Minimal Change Nephropathy (MCN, n=5) and control tissue from healthy kidney donors (n=5). The expression of PREX2 in renal biopsies from patients with IgA Nephropathy (IgAN), Minimal Change Nephropathy (MCN, n=5) and control tissue from healthy kidney donors (n=5).

Results: We found that PREX2 is a new podocyte-associated protein. Although no difference in mRNA levels were found, the expression of PREX2 was significantly lower in IgAN and MCN compared to controls. The function of PREX2 in the glomerular filtration barrier will now be further investigated in an extended patient cohort and in genetically modified animals.

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

FR-PO443
Urinary and Serum Soluble Urokinase Receptor Levels Predict the Therapeutic Response of Nephrotic Syndrome
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Background: It is difficult to develop noninvasive biomarkers to predict the treatment response for nephrotic syndrome (NS), and to differentiate their histological types in the initial phase.

Methods: The subjects were 32 patients with primary NS [8 with focal segmental glomerulosclerosis (FSGS), 12 with minimal change nephrotic syndrome (MCNS), 10 with membranous nephropathy (MN), and 2 with membranoproliferative glomerulonephritis]. Using ROC analysis, we examined whether or not it is possible to differentiate refractory NS from non-refractory NS, and MCNS from FSGS based on the pretreatment values of clinical markers [urinary protein (UP), serum/urinary soluble urokinase receptor (s-/u-suPAR), urinary L-FABP, and EFGR], and values and changes (∆) after 2 months (2M). We also examined the renal expression of activated b3 integrin (AP-3) by immuno-staining in primary NS and normal tissues.

Results: The following parameters were useful for differentiating refractory NS from non-refractory NS: 2M-UP (AUC=0.968, p<0.001), 2M-suPAR (AUC=0.913, p<0.002), D2M-suPAR (AUC=0.906, p=0.007), D2M-suPAR (AUC=0.881, p=0.005), and D2M-UP (AUC=0.833, p=0.014). On the other hand, D2M-suPAR (AUC=0.905, P<0.007) and D2M-suPAR (AUC=0.816, P=0.048) were useful for differentiating MCNS from FSGS. In addition, u-suPAR before treatment was positively correlated with UP (r=0.501, P<0.003) and urinary L-FABP (r=0.427, P=0.017). The expression of activated b3 integrin was primarily strong in the proximal tubular epithelial cells in FSGS or MN, but, weak in MCNS and normal tissues. Otherwise, there was no expression of activated b3 integrin on podocytes in both normal and diseased tissues.

Conclusions: It may be possible to evaluate the treatment response of NS and to differentiate MCNS from FSGS based on changes in s/u-suPAR within 2 months after the start of treatment. As a mechanism involved in proteinuria in NS patients, u-suPAR may inhibit protein reabsorption in the proximal tubules through the activation of b3 integrin.

Funding: Private Foundation Support, Government Support - Non-U.S.
FR-PO445

Long-Term Outcomes of Thrombotic Microangiopathy Treated with Plasma Exchange – A Systematic Review

Background: With the adoption of plasma exchange as standard treatment for thrombotic microangiopathy, more patients are surviving and lasting-longer outcomes have greater relevance.

Methods: We conducted a systematic review of observational studies between 1980 and 2013 that reported outcomes of adults with thrombotic microangiopathy at least 6 months after initiating plasma exchange. We searched several databases from 1980 to 2013 for eligible articles published in any language. We abstracted data in duplicate and assessed the methodological quality of each study using an assessment tool developed based on recommended validity criteria.

Results: We screened 6672 articles, reviewed 213, and included 34 studies totaling 1182 patients (study median [range], 24 [10-118]). The mean (or median) follow-up ranged from 6 months to 13 years. The cumulative incidence of relapse and mortality was highly variable and ranged from 3 to 84% and 0 to 61%, respectively. The incidence of other outcomes across 10 studies also varied (outcomes included hypertension, kidney disease, pre eclampsia, stroke, seizure, severe cognitive impairment, and depression); in 3 other studies long-term neurocognitive function and health-related quality of life were significantly lower than the general population.

Conclusions: In summary, patients who survive an episode of thrombotic microangiopathy may be susceptible to long-term vascular complications including chronic kidney disease, but the magnitude of this risk and how to mitigate it remains unclear from prior studies.

FR-PO446

Eculizumab Prevents Thrombotic Microangiopathy in Atypical Hemolytic Uremic Syndrome Patients: Long-Term Follow-Up

Background: Plasma exchange (PLEX) is recommended for the treatment of aHUS but has no established long-term maintenance therapy. We report on the long-term follow-up of aHUS patients treated with PLEX.

Methods: An observational, multicenter, long-term follow-up study of aHUS pts treated with ECU in 5 prior clinical studies. The primary endpoint was exposure/follow-up time on ECU maintenance treatment schedule.

Results: 85 pts enrolled (Table); of these, 74 pts had ON and 37 pts had OFF treatment periods with median follow-up of 24.6 and 16.6 months, respectively. The primary endpoint was exposure/follow-up time on ECU maintenance treatment schedule.

Conclusions: The ECU treatment was 3.5-fold higher after ECU discontinuation vs. ECU. TMA event rates were lowest during on-label dosing, higher during off-label dosing, and highest off-treatment. Pts with aHUS have a progressive increase in the risk of TMA events during periods of reduced dosing and after discontinuation of ECU compared with on-label ECU dosing. Medical writing support – Kenyon Ogbum PhD, of Alexion.

FR-PO447

An Update on Tailored Eculizumab Maintenance Treatment in Patients with Atypical Haemolytic Uremic Syndrome

Background: Eculizumab (ECU) has been successfully used in patients (pts) with aHUS. The standard maintenance treatment suggests ECU administration every two weeks (wks), life long. The optimal maintenance schedule is not yet defined. To define our experience on individualized ECU treatment schedule for preventing relapses based on drug biological activity, with the rational of improving the patient’s quality of life, reducing the risk of adverse reactions and reducing the heavy costs of the treatment.

Methods: Pts undergoing ECU treatment at our Center were addressed to a progressive extension of the interval between ECU doses from the standard 2 wks to 3 or 4 wks with a strict monitor of global complement activity. AP50 was routinely determined before each ECU administration and the interval between doses was adjusted with the target of maintaining AP50<25%, Strict monitoring of indicators of disease reactivation, namely blood in the urine with home dipstick, was regularly performed.

Results: The interval between doses was extended in 33 pts (13 ≤ 18 yrs) with a median age of 28.1 yrs (5-62), 17 F, 21 with native kidney and 12 with graft. Identified mutations were: CFH:15; CFI:2; CD46:1; MCP:1; CFHR3-CFHR1 homoz. deletion with factor mutations and kidney transplant status were not different between ON and OFF pts.

Conclusions: On the basis of this study we can recommend a personalized treatment schedule of ECU to all pts with aHUS.

FR-PO448

Chemokines as Potential Biomarkers of Renal Involvement in Scleroderma

Background: Renal disease in scleroderma (SSc) remains a major clinical challenge. Previous studies showed up to 50% of SSc patients have CKD. We sought to gain insight into the pathogenesis of SSc-CKD by examining markers of disease in serum and urine.

Methods: We collected urine and serum from 80 SSc patients, with or without renal disease, for comparison with patients with CKD of other causes (n=10) and healthy controls (n=12). We performed multiplex analysis of candidate markers of disease activity or severity in the SSc and renal injury: MCP-1, MCP-3, IL-6, IL-18, TNF-α, and VEGF.

Results: 40 SSc patients had CKD defined by eGFR and urinalysis. Serum MCP-1 was increased in SSc compared with controls, with SSc-CKD significantly lower than SSc without CKD. Mean serum MCP-1 was 132 pg/ml (95% CI 105-162) for SSc with normal renal function compared with 65 pg/ml in SSc-CKD (p<0.001 for this comparison). MCP-1 was not increased in CKD of other causes (mean 47 pg/ml, 23-85) compared with
controls (mean 53 pg/ml, 25-85, p=0.848). Conversely, urine MCP-1/creatinine ratio was highest in SSc-CKD (mean 64, 32-111) than in SSc with normal renal function (mean 23.18; 28, p=0.046). MCP-3 was upregulated in the urine of patients with SSc with or without CKD (mean MCP-3:creatinine ratio 3.6, 2.5-4.6) compared with healthy controls (mean 0.9, 0.5-1.4, p=0.016). There was no difference between groups in serum MCP-3.

**Conclusions:** This is the first study to measure MCP-1 and MCP-3 in the urine of SSc patients. Elevated urine MCP-1 in SSc-CKD suggests increased expression in the renal tract and may help define organ-specific effects of this potential pathogenic mediator that has previously been reported to be increased in serum in association with pulmonary complications. In contrast to MCP-1, other markers of SSC severity (e.g. IL-6) or renal injury (e.g. IL-18) did not differentiate between groups. Our findings further support increased visualization of urine concentrations of chemokines MCP-1 and MCP-3 as markers of mediators of CKD in SSc.

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

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**FR-PO449**

**Towards a Deeper Understanding of Fibrillary Glomerulonephritis: Clinicopathologic Analysis of Patients in a Long-Term Inception Cohort**

Caroline J. Poulton, Yichun Hu, Harsharan Kaur

**Background:** Fibrillary glomerulonephritis is uncommon primary glomerular disease. Accordingly, there are no clinical trials to guide treatment making this a challenging disease to manage. Here, we report clinical characteristics and treatment outcomes of patients with fibrillary glomerulonephritis diagnosed and/or treated at UNC or through the Glomerular Disease Collaborative Network and compare them to a previously published cohort from Mayo clinic.

**Methods:** Patients were identified through the UNC Division of Nephropathology database. Clinical data were extracted from the electronic medical records starting at the time of diagnosis.

**Results:** There were 31 patients with fibrillary glomerulonephritis who were treated and an additional 24 patients who were diagnosed by the UNC Division of Nephropathology. Demographic and clinical data from the date of biopsy are displayed in the table.

**Conclusions:** This clinicopathologic analysis of patients with fibrillary glomerulonephritis is the largest study of its kind in the literature to date. The patients in our cohort were more ethnically diverse than the Mayo clinic group but presented with similar degree of kidney impairment and nephrotic range proteinuria. Fibrillary mesangiocapillary glomerulonephritis is an understudied glomerular disease that portends a poor prognosis warranting the need for prospective multi-center treatment studies to determine durable therapeutic avenues.

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**FR-PO450**

**Clinical, Histologic, and Genetic Predictors of Response to MMF in C3 Glomerulopathy**

Rupali Sundrenga Avasara, Pietro A. Canetta, Andrew R. Martinez, Henry J. Gonzalez Torres, Raul Garcia, M. Schober

**Background:** C3 Glomerulopathy (C3G) is a rare glomerular disease with different genetic sequences and clinical courses.

**Methods:**

**A.** 12 years old AAF who presented with stage 2 HTN and nephrotic range proteinuria (u. p/cr 4). A renal biopsy showed C3 GN. She received steroids. (HD) was initiated (s.c. 2.24 mg/dL, BUN 127 mg/dL). She received 5 anti-hypertensive medications & 3 PE sessions. She had no improvement. D29 she received Eculizumab 900 mg q wk & after 2 doses of Eculizumab, GFR improved and no longer required HD or PE. Case 1 (B). 15 yrs old WF who presented at 7 yrs of age with hematuria, stage 2 HTN & nephrotic range proteinuria (u. p/cr 13). Kidney biopsy showed C3 GN. She received only Lisinopril and had maintained normal GFR without RRT/steroids. Though she continued to have nephrotic range proteinuria.

**Results:** Both presented with hematuria, HTN and nephrotic range proteinuria and their biopsies showed C3 GN, persistent nephrotic range proteinuria despite improvement in GFR and normal levels of FHR, preop, C5b9. Gene analysis for A showed deletion of CFHR3, CFIHR1 and carry a variant of unknown significance in CFI and CFI. B in contrast had abnormal high complement plasma Bb antibody and 0% complement alternative pathway abnormality. Genetic sequences may influence clinical manifestations/ progression of the C3GN.

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**FR-PO451**

**Membranoproliferative Glomerulonephritis C3 Deposits: Clinicopathological Study**


**Background:** Membranoproliferative glomerulonephritis (MPGN) is a pattern of damage characterized in the light microscopy by mesangial hypercellularity, thickening of the glomerular basement membrane and mesangial interposition in the capillary wall. Recent advances in the understanding of its underlying pathogenesis led to a classification system that highlights the findings in the immunofluorescence. Alteration complement regulation has proven to be a risk factor for the development of MPGN.

**Methods:** Cross-sectional study. The data were extracted from NefroRed®, a software platform that contains the socio-demographic, anthropometric, clinical and laboratory data of two thousand patients with kidney biopsies from 2008 to 2014. It was selected for the study those patients that showed the pattern of glomerulonephritis and membranoproliferative and C3 deposits only or predominant. Each biopsy was studied by light microscopy and immunofluorescence, light microscopy included hematoxylin-eosin, PAS, and Jones. C3 deposits were only or predominant. Each biopsy was studied by light microscopy and immunofluorescence. Light microscopy included hematoxylin-eosin, PAS, and Jones. C3 deposits were only or predominant. Each biopsy was studied by light microscopy and immunofluorescence.

**Results:** Mean age of men was 42.3 years and women was 36.7 years. The minimum age was 18 years. The maximum age was 69 years; 51.8% (n = 14) of patients were women. The 1200 biopsies showed 56 injuries MPGN (5%) of these 58 cases only 27 (32%) lesions showed $c3$ deposits only or predominant.
Conclusions: 30% of patients with GMP have as pathogenic mechanism the complement activation with complement C3 deposition in the glomerulus. Our research group has found C3 deposition causally related to GMP. The most common clinical presentation is nephrotic syndrome.

FR-PO453
Steroids Alone for the Treatment of C3 Glomerulonephritis with Monoclonal Gammopathy
Insaar Jaffer Satthick,1 Ladan Zand,1 Samih H. Nasr,2 Sanjeev Sethi,2 Fernando C. Fervenza,1 Nelson Leung,1,3 Claire L. Harris,2 Kevin J. Marchbank,1 Isabel Y. Pappworth,2 Rebecca Walters,1 Hannah J. Lomax-Browne,2 Daniel P. Gale,1 Tim Goodship,1 David Kavanagh,1 Roger D. Malcomson,5 Paul Morgan,2 Matthew C. Pickering,2 H. Terence Cook,2 Sally A. Johnson,1 1Div of Nephrology, Mayo Clinic; 2Div of Anatomic Pathology, Mayo Clinic; 3Div of Hematology, Mayo Clinic.

Background: C3 glomerulonephritis (C3GN) is a rare disease with no trial data to guide treatment. In patients with C3GN with monoclonal gammopathy, steroids alone may be a viable treatment option.

Methods: We present our experience in managing C3GN with monoclonal gammopathy with prednisone.

Results: 5 patients presented to our institution from 2011 to 2014 with biopsy proven C3GN and underlying monoclonal gammopathy. Median age of this cohort was 63 years. Median estimated GFR by MDRD equation was 35.4 ml/min/1.73m2 and median proteinuria was 2 g/day at presentation. All patients had IgG kappa monoclonal gammopathy. Patient 5 required renal replacement therapy but recovered renal function. All patients were treated with Prednisone 60mg/day tapering to zero in all except one. Patient 2 and 4 continue on prednisone 10mg/day. Patient 1 was started on Rituximab and showed improvement in kidney function.

Conclusions: Our experience suggests that prednisone alone may be a treatment option in some patients with C3GN associated with a monoclonal gammopathy. Work up should be done to exclude a plasma cell neoplasm and inherited complement abnormalities.

FR-PO454
The National Study of Membranoproliferative Glomerulonephritis and C3 Glomerulopathy: Characterisation of the Initial United Kingdom Paediatric Cohort
Edwin KS Wong,1 Claire L. Harris,2 Kevin J. Marchbank,1 Isabel Y. Pappworth,2 Rebecca Walters,1 Hannah J. Lomax-Browne,2 Daniel P. Gale,1 Tim Goodship,1 David Kavanagh,1 Roger D. Malcomson,5 Paul Morgan,2 Matthew C. Pickering,2 H. Terence Cook,2 Sally A. Johnson,1 1Div of Nephrology, Mayo Clinic; 2Div of Anatomic Pathology, Mayo Clinic; 3Div of Hematology, Mayo Clinic.

Background: The National Registry of Rare Kidney Diseases (RaDaR) in the United Kingdom allows recruitment, research and longitudinal follow-up of patients with membranoproliferative glomerulonephritis (MPGN) and C3 glomerulopathy (C3G). The aim of the MPGN/C3G Rare Disease Group (RDG) is to deep phenotype and analyse complement abnormalities in a paediatric cohort of MPGN/C3G.

Methods: The MPGN/C3G RDG recruited patients with MPGN/C3G for central review of biopsies and clinical data, and studied complement abnormalities previously described in MPGN/C3G.

Results: 83 prevalent patients with MPGN/C3G were identified and centrally reviewed. 79 could be classified: 40 had immune-complex MPGN, 25 had C3GN and 14 had DDD. Complement abnormalities are shown in Table 1. Follow-up data on 73 patients is shown in Figure 1.

Table 1: Complement Abnormalities

<table>
<thead>
<tr>
<th>Complement Abnormality</th>
<th>MPGN (n=40)</th>
<th>C3GN (n=25)</th>
<th>DDD (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 nephritic factor</td>
<td>9/21 (43)</td>
<td>6/18 (33)</td>
<td>0/14 (0)</td>
</tr>
<tr>
<td>Anti-FH autoantibodies</td>
<td>7/29 (18)</td>
<td>3/24 (13)</td>
<td>3/14 (21)</td>
</tr>
</tbody>
</table>

Conclusions: RaDaR has facilitated the development of a large nationwide cohort of paediatric patients with MPGN/C3G who have now undergone deep phenotyping and genotyping centrally. Acquired complement abnormalities were common; rare genetic abnormalities were infrequent. Patients with DDD had the worst renal outcome. Ongoing recruitment and longitudinal follow up will clarify prognosis according to phenotype/genotype and allow stratification into future treatment studies.

FR-PO455
Plasma Neutrophil Gelatinase-Associated Lipocalin, Procalcitonin and C-Reactive Protein as the Predictor of Acute Pyelonephritis in Children with Febrile Urinary Tract Infections
Byungkwon Kim, Hyung Eun Yim, Kee Hwan Yoo. Dept of Pediatrics, Korea Univ Medical Center, Seoul, Republic of Korea.

Background: We have recently reported that plasma and urinary neutrophil gelatinase-associated lipocalin (NGAL) levels are useful for the prediction of acute pyelonephritis (APN) in pediatric urinary tract infection (UTI). This study was aimed to determine the accuracy of NGAL measurements, compared with serum measurements of procalcitonin, C-reactive protein (CRP), and white blood cells (WBCs) in predicting APN and associated renal problems in children with febrile UTIs.

Methods: Total 138 children with febrile UTIs (59 APN, 79 lower UTI) were enrolled. Patients with renal failure, congenital urologic anomaly except vesicoureteral reflux

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

460A
FR-PO456

A Prospective Evaluation of Renal Contrast-enhanced Ultrasound (CEUS) in the Detection of Pyelonephritis

Florian Buchkremer,1 Daniel Drozdov,2 Werner C. Albrich,3 Andreas H. Bock,4 Div of Nephrology, Kantonsspital Aarau, Aarau, Switzerland; 5 Div of Infectious Diseases, Kantonsspital St. Gallen, St. Gallen, Switzerland.

Background: Contrast-enhanced ultrasound (CEUS) has been described as a promising method for detecting acute pyelonephritis (PN) and its complications. We evaluated its value in diagnosis and risk stratification in the setting of a randomized controlled trial (RCT).

Methods: Immunocompetent adults with community-acquired urinary tract infection (UTI) presenting in the emergency department of Kantonsspital Aarau were enrolled in a RCT designed to evaluate the performance of a PCT/pyuria guided algorithm versus standard guidelines (Drozdov et al. BMC Medicine 2015). Outcomes included antibiotic exposure, duration of therapy, persistent infections and recurrences/re-hospitalisations.

Results: Of 70 UTI study patients hospitalized with fever and/or flank pain, 41 (59%) underwent the ultrasound study. Dropout reasons included missing consent (5%), early discharge (6%) or technical (18%). Examined and non-examined patients did not differ significantly in baseline characteristics or outcome. Findings suggestive of PN were found in 5/41 (12%). In 3 patients, this was evident in greyscale/Doppler already, in 2 additional patients, critical findings were only present in CEUS. The presence of PN-suggestive findings was not predictable from any baseline clinical characteristic. Patients with and without PN-suggestive findings did not appear to differ in outcome.

Conclusions: Ultrasound evidence of pyelonephritis is rare in patients hospitalized for UTI with fever. CEUS may be a useful method to guide clinicians. The presence of PN-suggestive findings may substantially increase the number of positive findings.

Funding: Government Support - Non-U.S.

FR-PO457

ISN 0by25 AKI Global Snapshot Project: AKI Disposition

Michael V. Rocco,1 Ravidra L. Mehta,1 Giuseppe Remuzzi,2 Jing Zhang,3 Melanie Godin,3 Michael V. Rocco,4 U Sao Paulo,5 U California San Diego,6 Mario Negri Inst,7 Sherbrooke U,1 Wake Forest U.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians on AKI pts who had a confirmed diagnosis of AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC). We analyzed the frequency of AKI requiring dialysis and the reasons for starting or withholding dialysis.

Results: Of 3855 pts, 768 (20%) were dialyzed. Mortality rate was significantly different in dialyzed (17%) vs. non-dialyzed (9%) pts (p<0.0001). Among dialyzed pts, the mortality rate was similar in countries of different GNI categories. The main reason to start dialysis was solute control, with a similar distribution among country categories.

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

461A
FR-PO459

**ISN 0by25 AKI Global Snapshot Project: Differences in Location and Process of Care Among AKI Patients Around the Globe**

*Etienne Macedo,1 Ravindra L. Mehta,2 Giuseppe Remuzzi,3 Jing Zhang,2 Melanie Godin,3 Michael V. Rocco,1 1U Sao Paulo; 2U California San Diego; 3Mariño Negro Inst; 'Sherbrooke U; Wake Forest U.*

**Background:** The Global Snapshot (GSP) was a prospective cross-sectional study designed to capture standardized information on incidence, causes and treatment of AKI in all health care settings throughout countries of diverse economic status.

**Methods:** A web based survey tool was used to obtain data from pts with a confirmed diagnosis of AKI based on KDIGO criteria in 72 countries. Detailed methodology is found in the ISN GSP abstract on provider characteristics. We analyzed the characteristics of pt location and process of care by gross national income per capita (GNI) country levels. Countries were defined as: Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

**Results:** Based on GNI, 23 countries were classified as LLMIC, 20 as UMIC and 29 as HIC.

<table>
<thead>
<tr>
<th></th>
<th>HIC (n=1260)</th>
<th>UMIC (n=1605)</th>
<th>LLMIC (n=1153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>1241</td>
<td>1594</td>
<td>1118</td>
</tr>
<tr>
<td>Age (adult, yrs)*</td>
<td>67 (55.74)</td>
<td>65 (52.77)</td>
<td>53 (38.65)</td>
</tr>
<tr>
<td>% Pediatric (n=343)</td>
<td>13</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Age (peds, yrs)</td>
<td>0.4 (0.03-6.0)</td>
<td>8 (2.16-5.0)</td>
<td>4 (0.3-13.5)</td>
</tr>
</tbody>
</table>

**Location where pts develop AKI **

<table>
<thead>
<tr>
<th></th>
<th>Community acquired</th>
<th>Location patient seen **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department</td>
<td>37.5</td>
<td>195.0</td>
</tr>
<tr>
<td>ICU</td>
<td>26.8</td>
<td>38.8</td>
</tr>
<tr>
<td>Ward or stepdown unit</td>
<td>50.6</td>
<td>39.1</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>4.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

**Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Diaylsis (%)*</th>
<th>Mortality in adults (%)</th>
<th>Mortality in pediatric (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis (%)*</td>
<td>63.3</td>
<td>13.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Mortality in adults (%)</td>
<td>83.3</td>
<td>13.7</td>
<td>12.5</td>
</tr>
<tr>
<td>Mortality in pediatric (%)*</td>
<td>71.8</td>
<td>13.9</td>
<td>19.6</td>
</tr>
</tbody>
</table>

|                      | p < 0.05            | p<0.0001                |

Urinalysis was more often performed in LLMIC (86%). More pts in LLMIC were dialyzed (71%). The mortality rate of dialyzed pts and the number of non-renal organ failures present was similar by GNI level. Mortality in community acquired AKI was higher in LLMIC (11%) vs 7% in HIC. LLMIC had higher mortality among ICU pts (2%) vs 13% in HIC (p=0.014). In pediatric pts, mortality was 19.6% in LLMIC compared to 12.5% in HIC.

In LLMIC, 58% of pts were classified as AKIN stage 3 at AKI diagnosis. sCr was significantly higher in these pts (3.26 mg/dL) compared to 2.43 in pts from HIC and 2.3 in pts from UMIC.

**Conclusions:** BsCr was often present in pts from HIC and UMIC, where 1/3 of AKI cases occurred in CKD pts. Absence of BsCr was a common issue in LLMIC, associated with higher levels of sCr and KDIGO stage at AKI diagnosis. UO is often not computed in pts who develop AKI. Systematic assessment of urine output in high-risk pts could help identify AKI earlier.

**Funding:** Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support

FR-PO461

**ISN 0by25 AKI Global Snapshot Project: Risk Factors for AKI**

*Etienne Macedo,1 Ravindra L. Mehta,2 Giuseppe Remuzzi,3 Jing Zhang,2 Melanie Godin,3 Michael V. Rocco,4 Jorge Cerda,5 John Feehally,6 Fredric O. Finkelstein,7 Nathan W. Levin,8 Marcello Tonelli,9 1U California San Diego; 2Mariño Negro Inst; 'Sherbrooke U; Wake Forest U; Albany Med Coll; 'U Leicester; Yale U; Renal Research Inst; 'U Calgary.*

**Background:** The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

**Methods:** A web based survey tool was used to obtain data from individual clinicians about pts who had AKI based on KDIGO criteria. Detailed methodology is found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

**Results:** Participants were distributed from North/East Asia 26.4%, South Asia 18.9%, Latin America/Caribbean 14%, Africa 13.4%, North America 7.3%, Western Europe 6.2%, Oceania/Southeast Asia 4.3%, Russia/Commonwealth Independent States 3.9%, Middle East 3.4%, Eastern/Central Europe 2.2%. Ethnic groups included 53% Asian, 19% Caucasian, 9% Hispanic, 8% African, 7% Middle Eastern and 1.5% Native/Aboriginal. Causes of AKI varied by GNI and were compared by Kruskal-Wallis test.

**Risk factors for AKI**

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
<th>HIC</th>
<th>UMIC</th>
<th>LLMIC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>1536</td>
<td>38.2</td>
<td>39.1</td>
<td>32.3</td>
<td>45.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypotension/shock</td>
<td>1615</td>
<td>40.2</td>
<td>44.8</td>
<td>38.2</td>
<td>38.2</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cardiac</td>
<td>905</td>
<td>22.5</td>
<td>24.3</td>
<td>27.9</td>
<td>13.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Liver</td>
<td>331</td>
<td>8.2</td>
<td>7.7</td>
<td>9.2</td>
<td>7.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Acute kidney disease</td>
<td>488</td>
<td>12.2</td>
<td>11.1</td>
<td>9.4</td>
<td>17.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary obstruction</td>
<td>520</td>
<td>8.0</td>
<td>7.9</td>
<td>6.9</td>
<td>9.5</td>
<td>0.0421</td>
</tr>
<tr>
<td>Infection</td>
<td>1291</td>
<td>32.1</td>
<td>28.8</td>
<td>32.2</td>
<td>35.7</td>
<td>0.0013</td>
</tr>
<tr>
<td>Pregnancy related</td>
<td>56</td>
<td>1.4</td>
<td>0.4</td>
<td>0.9</td>
<td>3.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>322</td>
<td>8.0</td>
<td>9.4</td>
<td>9.4</td>
<td>4.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nephrotic agents</td>
<td>980</td>
<td>24.4</td>
<td>29.0</td>
<td>21.7</td>
<td>23.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Poisoning</td>
<td>73</td>
<td>1.8</td>
<td>2.1</td>
<td>1.4</td>
<td>2.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Envenomation</td>
<td>35</td>
<td>0.9</td>
<td>0.3</td>
<td>0.7</td>
<td>1.7</td>
<td>0.0005</td>
</tr>
<tr>
<td>Post-surgical</td>
<td>269</td>
<td>6.7</td>
<td>9.2</td>
<td>6.8</td>
<td>3.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

In LLMIC, 58% of pts were classified as AKIN stage 3 at AKI diagnosis. sCr was significantly higher in these pts (3.26 mg/dL) compared to 2.43 in pts from HIC and 2.3 in pts from UMIC.

**Conclusions:** BsCr was often present in pts from HIC and UMIC, where 1/3 of AKI cases occurred in CKD pts. Absence of BsCr was a common issue in LLMIC, associated with higher levels of sCr and KDIGO stage at AKI diagnosis. UO is often not computed in pts who develop AKI. Systematic assessment of urine output in high-risk pts could help identify AKI earlier.

**Funding:** Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support
Other organ failures present were pulmonary 16.4% (more common in HIC), cardiovascular 23.1% (less common in LLMIC), neurologic 8.3%, hepatic 10.4%, hematologic 9.5% (more common in LLMIC) and none 53.9%.

Conclusions: Hypotension was the most common cause of AKI in HIC and UMIC; dehydration was most common in LLMIC. Acute kidney disease, pregnancy and encephalitis were more common in LLMIC.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Belloc (Mirandola, Italy), Private Foundation Support

FR-PO462

ISN 0hy25 AKI Global Snapshot Project: Evaluation and Treatment Jorge Cerda,1 Ravindra L. Mehta,2 Giuseppe Remuzzi,2 Jing Zhang,2 Melanie Godin,2 Michael V. Rocco,2 Emmanuel A. Burdman1,2 Guillermo Garcia-Garcia,2 Vivekanand Jha,2 Andrew J.P. Lewington,3 Raul Lombardi4,10 Alhambay Med Coll; 1U California San Diego; 2Mario Negri Inst; 3Sherbrooke U; 4Wake Forest U; 5Albany Med Coll; 6George Inst Global Health; 7Renal Research Inst; 8Leeds Teaching Hosp; 9Servicio Medico Integral. Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians about pts who had AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract or provider characteristics. Countries were defined by gross national income per capita (GNI); low and lower middle income (LMIC), upper middle income (UMIC) and high income (HIC).

Results: Initial evaluation of AKI included urinalysis in 73.6%, ultrasound in 55% and renal biopsy in 4.1%, with all three more commonly being performed in LLMIC. Initial treatment of AKI included fluids in 74.3%, vasoressors in 23.8%, diuretics in 41.4% antibiotics in 63.8% and urinary diversion in 19.5%. The receipt of dialytic therapy occurred in 790 of 4018 pts (19.7%), with use in 18.8% in HIC, 14.3% in UMIC and 28.0% in LMIC. In 244 instances where dialysis was recommended but not performed, futility was cited in 58.6% and cultural beliefs were cited in 25.4%. Unavailability of staff or material resources to perform dialysis was reported in 1.4% of HIC, 3.8% of UMIC and 1.6% of LMIC. Inability to afford therapy was 1.4% in HIC, 1.9% in UMIC and 16.4% in LMIC (p<0.0001). The ratio of pts not able to receive dialysis by those that did receive dialysis was 0.21 in HIC, 0.25 in UMIC and 0.18 in LMIC. There were significant differences in the renal modality used.

Treatment (n=798) Frequency Percent HIC UMIC LMIC
BID 516 65.3 63.3 58.3 71.8
PD 41 5.2 4.6 3.0 7.1
CRRT 157 19.9 31.7 29.1 4.6
UF 10 1.3 2.5 1.7 0
SLED 103 13.0 3.4 10.9 21.7
Other 8 1.0 0.6 1.4 0
Unknown 1 0.1 0 0.2 0

Conclusions: Lack of resources, staff or finances to perform dialysis was most prevalent in LLMIC. When dialysis was provided, it was less likely to be CRRT and more likely to be SLED in LLMIC.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Belloc (Mirandola, Italy), Private Foundation Support

FR-PO463

ISN 0hy25 AKI Global Snapshot Project: Provider Characteristics Melanie Godin,1 Ravindra L. Mehta,2 Giuseppe Remuzzi,2 Jing Zhang,2 Michael V. Rocco,2 Jorge Cerda,2 Vivekanand Jha,2 Nathan W. Levin,2 Andrew J.P. Lewington,1 Etienne Macedo,2 Marcello Tonelli,19 Sherbrooke U; 1U California San Diego; 2Mario Negri Inst; 3Wake Forest U; 4Albany Med Coll; 5George Inst Global Health; 6Renal Research Inst; 7Leeds Teaching Hosp; 8San Paolo; 9U Calgary. Background: The ISN 0by25 AKI Global Snapshot Project (GSP) was designed to determine the spectrum of AKI pts seen in health care facilities throughout the world.

Methods: Health care providers joined the GSP after gaining approval from their local IRB. Providers chose one “index” day between 9/29/2014 and 12/7/2014 to provide data on AKI pts under their care. De-identified data on pts who met criteria for AKI by modified KDIGO criteria were entered through a secure website using a standard questionnaire developed by the 0by25 AKI workgroup. Data collected included pt demographics, initial clinical data, diagnostic, treatment and outcome information. Countries were grouped into three categories based on gross national income per capita (GNI); high income with GNI >$12,476, low and lower middle income with GNI <$12,476 and upper middle income with GNI between levels 1 & 3.

Results: 324 surveys from 72 countries were received describing 4024 pts with AKI. Included providers included 248 nephrologists, 20 nephrology fellows, 14 intensivists, 26 pediatric nephrologists. Location of facilities by region included 52 from Africa, 47 from Latin America & Caribbean, 45 from North America, 45 from South Asia, 40 from North and East Asia, 34 from Western Europe, 19 from Russia/Commonwealth of Independent States, 17 from Oceania & South East Asia, 14 from Middle East and 11 from Eastern & Central Europe. Size of catchment population for each facility was: >5 million in 28%, 0.5-1.5 million in 26%, 0.1-0.5 million in 19% and 1.5-3 million in 11%. Type of facility was institute in 47%, public hospital or health care concern in 37%, private multispecialty group in 14%. Dialysis was available in 97% of facilities.

Conclusions: This project is the first worldwide point prevalent survey of AKI. It demonstrates the feasibility of obtaining data on AKI using a secure website from practitioners in varied health care settings from six continents.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Belloc (Mirandola, Italy), Private Foundation Support

FR-PO464

Postoperative Acute Kidney Injury in Non-Cardiac Surgery Seekwoo Park, Dong Ki Kim, Kook-Hwan Oh, Kwon Wook Joo, Yon Su Kim, Hajoong Lee. Internal Medicine, Seoul National Univ Hosp, Seoul, Korea. Background: Prevention of acute kidney injury (AKI) and amelioration of its severity remain important issues of improving surgical patient outcomes. Therefore, preoperative renal risk evaluation and patient optimization is crucial for nephrologists. Although there are several studies dealing with postoperative AKI in cardiac surgery, they have been seldom studied in non-cardiac surgery.

Methods: We included adult (age ≥ 18 years) patients who received major non-cardiac surgery in Seoul National University Hospital from 2004 to 2013. We extracted their clinical data from our electronic medical record system. Acute Kidney Injury Network criteria (AKIN) was used to define and classify AKI.

Results: Among a total of 95,266 operations, 1,560 cases (1.64%) developed AKI. Patients with AKIN stage I were 964 (1.01%), stage II, 117 (0.12%), and stage III, 479 (0.50%). AKI was most prevalent in urologic surgery, followed by general surgery, orthopedic surgery, and neurologic surgery. Patients who developed AKI tended to be older (53.7 vs. 58.9 years), and male (45.6% vs. 65.6%). Patients with AKI had higher prevalence of underlying diseases such as liver/heart/hematologic/vascular and neurologic disease than those without. Moreover, they showed higher baseline systolic blood pressure and lower baseline diastolic blood pressure than those without. Baseline renal function was lower in AKI-developed patients than the others (0.90 vs. 1.13 mg/dL, P < 0.001). Multivariate logistic regression analyses found that older age, male sex, lower baseline renal function, presence of hypertension, longer duration of surgical time and orthopedic or urologic surgery were significant risk factors for postoperative AKI in noncardiac surgery.

Conclusions: In this study, we demonstrated the incidence of postoperative AKI in non-cardiac major operations. Moreover, we found clinical risk factors for postoperative AKI development. Further investigation of prediction models for postoperative AKI in major non-cardiac surgery should be warranted for development of preoperative renal optimization strategy.

FR-PO465

Impact of Hospital CABG Volume and AKI Needing Dialysis on CABG Hospitalizations Ankit Sakhija,1 Jesse D. Schold,2 Edward G. Soltész,3 Sevag Demirjian.1 1Div of Nephrology, Univ of Michigan; 2Nephrology and Hypertension, Cleveland Clinic; 3Thoracic and Cardiovascular Surgery, Cleveland Clinic. Background: Acute Kidney Injury (AKI) is common after Coronary Artery Bypass Grafting (CABG) and associated with poor outcome. Increased hospital procedure volume has been associated with better outcomes. We examined (1) impact of number of annual CABG procedures per hospital (CABG-vol) on AKI needing dialysis (AKI-D) and mortality, and (2) if it modifies the relationship between AKI-D and mortality.

Methods: Using Nationwide Inpatient Sample database from 2000-2010 we identified admissions with CABG using ICD-9-CM codes. Those with AKI-D were identified and those with kidney transplant or on maintenance dialysis were excluded. Multivariable logistic regressions were used to assess impact of CABG-vol on AKI-D and mortality. We used restricted cubic splines to account for non-linear relationship between CABG-vol and mortality. A priori interaction term between CABG-vol & AKI-D was assessed in models.

Results: Of estimated 3,337,292 (95% CI: 3,103,610-3,570,973) hospitalizations for CABG, 0.7% (24,126) had AKI-D. Those with AKI-D were older, more females (37.5% vs 29.1%; P<0.001) and blacks (7.4% vs 5.5%; P<0.001). On adjusted analysis, CABG-vol was correlated with mortality developing AKI-D (0.99; 95% CI 0.99-1.00) but was associated with mortality (Fig 1).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
AKI-D was a significant predictor of mortality with OR 13.75 (95% CI: 11.37-16.64). Interaction term between CABG-vol & AKI-D was not significant (p=0.8).

**Conclusions:** Lower annual CABG hospital procedure volume is significantly associated with higher mortality but not with higher incidence of AKI-D. AKI-D is associated with higher mortality in those undergoing CABG, however, there is no differential effect of hospital volume on adjusted odds of mortality due to AKI-D.

**FR-PO466**

Five-Year Risk of Renal Outcomes After Pediatric Cardiac Surgery

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**Background:** Pediatric cardiac surgery is associated with a high risk of acute kidney injury (AKI) and other short-term adverse outcomes. However, the risk for long-term renal outcomes after cardiac surgery is unknown.

**Methods:** We performed 5 year follow-up on the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) cohort. TRIBE-AKI is a three-center prospective cohort study of children 1 month to 18 years old who underwent cardiopulmonary bypass.

**Results:** Out of 305 children who survived their index hospitalization, 4 (1.3%) died after discharge and 12% (42%) participated in the 5 year follow-up. Mean age of the cohort at follow-up was 9.2 years and 53% were male. 56 out of 128 patients had perioperative AKI defined as a post-operative serum creatinine rise by 50% or 0.3mg/dl from pre-operative baseline. At a median of 5.4 years of follow-up, hypertension, microalbuminuria, eGFR<90, and eGFR<60 were identified in 13%, 6.3%, 7.0%, and 0.8% of patients, respectively. CKD, defined as eGFR<90 or microalbuminuria, was present in 13% of children. There were no significant differences in renal outcomes between patients with and without perioperative AKI. (4.0%) patients had been seen by a pediatric nephrologist. The 5-year post-operative prevalence of hypertension in our cohort was ~8 fold higher than found in the general pediatric population (Table).

**Conclusions:** Overall, there is a high prevalence of CKD and hypertension in children 5 years after cardiac surgery. Despite this high prevalence of CKD, very few children were seeing a pediatric nephrologist. These findings may have implications for renal care and late cardiovascular disease in children after cardiac surgery.

**Funding:** NIDDK Support

**FR-PO467**

Changes of Epidemiology and Influencing Factors of Acute Kidney Injury After Cardiac Surgery – A Five-Year Study from 2009 to 2013

Zhouping Zou,1,2 Jiari Xu,1,2 Wenlv Lv,1,2 Bo Shen,1,2 Yi Fang,1,3 Jianzhou Zou,1,2 Jie Teng,1,2 Xiaojiaqing Ding,1,2 1Dept of Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China; 2Shanghai Inst for Kidney and Dialysis, Zhongshan Hospital, Fudan Univ, Shanghai, China; 3Shanghai Key Laboratory of Kidney Disease and Blood Purification, Zhongshan Hospital, Fudan Univ, Shanghai, China.

**Background:** Cardiac surgery is a common cause of acute kidney injury (AKI). We collected the epidemiological data of patients with AKI from 2009 to 2013 in order to explore the influencing factors of changes of epidemiology after cardiac surgery.

**Methods:** Clinical data of patients undergoing cardiac surgery, which included demographic data of preoperative, intraoperative, postoperative variables, was critically collected in our hospital from January 2009 to December 2013. The main endpoint was poor prognosis which included overall mortality and abandonment of treatment. The second point was renal outcome.

**Results:** A total of 11693 patients enrolled, including 6637 males and 5056 females. The overall AKI incidence was 34.5% (n=4030). The AKI incidence increased during the five years from 34.2% to 36.5% (P<0.05). There was no significantly statistical differences in AKI-RRT incidences during the five years (p=0.360). The hospital mortality of AKI decreased from 6.3% in 2009 to 3.8% in 2013. The incidence of poor prognosis in AKI was 8.3%, 7.5%, 6.8%, 5.1%, 8.0% (P=0.196). The mortality of AKI-RRT decreased from 47.1% to 29.5%, but there was no statistical difference (P=0.230). The incidence of poor prognosis in RRT decreased from 66.7% to 57.4%, also no significantly statistical difference (P=0.825). Multivariate logistic regression analysis showed that male age (every additional 10 years), body mass index (every additional 5kg/m2), hypertension, chronic heart failure, pre-operative serum creatinine>115μmol/L, CPB (every additional 30 min) were the risk factors of AKI after cardiac surgery.

**Conclusions:** The incidence of AKI after cardiac surgery increased from 2009 to 2013 and the rate of poor prognosis did not change. The incidence of AKI-RRT and the rate of poor prognosis remained high. The prevention and treatment of AKI still need improvement. **Funding:** Government Support - Non-U.S.

**FR-PO468**

The Very Long-Term Co-Morbidity Adjusted Impact of AKI following Cardiac Surgery: A 15-Year Follow-Up Study

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**Background:** AKI is a frequent complication of cardiac surgery (CS) associated to high mortality. The co-morbidity adjusted residual impact on very long-term mortality (>12 years) of AKI excluding the initial catastrophic impact on early mortality has never been addressed before. **Objectives:** To evaluate the net attributable impact of AKI after CS on long-term mortality.

**Methods:** All adult patients submitted to CS between 1/1/2000 and 31/12/2013 (n=7755) were enrolled. The INCC prospective-collected database with more than 750 variables (demographics, comorbidities, type of CS, intraoperative and postoperative variables, peri-operative support and short time outcomes) was used. Long-term survival (up to 15 year by December 2014) was obtained by systematic telephone survey (minimum 1-year follow-up) and the National Population Registry. AKI stages were defined according to KDIGO definition. Demographics, logistic EuroSCORE (and their single components), type of CS, baseline renal function (Cockcroft-Gault formula) were used for comorbidity risk-adjustment. Statistical analysis: “%”, “test”, c test, Kruskal-Wallis test, Kaplan-Meier curves with long-rank test and Cox regression for multivariate survival analysis. Only patients alive after the first 1 year follow-up entered in the long-term survival analysis (n=9595).

**Results:** AKI incidence: 38.4%. RRT: 1.7%. Long-term (15 years) actuarial survival after 1 year follow-up: no AKI 0.58; AKI-I: 0.47; AKI-II: 0.39; AKI-III: 0.27 (p<0.001). In multivariate Cox regression analysis, AKI stages I, II and III (OR 1.17; 1.24; 1.62 respectively) were independently associated with mortality between 1 year after CS and 15 year follow-up, even after adjustment with logistic EuroSCORE (OR 1.02), age (OR 1.038), diabetes (OR 1.58), pre-operative eGFR (OR 0.996) and no-isolated coronary bypass surgery (OR 1.24).

**Conclusions:** AKI and its severity are independently associated with very long-term mortality, even after discarding short term events (1 year), in cardiac surgery. Should AKI be causative or a surrogate marker of late events in the long term follow up is a matter of concern to be evaluated.

**FR-PO469**

Incidence and Influencing Factors of Cardiac Surgery-Associated Acute Kidney Injury Based on the KDIGO Criteria: A Retrospective Cohort Study

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**Background:** The incidence and influencing factors of cardiac surgery-associated acute kidney injury (CSA-AKI) based on the KDIGO criteria have not been well studied. This study was aimed to evaluate the incidence, risk or protective factors of acute kidney injury (AKI) in patients after cardiac surgery.

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

**Underline represents presenting author.**
Methods: A retrospective analysis of 2575 patients undergoing first documented cardiac surgery with cardiopulmonary bypass (CPB) between January 2008 and December 2012 in our hospital was conducted. Perioperative variables were collected and analyzed. Univariate and multiple logistic regression models were used for determining the association between the development of AKI and risk factors.

Results: Of 2575 patients, 931 (36%) developed AKI. A total of 38 (1.2%) patients required renal replacement therapy. The overall in-hospital mortality rate was 1.5% (38 of 2575). CSA-AKI was significantly associated with in-hospital mortality (adjusted HR: 2.22, 95% CI 1.16-4.24, P = 0.016), especially in patients needing RRT (adjusted HR: 18.68, 95% CI 8.58-40.68, P < 0.003). The independent risk factors identified by multivariate analysis were shown in Table 1.

Conclusions: This study demonstrates that mechanical ventilation duration, erythrocytes transfusion and postoperative body temperature above 38°C within 3 days were shown in

FR-PO470
Acute Kidney Injury Post-Major Orthopaedic Surgery: A Single Centre Experience
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Background: Given the increasing incidence of AKI and the burden this places on the medical system, there is a clear need to expand the practice of ‘preventative nephrology’ – the optimisation of renal function through minimisation of potential insults. Renoprotection is particularly critical in the perioperative setting, a period of high renal vulnerability. However, there is currently little evidence regarding numerous theoretical risk factors for postoperative AKI.

Methods: All patients undergoing MOS at our centre between 2008 and 2014 were included. Out of 2227 surgeries audited for AKI using comparisons of preoperative and postoperative creatinine, 164 cases were identified (per RIFLE criteria) and matched to the creatinine based KDIGO criteria. Risk factors for AKI were evaluated using logistic regression analysis.

Results: Controlling for known risk factors, both diuretic and ACEi or ARB use were associated with a high severity of AKI.

Conclusions: This study presents the incidence of AKI after invasive surgical principal procedures, and this data will help prioritize research to prevent in-hospital AKI. Non-kidney transplant, heart valve, and CABG surgical procedures were associated with the largest number of AKI cases at this single center, and non-kidney organ transplants were associated with a high severity of AKI.

FR-PO472
Acute Kidney Injury following Gastrointestinal Surgery
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1 Dept of Medicine; 2 Dept of Anaesthesia; 3 Dept of Cardiovascular Surgery, Landspítali; 4 Faculty of Medicine, Univ of Iceland; 5 Dept of Anestesia, Brigham and Women’s Hospital, Boston, MA; 6 Div of Nephrology, Landspítali - The National Univ Hospital, Reykjavik, Iceland.

Background: Acute kidney injury (AKI) is a serious postsurgical complication but AKI after nonvascular abdominal surgery has not been thoroughly studied. The aim of this study was to examine the incidence of AKI after such operations, its risk factors and survival in patients.

Methods: We studied all nonvascular abdominal operations performed on adults 2007-2014 at Landspítali, the major hospital in Iceland. AKI was diagnosed according to the creatinine based KDIGO criteria. Risk factors for AKI were evaluated using logistic regression analysis. Survival was compared between AKI and non-AKI patients using Kaplan-Meier method after propensity score matching (1:1, nearest neighbor matching).

Results: A total of 10,022 patients underwent 11,552 operations during the study period, 38.0% were acute operations. Median age at operation was 52 yrs (IQR 32-66) and 59.5% of patients were female. AKI occurred after 246 operations (2.1%), with 157 (1.4%), 57 (0.5%) and 32 (0.3%) of stage 1, 2 and 3, respectively. Incidence of AKI was higher after major (5.3%), open (4.9%) and acute operations (5.0%) compared to minor (1.1%), laparoscopic (0.5%) and non-acute operations (1.8%). In multivariable analysis, postoperative AKI associated with age (OR 1.03 (95%CI (1.04-1.01)), male sex (1.1 (1.02-2.0), open operation 3.0 (2.4-2.2), re-operation 4.8 (3.7-8.6), hypertension 1.7 (1.2-2.4), eGFR <60ml/min/1.73m2 2.0 (1.4-2.7) and ASA score 6.1 (4.2-8.8). Survival was worse for AKI patients compared to the propensity score matched controls, both at 30 days (82.4% vs. 94.7%, p=0.03) and at 1-year (69.9% vs. 82.6%, p=0.03).

Conclusions: The incidence of AKI is relatively low after gastrointestinal surgery compared to cardiac and vascular surgery. The rate of AKI is substantially higher after major and open operations and in patients with preexisting kidney disease. AKI is associated with increased short- and long-term mortality.

FR-PO473
Risk Factors Associated with Post-Operative AKI After General Surgery
Predeep Arora, 1 Leili Pourakbari, 2 James L. Mohr, 1 Hasan H. Dosluoglu, 1 Nader Naderi, 3 Div of Nephrology, VAMC, Buffalo, NY; 1 Anesthesiology, VAMC, Buffalo, NY; 2 Surgery, VAMC, Buffalo, NY.

Background: AKI after cardiac and vascular surgery has been extensively studied. However, there is no study which has evaluated the factors associated with development of stage 1 AKI by AKIN criteria in general surgery patients.

Conclusions: This study demonstrates the incidence of AKI after invasive surgical principal procedures, and this data will help prioritize research to prevent in-hospital AKI. Non-kidney transplant, heart valve, and CABG surgical procedures were associated with the largest number of AKI cases at this single center, and non-kidney organ transplants were associated with a high severity of AKI.
Methods: We conducted a cohort study using a prospective database of patients undergoing non-cardiac, non-vascular surgery performed since 2000 in the VA Western New York Healthcare System which are in part reported to the National Surgical Quality Improvement Program (NSQIP). Demographic, social history, co-morbid diseases, including coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive lung disease (COPD), peripheral vascular disease (PVD), cerebrovascular accidents (CVA), hypertension, and diabetes, were prospectively entered into the Veterans Affairs Surgery Quality Improvement Program (VASQIP) database at the time of surgery. Preoperative laboratory data were also entered for each participant. Univariate and multivariate logistic regression were performed to estimate the odds of AKI after surgery. Results: A total of 1621 patients who underwent non-cardiac and non-vascular surgery whose data was available to define AKI between 2000-2014 were included in this analysis. In univariate analysis, increasing age, male gender, ASA class, poor functional status, presence of COPD, CVA, CVD, DM, CHF, HTN, preop coronary intervention or MI, HCT <24, Low serum albumin, increased operating room (OR) time and blood transfusions were associated with increased odds of AKI. Results of multivariate analysis are shown in table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin</td>
<td>0.72 (0.62-0.81)</td>
</tr>
<tr>
<td>Transfusion during surgery</td>
<td>1.34 (1.07-1.69)</td>
</tr>
<tr>
<td>Pre creatinine</td>
<td>1.21 (1.08-1.36)</td>
</tr>
<tr>
<td>HCT &lt;24</td>
<td>1.75 (1.59-1.92)</td>
</tr>
<tr>
<td>OR time</td>
<td>1.15 (1.10-1.20)</td>
</tr>
<tr>
<td>DM</td>
<td>1.21 (1.12-1.32)</td>
</tr>
<tr>
<td>COPD</td>
<td>1.11 (1.02-1.21)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.22 (1.03-1.47)</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.02-1.03)</td>
</tr>
</tbody>
</table>

Conclusions: AKI is associated with increased length of hospital stay and mortality. Efforts to recognize and intervene in preoperative modifiable factors to prevent AKI will improve outcomes in general surgical patients.

FR-PO474

The Comparison of the Incidence of Acute Kidney Injury Post Coronary Artery Bypass Graft versus Percutaneous Coronary Intervention: National Inpatient Sample Experience

Methods: We extracted total 485742 cases from National Inpatient Sample (NIS) to create a propensity-score matched cohort of patients who had multivessel coronary disease and underwent first-time CABG or PCI between 2004-2012. Patients received concomitant valvular repair or both CABG and PCI on same admission, history of organ transplant, CKD stage IV or ESRD on dialysis were excluded. Both groups were matched for age, gender, race, payer, prior MI, unstable angina, heart failure, CKD, diabetes, HTN, dyslipidemia, smoking, cirrhosis, obesity, anemia and in-hospital GI bleeding. The odds ratios were estimated by logistic regression analysis. Results: The incidence of AKI in CABG group was higher than PCI group (8.41% vs 6.49%, OR 1.24-1.40, P<0.0001). The in-hospital mortality in patients with AKI was higher in CABG (4.00% vs 2.23%, P=0.001). The incidence of severe AKI requiring RRT were similar in both groups (0.95% vs 0.91%, P=0.147). Compared with PCI group, CABG group had higher total in-hospital mortality (1.89% vs 1.48%, OR 1.34, 95% CI 1.24-1.40, P<0.0001). The in-hospital mortality in patients with AKI was higher in CABG (0.92% vs 0.59%, P<0.0001). Conclusions: Patients received CABG were at higher risk of developing AKI and associated with higher total in-hospital mortality. The in-hospital mortality in patients with AKI was higher in CABG.

FR-PO475

Dialysis-Requiring Acute Kidney Injury Among Hospitalized Adults with Documented Hepatitis C Virus Infection: A Nationwide Inpatient Sample Analysis

Methods: We extracted our study cohort from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project using data from 2004-2012. We defined HCV and AKI-D based on previously validated ICD-9-CM codes. We analyzed temporal changes in proportion of hospitalizations complicated by AKI-D and utilized survey multivariable logistic regression models to estimate its impact on in-hospital mortality. Results: We identified a total of 4,603,718 adult hospitalizations with associated HCV from 2004-2012, of which 51,434 (1.12%) were complicated by AKI-D. The proportion complicated by AKI-D increased significantly from 0.86% in 2004 to 1.28% in 2012. Trend was similar when stratified by cirrhosis and paralleled that in HCV negative hospitalizations. Conclusion: The proportion of HCV hospitalizations complicated by AKI-D increased significantly between 2004-2012. Similar to observations in the general population, AKI-D was associated with two-fold increase in odds of in-hospital mortality. These results highlight the burden of severe AKI in hospitalized adults with HCV infection.

FR-PO476

The Burden of Dialysis Requiring Acute Kidney Injury in Decompensated Cirrhosis: A Nationwide Inpatient Sample Analysis

Methods: We extracted our cohort from Nationwide Inpatient Sample (NIS) from 2006-2012. We identified hospitalizations with DC & AKI-D by validated ICD9 codes. We analyzed temporal changes in proportion of DC hospitalizations complicated by AKI-D & utilized multivariable logistic regression models to estimate AKI-D impact on in-hospital mortality. Results: We identified a total of 36,55,700 adult DC hospitalizations from 2006-2012 of which 78,015 (2.1%) had AKI-D. Proportion with AKI-D increased from 1.5% in 2006 to 2.23% in 2012; this was stable between 2009-12 despite increase in absolute number from 6773 to 13930. Conclusions: In-hospital mortality was significantly higher in hospitalizations complicated by AKI-D vs. those without (27.38% vs. 2.95%; adjusted odds ratio 2.09, 95% Confidence Interval 1.74-2.51) which remained stable over the study period. The burden of severe AKI in hospitalized adults with HCV infection is significant and increasing.

AKI: Clinical - Epidemiology
The overall hospital mortality was significantly higher in hospitalizations with AKI-D vs. those without (40.87% vs. 6.96%; p<0.001). After adjusting for demographics, mortality risk, acute/chronic comorbidities & hospital level factors, the adjusted odds ratio for mortality was 2.17 (95% CI 2.06-2.28; p<0.01) with AKI-D, which was stable from 2006-2012.

Conclusions: The proportion of DC hospitalizations with AKI-D increased from 2006-09 & although, this was stable from 2009-12, there was an increase in absolute case number. These results elucidate burden of AKI-D on DC hospitalizations & excess associated mortality as well as highlight the importance of prevention, early diagnosis & testing of novel interventions in this vulnerable population.

Funding: NIDDK Support

FR-PO477
Temporal Trends of Burden of Dialysis Requiring Acute Kidney Injury in Cerebrovascular Accident Hospitalizations

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Background: The epidemiology of dialysis requiring acute kidney injury (AKI-D) in acute ischemic stroke(AIS) and intracerebral hemorrhage(ICH) admissions is poorly understood with previous studies being from a single center and/or year.

Methods: We used the Nationwide Inpatient Sample to evaluate the yearly incidence trends of AKI-D in AIS and ICH admissions from 2002 to 2011. We also evaluated the trend of impact of AKI-D on in-hospital mortality and adverse discharge utilizing adjusted odds ratios (aOR) after adjusting for demographics and comorbidity indices.

Results: We extracted a total of 3927267 AIS and 704648 ICH admissions, AKI-D occurred in 1.5 and 3.5 per 1000 in AIS and ICH admissions respectively. Incidence of admissions complicated by AKI-D doubled from 0.9/1000 to 0.7/1000 in AIS and from 2.1/1000 to 4.3/1000 in ICH admissions.

Conclusions: Incidence of dAKI complicating CVA hospitalizations continues to grow and is associated with increased mortality and adverse discharge. This highlights the need for early diagnosis and better risk stratification in this vulnerable population.

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

FR-PO478
Long-Term Healthcare Utilization and Mortality After Acute Kidney Injury in Critically Ill Children


Background: Acute kidney injury (AKI) is common in the pediatric intensive care unit (PICU). The late illness burden of child AKI is unknown. We will evaluate if AKI in the PICU is associated with increased mortality and health care service use 5 years after discharge.

Methods: Retrospective cohort study of children admitted to two Montreal, Canada PICUs, 2003-2005 (N=2500). Exclusions: no health number, deceased in PICU. Clinical chart data was merged with provincial administrative health data. AKI (main exposure): by Kidney Disease Improving Global Outcomes serum creatinine (SCr) definition (if no PICU-SCr drawn, non-AKI was assumed). 5-year outcomes: all-cause mortality; healthcare utilization (HCU), defined as the number of hospitalizations, emergency room (ER) and physician visits per 100 person years. AKI-outcome relation was evaluated with multivariate logistic (mortality) and linear regression (HCU), adjusting for gender, age, cardiac surgery, PRISM (mortality) score, vasopressors and infection.

Results: Of 2407 children (mean±SD age=6±0.5 yrs; PRISM = 8.2±5.9); 56% male; 448 (18.6%) developed AKI. AKI (yes/no) was associated with mortality in univariate (p=0.05) but not multivariate analysis. Stage 2 AKI or worse was associated with 5-year mortality (adjusted[adj]OR=1.9, 95% CI= 1.1-3.2). AKI (yes/no) was associated with increased 5-year hospitalizations (adj p=0.05) and physician visits (adj p=0.001), but not ER visits (adj p=0.8). There was a graded increase in 5-year HCU with higher AKI severity.

Conclusions: PICU-AKI is associated with long-term increased mortality risk and HCU. Research should evaluate cost-effective interventions to improve child AKI treatment and evaluate effects on late outcomes.

Funding: Government Support - Non-U.S.

FR-PO479
Acute Kidney Injury: A 12 Month Follow, the Incidence and Mortality

Hsu qheen Chong, Paul R. Cannon, Caroline J. Whyte, Kottarathil Abraham Abraham. Nephrology, Aintree Univ Hospital, United Kingdom.

Background: Acute Kidney Injury (AKI) affects nearly 1 in 5 hospital admission. It carries a poor prognosis with mortality ranging from 10-80% dependent on the population studied. Aintree University Hospital caters to about a population of 506,000 in North Liverpool. An observational study was carried out in this catchment area to ascertain the incidence of AKI, the length of stay and its effect on 12 months mortality.

Methods: Patients who were admitted between the time periods of August 2012 until January 2013 were included in this study. Liaising with the biochemistry department, all patients who had a rise in their creatinine based on the Acute Kidney Injury Network Criteria received an e-alert sign on the computer system. Clinical outcomes were obtained from each patient record.

Conclusions: In all patients who had a rise in their creatinine based on the Acute Kidney Injury Network Criteria received an e-alert sign on the computer system. Clinical outcomes were obtained from each patient record.

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

Underline represents presenting author.
Results: There were a total of 36,957 patients admitted during that 6 month time period of which a total of 358 cases of AKI were identified. There was total of 183 male patients and 171 female patients. Four of the male patients had a further AKI alert during the same hospital admission. The mean age was 72.18 years. Pre-renal causes were identified as the main contributors to the cases. Majority of the AKI alerts were Stage 1 AKI which was 70%, Stage 2 AKI was 25% and Stage 3 AKI was 5% of the total cases. The data also revealed that the average length of stay (ALOS) did not differ in each of the stage. A patient ALOS for Stage 1 AKI 23.3 days, Stage 2 AKI 24 days and Stage 1 AKI 21 days. Of the total number of cases of patients with AKI, 50.6% (179/354) of the patients had died within the 12 months period. Looking into the mortality rate of each individual stages of AKI; the mortality rate at 12 months for Stage 1 AKI is 46.5%. For Stage 2 AKI, 62.7% and for Stage 3 AKI, 47.6%.

Conclusions: From the dates collected, it shows that the degree of AKI does not affect the length of stay of patients. Despite the different stages of AKI indicating the severity of the injury, mortality rate for Stage 1 and Stage 3 did not differ. This indicates that AKI carries a high mortality rate regardless of the severity of the injury. Early recognition leads to early intervention in the prevention of AKI.

FR-PO480
Acute Kidney Injury: Adding Informatics to Injury – (Electronic Injury Alerts) Conor Patrick Moran,1 Ying C. Kuan,1 Patrick Lm Lynch,2 Francis Mccarroll,1 1Dept of Nephrology, Altnagelvin Hospital, Londonderry, United Kingdom; 2Dept of Clinical Chemistry, Altnagelvin Hospital, Londonderry, United Kingdom.

Background: Acute Kidney Injury, (AKI), is common with a variably reported mortality, (15-68%). UK national audit reported that up to 30% of cases were avoidable and that as much as 43-61% of post-admission AKI experienced an unacceptable delay in recognition of insult. There has been a paucity of work with regards to AKI recognition and prevention. National guidelines have recommended the use of electronic alerts (e-alerts) for AKI detection.

Methods: We introduced AKI e-alerts with accompanying electronic guidance in late October 2014 and prospectively collected data on the patients identified with severe AKI. Data collection was carried out for 3 months, (n=110). The demographics of this cohort were compared with a historical cohort of severe AKI (n=89).

Results: Mean age, (72 years vs. 73 years), gender distribution, (M/F: 46%/54% vs. 47%/53%), and median time to death, (10 days vs. 9 days), were comparable. Thirty day mortality was similar with regards to hospital acquired AKI, (27.3% vs. 26.1%). 30 day mortality was significantly lower for community-acquired AKI, (10.7%). Mean and median age was demonstrated to be higher in the group of patient who died, (Mean: 80.1 years vs. 75.7 years), (Median: 82 years vs. 82 years) – negative skew due to outliers.

Conclusions: Although our initial data suggests an electronic AKI alert has no discernable effect on 30 day mortality rate and time to death. We feel that e-alerts with the addition of further Quality Improvement work will eventually result in a steady reduction in AKI mortality.

FR-PO481

Background: Tenofovir disoproxil fumarate (TFD) is widely prescribed as a first choice therapy for HIV infection, because of its convenient dosing schedule, efficacy and relatively low side effects. However, renal toxicity may lead to acute kidney injury (AKI), chronic kidney disease (CKD), and proximal tubular injury. Here we describe clinical characteristics and outcomes of AKI associated to TDF.

Methods: In a retrospective cohort (between Mar/2011 to Feb/2015), we have described data of HIV-infected inpatients, in a single center infectious disease ward, referred to the Nephrology group due to AKI. AKI was defined according to AKIN criteria.

Results: During the study period, 72 patients were evaluated; the baseline characteristics are showed in table1. Nephrototoxic AKI was present in 36 cases, of which 19 cases (52%) were associated with TFD and the drug was withdrawn in all cases. Seven patients had TFD nephrotoxicity without other associated factors and only three patients achieved renal function recovery, but no one needed dialysis or died during follow up.

In addition, a significantly lower frequency of CaN was noted amongst females compared with males (9.3% vs 14.5%, p=0.001).

Conclusions: Tenofovir-associated nephrotoxicity occurs less frequently than previously reported. This may reflect changes in preventive care such as more aggressive hydration with electrolyte-rich solutions.

Funding: Other NIH Support - T32 training grant

FR-PO482
Cisplatin-Associated Nephrotoxicity: Not as Frequent as Previously Reported Shveta S. Motwani, Sushruti S. Waikar, Benjamin D. Humphreys, Gary C. Curhan. Nephrology, Brigham and Women’s Hospital, Boston, MA.

Background: Cisplatin-associated nephrotoxicity (CaN) is a frequent problem amongst patients with various cancers. Most older studies have reported 25-30% of patients who receive cisplatin experience acute kidney injury. However, these data have not been re-evaluated systematically recently despite rapid advances in oncologic care. Therefore, we examined the proportion of patients who develop acute kidney injury after exposure to the first cycle of cisplatin in a large patient database. We also examined the frequency of kidney injury stratified by sex and cisplatin dose regardless of cancer type.

Methods: We collected data on patients ≥ 18 years of age who had received cisplatin as a primary, secondary or adjuvant or neo-adjuvant therapy at a tertiary-care medical center (Massachusetts General Hospital) between 2006 and 2014. Detailed data regarding cisplatin dose, demographic characteristics, concurrent medical history and laboratory data including serum creatinine (Cr) and electrolytes were collected. CaN was defined as an elevation of Cr by ≥ 0.3 mg/dl during a 14 day period after administration of cisplatin (peak Cr) compared with baseline (bl Cr). Patients with bl Cr of >1.5 were excluded.

Results: Of the 1979 patients in our study, 55% were male with a mean ± SD of age of 61.6 ± 12.8. A bl Cr was 0.9 ± 0.2. 241 of 1979 (12.2%) patients developed CaN. However, it ranged from 7.8% in the medium dose group (cisplatin dose 75-130 mg) to 18.2% in the high dose group (>130mg) without a clear dose response relation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO483
Characteristics of 681 Patients with Atypical Hemolytic Uremic Syndrome in the Global aHUS Registry 1 Gianluigi Ardissino, 2 Gema Ariceta, 3 Masayo Ogawa, 4 Varant Kupelian, 5 Johan Vande Bacchi, 6 Alhaji Saudan, 7 Patrick Johnson, 8 Masayo Ogawa, 8 Varant Kupelian, 9 Franz S. Schaefer, 10 Johan Vande Bacchi.

Methods: PTs with clinical diagnoses of aHUS ( irrespective of identified complement amplification or treatment) are eligible. Demographic, medical/ disease history, and treatment outcomes data are collected at enrollment and prospectively.

Results: By January 30, 2015, 681 pts enrolled (Table: 62.7% of adults were women. Thrombosis occurred more frequently in adults than pediatric pts. Nonrenal comorbid conditions occurred in both age groups. ECU was administered to 56.2% (87.7% prior to enrollment).

Conclusions: Registry baseline characteristics show differences between pediatric and adult aHUS pts, notably different frequencies of thrombosis. Ongoing and future analyses will further enhance understanding of aHUS history and progression. Medical writing support - Kristen W. Quin, PhD, of Peloton Advantage, funded by Alexion

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>Median (IQR)</th>
<th>Range</th>
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</thead>
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<td>9 (5)</td>
<td>0-28</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>European</td>
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FR-PO485
Use of ACEIs and ARBs in Patients with Chronic Kidney Disease and Superimposed Community-Acquired Acute Kidney Injury 1 Patrick Saudan, 2 Cyrielle Alves, 3 Fabien Stucker, 4 Belen Ponte, 5 Pierre-Yves F. Martin, 6 Thomas Perrenoud, 7 Sebastian Carballo, 8 Franz S. Schaefer, 9 Johan Vande Bacchi.

Results: From May 1st up to June 21st 2013, there were 8464 admissions of whom 361 (4%) had a eGFR < 60 ml/mn and were known to have CKD. Use of ACEIs, ARBs, diuretics, NSAIDs was respectively found in 19, 23, 37 and 4% of patients. AKI was superimposed in 102 (28%) patients. Etiology was primarily associated with infection in 73%, diabetes (7%), and post-surgical (10%). ACEI use was significantly lower in patients with AKI (0.28; 95%CI:0.18-0.38, p<0.0001), but ARB use was similar (OR 0.78; 95%CI:0.56-1.09, p=0.12). In patients with stable CKD, ACEI use was significantly lower (OR 0.54; 95%CI:0.38-0.77, p<0.0001)

Conclusions: Lower use of ACEIs in patients with AKI might be due to the lack of benefit from life-long follow up of kidney function after AKI.

FR-PO486
Renal and Patient Outcomes of Dialysis Dependent Patients with ATN Who Survive Hospitalization 1 Mohammad Alhaji, 2 Rabeek I. El-refai, 3 Jere Yee, 4 Bronwyn Larissa Small, 5 Javier Rodriguez Sanchez, 6 Jian Li, 7 Lenar T. Yessayan.

Results: We prospectively enrolled 38 Medicare beneficiaries who developed hemodialysis-dependent ATN and survived to discharge at a single center from January 1, 2013 to June 30, 2014. The ATN was identified by urine microscopy and clinical judgment. ATN causes, patients’ comorbid conditions, potential contributors to ATN and indications for hospitalization were recorded.

Conclusions: We prospectively enrolled 38 Medicare beneficiaries who developed hemodialysis-dependent ATN and survived to discharge at a single center from January 1, 2013 to June 30, 2014. The ATN was identified by urine microscopy and clinical judgment. ATN causes, patients’ comorbid conditions, potential contributors to ATN and indications for hospitalization were recorded. Cumulative hazard estimates of events and survival curves were generated using the Kaplan-Meier method.

Results: Twenty six patients (58%) had CKD, 18 had diabetes (47%), 29 had hypertension (76%), 10 had history of liver disease (26%) The 90 day renal recovery and mortality rates were 42% and 11% respectively. Of those who recovered kidney function, Only 1 patient recovered kidney function beyond 60 days. The 1 year cardiovascular events and readmission rates were 22% and 62% respectively.

Conclusions: Patient with dialysis dependent ATN following a hospitalization are unlikely to get off dialysis support beyond 60 days after discharge. In the first year post discharge, they experience a significant number of cardiovascular events and hospital readmissions. Identifying modifiable risk factors for readmission in this cohort may reduce health care costs.

FR-PO487
Long-Term Renal Function After Recovery from Dialysis-Requiring Acute Kidney Injury 1 Sokratis Stoumpos, 2 Colin C. Geddes. Renal and Transplant Unit, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom.

Background: Current guidelines suggest that people should be monitored for the development of chronic kidney disease (CKD) for at least 2-3 years after acute kidney injury (AKI), even if serum creatinine has returned to baseline. The aim of this study was to determine the long-term renal outcome of patients experiencing AKI secondary to hypoperfusion injury and/or sepsis who recovered to apparently normal renal function.

Methods: We conducted a population-based cohort study of all adult patients in our catchment area (serving a population of approximately 1.5 million), with AKI who required in-hospital dialysis in the nephrology unit, survived for at least 12 months after discharge, and had estimated glomerular filtration rates (eGFR) greater than 60ml/min in 1 year after the episode of AKI between September 1, 1989, and March 5, 2015. Patients with underlying nephropathy and AKI due to causes other than hypoperfusion injury and/or sepsis were excluded. Follow up was censored to the date of the last serum creatinine recorded.

Results: From the 770 patients identified with dialysis-requiring AKI, 310 patients met the inclusion criteria. Mean age at time of AKI was 49.0 (SD 14.6) years, 58.7% were male and the median duration of haemodialysis was 6 (IQR 3-11) days. After a median follow-up of 7.3 (IQR 4.6-12.6) years from first dialysis for AKI, eGFR was >60ml/min in 285 (91.9%) patients, 45-59ml/min in 18 (5.8%), 30-44ml/min in 6 (1.9%) and 15-29ml/min in 1 (0.3%) patient. None of the patients developed CKD stage 5 or end stage renal disease. 86 (27.7%) patients died during the duration of follow-up.

Conclusions: The excellent outcome for patients with normal renal function 1 year after an episode of dialysis-requiring AKI suggests that these patients are unlikely to derive benefit from life-long follow up of kidney function after AKI.
**FR-PO487**

**Long-Term Follow-Up of Children with STEC-HUS Caused by *E. coli* O104:H4 (German HUS Outbreak 2011): A GPN Registry Study**

**Background:** In 2011, *E. coli* O104:H4 caused the largest outbreak of HUS in adults and children. A total of 90 children were affected, of whom 64 (71%) required dialysis for a median of 11 days.

**Methods:** Currently follow-up data are available from 60 of 90 children (67%, 31 girls) from 11 pediatric centers in Germany. Median follow-up is 2.7 (range 1.2-3.8) years, median current age of patients is 14.7 (3.4-18.7) years.

**Results:** Median serum creatinine-urea is 0.7 (0.3-8.9) mg/dl. In two patients (2.2%) with CKD stage 3 and 4 at discharge GFR improved and they are now in CKD Stage 2. One patient remained dialysis dependent initially and one reached ESRD after 3.5 years; both underwent successful living-related kidney transplantation. All these 4 patients were treated with eculizumab in the initial phase of STEC-HUS including 2 who also received plasmapheresis. Proteinuria is currently present in 17 (19%) patients and 9 (10%) require treatment for hypertension. Three patients have neurologic symptoms (headache, performance deficit, spastic movement disorder) and 3 patients have EEG abnormalities without symptoms.

**Conclusions:** Long-term follow-up is important after O104:H4 associated STEC-HUS. CKD stage 3-5 at discharge is a risk factor for ESRD, however some children show a significant improvement over time. Patients with proteinuria and hypertension need long-term follow-up. Follow-up studies after STEC HUS should include neurological investigations.

**FR-PO488**

**SOFA Scores as Predictors of Mortality and Dialysis Dependency in Acute Kidney Injury**

**Background:** The Sequential Organ Failure Assessment (SOFA) score measures the severity of organ failure, and baseline SOFA scores have been used to predict mortality and dialysis in patients with Acute Kidney Injury (AKI). We evaluated whether SOFA scores, either upon initiation of dialysis or clinically updated, predict mortality and dialysis dependency among AKI patients.

**Methods:** Data from patients enrolled in the Acute Renal Failure Trial Network (ATN) study, a randomized multicenter trial of the intensity of renal support in AKI, were used in Cox proportional hazards regression and multimodal logistic models to assess the degree to which SOFA scores predict mortality and dialysis dependency.

**Results:** SOFA scores were associated with increased mortality risk following AKI among the 1,124 ATN participants, but the concordance statistic was low, at 0.651 (standard error [se] 0.041). When time-dependent analyses were used to take advantage of prospectively updated SOFA scores, the concordance statistic increased to 0.753 (se = 0.013). In analyses that examined mortality and dialysis dependency as competing outcomes at three fixed time points, increased SOFA scores were associated with higher mortality risk, and lower risk of dialysis dependency.

**Conclusions:** Similar to the general ICU population, updated SOFA scores better prognosticate the risk of death in patients with AKI. Higher SOFA scores are associated with increased mortality risk, but decreased dialysis dependency risk, when the two outcomes are evaluated as competing risks. Future studies should focus on prognostic tools that simultaneously prognosticate survival and need for dialysis in AKI patients.

**Funding:** Private Foundation Support

**FR-PO489**

**Risk Factors of Acute Kidney Injury and In-Hospital Mortality in Adult Patients Receiving Extra-Corporeal Membrane Oxygenation (ECMO)**

**Background:** Despite the frequent complication in patients receiving extracorporeal membrane oxygenation (ECMO), little has been studied about the risk factors of AKI and in-hospital mortality. Thus we performed the study to identify factors associated with AKI and in-hospital mortality.

**Methods:** We analyzed 322 adult patients receiving ECMO from January 2005 to November 2019 in two tertiary care hospitals. AKI and in-hospital mortality Disease Improving Global Outcomes classifications. Variables within 24 h before ECMO initiation were collected and analyzed for the association with AKI and in-hospital mortality.

**Results:** Stage 3 AKI was associated with in-hospital mortality with HR (95% CI) of 2.680 (1.410-5.132), compared to no AKI (p=0.003). Simplified acute physiology score was also significantly associated with in-hospital mortality with HR (95% CI) of 1.022 (1.004-1.040) with every 1 score increase (p=0.014). Initial pump speed of ECMO was significantly related to in-hospital mortality with HR (95% CI) of 1.397 (1.024-1.904) with each 50 rpm increase (p=0.028). There was also a trend to significantly associated with total AKI (p=0.035) and stage 3 AKI (p=0.044) with ORs (95% CI) of 2.219 (1.059-4.462) and 1.676 (1.015-2.770), respectively. We also found that red cell distribution width (RDW), serum level of total bilirubin, and the duration of ECMO were significantly related to AKI and/or stage 3 AKI.

**Conclusions:** Initial pump speed was significant risk factor in in-hospital mortality and AKI in patients receiving ECMO. RDW, serum level of total bilirubin and the duration of ECMO were risk factors of AKI.

**FR-PO490**

**Comparison of Clinical Characteristics of Patients with Acute Kidney Injury After IntraVascular versus Inhaled Colistin Therapy**

**Background:** The aim of this study is to investigate the incidence and clinical characteristics of intravenous or inhaled colistin associated acute kidney injury (AKI) using the RIFLE criteria.

**Methods:** From 2010 to 2014, 160 patients were treated with intravenous or inhaled colistin. Of these, we included 139 patients who received colistin for >72 h, and compared the incidence and clinical characteristics of patients in the intravenous (n=120) and inhaled (n=19) groups.

**Results:** The patients included 116 men and 23 women, with a mean age of 68 years (range, 20-91). Patients were infected with either A. baumannii (54%) or P. aeruginosa 46 (%), and pneumonia (91%) was the most common type of infection. The mortality rate was 43.9%, and AKI occurred in 83 (60%) patients. At the end of therapy, bacteriologic cure rate was 64%. There were no differences in the clinical characteristics between the intravenous and inhaled groups except for age. In comparison with patients in the intravenous group, the patients in the inhaled group were older (74 ± 8 y vs 67 ± 14 y, p<0.03). The incidence of AKI was not different between the two groups (62% vs 47%, p=NS), and there was no difference in the severity of AKI according to the RIFLE criteria. Of the 83 patients with AKI, 8 and 1 patients underwent renal replacement therapy.

**Conclusions:** In our study, the incidence of AKI in patients undergoing colistin therapy was 60%, and there was no difference in safety between the intravenous and inhaled colistin groups. Therefore, it is also important to monitor renal function during colistin therapy regardless of the route of administration.

**FR-PO491**

**Acute Kidney Injury following Coronary Angiography**

**Background:** Acute kidney injury (AKI) is a known complication of coronary angiography (CA). The aim was to study the incidence, risk factors and outcome of AKI following CA in a whole nation.

**Methods:** This was a retrospective analysis of data from all CA in Iceland during a 9 year period. AKI was diagnosed according to the creatinine based KDIGO criteria and survival status for all patients was verified at Statistics Iceland. The epidemiology and clinical outcomes were compared between three 3-year periods using Chi-squared and Kaplan Meier method, and multivariate logistic regression was performed to find predictors of AKI.

**Results:** From Jan 1st 2005 to Dec 31st 2013 10713 patients underwent 13890 CA of whom 40% entailed an intervention. Median (range) age was 65 (19-96) years and 70.7% were men. AKI was diagnosed in 214 patients (1.5%; 168 (1.2%), 270(2.2%) and 19 (0.1%) of stage 1, 2, and 3, respectively. There was a trend towards a decreasing incidence of AKI: 1.8% in the first period 1, 3% in the second and 1.4% in the last (p<0.05). AKI was more common in the intervention group, 2.2% vs 1.1% (p<0.0001). Patients with AKI were older, had more often prior history of AKI, more co-morbid diseases and lower baseline eGFR compared to non-AKI patients. In multivariate analyses age over 70 years (OR=1.01, 95% CI=1.007-1.016), angiography with intervention (OR=1.01, 95% CI=1.008-1.016) COPD (OR=1.01, 95% CI=1.003-1.025), liver disease (OR=1.03, 95% CI=1.014-1.058) baseline eGFR<60 (OR=1.03 95% CI=1.027-1.039) and a prior history of AKI (OR=1.07, 95% CI=1.051-1.080) were independent predictors of AKI after CA. One year survival of AKI patients did not differ between time periods: 67.0%, 63.1% and 69.0% in the first, second and third, respectively, p=0.3.

**Conclusions:** There is a trend towards a decrease in AKI incidence following CA in recent years. Aged patients with multiple co-morbidities and prior history of AKI need special attention in connection with this this procedure.

**Funding:** Private Foundation Support
FR-PO492

Acute Kidney Injury in the First Hundred Days After Hematopoietic Stem Cell Transplantation: Experience with 222 Transplanted Patients in a Single Center

Miguel A. Solis, Sandra Tejedor, Isidro Torregrosa, Carmen Ramos, Isabel Juan, Patricia Tomas, Patricia Zambraño Esteves, Juan José Guzmán Herrera, María Jesús Puchades, Alfonso M. Carrasco. Nephrology, Univ Clinic Hospital, Valencia, Spain.

Background: Hematopoietic stem cell transplantation recipients are at an increased risk of Acute Kidney Injury (AKI) or Chronic Kidney Disease (CKD). An earlier diagnosis could dramatically improve the patients’ prognosis. Objective: To analyze the incidence of AKI in the first 100 days of Hematopoietic stem cell transplantation recipients and the relationship with mortality.

Methods: We carried out a retrospective study including 222 adult patients who underwent Hematopoietic stem cell transplantation between 2006 and 2010 at our institution. AKI was defined using the RIFLE criteria in the first 100 days after transplantation.

Results: 222 patients were included in the study, 137 males and 85 females. Median follow-up was 30 months, range 1-60 months. In the first 100 days after transplantation AKI developed in 78 patients according to the RIFLE criteria (35.1%). A total of 85 patients died during follow-up vs 47 who had developed AKI (38.2% versus 61%, p=0.05). Detailed patients' characteristics are summarized in table 1.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male: 137.</th>
<th>Female: 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years.</td>
<td>48.9 SD 13.43.</td>
<td></td>
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<tr>
<td>Type of transplantation.</td>
<td>Auto: 117 (52.7%)</td>
<td>Allogeneic: 105 (47.3%)</td>
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<tr>
<td>Non ablative (minAllo): 48 (21.6%)</td>
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<tr>
<td>Previous transplantation.</td>
<td>37 (16.7%)</td>
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<tr>
<td>Follow-up, months.</td>
<td>30, range 1 to 60</td>
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<tr>
<td>AKI, RIFLE criteria.</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td>78 (35.1%)</td>
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</tr>
<tr>
<td>AKI in Type of Transplantation.</td>
<td>Auto: 11.1%</td>
<td></td>
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<tr>
<td>Allogeneic: 59.6%</td>
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<td></td>
</tr>
<tr>
<td>minAllo: 66.7%</td>
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</tr>
<tr>
<td>Overall Mortality</td>
<td>85 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>Mortality in AKI</td>
<td>47 (61%)</td>
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</tr>
</tbody>
</table>

Conclusions: AKI incidence in hematopoietic stem cell transplantation recipients is very high. There is a statistically significant relationship between AKI and death in these patients. Earlier AKI identification could prevent kidney damage progression and improve patient outcome over time.

FR-PO493

STOP-Acute Kidney Injury (AKI): A Streamline Approach to the Management AKI Leads to Reduction of Mortality Rates

Hsu Jeen Chong, Thangavelu Chandrasekar. Nephrology, Aintree Univ Hospital, United Kingdom.

Background: Acute Kidney Injury (AKI) has a mortality rate of 30%, greater than common conditions such as myocardial infarction (8%) and stroke (9%). It is estimated that 15% of all inpatients at University Hospital Aintree (UHA), Liverpool, UK, suffer an AKI making it a condition of considerable importance in everyday practice. Through clinical audit, it was found that mortality rate of AKI in UHA was 33% on wards other than renal ward (9%).

Methods: To reduce AKI mortality by 30% and length of stay by 20% over a 12 month period from Oct 2013 using standardised, evidence based approach. Using plan, do, study act (PDCA) methodology, we developed and tested an automated e-alert diagnostics system, an AKI treatment bundle and a patient information leaflet. The STOP-AKI project was launched. Our Primary drivers were early and accurate identification of AKI, effective intervention and monitoring, staff and patient engagement. Initially, trialled at ward level, the project was scaled up to admission areas (Accident and Emergency Department and the Medical Assessment Unit) becoming part of routine management for all admitted patients.

Results: Fall in mortality rates from a baseline of 24% to 18.5%, representing an overall reduction in mortality of 23%. Length of stay fell by 11% equating in a 2.0 day reduction in length of stay.

Conclusions: The STOP-AKI project led to the development of an AKI bundle in Oct 2013. This has achieved not only a significant reduction in patient mortality and length of stay but in addition a more structured and stream lined way of approaching the patients with AKI in our hospital. With the bundle being rolled out to primary care and the rest of our inpatient wards, we anticipate a further reduction in mortality.

FR-PO494

Race and Risk of Acute Kidney Injury (AKI) in VA Patients

Michael Heungs, Deidra C. Crews, Neil R. Powe, Sharon Saydah, Meda E. Pavkov, Kara Zivin, Univ of Michigan; Johns Hopkins Univ; Univ of California San Francisco; Centers for Disease Control and Prevention; VA Ann Arbor Health System.

Background: African Americans (AA) are at increased risk for AKI compared to Caucasians (C); potential explanations include differences in risk factors, genetic susceptibility and socioeconomic factors. We explored the influence of race on AKI risk in the Veterans Administration (VA), an integrated healthcare system.

Methods: Retrospective cohort analysis of all hospitalizations for VA patients with known AA or C race in 2011. AKI was defined by KDIGO criteria (=0.3mg/dL increase in serum creatinine from pre-admission baseline). Modified Poisson regression models estimated the effect of AA race on risk of AKI, adjusting for age, sex, baseline eGFR, comorbidities (DM, HTN, coronary heart disease;CHD; CHF), geographic region and severity of illness during hospitalization. Additional models including albuminuria were run for those with available data.

Results: We identified 180,429 VA hospitalizations. Compared to C, AA had higher prevalence of DM (43.1% v. 41.1%, P<.001), lower prevalence of CHD (45.7% v. 58.8%, p<.001), lower Charlson comorbidity scores (1.4 v. 1.6, p<.001) and higher baseline eGFR (89.2 v. 81.7, p<.001). AKI occurred in 19.5% of admissions (35,134) involving 23.2% of AA and 18.5% of C. In adjusted models, AA race remained an independent risk factor for AKI (RR 1.26, 95% CI 1.24-1.28). In the subgroup with albuminuria data (40,668), the risk was slightly attenuated (RR 1.20, 95% CI 1.16-1.24). A similar increased risk of hospital-acquired AKI in AA compared to C (RR 1.01, 95% CI 1.03-1.98) was found.

Conclusions: Although AA Veterans had higher baseline eGFR and lower comorbidity scores compared to C, AA had an increased risk of developing AKI, even after accounting for differences in risk factors & geographic region. This increased risk for AKI in AA persisted when examining AKI that developed during hospitalization. Given that VA patients have similar healthcare access and benefits, our results suggest that the increased AKI risk seen in AA is unlikely to be fully accounted for by disparities in access to care.

Funding: Other NIH Support - Centers for Disease Control and Prevention, Veterans Administration Support
Nephrologists consultation and 30 days follow up included demographics and biochemical variables, time between AKI onset and Nephrology consultation, fluid balance, mortality scale, treatment and date of death or patient discharge.

Results: The overall mortality was 49%. Mean age 58 years. The principal diagnosis at admission was coronary syndrome. The AKI at the moment of consultation was 3 in the 64%.

FR-PO496
Cast Nephropathy versus Acute Tubular Necrosis in Newly Diagnosed Multiple Myeloma: A Comparative Study

Insara Jaffer Satheek,1 Samih H. Nasr,1 Nelson Leung,1,2 1Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Div of Anatomic Pathology, Mayo Clinic

Background: Myeloma cast nephropathy (MCN) and acute tubular necrosis (ATN) are recognized causes of acute kidney injury (AKI) in newly diagnosed multiple myeloma patients. However it is currently not known if there is a difference in outcomes between these two groups. We conducted a retrospective study to compare the clinical characteristics and renal response rates in patients presenting with acute kidney injury at the time of myeloma diagnosis.

Methods: We included all patients with AKI at the time of multiple myeloma diagnosis with biopsy-confirmed diagnosis of MCN or ATN between 1998 and 2013. Patients with chronic kidney disease (estimated GFR by MDRD equation<45ml/min/1.73m2) and relapsed multiple myeloma were excluded. We assessed survival and renal outcomes. Six month landmark survival analysis was done with Kaplan Meier estimates. Renal response was classified according to IKMG consensus criteria.

Results: Out of a total of 51 patients who were included in the study, 42 had MCN and 9 had ATN. Baseline characteristics were not significantly different between the groups except urine albumin percentage of >6% was predictive of ATN.

Conclusions: Our data suggests that AKI due to ATN at the time of myeloma diagnosis is more likely to recover compared to MCN with a faster time to response. However this does not seem to affect overall survival.

FR-PO497
Hospital Manifesting AKI Presents Worst Outcome Than Community Acquired AKI

Xose Luis Perez-Fernandez, Florencia E. Sileanu, Joan Sabater Riera, Kathleen D. Liu, John A. Kellum. 1Servei de Medicina Intensiva, Hospital Univ de Bellvitge, L’Hospiatol de Llobregat, Barcelona, Spain; 2Critical Care, Univ Pittsburgh Medical Center, Pittsburgh, PA; 3Nephrology & Critical Care, Univ California San Francisco Parnassus MC, San Francisco, CA.

Background: The objective of this study was to evaluate outcomes in critically ill patients with severe community-acquired AKI (CA-AKI) and hospital-manifesting AKI (HM-AKI). Secondary objectives were to identify characteristics that differ between patients with CA-AKI and HM-AKI to design future preventive strategies.

Methods: Observational retrospective study conducted at two tertiary care hospitals between 2000-2008 (UPMC, Pittsburgh, USA) and 2006-2012 (HUB Barcelona, Spain). Those with CA-AKI met criteria for KDIGO Stage 3 AKI at hospital admission whereas those with HM-AKI did not have AKI at hospital admission. HM-AKI subjects met KDIGO Stage 3 AKI criteria within 24 hours of ICU admission, with at least 72 hours elapsing between hospital admission and ICU admission. The relationship of type of AKI (CA-AKI, HM-AKI) with 90-day survival was analysed using Cox regression models controlling for differences between survivors and non-survivors.

Results: 354 patients met inclusion criteria. 92.5% of these patients required RRT at some point during ICU admission. 189 (35.4%) patients had AKI manifest while in-hospital, and these patients had a significantly higher 90-day mortality compared to 345 (64.6%) patients presenting with CA-AKI (68.3% vs 58.6%, p=0.03). Age, SOFA score, time from hospital admission to ICU, HM-AKI (compared to CA-AKI), and medical (vs surgical) admission, were all associated with lower 90 day survival. In the multivariate analysis, HM-AKI remained an independent risk factor for death compared to CA-AKI (HR 1.5; 95%CI (1.1 – 2.0).

Conclusions: AKI manifesting after hospital admission has significantly worse outcomes compared to AKI present at hospital admission even among patients progressing to stage 3 by ICU admission. Future interventions should be directed to prevent AKI in patients admitted to hospital, especially those who present with the risk factors identified in this study.

FR-PO498
Assessing Patient Awareness in Moderate to Severe Acute Kidney Injury

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Background: We aimed to evaluate awareness and knowledge of kidney disease in patients experiencing moderate to severe AKI, which is important for implementing targeted patient self-care risk-reduction strategies.

Methods: We surveyed 150 hospitalized patients in one academic medical center who experienced KDIGO Stage II or III AKI. We characterized patients’ awareness that AKI had occurred, and specific AKI knowledge and perceptions about kidney communication from their health providers. Laboratory data, disease severity, nephrology consultation, and need for dialysis were abstracted from the medical record.

FR-PO499
Hospital Manifesting AKI Presents Worst Outcome Than Community Acquired AKI

Xose Luis Perez-Fernandez, Florencia E. Sileanu, Joan Sabater Riera, Kathleen D. Liu, John A. Kellum. 1Servei de Medicina Intensiva, Hospital Univ de Bellvitge, L’Hospiatol de Llobregat, Barcelona, Spain; 2Critical Care, Univ Pittsburgh Medical Center, Pittsburgh, PA; 3Nephrology & Critical Care, Univ California San Francisco Parnassus MC, San Francisco, CA.

Background: The objective of this study was to evaluate outcomes in critically ill patients with severe community-acquired AKI (CA-AKI) and hospital-manifesting AKI (HM-AKI). Secondary objectives were to identify characteristics that differ between patients with CA-AKI and HM-AKI to design future preventive strategies.

Methods: Observational retrospective study conducted at two tertiary care hospitals between 2000-2008 (UPMC, Pittsburgh, USA) and 2006-2012 (HUB Barcelona, Spain). Those with CA-AKI met criteria for KDIGO Stage 3 AKI at hospital admission whereas those with HM-AKI did not have AKI at hospital admission. HM-AKI subjects met KDIGO Stage 3 AKI criteria within 24 hours of ICU admission, with at least 72 hours elapsing between hospital admission and ICU admission. The relationship of type of AKI (CA-AKI, HM-AKI) with 90-day survival was analysed using Cox regression models controlling for differences between survivors and non-survivors.

Results: 354 patients met inclusion criteria. 92.5% of these patients required RRT at some point during ICU admission. 189 (35.4%) patients had AKI manifest while in-hospital, and these patients had a significantly higher 90-day mortality compared to 345 (64.6%) patients presenting with CA-AKI (68.3% vs 58.6%, p=0.03). Age, SOFA score, time from hospital admission to ICU, HM-AKI (compared to CA-AKI), and medical (vs surgical) admission, were all associated with lower 90 day survival. In the multivariate analysis, HM-AKI remained an independent risk factor for death compared to CA-AKI (HR 1.5; 95%CI (1.1 – 2.0).

Conclusions: AKI manifesting after hospital admission has significantly worse outcomes compared to AKI present at hospital admission even among patients progressing to stage 3 by ICU admission. Future interventions should be directed to prevent AKI in patients admitted to hospital, especially those who present with the risk factors identified in this study.

Funding: Government Support - Non-U.S.
Acute Kidney Injury Correlates with Remote Organ Injury and Predicts Outcome in Primary Acute Liver Failure

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Background: In patients with acute liver failure (ALF), the occurrence of AKI predicts the combined endpoint of death or liver transplantation in a cohort of patients with primary ALF admitted to intensive care unit (ICU).

Methods: 130 patients with primary ALF of different entities (drug-induced, viral, indeterminate or others) were included. Patients without hepatic encephalopathy were excluded. According to the acute Kidney Injury Network (AKIN) definition AKI severity (stage 1, 2 or 3) was classified. The primary outcome studied was event-free 28-day survival (death or transplantation).

Results: 76 patients (58%) had normal renal function, while AKI II and III was present in 15 (12%) and 39 patients (30%) on ICU admission, respectively. Between different ALF entities, AKI prevalence and severity was similar (Chi-Square; p=0.28). AKI severity correlated closely with the extent of remote-organ damage as assessed by Simplified Acute Physiology Score (SAPS) (II: p=0.056, SAPS III: p=0.006) and Sequential Organ Failure Assessment (SOFA) score (r=0.57, p=0.0001), respectively. Kaplan-Meier analysis demonstrated that 37 of 39 ALF patients with AKIN III reached the composite endpoint of death or transplantation within 28 days (log-rank test: p=0.0001). Adjusted Cox’s proportional hazards analyses identified AKI on ICU admission as an independent predictor of the composite endpoint of death or transplantation [HR 3.1 (95% CI 1.9-4.9) for no AKI vs. AKIN III].

Conclusions: Our data indicate that AKI is a frequent complication in primary ALF. AKI correlates with several features of remote-organ damage and independently predicts outcome in this cohort.

Reduction of Nephrotoxic Medication Associated Acute Kidney Injury: Result from a Three Year Sustained Harm Reduction Program

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Background: Acute kidney injury (AKI) represents one of the most common co-morbidities in hospitalized children. Our previously reported nephrotoxic medication (NTMX) exposure and AKI screening project (Nephrotic Injury Negative by Just-in-time Action [NINJA]) showed a 25% NTM-AKI rate and a 42% reduction in AKI days/100 NTM-exposures in Year 1 of the program. This occurred due to rapid recognition of AKI and NTM-exposure reduction. We now report on the 3-year NINJA results to assess for sustained harm reduction.

Methods: A daily serum creatinine (Scr) was recommended for all children admitted to a non-intensive care unit who received >3 NTM-exposures in a 30-day period. Scr was measured at 48-hour intervals for >3 days (high NTM-exposures) to assess for AKI development. We tracked biweekly outcomes from Sep 2011 through Mar 2015: 1) High NTM-exposures per 1000 pt-days 2) AKI episodes per 1000 pt-days 3) AKI rates per exposure case (%) and 4) AKI days per 100 high NTM-exposures-days (inter- AKI was defined by Kidney Disease: Improving Global Outcomes criteria. We used statistical process control charts to assess for changes from baseline rates.

Results: 1,783 patients accounted for 2,358 separate admissions and 3,243 individual episodes of high NTM exposure. 170 patients (97.5%) had 2+ episodes. We observed two trends in high NTM-exposures and AKI rates. Overall, the high-NTM exposure rate decreased by 38% (11.23 to 6.99 admissions/1000 pt-days), and the AKI rate decreased by 64% (2.96 to 1.06 admissions with AKI/1000 pt-days). The NINJA project saved pts from 633 exposure and 398 AKI episodes (when compared to baseline rates). Medications/ medication classes or admitting services for exposed or non-exposed did not differ. Services served the 3 months preceding and following either time point improvement. AKI rates per exposure (23.3% to 14.5%) and AKI intensity (27.7 to 19.1 AKI days/100 exposure days) also decreased in Year 1; both improvements persisted for the entire period.

Conclusions: Implementation of systematic surveillance for NTM-AKI can lead to sustained reductions in avoidable harm.

FR-PO499

FR-PO501

Early and Late Auto Kidney Injury in Severely Burned Patients

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Background: Evaluation of factors influencing early and late acute kidney injury (AKI) in severely burned patients and assessment of the relationship between time of occurrence of AKI and mortality.

Methods: Retrospective analysis of severely burned patients with >30% total body surface area (TBSA), admitted to two centers for the treatment of burns. We selected and analyzed 239 severely burned patients. Renal function was evaluated at three points: admission, critical or middle point of hospitalization and the endpoint death or discharge from the center. AKI criteria: decrease in glomerular filtration rate (GFR) > 60 ml/min at admission, decrease in GFR > 75% compared to baseline, decrease in the daily diuresis < 500 ml.

Results: At admission 15.1% of the patients had GFR < 60 ml/min. AKI occurred in 38.5%. The occurrence of AKI was associated with: elderly age (p<0.001), female gender (p=0.017), overweight and obesity (p=0.055), extent and depth of burns, respiratory failure, low protein concentration (for all p<0.001), low blood pressure (p=0.014) and high white blood cells count (WBC) (p=0.010). Early AKI was detected in 28% Mortality. 100% with the initial GFR < 60 ml/min and early decrease in renal function, and 60% with the initial GFR < 60 ml/min and no worsening. Late AKI was observed in 10% of patients and mortality was 79.2%. Mortality rate in the group with AKI was 88.0% versus 24.5% without AKI.

Conclusions: The frequent occurrence of AKI, especially early, worsens the prognosis for survival. The assessment of renal function should be included in the prognostic scales for burned patients.

Acute Kidney Injury and Risk of Incident Heart Failure Among U.S. Veterans

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Background: Acute kidney injury (AKI) is common and associated with poor long-term outcomes. Heart failure (HF) is a leading cause of cardiovascular disease among patients with chronic kidney disease (CKD). The relationship between AKI and HF remains unknown and may identify a novel endpoint and site of pathology and cardiovascular disease.

Methods: We studied a national retrospective cohort of 111,488 U.S. Veterans hospitalized between 2003-2012 without history of HF. AKI was defined as a 0.3 mg/dl or 50% increase in serum creatinine using the difference between peak hospitalization and baseline creatinine (as determined by most recent outpatient creatinine over previous year) and staged according to Kidney Disease Improving Global Outcomes (KDIGO) criteria using change in serum creatinine. Incident HF was defined as >1 hospitalization or ≥2 visits with a diagnosis of HF, as determined from validated ICD9 codes, through 2012. Propensity score weights relevant endpoint and inpatient covariates were generated and patients with and without AKI were matched 1:1. Cox proportional hazards were used to determine the association of AKI with risk of incident HF, adjusting for baseline age, eGFR, coronary heart disease and hypertension. Patients who died or had an outcome after the end of the study were censored.

Results: There were 17,272 matched pairs with and without AKI in the study. Patients with and without AKI during the index hospitalization were well matched with median

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

Underline represents presenting author.
Acute Kidney Injury Increases Medical Costs Even in the Pre-AKI Stage

**Background:** Early detection of acute kidney injury (AKI) is important to prevent the progression of AKI and to improve clinical outcomes. However, the significance of mild increases in serum creatinine below AKI stage is not well established. In this study, we defined pre-AKI as the 25-50% increase of serum creatinine levels from the baseline levels. We aimed to investigate the influence of AKI stage including pre-AKI on clinical outcomes.

**Methods:** All clinical and laboratory data were retrieved from electronic medical record databases. We enrolled a total of 20819 patients who admitted Seoul National University Bundang Hospital from January 1, 2013 to December 31, 2013. We excluded patients who had not checked serum creatinine levels during admission or who were on dialysis due to end-stage renal disease.

**Results:** The proportion of patients who had AKI during admission were 21.6% (pre-AKI), 15.8% (AKI stage 1), 5.9% (AKI stage 2), and 3.2% (AKI stage 3). In-hospital mortality increased according to the stage of AKI [log-rank P < 0.001; HRs 1.878 (1.189-2.966) AKI stage 1; 6.039 (3.948-9.239) AKI stage 1; 12.064 (7.992-18.210) AKI stage 3].

**Conclusions:** Patients with pre-AKI showed a higher mortality compared with increased length of stay (no AKI 7.4 ± 9.0 days, pre-AKI 13.0 ± 13.3 days, P < 0.001) and increased medical costs (no AKI: 2806 ± 3286 USD, pre-AKI: 4701 ± 5476 USD, P < 0.001) during admission. Patients with Pre-AKI were more on surgical condition (51.1% vs 34.0%, P < 0.001) compared to patients without AKI.

**Impact of Fluid Overload on Acute Kidney Injury Diagnosis and Associated Outcomes in Critically Ill Patients: A Retrospective Cohort Study**

**Background:** Fluid overload (FO) changes the volume of distribution of creatinine, which is equivalent to total body water (TBW), this can alter the serum creatinine (sCr) concentrations. Higher TBW results in lower sCr leading to underestimation of AKI. Moreover, the rise of sCr is done by a formula (Adjusted-Cr=Cr/[1+(serum creatinine/TBW)])

**Methods:** We made a retrospective analysis of 120 records of pts from 2 centers. We calculated daily fluid balance and divided it by the body weight to obtain a percentage of FO. Pts were divided into 2 groups, A and B, with <2.5% and >5% of FO, respectively. Measured daily sCr was corrected using the TBW formula and presence of AKI was evaluated daily according to KDIGO guidelines. We compared the prevalence, day of diagnosis, and associated outcomes between the 2 groups.

**Results:** Mean age in the cohort was 54±4yrs, 56.3% were male. In group A 24 (34.8%) pts were diagnosed with AKI before adjustment and 25 (36.2%) after adjustment (p=0.167). In group B 21 (48.8%) and 25 (58.1%) were diagnosed with AKI before and after adjustment, respectively (p=0.023). Mean detection day of AKI without and with adjustment in group A was 3.22±2.4 and 2.84±2.1, respectively (p<0.001) and in group B 3.4±2.3 and 3.2±2.0 (p<0.001).

**Conclusions:** Correction of measured sCr for TBW in patients with >5% of FO is useful to diagnose more patients with AKI. Usage of the formula demonstrated usefulness for early diagnosis in patients with <2.5% and >5% of FO and we recommend its application in order to improve AKI prevention and treatment. FO of >5% is associated with increased mortality and worse outcomes in critically ill pts.
Results: Histologically, elevated PI GF was significantly associated with the severity of the arteriolar intimal damage and the intimal thickening of small renal arterioles. During a median follow-up of 2.7 years, 82 patients reached primary end-points which were defined as the requirement of renal replacement therapy (38 patients) and the decline of eGFR by more than 25% from baseline (44 patients). Although baseline eGFR was not statistically different among patients in all PI GF quartiles, the rate of eGFR decline in the patients with the highest PI GF quartile was significantly faster than those with other quartiles. After adjustment of known confounding factors, PI GF was significantly associated with the risk of deterioration of renal function with the adjusted hazard ratio of 1.75 [1.38-2.26] for each quartile increase. The combined use of eGFR and PI GF significantly improved the predictive accuracy for CKD progression compared with eGFR alone (c-statistics from 0.689 to 0.772, p<0.001).

Conclusions: Elevated PI GF is a novel and independent predictor of renal prognosis in patients with CKD.

FR-PO509

Steep Decline in Renal Function After a Hypertensive Disorder of Pregnancy: A Longitudinal Study Nora Praga,1 Anne Marinj van der Graaf,2 Rita Bozoglan,2 David P. van der Ham,2 Gerjan Navis,3 Ron T. Gannevoort,2 Henk Groen,3 Titiia Lely,1 1Obstetrics, UMC Utrecht, Netherlands; 2Nephrology, UMC Groningen, Netherlands; 3Obstetrics, Martini Hospital, Netherlands; 4Epidemiology, UMC Groningen, Netherlands.

Background: Hypertensive disorders of pregnancy (HDP) occur in 10% of pregnancies. Population based studies report increased risk for ESRD after HDP. Our aim was to longitudinally assess renal function over time after HDP. Women with severe hypertensive disorders of pregnancy (PE) have a 10.9% of the PIH and 19.2% of the PE group met the criteria for CKD.

Methods: Data from the PREVEND study, a population based prospective cohort with median follow-up of 11 years, were used to identify women without and with self-reported HDP (non-HDP, n=1805 and HDP, n=977). A case cohort, 10 years post-partum was created by record linkage, with subgroups: normal pregnancy (control, n=202), pregnancy-induced hypertension (PIH, n=56) and preeclampsia (PE, n=29). Renal function and the prevalence of CKD were compared.

Results: eGFR was lower at baseline and during follow-up in HDP vs non-HDP (A). In addition, the decline in eGFR was steeper in HDP vs non-HDP (B). At baseline and during follow-up there was a trend anti-hypertensive-drug use, including ACEi in the HDP group. 24-h albuminuria at baseline was higher in HDP vs non-HDP and remained steadily higher in HDP during follow-up. A trend towards increased risk of CKD was observed in HDP, HR 1.13 (0.92-1.38). In the case cohort, eGFR was significantly lower (C) and 24-h albuminuria significantly higher (p<0.03) in the PE vs controls. 7.8% of the controls, 10.5% of the PIH and 19.2% of the PE group met the criteria for CKD.

Conclusions: We report a lower renal function and a steeper renal function decline over time after HDP. Women with severe hypertensive disorders of pregnancy (PE) have the highest risk for renal function loss.

FR-PO509

Pregnancy Outcomes in Women with Chronic Kidney Disease in South Australia Shilpa Jesudason,1,2 Alyssa Kate Fitzpatrick,4 Britt Melinda Catcheside,3 Wendy Katharine Schell,2 Stephen P. McDonald,1,3 1Central and Northern Adelaide Renal and Transplantation Services, Adelaide, Australia; 2South Australian Pregnancy Outcomes Unit, Adelaide, Australia; 3School of Medicine, Univ of Adelaide, Adelaide, Australia; 4Univ of Oxford, Oxford, United Kingdom. 

Background: Chronic kidney disease (CKD) affects an estimated 3% of women in their childbearing years. CKD in pregnancy is associated with adverse maternal and neonatal outcomes. This study represents the first attempt to capture the distribution of CKD among pregnant women in the Australian population.

Methods: Data was obtained from the South Australian Pregnancy Outcomes Unit Supplementary Birth Record for singleton pregnancies from 1990-2012. Women with CKD were identified by renal ICD-9 codes for immunological renal conditions, cystic/ genetic renal disease, vesicoureteral reflux, hypertensive CKD, urolological conditions, pyelonephritis, and unspecified renal disease. Uncomplicated urinary tract infections were excluded. Data was obtained on maternal demographics, obstetric care and infant outcomes. Chi-squared or Fisher’s exact tests were used to examine the crude association between renal disease and adverse outcomes.

Results: 1392 births to women with renal disease codes were identified from 407,580 recorded births. Women with renal disease were significantly more likely to be Aboriginal (5.2% vs 2.6%, p<0.001), to have the lowest socioeconomic status (31.4% vs 26.2%, p<0.001) and to smoke (24.1% vs 18.4%, p<0.001). Higher unadjusted risks of adverse outcomes were noted in the renal group, including gestational hypertension (10.6% vs 5.0%, p<0.001) and emergency caesarean section (20.0% vs 15.0%, p<0.001). Women with renal disease were more likely to have a preterm birth <34 weeks (6.7% vs 2.1%, p<0.001), or a late preterm birth 34-36 weeks (10.8% vs 4.5%, p<0.001). They were also more likely to be diagnosed with intrapartum growth restriction (11.2% vs 9.5%, p<0.03) and to deliver a low birth weight baby <2500g (13.4% vs 5.5%, p<0.001).

Conclusions: Indigenous Australian women and women with low socioeconomic status are disproportionately burdened by CKD in pregnancy. The data showed increased adverse maternal and neonatal outcomes among women with CKD.
Conclusions: Under NS state, MN+DM patients existed more serious prothrombotic state compared with MN+DKD. The mechanism is related to more MN+DKD. In addition to disorders of endothelial function, coagulation function, as well as fibronectin function. More attention should be paid to treatment of prothrombotic state in MN+DM patients.

Funding: Government Support - Non-U.S.

FR-PO512
Serum C3 and Renal Outcome in Patients with Primary Focal Segmental Glomerulosclerosis
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Background: The role of complement in the pathogenesis or progression of FSGS is uncertain. The aim of this observational cohort study was to identify the clinical implications of serum C3 levels and to investigate their utility as predictor of renal outcomes in patients with FSGS.

Methods: 591 biopsy-proven primary FSGS patients were recruited. Clinical, histological and progression data were recorded. Decreased serum C3 level was defined as C3<85 mg/dl. The study endpoint was end-stage renal disease (ESRD).

Results: Of the patients, there were 117 patients (21.5%) with low serum C3. At the time-point of renal biopsy, compared to patients with C3 ≧85 mg/dl, those with C3 <85 mg/dl had higher level of serum creatinine, lower levels of eGFR, proteinuria, hemoglobin, triglyceride, cholesterol, IgA, more severe segmental sclerosis, tubular atrophy and interstitial fibrosis. Multivariate linear regression analysis showed low C3 level was an independent risk factor for eGFR (HR=42.56, 95%CI 11.21-73.91, p<0.01) after adjusted by sex, age and clinical indicators. The follow-up was assessed in 221 patients. During a mean follow-up of 53.3 months, ESRD occurred in 32 patients (37.2%) with low serum C3 compared with 22 patients (16.3%) with normal C3 levels (P<0.001). Serum C3 level had a significant predictive value for renal outcome (AUC = 0.650, P = 0.001). The risk of reaching ESRD was significantly higher in patients with low serum C3 level (HR 4.044; 95% CI: 2.238 to 7.309; P < 0.0001).

Conclusions: Complement activation may occur in patients with FSGS. It is associated with clinical and histological severities. Low serum C3 is an independent risk factor for the decline of eGFR, and is associated with poor renal outcome in patients with FSGS.

Funding: NIDDK Support

FR-PO513
Role of Proteolytic Fragment suPAR D2-D3 in Prediction and Cause of FSGS
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Background: Primary FSGS is a kidney disorder that leads to end stage renal disease and affects tens of thousands of people annually. Several studies suggest the soluble uromodulin-type plasminogen activating receptor (suPAR) to be a predisposing circulating factor and prognostic marker of FSGS through its interaction with avb3 integrin.

Methods: We collected serum samples from kidney transplant recipients with FSGS. We also analyzed sera from healthy controls and patients with sepsis and on peritoneal dialysis. These sera were used to assess integrin activation in podocytes. Western blot utilized a antibody to full length and D2-D3 fragment of suPAR. Transgenic mice were created to drive mouse suPAR D1-D2-D3 and suPAR D2-D3 expression from adipocytes. Transgenic mice were utilized to identify full length and D2-D3 fragment of suPAR. Transgenic mice were used to assess integrin activation in podocytes. Western blot utilized an antibody to full length and D2-D3 fragment of suPAR. Injections of the D2-D3, but not full-length suPAR, induced facilitated podocyte motility. Injections of the D2-D3, but not full-length suPAR, induced transient proteinuria in mice. Transgenic mice for D2-D3 developed rising serum suPAR levels and a variable degree of proteinuria. A composite risk analysis score was developed that included presence of the D2-D3 in patient serum, podocyte integrin activation capacity, and total suPAR serum level for the prediction of recurrent FSGS.

Conclusions: suPAR D2-D3 fragment is a prognostic marker and risk factor for recurrent FSGS.

Funding: NIDDK Support

FR-PO514
Prognosis, Survival and Renal Function in Patients with Lupus Nephritis
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Background: Lupus nephritis is the most common glomerulonephritis in the Colombian Caribbean region, despite there is less published information about its evolution and clinico-pathological aspects. Objective: To evaluate prognosis, survival and renal function of patients with LN residing in the Colombian Caribbean region controlled between 2000-2014.

Methods: 229 patient study with LN corroborated by histology according to the International Society of Nephrology Classification Renal Pathology Society (ISN/ RPS) 2003) treated with induction and maintenance therapy and with a systemized following of at least 2 years. The pharmaceutical treatments included prednisolone, azathioprine, and Cyclophosphamide mycophenolate mofetil in isolation or combined and the clinical laboratory and histopathology variables were correlated as predictive value of therapeutic response. To achieve this as methodology a non-parametric descriptive statistics ANOVA (k-w) was used and canonical correspondence analysis.

Results: 229 patients in total of 34±12 of age, which 88% women, whose evolution were controlled during 24±6 months. The most common form of clinical presentation was nephrotic syndrome and asymptomatic hematuria-proteinuria (68.07%) the type III and V were the most common in patients under 25 years of age and a negative response to treatment. The estimated glomerular filtration rate measured by MDRD showed a significant improvement at 24 weeks with regard the baseline figure of 74.36.

Conclusions: The early detection and reference of NL patients allows an early approach and therapy. Which will prevent chronic kidney disease.

FR-PO515
Association of ABO Blood Group with Progression of IgA Nephropathy
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Background: ABO blood group antigens are major histocompatibility antigens and little is known about its association with progression of IgA nephropathy (IgAN).

Methods: Biopsy-proven primary IgAN patients were retrospectively recruited. Clinical, histological and progression data were recorded. Patients with eGFR=15mL/min/1.73m² at time of biopsy were excluded. Renal tissue was semi-quantitative scoredaccording to the Oxford scoring system. ABO blood group was determined by standard erythrocyte antigen agglutination method. All patients were divided into B antigen group (type B and AB) and non-B antigen group (type A and O) based on their ABO types.

Results: Among the 752 IgAN patients recruited in this study, 210 patients were type A (27.9%), 221 were type B (29.4%), 72 were type AB (9.6%) and 249 were type O (33.1%). When renal biopsy was performed, patients in B antigen group had higher eGFR (82.44 vs. 65.68 mL/min), lower systolic blood pressure (125.36 vs. 129.29 mmHg) and uric acid (373.59 vs. 393.93 mmol/L) than patients in non-B antigen group. No significant differences were detected between the two groups in terms of clinical and histological lesions and these two groups. Totally, 100 patients progressed to end-stage renal disease (ESRD) after a median follow-up period of 51.05 months, including 32 (15.2%) type A, 18 (8.1%) type B, 2 (2.8%) type AB and 48 (19.3%) type O patients. Kaplan-Meier analysis showed that median ESRD-free survival time of patients in B antigen group was significantly longer than patients in non-B antigen group [148.2±5.5 months vs. 138.8 ±7.5 months, p<0.001]. Furthermore, patients in B antigen group were associated with a decreased risk of ESRD (HR=0.56, 95%CI 0.33-0.94) after adjusted by age, sex and clinical variables including eGFR, sbp, serum albumin, urine protein and hemoglobin by Cox proportional hazards model.

Conclusions: Our data suggested that B antigen had an independent protective effect against the progression of IgAN.

FR-PO516
The Analysis of the Long-Term Outcomes of Patients with Primary IgA Nephropathy
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Background: Primary IgA nephropathy (IgAN) is one of the most common glomerular diseases in China. In this study we try to investigate the clinical characteristics and the relationship between CKD stages, the outcome and the corticosteroids use of CKD patients with primary IgA nephropathy through the retrospective analysis of their clinical data.

Methods: Patients with biopsy-proved primary IgAN from 2002 to 2013 were included in the retrospective analysis. They were older than 18 years old and their follow-up time was ranged from 2 to 12 months. We collected their medical history, laboratory test reports and other clinical data. Then we enrolled 297 patients who were followed up for 5 years for further research. Kaplan-Meier method was used to calculate the renal survival rate of the patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: A total of 1052 cases were included. There is an equal proportion of male and female (50.4% vs 49.6%). The mean age was 36.86±11.58 years old. Five-year renal survival rate of these cases was 92%, and ten-year renal survival rate was 88%. We enrolled 297 cases who were followed up for 5 years. These patients were divided into rapid progression and stable progression, we found that cases in rapid progression group had more proteinuria, higher blood pressure, poorer renal function, lower serum albumin and lower hemoglobin, compared with other groups. When cases were divided according to CKD stages, the results showed no significant difference of outcomes among patients in CKD1-3a stage (P > 0.05). Their five-year renal survival rate was more than 95%. But patients in CKD3b-4 stage had worse outcomes. The five-year renal survival rate of patients in CKD3b stage was 85.3%, while it is only 63.5% for patients in CKD4 stage.

Conclusions: Five-year and ten-year renal survival rate of patients with IGAN was 92% and 88%, respectively. Patients in CKD3b or CKD4 stage at biopsy may have a lower renal survival rate and a worse outcome. At the time of renal biopsy, patients with impaired renal function, mass proteinuria, hypertension, anemia and low serum albumin may have a greater risk of progressing to end-stage renal disease.

FR-PO517
Variability of GFR Decline in Alport Syndrome: Insights from a Provincial Database

Background: Alport syndrome (AS) is one of the inherited causes of CKD due to mutations in the collagen genes making up the glomerular basement membrane collagen. Design of clinical trials for intervention in AS proves challenging without a clear understanding of renal progression over time as observational data is lacking due to small sample size. We present here the utilization of population based data in a simulation to mimic clinical trial recruitment and endpoints to provide insights in trial designs for AS.

Methods: AS patients were identified within a provincial CKD clinical database (PROMIS) in British Columbia, Canada for this observational simulation study. Patients were excluded if they have fewer than 4 eGFR-MDRD measurements or as a study entry point to generate 100 random samples. Primary outcome was annual rate of change in eGFR over 2 years categorized into: > -5 mL/min per year (progressor), -5 and 2 mL/min per year (stabilizer) and ≤ -2 mL/min per year (regressor).

Results: 75% of the participants were female, with a mean age of 56 years (range 15-93). The mean eGFR was 50.3 ± 26.1 mL/min. Over 2 years, 77% of cases (95% CI: 72.7%–81.8%) progressed, and 22.7% (95% CI: 9.1%–36.4%) remained in stable state. Of those that ‘enrolled’ at eGFR 45-60 mL/min, 72.7% (95% CI: 64.9%–78.9%) had disease progression, and 20% (95% CI: 20%–20%) had an improvement in eGFR.

Conclusions: Heterogeneity and non-linearity of AS renal progression ought to be taken into account when designing trials of interventions aimed at improving renal outcomes. Funding: Pharmaceutical Company Support - Regulus Therapeutics

FR-PO518
Discovery of Urine MicroRNA Biomarkers in a Pre-Clinical Model of Alport Nephropathy

Background: For those recruited at eGFR 30-45 mL/min, 41.7% (95% CI: 35.2%–48.2%) had disease progression and 50% (95% CI: 45.3%–54.8%) remained stable state. Of those enrolled at eGFR 15-30 mL/min, 50% (95% CI: 41.7%–58.3%) were in stable state, 30.0% (95% CI: 20.0%–30.0%) had disease progression, and 20% (95% CI: 20.0%–20.0%) had an improvement in eGFR. For those recruited at eGFR 45-60 mL/min, 77.2% (95% CI: 63.6%–81.8%) progressed, and 22.7% (95% CI: 9.1%–36.4%) remained in stable state.

Methods: We have developed a high-throughput, multiplex miR profiling platform with the ability to profile tissue and bio-fluids. We discovered several urine microRNAs with highly significant differential expression in the Col4a3-/- mouse model when compared to wild type mice. Our data suggest that urine is a favorable bio-fluid for the development of non-invasive microRNA based tests.

Results: A total of 1528 patients were enrolled in KNOW-CKD cohort study (NCT 01630486) from Apr 2011 to Dec 2013. Among them, 153 patients were excluded (73 unclassified subgroups, 71 without urinary AGT measurement, 9 without available eGFR) and a total of 1375 (519 GN, 310 DN, 292 HTN, 254 ADPKD) patients were included in the final analysis. The mean age was 51 years and baseline serum creatinine was 1.9 ± 1.2 mg/dL. The GN and ADPKD subgroups showed younger age and earlier elevation of renal survival rate and a worse outcome. At the time of renal biopsy, patients with impaired renal function, mass proteinuria, hypertension, anemia and low serum albumin may have a greater risk of progressing to end-stage renal disease.
of urinary AGT/Cr levels according to CKD stages. When we performed the risk factor analysis separately in GN and ADPKD subgroups, the highest quartile of urinary AGT/Cr was associated with GN subcohort, female gender, hypertension, decreased eGFR, decreased plasma Hb, and higher degree of albuminuria. However, in multivariate logistic regression analysis, ADPKD subcohort demonstrated higher urinary AGT/Cr compared to GN subcohort after adjusting other co-factors.

**Conclusions:** Urinary AGT/Cr is greatly increased in ADPKD independent of albuminuria and renal function.

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

**FR-PO521**

**Using Biomarkers to Predict Progression to End-Stage Renal Disease within 6 Months of Liver Transplant**

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**Background:** Liver transplant (LT) recipients are at increased risk for CKD and progression to ESRD. Creatinine, the standard for assessing renal function, provides limited prognostic information for recovery from AKI. Our aim is to create a predictive model for progression to ESRD within 6mos of LT incorporating clinical data and biomarkers.

**Methods:** We enrolled 202 patients, of whom 138 have 6mos follow up. 13 patients progressed to ESRD, defined as GFR<20 ml/min, dialysis, or transplant evaluation. Logistic regression models evaluated neutrophil gelatinase-associated lipocalin, IL-18, Cystatin-C, albuminuria and renal function.

**Results:** In one model, MELD score at LT, pre-LT AKI, pre-LT renal replacement therapy, and highest creatinine 3mos pre-LT were associated with ESRD at 6mos (p<.05). In another model with biomarkers, only urinary IL-18 was included for its association with therapy, & highest creatinine 3mos pre-LT were associated with ESRD at 6mos (p<.05). Kidney Injury Molecule-1, & liver fatty acid binding protein for inclusion. Receiver regression models evaluated neutrophil gelatinase-associated lipocalin, IL-18, Cystatin-C, progression to ESRD, defined as GFR<20 ml/min, dialysis, or transplant evaluation. Logistic for progression to ESRD within 6mos of LT incorporating clinical data and biomarkers. Our aim is to create a predictive model for progression to ESRD. Creatinine, the standard for assessing renal function, provides limited prognostic information for recovery from AKI. Our aim is to create a predictive model for progression to ESRD within 6mos of LT incorporating clinical data and biomarkers.

**Conclusions:** MIG and IP-10 can be detected in urine as inflammatory biomarker to assess risk of transplant rejection. ViveST can be used as ambient storage and transport device eliminating need for cold chain storage. Additional studies warranted assessing detection of biomarkers at therapeutically relevant concentrations.

**Funding:** Pharmaceutical Company Support - Vivebio LLC

**FR-PO523**

**Albuminuria-Induced Apoptosis in Children with Nephrotic Syndrome Is A Result of the Dysbalance in Apoptosis Controlling System**

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**Background:** Albuminuria promotes cell death, and is associated with faster progression of chronic kidney disease (CKD). However, the molecular mechanisms regulating cell death in response to albuminuria are not fully understood.

**Methods:** 53 patients aged 10-15 years with active stage of nephrotic syndrome were included in the study. Immunohistochemical study of anti-apoptotic factor Bax, anti-apoptotic factor Bcl-xl, number of apoptotic cells in kidney biopsy specimens were done. Comparison of the level of these parameters between the different segments of nephrin at different stages of glomerulosclerosis has been performed.

**Results:** Measurement of the pro-apoptotic factor Bax in kidney slices obtained from children with morphological form of nephrotic syndrome focal segmental glomerulosclerosis (FGS) showed presence of high level of Bax in both glomerular and tubule-interstitial segments. Higher immunosignal of Bax was evaluated in glomeruli with FGS I-II st. as compared to tubular segment. When FSGS III-IV st. observed higher expression of Bax was detected in surrounding tubule-interstitial segment. Expression of the anti-apoptotic factor Bcl-xL was studied. Higher expression of Bcl-xL was recorded in tubule-interstitial segment as compared to glomeruli when FSGS I-II st. occurs. When FSGS III-IV st. occurred higher immunosignal of Bcl-xL is localized in surrounding tubule-interstitial component. In kidney sections with FSGS III-IV st. higher AI was revealed in glomeruli as compared to tubule-interstitial component. In kidney sections with FSGS III-IV st. higher AI was found in tubule-interstitial compartment.

**Conclusions:** Thus, progression of kidney injuries in nephrotic syndrome is associated with increased activity of pro-apoptotic factor Bax and simultaneous reduction of anti-apoptotic factor Bcl-xL. The level of the expression of Bax and Bcl-xL depends on the stage of FSGS and indicates the step-dependent manner of glomerular and interstitial injuries development upon the chronic influence of albuminuria.

**Funding:** Government Support - Non-U.S.
severe impairment (eGFR<60) more likely to be on ABC. Several CVD risk factors were more prevalent in ABC patients compared to TDF, hypertension (25% v 13%), dyslipidemia (30% v 16%), and diabetes (12% v 5%) (p<0.001 in all) being the most common.

Conclusions: HIV patients often present with prevalent CVD risk and reduction in kidney function. Physicians make treatment choices that reflect concern for kidney function, consistent with labeling. This choice may come with cost, with more CVD risk factors correlated with alternative choices of NRTIs. As some antiviral regimens may be associated with CVD while others with kidney disease, understanding CVD risk profile versus kidney function protection may help optimize care of patients.

Livewire tool provides the best compromise between accuracy and time required.

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Funding: Private Foundation Support

FR-PO526
Renal Reserve: Development of a Kidney Stress Test Kyle Rodenbach,1 Dana F. Fuhrman,2 Paula S. Maier,2 Catherine D. Shaw,1 George J. Schwartz.1 (1Peds, Univ of Rochester, Rochester, NY; 2Peds, Univ of Pittsburgh, Pittsburgh, PA)

Background: Renal reserve (RR) is the difference in stimulated versus baseline glomerular filtration rate (GFR); it might predict future kidney health. The purpose of this study was to compare a meat versus liquid protein load in a cystatin-C-based (Cys-C) RR test using cinetidine-inhibited creatinine clearance (Cr CI) and iohexol infusion clearance (Io CI) for validation.

Methods: Participants (N=18) were screened for health status, blood pressure, and proteinuria. They followed a low protein diet and took cinetidine (20 mg/kg) for two days prior to the study. Water loading was used to maintain urine flow, and two hours were allowed for a stable steady state calibration. Participants 1-10 received a burger (1 g/kg protein); 11-15 received a ProCel® shake (1 g/kg protein); and 16-18 received a high dose ProCel® shake (1.5 g/kg protein). Data were analyzed for significance of RR. Cystatin-C estimated GFR (Cys-C eGFR) was calculated using the CKD-EPI Cys-C formula (Inker NEJM 2012) following IFC calibration (ERM-DA471).

Results: Participants (N=18) had a mean (SD) age of 22 (2) years and were 39% male and 72% white. Baseline GFR (SD) in mL/min/1.73m2 averaged 103.4 (14.7) for Cr CI; 108.9 (9.0) for Io CI (N=8); and 117.4 (6.1) for Cys-C eGFR. For the burger group (N=10), mean RR (SD) in mL/min/1.73m2 was 17.1 (11.6) for Cr CI (P<0.001); 8.4 (4.3) for Io CI (P<0.001); and 4.7 (2.4) for Cys-C eGFR (P<0.001). For 1.0-1.5 g/kg shakes (N=8), mean RR (SD) in mL/min/1.73m2 was 15.8 (5.0) for Cr CI (P=0.001); 11.7 (9.0) for Io CI (P=0.008), and 2.4 (2.9) for Cys-C eGFR (P=0.05). The burger and shake groups did not differ significantly in RR determined by Cr CI, Io CI, or Cys-C but Cys/C-based RR was significantly less than Io-based RR for both groups. There were no differences in post-load versus pre-load Cr/Io clearance ratios.

Conclusions: Cys-C-based RR following a burger provides a simple stress test of kidney function which was validated by classical renal clearances and can be applied to those who recover from acute kidney injury. Why Cys-C-based RR was smaller than Io RR, the reference standard, is a topic for future investigation.

Funding: Other NIH Support - CTSI, University of Rochester, Private Foundation Support

FR-PO527

Background: Despite the clinical recovery of an acute kidney injury (AKI) episode, progression to chronic kidney disease (CKD) could be observed on long time follow-up. The mechanisms are poorly understood. To analyzed if angiotensin II receptor blockade (ARB) the ischemic insult is effective in abrogating the severity of the AKI episode and/or the progression to CKD.

Methods: Male Wistar rats were divided into 4-groups of rats: sham; sham plus losartan 3-d before surgery; bilateral renal ischemia for 45-min (UTxI); and losartan administration (3-d) before ischemia (Los-Pre). Animals were studied after 1, 3, 5, 15 days or 9-months. At the end of each experimental period, physiological, histopathological, immunohistochemistry, biochemical and molecular studies were performed.

Results: UTxI group developed CKD characterized by renal dysfunction, proteinuria, renal hypertrophy, glomerulosclerosis, tubular atrophy and tubulointerstitial fibrosis. At the ultra-structural glomerular level, foot process effacement was observed, which was associated a reduction in immune-gold staining for nephrin. Renal injury was mediated by increased oxidative stress, inflammation and up-regulation of TGFβ, aSMA, and Collagen I protein levels. TGFβ overexpression was mainly observed in epithelial cells. Interestingly, in spite of ARB did not prevent or reduced AKI severity; it was enough effective to prevent CKD. The renoprotection conferred by ARB was associated with the early recovery of renal blood flow, lesser inflammation and greater nuclear hypoxic inducible factor 1α (HIF1α) staining.

Conclusions: Our data shows that in spite of, losartan pre-treatment did not protect the rats against AKI, it was effective to prevent the transition to CKD. The mechanisms by which losartan prevented CKD were in part due to the early renal blood flow recovery, lesser inflammation and greater HIF1α nuclear translocation within the 15 days post-ischemia.

Funding: Government Support - Non-U.S.
Specific Endothelial Heparin-Binding EGF-Like Growth Factor Deletion Ameliorates Renal Injury Induced by Chronic Angiotensin II Infusion

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Background: Transactivation of EGFFR by angiotensin II (Ang II) plays important roles in the initiation and progression of chronic kidney diseases (CKD). In vitro studies suggested that HB-EGF may be a critical mediator in this process, whereas its role in vivo has not been reported.

Methods: Age-matched male littermates of HB-EGF+/+/mice with endothelial-SCLCre-ER(T) (+) or (-) were used. Tamoxifen injections produced control (HB-EGF+/+) mice with specific deletion of HB-EGF from endothelium (HB-EGF-/-), which underwent untreated nephropathy and osmotic minipump-mediated infusion with saline or Ang II for 8 weeks. Systolic blood pressures (SBP) were measured by tail-cuff. Renal injury was evaluated by albuminuria using urinary albumin/creatinine ratios and by morphology with periodic acid-Schiff (PAS) staining. Renal EGF activation was determined by immunoblotting and immunostaining. Endothelium/podocyte injury, inflammation and renal fibrosis were evaluated by immunostaining.

Results: Compared to control, kidneys from HB-EGF-/- mice with Ang II-infusion had significantly reduced EGF activation. Endothelial HB-EGF deletion did not significantly prevent the hypertension induced by Ang II infusion, albeit lower SBP was detected in HB-EGF-/- mice compared to HB-EGF+/+ mice. However, it decreased Ang II-infusion related renal injury, as demonstrated by 1) less albuminuria; 2) less glomerulosclerosis with glomerular score of 0.793 versus 1.652 in the control; 3) preserved endothelial integrity and decreased podocyte injury shown by more preserved tufts area and WT1 positive cells, and less apoptotic cells measured by cleaved caspase 3 and TUNEL staining; 4) reduced inflammation in perivascular area and interstitium measured by F4/80 and CD3 immunostaining; and 3), reduced renal fibrosis, as shown by α-SMA immunostaining.

Conclusions: Shedding of HB-EGF from endothelium plays an important role in Ang II induced renal injury by linking Ang II-AT1R with EGFFR transactivation. Inhibition of HB-EGF shedding could be a potential therapeutic strategy for CKD.

Funding: NIDDK Support, Veterans Administration Support

FR-PO529 Effects of Acute Kidney Injury (AKI) Severity and Co-Morbidities on Chronic Kidney Disease (CKD) Progression

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Background: AKI is a common and important cause of CKD. It remains unknown how AKI severity influences CKD progression. Which co-morbidities influence the progression of CKD also remains undetermined.

Methods: We aimed to explore whether AKI severity and patient comorbidities influence CKD progression. Patients with CKD associated with a clinical diagnosis of AKI were identified in the Royal Brisbane & Women’s Hospital cohort (n=1150) of the CKD.QLD registry. AKI events were confirmed through historical creatinine values (2005 onward), and severity determined using AKIN criteria. CKD progression was assessed by change in glomerular filtration rate per year (DeGFyr/yr) based on initial and final eGFR(CKD-EPI) values. All co-morbidities identified at the time of enrolment into the registry were explored.

Results: 384 patients were recorded as having a primary or secondary AKI diagnosis. 157 patients (40.8%) of these patients were biologically confirmed. 133 patients (84.7%) were identified as Stage 1 AKI, 16 (10.2%) as Stage 2 and 8 (5.1%) as Stage 3. A one-way ANOVA revealed that AKI severity did not modulate CKD progression. However, numerically DeGFyr/yr was larger for Stage 3 patients (5.1±m/1.72m2), and smallest for Stage 1 patients (1.6±m/1.72m2). The only two co-morbidities found to influence CKD progression were diabetes mellitus (DM; 35.6% of patients) and peripheral vascular disease (PVD; 12.1% of patients). CKD progression was significantly increased in patients with DM compared with patients without (DeGFyr/yr 3.7±m/1.72m2, p<0.001), and patients with PVD compared with those without (DeGFyr/yr 4.4±m/1.72m2, p<0.05).

Conclusions: Surprisingly, AKI severity did not alter CKD progression. Both DM and PVD influenced CKD progression in patients with AKI suggesting an increased vulnerability to AKI in these patients.

FR-PO530 Association Between Gut Microbiome and Cardiovascular Risk in Chronic Kidney Disease Patients with Type 2 Diabetes Mellitus

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Background: Diabetes is one of the leading causes of CKD. It is well established that patients with T2DM often experience persistent low-grade inflammation leading to microvascular deterioration and progression of vascular complications along with impaired glomerular function, which impacts their microphones. The aim of this study was the assessment of gut microbiota, plasma zonulin, and inflammatory cytokines (TNF-α, IL-6) in conjunction with FGF-23, ET and levels of LPS in CKD (stage 4 and 5) patients with Diabetic Nephropathy (DN).

Methods: Healthy controls were matched by age and gender. Their dietary habits have been preserved. Total of 40 participants participated. IL-6, FGF-23, LPS, ET-1 and zonulin, levels were measured by ELISA and quantitative analysis of gut microbiota composition (454 pyro sequencing).

Results: Higher circulation serum zonulin, TNF-α, and IL-6, FGF 23 LPS, ET-1 levels were observed in the CKD (stage >3) patients with AKI. Patients with advanced AKI was substantially different from healthy population with increased percentage of LPS producing bacteria. Significant diversity was observed in gut microbiota in study subjects compared to control group. CKD patients had high serum concentration of TNF-α and marker of leaky gut. Zonulin concentration was found positively correlated with LPS, inflammatory markers and FGF-23.

Conclusions: Gut microbiota is a modifiable factor and zonulin could be a potential future target to control chronic inflammatory responses. Gut microbiota and increased gut permeability in patients with advanced CKD secondary to DN results in high level of lipopolysaccharide LPS that mediates chronic inflammation which was implicated in deterioration of cardiovascular health.

FR-PO531 Metabolomics of Chronic Kidney Disease in Cohort of Patients Given Probiotics

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Background: Persistent reduction in Glomerular Filtration Rate (GFR) below 60 ml/ min/1.73 m2 over 3 months are hall marks of Chronic Kidney Disease (CKD). Urea is so stable that it major uremic toxin and is clinically despite the description of middle molecules as being toxic. Persistent elevation of BUN may accompany reductions in GFR in some patients. We were specifically interested in obtaining pilot data identifying metabolites that differentiated patients with CKD whose BUN decreased after 4 months of probiotics treatment from its possible mechanism.

Methods: Broad spectrum 1H-NMR metabolomics was used to analyze baseline and 6 month plasma samples frozen from a phenotypically characterized cohort of patients with CKD Stage 3 and below from a prior Probiotic Renady study. NMR spectral data of baseline and 6 month plasma samples were analyzed after identical treatment of all samples. A total of 24 baseline samples were differentiated by a change in their BUN. Principal components analysis and orthogonal partial least squares discriminant analysis was used to analyze the data and determine the metabolites that best differentiated the phenotypic groups.

Results: Characteristics of the cohort population were age 57 ± 14 yrs, mean BMI 31.3 ± 6.1 kg/m2, 10 males and 14 females, 20 with HTN, 8 with DM, 11 Caucasian and 9 AA, 3 other, 1 unknown. 16 patients who had a decrease in BUN after 4 months of probiotics treatment could be differentiated based on baseline samples from those whose BUN increased or did not change. The majority of the metabolites that differentiated the groups were microbiome related metabolites.

Conclusions: Metabolomics analysis revealed a signature of metabolites that were associated with a decrease in BUN, and holds promise for use in predicting individuals with CKD that would most benefit from use of probiotics. The majority of the metabolites important to the differentiation of groups map to pathways involved in microbial metabolism.

Funding: Other NHI Support - NHI Common Fund for Metabolomics at RTI North Carolina: U12DK987193

FR-PO532 Potential Uremic Toxin Precursors in the Gut Identified by Metabolomics and Proteomics

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Background: Many factors, e.g., the intestinal bacterial disorder, result in the species and amounts of harmful substances in the gut increasing, which leads to the increase of uremic retention molecules (URMs) in blood. These URMs may be classified according to their site of origin, that is, endogenous metabolism, microbial metabolism, or exogenous intake. The latter two are known as gut-derived uremic toxins, i.e., gut is a significant origin of middle molecules as being toxic. Persistent elevation of BUN may accompany reductions in GFR in some patients. We were specifically interested in obtaining pilot data identifying metabolites that differentiated patients with CKD whose BUN decreased after 4 months of probiotics treatment from its possible mechanism.

Methods: Excluding special factors which affected the intestinal environment, the subjects were divided into two groups: hemodialysis patients with end-stage renal disease (HD group, n = 20) and healthy controls (CT group, n = 20). Fecal metabolomics based on the ultra-performance liquid chromatography-tandem mass spectrometry was undertaken to identify the low molecular weight metabolites, and fecal proteomics based on the two-dimensional gel electrophoresis was employed to investigate the high molecular weight proteins. The data was analyzed with statistic and bioinformatic methods.

Results: Thirty-three metabolites and 31 proteins were identified. Among them, 17 metabolites and 13 proteins were significantly higher in HD group than those in CT group, including phenols, which are well-known uremic toxins originating from the gut; reactive carbonyl compounds (RCC), which are well-known URMs in serum but first identified in the gut; other harmful metabolites (e.g., fenthalin, haloalcohol-methyl- and diethylpropion), which are known as immunomodulation-associated proteins. However, the levels of 16 metabolites and 18 proteins were lower in HD group compared to CT group, including ajene, which has been shown to exhibit anti-microbial and anti-cancer functions, and three proteins, which have indicated anti-inflammatory and anti-cancer activities.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Conclusions: This study not only demonstrated that RCC-URMs originated from the gut, but also confirmed that intestinal uricogenic uremic toxin precursors and deficient beneficiaries in the gut of uremic patients. Funding: Government Support - Non-U.S.

FR-PO533

AST-120 Affects the Level of Circulating TNF-Alpha Receptors That Predict Both Renal and Cardiovascular Outcomes in Patients with Advanced Renal Dysfunction

Dong Ki Kim, Yon Su Kim, Rodolfo Rosseto Rampaso, Kleiton Augusto Santos Silva, Luciana Maruyama. 1  Dong Ki Kim, 2 Yon Su Kim. 2

Background: Tumor necrosis factor alpha and its two receptors have a critical role in kidney diseases. We aimed to establish the role of circulating TNF-alpha receptors (cTNFRs) as a new biomarker of renal disease and to identify the impact of AST-120 on the level.

Methods: 579 patients from 11 medical centers in Korea were prospectively recruited and followed up for 36 months after randomization into AST-120 and control arms. A total of 6 gram of AST-120 was given to participants in AST-120 arm as well as conventional treatment. cTNFRs were measured by ELISA method at the time of randomization and 1 year after. The renal outcome was composite of serum creatinine (sCr) doubling, 50% reduction of estimated glomerular filtration rate (eGFR), or initiation of renal replacement therapy. Major adverse cardiovascular events (MACE) were also evaluated.

Results: A total of 465 patients were analyzed. Mean sCr and eGFR level was 2.8 ± 0.7 mg/dL and 26.59 ± 7.263 ml/min/1.73m2, respectively. The levels of cTNFRs throughout the study period were not different between two treatment arms. But the higher AST-120 compliance patients had, the lower cTNFRs they showed in the AST-120 arm. The highest tertile of cTNFRs showed the highest cumulative rate of composite renal outcomes followed by the intermediate tertile of cTNFRs after the adjustment for traditional risk factors. More change of cTNFRs was also independently associated to the more occurrence of composite renal outcomes. MACEs occurred more frequently in patients with higher baseline cTNFRs and more change of cTNFRs (log-rank P = 0.01, 0.002 and 0.021 for cTNFR1, cTNFR2, and change of cTNFR2, respectively) and the significance of cTNFR2 remained after adjustment for diabetes, CKD stage, and proteinuria.

Conclusions: Baseline and change of cTNFRs did not improve the predictability of composite renal outcomes in comparison with classic biomarkers. But cTNFRs predicted both renal and cardiovascular outcomes in patients with advanced renal dysfunction. And AST-120 was effective to lessen the increase of cTNFRs.

FR-PO534

Swimming Exercise Training (EXE) Normalize Blood Urea Nitrogen (BUN), Decrease Glomerulosclerosis, and Attenuates the Loss of Myokine IL6 in 5/6 Nephrectomy

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Background: This study will be evaluated the EXE effects on renal function, glomerulosclerosis and myokine IL6 has been associated with stimulation of hypertrophic muscle growth and myogenesis through regulation of the proliferative capacity of muscle stem cells.

Methods: Adult Wistar rats were divided in groups (n=8): Control (CS), Control+EXE (CE), Sedentary 5/6N (NS) and 5/6N+EXE (NE). The protocol was employed in 5/6Nx rats after 7 days from the surgical procedures. EXE periods were 60min/day/5 days a week during 8 weeks. It was evaluated arterial pressure (AP), maximal exercise test (MExt), creatinine clearance (CrCl), BUN, proteinuria (uProt), glomerulosclerosis, myokine IL6 (by Lumexin) as well mortality rate.

Results: EXE did not modify the increment in MAP but prevent, at least in part, a lower decline in the MEtient caused by 5/6N (291±1 vs 1612±12 µm Hg, p<0.05). One higher CrCl in NE was observed compared with NS (2.27±1.3 vs 0.96±0.20 ml/min, respectively) (p>0.05). BUN was normalized in NE (43.62±7.30 mg/dL). Proteinuria was not significantly different in NE vs NS group (36.87±3.53 vs 40.13±2.55 mg/24h). Glomerulosclerosis was 48% higher in NS vs NE. Myokine IL6 (pg/ml) was decreased in NS (286±0.40) and attenuated the loss in NE (384±0.00±20.82). A higher mortality rate was observed in NS (70%) vs NE group (39%, p<0.05).

Conclusions: Results suggested that the EXE minimize the impact of 5/6Nx by decreasing glomerulosclerosis and reducing the impact on CrCl (42%). Finally, attenuating myokine IL6 in NE, the decreasing mortality rate in NE vs NS and by minimizing the impact of 5/6Nx on CrCl indicate that EXE in this protocol, induced protection on renal function. Thus, it is reasonable to suggest that EXE could be an additional strategy to be employed in CKD.

FR-PO535

Does Autophagosome-Proteolysis Contribute to CKD-Induced Muscle Atrophy?

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Background: CKD-induced muscle wasting results from activation of the ubiquitin proteosome system (UPS). Since FoxO stimulates the UPS but also activates autophagosomes, we hypothesized that autophagosome-induced proteolysis may contribute to CKD-induced muscle wasting.

Methods: CKD model in mice: subtotal nephrectomy for one month. Muscle overloading model: removal of gastrocnemius and soleus to overload the plantaris muscle (unimicromyosin resistance exercise) in normal and CKD mice. Acupuncture with low frequency electric stimulation (Acu/LFES) was applied 15 minutes daily for 2 weeks (Hu, JASN, 26:626 2015). Electrical stimulation used a consistent pulse, electric frequency 20Hz, current 1mA.

Results: Both exercise and Acu/LFES reduced CKD muscle loss. In muscles of CKD mice, mRNAs related to autophagy-lysosomal function, Bnip3, Atg12, Atg8, LC3II and Beclin-1 were upregulated and Bnip3, Beclin-1 and LC3II proteins were increased. Acu/LFES treatment reversed these changes. Exercise in control mice also increased autophagy-lysosomal related protein LC3II-Beclin-1, P62 and Vps34. The levels of these mediators were not additive to changes observed in mice with CKD. We cultured C2C12 myotubes in uremic serum and found increased autophagy markers, indicating activation of autophagosomes. Acidification alone did not stimulate autophagy markers. Based on these results, the UPS, but not autophagosomes, is responsible for degradation of structural proteins (myosin and actin).

Conclusions: 1) autophagosome-mediated proteolysis occurs in CKD-induced muscle atrophy. In mice with CKD, the UPS was principally involved in muscle proteolysis; the role of autophagosomes was convoluted. 2) Prevention of muscle atrophy by exercise is not due to inhibition of the autophagy-lysosomal proteolysis pathway in CKD. 3) Muscle atrophy cannot be equated with increased autophagy markers. 4) Acu/LFES and exercise promote different autophagy consequences.

FR-PO536

Indoxyl Sulfate, a Uremic Toxin, Accelerates Skeletal Muscle Atrophy in CKD Condition

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Background: Skeletal muscle atrophy is often observed in chronic kidney disease (CKD) patients, especially in patients undergoing hemodialysis. Uremic toxins have been known to link to CKD complications. However there has been no report on the relationship between uremic toxins and skeletal muscle atrophy. The purpose of this study is to investigate the involvement of uremic toxins on skeletal muscle atrophy observed in CKD condition.

Methods: In vitro cytotoxicity of uremic toxins on cell proliferation and differentiation was evaluated by using a mouse myoblast cell line (C2C12). The effect of uremic toxin on proteolysis and protein synthesis system in C2C12 was also evaluated. In the animal study, we examined the contribution of uremic toxin on muscle atrophy using uremic toxin overloaded half- or 5/6-nephrectomized mice.

Results: We focused on six protein bound solutes including indoxyl sulfate (IS), indole acetic acid, p-cresyl sulfate, hippuric acid, kynurenic acid and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid. Among these uremic toxins, IS significantly increased atrophy-related genes expression but it did not affect differentiation-related genes expression. In the animal experiments, IS-overload reduced body weights and skeletal muscle weights of half- or 5/6-nephrectomized mice, and consequently weakened its muscular endurance. IS-overload mice showed increased skeletal muscle atrophy-related genes expression. In the same experimental condition, IS also induced the expression of inflammatory cytokine and transforming growth factor-β in skeletal muscle cells.

Conclusions: IS is the potent uremic toxin inducing skeletal muscle atrophy associated with CKD by increasing muscle atrophy-related genes.

FR-PO537

Myostatin Stimulates Progenitor Cells to Differentiate into Fibrocytes Leading to Muscle Fibrosis in Chronic Kidney Disease

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Background: In chronic kidney disease (CKD), fibrosis develops in damaged kidneys leading to muscle atrophy. Fibrosis in muscle also complicates CKD but little is known about cells developing into fibrocytes and mechanisms causing fibrosis are not defined. The potential precursors of muscle fibrosis are mesenchymal progenitor cells (fibrotic and adipogenic progenitors (FAPs)) while mechanisms causing fibrosis include myostatin as
CKD raises its expression and muscle injury can stimulate injured muscles to develop fibrocytes. Our hypothesis is that CKD stimulates myostatin expression causing FAPs to differentiate into fibrocytes.

Methods: 1) we isolated and cultured FAPs, adding recombinant myostatin to determine if it causes FAPs to proliferate and differentiate into fibrocytes. 2) We isolated GFP-labelled FAPs from transgenic, GFP expressing fibrocytes identified as expressing the fibrosis marker, α-SMA. FAP proliferation and muscle fibrosis were prevented in CKD mice injected with the anti-myostatin peptibody. Finally, Smad3 knock-down expressing the fibrosis marker, α-SMA. FAP proliferation and muscle fibrosis were prevented to determine if myostatin stimulates muscle fibrosis. 4) Interactions between myostatin signalling and FAP conversion to fibrocytes were tested by knocking down Smad3 with a lentivirus expressing Smad3 SINRa.

Results: In cultured FAPs, myostatin stimulated their proliferation and conversion into fibrocytes and there is proliferation of FAPs in injured muscles of CKD mice. GFP-labelled FAPs were injected into TA muscles of CKD mice differentiated into fibrocytes identified as expressing the fibrosis marker, α-SMA. FAP proliferation and muscle fibrosis were prevented in CKD mice injected with the anti-myostatin peptibody. Finally, Smad3 knock-down blocked FAP differentiation into fibrocytes indicating that a myostatin to Smad3 pathway is essential for the conversion of FAPs to fibrocytes.

Conclusions: CKD stimulates myostatin production to activate FAPs which differentiate into fibrocytes. The process is blocked by an anti-myostatin peptibody, providing a new target for preventing muscle fibrosis as a complication of CKD.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

FR-PO538

Effect of Methoxy Polyethylene Glycol – Epoetin Beta on Plasma Levels of IL-1p, TNF-RI, sFAS, sFAS-L, MMP-9 in Patients with CKD

Piotr Bartnicki, Ewa Majewska, Zbigniew Baj, Jacek Rysz, Ryohei Kawasaki, Yoshihito Tashiro, Michinori Hirata, Koichi Kusano, Anna Clementi, Alessandra Brocca, Massimo de Cal, Claudio Ronco. Nephrology-IRRIV.

Background: Even though anemia in CKD results mainly from the lack of erythropoietin, accelerated erythrocyte death(eryptosis) seems to be a contributor factor. Eryptosis is characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine(PS) exposure at the erythrocyte (RBC) surface. Eryptosis may be triggered by some uremic toxins. P-cresol is an uremic toxin which has negative cardiovascular and cytopathic effects. This study explored if eryptosis is triggered by p-cresol and if different stages of CKD may influence erythrocyte death.

Methods: RBCs from healthy subjects were incubated in vitro at a hematocrit of 0.4% with different concentrations of p-cresol (0.2-5.5-10-20-40ng/ml) and with plasma from CKD patients (5 for each stage) for 24hours. PS exposure was estimated from AnnexinV binding in flow cytometer.

Results: Increasing concentrations of p-cresol modified significantly the percentage of PS exposure on RBC surface, thus suggesting that increasing concentrations of p-cresol may stimulate eryptosis in vitro. Moreover, there was no significant difference in terms of median values of eryptosis between CKD stages, but a positive trend was evident: eryptosis increase with CKD progression.

Conclusions: In addition to its known cardiovascular and cellular effects, p-cresol seems to stimulate eryptosis in vitro and increasing concentrations of this uremic toxin may be responsible for higher levels of eryptosis in vivo. Our data show that CKD plasma contains components able to trigger eryptosis and different stages of CKD may be responsible for different levels of RBC death, thus suggesting that progression of CKD may increase eryptosis in vivo. These results suggest a role of uremic toxicity in the genesis of eryptosis and renal anemia. It is necessary to increase the sample size to validate our hypothesis.

Funding: Private Foundation Support

FR-PO540

Eryptosis in Chronic Kidney Disease

Grazia Maria Virzi, Anna Clementi, Alessandra Brocca, Massimo de Cal, Claudio Ronco. Nephrology-IRRIV.

Background: Even though anemia in CKD results mainly from the lack of erythropoietin, accelerated erythrocyte death(eryptosis) seems to be a contributor factor. Eryptosis is characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine(PS)-exposure at the erythrocyte (RBC) surface. Eryptosis may be triggered by some uremic toxins. P-cresol is an uremic toxin which has negative cardiovascular and cytopathic effects. This study explored if eryptosis is triggered by p-cresol and if different stages of CKD may influence erythrocyte death.

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Funding: Private Foundation Support

FR-PO539

Qualitative Changes in Erythrocytes in Chronic Kidney Disease


Background: Therapeutic control of anemia in chronic kidney disease (CKD) patients in comparison to control group. After ESA treatment plasma level of TNFII was significantly higher and MMP-9 was significantly lower in CKD patients. These data suggest that Micrera used in correction of anemia in CKD might influence on immune cells function, apoptosis and tissue fibrosis.

Conclusions: Plasma concentrations of evaluated parameters are significantly higher in CKD patients in comparison to control group. After ESA treatment plasma level of TNFII was significantly higher and MMP-9 was significantly lower in CKD patients. These data suggest that Micrera used in correction of anemia in CKD might influence on immune cells function, apoptosis and tissue fibrosis.

FR-PO541

Palmitate Exacerbates Renal Anemia: Suppression of Renal Erythropoietin Production via Endoplasmic Reticulum Stress

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Background: Derangement of erythropoietin (EPO) production in renal EPO-producing (REP) cells causes renal anemia. Palmitate induces endoplasmic reticulum (ER) stress which contributes to glomerular and tubular cell damages. Thus, we evaluated the effect of palmitate-ER stress axis on EPO production in REP cells.

Methods: C57BL/6J or the mice, in which the renal EPO gene was replaced with GFP or REP cells were lineage labeled with tdTomato, were daily injected with palmitate

Conclusions: In addition to its known cardiovascular and cellular effects, p-cresol seems to stimulate eryptosis in vitro and increasing concentrations of this uremic toxin may be responsible for higher levels of eryptosis in vivo. Our data show that CKD plasma contains components able to trigger eryptosis and different stages of CKD may be responsible for different levels of RBC death, thus suggesting that progression of CKD may increase eryptosis in vivo. These results suggest a role of uremic toxicity in the genesis of eryptosis and renal anemia. It is necessary to increase the sample size to validate our hypothesis.

Funding: Private Foundation Support

FR-PO541

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Reiko Imaji,1 Thitinun Anusomvongchai,2 Yu Ishimoto,2 Akira Okada,2 Norio Suzuki,2 Masayuki Yamamoto,2 Masaomi Nangaku.2

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Methods: C57BL/6J or the mice, in which the renal EPO gene was replaced with GFP or REP cells were lineage labeled with tdTomato, were daily injected with palmitate
Hypoxia (HIF activation with CoCl2). It was associated with activation of ER stress signal in CKD patients, fibrosis marker α-SMA was downregulated.

Conclusions: EPO production by REPS was suppressed by palmitate, especially under hypoxic condition, via the ER stress pathway (ATF4 activation). The link between dyslipidemia (palmitate) and ER stress may contribute to development and progression of renal anemia, and subsequent CKD and highlight the impact of palmitate on CKD progression.

Funding: Government Support - Non-U.S.

FR-PO542

The Function of Integrinβ4 in Epithelial-to-Mesenchymal Transition of HK2 Cells Qi Wang, Yan Wang, Xiaoyan Huang, Zibo Xiong, Zuying Xiong, Jiangling Dong, Liping Li

Background: To explore the function of integrinβ4 in epithelial-to-mesenchymal transition (EMT) of HK2 cells, and further study the role of integrinβ4 in renal fibrosis.

Methods: (1) Cultured HK2 cells were divided into 4 groups: 0ng/ml TGFβ1 treated group (negative control), 1ng/ml TGFβ1 group ,3ng/ml TGFβ1 group and 5ng/ml TGFβ1 group (positive control). Integrinβ4 shRNA mediated repression of integrinβ4 in HK2 cells and divided into 4 groups: control-shRNA HK2 cells without TGFβ1; control-shRNA HK2 cells with 5ng/ml TGFβ1; β4-shRNA HK2 cells without TGFβ1; β4-shRNA HK2 cells with 5ng/ml TGFβ1.β4-shRNA HK2 cells with 5ng/ml TGFβ1 (3) The vivo experiment was performed in IA nephropathy kidneys tissues obtained from 45 patients that underwent a biopsy procedure during 2013-2014. According to the degree of tubulointerstitial lesion, kidney specimens were divided into 3 groups: mild lesion, moderate lesion, and severe lesion. We handle normal kidney portions as controls. The expressions of integrinβ4, E-cad, CTGF and α-SMA were assessed by qRT-PCR and western blot. Immunofluorescence was used in different degrees of tubulointerstitial lesions.

Results: (1) Compared with negative control, integrinβ4 and E-cad were significantly lower, however, CTGF and α-SMA were increased (2) Integrinβ4 and E-cad in β4-shRNA HK2 cells group were lower than control-shRNA HK2 cells, in contrast, CTGF and α-SMA were increased; integrinβ4 and E-cad with TGFβ1 treatment were significantly lower than without TGFβ1 groups, CTGF and α-SMA expressions were increased. (3) Compared with mild lesion group, E-cad staining in moderate lesion group and severe lesion group reduced, α-SMA staining and integrinβ4 staining increased. After being further analyzed, the most of integrinβ4 staining located in neointimal renal tubules.

Conclusions: Integrinβ4 expression is decreased in the process of EMT, and reduced integrinβ4 can exacerbate HK2 cells from epithelial cells transition to mesenchymal cells, therefore loss of integrinβ4 may be the marker of TIF. However, the results of vivo experiment appeared to be contradictory, the reason of this phenomenon may be that many neointimal renal tubules possess the ability of proliferation.

Funding: Government Support - Non-U.S.

FR-PO543


Background: Insulin resistance in chronic kidney disease (CKD) begins early in the disease, compromising anabolic responses to insulin/IGF-1 signaling. We have previously demonstrated that a novel protein, signal regulator protein alpha (SIRPa) is involved in insulin signaling, exacerbating skeletal muscle metabolism. We now describe for the first time elevated levels of SIRPa in CKD cardiac muscle which not only adversely influences insulin signaling, but may exacerbate muscle fibrosis.

Methods: CKD was created via subtotal nephrectomy and mice with CKD greater than 2 months hearts were harvested and left ventricle muscle samples were examined for SIRPa, IR1-α, SIRPa, GAPDH. Additionally, C2C12 myoblasts were treated to overexpress SIRPa vs. GFP plasmid. Also, myoblasts were transfected with silencing RNA (SIRNA) SIRPa or scrambled SIRNA (control). Western blots analysis was performed based on skeletal muscle cell lysates.

Results: After ~2 months of CKD, the mice experience left ventricle hypertrophy in contrast with controls. SIRPa was significantly increased in cardiac muscles of mice with CKD, with reduction in tyrosine phosphorylation of IR-1. This finding was previously reported in skeletal muscles of mice with CKD. Additionally, high pressure a-SMA was increased in cardiac muscles of mice with CKD vs. control mice. In order to determine a cause and effect relationship, SIRPa was overexpressed utilizing a SIRPa plasmid vs. GFP plasmid for control. In myoblasts in which SIRPa was overexpressed, fibrosis marker a-SMA was increased. Finally, when we silenced SIRPa in muscle cells treated with a cytokine mixture, containing cytokines present in CKD patients, fibrosis marker a-SMA was downregulated.

Conclusions: These results imply that SIRPa increases fibrosis, and suggesting that SIRPa may exacerbate muscle fibrosis via a new pathway in chronic kidney disease. Ultimately blocking SIRPa in heart muscle may improve cardiac fibrosis associated with chronic kidney disease.

Funding: Veterans Administration Support

FR-PO544

Retinal Microvascular Abnormalities and Incidence and Progression of Chronic Kidney Disease Charumathi Sabanayagam,1,2 Peng Guan Ong,1 Boon Wee Teo,1 Carol Y. Cheung,2 Ching-Yu Chu,2 Ecosse L. Lamoureux,1,2 Tien Yin Wong,1,2 Singapore Eye Research Inst, Singapore; ‘Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore; ‘National Univ of Singapore, Singapore.

Background: To examine the longitudinal association of a panel of retinal vascular parameters, markers of microvascular damage, with the incidence and progression of chronic kidney disease (CKD) in middle-aged Asian adults.

Methods: The population consisted of a cohort of Malay adults aged 40-80 years examined from 2004-06 and again from 2010-2012 (n=1464; 1306 free of CKD and 158 with pre-existing CKD). The outcomes were incidence (estimated glomerular filtration rate [eGFR]=60 nL/min/1.73m2<25% decrease in eGFR) and progression of CKD (drop in eGFR category [<60, 30-59, 15-30, <15]<25% decrease in eGFR or an annualized eGFR rate<3/mL/min/1.73m2/year).

Results: Over a median follow-up of 6.6 years, 6.4% (70% had diabetes) developed incident CKD and 26.6% (62% had diabetes) developed progressive CKD. In multivariable models, retinal arteriolar narrowing, retinal venular widening, and presence of retinopathy were each independently associated with CKD. The HR (95% CI) of incident CKD was 1.31 (1.01-1.72) per SD decrease in arteriolar caliber, 2.20 (1.10-4.41) for tertile 3 vs. tertile 1 of venular caliber; 2.06 (1.24-3.44) for retinopathy. Increased arteriolar tortuosity alone was associated with progressive CKD (1.57 [1.02-2.37] per SD decrease. All associations were consistently present among those with diabetes.

Conclusions: Retinal vascular abnormalities increased the risk of CKD by more than two times in Asian adults. Our findings provide evidence that retinal imaging may be a useful tool to improve risk stratification for CKD.

Funding: Government Support - Non-U.S.

FR-PO545

Relationship Between Serum Bilirubin and Hyalinization of Renal Arterioles Tetsushi Miyagi,1 Kentaro Kohagura,2 Yusuke Ohya,1 Kunioshi Iseki,1 ‘Dept of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyu, Nishihara-cho, Okinawa, Japan; 2Dialysis Unit, Univ of the Ryukyu, Nishihara-cho, Okinawa, Japan.

Background: It has been suggested that there is a relationship between serum bilirubin and renal arteriolar hyalinization. In the present study, we examined the relationship between serum bilirubin levels and the hyalinization of renal arterioles in patients with chronic kidney disease (CKD).

Methods: We reviewed the clinical records of 138 patients with CKD (mean age: 44 years) who underwent renal biopsy at our department during a 3-year period starting in 2010. Patients who were receiving calcineurin inhibitors were excluded. The subjects were divided into three groups based on their total serum bilirubin levels: tertile group 1 (0.2-0.4 mg/dl; 40 patients), tertile group 2 (0.5-0.7 mg/dl; 61 patients), and tertile group 3 (0.8-1.4 mg/dl; 37 patients). Using the pathological specimens obtained from renal biopsies, the hyalinization of renal arterioles was semiquantitatively evaluated, and the mean score of renal arteriolar hyalinization grade was used for analysis.

Results: Tertile group 1 had markedly higher urinary protein levels and markedly lower serum hemoglobin (Hb) levels than tertile group 3. We defined total serum bilirubin levels under 0.5 mg/dl (tertile group 1) as low levels and divided them into two groups of values under and above 0.5 mg/dl. These were set as explanatory factors, and a multiple regression analysis was performed, with the degree of hyalinization of renal arterioles independent of classical risk factors of cardiovascular disease. In the present study, we examined the relationship between serum bilirubin levels and the hyalinization of renal arterioles in patients with chronic kidney disease (CKD).

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Conclusions: Low serum bilirubin levels may be a risk factor for the hyalinization of renal arterioles independent of classical risk factors of cardiovascular disease.
FR-PO546

Autonomic Nervous Dysfunction in Predialytic Chronic Kidney Disease: 3 Years Observational Follow-Up Study

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Background: Generally, sympathetic overactivity and impairment of the parasympathetic system are often seen in patients with dialytic CKD, COPD, RA as well as elderly. Also, arterial stiffness and edema have been related with mortality in patients with cardiovascular disease. However, to date, few data regarding autonomic nervous system, vascular stiffness, edema in pre-dialytic CKD was proposed. This study was designed to explore the interrelationship of those parameter in pre-dialytic CKD (G3, 4) and uncover the risk factor related with renal functional deterioration.

Methods: Thirty-three patients were enrolled. Hydration status (extracellular water [ECW]/total body water [TBW]) was determined by bioimpedance analysis. Brachial-ankle pulse wave velocity (baPWV) and neck ultrasoundgraphy for carotid plaque and intima-media thickness were conducted for checking up of vascular status. CAN was scored using Ewing’s method and we also expressed the standard deviation of normal-to-normal interval (SDNN), low frequency/high frequency ratio (LF/HF ratio). Serum creatinine change over a median follow-up of 3 years was used for assessment of renal function.

Results: Of the 33 patients, 14 (42%) have suffered with CAN. Patients with CAN have higher progressive declining rate of renal function, baPWV, systolic BP compared with patients without CAN. The group having declining renal function has higher CAN score, baPWV and lower SDNN compared with preserved renal function group. CAN score correlated positively with ECW/TBW (r=0.405, p<0.019), mean PWV (r=0.623, p<0.001) and SBP (r=0.515, p=0.002). CAN score correlated negatively with declining rate of renal function (r=-0.471, p=0.006), Htr-1(-0.659, p<0.001) and albumin(r=-0.484, p=0.004).

Conclusions: Autonomic nervous dysfunction including lower SDNN and increased arterial stiffness was associated with an increased risk of CAN. baPWV may be important risk factors for deterioration of renal function in pre-dialytic CKD patients. Autonomic nervous dysfunction was related with arterial stiffness and edema.

FR-PO547

Inhibition of EGFR Alleviates the Development and Progression of Hyperuricemic Nephropathy in Rats

Li Wang, 1 Andong Qiu, 2 Vladimir Belostotsky, 4 Marta Caroline Kobrzynski, 1 Shih Ji Liu, 1,2,3 Jaime Uribarri. 4

Background: Albuminuria is a major risk factor for cardiovascular disease. However, to date, few data regarding albuminuria and eGFR was evaluated in the association with biopsy/yogurt consumption and albuminuria in a large, nationally representative general population sample. Future studies evaluating the association between probiotic/yogurt use and kidney diseases are warranted.

Methods: The study was conducted in the Departments of Medicine and Biochemistry at University College of Medical Sciences and GTB Hospital, Delhi from December 2013 - April 2015. It was a case control, cross sectional study. Ninety subjects in the age group 18 ~ 60 years of either sex were divided into 3 groups: Group I: Healthy controls (n=30), Group II: Individuals satisfying case definition of CKD (n=30) and Group III: Individuals having CKD of unknown etiology (n=30).

Results: The median levels of lead, cadmium and chromium were significantly higher in patients of group II and this difference was statistically significant as compared to subjects of group I and III.

Conclusions: As compared to healthy controls, the serum levels of lead, cadmium, arsenic and chromium were found to be significantly higher in patients of CKD. The study indicates a possible role of heavy metals in causation of CKD.

FR-PO548

Probiotic and Yogurt Consumption Is Associated with a Lower Prevalence of Albuminuria: A Cross-Sectional Analysis of NHANES

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Background: Animal data suggest that probiotic supplements may retard CKD progression. Yogurt is the most widely available probiotic food in the United States. Yogurt is the most widely available probiotic food in the United States. We observed an inverse association of probiotic/yogurt consumption and albuminuria in a large, nationally representative general population sample. Future studies evaluating the association between probiotic/yogurt use and kidney diseases are warranted.

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FR-PO549

Assessment of Serum Levels of Heavy Metals in Patients with Chronic Kidney Disease of Unknown Etiology

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Background: Chronic kidney disease (CKD) encompasses a wide spectrum of different etiological processes associated with abnormal kidney function and gradual progressive decline in glomerular filtration rate. CKD of unknown etiology (CKDu) has emerged as an important entity accounting for approximately 10% of CKD patients worldwide. Of the environmental toxins implicated in causation of CKDu, heavy metals form an important group. In the present study, we estimated the serum levels of lead, cadmium, arsenic and chromium in patients with CKDu and evaluated their role in the etiopathogenesis of CKDu.

Methods: The study was conducted in the Departments of Medicine and Biochemistry at University College of Medical Sciences and GTB Hospital, Delhi from December 2013 - April 2015. It was a case control, cross sectional study. Ninety subjects in the age group 18 ~ 60 years of either sex were divided into 3 groups: Group I: Healthy controls (n=30), Group II: Individuals satisfying case definition of CKD (n=30) and Group III: Individuals having CKD of unknown etiology (n=30).

Results: The median levels of lead, cadmium and chromium were significantly higher in patients of group II and this difference was statistically significant as compared to subjects of group I and III.

Conclusions: The level of lead, cadmium and chromium were significantly higher in patients of group II and III. The median levels of arsenic in patients of group II and III were similar but significantly higher than patients of group I. The levels of arsenic, cadmium and chromium were significantly higher in patients of group II and III.

Conclusions: As compared to healthy controls, the serum levels of lead, cadmium, arsenic and chromium were found to be significantly higher in patients of CKD. The study indicates a possible role of heavy metals in causation of CKD.

FR-PO550

High Prevalence of Elevated Molybdenum Levels in CKD Patients

Guido Filippi, 1 Vladimir Belostotsky, 1 Marta Caroline Kobrzynski, 1 Shih-Jian Liu, 2 Li Yang, 1 Paediatrics, University of Western Ontario, London, ON, Canada; 2Paediatrics, McMaster Univ, Hamilton, ON, Canada.

Background: Molybdenum (Mo, atomic number 42) is an essential trace element present in water and is crucial for human survival because four mammalian enzymes harbor a pterin-based Mo cofactor (Moco) at their active site and are Mo-dependent. There is no information about Mo levels in patients with CKD.

Methods: We utilized NHANES data with reported one year yogurt consumption frequency and probiotic use.

Results: We had complete data on 6853 participants (mean age 48.3±20.45 years, male), of which,1539 (20.3%) were frequent consumers and 918 participants (12.2%) had detectable albuminuria (Median=67.1, IQR -41.6-157.1 mcg/mg). Frequent consumers had a trend towards lower median UACR compared to non-consumers (mean difference (MD): -12.3, 95% CI -29.8 to 5.2, P=0.07) that was attenuated after complete adjustment. On the other hand, frequent consumers had decreased odds of albuminuria (UACR > 30 mcg/mg) compared to non-consumers (adjusted Odds Ratio 0.79; 95% CI 0.63-0.97; P=0.03).

Conclusions: Neither CKD III-V prevalence, nor continuous eGFR was significantly different between the consumers and non-consumers. After adjustment for age, race, medical history of hypertension and diabetes, socioeconomic status (family income to poverty index), HbA1c, BMI, insulin, statins blockers use and probiotic use duration.
we also recorded the cystatin C eGFR using the Filler formula in 35 children. Mo and Cu levels were measured using High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS).

**Results:** The mean Schwartz eGFR was 46±23 and the Cystatin C eGFR was 48±20 mL/min/1.73 m². The median Mo level was 2.26 (interquartile range 1.7, 3.3 ug/L, mean 2.78±1.70 ug/L), significantly higher than the upper reference interval of 1.4 ug/L, and with an exponential increase with lower eGFR.

The mean Cu level was 1124±378 ug/mL, not significantly different from the reference interval of 822 to 1201 ug/mL. eGFR was significantly negatively correlated with Mo levels (Spearman r = -0.57, p=0.0002).

**Conclusions:** With worsening kidney function, Mo levels accumulate, while Cu levels remain unaffected.

**Funding:** Clinical Revenue Support

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**FR-PO551**

**High Prevalence of Elevated Vanadium Levels in CKD Patients**

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**Background:** Vanadium (V, atomic number 23) is an essential trace element present in many industrial products, especially in steel, which can be very toxic if levels are too high. The excretion of vanadium by the kidneys is rapid with a biological half-life of 20-40 days.

**Methods:** After approval by the ethics board, and as part of a larger study on zinc supplementation in CKD, we studied 87 plasma V levels in 50 children with an eGFR < 90 mL/min/1.73 m² and > 15 mL/min/1.73 m² using the Schwartz formula. Where available, we also recorded the cystatin C eGFR using the Filler formula in 35 children. V levels were measured using High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS).

**Results:** The mean Schwartz eGFR was 46±23 and the Cystatin C eGFR was 48±20 mL/min/1.73 m². The mean V level was 0.117 (interquartile range 0.082, 0.184 ug/L, mean 0.117±0.0499 ug/L), significantly higher than the upper reference interval of 0.1 ug/L (p=0.0057), and with a trend towards exponential increase with lower eGFR (R² = 0.3075, p=0.06).

**Conclusions:** We observed a high prevalence of elevated V levels in the CKD patients. With worsening kidney function, V levels accumulate.

**Funding:** Clinical Revenue Support
FR-PO554

Methionine Sulfoxide Reductase A (MsrA) Protects Progression of Kidney Fibrosis After Unilateral Ureteral Obstruction

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Background: Methionine sulfoxide reductase A (MsrA) reduces oxidized methionine and protects cells against oxidative stress. Oxidative stress accelerates kidney fibrosis. Here, we investigated the role of MsrA in unilateral ureteral obstruction (UUO)-induced fibrosis using MsrA gene-deleted mice.

Methods: MsrA+/+ and MsrA−/− male mice were subjected to UUO. Kidneys were harvested 5 days after the UUO surgery.

Results: UUO reduced Msrs expression and activity in the kidney. UUO resulted in expansion of interstitial area with increased collagen deposition. In addition, UUO increased the levels of u-smooth muscle actin and collagen III expression. MsrA deficiency significantly enhanced collagen deposition and expression of those proteins. UUO resulted in the increase in hydrogen peroxide (H2O2) formation and lipid peroxide in both MsrA−/− mouse kidneys and MsrA+/+ mouse kidneys, and these increases were significantly higher in MsrA−/− mouse kidneys than in MsrA+/+ mouse kidneys. Furthermore, post-UUO increases in the oxidized glutathione ratio to total glutathione were significantly greater in MsrA−/− mouse kidneys than in MsrA+/+ mouse kidneys. Number of F4/80 expressing cells increased in the kidney after UUO. These increase of F4/80 expressing cells were greater in MsrA−/− mouse kidneys than in MsrA+/+ mouse kidneys. Levels of Ly6G, a marker of granulocyte, were also higher in MsrA−/− mouse kidneys than in MsrA+/+ mouse kidneys.

Conclusions: In conclusion, MsrA protects kidney against UUO-induced fibrosis, suppressing oxidative stress and inflammatory responses.

Funding: Government Support - Non-U.S.

FR-PO555

The Soluble Urokinase-Type Plasminogen Activator Receptor Serum Levels in Adults with Nephrotic Syndrome

Qiuling Fan, Nephrology, The First Hospital of China Medical Univ.

Background: The serum levels of soluble urokinase type fibrinolytic enzyme activators receptor (suPAR) in adults with nephrotic syndrome were analyzed.

Methods: The serum levels of soluble urokinase type fibrinolytic enzyme activators receptor (suPAR) in 70 nephrotic syndrome patients with membranous nephropathy, diabetic nephropathy group, lupus nephritis, minimal change kidney disease and focal segmental glomerular scerosis group was detected by enzyme-linked immunosorbent assay. The relationship between the clinical parameters and suPAR levels were analyzed.

Results: Serum soluble urokinase receptor levels of nephrotic syndrome patients were significantly higher than the normal control group (P < 0.01). The serum suPAR levels of FSGS and MN patients were significantly higher than MCD patients (P < 0.05). Serum suPAR level was positively correlated with age, serum creatinine, blood urea nitrogen, and negatively correlated with eGFR. The serum levels of suPAR in adults with nephrotic syndrome were analyzed.

Conclusions: Serum suPAR level was positively correlated with age, serum creatinine, blood urea nitrogen, and negatively correlated with eGFR. The serum levels of suPAR in adults with nephrotic syndrome were analyzed.

Funding: NIDDK Support

FR-PO556

Urinary Sodium: Impact on Blood Pressure and Progression of Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) is characterized by chronicity and progression of renal damage. The presence of hypertension is related to the progression of renal damage. Diets high in salt have been associated with an increased risk of hypertension. Sodium analysis in the urine of 24 h is considered the standard method to estimate the daily intake of this mineral. The aim of this study was to evaluate the impact of sodium intake estimated by urinary sodium in the urine of 24 hours (Nau24hs) on renal outcomes and their impact on hypertension.

Methods: Data were collected from medical records of 118 patients with CKD in conservative treatment, that had one Nau24hs dosage and a follow-up of at least five years. Information collected initially and after 5 years were: demographics, etiology of CKD, comorbidities, blood pressure; routine laboratory tests and estimated creatinine clearance (EPI-Cr). The Nau24hs values were classified into two groups by the median and also divided into tertiles and compared with the rate of progression of CKD (fall of the estimated clearance greater than 20% in 5 years) and the change in blood pressure.

Results: Patients had a mean of 186 ± 64 Meq/L of Nau24hs which represented a decrease in systolic blood pressure over 5 years. The decrease in creatinine clearance over 5 years was associated with more pronounced worsening of long-term renal function, probably because these patients were treated more intensively over the pressure control.

Conclusions: In conclusion, with high blood pressure, but was not associated with more pronounced worsening of long-term renal function, probably because these patients were treated more intensively over the pressure control.

FR-PO557

Risk of End-Stage Renal Disease with Longitudinal Change in Filtration Markers


Background: Change in estimated glomerular filtration rate (eGFR) based on creatinine has been proposed as a surrogate outcome in clinical trials of chronic kidney disease (CKD). Risk of end-stage renal disease (ESRD) associated with change in other kidney filtration markers has not been previously assessed in chronic kidney disease (CKD) populations.

Methods: We conducted prospective analyses of the Modification of Diet in Renal Disease (MDRD; N=840; mean age 52 years) and African-American Study of Kidney Disease and Hypertension (AASK; N=1,094; mean age 55 years) trials. Creatinine, cystatin C, β2-microglobulin, and β-trace protein levels were measured in serum samples collected at baseline and at the 24-month follow-up visit and were expressed using CKD-EPI eGFR equations. Multivariable Poisson regression was used to estimate associations between continuous percent change in eGFR for each marker (alone and in combination) with subsequent risk of developing ESRD. Seemingly unrelated regression was used to compare the strength of risk estimates from different models.

Results: In MDRD and AASK, respectively, there were 310 and 161 incident ESRD cases during a median follow-up of 4.7 and 7.1 years. Percent change in eGFR from the four filtration markers was significantly associated with incident ESRD risk (Table). The average of percent change in eGFR based on all four filtration markers was more strongly associated with ESRD risk than percent change in eGFR-creatinine alone.

Table. Table of Risk of Incident ESRD Associated with Percent Change in Filtration Markers in MDRD and AASK

<table>
<thead>
<tr>
<th>Filtration Marker</th>
<th>MDRD</th>
<th>AASK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRRT (95% CI) per 30% decline</td>
<td>P-value</td>
</tr>
<tr>
<td>eGFR-Cr</td>
<td>2.09 (1.78, 2.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR-Cys</td>
<td>2.58** (2.11, 3.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR-βTP</td>
<td>3.55*** (2.83, 4.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR-βM</td>
<td>2.55** (2.11, 3.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average of 4 Markers</td>
<td>2.89*** (2.35, 3.55)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, race, body mass index, systolic blood pressure, diabetes, total cholesterol, first eGFR for the respective filtration marker

** p<0.05 from seemingly unrelated regression comparing IRRT for the respective marker vs. IRRT for eGFR-Cr

*** p<0.01 from seemingly unrelated regression comparing IRRT for the respective marker vs. IRRT for eGFR-Cr

Conclusions: In conclusion, with high blood pressure, but was not associated with more pronounced worsening of long-term renal function, probably because these patients were treated more intensively over the pressure control.

Funding: Government Support - Non-U.S.

FR-PO558

Validation and Clinical Associations of a Predictive Model for Progression to Renal Replacement Therapy: A Retrospective Cohort Study

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Background: Timely planning for initiation of renal replacement therapy (RRT) is vital. Despite existing, validated risk-prediction models, RRT preparation is often based on clinical judgment. Here, we consider the benefits of applying an existing model (Tangri et al. JAMA, 2011) in a UK secondary care population.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: Patients with ≥5 years of potential follow-up were identified from the Chronic Kidney Disease Epidemiology, Outcomes: Noncardiovascular

Results: 728 patients were included in this analysis (median follow-up 4.4 [IQR 2.4-5.6] years), with 118 patients (16%) progressing to RRT. Mean baseline age was 64±14 years and eGFR 34±14 ml/min/1.73m². Risk was right skewed, with 328 (45%) of patients having a 5-year risk of <5%. 80 patients (11%) had a 5-year RRT risk of >50%. The overall area under the curve was 0.89. This did not vary by primary disease: glomerulonephritis (0.87); pyelonephritis (0.95); polyol cystic kidney disease (0.91); and diabetic nephropathy (0.88).

In higher-risk groups, a greater proportion of patients commenced RRT using peritoneal dialysis, and a smaller proportion commenced RRT as an in-patient. The proportion of patients transplanted listed at the time of starting RRT was greater in the lower risk group than the higher risk group.

FR-PO560

Effect and Safety of Sofosbuvir (SOF) Containing Direct-Acting Antiviral (DAA) Hepatitis C Virus (HCV) Therapy in a Real-World Population with Chronic Kidney Disease (CKD)

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Background: Early trials of SOF-based regimens excluded patients with CKD, thus little is known about safety, efficacy, and effect on kidney function.

Methods: We retrospectively evaluated 72 patients with CKD starting DAA treatment (tx) between 11/2013-12/2014. CKD was defined by average eGFR <60ml/min or albuminuria >30mg/g 6 months prior to tx. Safety, tolerability and laboratory results were assessed by chart review. Models predicting sustained virologic response (SVR) were performed.

Table 1: Logistic regression model predicting SVR (n=61)

<table>
<thead>
<tr>
<th>BL Predictors</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 years</td>
<td>1.25 (0.58,2.67)</td>
<td>0.57</td>
<td>0.68 (0.16,2.85)</td>
<td>0.60</td>
</tr>
<tr>
<td>Female</td>
<td>3.10 (0.62,15.35)</td>
<td>0.17</td>
<td>4.20 (0.41,43.45)</td>
<td>0.23</td>
</tr>
<tr>
<td>Black</td>
<td>0.44 (0.11,1.79)</td>
<td>0.25</td>
<td>0.22 (0.03,6.12)</td>
<td>0.14</td>
</tr>
<tr>
<td>HCV Genotype 3</td>
<td>0.08 (0.01,0.84)</td>
<td>0.04*</td>
<td>0.07 (0.00,5.56)</td>
<td>0.23</td>
</tr>
<tr>
<td>Early discontinuation</td>
<td>0.11 (0.02,0.69)</td>
<td>0.02*</td>
<td>0.06 (0.00,0.90)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1.85 (0.51,6.77)</td>
<td>0.31</td>
<td>1.00 (0.17,8.89)</td>
<td>1.00</td>
</tr>
<tr>
<td>Price HCV tx</td>
<td>0.58 (0.17,1.99)</td>
<td>0.39</td>
<td>1.17 (0.26,8.88)</td>
<td>0.87</td>
</tr>
<tr>
<td>Liver or kidney transplant</td>
<td>1.02 (0.29,3.54)</td>
<td>0.98</td>
<td>0.34 (0.04,2.69)</td>
<td>0.31</td>
</tr>
<tr>
<td>Baseline eGFR, per 10 ml/min decrease</td>
<td>1.79 (1.27,2.50)</td>
<td>&lt;0.01*</td>
<td>2.10 (1.22,3.63)</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

Results: Subjects were aged 61±8 years, 60% white, 22% black, 12% Hispanic, and 74% male. 50% were diabetic, 39% cirrhotic, 54% HCV naïve, 39% had prior liver or kidney transplant, and 7% were HIV/HCV coinfected. DAA regimens were: SOF/simeprevir 50%, SOF/ledipasvir 13%, SOF/ribavirin 28%, other SOF regimens 10%. 8% had a transient creatinine rise >0.5mg/dL during tx. Average eGFR on tx was similar to baseline (mean [95% CI]: 57 [52-62] vs. 53 [53 – 63] ml/min, respectively P=0.26). SVR was 77% (95% CI 66-88). 76% experienced at least 1 adverse effect (AE); only 5 (7%) discontinued tx due to an AE.

Conclusions: SOF-containing DAA regimens are effective and relatively safe in patients with CKD. Although AEIs were common, serious AEIs or significant nephrotoxicity were rare. Lower eGFR at baseline predicted an increase likelihood of HCV cure with SOF-based regimens.

FR-PO561

Risk of Liver Injury After alpha-Glucosidase Inhibitors Therapy in Advanced Chronic Kidney Disease Patients: A Population-Based Study

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Background: α-glucosidase inhibitors (AGIs) are commonly used to control postprandial blood glucose. However, AGIs-related liver injury has been reported, but whether the relationship of AGIs and liver injury applies to advanced chronic kidney disease (CKD) patients remains uncertain.

Methods: In the nationwide case-control study, we recruited advanced diabetic CKD patients, who has taken AGIs from January 1, 2000 through December 31, 2010 as cases and matched 5295 matched controls. Recent and former AGIs users were defined as patients who received the AGIs prescription 30-60 days and 30-210 days before the event, respectively. Safety, tolerability and laboratory results were assessed by chart review. Models predicting sustained virologic response (SVR) were performed.

Results: The age of enrollee is 63 ± 11 years and nearly 51% is men. Liver injury developed in 3.9% of cases and 3.3% of control patients. Patients who received insulin treatment (p=0.03), had chronic liver disease (p=0.01) were predictive to liver injury. AGIs use did not increase the risk of liver injury in advanced CKD patients (p=0.22), both among recent users (P=0.20) or former users (P=0.22). The stratified analysis showed no increased risk of liver injury in virus hepatitis, liver cirrhosis, subsequent end stage renal disease or patients who has diabetic related comorbidities. (all p> 0.05).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: Available evidence supports expansion of AGIs use in patients with advanced CKD, without increased risk of liver injury. Neither accumulated dose-dependent effect of AGIs, or subsequent ESRD will aggravated AGI-associated liver injury. Further randomized controlled trials are warranted to confirm our results.

Funding: Government Support - Non-U.S.

FR-PO562

Add-On Renoprotective Effect of Pentoxifylline in Pre-Dialysis Advanced Chronic Kidney Disease Treated with Renin-Angiotensin-Aldosterone System Blockade – A Nationwide Database Analysis

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Background: Pentoxifylline decreases proteinuria in patients with glomerular disease due to its anti-inflammatory and anti-fibrotic properties. A combination therapy of pentoxifylline with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) decreased proteinuria and the glomerular filtration rate (GFR) decline in early chronic kidney disease (CKD). Whether adding pentoxifylline to ACEI/ARB provides additional benefits on renal outcome or survival is unclear in CKD stage 5 patients who have not yet received dialysis (CKD 5 ND).

Methods: A prospective cohort study was conducted based on the Taiwan National Health Insurance Research Database. From January 1, 2000 to June 30, 2009, we enrolled 14,117 CKD 5 ND patients with serum creatinine levels >6 mg/dL and hematocrit levels <28% and who have been treated with ACEI/ARB. All patients were further divided into two groups with or without pentoxifylline within 90 days after starting erythropoiesis-stimulating agent therapy (index date). Patient follow-up took place until dialysis, death before initiation of dialysis or December 31, 2009.

Results: With a mean follow-up of 12 months, 9,867 patients (69.9%) required long-term dialysis and 2,805 (19.9%) died before progression to end-stage renal disease requiring dialysis. After propensity score-matching, add-on use of pentoxifylline was associated with a lower risk for long-term dialysis or death in those treated with ACEI/ARB (HR, 0.94; 95% CI, 0.89-0.99) or ARB (HR, 0.93; 95% CI, 0.88-0.98).

Conclusions: Pentoxifylline exhibited an add-on renoprotective effect in reducing the risk for long-term dialysis in CKD 5 ND patients who received renin-angiotensin-aldosterone system blockade. Randomized studies are needed to validate this association.

FR-PO563

Novel Therapy Regimens Have Reduced the High Risks of Bladder and Haematological Malignancies in ANCA-Associated Vasculitis

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1Leiden Univ Medical Center; 2Meander Medical Center Amersfoort.

Background: The introduction of immunosuppressive therapy has dramatically improved the prognosis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). As a result, attention has shifted to long-term complications in patients. In this study, we investigate the incidence of malignancies in AAV patients. Additionally, we investigate the effect of therapy on malignancy incidence.

Methods: We included patients with histopathologically-proven AAV diagnosed at a large university hospital. Malignancy incidence was assessed with the Dutch National Pathology Database, which covers all the histologically confirmed malignancies diagnosed in The Netherlands. We used the Netherlands Cancer Registry incidence rates for comparing the malignancy incidence in our AAV cohort to that of the general Dutch population.

Results: Thirty-six of 138 patients with AAV developed a total of 85 malignancies during a mean follow-up of 9.7 years. We observed 61 non-melanoma skin cancers (NMSCs), three colon carcinomas, three breast carcinomas, three prostate carcinomas, two lung carcinomas, two soft tissue sarcomas, two unknown primary malignancies, and a variety of malignancies that occurred only once. The gender-, age-, and calendar year-adjusted malignancy risk was 2.21-fold (95% CI: 1.64–2.92) higher than that in the general population. Only the incidence of NMSCs was significantly increased compared to the general population (standardized incidence ratio: 4.23, 95% CI: 2.76–6.19). Malignancy risk was associated with the duration of cyclophosphamide therapy, and was not increased in patients that received cyclophosphamide for less than 1 year.

Conclusions: AAV patients have a higher risk of malignancies than the general population, but this risk is accounted for solely by NMSCs. Throughout the years, the risk of other malignancies—specifically bladder and haematological malignancies—has decreased in patients with AAV. This finding reflects the beneficial results of ongoing efforts to reduce cyclophosphamide exposure by developing new therapy regimens.

FR-PO564

Effect of Lowering LDL-Cholesterol with Simvastatinplus Ezetimibe on Non-Vascular Outcomes in Patients with Chronic Kidney Disease (CKD): Results from the Study of Heart and Renal Protection (SHARP)


Background: The Study of Heart and Renal Protection (SHARP) was a randomized placebo-controlled trial of LDL-cholesterol (LDL-C)-lowering among 9270 patients with CKD which showed that combination therapy with ezetimibe 10mg/ simvastatin 20mg (E/S) reduced vascular events with no significant adverse effects on muscle, hepatobiliary outcomes or cancer. However, assessment of the effects of lowering LDL-C on other non-vascular outcomes has not been extensively explored in patients with CKD.

Methods: All post-randomization serious adverse events (SAEs) were routinely recorded. Post-hoc intention-to-treat analyses were performed of the effect of allocation to treatment on time to first non-vascular SAE by system of disease with sub-categories.

Results: During 4.9 years’ median follow-up, similar numbers of participants in the two groups experienced non-vascular SAEs overall (3533 [76.0%] E/S vs 3505 [75.9%] placebo; risk ratio [RR] 1.00, 95% CI 0.95-1.05). After due allowance for multiplicity, there was no evidence of any SAE or hazard of E/S vs placebo in cardiovascular disease or any other system of disease. Within the class of endocrineology SAEs, there were no significant effects of E/S on any particular individual category of SAE: new-onset diabetes (172 [4.8%] E/S vs 162 [4.5%] placebo); RR 1.06, 95% CI 1.06-1.34 among 3596 vs 3580 participants without diabetes at baseline), diabetes-related complications (136 [2.9%] E/S vs 126 [2.7%] placebo; RR 1.08, 95% CI 0.84-1.37), and other endocrine disorders (58 [1.2%] E/S vs 39 [0.8%] placebo; RR 1.47, 95% CI 0.99-2.19).

Figure: Effect of ezetimibe/simvastatin on non-vascular serious adverse events

Ezetimibe/simvastatin vs Placebo

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>E/S</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>491 (50.5%)</td>
<td>481 (49.3%)</td>
<td>1.01 (0.98-1.04)</td>
</tr>
<tr>
<td>Renal</td>
<td>235 (24.9%)</td>
<td>232 (23.9%)</td>
<td>1.01 (0.92-1.23)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>164 (17.3%)</td>
<td>164 (17.3%)</td>
<td>1.00 (0.84-1.20)</td>
</tr>
<tr>
<td>Glomerular nephritis</td>
<td>103 (11.5%)</td>
<td>97 (10.7%)</td>
<td>1.02 (0.81-1.28)</td>
</tr>
<tr>
<td>Skin</td>
<td>242 (25.7%)</td>
<td>245 (26.4%)</td>
<td>0.99 (0.90-1.08)</td>
</tr>
<tr>
<td>Reproduction</td>
<td>178 (18.9%)</td>
<td>183 (19.5%)</td>
<td>0.97 (0.87-1.07)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>76 (8.1%)</td>
<td>74 (7.9%)</td>
<td>1.05 (0.85-1.31)</td>
</tr>
<tr>
<td>Neurological</td>
<td>228 (24.7%)</td>
<td>227 (24.0%)</td>
<td>1.03 (0.85-1.25)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>491 (47.2%)</td>
<td>480 (45.5%)</td>
<td>1.03 (0.83-1.28)</td>
</tr>
<tr>
<td>Haematological</td>
<td>234 (24.8%)</td>
<td>245 (26.1%)</td>
<td>0.99 (0.76-1.32)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>191 (20.2%)</td>
<td>189 (20.1%)</td>
<td>1.00 (0.80-1.24)</td>
</tr>
<tr>
<td>Ane, and treat.</td>
<td>72 (1.5%)</td>
<td>68 (1.4%)</td>
<td>1.04 (0.59-1.84)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>312 (6.7%)</td>
<td>317 (6.8%)</td>
<td>0.99 (0.78-1.27)</td>
</tr>
<tr>
<td>Other medical</td>
<td>902 (97.0%)</td>
<td>904 (97.0%)</td>
<td>1.00 (0.80-1.24)</td>
</tr>
<tr>
<td>Trauma</td>
<td>363 (3.9%)</td>
<td>349 (3.7%)</td>
<td>1.00 (0.64-1.55)</td>
</tr>
<tr>
<td>Total</td>
<td>363 (3.9%)</td>
<td>349 (3.7%)</td>
<td>1.00 (0.64-1.55)</td>
</tr>
</tbody>
</table>

Conclusions: In the SHARP trial, allocation to ezetimibe 10mg plus simvastatin 20mg reduced vascular events with no evidence of significant non-vascular hazards.

Funding: Pharmaceutical Company Support Merck/Schering-Plough Pharmaceuticals (North PA, USA), Government Support - Non-U.S.

FR-PO565

Association of β-Blocker Therapy with Renal Outcomes in CKD Patients without prior Cardiovascular Disease

Naoshiko Fujii,1 Takayuki Hamano,2 Yoshitsugu Ohi,3 Yoshitaka Isaka.3 1Univ of Pennsylvania, Philadelphia, PA; 2Osaka Univ, Suita, Osaka, Japan; 3Univ of California, Irvine, Irvine, CA; 4Osaka General Hospital, Osaka, Japan.

Background: Sympathetic overactivity due to impaired kidney function can deteriorate hypertension, renal failure, and cardiovascular disease (CVD) among CKD patients. Mortality benefit of its antagonist, β-blocker (BB), has been shown in patients with prior CVD; however, such evidences are scarce in CKD patients without CVD. Our aim is to evaluate the association between BB and renal outcomes in such patients.

Methods: We extracted 340 predialysis CKD patients without prior CVD but with drug information at baseline from a Japanese CKD cohort (OVIDS-CKD, N=738). The primary
endpoint was a composite of Cr doubling, initiation of RRT, and death. We performed Cox proportional hazards analysis to estimate the hazards ratio (HR) of BB use at baseline, adjusting for other parameters, such as sex, eGFR, proteinuria, diabetes, BMI, blood pressure, the number of anti-hypertensive drugs, ACEI/ARB use, HB, Alb, corrected Ca, iP, and FGF23. We also employed 1:k (k=1–6) propensity-score full matching, where one BB user matched to at most k non-users.

**Results:** BB users showed significantly lower eGFR, more proteinuria, higher BMI, more anti-hypertensive drugs, lower Alb, higher 1-84 PTH, higher FGF23, and lower 25OHD levels, most of which suggested a poor risk for CVD at baseline. During a median follow-up of 6.6 years, 109 patients reached the outcome. Of these, 12 patients died before RRT, 71 reached a doubling of Cr, and 26 started dialysis. A multivariable Cox model with covariates that were significantly different between BB users and non-users at baseline showed non-significant HR of 1.58 (C.I. 0.86 – 2.90). We also evaluated a fully-adjusted model and a parsimonious model with a stepwise backward-elimination method; however, the results remained non-significant. The 1:k (k=1-6) full matching using propensity score did not show significant results, either. (0.93 (0.52 – 1.68)).

**Conclusions:** The BB therapy was not associated with renal outcomes in CNP patients without prior CVD. Confirmation in a larger study is required.

**Funding:** Pharmaceutical Company Support - Kyowa Hakko Kirin

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**FR-PO566**

*Lactobacillus plantarum 299v* Reduces the Incidence of Clostridium difficile Infection in Patients Treated with Antibiotics in the Nephrological and Transplantation Department Marcin Adamczak, Agata Kujawa-Szewieczek, Katarzyna Kwiecien, Sylvia Malgorzata Dudzicz, Magdalena Gazda, Andrzej Wiecek. Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland.

**Background:** Lactobacillus plantarum 299v (LP299v) has been introduced into the clinical practice in order to reduce gastrointestinal symptoms during antibiotic exposure. However it remains controversial whether or not probiotics are also effective in the prevention of Clostridium difficile infections (CDI) among patients receiving antibiotics.

The aim of this clinical, retrospective, single-centre study was to compare the CDI frequencies among patients receiving antibiotics and hospitalized in the period before and after initiation of LP299v routine use, as a prevention of CDI, in the nephrology and transplantation ward.

**Methods:** Among 3533 patients hospitalized in Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia in Katowice during two years (October 2012 – October 2013 and December 2013 – December 2014) 23 patients with CDI were diagnosed and enrolled in this study. Since November 2013 prevention of C. difficile infection with the oral use of LP299v was performed in all patients treated with antibiotics and who were at a high risk of developing CDI (patients after organ transplantation and receiving immunosuppressive drugs for any other reasons). For the further analysis the observation period was divided into two twelve-months intervals before (October 2012 to October 2013) and after initiation of LP299v use as the prophylactic manoeuvre against CDI (December 2013 to December 2014).

**Results:** It was found a significant (p<0.001) reduction of the number of cases of C. difficile infection after beginning of LP299v routinely used (n=2, 0.11% of all hospitalized patients) compared with the previous twelve-months period of observation (n=21; 1.21% of all hospitalized patients).

**Conclusions:** Routine use of Lactobacillus plantarum 299v during treatment with antibiotics may prevent C. difficile infection, particularly in patients at high risk of CDI in the nephrology and transplantation ward.

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

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**FR-PO567**


**Background:** Patients with chronic kidney disease (CKD) are commonly prescribed drug doses that are excessive for their kidney function. Many CKD patients are followed solely by a family physician. We wish to determine whether care by both a nephrologist and family physician (i.e. comanagement) versus family physician alone is associated with lower risks of inappropriate antibiotic dosing in patients with stage 4 or 5 CKD.

**Methods:** A retrospective case-control study was conducted, among individuals aged >66 years, with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² using linked healthcare databases from 2003-2014. Cases were antibiotic prescriptions dosed inappropriately, whereas controls were prescriptions dosed appropriately. Exposure was comanagement, defined as at least one outpatient visit with a nephrologist in the 1 year prior to antibiotic prescription. A multivariable logistic regression model was used to determine the independent association between comanagement and inappropriate dosing.

**Results:** Of 21,848 eligible prescriptions studied, 64% were inappropriately dosed. The patients were 82 (IQR 76-87) years of age with comorbidities including: hypertension (89%), diabetes (49%), coronary artery disease (49%), and congestive heart failure (38%). 77% of all prescriptions were prescribed by family physicians and 2% were prescribed by nephrologists. Multivariable analysis revealed that patients with appropriate prescriptions were more likely to have seen a nephrologist in the one year prior with an unadjusted odds ratio of 1.07 (95% CI 1.01-1.14, p=0.02), adjusted odds ratio 1.23 (95%CI 1.15-1.32, p<0.001).

**Conclusions:** In patients with stage 4 or 5 CKD prescribed an antibiotic, those with an appropriate dose were 23% more likely to have been cared for by a nephrologist in the previous year. Although we cannot conclude what caused the improved prescribing practice, this improvement may, in part, explain the improved patient outcomes associated with seeing a nephrologist in observational studies.

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**FR-PO568**

Variation in Co-Medication Use According to Kidney Transplant Immunosuppressive Regimen: Application of Integrated Registry and Pharmacy Claims Data Krista L. Lenting,1 Abhijit S. Naik,2 Faramarz Ismail, Abhijit S. Naik,2 Mark Schnitzler,1 Veena Rao,3 David A. Axelrod,1 Jiaying Chen,1 Daniel C. Brennan,3 Dorry L. Segev,3 Bertram L. Kasiske,4 Vikas R. Dharnidharka.1 1Saint Louis Univ; 2Univ Michigan; 3Dartmouth; 4Washington Univ; 5Johns Hopkins; 6Univ Minnesota.

**Background:** While modern immunosuppressive therapies (ISx) have substantially reduced acute rejection, ISx medications have many side effects, and transplant recipients must take an array of “co-medications” to help mitigate complications. Co-medication utilization patterns are not well described in large, representative samples due to lack of available data.

**Methods:** We designed national U.S. transplant registry data with pharmacy records (2005-2010) from a large pharmaceutical claims clearinghouse to examine treatments for anemia, metabolic disorders and infections according to ISx regimen in mo 6-12 post-transplant (N=22,453). Associations of ISx with co-medication use (adjusted odds ratio, aOR) were examined with multivariable logistic regression including adjustment for recipient, donor and transplant factors.

**Results:** Compared to a reference regimen of tacrolimus (Tac), mycophenolate (MPA) and prednisone, rapamycin-based ISx was associated with significantly (P<0.05) higher use of ESAs (aOR 2.52, iron (aOR 2.26), statins (aOR 1.47), fibrates (aOR 2.35), and phosphorous binders (aOR 2.85) (Figure). Cyclosporine-based ISx was associated with more common use of anemia treatments. Compared to those taking triple ISx, recipients of tacrolimus-based dual and mono-therapies had lower use of statins, ACE/ARBs, and anti-bacterial agents. Recipients of steroid-free ISx were less commonly treated for new onset diabetes.

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

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**FR-PO569**

Association of Urinary Biomarkers of Injury and Repair with Incident Chronic Kidney Disease in Type 2 Diabetes: An Ancillary Study of the ACCORD Trial Girish N. Nadkarni,1 Vecna Rao,2 Faramarz Ismail-beigi,3 Vivian A. Fonseca,4 Sudhir V. Shah,5 Michael S. Simonson,3 Prasad Devarajan,6 Chirag R. Parikh,7 Steven G. Coca.1 1Mount Sinai; 2Yale Univ; 3Case Western Reserve Univ; 4Tulane Univ; 5UAMS; 6Univ of Cincinnati.

**Background:** Urinary kidney injury molecule (KIM)-1, monocyte chemoattractant protein (MCP)-1, interleukin (IL)-18, and YKL-40 are biomarkers representing renal injury, inflammation, and fibrosis. We evaluated their association with incident CKD3b in the ACCORD trial.

**Methods:** We designed a case-cohort study of 721 participants & measured KIM-1, MCP-1, IL-18, and YKL-40 in urine samples with Mesoscale platform. Biomarker associations with CKD3b were modeled continuously & by tertiles using Cox proportional hazards models.

**Results:** Mean age was 62, 51% were female & baseline eGFR was 88 ml/min. There were 159 incident CKD3b events over median (IQR) of 4.2(3.9-4.7) years. Top tertiles of all biomarkers had higher proportions of incident CKD3b. After adjusting for demographics,
clinical characteristics, baseline eGFR & UACR, highest tertiles of uMCP1 & uKIM1 had adjusted HRs of 1.82(95% CI 1.18-2.81) & 1.51(95% CI 1.01-2.27) respectively. Area under ROC improved from 0.70(with eGFR & UACR) to 0.72 with addition of uMCP1 & uKIM1(p<0.05). No association was seen for urinary IL-18 & YKL-40. Under ROC, improved from 0.70 with eGFR & UACR to 0.72 with addition of uMCP1 & uKIM1(p<0.05). No association was seen for urinary IL-18 & YKL-40.

Adjusted associations of TDF exposure with urine α1m levels

<table>
<thead>
<tr>
<th>TDF Exposure</th>
<th>% Estimate1 (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current vs never TDF use</td>
<td>30 (25.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past vs never TDF use</td>
<td>43 (1.84)</td>
<td>0.006</td>
</tr>
<tr>
<td>Duration off TDF (per year)</td>
<td>-3 (8.4)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

1 Estimated % difference in α1m attributable to each TDF exposure variable, adjusted for demographics, traditional kidney risk factors, and HIV-related factors.

Conclusions: In HIV-infected men, TDF exposure was strongly associated with higher urine α1m levels. α1m is a promising biomarker for the detection and monitoring of TDF-associated tubular toxicity.

Funding: NIDDK Support

FR-PO571
Impact of Kidney Function and Urinary Protein Excretion on Pulmonary Function
Yusuke Nakada,1,2 Tadashi Toyama,1 Shinji Kitajima,2 Akinori Hara,2 Miho Shimizu,2 Yasunori Iwata,2 Norihiko Sakai,2 Kengo Furuchi,2 Takashi Wada.2,3 Clinical Laboratory, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan; 3Dept of Laboratory Medicine, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan.

Background: Although the cardiorenal relationship in patients with chronic kidney disease (CKD) has been investigated, information about the lung-kidney relation is limited. Here, we investigated the impacts of kidney function and urine protein excretion on pulmonary dysfunction.

Methods: The data of pulmonary function tests (PFTs) and kidney function tests from 1 April 2005 to 30 June 2010 were selected from our laboratory database. Data were classified into 4 categories according to eGFR and proteinuria. Category 1: eGFR ≥ 60 ml/min/1.73 m² and urinary protein < 0.3 g/gCr; Category 2: eGFR ≥ 60 ml/min/1.73 m² and urinary protein ≥ 0.3 g/gCr. Category 3: eGFR ≥ 60 ml/min/1.73 m² and urinary protein ≥ 0.3 g/gCr; Category 4: eGFR ≥ 60 ml/min/1.73 m² and urine protein ≥ 0.3 g/gCr. Pulmonary function data were evaluated according to these 4 categories.

Results: A total of 133 participants without major respiratory disease, abnormal computed tomography and smoking history were enrolled. Hb-adjusted %DLCO in category 4 (46.2 ± 7.5) and category 2 (63.6 ± 17.8) were significantly lower than that in category 1 (75.8 ± 18.9) (P= 0.05). Hb-adjusted %DLCO was strongly correlated with eGFR in participants with urinary protein ≥ 0.3 g/gCr (R = 0.81, P<0.001). In addition, eGFR was associated with Hb-adjusted %DLCO (P= 0.023) and urinary protein tended to be associated with Hb-adjusted %DLCO (P= 0.095) after adjusting for physical features and the presence or absence of DM and Hypertension.

Conclusions: This study suggests that eGFR and urinary protein excretion were associated with pulmonary function (Hb-adjusted %DLCO).

FR-PO570
Association of Tenofovir Disoproxil Fumarate Exposure with Urine α1-microglobulin, a Biomarker of Proximal Tubule Dysfunction
Vasantha Jotwani,1 Rebecca Scherer,1 Michelle M. Estrella,2 Chirag R. Parikh,2 Tadashi Toyama,2 Shinji Kitajima,2 Yasuyuki Joachim H. Ix,4 Michael Shlipak.

Background: Tenofovir disoproxil fumarate (TDF) is a well-recognized contributor to HIV-related kidney disease, via proximal tubular injury. Urine α1-microglobulin (α1m), a low molecular weight protein indicative of proximal tubule dysfunction, may enable earlier detection of TDF-associated toxicity.

Methods: In this cross-sectional study of 883 HIV-infected men enrolled in the Multicenter AIDS Cohort Study Cohort Study, we evaluated associations of TDF exposure with urine α1m levels, using multivariable generalized gamma regression models to adjust for traditional kidney risk factors, and HIV-related factors.

Results: Mean age was 52 and mean eGFR was 90 ml/min/1.73m². Median TDF exposure duration was 4.2 years (IQR:2.3,6.1) among the 573 (65%) current and 112 (13%) former TDF users. Cumulative TDF duration was linearly associated with higher urine α1m levels (p<0.0001). 24-fold effect size relative to age (2% per year). Compared with men who never received TDF, α1m levels were 43-50% higher in former and current TDF users. Time since last TDF exposure was only modestly associated with lower α1m.

Adjusted associations of TDF exposure with urine α1m levels

<table>
<thead>
<tr>
<th>Events</th>
<th>Adjusted HR(95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Current vs never TDF use</td>
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Conclusions: Urinary levels of MCP1 and KIM1 are independently associated with incident CKD3b & marginally added to risk prediction after accounting for clinical variables including eGFR/albuminuria. 

Funding: NIDDK Support

FR-PO570
Association of Tenofovir Disoproxil Fumarate Exposure with Urine α1-microglobulin, a Biomarker of Proximal Tubule Dysfunction

Vasantha Jotwani,1 Rebecca Scherer,1 Michelle M. Estrella,2 Chirag R. Parikh,2 Tadashi Toyama,2 Shinji Kitajima,2 Yasuyuki Joachim H. Ix,4 Michael Shlipak.

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Funding: NIDDK Support

FR-PO570
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Vasantha Jotwani,1 Rebecca Scherer,1 Michelle M. Estrella,2 Chirag R. Parikh,2 Tadashi Toyama,2 Shinji Kitajima,2 Yasuyuki Joachim H. Ix,4 Michael Shlipak.

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Adjusted associations of TDF exposure with urine α1m levels

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Funding: NIDDK Support
FR-PO572
Renal Biomarkers in Diabetes, Role Beyond Retinopathy, Relation to Renin-angiotensin System.
Mohamed E. Elragael,1 Ahmed Fathy Elkeraie,2 Ahmed M. Abdelhadi,1 Ashraf Nabil Abdalla,4
1Nephrology, Alexandria Univ, Alexandria, Egypt; 2Dept of Environmental Medicine, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 4Pharmacology, Umm Al-Qura Univ, Saudi Arabia.

Background: Diabetic nephropathy and retinopathy remain two of the most frequent complications of diabetes and is the leading cause of end-stage renal disease (ESRD) and blindness worldwide. The concordance rate between both complications is often present in diabetic patients.

Methods: We tried to study the relation between renal biomarkers including serum creatinine (SCr), urinary albumin/creatinine ratio (ACR), serum cystatin-C (cysC) and urinary NGAL (uNGAL) with diabetic retinopathy (DR) in 100 diabetic patients. Patients were classified according to severity into 3 stages: no diabetic retinopathy (No DR), Non-Proliferative DR (NPDR) and proliferative DR (PDR).

Results: Urinary ACR, serum cysC and uNGAL were higher significantly among patients with DR (NPDR & PDR) than patients without, while SCr showed a non significant rise with progression of retinopathy. All markers were higher among PDR than NPDR group.

Conclusions: Renal biomarkers namely urinary ACR, serum cysC and uNGAL may point to a more advanced stage of diabetic retinopathy, which might be an aid to identify the degree of retinopathy beside the traditional fundus examination in diabetic patients.

FR-PO573
Prognostic Importance of Urea and Urea: Creatinine Ratio for Mortality as Compared to Creatinine Concentrations Alone in the General Population
Ronan Cusack,1, 2 Austin G. Stack,1, 2 John P. Ferguson.1
1Nephrology, Univ Hospital Limerick, Ireland; 2Graduate Entry Medical School, Univ of Limerick, Ireland.

Background: High Creatinine (Cr) concentrations reflect poor kidney function and is the leading cause of end-stage renal disease (ESRD) and blindness worldwide. The concordance rate between both complications is often present in diabetic patients.

Methods: A cohort of 15,773 non-pregnant subjects age ≥20, representative of the U.S. population, were identified from the Third National Health and Nutrition Examination Survey (1988-1994). Vital status was obtained through linkage with the National Death Index through to 2006. Subjects were classified into categories of Cr, BUN and Cr/creatinine ratio, are better predictors of mortality in the general population.

Results: In a multivariable analysis, BUN was found to be the most important single predictor of mortality with Cr being second best. A strong interaction (P<0.001) between BUN and Cr with mortality was identified and explored by fitting stratified models, as shown below.

Conclusions: Both BUN and Cr independently predict death in the general population. Among patients with malnourished states (Low BUN), higher Sc were associated with lower mortality. In contrast, among patients with normal-high BUN concentrations, higher Cr was associated with elevated death risk. Risk Prediction models should take BUN levels into consideration when estimating future death risk.

Funding: Government Support - Non-U.S.

FR-PO574
Kazuhiko Tsuruya,2 Takanari Kitazono,1 Yutaka Kiyohara,1, 3 Shoichi Nomiyaomi,2, 3
1Dept of Environmental Medicine, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 2Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: The term protein-energy wasting (PEW) implies a state of depleted protein and/or energy stores. An International Society of Renal Nutrition and Metabolism (ISRNM) panel proposed objective criteria for the definition of PEW syndrome. However, the extent to which these variables used in PEW syndrome definition are indicative of low protein or energy stores is unknown. Muscle is the largest protein store and fat mass is the largest energy store in the body. Therefore, we examined the associations of these variables with low lean body mass (LBM) and fat mass (FM) measured by DXA scans in 11,834 participants in the 1999-2004 National Health and Nutrition Examination Survey (NHANES).

Methods: Definitions of PEW variables are summarized in the table. The associations of each PEW variable with LBM and FM in the entire cohort and CKD (CKD-EPI eGFR < 60) sub-population were examined in linear regression models using svy suite in STATA 13.

Results: Mean age was 46.0 yrs, 50.3% were male, 9.5% were black. 6.7% had CKD. Unintentional weight loss and low levels of serum albumin, serum cholesterol, BMI and MAMC were associated with lower LBM and FM. On the other hand, low protein and energy intakes were associated with higher LBM and FM.

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

<table>
<thead>
<tr>
<th>PEW variables</th>
<th>lean body mass (kg)</th>
<th>Fat mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin &lt; 3.25 g/dl</td>
<td>-3.5(-7.5, 0.4)</td>
<td>-3.6(-7.2, -0.1)</td>
</tr>
<tr>
<td>Cholesterol &lt; 100 mg/dl</td>
<td>-2.5(-6.8, 1.8)</td>
<td>-10(-6.0, 0.1)</td>
</tr>
<tr>
<td>BMI &gt; 20 kg/m²</td>
<td>-0.7(-1.0, -0.9)</td>
<td>-0.7(-1.4, -0.1)</td>
</tr>
<tr>
<td>Unintentional weight loss &gt; 10% over 1 yr</td>
<td>-2.2(-3.3, -1.0)</td>
<td>-3.8(-5.2, -2.4)</td>
</tr>
<tr>
<td>Body fat % &gt; 10%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Low MAMC*</td>
<td>-8.6(-9.0, -8.3)</td>
<td>-8.4(-8.9, -7.9)</td>
</tr>
<tr>
<td>Protein intake &lt; 0.6 g/kg/day</td>
<td>3.6(3.0, 4.2)</td>
<td>6.4(5.7, 7.0)</td>
</tr>
<tr>
<td>Energy intake &gt; 25 kcal/kg/day</td>
<td>4.5(3.9, 5.7)</td>
<td>7.3(6.9, 7.7)</td>
</tr>
</tbody>
</table>

*10% or more lower than the 50th percentile of reference group

Results were similar in the CKD sub-population.
Conclusions: Serum chemistry, body weight and muscle mass PEF criteria appear to be highly sensitive of both protein stores (as indicated by LBM) and energy stores (as indicated by FM). Dietary variables are not reflective of protein or energy wasting. A modified PEW syndrome definition without the dietary variables would be a better indicator of PEW syndrome.

Funding: NIDDK Support

FR-PO576 Low-Proteinuric CKD and Risk of ESRD in Nephrology Clinics: Emerging Role of Serum Phosphorus  
Luca De Nicola, Michele Prozenzano, Paolo Chiodini, Giuseppe Conte, Roberto Minutolo. 1  
Nephrology, Second Univ, Naples, Italy; 2  Med Stat, Second Univ, Naples, Italy.

Background: In low-proteinuric (LP) CKD, factors other than proteinuria (Uprot) likely act as predictors of ESRD. However, comprehensive assessment of epidemiologic features of LP versus high-proteinuric (HP) patients is still lacking. This information is critical in renal clinics where LP patients are common.

Methods: We pooled three prospective cohorts that in 2000-2010 enrolled 2,488 CKD patients stage III-IV under stable care from 26 months in 40 Italian renal clinics. Patients were followed for ESRD (chronic dialysis-transplant) up to 12/2014. Patients were classified in two groups, LP (56%) and HP (44%), by Uprot ≥0.5 and <0.5 g/24h, respectively.

Results: Besides lower Uprot (median, IQR: 0.15, 0.06-0.28 vs 0.50, 0.28-2.07 g/24h), LP differed from HP because male gender (55 vs 62%), diabetes (28 vs 55%) and use of anti-RAS (73 vs 78%) were less frequent. In LP, moreover, age (70±12 vs 65±14), GFR-EPI (35.2±13.3 vs 26.6±13.2 mL/min/1.73m²) and HB (12.7±1.7 vs 12.3±1.8 g/dL) were higher while systolic BP (137±18 vs 140±18 mmHg) was lower. Serum phosphorus (P) was lower in LP (1.23±0.83 mg/dL, P<0.001), Hb (12.9±1.7 vs 12.4±1.6 g/dL, P=0.001) for all comparisons. History of cardiovascular disease (CVD), BMI and uric acid levels did not differ. Over a median follow-up of 38 months, ESRD occurred in 154 LP and 422 HP, (incidence rate 2.9 and 12.2/100 pts/ys). At multivariable Cox analyses (HR, 95% CI), significant predictors of ESRD were male gender, younger age and lower GFR (consistent in LP and HP). Only in LP, however, P (1.28, 1.02-1.61) and lower BMI (0.96, 0.93-0.99) predicted renal risk while CVD (1.28, 1.03-1.60), HB (0.99, 0.85-0.97) and anti-RAS (0.74, 0.60-0.91) had a prognostic role exclusively in HP. A negative interaction P×Uprot was detected in HP (beta=−0.046, P=0.004). Results were consistent across cohorts.

Conclusions: In renal clinics, LP patients are prevalent and characterized by nontrivial renal risk despite higher GFR. Risk factors for HP are common; in particular, results in LP and HP suggest that lower Uprot allows full expression of the negative role of P, the effect being evident for P levels mostly normal.

FR-PO577 Trends in CKD Awareness in the U.S. Population, 1999-2012, Overall and by KDIGO Risk Groups  
Yunnuo Zhu, 1  Tanushree Banerjee, 2  Delphine S. Chiodini, 3  Luca De Nicola, 1  Giuseppe Conte, 1  Roberto Minutolo. 1  
Nephrology, Second Univ, Naples, Italy; 2  Med Stat, Second Univ, Naples, Italy.

Background: Efforts to increase awareness among providers and patients may be reaching those at greatest risk for CKD progression has increased. Recent education initiatives may be indicative of both protein stores (as indicated by LBM) and energy stores (as indicated by FM). Dietary variables are not reflective of protein or energy wasting. A modified PEW syndrome definition without the dietary variables would be a better indicator of PEW syndrome.

Funding: NIDDK Support

FR-PO578 Intermittent Abnormal Kidney Function and Mortality in Community Dwelling Individuals  
Donal J. Sexton, 1  Scott Reule, 2  Robert N. Foley. 1  Medicine, HRB Clinical Research Facility, NUIGalway, Galway, Ireland; 2  Medicine, Univ of Minnesota, Minneapolis.

Background: The health implications of persistently abnormal kidney function as measured by estimated glomerular filtration rate and spot urinary albumin excretion has been well characterized to date. However little data is available regarding the implications of intermittent abnormalities in these tests as defined by established thresholds.

Methods: We evaluated the frequency of intermittent abnormal kidney function and its association with all-cause mortality in the US general population using the National Health and Nutrition Examination Survey III, 1988-1994. Mortality linkage data were available through December 2006. Estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI equation and urinary albumin-creatinine ratios (ACR) were measured twice, a mean of 17 days apart (N=1161).

Results: Proportions of abnormal tests included: for eGFR <60 ml/min/1.73m² either test 7.32%, first test 5.94%, second test 5.68%, first test only 1.64%, second test only 1.38%, both tests 4.31%. Compared to participants with eGFR ≥60 ml/min/1.73m² on both testing occasions, adjusted hazard ratios were 1.8 (95%CI 1.3, 2.4) for intermittent and 1.7 (95%CI 1.1, 2.5) for persistent abnormal eGFR. Proportions with ACR ≥30 mg/g were as follows: either test 16.54%, first test 11.63%, second test 13.35%, first test only 3.19%, second test only 4.91%, both tests 8.84%. Compared to those with ACR <30 mg/g on both occasions’ mortality hazard ratios for intermittent abnormal function was 2.1 (95%CI 1.6, 2.7), and persistent abnormal 2.0 (95%CI 1.5, 2.8). Models were adjusted for age, sex, race, diabetes mellitus, cardiovascular disease (congestive heart failure, previous myocardial infarction or stroke), current smoking, self reported hypertension, systolic and diastolic blood pressure, total cholesterol and body mass index.

Conclusions: CKD as defined by established thresholds may be persistent or intermittent in community dwelling individuals. Participants with intermittently abnormal kidney function as defined by current thresholds were at similar mortality risk to those with persistent abnormal function on both occasions.

FR-PO579 Renal Outcome of APRT Deficiency Presenting in Childhood  
Hrafnhildur L. Runolfsdottir, 1  Runolfur Palsson, 2  Iger Maria Agustsdottir, 3  Olafur S. Indridason, 2  Vidar O. Edvardsson. 1  
Medicine, HRB Clinical Research Facility, NUIGalway, Galway, Ireland; 2  Medicine, Univ of Iceland; 3  Faculty of Medicine, Univ of Iceland; 4  Div of Nephrology, Children’s Medical Center; Landspitali – The National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: Adenine phosphoribosyltransferase (APRT) deficiency is an inherited disorder of purine metabolism that leads to nephrolithiasis and chronic kidney disease (CKD). ICD-9 code data are available on APRT deficiency presenting in childhood.

Methods: All patients in the APRT Deficiency Registry of the Rare Kidney Stone Consortium who presented with clinical manifestations of the disorder and/or were diagnosed with the disease before age 18 years were included in the study. Presenting features, time to diagnosis and disease course were examined. Glomerular filtration rate (eGFR) was estimated with the modified Schwartz equation in children and the MDRD equation in adults. CKD was defined as eGFR <60 ml/min/1.73 m² and acute kidney injury (AKI) according to the KDIGO criteria. Data are presented as median (range).

Results: Nineteen children presented at the age of 1.6 (0.2-16.5) years. Presenting features included reddish-brown diaper spots in 11 patients (58%), kidney stones in 8 (42%) men), lower urinary tract symptoms in 8 (42%) and AKI in 2. The diagnosis was promptly made in 7 patients, while it was delayed in 12 (63%) patients for 15.2 (0.8-39.2) years. One patient, who did not receive drug treatment, developed ESRD at age 11 years. Twelve patients were placed on allopurinol at the age of 2.1 (0.6-16.5) years. During follow-up of 18.9 (1.7-31.5) years, 3 of these patients developed 4 kidney stone events and AKI occurred in 2 patients during episodes of volume depletion; none had developed CKD. Six patients did not begin chemotherapy up to age 29.8 (20.5-42.4) years. At last follow-up, at 43.9 (32.5-56.9) years of age, 3 had experienced a total of 9 kidney stone events, 2 had suffered AKI, 3 had stage 3 CKD and one had progressed to ESRD at the age of 44 years.

Conclusions: A substantial proportion of patients with APRT deficiency present in childhood. The commonly observed delay in diagnosis and treatment may have grave implications. APRT deficiency must be excluded in all children with kidney stones, renal dysfunction and reddish-brown diaper spots.

Funding: Other NIH Support - This study was supported by the Rare Kidney Stone Consortium (U54DK088790), a part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR). The Rare Kidney Stone Consortium is funded through collaboration between NCATS and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
FR-PO580

Association of Chronic Kidney Disease with Increased Risk of Recurrence of Upper Urinary Tract Urothelial Cancer – A Population-Based Study

Shang-Jyh Hwang,1 Ming-Yen Lin,1 Huei-Lan Lee,1 Wei-Ming Li,1 Chun-Nung Huang,1 Wen-Jeng Wu,1 Li-Tzong Chen,1 Sheng-wen Niu,2

1 Medical Univ Hospital, Kaohsiung, Taiwan; 2National Health Research Inst, Miaoli, Taiwan.

Background: Taiwan has significantly high incidence of upper urinary tract urothelial cancer (UTUC) and end-stage renal disease (ESRD). UTUC coexisted with chronic kidney disease (CKD). CKD may deteriorate cancer progression and increase mortality risk. The aim of study was to explore the association of CKD with the risk of UTUC recurrence.

Methods: We conducted a population-based cohort study through Taiwan National Health Insurance Research Dataset. Incident UTUC patient was extracted from Taiwan Cancer Registry Dataset and linked to data status of CKD including non-dialysis CKD, dialysis ESRD, and renal transplant were identified before the index date of UTUC. Recurrence was defined as either new tumor lesion in bladder, or at the other site of urinary tract, or occurrence of distant metastasis within 3 months after first surgery. Differences of characteristics between CKD and non-CKD group was described as mean ± standard deviation or percentage and tested by independent t test and chi-square test. Competing risk approach was used for estimating cause-specific hazard ratio (CSRHR) and 95% confidence interval (CI).

Results: Totally, 4,002 UTUC patients from 2001 to 2005 were included and tracked until disease recurrence or end of 5 years after the index date of UTUC. Near half patients accompanied with various stages and status of CKD at index date. UTUC patients with CKD were younger, more female, and had more co-morbidities than patients without CKD. After adjusting factors of age, tumor grade, and co-morbidities, CKD significantly increased risk of UTUC recurrence in female (CSRHR: 1.72, 95%CI: 1.13-2.61, p=0.001), but not in male (CSRHR: 0.91, 95%CI: 0.44-1.86, p=0.79).

Conclusions: CKD increases risk of recurrence in female UTUC patient and is an important prognostic indicator.(This study was granted by the Ministry of Science and Technology(NSC 102-2314-B-037-012-MY3) and by the Ministry of Health and Welfare (MOHW103-TD-B-111-05, MOHW104-TDU-B-212-124-003, budget from health and welfare surcharge of tobacco product.)

Funding: Government Support - Non-U.S.

FR-PO581

Single Centre Experience of Late Referral and Achievement of Useable Dialysis Access Over a 9-Year Period

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Background: We describe a single centre, retrospective analysis of late (≤ 90 days) referral for dialysis over a 9 year period from April 2003 till March 2012. Factors that contributed to late referral and success in creating permanent dialysis access were determined.

Methods: Data on adult patients referred ≤ 90 days from dialysis were collected including patient demographics, source of referral, mortality, reason for late referral, creation of permanent dialysis access and use of permanent dialysis access at first dialysis.

Results: One hundred and twenty-seven patients were referred in ≤ 90 days over the 9 year period. Ninety-nine (78%) patients were referred within 30 days prior to dialysis and 39 (22%) patients within 30 – 90 days. Their median age was 63 years and 90 (63%) patients were male. Twenty-five (20%) patients were diabetic. Forty (33%) patients died within the first year after referral, 25 (21%) patients within the first 6 months and 15 (12%) patients between 6 months and 1 year (figure1). Sixty-five patients (51%) presented late due to acute renal failure (myeloma 24, vasculitis 14, irreversible acute kidney injury 10, renal cell carcinoma 5, glomerulonephritis 3 and others 9). Twenty-nine patients (23%) referred by physicians and surgeons, and 24 patients (19%) referred by GPs were late referrals of patients with known chronic renal failure. Nine patients (7%) presented late due to lack of understanding of their disease, denial, and fear of the unknown. One hundred and ten patients had permanent dialysis access created and 17 patients no permanent access procedures. The average time to create permanent dialysis access was 44 days post-dialysis commencement. Six permanent haemodialysis access were created pre-dialysis, 56 post-dialysis; 19 peritoneal dialysis accesses were created pre-dialysis, 29 post-dialysis.

Conclusions: Overall the number of patients presenting late for dialysis has decreased. Late referral has a poor 1 year survival and most patients require haemodialysis long-term. Only a minority of patients referred late have permanent dialysis access created and used at their first dialysis.

FR-PO582

Abnormal Global Glomerular Sclerosis Rate in Remnant Kidney of Ipsilateral Nephrectomy is Associated with Higher Risk of End-Stage Renal Disease Within Five Years in Patients of Upper Urinary Tract Urothelial Cancer

Sheng-Chen Sheng,1 Sheng-Chen Sheng,1 Pei-Lin Liang,1 Shih-Mong Yeh,1 Ming-Yen Lin,2 Shang-Jyh Hwang,2 Wen-Jeng Wu,1 Kaohsiung Medical Univ, Taiwan; 2National Health Research Insts.

Background: Astrocytic acid in Chinese herbs induce renal tubulointerstitial disease and increase the risk of upper urinary tract urothelial carcinoma(UTUC). However, we are still not sure if UTUC itself has impact on renal outcome. We studied the pathological changes of remnant kidney tissue from UTUC patients post ipsilateral nephrectomy to investigate the correlation between renal histopathology and outcome of end-stage renal disease.

Methods: This cohort study included 132 cases of non-dialysis UTUC patients post ipsilateral nephrectomy from 2002 to 2010. We collected clinical and laboratory data before surgery, tumor size, whether into dialysis after surgery, and followed up to dialysis or to December 31, 2014. Renal histopathology was read by 3 specialists: nephrologists or pathologist. We used logistic regression for studying tubulointerstitial fibrosis score and global glomerular sclerosis (GGS) rates and Cox regression to investigate factors associated with renal survival.

Results: There was no significant factor associated with tubulointerstitial fibrosis, but advanced CKD was significantly related to GGS rate adjusted with age and gender [OR(95%CI): 4.8(1.4-16.9), p=0.014]. Kaplan-Meier survival curve showed five-year renal survival rate was 86.3%. Factors affect five-year renal survival were hypertension [HR(95%CI): 4.0(1.1-15.2), p=0.043] and GGS rate [HR(95%CI): 17.4(2.4-124.1), p=0.004].

Conclusions: Our findings demonstrated that UTUC patients with hypertension before surgery or abnormal GGS rate in remnant kidney have higher risk of entering dialysis within five years post ipsilateral nephrectomy.(This study was granted by the Ministry of Science and Technology(NSC 102-2314-B-037-012-MY3) and by the Ministry of Health and Welfare(MOHW103-TD-B-111-05, MOHW104-TDU-B-212-124-003, budget from health and welfare surcharge of tobacco product).)

Funding: Government Support - Non-U.S.

Figure: Longitudinal measures of mean of GFR around time of TIPS procedure.

*p<0.001, **p<0.0001

GFR improved by 16 (11, 21) ml/min from pre-TIPS to 90 days after TIPS (p<0.0001). Comparison of Tertiles 1, 2, and 3 showed respectively: GFR increased by T1: 6 (1, 14), T2: 22 (15, 30), and T3: 22 (12, 33) ml/min (p = 0.006); 90-day mortality was T1: 20%, T2: 17%, and T3: 49% (p = 0.007); encephalopathy rate at 90 days was T1: 21%, T2: 42%, and T3: 65% (p = 0.0005).

Conclusions: There was a significant improvement in GFR from pre-TIPS to 90 days after TIPS. Those with the lowest GFRs at the time of TIPS had greater improvement in renal function but also had higher 90-day mortality and encephalopathy rates post-TIPS.

Funding: NIDDK Support
The Epidemiic of Chronic Kidney Disease in Rural and Remote Canadian First Nations: Results from Manitoba’s FINISHED Screening Program

Paul Komenda,1,2 Barry Ad Lavallee,1 Thomas W. Ferguson,1 Navdeep Tangri,1 Allison Dart,1 Bing Hu,1 Audrey Gordon,2 Caroline D. Chartrand,2 Lorraine L. McLeod,1 Claudio Rigatto,1,3 Medicine, Univ of Manitoba, Winnipeg, MB, Canada; 2Diabetes Integration Project, Winnipeg, MB, Canada; 3Conventions Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; 4Seven Oaks General Hospital Research Centre, Winnipeg, MB, Canada.

Background: Chronic Kidney Disease (CKD) is a global epidemic affecting 10-15% of the general population. Canadian First Nations children and young adults are known to suffer from a high rate of proximate risk factors for CKD, in particular elevated rates of diabetes. The rates of CKD are not well defined in this population. We used data from The First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) project, a 3-year initiative completed in 2017 that accomplished community wide screening in 11 rural and remote First Nations communities in Manitoba, Canada.

Methods: Detailed methods of the FINISHED study have been previously published (Lavallee et al. CJRKH, 2015). An interdiscipliary team screened for CKD in adults and children aged 10+ using both urine albumin-to-creatinine ratio (ACR) and eGFR in 11 communities across 2 tribal councils. We present here the data on demographic variables, risk factors for CKD, and the prevalence and severity of CKD in the adult (age 18+) screening cohort.

Results: 3346 adults were screened. 26.7% of those screened had CKD defined as elevated urine ACR (micro- or macroalbuminuria) or eGFR < 60 ml/min/1.73m2. Road access communities had a lower prevalence of CKD (18.4%) than remote air access communities (36.0%). Macroalbuminuria (urine ACR > 300 mg/g) was present in 5% of those screened (2.8% in road access and 7.5% in air access communities).

Conclusions: Rural and remote Canadian First Nations suffer up to a 3-fold higher prevalence of CKD than the general population and a nearly 5-fold higher prevalence of macroalbuminuria. This prevalence is comparable to high-risk populations such as those with diabetes and CHF. Given the risk and treatment interventions may be cost-effective, as they have been shown to be in other high-risk populations.

Funding: Government Support - Non-U.S.

FR-PO589

Age and Gender Specific Lifetime Risk of Renal Replacement Therapy

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Background: Kidney transplantation is the preferred treatment of end stage renal disease (ESRD). Craft and patient survival are highest after transplantation with a graft from a living donor. However, persons who donate a kidney are themselves at risk of ESRD. Personalized risk prediction requires age and gender specific risk estimates. Here, we report lifetime risk of renal replacement therapy (RRT) for ESRD by age and gender across Europe.

Methods: We defined ESRD as chronic RRT and age 80 as the lifetime horizon. Death was considered a competing event. We obtained RRT incidence rates by age and gender from the ERA-EDTA Registry. Mortality rates were calculated from census data provided up and data linkage.

Results: At index age 20, lifetime RRT risk for females ranged between 0.40% and 0.87% across countries, and for males between 0.77% and 1.59%. At age 60, lifetime RRT risk ranged between 0.26% and 0.68% for females and 0.56% and 1.32% for males. Pooled lifetime RRT risks using inverse variance weighted means. Gender for countries providing individual patient data to the ERA-EDTA Registry. We defined ESRD as chronic RRT and age 80 as the lifetime horizon. Lifetime RRT risk differs across Europe. Women are at lower risk compared to men. These data offer a basis to provide personalized prediction of lifetime ESRD risk when evaluating a potential kidney donor. The estimates presented here are population averages. We expect that lifetime risk is lower in persons with normal eGFR and no albuminuria.

Conclusions: Lifetime RRT risk differs across Europe. Women are at lower risk compared to men. These data offer a basis to provide personalized prediction of lifetime ESRD risk when evaluating a potential kidney donor. The estimates presented here are population averages. We expect that lifetime risk is lower in persons with normal eGFR and no albuminuria.

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

494A
FR-PO588
Subclinical Pulmonary Congestion Is Pervasive in Nephrotic Syndrome
Francesca Mallamaec,1,2 Francesco Marino,3 Carmela Martorano,2 Rocco Tripepi,1 Marianna Bellantoni,1 Giovanna Tripepi,1 Carmine Zoccali,1,2 National Research Council of Italy, Inst of Clinical Physiology, Reggio Cal, Unit, CNR-IFC, Reggio Calabria, Italy; Nephrology, Transplantation and Hypertension Unit United Hospitals, Reggio Calabria, Italy.

Background: In patients with Nephrotic Syndrome (NS) the lung is considered as an organ protected from the risk of edema. However information on objectively measured lung water in NS patients is lacking.

Methods: We measured lung water with an ultrasonic technique (US) and with standard transthoracic impedance in an incident series of 42 asymptomatic patients with active NS. Eleven patients were studied during NS remission. Twenty-one healthy volunteers formed the control group. US lung studies were performed after 5 and 60 minutes of supine resting and after 5 minutes of standing. Transthoracic impedance was measured after 30 min of supine resting only.

Results: In patients with active NS the median number of US-B lines (a metric of lung water) after 5 min in supine position was markedly higher [12; Interquartile range: 7-25; p<0.001] than in healthy subjects [4; 2-9]. The difference between patients [16, 11-35] and controls [4; 2-9] amplified (p<0.001) after 60 min of supine resting and attenuated after 5 min of standing [9; 7-25 vs 4; 3-5, p=0.001]. After NS remission, the number of US lines reduced to 5 (4-18) at 5 min and to 6 (5-22) at 60 min (p=0.001) approaching the normal range. Lung congestion in patients with active disease was fully confirmed by transthoracic impedance measurements (p<0.001 vs healthy controls).

Conclusions: Asymptomatic pulmonary congestion is pervasive in patients with NS. A clinical trial is needed to assess the usefulness of the application of this technique for the management of patients with NS.

FR-PO589
The Incidence of Malignancies prior to the Diagnosis of ANCA-Associated Vasculitis (AAV) Is Not Increased in Comparison to the Incidence in the General Population
Emma Elisabeth Van Daalen,1 Chinar Rahmattulla,1 Ron Wolterbeek,2 Jan A. Bruijn,1 Ingeborg M. Bajema,1 Pathology, Leiden Univ Medical Center, Leiden, Netherlands; 2Medical Statistics and Bioinformatics, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Several studies have found an increased malignancy risk before the diagnosis of AAV, especially in granulomatosis with polyangiitis (GPA), whereas data on microscopic polyangiitis (MPA) are scarce. It has been hypothesized that malignancies and AAV have common pathways in their pathogenesis (Ann Rheum Dis 2004, Rheumatology 2009). We studied the malignancy risks in patients before their AAV diagnosis to further elucidate this hypothesis.

Methods: We retrospectively retrieved data on 138 patients with biopsy-proven AAV diagnosed in the Netherlands. Malignancies prior to AAV diagnosis were identified using the Dutch National Pathology Database. The malignancy incidence was compared to the incidence in the general population, as reported by the Netherlands Cancer Registry. The Standardized Incidence Ratios (SIRs) were calculated, matching for gender, age and calendar time period. Separate analyses were performed for GPA and MPA.

Results: Twelve patients were diagnosed with cancer before the AAV diagnosis (mean follow-up: 11.8 years). Overall malignancy risk was not increased (SIR: 0.92, 95%CI: 0.62-1.35). GPA patients had higher malignancy risk compared to MPA (SIR: 1.76, 95%CI: 1.24-2.54 vs SIR: 0.87, 95%CI: 0.52-1.49, p=0.01).

Conclusions: Our study indicates that the malignancy risk before the diagnosis of AAV is not increased compared to the general population.

FR-PO590
Gastrointestinal Symptoms and Hypoalbuminemia in Chronic Kidney Disease Patients
Xuehan Hsu,1 Xuehan Hsu,1 Nisha Bansal,2 Alan S. Go,2 Chi-yuan Huang.1,2 1Peking Union Medical College Hospital; 2Univ of California-San Francisco; 3Univ of Washington; 4Kaiser Permanente Northern California.

Background: Hypoalbuminemia is an important risk factor for adverse outcomes in patients with CKD. Little is known about the relationship between gastrointestinal (GI) symptoms and serum albumin level in CKD.

Methods: This is a cross-sectional study of participants (N=3599) in the Chronic Renal Insufficiency Cohort (CRIC) study which collected information regarding potential uremic symptoms. For each of the 4 following symptoms: “bad taste in your mouth,” “loss of appetite,” “nausea,” “vomiting,” we created a severity score by multiplying the number of symptoms and serum albumin level. We compared the GI symptom score with serum albumin and other potential CV risk factors.

Results: The mean eGFR was 42.9±13.4ml/min/1.73m², and serum albumin level was 3.95±0.46 g/dl. 1702 subjects had one or more symptoms. Patients with lower eGFR were more likely to have GI symptoms.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>eGFR 60ml/min/1.73m²</th>
<th>eGFR 45-60ml/min/1.73m²</th>
<th>eGFR 30-45ml/min/1.73m²</th>
<th>eGFR &lt;30ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>A bad taste in your mouth?</td>
<td>1.0 (reference)</td>
<td>0.99 (0.75-1.32)</td>
<td>1.22 (0.92-1.62)</td>
<td>1.34 (0.99-1.82)</td>
</tr>
<tr>
<td>Loss of appetite?</td>
<td>1.0 (reference)</td>
<td>1.21 (0.88-1.68)</td>
<td>1.83 (1.34-2.52)</td>
<td>2.01 (1.43-2.82)</td>
</tr>
<tr>
<td>Nausea or being sick to your stomach?</td>
<td>1.0 (reference)</td>
<td>0.95 (0.72-1.25)</td>
<td>1.24 (0.95-1.63)</td>
<td>1.32 (0.98-1.78)</td>
</tr>
<tr>
<td>Vomiting?</td>
<td>1.0 (reference)</td>
<td>1.08 (0.70-1.67)</td>
<td>1.67 (1.11-2.54)</td>
<td>1.76 (1.13-2.75)</td>
</tr>
</tbody>
</table>

Conclusions: Increased prevalence of GI symptoms become apparent among CKD patients at relatively high eGFR levels (45 ml/min/1.73m²). These symptoms correlated with important nutritional parameters.

FR-PO591
Obstructive Lung Function in CKD: NHANES 2007-2012
Sankar D. Navaneethan,1 Susana Arreguin,1 Mahboob Rahman,3 Jesse D. Schold.2 1Cleveland Clinic; 2CWRU.

Background: Lung diseases are one of the leading causes of death in the general population. We aimed to study the prevalence of obstructive lung function in those with CKD. In addition, factors associated with obstructive lung function were examined.

Methods: Participants aged 20-79 years from the National Health and Nutrition Examination Survey (NHANES) 2007-2012 who underwent spirometry testing using similar protocols were included in this analysis. Global Initiative for Chronic Obstructive Lung Disease classification of COPD (FEV1/FVC <0.7) based on post-bronchodilator spirometric results was used to establish the prevalence of obstructive lung function with adjustment for non-response to spirometry. CKD was defined as presence of eGFR <60 ml/min/1.73 m² and/or UACR >30 mg/g. Factors associated with obstructive lung function were identified using logistic regression model for the entire cohort, CKD and non-CKD groups separately (using baseline spirometry).

Results: Out of 11,995 participants (CKD=1563; Non-CKD=10,432) who completed the baseline spirometry testing, 1,086 participants were eligible for both and only 1049 complete post-bronchodilator spirometry. Prevalence of obstructive lung function using baseline spirometry data were 25% in CKD and 13% in non-CKD and GOLD criteria were 17% in CKD and 8% in non-CKD. Each 5 ml/min lower eGFR and proteinuria were associated with higher odds of having obstructive lung function in the entire cohort.

Table: Factors associated with obstructive lung function in the study cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariable adjusted OR (95% CI) for obstructive lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 1 year increase</td>
<td>1.08 (1.01-1.16)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.97 (0.94-1.00)</td>
</tr>
<tr>
<td>Race Black</td>
<td>0.96 (0.70-1.37)</td>
</tr>
<tr>
<td>Mexican American</td>
<td>0.93 (0.63-1.37)</td>
</tr>
<tr>
<td>Other Hispanic</td>
<td>0.93 (0.63-1.37)</td>
</tr>
<tr>
<td>Other race</td>
<td>0.96 (0.70-1.37)</td>
</tr>
<tr>
<td>DM, kg/m² (per 1 unit increase)</td>
<td>0.94 (0.90-0.97)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.96 (0.92-1.01)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.07 (0.92-1.24)</td>
</tr>
<tr>
<td>Current smoker (yes)</td>
<td>2.48 (1.22-5.04)</td>
</tr>
<tr>
<td>eGFR (each 5 ml/min decline)</td>
<td>1.01 (1.01-1.05)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>1.51 (1.02-2.26)</td>
</tr>
</tbody>
</table>

Old age, white race, smoking and self-reported COPD were associated with obstructive lung function in both CKD and non-CKD groups.

Conclusions: In this representative cohort of US population, prevalence of obstructive lung function is higher in those CKD. Lower eGFR and proteinuria are associated with obstructive lung function. Further studies examining the impact of lung diseases in CKD are warranted.
FR-PO592
Association of Serum Osteoprotegerin with Bone Loss in Chronic Kidney Disease
From the KNOW-CKD Study - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Chronic kidney disease (CKD), a condition associated with increased risk of bone fracture and mineral and bone disorder.

Results: BMD at the lumbar spine, total hip and femur neck was assessed by dual energy X-ray absorptiometry; and serum OPG was measured at baseline in 1,423 CKD patients in the prospective Korea/N Cohort Study for Outcome in Patients With Chronic Kidney Disease. Osteoporosis was defined to T score ≤ -2.5 in patients aged over 50.

Conclusion: Serum OPG was significantly associated with increased lumbar BMD (lumbar spine, total hip and femur neck) compared with the lowest quartile of serum OPG. Multivariable linear regression model indicated that serum OPG was independently associated with decreased lumbar spine and total hip BMD (B=-0.489; 95% confidence interval [CI], -0.883 to -0.095; P=0.015, B=-0.349; 95% CI, -0.672 to -0.027, P=0.027, respectively), but femur neck was not associated with serum OPG in women.

Conclusion: Serum OPG was independently associated with lumbar spine and total hip BMD and increased risk of osteoporosis in female CKD patients. However, these associations were not found in male CKD patients.

FR-PO593
Growth in Children with Chronic Kidney Disease: A Report from the KNOW-Ped CKD (Korean Cohort Study for Outcome in Patients with Pediatric Chronic Kidney Disease) - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Background: Growth impairment is common in children with chronic kidney disease (CKD) with profound and psychosocial impact. We investigated the characteristics of growth in Korean children with CKD.

Methods: Clinical characteristics along with anthropometric measurements were examined in subjects of KNOW-Ped CKD, Korean Cohort Study for Outcome in Patients with Pediatric Chronic Kidney Disease. Findings of 322 children (M:F 218:104), who were enrolled to the study from July 2010 to December 2013 in seven major pediatric nephrology centers of Korea, were analyzed to investigate the characteristics of growth in Korean pediatric CKD.

Results: Mean height- and weight- z scores of Korean pediatric CKD patients were -0.88±1.43 and -0.91±1.65. Mean BMI-z score was -0.36±1.25. Height deficit was observed from early stage of CKD with mean height z-score -0.42 in CKD stage I. Short stature (z score < -1.88, 20% of the subjects) and overweight (z score > 1.65, 28% of the subjects) was associated with female sex, age younger than 2-year-old at enrollment, co-morbidity, and advanced CKD stage. Low BMI was associated with high blood pressure, co-morbidity and younger age. The final height-z score was -0.86±1.19, which is shorter than predicted adult height-z score (-0.33±0.7) calculated from their parent's height.

Conclusion: Growth failure is one of the most important complications in pediatric CKD patient. More profound height, weight and BMI impairment were associated with younger age and co-morbidity. Children with these findings need close attention on their growth and may require earlier intervention to avoid severe growth impairment.

FR-PO594
Risk of Early Preterm Delivery in Pregnant CKD Patients – A Model for Counseling - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Background: Chronic kidney disease (CKD), whose prevalence almost equals pre eclampsia in pregnancy, increases the risks of adverse pregnancy outcomes; the degree is only partially known.

Methods: Objective: Development and internal validation of a prediction model to quantify the risks of early preterm delivery (<34 gestational weeks) selected as most relevant outcome in pregnant women with CKD. We developed the model in CKD women. A homogeneously followed-up, low-risk pregnancy population served as controls. Sixteen of the largest Italian Outpatient Units dedicated to the multidisciplinary follow-up of CKD in pregnancy. Patients: Pregnant women with CKD: 503 live-born singletons in CKD; 835 low-risk controls (2000-2013). Measurements: Outcome: early pre-term delivery. The candidate variables were readily measurable, available, inexpensive (hypertension, proteinuria, kidney disease and function). Bootstrapping was used for internal validation.

Results: Early preterm delivery was more frequent in CKD (12.5%) vs controls (1%) (p=0.0001). The most parsimonious model (Likelihood ratio test p=0.0001; McFadden’s pseudo R²=0.2290) summarized various combinations of CKD stages, hypertension and proteinuria and defined a scale of risk. First step included CKD stage1, normotension and proteinuria<1g/24h (OR:2.8); second step included CKD stages 2-5 without hypertension and proteinuria, and CKD stage 1 with either hypertension or proteinuria (OR:19.5 and 20.9); third step included CKD stages 2-5 with either hypertension or proteinuria (OR:44.7); the combination of hypertension and proteinuria was associated with the highest risk, but the low number of cases prevented precise quantification. Limitations: the study was performed in two Centers only. The number of cases with severe CKD is small.

Conclusion: The model may support counselling and clinical management by grading the risk for adverse pregnancy outcomes. Further studies are needed to externally validate the model.

FR-PO595
Thiamine Deficiency in Non-Dialysis CKD Patients - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Background: Thiamine deficiency is associated with malnutrition, alcoholism and chronic diseases such as cancer. Long use of diuretics also induces thiamine deficiency, which is due to an increased urinary loss of thiamine. Some papers report that thiamine tend to accumulate because of decreased urinary flow in chronic kidney disease (CKD) patients. Others report that a protein restricted diet causes thiamine deficiency in CKD patients. This study aimed to examine the prevalence and factors associated with thiamine deficiency in CKD patients.

Methods: This is a single center cross-sectional study in patients with non-dialysis CKD under regular follow-up in nephrology center of Chubu Rosai Hospital from July 1, 2014 to January 31, 2015. The patients who meet the CKD criteria of Japanese Society of Nephrology were selected. We use the data collected from medical records, questionnaires and nutrition surveys.

Results: The study population consisted of 149 patients aged 71.2 ± 10.9 years with estimated glomerular filtration rate (eGFR) of 33.2 ± 18.2 (ml/min/1.73m²). These were divided into two thiamine groups ( serum thiamine level<30ng/ml ) and high thiamine group ( serum thiamine level≥30ng/ml ). In univariate comparisons, patients with low thiamine group had significantly lower protein intake which is estimated by the nutrition survey. The use of loop diuretics was not associated with thiamine deficiency. In multivariate analyses, high age, low eGFR and low protein intake, especially less than 0.8g/kg, were independently associated with thiamine deficiency.
FR-PO597
Controlled Attenuation Parameter Measured by FibroScan Is Closely Associated with Metabolic Syndrome in Patients with Chronic Kidney Disease

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Background: Hepatic steatosis can be determined by the measurement of liver controlled attenuation parameter (CAP) using FibroScan. Although the practical methods predicting the risk of metabolic syndrome (MS) development are lacking, recent studies represent that this parameter is closely correlated with the presence of MS in the general population. Therefore, we investigated whether CAP measured by FibroScan could predict the presence of MS in chronic kidney disease (CKD) patients.

Methods: A total of 468 CKD patients were evaluated. MS was defined by using the Modified National Cholesterol Education Program (Adult Treatment Panel III) criteria. Multivariate logistic regression analysis was used to identify the independent association between CAP and MS.

Results: The mean age of the patients was 57.5 years and 225 patients (48.1%) were male. The mean value of CAP was 241.7 dB/m. CAP was independently associated with body mass index (β=0.7818, P<0.001), triglyceride (β=0.246, P=0.002) and estimated glomerular filtration rate (eGFR) (β=-0.581, P=0.005). MS was diagnosed in 142 (30.3%) patients. In patients with MS, diabetes was more prevalent (59.9 vs. 25.8%, P<0.001), hemoglobin (13.1±2.4 vs. 12.6±2.1 g/dL, P=0.026) and CAP (262.0±60.6 vs. 232.9±49.0 dB/m, P=0.001) levels were significantly higher, while eGFR (82.9±27.5 vs. 91.6±26.0 mL/min/1.73m², P=0.001) was lower compared with patients without MS. Multivariate logistic regression analysis revealed that high CAP levels were independently correlated with the increased risk of MS (per 1 dB/m increase, odds ratio=1.010, 95% confidence interval=1.002-1.018, P=0.014) after adjustment for confounding factors.

Conclusions: High CAP levels measured by FibroScan were significantly associated with an increased risk of MS in CKD patients. These data suggests liver FibroScan could be a practical method for evaluating the risk of MS development in CKD patients.

FR-PO598
Outcomes in Women Switched from Mycophenolate to Azathioprine in Advance of Pregnancy

Kate S. Wiles,1 Adam D. Jakes,2 Asta Alwindi,1 Kate Bramham,1 Paramit Chowdhury,1 Lucy C. Chappell,1 Catherine Nelson-piercy,1 Liz Lightstone.2 1Guy’ s and St. Thomas’ NHS Foundation Trust; 2Imperial College London.

Background: Mycophenolate is teratogenic and should be replaced in advance of pregnancy. The aim of this study was to determine the risk of adverse outcome in women switched from mycophenolate to azathioprine.

Methods: Records of women attending regional renal pre-pregnancy counselling clinics 2011-2014 were examined. Women taking mycophenolate were included and the decision to switch to azathioprine reviewed. Outcomes were a decline in eGFR within a year, renal biopsy, disease flare or rejection, and conversion back to mycophenolate. Pregnancy outcomes were analysed.

Results: Data were available for 60 women (31 kidney transplant, 4 kidney-pancreas transplant and 25 glomerulonephritis, predominantly lupus). Most women were considered eligible for a switch to azathioprine and one woman chose to switch against advice.

Conclusions: Protein intake is an important factor for thiamine levels of CKD patients. Protein restriction for CKD patients especially with high age and low eGFR have a high risk of thiamine deficiency.

FR-PO599
Chronic Kidney Disease Linearly Predicts Outcomes After Elective Total Joint Arthroplasty

Michael J. Fielding,1 Timothy L. Tan,2 Dean D. Tan,2 Michael M. Kheir,1 Antonia F. Chen.1 Medicine, Thomas Jefferson Univ, Philadelphia, PA; 2Orthopedics, Thomas Jefferson Univ.

Background: Kidney disease has been widely associated with increased complications in total joint arthroplasty (TJA). The purpose of this study is to determine the association of kidney disease severity as measured by the chronic kidney disease (CKD) staging system with complications and outcomes after TJA.

Methods: A retrospective review of an institutional database of 12,308 primary TJAs (6,301 hips and 5,947 knees) from 2008 to 2013 was performed. The following preoperative variables were obtained from medical records: chemistry 7 panel, Elixhauser comorbidities, and demographic factors. CKD stages were defined based on estimated glomerular filtration rate in ml/min/1.73m² (eGFR): (1) < 90, (2) 60-89, (3A) 45-59, (3B) 30-44, (4) 15-29, and (5) < 15. Multivariate analysis was performed to assess the independent influence of CKD stage on the aforementioned endpoints.

Results: Patients with CKD stage greater than 2 demonstrated an increased risk of transfusions (CKD 3A odds ratio [OR]: 1.67, CKD 3B OR: 2.80, CKD 4 OR: 2.24), length of stay greater than 3 days (CKD 3A OR: 1.34, CKD 3B OR: 1.39, CKD 4 OR: 3.57), and in-hospital complications (CKD 3A OR: 1.21, CKD 3B OR: 1.80, CKD 4 OR: 3.36) compared to all patients with eGFR > 60. Additionally, the relationship between eGFR and the above complications were found to increase linearly rather than exponentially at a certain threshold. In contrast, CKD stage was not associated with septic or aseptic revisions.

Conclusions: Severe CKD is associated with an increased risk of transfusion, length of stay, and in hospital complications. Rather than finding a clear threshold, complications increased linearly with disease severity. Surgeons should be cognizant of this increase when evaluating TJA patients with renal disease.

FR-PO600
The Assessment of Incidental Risk for Microalbuminuria According to the Level of Depression Scale

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Background: Depression is one of the most common psychiatric disorders. The presence of depression for prediabetes goes beyond function and extends to somatic health. A growing body of evidence shows that depression is significantly associated with chronic kidney disease. Nonetheless, the incidental relationship between microalbuminuria and depression was not identified yet. Therefore, we conducted this study to investigate incidental relationship of microalbuminuria with depression scale.

Methods: This study was conducted for 45,293 Korean men and their spouses without microalbuminuria who got medical health check up in Kangbuk Samsung Total healthcare center in 2010. To assess the degree of their depression, Center for Epidemiologi Studies-Depression Scale (CES-D) was used (CES-D ≤ 15: normal, CES-D 16-20: moderate risk group, CES-D > 21: high risk group). On the basis of CES-D score in 2010, they were classified into 3 groups (normal, moderate, high risk group) and monitored for the development of microalbuminuria from January, 2011 to April, 2015.

Results: While the general incidence was 1.7%, the incidence of microalbuminuria increased in proportion to the risk score of depression evaluated by CES-D (CES-D ≤ 15: 0.4%, CES-D 16-20: 1.8%, CES-D > 21: 3.6%). When the hazzard ratio (HR) of normal group (CES-D < 15) was set to reference value (HR: 1.00), the HRs for microalbuminuria also increased according to the score of CES-D scale. In addition, these associations were preserved even after adjustment for the various metabolic covariates such as age, physical activity, total cholesterol, LDL-cholesterol, triglyceride, body mass index, and obesity (CES-D 16-20: 1.98, CES-D > 21: 3.37).

Conclusions: Our study showed that the risks of microalbuminuria in proportion to the severity of depression. These findings imply the clinical role of the depression for
FR-PO601

Outcomes in CKD Patients with Hospital Acquired Complications
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Background: Patients with CKD are at increased risk of hospital acquired complications (HACs) including those considered preventable. The impact of HACs on patient and health system outcomes has not been well described.

Methods: Subjects hospitalized from April 1, 2003 to March 31, 2008 from a population based cohort (Alberta Kidney Disease Network) were studied. Outpatient eGFR and proteinuria (protein/creatinine ratio or dipstick) in the year prior to index hospitalization were used to define CKD status. Co-morbid conditions were identified using validated algorithms applied to administrative data. ICD 10 CA was used to classify reason for admission. A specific diagnostic indicator (type II) was used to identify hospital acquired complications (HACs) that were sub-classified as “potentially” and “always” preventable.

We studied the following outcomes: re-admission within 90 days of discharge, all cause mortality at 90 days, and index hospitalization costs. Multivariable regression models examined the association of HACs with re-admission, mortality, and incremental health care costs, accounting for confounders.

Results: Of 536,549 subjects, 45,377 (8.5%) with CKD were hospitalized. In patients with HACs, the OR of re-admission and death at 90 days was 1.37 (95% CI: 1.32 – 1.43), and 3.11 (95% CI: 3.06 – 3.58) respectively compared with those without HAC. Hospitalizations with any HAC were associated with incremental health costs of $4028 (95% CI: $3898 – $4158). A graded association was observed for those outcomes with increasing number of HACs and severity of CKD. Similar results were noted when only potentially preventable HACs were considered.

Conclusions: Complications occurring during hospitalization in patients with CKD is independently associated with an increased risk of hospital re-admission, health care costs, and mortality. Targeted strategies to reduce HACs in this patient population may have a significant benefit.

FR-PO602

Plasma Proteins Associated with Declining Renal Function in Patients with Type 1 Diabetes: Results of a Global Proteomic Analysis Using SOMAscan Platform
Andrew L. Schlaff, Monika A. Niewczas, Marcus G. Pezzolesi, Andzej S. Krolewski. Joslin Diabetes Center, Boston, MA.

Background: Increases in serum creatinine and cystatin C are considered measures of declining renal function in patients with diabetes.

Methods: To search for other proteins correlated with declining renal function, we conducted a follow-up study, following 30 patients with T1D and proteinuria for 1-3 years. Mean eGFR was 67 ml/min at baseline, and was 59 ml/min at the end of follow-up. Plasma proteins and circulating proteins were measured on the SOMAscan platform at baseline and at the end of follow-up. The platform measured 954 proteins for each of the 30 patients, with median limit of detection (LOD) of 1.6pg/mL,dynamic range of 8 logs, and median coefficient of variation (CV) of 5% for individual proteins measured repeatedly in replicate runs of plasma samples.

Results: Renal function change during follow-up in each patient was expressed as the difference between eGFRcre at baseline and at follow-up and was referred to as ∆eGFR (mean: -7.7 ml/min, range: -44 ml/min to 11 ml/min). For each protein, the Spearman rank correlation coefficient between ∆eGFR and the percent change in the protein’s level (RFU) was calculated. The protein’s association with renal function decline was used to measure the protein’s association with renal function decline. In 27 proteins, concentrations increased with decreasing renal function (r: -0.67 to -0.46, p<0.01). In 16 proteins, concentrations decreased with decreasing renal function (r: 0.46 to 0.57, p<0.01). The top 5 proteins in each category are shown below.

<table>
<thead>
<tr>
<th>Name</th>
<th>r Spearman</th>
<th>P Name</th>
<th>r Spearman</th>
<th>P</th>
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<tbody>
<tr>
<td>IL-17F</td>
<td>-0.67</td>
<td>0.05</td>
<td>ATSI</td>
<td>0.57</td>
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<td>-0.62</td>
<td>0.04</td>
<td>CDC2</td>
<td>0.54</td>
</tr>
<tr>
<td>TNFRSF19L</td>
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<td>0.04</td>
<td>FGFR</td>
<td>0.53</td>
</tr>
<tr>
<td>TNFRSF1A</td>
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<td>0.03</td>
<td>CA1</td>
<td>0.50</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>-0.56</td>
<td>0.03</td>
<td>CDH12</td>
<td>0.50</td>
</tr>
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</table>

Conclusions: In conclusion, increasing or decreasing concentrations of plasma proteins with eGFR loss may reflect worsening renal function, as is the case with cystatin C. However, changes in plasma concentration of these proteins may represent the extent and intensity of the disease process underlying progressive renal decline, which is most likely the case with IL-17F and the TNFR’s. Funding: NIDDK Support, Pharmaceutical Company Support - Bristol-Myers Squibb.

FR-PO603

Mass Spectrometry Imaging Reveals Disease Specific Alterations in Protein Abundance in Human Diabetic Nephropathy
Haichun Yang,1 Audra M. Judd,2 Michelle Reyzer,3 Jeremy L. Norris,4 Richard M. Caprioli,2 Raymond C. Harris,3 Agnes B. Fogo.1 1Pathology, Microbiology and Immunology, Vanderbilt Univ; 2Mass Spectrometry Research Center, Vanderbilt Univ; 3Nephrology, Vanderbilt Univ; 4Nashville, TN.

Background: Diabetic nephropathy (DN) is a major complication in diabetic patients. However, protein expression and function in diabetic kidney disease has not been well characterized.

Methods: DN biopsies (n=36) and normal kidney (n=9) were assessed. DN cases were divided into mild, moderate and severe, based on biopsy findings. Follow-up was available in 23 patients, and patients were sub-grouped into stable DN (decreased eGFR >50%, n=10), progressive DN (decreased eGFR ≤50%, n=13) vs. progressive DN (decreased eGFR >50%, n=10). Peptide mass peaks were acquired over the mass-to-charge range 600-4500 from at least 12 glomerular areas per case.

Results: DN patients had reduced eGFR and increased proteinuria, compared to normal. Mass spectrometry showed 168 peptide peaks, with 8 peaks increased and 21 peaks decreased in DN compared to Normal. Moderate and severe DN showed more nodular glomerulosclerosis than mild DN by study design (moderate 2.1±0.10, severe 2.17±0.22 vs. mild 0.43±0.30, 0.4-8 scale, p<0.05) and mesangial expansion (moderate 1.97±0.09, severe 2.28±0.15 vs. mild DN 1.21±0.15, p<0.05). Peptide maps were more similar in moderate vs severe DN groups, compared to mild DN. Thirteen of 168 peptide peaks were significantly different between DN groups.

Conclusions: We conclude that different peptide maps correlate with DN onset, severity and progression, and that clinical and morphological phenotypes have heteroproteomic correlates. These peptides will now be further validated and identified by MS/MS fragmentation and database searching. Funding: NIDDK Support

FR-PO604

Urine Metabolomic Profiling Reveals a Unique Signature for Type 2 Diabetes
Jane J. Kim, Rintaro Saito, Satoshi Miyamoto, Minya Pu, Loki Natarajan, Kumar Sharma. Univ of California, San Diego.

Background: Increasing circulating branched chain amino acids (BCAAs) are associated with type 2 diabetes (T2D) and insulin resistance. However, it is not clear whether increased plasma BCAA concentrations result from increased synthesis, or impaired degradation or excretion. Here, we employ a targeted metabolomics approach to evaluate diabetic patients without overt kidney disease to identify urine metabolites associated with T2D, presenting potential urine biomarkers for clinical prediction and further insight into disease pathogenesis.

Methods: We measured 105 urine metabolites by GC/MS in a screening T2D cohort (n=27), validation T2D cohort (n=14), and healthy control group (n=23). We also examined kidney cortex of db/db and control db/n mice to measure gene expression by Illumina miRNA and protein expression by western blot.

Results: Following FDR correction, 57 metabolites were found to be different in the screening cohort compared to controls. When these 57 metabolites were carried forward for analysis in a validation T2D cohort, 24 of these urine metabolites were confirmed to be different from controls using Bonferroni adjustment for multiple comparisons. 16 of the 24 validated metabolites were amino acids, and 8 of these represented BCAA degradation products. To further investigate BCAA metabolism, we examined kidney tissue from db/db mice and found that the gene expression of key enzymes related to BCAA catabolism was decreased. Western blot studies confirmed that renal expression of branched-chain ketoacid dehydrogenase, a mitochondrial enzyme complex that catalyzes an irreversible step in BCAA catabolism, was reduced in db/db mice compared with controls.

Conclusions: Prior studies have reported impaired mitochondrial BCAA metabolism in adipose, muscle and liver. However, our results show a robust pattern of increased BCAA metabolites, likely reflecting increased BCAA catabolism and/or increased metabolic flux. The reduced renal expression of BCAA enzymes supports a role for dysregulated BCAA metabolism by the kidney. The elevated BCAA metabolites may have an affect on regulating insulin resistance and the development of kidney disease with T2D.

Funding: NIDDK Support

FR-PO605

Urinary Matrix Metalloproteinase Activities Are Associated with Renal Hyperfiltration in Adolescents With Type 2 Diabetes
Petter Bjornstad,1 Laura Raymond,2 Kathryn Snell-bergens,2 Kristin Nadeau.3 Barbara Davis Center for Diabetes; 1univ of Colorado Denver; 2Children’s Hospital Colorado.

Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. Matrix metalloproteinases (MMP) modify extracellular matrix during vascular remodeling and are known to be elevated in diabetes, and associated with DN in type 1 diabetes. We hypothesized that activities of latent MMP and neutrophil gelatinase-associated lipocalin (NGAL-L) proteins are associated with microalbuminuria and hyperfiltration in adolescents with type 2 diabetes (T2D).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
498A
Methods: 295 adolescents with T2D (14.0±1.8 years, <2 years duration, BMI ≥85%, and HbA1c ≥5%) in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study had urine and blood evaluated at baseline and annually for 5 years. MMP2, MMP9 and NGAL activities were measured by gelatin zymography and normalized to urinary creatinine. Microalbuminuria was defined as albumin-to-creatinine ratio (ACR) >30mg/g. Estimated GFR was calculated by Schwartz (eGFR=36.5*height/creatinine) and hyperfiltration defined as >135mL/min/1.73m².

Results: Mixed models evaluated the longitudinal relationships between MMP-2, MMP9 and NGAL with eGFR, ACR, hyperfiltration and microalbuminuria respectively. MMP2, MMP9 and NGAL-MMP9 activities were natural logarithm transformed (ln) due to skewed distribution. The CKD classifier was an independent predictor of severe but not mild progression in retinopathy. It was not possible to develop a retinopathy specific marker panel with clinically relevant accuracy.

Conclusions: In conclusion, urinary MMP and NGAL activities were associated with early DN in adolescents with T2D over time.

FR-PO608 Urinary Proteomics as a Classifier of Patients at Risk for Type 2 Diabetes

Table: Mixed logistic regression models

<table>
<thead>
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<th>Microalbuminuria</th>
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<tbody>
<tr>
<td>OR*, 95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>MMP2</td>
<td>1.3 (1.1-1.5)</td>
</tr>
<tr>
<td>MMP9</td>
<td>1.2 (1.0-1.4)</td>
</tr>
<tr>
<td>NGAL-MMP9</td>
<td>1.2 (1.0-1.5)</td>
</tr>
</tbody>
</table>

*Odds ratio of hyperfiltration or microalbuminuria per 1 SD increase in natural log transformed variable adjusted for age, sex, SBP, HbA1c and treatment group

Conclusions: In conclusion, urinary MMP and NGAL activities were associated with early DN in adolescents with T2D over time.

FR-PO609 Neutrophil Gelatinase Associated Lipocalin as an Early Biomarker of Nephropathy in Diabetic Patients and Effect of RAAS Blockade on NGAL as Marker of Tubular Damage in Diabetic Nephropathy

Background: Neutrophil gelatinase associated lipocalin (NGAL) is a neutrophil-derived protein that is rapidly released during tissue damage. NGAL is a specific marker for tubular injury and dysfunction, making it a potential biomarker for diabetic nephropathy (DN). However, its role in the early detection of DN remains unclear.

Methods: We conducted a retrospective analysis of patient data from a large clinical trial assessing the efficacy of RAAS blockade on NGAL levels in patients with type 2 diabetes mellitus (T2DM). The trial enrolled 300 patients with T2DM and followed them for 2 years. Plasma NGAL levels were measured at baseline, 6 months, and 2 years post-randomization.

Results: The mean baseline plasma NGAL level was 2.5 ng/ml. At 2 years, the mean plasma NGAL level had increased to 3.2 ng/ml, indicating progressive kidney damage. There was a significant correlation between the increase in NGAL levels and the decrease in eGFR (p=0.03). Patients treated with RAAS blockade showed a significant reduction in NGAL levels (p=0.01), indicating improved kidney function.

Conclusions: NGAL is a promising biomarker for early detection of diabetic nephropathy. RAAS blockade appears to have a beneficial effect on NGAL levels, suggesting its potential in preventing kidney damage.
Mechanism of Increased Urinary Full-Length Megalin Excretion in Type 2 Diabetes Mellitus Patients with Nephropathy

By: Maria Celeste Nicoletti, Monica Carmosino, Bladzinska-Bladzinska, Gudeta D. Fufaa, Robert G. Nelson, Paulina Dumnicka, Agnieszka Zylka, Beata Kustomierz-cabala, Marek Kazniewski, Shi Queen Jadwiga Hospital No 2, Rzeszow, Poland; Dept of Medical Diagnostics, Jagiellonian Univ Medical College, Krakow, Poland; Dept of Nephrology, Jagiellonian Univ Medical College, Krakow, Poland.

Background: Two clinical phenotypes of diabetic kidney disease (DKD) have been identified, i.e. with or without increased albuminuria. The aim of this study was to assess the usefulness of uNGAL for the preclinical diagnosis of DKD in the course of diabetes mellitus type 2 (DM2).

Methods: The study group consisted of 115 DM2 patients (63F, 58M) aged 18 and over (62±14), with normal to moderately increased albuminuria (i.e. urine albumin/creatinine ratio (UACR) <300 mg/gCr) and eGFR (CKD-EPI) ≥60ml/min/1.73m². Control group included 22 non-diabetic persons with comparable age (57±14; p=0.1) and sex (9F, 13M, p=0.5), and with similar comorbidities. Urine concentrations of NGAL, albumin and creatinine (uCr) were measured in the first morning urine sample. Urine albumin/creatinine ratio (UACR), and analogically, uNGAL/uCr were calculated.

Results: In control group, maximum uNGAL/uCr was 39.64 µg/g. In DM2 group, 24 patients (21%) had higher results, with the maximum value of 378.6 µg/g. Twenty three (20%) of DM2 patients had UACR >30 mg/g; of these, 11 had uNGAL/uCr <39.64 µg/g. Among patients with uNGAL/uCr >39.64 µg/g, 13 did not have markedly increased albuminuria (in uraemic patients those ranged from 2.35 to 16.10 mg/g). Women with DM2 had significantly higher uNGAL/uCr than men (median 28.06; IQR 9.05-65.60 versus 11.40; 3.36-18.02 µg/g; p=0.001), without significant difference in UACR (p=0.09). uNGAL/ uCr in DM2 patients correlated significantly with HbA1c (R=0.28; p=0.013), however, it did not correlate with eGFR (R=0.54; p=0.1), age (R=0.14; p=0.1), or time from DM2 diagnosis (R=0.13; p=0.1).

Conclusions: Increase in urine NGAL and uNGAL/uCr may indicate early tubular damage particularly worse diabetes control patients, especially female with DM2.

Funding: Private Foundation Support, Clinical Revenue Support

Plasma Bradykinin and Early Diabetic Nephropathy in Type 1 Diabetes Mellitus


Background: Bradykinin (BK) and its modified forms are potential biomarkers of diabetic nephropathy (DN). We examined their association with development of DN lesions in normoalbuminuric normotensive subjects with normal or increased glomerular filtration rate (GFR) and type 1 diabetes (T1D) from the Renin-Angiotensin System Study (N Engl J Med 2009;361:40-50).

Methods: Plasma concentrations of BK and modified BKs were measured at baseline and 5 years using a mass spectrometry-based multiple reaction monitoring assay in samples from 246 subjects who underwent kidney biopsies at baseline and after 5 years. Relationships of BK and modified BKs with morphometric variables were assessed using multiple linear regression after adjustment for age, sex, T1D duration, HbA1c, mean arterial pressure, albumin excretion rate (AER) and eGFR.

Results: Baseline mean age was 29.8 years, mean duration of T1D 11.3 years, median AER 5.1 mg/min, and mean GFR 128 mL/min/1.73 m². At multivariable adjustment, higher BK concentration was associated with the peripheral glomerular basement membrane surface density (p=0.001), and analogically with the thickness of the basement membrane at the podocyte-mesangial cell interface (p=0.03). Elevated plasma BK concentration measured before clinical findings of DN in people with T1D was associated with increased peripheral glomerular basement membrane surface density, suggesting that it may reflect an adaptive response to early glomerular changes in DN.

Funding: NIDDK Support
FR-PO614
Serum Omentin and Progression of Diabetic Nephropathy. Tetsuharu Oku,
Fumihiko Furuya, Takeyuki Takamura, Kenichiro Kitamura. Third Dept of
Internal Medicine, Univ of Yamanashi, Chuo, Yamanashi, Japan.

Background: A novel adipokine, omentin, preferentially produced by visceral
adipose tissue compared with subcutaneous adipose tissue. Animal experiments indicated that
treatment with recombinant omentin enhanced insulin-stimulated glucose uptake in
subcutaneous and omental adipocytes. Furthermore, serum omentin levels are decreased in
obesity and diabetics. The purpose of this study was to elucidate whether serum omentin is
associated with progression of diabetic nephropathy in diabetic patients.

Methods: The prospective follow-up study; 114 diabetes patients were followed for
5 ± 1.1 years. Patients were divided at baseline into three groups according to their
urinary albumin-to-creatinine ratio (UACR): 68 patients with normoalbuminuria (UACR <30
mg/gCr), 31 patients with microalbuminuria (30 mg/gCr ≤ UACR < 300 mg/gCr), and 17 patients
with macroalbuminuria (UACR >300 mg/gCr). Progression of albuminuria was the main outcome.
Omentin was measured by ELISA, and the values were adjusted for age, BMI, and sex before analysis.

Results: Progression either to the next albuminuria level in 16 patients or to end-stage
renal disease (ESRD) occurred in 5 patients. No difference in adiponectin concentrations was
observed between progressors and nonprogressors in patients with normoalbuminuria. In the
patients with microalbuminuria and macroalbuminuria, progression of albuminuria was
associated with higher omentin. Progression to ESRD was also associated with estimated
glomerular filtration rate (eGFR). When these covariates were inserted in a Cox regression
analysis, eGFR and omentin were significantly associated with progression of albuminuria.
Conclusions: Serum omentin levels predict the progression from microalbuminuria to macroalbuminuria and from albuminuria to ESRD in diabetic patients.

FR-PO615
The Expressions of Vitamin D and Its Receptor in Patients with Diabetes
Associated with Proteinuria and Diabetic Nephropathy. Yang Yang, Jia Guo,
Zhiangso Liu. The Firs Affiliated Hospital of Zhengzhou Univ, Zhengzhou,
Henan, China.

Background: Vitamin D receptor (VDR) is a member of the nuclear receptor
superfamily, and there was no report about the expression of Vitamin D and its receptor
in patients with diabetes associated with proteinuria and diabetic nephropathy. So, this study
aimed to test the expression trends of VDR in blood, urine specimens and renal tissues
of diabetic nephropathy patients who were diagnosed by renal biopsy (DN3 group). 2. The expressions
of peritubular capillaries in renal tissues with DN. Increased serum omentin levels predict the progression from
microalbuminuria to macroalbuminuria and from albuminuria to ESRD in diabetic patients.

Conclusions: There was no report about the expression of Vitamin D and its receptor
in patients with diabetes associated with proteinuria and diabetic nephropathy. So, this study
aimed to test the expression trends of VDR in blood, urine specimens and renal tissues
of diabetic nephropathy patients who were diagnosed by renal biopsy (DN3 group). 2. The expressions
of peritubular capillaries in renal tissues with DN. Increased serum omentin levels predict the progression from
microalbuminuria to macroalbuminuria and from albuminuria to ESRD in diabetic patients.

Conclusions: There was no report about the expression of Vitamin D and its receptor
in patients with diabetes associated with proteinuria and diabetic nephropathy. So, this study
aimed to test the expression trends of VDR in blood, urine specimens and renal tissues
of diabetic nephropathy patients who were diagnosed by renal biopsy (DN3 group).
FR-P0619
Macrophyage Accumulation and Phenotype in Human Diabetic Nephropathy
Yang Ying, Yinfeng Guo, Zhixia Song, Min Zhou, Xiaoliang Zhang. Southeast Univ.

Background: Macrophage, especially its distinct phenotype is involved in the progression of DN. M1 is characterized with pathogenic function, while M2 displays anti-inflammatory. This study tries to examine the macrophage phenotype and its relationship to the renal function and histological changes in human DN.

Methods: We studied retrospectively 46 patients with DN who were confirmed by diagnosis of renal biopsy. Biopsies were divided into I Ha Ib III IV classes according to the pathologic classification of DN. Patients with renal trauma or renal tumor were considered as control group. Serum creatinine, proteinuria were calculated. Kidney tissues were used to assess histological changes and the presence of macrophage marker CD68, M1 marker iNOS, M2 marker CD206, Arg-1, TREM1 and TREM2.

Results: In biopsy renal tissue of human DN, Expression of CD68, M1 were significantly increased in the glomeruli (2.835±1.045/pcs VS 1.203±0.547/pcs for normals P=0.031; 2.330±1.343/pcs VS 0.896±0.548/pcs for normals P=0.046) and interstitium (0.037±0.142%area VS 0.019±0.002%area P=0.016; 0.018±0.008%area VS 0.009±0.005%area P=0.023). While M2 were mainly observed in the interstitium (0.019±0.008%area VS 0.010±0.004%area P=0.038). Interstitium M2 correlated strongly with interstitium M1 infiltration. Additionally there was a positive correlation between the glomerular CD68, M1 numbers and serum creatinine (r=0.619, p<0.001; r=0.463, p=0.017), proteinuria (r=0.641, P=0.000; r=0.508, P=0.008), mesangial matrix, interstitial collagen deposition. Likewise, the expression of interstitial CD68, M1, M2 also correlated strongly with serum creatinine (r=0.638, P=0.000; r=0.606, P=0.001; r=0.520, P=0.006), proteinuria (r=0.749, P=0.000; r=0.651, P=0.000; r=0.694, P=0.000), mesangial matrix, interstitial collagen deposition. Besides TREM1,2-positive cells were apparent in the interstitium and the expression levels significantly correlated with interstitium M1, M2 expression.

Conclusions: Macrophage infiltration and polarization participate in the development of diabetic nephropathy.

Funding: Government Support - Non-U.S.

FR-P0620
Risk of Diabetes Increased According to the Level of Urinary Albumin Excretion Even Within Normal Range
Dong-Young Lee, Beom Kim, Kyounghyub Moon, Sung Keun Park, Youngou Jung. Internal Medicine, VHS Medical Center, Seoul, Republic of Korea; Total Health Care Center, Kangbuk Samsung Hospital, Sungkyunkwan Univ; School of Medicine, Seoul, Republic of Korea.

Background: Urine albumin creatinine ratio (UACR) as a reliable index of urinary albumin excretion is getting great attention on its predictive role for various diseases related with diabetes. Nevertheless, predictive value of UACR within normal range was not clarified for diabetes yet. Therefore, this study was aimed at examining the clinical association between normal range of UACR and development of diabetes.

Methods: We identified 1,274 non-diabetic Korean men within normal range of UACR in 2005, and followed them up until 2010. All subjects were classified into three categories with respect to baseline UACR, from the lowest to the highest. The incidence rates of diabetes were compared according to the tertile groups of UACR, and the independent hazard ratios (HRs) of UACR levels for diabetes was measured by Cox proportional hazards analysis.

Results: During follow-up, diabetes developed in 97 out of 1,274 subjects (7.6%). Incidence rate of diabetes increased in proportion to the levels of UACR (tertile 1; 4.9%, tertile 2; 7.3%, tertile 3; 10.6%, p<0.001).

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Tertile 1 (&lt;1.17)</th>
<th>Tertile 2 (1.17≤&lt;4.95)</th>
<th>Tertile 3 (≥4.95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>49.5</td>
<td>52.6</td>
<td>53.9</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
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<tr>
<td>DBP (mmHg)</td>
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<td>78.3</td>
<td>81.4</td>
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<td>FBG (mg/dL)</td>
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<td>98.5</td>
<td>99.8</td>
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<tr>
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<td>2.07</td>
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<tr>
<td>HbA1C (%)</td>
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<td>5.4</td>
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<tr>
<td>eGFR (ml/4L)</td>
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<tr>
<td>Hypertension (%)</td>
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<td>23.7</td>
<td>37.5</td>
</tr>
<tr>
<td>Development of diabetes (%)</td>
<td>4.9</td>
<td>7.3</td>
<td>10.6</td>
</tr>
</tbody>
</table>

Conclusions: Elevated UACR, even within normal range, was significantly associated with the future development of diabetes.

FR-P0621
Albuminuria Is Positively Associated with Elevated Numbers of Circulating Endothelial Pre- and Mature Cells, but Inversely Associated with Circulating Fibrocytes

Background: Diabetic nephropathy is characterized as a microvascular disease with enhanced vascular leakiness in the kidney and aberrant tissue remodelling. Abnormal number and function of endothelial cells, stem cells and activation of leucocytes is considered as contributing mechanisms to the “kidney-micro”-vascular leaky syndrome. We determined if circulating endothelial pre- and mature cells, fibrocytes or monocyte sub-populations were abnormally regulated in type 2 diabetic patients with albuminuria.

Methods: Cross-sectional study of 37 type 2 diabetic patients; 18 with normalalbuminuria (<30mg/24h) and 19 with albuminuria (³30mg/24h). 8-color flow cytometry analysis of peripheral blood was performed. ANCOVA compared expression of cell markers and absolute number of specific cell populations in patients with normalalbuminuria vs. albuminuria.

Results: Expression of VEGFR2 was significantly enhanced in patients with albuminuria (p=0.009). Also, the total number of circulating mature endothelial cells (CEC) was significantly enhanced in albuminuria (p=0.001). Circulating fibrocyte number and collagen-1 expression was inversely associated with albuminuria (r=0.39, P<0.037) and TGFbeta stabilizing and M2-associated galectin-3 expression on M1-like and M0-like monocytes was positively associated with albuminuria (r=0.029). In contrast, expression of the M1-associated marker CD11c (p=0.042) was inversely associated with albuminuria on all monocytes, particularly on M0-like macrophages (p=0.014).

Conclusions: The enhanced number of CEC together with elevated expression of VEGFR2 may indicate an aberrant function of the CEC with reduced capacity to heal the kidney microvascular disease. The imbalanced M2-polarization of monocytes and aberrant fibrocyte count may favour improper repair leading to excessive tissue fibrosis. Hence therapeutic approaches addressing migratory pattern of CEC, providing adjuvant activating signals or restoring the immune balance might provide novel individualized treatment regimes.

FR-P0622
Prognostic Value of Tubulointerstitial Lesions and Urinary N-Acetyl-b-D-Glucosaminidase in Patients with Type 2 Diabetes and Biopsy-Proven Diabetic Nephropathy
Koki Mise, Junichi Hoshino, Toshiharu Ueno, Masayuki Yamanouchi, Noriko Hayami, Tetutsu Suwabe, Kenmei Takaichi, Yoshifumi Ubara. Nephrology Center, Toranomon Hospital Kajigaya, Kavasaki, Kanagawa, Japan; Nephrology Center, Toranomon Hospital, Tokyo, Japan.

Background: Recently, it has been reported that some biomarkers of renal tubular injury are useful to predict the renal prognosis in the early stage of diabetic nephropathy (DN). However, how closely such biomarkers reflect actual tubulointerstitial damage remains unknown.

Methods: Among 210 patients with type 2 diabetes and biopsy-proven DN, 152 patients were enrolled, 89% of whom had overt proteinuria. The endpoint was defined as 50% or more decrease of the estimated glomerular filtration rate (eGFR) from baseline or commencement of dialysis due to end-stage renal disease. The Cox proportional hazard model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the death-censored endpoint.

Results: A significant correlation was found between baseline urinary N-acetyl-b-D-glucosaminidase (NAG) excretion and the score for interstitial fibrosis and tubular atrophy (IFTA score) (r=0.39, P<0.001). The influence of urinary NAG on the renal prognosis was attenuated after adjustment for known promoters of progression (+1SD for log NAG, HR: 0.87 [95% CI: 0.66-1.13]). On the other hand, the IFTA score was significantly related to the outcome even after adjustment for those covariates (+1 for IFTA score, HR: 2.20 [1.50-3.21]).

Conclusions: The assessment of urinary NAG excretion did not improve the prognostic power of known indicators of progression, whereas the IFTA score did. The IFTA score may be more useful for predicting the renal prognosis than current tubulointerstitial markers, especially in patients with advanced DN.

Funding: Private Foundation Support
Is There Any Benefit of Performing Renal Biopsies in Patients with Diabetic Nephropathy when No Other Diagnosis Than Diabetic Nephropathy Is Found?  
Rosa M. Montero, 1 Dimitrios Anestis Moutzouris, 1 Ranmith Perera, 2 David Goldsmith. 1 \textit{Nephrology & Transplantation, Guy’s & St Thomas’ NHS Foundation Trust, London, United Kingdom}; 2 \textit{Histopathology, Guy’s & St Thomas’ NHS Foundation Trust, London, United Kingdom.}

\textbf{Background:} The risk of renal biopsy has long been thought to outweigh the benefit of performing these on patients with diabetes mellitus (DM) leading to small numbers of renal biopsies in this population. Those biopsied have a propensity to more proteinuria or haematuria precipitating biopsy. Glomerular lesions alone have long been the hallmark of diabetic nephropathy (DN) however looking back at the biopsy can there be more to see?  

Methods: \textbf{All native renal biopsies diagnosed with DN from 2009-2014 were retrieved from archive at Guy’s & St Thomas’ NHS foundation trust. Renal biopsies were performed in patients with DM who had heavy proteinuria or haematuria on presentation. Biopsies with a DN diagnosis alone were identified and Tervaert’s new DN classification was applied. Clinical outcome data was collected from electronic patient records. Cox regression models were used to perform statistical analysis.}  

\textbf{Results:} 3000 native kidney biopsies were performed from 2009-2014. 34 DM patients had DN alone on renal biopsy, 12 T1DM and 22 T2DM. 20 male, 14 females. Ethnicity: 35% white, 35% black, 3% asian, 27% other. Age range: 24-86 years (median 55). UPCR: 13.492 mg protein/mmol creatinine (median 392) eGFR 7-74.9 (median 23). 8.8% 5 year mortality. Glomerular IV and Interstitial III lesions were significant predictors of renal survival (p=0.013 HR 27.5, p=0.066 HR 21, respectively). Renal survival ranged from 1-60 months post renal biopsy (median 3).  

\textbf{Conclusions:} Interstitial fibrotic lesions are as important as glomerular lesions in predicting renal survival. Determining the significance of the compartments in predicting outcome may be more sensitive; however few biopsies are undertaken in this population. The role of an earlier renal biopsy showing less well established features in the DN population may be more sensitive; however few biopsies are undertaken in this population. The risk of renal biopsy has long been thought to outweigh the benefit of performing these on patients with diabetes mellitus (DM) leading to small numbers of renal biopsies in this population. Those biopsied have a propensity to more proteinuria or haematuria precipitating biopsy. Glomerular lesions alone have long been the hallmark of diabetic nephropathy (DN) however looking back at the biopsy can there be more to see?  

Understanding the Relationship Between Histopathology and Renal Function in Hypertension and Diabetes  
Matthew Palmer, 1 Jordana B. Nagata, 2 Holly J. Cornish, 3 Michaela J. Obel, 4 Ana M. Ramos, 5 Emily Ansell, 6 Reuben Wilkins, 7 David G. Cooper. 1 \textit{Nephrology & Transplantation, Guy’ s & St Thomas’ NHS Foundation Trust, London, United Kingdom}; 2 \textit{Histopathology, Guy’s & St Thomas’ NHS Foundation Trust, London, United Kingdom}.  

\textbf{Background:} The link between obesity and renal disease is unclear. Hyperfiltration is suspected to induce arteriolar hyalinosis and glomerular hypertrophy in moderate to severe obesity. To assess morphological changes in obesity, we investigated human normotensive renal tissue from 7 mild obese cases (Ob)(BMI 27) and 7 non-obese cases (Con) and compared with 7 hypertensive case (HT) and 4 control(Con).  

\textbf{Methods:} Total 130 of serially cut paraffin sections were double immunostained with CD34 as endothelial marker, and smooth muscle actin as medial marker, followed by PAS staining. Incidence of hyalinosis in afferent and efferent arterioles, intraglomerular cleft dilatation connecting to efferent arterioles, segmental sclerosis, sclerotic glomerul(GS) and average size of glomeruli were assessed using 50-40 glomeruli per case. \textbf{Results:} The morphological data were as follows; average glomerular diameter 203±26, 181±19, 136±14, incidence of arteriolar hyalinosis 43±13, 47±29, 20±16%, incidence of that of efferent arterioles, 30±10**, 13±14, 5±4% for Ob, HT and Con, respectively (**P<0.05 vs Con, **P<0.05 vs Con and HT). Higher incidence of cleft dilatation near efferent arterioles was noticed in Ob (21±15%) than HT and Con (2±15%, 0%, respectively)(P<0.05). Obese cases revealed neither significant intimal thickening nor distortion in the interlobular arteries, no segmental sclerosis, low incidence of GS (11±7%) and minimal interstitial damage(<10%).  

\textbf{Conclusions:} Effector arterioles are targets for obesity, which suggest that specific mechanism of glomerular hyperfiltration involves obese cases, even in mild form.  

Fundings: \textit{Government Support - Non-U.S.}
Methods: A total of 396 patients with T2D and biopsy-proven DN from Nanjing DN registration system who were followed-up for at least 1 year were recruited and median 5-year follow-up. Renal outcomes were defined by progression to end-stage renal disease and doubling of serum creatinine.

Results: Of the participants, the mean baseline eGFR was 73.86±33.52 mL/min per 1.73 m². The levels of the urinary tubulointerstitial injury markers including the NAG, RBP and NAGL were significantly different among quintiles of serum phosphorus (P<0.01). The participants whose eGFR<90 mL/min per 1.73 m² had a higher rate of tubulointerstitial injury (interstitial fibrosis tubular atrophy scores of 2 and 3, P<0.005; interstitial inflammation scores of 1 and 2, P<0.035) in hyperphosphatemia (>1.45 mmol/L) group than in lower phosphorus group (<1.17 mmol/L). Participants with baseline levels of serum phosphorus in higher quintiles had a higher cumulative incidence of ESRD (log-rank, P<0.001). In the analyses adjusted by age, sex, diabetes status, BP, Fbg, BMI, proteinuria, cholesterol, and eGFR, the relationship between higher serum phosphorus and an increased risk of ESRD remained. The association between serum phosphorus and ESRD risk persisted and was stronger when the sample was restricted to those with a baseline eGFR equal to 60-90 mL/min per 1.73 m², but not when it was restricted to patients with a baseline eGFR of 30-60 mL/min per 1.73 m².

Conclusions: These findings indicated the baseline serum phosphorus is associated with tubulointerstitial injury of T2D patients. And serum phosphorus >1.45 mmol/L is an independent risk factor of ESRD in T2D, especially in the patients with eGFR>60 mL/min per 1.73 m².

Funding: Government Support - Non-U.S.

FR-P0628
Longitudinal Changes in Estimated Glomerular Filtration Rate in Youth with Type I Diabetes
Nora Fino,1,3  Maryam Bjorn Eliasson,3  Kiran Kalia.

FR-P0630
The Relationship Between Diabetic Retinopathy and Diabetic Kidney Disease in a Population-Based Study in Korea (KNHANES V2-3)

Methods: Urinary/serum cyst c and NAG were estimated in total 491 age-matched patients enrolled for our cross-sectional study. Their efficacy was compared with conventional microalbuminuria, serum creatinine and eGFR in patients with varying type 2 diabetes (T2DM) duration and various stages of DN.

Results: Patients with 5-10 yrs of T2DM duration showed a significant increase in cyst of urinary NAG in patients with nonproteinuric DN (p<0.001) in all stages of T2DM duration. The ROC curve signifies diagnostic efficacy of urinary cyst c (AUC = 0.820) over urinary NAG (AUC = 0.678), in detecting T2DM patients susceptible to develop DN. Figure 1: Comparison of urinary Cystatin c and NAG in various groups.
previous congestive heart failure (n=23 799) (HR 1.26, 95% CI 1.17, 1.36). In addition, a 25-50 mmHg decrease in SBP from the last observation was associated with an increase in risk of all-cause mortality (HR 1.44, 95% CI 1.33, 1.56) compared to a change in the range -10 to 10 mmHg.

Conclusions: A systolic blood pressure < 130 mmHg and a decrease in systolic blood pressure during follow up with or without previous congestive heart failure, is associated with an increase in the risk of all-cause mortality in patients with type 2-diabetes and renal impairment. Intensity of hypertensive medication and co-morbidities are important confounders and will be further evaluated.

FR-PO632 Increased Expression of WNT5a in Renal Tubules Is Associated with Diabetic Nephropathy in Humans Malik Asad Anjum, An Xiao, Dean Troyer, Michael J. Solhaug, Anca Dobrian, Jerry L. Nadler, Liwei Huang.

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease worldwide. In recent years, convincing data has come forward suggesting that inflammatory pathways play a pivotal role in the pathogenesis and progression of DN. Identification of these inflammatory pathways and associated biomarkers may help in the early diagnosis of DN and development of novel targeted therapeutic strategies to help prevent, treat and even slow the progression of DN. Wnt5a, a secreted glycoproteins, plays an important role in normal kidney development and is also a pro-inflammatory factor which has been associated with renal fibrosis and disruption of matrix metabolism. The objective of our study was to investigate the expression of WNT5a in diabetic kidneys in humans.

Methods: 11 subjects with biopsy confirmed DN were included in our experimental group. Normal kidney tissues from non-diabetic subjects who underwent nephrectomy for renal cell carcinoma were used as controls. Exclusion criteria for the experimental group were HIV positivity, chronic/acute inflammatory diseases (including hepatitis C) and steroids-immunosuppressant medication. WNT5a expression was evaluated in paraffin embedded tissues.

Results: Immunohistochemical analysis of WNT5a expression showed positive staining on the apical side of the plasma membrane of the renal tubular epithelial cells in control kidney tissues. The intensity of the staining is increased in patients with DN compared to normal kidney control tissues. In patients with DN, WNT5a expression is localized both in the cytoplasm and on the apical side of the plasma membrane of the renal tubular cells. WNT5a is also expressed on glomerular cells, but there are no differences in Wnt5a expression between the tissues from diabetic subjects and controls.

Conclusions: Our results suggest that WNT5a expression in renal tubules might have a pathogenic role in the development of human renal tubular fibrosis. These studies are the first to demonstrate an increase in WNT5a expression in renal tubules in DN.

Funding: NIDDK Support

FR-PO633 Accuracy of Serum Creatinine and Glomerular Filtration Rate Estimation for Adjusting Metformin Prescription in European Type 2 Diabetics Olivier Moranne, Coraline Faïfin, Pierre Delanaye, Martin Flamant.

Background: There is a debate in the literature about the thresholds of serum creatinine (Scr) above which the drug is contraindicated (1.5 mg/dL in men & 1.4mg/dL in women). For KDIGO, recommendation is a dose-adjustment between 45 and 30 mL/min and a withdrawal below 30 mL/min. However, in DM2, estimation of renal function based on Scr alone or on eGFR may vary from the true renal function (mGFR). The purpose of our study was to define the performance of the GFR assessment method (Scr or eGFR) calculated with Cockcroft-Gault (CG) or CKD-EPI in terms of metformin dose adjustment in DM2 who underwent a GFR measurement.

Methods: In 243 DM2 patients, GFR was measured by urinary clearance of CrEDTA. Non indexed GFR was used. We analyzed the agreement between classification of patients based on mGFR and, first, Scr alone with a cutoff value of 1.5 mg/dL in men and 1.4 mg/dL in women, second, on eGFR with threshold values of 45 or 30 mL/min. When both methods classified the patient in the same subgroup, the data were considered concordant otherwise overprescription (underprescription) was defined for discordance according to mGFR.

Results: Age was 61 ± 12 y/o, median mGFR was 42 [30-61] mL/min. Based on mGFR, the distribution of the patients according the following GFR class: [90-45] 110(45%), [44-30] 74(30%), < 30: 59(24%). In patients with a Scr above the cutoff value, mGFR(Scr) was <30 mL/min in respectively 23/40 women and 33/106 men. With a threshold of 45 mL/min then 30 mL/min, concordance was found in 80/85% then 88/88% of the patients for the CG and CKD-EPI. With a threshold of 30 mL/min, discordance was an overestimation (or underestimation) in 22(9%) and 19(8%) or 14(6%) and 11(5%) of the patients with the CG and CKD-EPI.

Conclusions: In this population creatinine-derived equations outperformed Scr alone in correctly classifying the patients in prescription subgroups. However, even with creatinine-based equations, discordance with mGFR occurs in 12-20% of the patients. New strategies such as drug concentration monitoring may be necessary to improve appropriate prescription of metformin in DM2.

FR-PO635 Changes in Glycaemia During Haemodialysis (HD) Are Not Associated with Changes in QTc Interval in Insulin-Treated Diabetic Patients Naveen H. Siddaramahal, Ddidem Tez, Thanh Phan, Nicholas J. Linker, Mary Bilous, Sue Winship, Sally M. Marshall, RudolfW. Bilous.

Background: Changes in albuminuria may have useful prognostic value. We sought to assess the association between change in urine albumin-to-creatinine ratio (UACR) and the risk of all-cause death, cardiovascular disease (CVD), and end-stage renal disease (ESRD) in the ADVANCE trial.

Methods: We defined UACR change (baseline to 2 years) as ≥30% decrease, <30% decrease to >30% increase (minor change; reference), and >30% increase. Follow-up for outcome ascertainment commenced at the second UACR measurement. We used Cox regression to estimate the hazard ratio (HR), after adjustment for demographics, ADVANCE randomized treatment assignments, comorbidities, laboratory measurements (including baseline UACR), and drug use.

Results: From baseline to 2 years, 34% of 9195 patients experienced a UACR decrease of ≥30%, 26% experienced a minor change, and 40% experienced an increase of ≥30%. Over the next 2.9 years (median), 520 deaths, 524 CVD events, and 12 ESRD events were recorded. An increase of >30% in UACR was associated with 30% higher mortality when compared to a minor change ([Figure 1] HR 1.30, 95% CI 1.18-1.40). Increase in UACR associated with increased CVD or ESRD, although the direction of effect was similar. A >30% UACR decrease was not significantly associated with the risk of death or CVD when compared to those with minor change but was significantly associated with lower ESRD risk (HR 0.10, 95% CI 0.01-0.79).

Conclusions: In type-2 diabetes patients, ≥30% increase in albuminuria predicted higher mortality while >30% decrease was associated with decreased ESRD risk. Our results suggest change in albuminuria may be a potential prognostic marker for clinical outcomes in type-2 diabetes.
Results: QTc interval was prolonged significantly at the end of HD in all sessions (p<0.001). Change in glucose level (mean±SD -1.8±4.2 vs. -1.7±3.0) did not have a significant effect on the change in QTc interval (p=0.396), which was not different in diabetic subjects compared to non-diabetic group (p=0.390). Serum K+ , Mg++ and Ca++ levels dropped significantly (p<0.001) during all 3 HD sessions. There was no significant difference in Mg++ levels and the drop in K+ , Mg++ and Ca++. The change in Mg++ (p<0.05) and Ca++ (p<0.05) levels but not K+ (p=0.202) were more pronounced in diabetic subjects. The change in Mg++ levels in diabetic subjects was associated with QTc prolongation (p<0.05).

Conclusions: Significant QTc prolongation occurs at the end of HD in people with and without diabetes, often reaching abnormal levels and appears to be related more to changes in blood electrolytes than glycaemia. The fall in serum Mg++ levels during HD had a larger effect on QTc than K+ or Ca++ and this appears to have a more pronounced effect in diabetic subjects. The changes in QTc may increase the risk of cardiac dysrhythmia and sudden death in HD patients.

FR-PO636

Markers of Inflammation and Endothelial Dysfunction Are Associated with Cardiovascular Morbidity and Mortality in Type 2 Diabetic Patients with Microalbuminuria

Bernt Johan Ilmum von Scholten,¹ Henrik Reinhard,¹ Tine Hansen,¹ Casper Schalkwijk,² Coen Stenhouse,² Hans-Henrik Parving,² Peter Karl Jacobsen,¹ Peter Rossing,¹ Steno Diabetes Center, Denmark;² Maastricht Univ Medical Center, Netherlands;³ Rigshospitalet, Denmark.

Background: Accumulating evidence suggests that inflammation and endothelial dysfunction link type 2 diabetes (T2D) to cardiovascular disease (CVD). We evaluated the predictive value of markers of inflammation and endothelial dysfunction for combined fatal and non-fatal CVD and for all-cause mortality in patients with T2D and microalbuminuria but without known coronary artery disease (CAD).

Methods: Prospective study including 200 patients. All received intensive multifactorial treatment. Markers of inflammation (TNF-α, ICAM-3, hsCRP, SAA, IL-1β, IL-6, IL-8) and endothelial dysfunction (thrombomodulin, VCAM-1, ICAM-1, E-selectin, P-selectin) were measured at baseline. Adjusted multiregression models included sex, age, total cholesterol, smoking, HbA1c, creatinine, systolic blood pressure and urinary albumin excretion. Fully adjusted models additionally included NT-proBNP and coronary artery calcium score (CAC).

Results: Participants were 76% men, age (± SD) 59 ± 9 years, HbA1c was 7.9 ± 1.3%. Occurrence of CVD (n=40) and mortality (n=26) was traced after 6.1 years (median). In adjusted Cox analysis, higher TNF-α predicted the CVD endpoint and mortality (p<0.002). After full adjustment higher TNF-α remained predictive of both endpoints (p<0.007). Higher thrombomodulin and ICAM-3 were associated with risk of CVD and mortality in adjusted analyses (p<0.05) and predicted mortality after full adjustment (p<0.001). Higher VCAM-1 and ICAM-1 were associated with risk of mortality in adjusted (p<0.002) and fully adjusted models (p<0.005). The composite z-score of all markers of inflammation and of endothelial dysfunction predicted CVD and mortality (p<0.008).

Conclusions: In patients with T2D and microalbuminuria without known CAD, biomarkers of inflammation and endothelial dysfunction were independently associated with risk of CVD and mortality. Especially TNF-α was a robust predictor, even after adjusting for albuminuria, NT-proBNP and CAC.

FR-PO637

Predictors of Glycemic Status and Associations with Mortality in Incident Diabetic Hemodialysis Patients

Connie Rhee,¹ Steven B. Kim,¹ Rajnish Mehrotra,¹ Elani Streja,¹ Danh V. Nguyen,¹ Steven M. Brunelli,³ Gregory Brent,¹ Csaba P. Kovessy,¹ Kamyar Kalantar-Zadeh,¹ UC Irvine;² Univ Washington;³ DaVita Clinical Research; ¹UCLA; ²UTHSC.

Background: In the general population, intensive glycemic targets confer higher mortality in diabetics with cardiovascular risk. In diabetic hemodialysis (HD) patients, some but not all studies show that lower glycemic levels defined by HbA1c are associated with higher mortality. We sought to examine predictors of low glycemic status in HD patients with one or more HbA1c measures during the first 91-days of dialysis, we examined the association, respectively, were examined using case-match laboratory adjusted Cox models.

Results: Among 63,607 diabetic HD patients, 37% had low HbA1c levels. Female gender and non-Hispanic race/ethnicity; lower BMI and nPCR; and higher serum bicarbonate, creatinine, and albumin were associated with higher risk of low HbA1c. Baseline HbA1c levels <7% were associated with lower mortality. However, time-dependent HbA1c levels <5% were associated with higher mortality.

Methods: We performed a cross-sectional study of a representative sample of 1594 persons recruited from the general population of the municipality of Tromso, Norway, aged 50-62 without prevalent cardiovascular disease, diabetes or renal disease. GFR was measured by iohexol clearance. Obesity was classified according to body mass index (BMI), waist circumference (WC) and waist-hip ratio (WHR). RHF was defined as >90th percentile of residuals from a linear regression of absolute GFR on age, sex, weight and height.

Results: In multivariable adjusted logistic regression models, the odds ratios (95% confidence intervals) for RHF were 1.56 (1.11-2.18) per 0.10 increase in WHR, 0.82 (0.51-1.32) per 2 kg/m2 of BMI and 1.23 (0.92-1.65) per 10 cm of WC. WHR was consistently associated with RHF across different models. Higher BMI and WC were significantly associated with RHF only when an alternative definition of RHF, not adjusted for body weight, was used. Higher BMI, WC and WHR were also independently associated with increasing GFR analyzed as a continuous variable.

Conclusions: Baseline HbA1c levels <7% were associated with lower mortality, suggesting that moderately low glycemic status has long-term benefits in diabetic HD patients. Yet time-dependent HbA1c levels <5% were associated with higher mortality, suggesting that very low glycemic status carries short-term risk. Further studies are needed to determine if pharmacotherapies targeting these glycemic ranges reduce mortality in diabetic HD patients.

Funding: NIDDK Support, Private Foundation Support

FR-PO638

Waist-Hip Ratio Is Associated with Renal Hyperfiltration in the Non-Diabetic, Middle-Aged General Population

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Background: Renal hyperfiltration (RHF) is a maladaptive response to increased metabolic stress in the kidneys which may result in chronic kidney disease. Diabetes causes RHF, but whether obesity in non-diabetic persons is a cause of RHF has not been adequately studied in the general population. This study aimed to establish whether RHF assessed by measured glomerular filtration rate (GFR) is associated with obesity independently of metabolic and cardiovascular risk factors.

Methods: We performed a cross-sectional study of a representative sample of 1594 persons recruited from the general population of the municipality of Tromso, Norway, aged 50-62 without prevalent cardiovascular disease, diabetes or renal disease. GFR was measured by iohexol clearance. Obesity was classified according to body mass index (BMI), waist circumference (WC) and waist-hip ratio (WHR). RHF was defined as >90th percentile of residuals from a linear regression of absolute GFR on age, sex, weight and height.

Results: In multivariable adjusted logistic regression models, the odds ratios (95% confidence intervals) for RHF were 1.56 (1.11-2.18) per 0.10 increase in WHR, 0.82 (0.51-1.32) per 2 kg/m2 of BMI and 1.23 (0.92-1.65) per 10 cm of WC. WHR was consistently associated with RHF across different models. Higher BMI and WC were significantly associated with RHF only when an alternative definition of RHF, not adjusted for body weight, was used. Higher BMI, WC and WHR were also independently associated with increasing GFR analyzed as a continuous variable.

Conclusions: Central obesity measured as WHR is associated with RHF and higher GFR independently of age, sex, body weight, metabolic indices (including fasting glucose,
insulin and HbA1C) and cardiovascular risk factors (including ambulatory blood pressure, antihypertensive medication and smoking status). WHR may be a better indicator of the renal effects of obesity than BMI or WC.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Private Foundation Support, Government Support - Non-U.S.

FR-PO639

Obesity Associates with High Hemoglobin A1c but Low Alternative Indices in Both Diabetic and Nondiabetic Hemodialysis Patients

Mark E. Williams,1 Neal Mittleman,2 Lin Ma,1 Julia I. Brennan,2 Chiuin M. Jani,1 Curtis D. Johnson,3 Franklin W. Maddux,1 Eduardo K. Lacson,4,5 *Joslin Diabetes Center, Boston, MA; 2Kidney Care of Brooklyn and Queens, Brooklyn, NY; 3Prescient Medical Care North America, Waltham, MA; 4Spectra Laboratories, Rockleigh, NJ; 5Physician, Lexington, MA.

Background: The GIDE (Glycemic Indices in Dialysis Evaluation) study is evaluating several glycomic markers inhemodialysis (HD) cohorts with and without diabetes. We have reported that alternative glycomic indices may be elevated out of proportion to hemoglobin A1c (HgbA1c). Because obesity is known to affect markers of glycemia, we examined its association with these indices.

Methods: A combined cohort of 2,394 active HD patients (1,424 with diabetes, 970 without) from 26 U.S. FMCNA facilities had baseline indices [HgbA1c; albumin-adjusted and unadjusted fructosamine (AlbF; F) and glycated albumin (GA) or percent GA] measured Jan-Mar 2013 and monthly until April, 2015. Mean of body mass index (BMI) was determined for the entire cohort. Obesity—BMI ≥30 kg/m². Cox models adjusted by age, sex, race, ethnicity, vintage, HD cather, baseline comorbidity and laboratory albumin values were utilized to determine associate between obesity with death outcome.

Results: Average BMI (kg/m²; mean±SD) by risk as determined by indices (low=within target range, high=above target range) are shown in (table 1).

<table>
<thead>
<tr>
<th>Indices</th>
<th>Low Risk</th>
<th>High Risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgbA1c ≥ 7%</td>
<td>28.8 ± 11.4</td>
<td>31.6 ± 8.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent Glycated Albumin &gt; 15.7%</td>
<td>29.8 ± 12.4</td>
<td>28.9 ± 9.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fructosamine &gt; 285 μmol/L</td>
<td>31.0 ± 14.6</td>
<td>28.7 ± 9.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AlbF ≥ 974 μmol/L</td>
<td>29.5 ± 11.8</td>
<td>28.6 ± 7.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glycated Albumin ≥ 300 μmol/L</td>
<td>29.3 ± 11.4</td>
<td>29.2 ± 10.4</td>
<td>0.0008</td>
</tr>
<tr>
<td>HgbA1c &gt; 2.8%</td>
<td>29.1 ± 11.1</td>
<td>31.6 ± 8.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The Hazard Ratio (HR) for death was reduced with obesity [HR=0.76, 95% CI (0.62, 0.94), p=0.01].

Conclusions: Obesity is positively correlated with HgbA1c but negatively correlated with other glycomic indices in hemodialysis patients. Further studies are needed to elucidate underlying mechanisms and assess the relationship of these findings to superior survival outcomes in obese HD patients.

FR-PO640

BMI and Causes of Death in Chronic Kidney Disease

Sankar D. Navaneethan,1 Jesse D. Schold,2 Susana Arrigain,2 John P. Kirwan,3 Joseph V. Nally,3 Nephrology, Cleveland Clinic; 2Quantitative Health Sciences, Cleveland Clinic; 3Pathobiology, Cleveland Clinic.

Background: Chronic kidney disease (CKD) is associated with higher risk for cardiovascular related death. In CKD, a higher body mass index (BMI) is associated with a lower risk for death, but cause specific death details are unknown across the BMI range.

Methods: We included 54,506 patients with CKD (two estimated glomerular filtration rate <60 ml/min/1.73 m²); 90 days apart; January 2005 – December 2012) from our institutional electronic medical record-based CKD registry. We examined the associations between various causes of death (cardiovascular, malignancy and non-cardiovascular/ non-malignancy related deaths obtained from the State of Ohio mortality files) across the BMI range using the Cox proportional hazards model.

Results: During a median follow-up of 3.7 years (25th percentile,75th percentile: 1.8-5.8), 14,151 patients died. In the multivariable model, an inverted J-shaped association was noted between BMI and overall, cardiovascular, malignancy-related, and non-cardiovascular/ non-malignancy related deaths.

FR-PO641

Weight Reduction with Low Calorie Diet Reduces Urinary Megalin and Improves Albuminuria in Obese Men

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Background: Megalin, an endocytic receptor in proximal tubules, is involved in the mechanisms of albuminuria in diabetic nephropathy. A urinary full-length megalin (C-megalin) assay is linked to the severity of diabetic nephropathy and IgA nephropathy. Also, albuminuria is a frequent sign of obese individuals and could be reduced by losing body weight. We investigated the relationship between level of urinary C-megalin and albuminuria on a weight reduction program in obesity.

Methods: Thirty-three obese male volunteers (age 36.6 ± 6.9 years, BMI >25 kg/m²) were enrolled but 30 subjects completed the 12-week weight reduction program. The program consisted of replacement of evening meal by a low calorie formula food (MICRO-S®) for first 4 weeks and followed by bi-weekly dietary counseling session with nutritionist. Of these, 20 subjects with metabolic syndrome were included (based on the Japanese criteria). Urinary albumin/C-megalin ratio (ACR) and urinary C-megalin were measured at baseline and after the program.

Results: The mean weight loss was 5.2 ± 2.9 kg (5.6% of the original BW). The baseline ACR ranged from 2.8 to 52.9 mg/gCre. After the program, BMI, waist circumference, BP, total cholesterol and FFA were significantly decreased. HDL-cholesterol and adiponectin were significantly increased. Overall, ACR was not changed (11.9 ± 12.4 to 8.8 ± 5.3 mg/gCre). However, in the cases with ACR >8 mg/gCre at baseline (n=11), ACR was more effectively reduced (22.9 ± 15.1 to 12.7 ± 6.4 mg/gCre) without a change in eGFR. The reduction of ACR was correlated with the reduction of urinary C-megalin. No other parameters like insulin resistance were associated with the reduction of ACR or C-megalin.

Conclusions: Losing BW with a formula food is effective in reducing urinary ACR in obese men. This improvement of ACR is related to the reduction in urinary C-megalin. Since albumin is excreted into urine by its increased glomerular leakage and/or decreased proximal tubular reabsorption via megalin and cubilin, our observations suggest that megalin metabolism in proximal tubules may determine albuminuria in obesity.

Funding: Pharmaceutical Company Support - CCF CKD registry creation was supported by an unrestricted grant from Apen to the Department of Nephrology and Hypertension at Cleveland Clinic.
FR-PO642
Obesity Management in Patients with Chronic Kidney Disease (CKD): A National Survey
Christopher Lawrence,1 Helen L. MacLaughlin,2 Ken Farrington,1 Andrew H. Frankel.1 1Lister Hospital, United Kingdom; 2Kings College London, United Kingdom.
Background: Obesity contributes to the development and progression of CKD and may be a barrier to, or increase risks of, transplantation. Evidence for how the renal multi-disciplinary team (MDT) should proceed is limited and sometimes counterintuitive i.e., association of increased weight and better survival on hemodialysis. The study assessed approaches to obese patients with CKD across the UK and describes the availability of, and extent of co-working with, bariatric services.
Methods: An online survey tool was designed and sent by the British Renal Society to UK renal clinical directors and dieticians. The survey focussed on patients with CKD stage ≥ 3, with proteinuria and co-existent Obesity stage II (BMI ≥ 35kg/m²) as these patients are most likely to progress to ESRD.
Results: 58/71 (82%) of UK units responded with respondents split between dieticians (53%) and nephrologists (47%). Most respondents (78%) thought the prevalence of obesity has increased over the last decade. There was no consensus on the BMI cut off for kidney transplantation: 30%, 16%; 35%, 71%; ≤40, 12%; none, 2%. The 3 most common actions for initial obesity management were: to provide education/motivation (81%); dietary referral (60%) and test fasting glucose and lipids (43%). The other 17% did not feel confident to bariatric services. The main perceived barriers to weight loss were: lack of patient motivation (79%); no funding (60%); lack of services (53%). 54% of renal units co-locate with bariatric services. Only 35% of renal units can refer directly to local/regional bariatric service, the remainder were uncertain of referral pathways (27%) or relied on primary care physicians to refer. Only 5 units (9%) have a joint care pathway for obese patients with CKD undergoing bariatric surgery.
Conclusions: The response to obesity in CKD falls short of National (NICE) guidelines. The increasing prevalence of obesity is a challenge to the renal MDT. Strategies to tackle this include wider recognition of the problem; identifying and sharing best practice and development of a robust evidence base to foster investment in renal dietetic and support services.

FR-PO643
Effects of Renin-Angiotensin Blockade (RASB) on the Components of Early Interstitial Expansion in Patients (pts) with Type 1 Diabetes (T1D) Zarah Khan, Michael Maurer, Maria Luiza A. Caramori. Medicine and Pediatrics, Univ of Minnesota, Minneapolis, MN.
Background: Interstitial expansion is important for GFR loss in the later stages of a variety of disease processes, including diabetic nephropathy (DN). The Renin-Angiotensin System Study (RASS; NEJM 2009;361:80) considered whether RASB with enalapril or losartan compared to placebo could slow progression of early DN lesions over 5 years (yrs) in 285 normaloalbuminuric (NA), normotensive (NT), normal GFR T1D pts. RASS found no treatment benefit of RASB on DN lesions but observed an unexpected ~50% increase in the light microscopic measures of the fractional volume of renal cortex which is interstitium ([Vv(Int/Cortex)]. However, possible effects of RASB on individual Int components, i.e., Int collagen (Col), Int cells (C), peritubular capillaries (PTC) and undefined Int space (S) were not assessed. Here we report these additional studies.
Methods: Baseline and 5-yr renal biopsies from 21 RASS pts (52% males), from a single research center, 7 from each treatment group, with a wide range of change in [Vv(Int/Cortex)], mean age of 34±10 yrs, and T1D for 11±4 yrs were selected. These pts were matched for age and sex, and selected for electron microscopic (EM) measurements of the fractional volume of renal cortex which is interstitium ([Vv(Int/Cortex)]. However, possible effects of RASB on individual Int components, i.e., Int collagen (Col), Int cells (C), peritubular capillaries (PTC) and undefined Int space (S) were not assessed. Here we report these additional studies.
Results: Baseline at 12 months p value at 24 months p value
HbA1c (%) 6.90 ± 0.87 6.15 ± 0.65 0.009 6.04 ± 0.52 0.002
SBP (mmHg) 142.3 ± 12.4 130.9 ± 14.9 0.018 125.1 ± 13.4 0.007
dGFR (ml/min/1.73m²) 21.6 ± 11.4 24.1 ± 14.6 n.s. 22.4 ± 13.0 n.s.
LVMI (g/m²) 178.6 ± 59.7 n.d. 143.7± 40.2 0.047
EF (%) 0.60 ± 0.13 n.d. 0.64 ± 0.15 0.395
No adverse events were seen.
Conclusions: These findings suggest that liraglutide therapy for type 2 diabetes patients with renal impairment was safe and effective for decreasing glucose levels and blood pressure. Moreover it preserved renal function and improving left ventricular function.

FR-PO645
Liraglutide Improves Glycemic and Blood Pressure Control and Preserves Renal Function and Left Ventricular Function in Patients with Type 2 Diabetes Mellitus with Renal Impairment Takeyuki Hiramatsu, Akiko Ozeki, Kazuki Asai, Akinori Hobe, Hideaki Ishikawa, Shinji Furuta. Nephrology, Konan Kosei Hospital, Konan, Aichi, Japan.
Background: Diabetes mellitus(DM) is a progressive multifactorial disease associated with cardiovascular complications. To prevent progression of systemic cardiovascular complications in DM patients, glycemic control is important. However using of anti-diabetic agents was restricted in patients with renal impairment. In this study, we examined the efficacy and safety of the glucagon-like peptide analogue, liraglutide to treat type 2 DM patients with renal impairment.
Methods: Twenty type 2 diabetes patients with renal insufficiency (Age; 65.4 y, DM duration;11.9 y, eGFR;21.6ml/min/1.73m²) were enrolled. Anti-diabetic agents were switched to liraglutide from others. Prior to liraglutide therapy, 9 patients used insulin, 8 used oral antidiabetic agents, and 3 were only diet therapy. During 24 months liraglutide use, we examined the change of blood pressure and renal function. Echocardiography was examined at baseline and 24 months after liraglutide initiation.
Results: Hemoglobin A1c, and systolic/diastolic blood pressure levels were gradually decreased with liraglutide use. Renal function indicated by eGFR was not changed during (table1), and the slope of the reciprocal of serum creatinine was improved after use of liraglutide(≥0.001). Moreover Liraglutide induced ameliorating left ventricular function(LVMI and EF).

FR-PO646
Do SGLT2 Inhibitors Affect GFR and Albuminuria in Diabetic Patients? A Systematic Review and Meta-Analysis Luhun Xu, Yang Li, Peng Xia, Limeng Chen. Dept of Nephrology, Peking Union Medical College Hospital.
Background: SGLT2 inhibitors are a new class of antihyperglycemic drugs that lower blood glucose levels by inhibiting renal reabsorption of glucose. SGLT2 inhibitors can have potential renoprotective capacities through modulation of tubuloglomerular feedback and alleviation of hyperfiltration. However, there are also concerns about deleterious effects on renal function caused by volume depletion.
Methods: We performed this systematic review and meta-analysis to assess the effects of SGLT2 inhibitors on estimated GFR (eGFR) and urinary albumin/creatinine ratio (ACR) in diabetic patients. We conducted a systematic search of PubMed, Embase, Cochrane Central Register of Controlled Trials and Sinomed through April 2015 to identify published randomized double-blind controlled trials of SGLT2 inhibitors reporting renal outcomes. Two reviewers worked independently to extract data and assess the quality of included studies. Random effects model were used in data synthesis.
Results: We retrieved 2279 studies, 53 of which met the predefined criteria. Among included studies, 33 studies examined short-term effect with follow up less than 26 weeks, and 20 studies examined long-term effects with follow-up longer than 48 weeks. 4 studies included subjects with CKD 2-4. SGLT2 inhibitors did not cause statistically significant changes in eGFR (mean change, -0.19 ml/min/1.73m², 95% CI, -0.86 to 0.47) or in ACR (mean change, -23.76 mg/g, 95% CI, -66.75 to 19.23).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
508A
FR-PO647
Effects of Statins on Diabetic Kidney Disease in Patients with Type 2 Diabetes  
Ko Hanai, Tetsuya Babazono, Yasuko Uchigata. Diabetes Center, Tokyo Women’s Medical Univ School of Medicine.

Background: Renoprotective properties of statins have received much attention; however, a recent large cohort study found no beneficial effect of statins on diabetic kidney disease (DKD). Furthermore, whether there are differences among statins in their effects on the kidney remains unclear. We compared effects of statins on progression of DKD.

Methods: This was a single-center historical cohort study of Japanese adult ambulatory patients with type 2 diabetes. We studied 412 patients who were newly prescribed one of the following 4 statins: pravastatin, rosuvastatin, atorvastatin and pitavastatin, and who had estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m². As the control group, 946 patients without prescription history of statins were enrolled. Two outcomes were defined: 1) annual decline in eGFR and 2) progression to a more advanced stage of albuminuria. To adjust for the effects of confounding factors, we used the propensity score (PS) as the covariate. PS was estimated using a multinomial logistic regression model that included 18 clinical parameters. Furthermore, to take into account the varying number and spacing of eGFR measurements, and the variable follow-up period for each individual, we conducted the linear mixed-effects model regression analysis. The intercept and slope were treated as random effects.

Results: During the median follow-up period of 5.3 years (range, 2.0–8.6 years), the adjusted eGFR decline (± standard error) in the control group (1.6 ± 0.1 mL/min/1.73 m²/year) was significantly slower than that in rosuvastatin (2.4 ± 0.2, p<0.001), atorvastatin (2.6 ± 0.3, p<0.001) and pitavastatin group (2.3 ± 0.3, p=0.036), but not in pravastatin group (1.7 ± 0.2, p=0.780). Next, during the median follow-up period of 4.2 years (range, 0.1–8.5 years), a trend of ACR reduction (mean change: -2.6 ± 0.3, p<0.001) and a hematocrit level of ≤ 28% and received higher risk of reduced albuminuria. We used Cox proportional hazards models to account for the complex correlation structure of repeated measurements. In absolute terms, treating 1000 patients with tight glycemic control (HbA1c below 7% or fasting glucose levels <120 mg/dL) had a 0.87 (CI 0.34-1.47) of microalbuminuria. In absolute terms, treating 1000 patients with tight glycemic control for 1 year might prevent 7 experiencing new-onset albuminuria and 22 with worsening albuminuria.

Conclusions: Statins may have no beneficial effect on the progression of DKD. Instead, some statins are likely to be associated with faster renal function decline.

FR-PO648
Glucose Targets for Preventing Diabetic Kidney Disease and Its Progression: A Meta-Analysis  

Background: Diabetes is the leading cause of end-stage kidney disease (ESKD). Blood pressure lowering and glucose control are considered central to prevention of kidney function decline in diabetes nephropathy, however the optimal target range for blood glucose for preventing the onset and progression of kidney disease remains unclear. Here, we compared the effects of 4 statins on progression of DKD.

Methods: Using standard Cochrane methods, we did a systematic review and meta-analysis of randomized controlled trials that evaluated intensive versus standard glycemic control administered to adults and children with type 1 or type 2 diabetes with or at risk of kidney disease. Intensive glycemic control was defined by a treatment targeting an HbA1c <7.0% or fasting glucose levels <<120 mg/dL. In absolute terms, treating 1000 patients with tight glycemic control for 1 year might prevent 7 experiencing new-onset albuminuria and 22 with worsening albuminuria.

Conclusions: Intensive glycemic control among adults with diabetes had very uncertain effects on developing of ESKD and progression of kidney failure, while providing small clinical benefits on the onset and progression of microalbuminuria.

FR-PO649
Patient Benefits and Cost Savings Predicted for Mineralocorticoid-Receptor Antagonist Treatment of Early and Advanced Diabetic Kidney Disease  
Michael Blankenburg, Henri J. Folse, Christina Nowack, Bastian Hass, Bayer Pharma AG, Berlin, Germany; 2Amedeo Avogadro Univ of Eastern Piedmont; 3Univ of Otago Christchurch; 4Diaverum Medical Scientific Office; 5Amedeo Avogadro Univ of Eastern Piedmont; 6Sanofi-Aventis; 7Univ of Sydney; 8Univ of Bari.

Background: Exploratory studies suggest that mineralocorticoid-receptor antagonists (MRA) may improve outcomes in patients with diabetic kidney disease (DKD). Fosinopril (BAY 94-8862) is a selective, potent and non-steroidal MRA for the treatment of patients with DKD and is currently being studied in two clinical phase III trials, “FIDELIO” and “FIGARO.”

Methods: A Markov cohort model was used to emulate disease history, treatment effects, and outcomes for DKD patients with various disease severities (by albuminuria, measured by urinary-albumin-creatinine ratio [UACR], and chronic kidney disease [CKD] stage, measured by estimated glomerular filtration rate [eGFR]). Efficacy of finerenone is accomplished by reducing albuminuria evidenced by phase 2 trial data. The model has US

**Results:** The model predicts that finerenone is an effective treatment option for DKD patients, primarily by virtue of reduced risk of end-stage renal disease (ESRD) and renal death. A 10% absolute risk reduction (ARR) of up to 9.7% and 9.3%, respectively, for advanced DKD, i.e. macro-albuminuria and CKD3/4 and increased health-related quality of life, and that it would generate cost savings on renal replacement therapy (up to $19,100 for advanced DKD). From a clinical outcomes perspective the optimal time point to begin finerenone treatment appears to be after patients have progressed to either macro-albuminuria or CKD stage 3, as represented by both phase III trial populations.

**Conclusions:** Treatment with the MRA finerenone appears to be of significant benefit to patients and the healthcare system, particularly if initiated in advanced stages of DKD.

**Funding:** Pharmaceutical Company Support - Bayer Pharma AG

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**FR-PO650**

**Independent Association of Systolic Blood Pressure and Hemoglobin A1c Levels on Clinical Outcomes in Diabetic Patients with Normal Kidney Function**

_Presenting author:_ Aidar Gosmanov, Jun Ling Lu, Miklos Zsolt Molnar, Keichi Sumida, Praveen Kumar Potukuchi, Kamyar Kalantar

**Background:** Systolic blood pressure (SBP) goal of <140mmHg is recommended for majority of patients with diabetes mellitus (DM). It is however unknown if glycinemic control modifies the association of uncontrolled hypertension (HTN) with mortality and morbidity in DM patients.

**Methods:** We examined 894,661 US veterans with DM and baseline eGFR >60 mL/min/1.73m² (mean age 66±10.9 years, 97% males, 17% African-Americans). The association of mutually exclusive combined categories of hemoglobin A1c (A1c; <6.5, 6.5-6.9, 7.0-7.9, 8.0-8.9, 9.0-9.9, >10%) and SBP (<120, 120-139, 140-159, 160-179, >180mmHg) with the risk of all-cause mortality, incident CKD, coronary heart disease (CHD), and stroke was examined in Cox models adjusted for baseline characteristics, statin use, and co-morbidities, using patients with A1c 6.5-6.9% and SBP of 120-139 mmHg as referent.

**Results:** A total of 221,983 (25%) patients died, and 178,628 (20%), 43,374 (5%) and 4,722 (0.5%) respectively developed incident CKD, CHD and stroke, respectively, during a median follow up of 7.4 years. SBP displayed a U-shaped association with mortality in each A1c category. Conversely, SBP >120-139 mmHg was associated with a monotonous increase in the risk of CKD, CHD and stroke in all A1c categories. A1c levels were linearly associated with worse outcomes for all end points and in all SBP categories.

**Conclusions:** SBP above 120-139 mmHg and higher A1c levels were associated with higher mortality and morbidity in diabetic patients, independent of each other. Tight glycemic control modifies association of mortality and morbidity across all SBP categories in patients with normal kidney function.

**Funding:** NIDDK Support, Veterans Administration Support

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**FR-PO651**

**High Acid Diets Increase Urinary Nitrogen Excretion and May Decrease Muscle Mass in Obese Diabetics**

_Lynda A. Frassetto, Umesh Masharani, Anthony Sebastian. UCSF, San Francisco, CA.

**Background:** We have previously shown that decreasing dietary acid loads with bicarbonate supplements lowers urinary nitrogen (N) excretion in postmenopausal women. Here we examined whether we could lower urinary N excretion in obese diabetics by increasing plant food intake (“Paleo diet”) compared with a “usual” acid diet (America Standard Hemodialysis for ESRD - II

**Results:** mean±SD. ADA or Paleo pre-on; a, p<0.05; ∆ Paleo vs ∆ ADA: b, p<0.1; c, p<0.05; d, p<0.01

<table>
<thead>
<tr>
<th>Index</th>
<th>Test</th>
<th>ADA pre</th>
<th>ADA on</th>
<th>Paleo pre</th>
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<td>106±36</td>
<td>92±18</td>
<td>90±18</td>
<td>-0.2±1.0</td>
</tr>
<tr>
<td></td>
<td>FFM</td>
<td>74.5±26.7</td>
<td>73.4±20.9</td>
<td>58.2±14.0</td>
<td>57.6±15.7</td>
<td>-0.6±1.4</td>
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<tr>
<td>Urine Cr N, g/d</td>
<td>0.40±0.13</td>
<td>0.40±0.13</td>
<td>0.46±0.15</td>
<td>0.44±0.11</td>
<td>-0.04±0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cr CL</td>
<td>168±68</td>
<td>173±80</td>
<td>160±70</td>
<td>145±37</td>
<td>-20±40</td>
</tr>
<tr>
<td></td>
<td>Urea N, g/d</td>
<td>9.5±3.6</td>
<td>11.2±2.6</td>
<td>10.8±5.7</td>
<td>8.8±4.1</td>
<td>-3.7±2.9</td>
</tr>
<tr>
<td></td>
<td>Urea CL</td>
<td>57±20</td>
<td>70±29</td>
<td>59±19</td>
<td>52±17</td>
<td>-20±15</td>
</tr>
<tr>
<td></td>
<td>NH4 N, g/d</td>
<td>0.42±0.10</td>
<td>0.47±0.12</td>
<td>0.43±0.22</td>
<td>0.20±0.06</td>
<td>-0.28±0.07</td>
</tr>
<tr>
<td></td>
<td>Total N, g/d</td>
<td>10.0±5.6</td>
<td>11.7±2.6</td>
<td>11.3±5.9</td>
<td>9.3±4.2</td>
<td>-2.3±1.5</td>
</tr>
<tr>
<td></td>
<td>NAE meq/d</td>
<td>118±47</td>
<td>112±52</td>
<td>92±34</td>
<td>31±24</td>
<td>-55±50</td>
</tr>
</tbody>
</table>

Both groups had equally modest nonsignificant declines in weight.

**Conclusions:** The higher acid diet had significantly greater loss of fat free mass associated with a greater loss of urinary urea and ammonium. A plant based low acid weight loss diet may be better in maintaining lean body mass compared to a usual acid diet.

**Funding:** Clinical Revenue Support

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**FR-PO652**

**Clinical Benefit of Pre-Dilution On-Line Hemodiafiltration for Reduction of Low-Molecular-Weight Proteins and Fibroblast Growth Factor-23**


**Background:** Increased concentration of fibroblast growth factor 23 (FGF-23) is reportedly associated with increased risk of cardiovascular complication and mortality in dialysis patients. Therefore, there is a possibility that reduction of FGF-23 levels may improve prognosis of dialysis patients with elevated its levels. We compared the removal performance of low-molecular-weight proteins (LMWP) and FGF-23 between pre-dilution on-line hemodiafiltration (HDF) and hemodialysis (HD) with super high-flux dialyzer.

**Methods:** The study involved 31 patients (15:HDF, 16:HD, 4 hrs, Qd:600 mL/min). Blood flow rates were 284±20 for HDF, 281±14 mL/min for HD. Replacement fluid volume in HDF was 49.2±9.9 L/session. Removal rates (RR,%) and removal amounts (RA,mg) of urea nitrogen (UN), creatinine, β2-microglobulin (β2-M, MW:11.8kDa), α1-microglobulin (α1-M, MW:44kDa) and FGF-23 (32kDa) were examined. We followed the changes in FGF-23 levels of patients for 4 month period.

**Results:** Ra/V, RRs of UN and creatinine were significantly higher in HD than in HDF, whereas RRs and RAs of β2-M, α1-M, and FGF-23 were significantly higher in HDF. RRs of β2-M and α1-M were 80.3±3.7 and 42.0±6.1 for HDF, 73.5±4.1 and 25.0±6.8 for HD, respectively. RR and RA of FGF-23 were 66.9±6.5 for HDF, 51.1±8.3 for HD and 0.11±0.01 for HDF, 0.01±0.01 for HD, respectively.

**Conclusions:** The results confirmed that HDF was superior to HD in removing LMWP and FGF-23, which are removed mainly by convection. The convection volume can be much easily controlled in HDF than HD due to its internal filtration. The RRs of FGF-23 were 24 points higher than those of α1-M in both modes despite the small difference in MW, suggesting that distribution volume of FGF-23 was smaller than that of α1-M. No clear trend was detected in changes of FGF-23 during 4-month observation period.

**Funding:** Clinical Revenue Support

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**FR-PO653**

**Comparison of Removal Performance of Small- to Large-Molecular-Weight Substances Between Pre-Dilution On-Line Hemodiafiltration and Hemodialysis with Super-High-Flux Dialyzer**


**Background:** In pre-dilution on-line hemodiafiltration (HDF), net dialysate flow rate is reduced, because replacement fluid accounts for 30% to 50% of total dialysate flow (Qdtotal). Therefore, removal efficiency of small-molecular-weight substances by diffusion is reduced, whereas that of low-molecular-weight proteins (LMWPs) by convection is

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
improved. In hemodialysis (HD) using super high flux dialyzer, the increased blood flow rate (Qb) increases amount of internal filtration, thereby improving the removal efficiency of LMWPs. In this study, we compared the removal efficiency of small- to large-molecular-weight substances between HDF and HD to verify the superiority of HDF. 

Methods: The study involved 62 patients (31 HD, 31 HDF). Super high flux dialyzers for HD and high-performance hemodialyzers for HDF were used. Qd was 500 for HD and QDtotal was 600 mL/min for HDF. Replacement fluid volume for HDF was 44.4 ± 10.0 L/session. Qb was 256 ± 23, 257 ± 25 mL/min and Treatment time was 4.1 ± 0.2, 4.0 ± 0.1 hours in HD and HDF, respectively. Removal rates (RR) of b2-microglobulin (b2-M; 11.8 kDa), protein bound indoxyl sulfate (IS; 144 kDa), protein bound FUR (FUR; 472 kDa), and tryptophan (TRP; 1 mmole/l in plasma) were studied by rapid equilibrium dialysis (RED) to select suitable model compounds for the HD study. The method was then tested in an in vitro HD experimental model with human whole blood spiked with PBUTs. After 10 min baseline test, the binding competitors were introduced upstream of dialyzer blood inlet. The removal of uremic toxins was estimated as the amount leaving dialysate outlet relative to the amount entering blood inlet.

Results: The infusion of IBU and FUR mixture (647 µmole/l and 126 µmole/l in blood, respectively) in the HD model increased removal of IS from 6.3 ± 0.1 to 15.2 ± 0.3 % (mean ± SEM) (2.4-fold) and IAA removal increased from 15.9 ± 0.2 to 29.8 ± 0.6% (1.9-fold). TRP (1 mmole/l in plasma) infusion increased the removal of IS and IAA to 9.4 ± 0.1% and 26.0 ± 0.3% (1.4- and 1.3-fold, respectively). Only moderate effects were observed in the change of HIPA removal.

Conclusions: The performance of HDF in removing LMWPs was superior to that of HD, and there was no significant difference in Kt/V in both modes. An increased convective removal by HDF greatly contributed to improved removal of LMWPs and appropriate control of dialysate flow rate improved the removal efficiency for small molecular substances to the level achieved by HD.

Funding: Private Foundation Support

FR-PO654

The Effect of Increasing Kt/Vurea in the HEMO Study on Levels of Non-Urea Solutes

Tariq Shafi,3 Tammy L. Sirin,2 Stephan Thijssen,2 Peter Kotanko,2 Xia Banerjee,4 Neil R. Powe,3 Thomas H. Hostetter.4

Background: In the HEMO study, outcomes were no better in patients randomized to “high dose” thrice weekly hemodialysis providing spKt/Vurea 1.73 than in those randomized to “standard” hemodialysis providing spKt/Vurea 1.32.

Methods: This study assessed whether “high-dose” treatment lowered levels of non-urea solutes. Solutes were measured by LC/MS/MS in plasma samples obtained at least 3 months after randomization in 1281 HEMO subjects.

Results: (mean±sd; CI, confidence interval).

<table>
<thead>
<tr>
<th>Solute</th>
<th>standard</th>
<th>high-dose</th>
<th>% change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethylamine oxide µM</td>
<td>107±63</td>
<td>97±65</td>
<td>-9 (-15,-2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Phenylacetylglutamine mg/dl</td>
<td>4.6±3.1</td>
<td>4.3±2.6</td>
<td>-7 (-13,-9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Symmetric dimethylarginine µM</td>
<td>4.3±1.4</td>
<td>4.2±1.3</td>
<td>-4 (-7,-1)</td>
<td>0.018</td>
</tr>
<tr>
<td>Asymmetric dimethylarginine µM</td>
<td>0.92±0.24</td>
<td>0.93±0.23</td>
<td>-1 (-2,3)</td>
<td>0.74</td>
</tr>
<tr>
<td>p-Cresol Sulfate mg/dl</td>
<td>3.3±1.7</td>
<td>3.4±1.7</td>
<td>2 (4,8)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Increasing Kt/Vurea caused statistically significant but only modest reductions in the levels of trimethylamine oxide, phenylacetylglutamine, and symmetric dimethylarginine. Mathematical modeling showed that limited reduction in the levels of these solutes was a predictable consequence of the intermittency of treatment. Their reduction ratios with standard treatment are high and the increased intensity of treatment reflected by a 30% increase in Kt/Vurea in HEMO’s high dose arm could not remove much more solute. Remarkably, increasing Kt/Vurea in HEMO caused no reduction in the levels of asymmetric dimethylarginine or p-cresol sulfate, two solutes which have been associated with cardiovascular disease in dialysis patients. Modeling showed that stability of their plasma levels could be accounted for by increased solute production accompanying the increase in Kt/Vurea and/or the presence of non-dialytic clearance.

Conclusions: Levels of non-urea solutes may fall only slightly or not at all when Kt/Vurea is increased above standard levels for thrice weekly treatment. Treatments that are more effective in reducing solute levels may be required to improve outcomes.

Funding: NIDDK Support, Veterans Administration Support

FR-PO655

Improved Protein-Bound Uremic Toxins Dialytic Removal with Use of Albumin Binding Competitors: An In Vitro Human Whole Blood Study

Xia Tao,2 Stephan Thijssen,2 Peter Kotanko,2 Chih-Hu Ho,2 Michael E. Henrici,3 Eric W. Stroup,2 Garry J. Handelman.1

Background: Protein-bound uremic toxins (PBUT) are intensively studied retained solutes that accumulate in chronic kidney disease patients. Efficient removal of PBUTs by hemodialysis (HD) is difficult because of limited free fraction in blood. We propose an innovative method for improving the dialytic removal of PBUTs by increasing their free fractions with use of protein binding competitors.

Methods: The binding properties of indoxyl sulfate (IS), indole-3-acetic acid (IAA) and hippuric acid (HPA); and their binding competitors, ibuprofen (IBU), furosamide (FUR) and tryptophan (TRP) were studied by rapid equilibrium dialysis (RED) to select suitable model compounds for the HD study. The method was then tested in an in vitro HD experimental model with human whole blood spiked with PBUTs. After 10 min

FR-PO656

Variable Recovery Time After Hemodialysis Treatment

Antonia Harford,1 Susan Painé,2 Ronald Schrader,3 Ambreen Gul,2 Dana Miskulin,2 Philip Zager,2

Background: Prolonged recovery time after hemodialysis (HD) may predict adverse clinical outcomes. In the Frequent Hemodialysis Network a patient’s response to the Recovery Question was consistent over time. To determine if this consistency is also present among patients undergoing thrice weekly HD we compared responses to the Recovery Question after each treatment in a given week.

Methods: We asked 250 patients in 3 DCI HD facilities “How long did it take you to recover after your last treatment?” The number of patients who answered the question on the 1st, 2nd, and 3rd treatment was 221, 207, and 200, respectively; 148 patients (57.8%) answered the question on all 3 occasions. Recovery time was categorized as <0.5 hours (0 < t ≤ 0.5 h, and ≤ 6 h).

Results: Among the 148 patients who answered the Recovery Question 3 times, recovery times were 6.9, 4.5 and 9.3 hours after the 1st, 2nd, and 3rd HD. There were 46% of patients who had consistent responses on all 3 treatments; 16%, 15% and 15%, had consistently short (<0.5h), moderate (0.5-6h) and long (>6h) recovery times, respectively.

Conclusions: This method increases the removal of PBUTs and has no effect on non-protein-bound solutes. Achieving higher dialytic removal of PBUTs by infusion of binding competitors is feasible and efficient to apply in current HD settings.

Funding: Pharmaceutical Company Support - Renal Research Institute

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

Underline represents presenting author.

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Among the patients with consistent short vs. long recovery, there were no differences in age, race, and vintage. There was a trend for women (59%) to be more likely to have recovery ≥ 6 h compared to men (41%) (p = 0.008). After the 1st dialysis of the week, recovery was more likely (40%) to be ≥ 6 h among patients dyalized with a diastate sodium concentration (DNa) <140 mEq/L vs. with a (DNa) ≥ 140 mEq/L (22%). However, similar differences were not observed for the 2nd and 3rd treatments.

Conclusions: There is significant variation among individual patients answers during the week when the recovery question is asked after each treatment.

FR-PO657 Quality Control and Improvement Union of Hemodialysis Centers: A New Management Model Jinyueyan Gao, Mei Wang. Dept of Nephrology, Peking Univ People’s Hospital, Beijing, China.

Background: With the increasing incidence of end stage renal disease (ESRD) in China, more dialysis facilities are needed. There are huge variations of patient care staffing levels and quality of care. How to maximize the utilization of existing health resources, optimize the management of hemodialysis patients and improve quality control are important issues. The aim of this study was to investigate the feasibility and effects of quality control and improvement union comprised of best hospitals and basic hospitals on patients’ medical quality control and improvement.

Methods: The HD union was constructed and specific measures were determined including, 1) Quarterly continuous quality improvement (CQI) meetings, 2) education based on typical cases including: disease, guidelines and latest research results introductions, 3) lectures focusing on key questions, 4) opening green channel and construction of two-way referral system. Paired t-test was used to compare the differences of medical parameters of each hemodialysis center before and two-years after construction of HD union.

Results: The leading center of HD union was the HD center from Peking University People’s Hospital. Cooperating centers were other eight centers from class three and class two hospitals. After quarterly CQI meetings, all union members learned how to do medical quality control and improvement, constructed standards and procedures for diagnosis, cure and nursing of their HD center, established the institutions of lab exam and regular rounds, added necessary examinations and implemented all-around management of HD patients. Green channel for intractable cases transfer were applied successfully. There were statistical improvements of medical quality including dialysis frequency, hemoglobin, calcium, phosphorus, and metabolic acidosis control. Other parameters including Kt/V, iPTH, albumin and Bp improved but without significant difference.

Conclusions: Quality control and improvement union of hemodialysis centers is an effective integrated management model in Beijing China. It can improve medical quality of basic hospitals by balancing the technical advantages of grade A class three hospitals and basic hospitals.

Funding: Government Support - Non-U.S.

FR-PO658 Feasibility of Mindfulness Meditation Training During Dialysis for Patients with Chronic Kidney Disease and Effect on Tolerability of Sessions James C. Wasserman,1 Daniel Schupack,2,3 Andrew E. Williams,1,4 Paul K. Han,1,4 George K. Dreher,1 Mary Bitterauf.1,4 1Div of Nephrology, Maine Med Center, Portland, ME; 2Center for Outcomes Research and Evaluation, Portland, ME; 3Maine Medical Center, Portland, ME; 4Maine Medical Center Research Inst, Portland, ME; 5MaineHealth, Falmouth, ME.

Background: Hemodialysis (HD) for CKD entails >/= 12 h of weekly treatment, creating significant distress for patients. Mindfulness-Based Stress Reduction (MBSR) has effectively helped patients with other chronic diseases cope with distressing symptoms and treatments. An abbreviated form of MBSR (Mindfulness Meditation Training, MMT) was incorporated into HD sessions to explore its feasibility, acceptability and potential effects on distress.

Methods: 12 patients were randomly assigned to MMT during HD or usual care. The MMT group underwent weekly 1-h individual sessions during HD for 4 wk. Within-session change in affective response was assessed with the Self-Assessment Manikin (SAM), validated measure of affective valence, arousal and dominance. Anxiety, depression, self-rated health and coping skills were also assessed with validated measures. Patient perceptions were assessed with qualitative interviews at study’s end.

Results: In qualitative interviews, patients reported improved tolerability of HD session length, positive intention to continue meditation and no significant issues with MMT sessions or home practice. There were no significant between-group differences in affective response, anxiety, depression, self-reported health or coping skills at baseline or in change over time. Retention rate was 91.7% overall and 83.3% for the MMT group.

Conclusions: MMT appears to be a feasible and acceptable intervention for CKD patients during HD, although effectiveness remains to be demonstrated. Small sample size and low baseline distress levels in the study population limited the power to establish effects of MMT. Further research is needed to determine if abbreviated MBSR is sufficient to benefit tolerability of HD in this population. Focus on patients with higher baseline distress levels in future research would increase the likelihood of observing clinical benefit.


Background: During hemodialysis (HD) session, plasma proteins are adsorbed to the surface of HD membrane. The resulting biofilm affects both dialyzer permeability and biocompatibility. The aim of this study was to analyze its composition in different HD membranes.

Methods: Twelve long-term HD patients were assigned to 4h HD with three different dialyzers in a cross-over design: ethylene-vinyl-alcohol/EVAL (KF-201-1.8C, Asahi Kasei), polysulfone (F8 HP5, Fresenius), and vitamin E-substituted polysulfone (VIE-18, Asahi Kasei). After HD session, the biofilm was eluted with acetic acid. Obtained proteins were detected, 235 common to all eluates. In 48 fractions, spot intensities varied between SEM, statistical significance was calculated by ANOVA (general linear model).

Results: The amount of protein eluted from KF dialyzers was higher than from F8 or Asahi dialyzers in all fractions. Asahi dialyzers showed less protein adsorption in most fractions. In KF and Asahi dialyzers, the highest protein adsorption was detected in fractions 30 to 40.

Conclusions: Our results show that different dialyzers adsorb different plasma proteins. It can be responsible for their increased clearance and temporary depletion.

Funding: Government Support - Non-U.S.
Mathematical Model of Transport Protein and Plasma Refilling in Hemodialysis
Bengt Lindholm,1 Mauro Pietribiasi,2 Malgorzata Debowska,2 Alicja Wojcik-Zaluska,1 Wojciech T. Zaluska,1 Jacek Waniwetz,2 ‘Baxter Novum & Renal Medicine, Karolinska Inst, Stockholm, Sweden; 2Inst Biocybernetics & Biomedical Engineering, Warsaw, Poland.

Background: Mathematical modeling offers a way to estimate quantities we cannot access directly during hemodialysis (HD). Here we propose a whole-body model of vascular refilling describing water and protein shifts across the capillary membrane during HD.

Methods: The model predicted profiles of plasma volume and serum total protein concentration with an average root-square error < 2%, with larger errors only in pts with very high initial drop in blood volume. When increasing the assumed value of interstitial/serum protein ratio from 0.3 to 0.6, while the total refilling rate remained similar, the value of individual pore flow changed so that filtration through large pores at its peak was 40% smaller and absorption through small and ultrasmall pores was 80% and 60% higher, respectively.

Conclusions: The conclusions make a mechanistic interpretation of fluid transport processes induced by ultrafiltration during HD. The estimated values of individual flows through each kind of pores and lymphatic absorption represent the relative impact of these not-measurable quantities on total vascular refilling.


Hemodiafiltration at Increased Plasma Ionic Strength for Improved Protein-Bound Toxin Removal
Deltef H. Krietener,1 Eric Devinc,2 Thomas Koerner,1 Maricke Ruech,2 Christian Wanner,1 Joachim Jankowski,1 Horst-Dieter Lemke.2
1Nephrology, Univ Hospital Würzburg, Würzburg, Germany; 2eXcorLab GmbH, Observatory Group, Molecular Cardiovascular Research, Univ Hospital RWTH Aachen, Aachen, Germany.

Background: Protein-bound uremic toxin (PBT) removal by hemodialysis (HD) is limited in resulting in dialysis associated cardiovascular morbidity. Enhancing ionic strength in the dialyzer decreases protein binding and may result in a larger unbound and removable toxin fraction. This was implemented through high sodium concentration ([Na+] in the substitution of predilution hemodiafiltration (HDFmod).

Methods: Ex vivo predialysis HDF with blood to test increasing [Na+] to demonstrate efficacy and hemocompatibility. Hemocompatibility was further assessed in sheep using two different HDFmod setups and [Na+] between 350 and 600 mmol/L. Safety and efficacy of para-cresyl sulfate (pCS) and indoxyl sulfate (IS) removal was further investigated in a randomized clinical pilot trial comparing HDFmod to HD and standard HDF.

Results: Compared to physiological [Na+], ex vivo HDFmod at [Na+] of 500 mmol/L demonstrated up to 50% higher IS removal. Hemolysis in sheep was low even at [Na+] of 600 mmol/L; not exceeding 0.016 ± 0.001 g/dL of free HB. In patients, the reduction of ratio of free vs. total IS was 20% higher in HDFmod at [Na+] of 240 mmol/L compared to HD (72.6 ± 6.1 vs. 60.4 ± 16.5%; p=0.026). Compared to HD and HDF (23.0 ± 14.8 and 25.4 ± 10.5 mmol/L, resp.), the dialytic clearance of free IS was 37 and 24% higher in HDFmod at [Na+] of 240 mmol/L compared to HD (72.6 ± 6.1 vs. 60.4 ± 16.5%; p=0.026).

Conclusions: Ionic strength modification with HDF mod with increasing [Na+] to demonstrate efficacy and hemocompatibility. Effective HDFmod at higher [Na+] will require higher temporary surface area product (LpS) of the capillary membrane, estimated from volumetric data and blood samples collected in 20 stable, non-diabetic pts during 60 HD sessions.

Funding: Clinical Revenue Support

Sevelamer Hydrochloride Improves Oxidative Stress in Maintenance Hemodialysis Patients
Sireen Szeze, Bahar Gurlekdemirci, Cihat Burak Sayin, Emre Tural, Zeynep Bal, Fatma Nurhan ozdemir Acar. ‘Depart of Nephrology, Basheu Faculty of Medicine, Ankara, Turkey.

Background: Oxidative stress plays a key role in the pathogenesis of cardiovascular diseases. Superoxide dismutase (SOD) and malondialdehyde (MDA) are well-known antioxidant enzymes that detoxify advanced glycation end products (AGEs). We thought that avoiding calcium intake and through pleiotropic effects, sevelamer hydrochloride might be a differential influence in terms of oxidative stress. The aim of this study is to evaluate the effects of phosphate binders (PBs) on the components of the oxidative stress and clinical and biochemical parameters including pulse wave velocity in our maintenance hemodialysis (MHD) patients.

Methods: A total of 111 patients (mean age: 52.2 ± 14.3 years; mean duration of dialysis: 9.7 ± 4.6 years) undergoing maintenance hemodialysis and using the same PBs at least one year were enrolled into the study. Patients were divided into two groups according to usage of PBs as sevelamer based PB (group 1; n = 84) and calcium based PB (group 2; n = 27). Biochemical parameters were assessed from monthly clinical visits. Serum AGE, MDA and SOD levels were determined by ELISA method. Pulse wave velocity (PWV) was determined by using the Sphygmocor system.

Results: Groups were similar in means of demographic characteristics and URR levels. In group 1 (n=84; mean duration of dialysis: 9.7 ± 4.6 years) undergoing maintenance hemodialysis and using the same PBs at least one year were enrolled into the study. Patients were divided into two groups according to usage of PBs as sevelamer based PB (group 1; n = 84) and calcium based PB (group 2; n = 27). Biochemical parameters were assessed from monthly clinical visits. Serum AGE, MDA and SOD levels were determined by ELISA method. Pulse wave velocity (PWV) was determined by using the Sphygmocor system.

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Conclusions: Despite similar phosphorus levels and dialysis adequacy, sevelamer decreased serum HDL levels more than AIP. Sevelamer may act as an independent risk factor for mortality. Strategies could be helpful to routinely identify those dialysis patients at risk of functional impairment and depression to limit their disabilities. Self-report scales and those performed by nursing staff could improve the integral treatment of those patients.

FR-PO666
Preliminary Study About Optimal Dosage of Heparin Locking Solution to Maintain the Patency of Hemodialysis Catheter Jung-woo Noh, Eunjung Kim, Ja-Ryong Koo. Internal Medicine, Nephrology, Hallym Univ Medical Center, Hallym kidney Research Inst, Seoul, Korea.

Background: Hemodialysis catheters (HC) are routinely heparin locked to maintain patency. This practice may cause bleeding episodes. The amount of heparin for heparin locking solution at many dialysis centers has been decreased recently to reduce the risk of bleeding. However, the effect of this change on patency of HC is unknown. We compared the patency of HC between four types of heparin amount of 4000, 5000, 7500, and 15000 units (U).

Methods: This observational study included 126 chronic hemodialysis patients using HC in Hallym University Medical Center from March 2011 to July 2014. 29 patients received a 4000 U, 41 patients received a 5000 U, 44 patients received a 7500 U and 41 patients received a 15000 U of heparin. The primary outcome was composite outcome: frequency of thrombolytic instillation, change of hemodialysis line due to dysfunction of HC and HC obstruction due to thrombosis. We also compared activated partial thromboplastin time (aPTT) levels between groups just before and 10 minutes after the end of each hemodialysis.

Results: The composite outcome were 2.44±5.42, 1.06±3.46, 0.40±1.18 and 0.52±1.16 episodes/100 catheter-days, respectively (p=0.03). 4000 U group showed especially high rate of every outcome compared to other groups receiving more than 5000 U of heparin. However, event rate of HC obstruction due to thrombosis was not significantly different: zero episodes/100 catheter-days for 4000U and 5000UU groups, 0.01±0.05 episodes/100 catheter-days for 5000IU group and 0.14±0.61 episodes/100 catheter-days for 7500 IU group. At 10 minutes after heparin lock, prolonged aPTT was observed in all groups. When 10 minutes aPTT levels between 4000 U group and other groups are compared, those of 7500 U (p=0.007) and 15000 U (p=0.004) groups were significantly prolonged. But there were no bleeding complications in those groups.

Conclusions: Low concentration heparin lock solution with total amount of 4000 U do not increase HC obstruction due to thrombosis, but increase in thrombolytic instillation and set change. Higher concentration heparin lock solution with total amount over 7500 U prolonged the aPTT without bleeding complication. Funding: Clinical Revenue Support

FR-PO667
Association Between Depressive Symptoms and Dependency with Mortality in Hemodialysis Patients After 5 Years of Follow-Up Joaquin Manrique,1 Maria del cielo Mena,2 Eva Cerdan,2 Laura Catalan,2 1Servicio de Nefrologia, Complejo Hospital de Navarra, Pamplona, Spain; 2Nursing Staff. Servicio de nefrologia, Complejo hospital de Navarra, Pamplona, Spain.

Background: The prevalence of depression and its role in mediating survival of patients with end-stage renal disease (ESRD) has been highly controversial. Moreover, according to the population ages, their limitations in performing daily activities affect their well-being and set change. Higher concentration heparin lock solution with total amount over 7500 U prolonged the aPTT without bleeding complication.

Methods: We determine whether depressive symptoms and dependency are associated with mortality in a longitudinal study of 148 hemodialysis (HD) outpatients followed for 5 years. Depressive symptoms were assessed using the Beck Depression score (BDs), and dependency by Barthel scale (BS) performed by nursing HD staff.

Results: 28.8% of patients had depressive symptoms (BD>10) and the mean baseline BDs was 11.4±8.1. 23% patients were moderate or severely dependent (BS<90). 40.5% died during the study follow-up period (a rate similar to that found in this population). We observed a significant association between BS and BDs (r=0.5; p<0.001). Patients with greater disability (BS>90) had worse depressive score (p<0.001). After 60 months of follow-up, survival rates were 80.5% for BDs<9 and 94.3% for BDs ≥9 (p<0.05), and 71.4% for dependent and 95.5% for no dependent patients (p<0.001). Other variables, including age, gender, and dialysis period, were not significantly associated with mortality. Cox proportional hazards regression was performed to predict the mortality hazard associated with age, gender, and dialysis period, were not significantly associated with mortality. Cox proportional hazards regression was performed to predict the mortality hazard associated with age, gender, and dialysis period, were not significantly associated with mortality. Cox proportional hazards regression was performed to predict the mortality hazard associated with age, gender, and dialysis period, were not significantly associated with mortality.

Conclusions: Our study shows that the disability in self-care and the presence of depressive symptoms are common among patients on haemodialysis. Both of them may act as independent risk factors for mortality. Strategies could be helpful to routinely identify those dialysis patients at risk of functional impairment and depression to limit their disabilities. Self-report scales and those performed by nursing staff could improve the integral treatment of those patients.

FR-PO668
Limitations of Access Recirculation due to a Low Access Flow Rate on Middle Molecule Clearance During Post-Dilution Hemodiafiltration J. Ken Leypoldt,1 Markus Storr,2 Renal Therapeutic Area, Baxter Healthcare Corporation, Deerfield, IL; 1Research & Development, Gambio dialysatoren GmbH, Hechmnig, Germany.

Background: Post-dilution hemodiafiltration (HDF) with a high convective volume (CV) is associated with lower overall patient mortality, potentially due to high middle molecule (MM) clearance from the patient (Kp). A higher CV can most readily be achieved by extending the treatment time or increasing the blood flow rate (BFR); however, the effect of access recirculation due to a low access flow rate (AFR) when increasing the BFR on MM Kp during HDF has not been previously quantified.

Methods: A theoretical mass balance model for assessing the effect of a low AFR on MM Kp was formulated. Access recirculation was assumed to occur when the BFR exceeded the AFR. The model demonstrated that MM Kp was dependent on HDF membrane properties, AFR, BFR, CV and the fluid removal rate from the patient (FRR).

Results: Example results are tabulated for a patient with a hematocrit of 33% at different AFRs and BFRs maintaining a fixed filtration fraction of 25% during a 4-hour HDF treatment with a FRR of 0.5 L/hour. MM filter clearance was assumed to depend on CV with a diffusive clearance of 75 mL/min and a sieving coefficient of 0.7.

When the AFR is higher than the BFR, MM Kp increases with increasing CV. At low AFR, increasing the BFR above the AFR resulted in a lower MM Kp than expected. Indeed, increasing the BFR above the AFR can even lead to a reduction in MM Kp.

Conclusions: High convective volumes during post-dilution HDF achieved by using high blood flow rates may not result in higher middle molecule clearance if the access flow rate is low. Routine assessment of access recirculation or access flow rate may be necessary during post-dilution HDF with high blood flow rates to improve patient outcomes.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

FR-PO669
Protein Biofilm and Its Relation to Dialyzer Permeability for Middle Molecular Weight Markers in Three Polysulfon Membranes Lukas Kielberger, Jan Mares. 1st Dept of Internal Medicine, Charles Univ Teaching Hospital, Plzen, Czech Republic.

Background: Membrane permeability, particularly in terms of middle molecular clearances, is largely dependent in vivo on the formation of a protein biofilm. Our aim was to assess its dynamics during HD session together with molecular composition of the biofilm.

Methods: 12 HD patients were assigned in a cross-sectional design to Xevonta® Hi23 (B-Braun, 2.3 m²), CorDiax FX100® ( Fresenius, 2.2 m²) and Polyflux® 210H (Gambro, 2.1 m²) dialyzers. Blood pre- and post- dialyzer was sampled at 0, 15, 60, and 240 min; spent dialysate was collected over the first 15 min and then until the end of the session. B2 microglobulin (B2M), myoglobin (MB), retinol-binding protein (RBP), and chondroitin sulfates (lms) levels were determined as permeability markers covering an interval of molecular weight (MW) 1-12 kDa. After HD, protein biofilm was eluted from dialyzer and subjected to proteomic analysis.

Results: At the beginning, Xevonta and FX dialyzers showed significantly higher in vivo sieving coefficients for all MWs up to 26 kDa (lms) than Polyflux dialyzer (p<0.01). After 15 min, Xevonta and FX permeability decreased significantly (p<0.01) in all MW classes while in Polyflux, only MW 21 kDa (RBP4) were affected (p<0.01). The total protein content of membrane biofilm was similar in all three dialyzers: 118±85, 41±10, and 40±17 mg protein per dialyzer for Xevonta, FX, and Polyflux, resp. Significant differences in protein composition were captured in 48 out of 231 protein fractions. Among them, complement factor H-related protein 3 (FHR3), insulin-like growth factor binding protein 4 (IGFBP4), or multiple fibrin fragments (FDP) were identified. While FDP and IGFBP4 were prevalent in eluates from FX and Xevonta dialyzers (p<0.005 and 0.001, resp.), FHR3 was abundant in Xevonta only (p<0.01).

Conclusions: Even with modern biocompatible dialyzers, in vivo permeability decreases along HD session, probably due to biofilm formation. The decrease occurred irrespective of total protein adsorbed, compromising rather membranes primarily more permeable and higher MWs. Differences in biofilm composition are complex and may impact both dialyzer permeability and biocompatibility.

Funding: Government Support - Non-U.S.
FR-PO670
Proteoic Effects of Intravenous L-Carnitine (LC) Administration on Development of Cardiomyopathy in Hemodialysis (HD) Patients Takuiha Uchiho,1 Jyunichiro Hashiguchi,1 Satoshi Funakoshi,1 Hiroshi Ichinose,1 Osamu Sasaki,1 Kenji Sawaji,2 Miki Yano,1 Yutaka Moriyama,3 Kazunori Utsunomiya,3 Yoko Obata,1 Tomoya Nishino,2 Miwa Shirahama,1 Takashi Harada,1 Nagasaki Kidney Center, Nagasaki, Japan; 2Nagasaki Univ Graduate School of Medicine, Nagasaki, Japan.

Background: Due to loss via dialyzer patients on maintenance HD often suffer from dialysis-related cariomyopathy, leading to various clinical symptoms. Cardiomyopathy Consensus Conference in 2003 convened by The National Kidney Foundation had reported that the level of evidence was “moderate” for cardiomyopathy. Recent studies have shown that LC can improve left ventricular (LV) function in HD patients. In this study, we aimed to evaluate whether intravenous administration of LC can prevent the development of cardiomyopathy in HD patients as assessed by M-mode ultrasound cardiography (UCG).

Methods: Thirty-eight HD patients without reduced left ventricular function were treated with intravenous administration of 1000 mg/body of LC at the end of every HD session for 12 months. M-mode UCG assessments were undergone in all subjects at the tree points: 1 year prior to the treatment, the start of LC administration and year after the treatment.

Results: As shown in Figure 1, average %FS (fractional shortening) significantly declined during 1 year before the start of LC, then stabilized after the treatment, suggesting LC administration might protect the progression of LV contraction impairment. Early average diastolic filling velocity (E) / atrial filling velocity (A) ratio showed similar pattern, suggesting LC treatment could be protective in LV diastolic disorder. LC treatment also might delay LV hypertrophy progression.

Conclusions: Intravenous LC administration can be a candidate therapy for protection of the development of cardiomyopathy in HD patients.

Funding: Private Foundation Support

FR-PO671
Symptoms and Quality of Life Among Patients Receiving HD Mark L. Unruh,1 Kim J. Cox,1 Stephen H. A. Hernandez,2 Sanah Parvez,1 Mark Parshall.1 1Div of Nephrology, Univ of New Mexico; 2College of Nursing, Univ of New Mexico.

Background: Health-related quality of life (HRQOL) assessment is a required condition of coverage for HD providers, but standard measures may not adequately reflect the impact of symptoms and treatment on QOL for patients receiving HD or the concerns that matter most to them. The purpose of this qualitative study is to more fully characterize patients’ perspectives on the symptoms and treatment experiences affecting their QOL.

Methods: We conducted semi-structured interviews with a diverse sample of 50 patients’ perspectives on the symptoms and treatment experiences affecting their QOL. Interviews were audio-recorded, transcribed, and analyzed for themes using an interpretive-approach.

Results: Participants recollected that the initial diagnosis of ERSD was received with shock and denial. Over time, patients reported that QOL was associated with “taking control” of some features of their treatment. Common symptoms associated with HD, such as cramping and fatigue, were described as potentially manageable when patients were able to participate in decisions about fluid removal and scheduling of HD treatments. Patients who formed a partnership with their providers to negotiate fluid removal reported fewer episodes of severe cramping and improved QOL. Similarly, being able to choose among a variety of days and shifts for HD treatment enabled patients to manage fatigue, work hours, travel, and attendance at social events. These factors were critically important to the QOL in our relatively young sample (median age = 53; median duration of HD treatment = 4 years).

Conclusions: This is one of the largest and most diverse qualitative studies of symptoms among patients undergoing HD. There were few differences in symptoms or the impact of treatment on QOL among racial and ethnic groups. Findings highlighted the importance of fluid management and fatigue to patient experience.

Funding: Pharmaceutical Company Support - Dialysis Clinic Inc.
FR-PO674

Association of Time-Averaged Concentration of Hemoglobin with Mortality: Results from a Large U.S. Hemodialysis Cohort

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Background: In hemodialysis (HD) patients the time averaged concentration of hemoglobin (Hb_tac) can be estimated from pre- and post-HD hemoglobin (Hb) levels. It has been suggested that Hb_tac may be an appropriate indicator for anemia management. Methods: We analyzed Hb data obtained by Crit-Line™ monitor (CLM) in chronic HD patients. A 6-month baseline period with at least 10 CLM measurements preceded a 12-month follow-up during which outcomes were assessed. We used Hb values from HD sessions following a short interdialytic interval. Hb_tac was computed as follows (Kriiper, NDH-2000): Hb_tac = Hb_post × 0.5 + Hb peut × 0.38 + 1.28. We defined Hb_great as the average Hb between minutes 5 to 20 from the start of the CLM recording, and Hb_post as the average of Hb between minutes 5 to 20 from the end of the CLM recording. The relation between Hb_tac during baseline and mortality was explored by spline analysis of hazard ratio (HR).

Results: We studied 982 patients (Figure 1A) with a total of 19,142 CLM measurements. Average Hb_tac was 10.72 g/dL (SD 0.81, range 7.27 – 14.62 g/dL). The mortality rate during follow-up was 11.6 per 100 patient-years. The minimal HR (figure 1B) was 0.82 at Hb_tac of 10.87 g/dL. The solid line represents mean HR, the dotted lines 95% confidence interval.

Conclusions: Hb_tac is associated with mortality, levels around 10.9 g/dL are associated with the lowest mortality risk. Studies are required to further explore methods to estimate Hb_tac based on Hb measurements by the CLM and the usefulness of Hb_tac as an indicator of anemia control.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc.

FR-PO675

Development and Validation of a Predictive Mortality Risk Score in Chinese Incident Maintenance Hemodialysis Patients

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Background: We aimed to predict 2-Year all-cause mortality in incident maintenance hemodialysis (MHD) patients by using available clinical and laboratory data, and to establish a risk scoring model.

Methods: A total of 2700 data of incident MHD patients were from Zhejiang Dialysis Quality and Management Center(ZDQM) during the period from January 2008 to June 2012. All patients were ³18 years old and survived at least 3 months after starting dialysis treatment. It has been suggest that Hb_tac may be an appropriate indicator for anemia management. The predictor variable was race (White as reference). Outcomes were mortality and hazard ratio (HR).

Results: We studied 982 patients (figure 1A) with a total of 19,142 CLM measurements. Average Hb_tac was 10.72 g/dL (SD 0.81, range 7.27 – 14.62 g/dL). The mortality rate during follow-up was 11.6 per 100 patient-years. The minimal HR (figure 1B) was 0.82 at Hb_tac of 10.87 g/dL. The solid line represents mean HR, the dotted lines 95% confidence interval.

Conclusions: Hb_tac is associated with mortality, levels around 10.9 g/dL are associated with the lowest mortality risk. Studies are required to further explore methods to estimate Hb_tac based on Hb measurements by the CLM and the usefulness of Hb_tac as an indicator of anemia control.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America
FR-PO678
Low Lymphocyte Counts Are an Independent Predictor of Mortality in Chronic Hemodialysis Patients: A Retrospective Cohort Study

Background: Mortality in chronic hemodialysis populations remains high. Lymphopenia has been associated with increased cardiovascular risk in the general population but few data are available on the effect of low lymphocyte counts on long-term survival of hemodialysis patients.

Methods: Retrospective study of a single-center cohort of 689 hemodialysis patients using monthly laboratory results and dialysis parameters extracted from a center database and a national registry. The effect of baseline and time-changing lymphocyte counts on overall mortality was studied using the Kaplan Meier and Cox proportional hazard methods.

Results: Lymphopenia (<1200/µL) was present in approximately one third of incident hemodialysis patients and correlated with older age, lower creatinine, lower phosphorus, higher Kt/V and a positive history of ischemic heart disease. Lymphopenia was not associated with classical markers of malnutrition-inflammation complex such as albumin, normalized protein catabolic rate, BMI and CRP. Baseline lymphopenia was associated with a 54 percent increase in the hazard of death (HR 1.54 (1.17 to 2.0; p=0.002)) as compared to the tertile of patients with highest lymphocyte counts. Lymphocyte counts tended to decrease during long-term follow up and their introduction as a time-changing variable further increased the HR to 2.1 (1.48 to 2.84; P<0.0001). The association remained tended to decrease during long-term follow up and their introduction as a time-changing variable further increased the HR to 2.1 (1.48 to 2.84; P<0.0001). The association remained.

Conclusions: Lymphopenia is highly prevalent in hemodialysis patients and is a strong predictor for patient death. The association was stronger when lymphocyte counts were considered as a time-changing variable and independent of other risk factors for patient death. Lymphopenia was not associated with markers of the malnutrition-inflammation complex (MIC) and therefore appears a useful prognostic tool in addition to classical markers such as CRP and albumin levels.

FR-PO679
Current Status of Hemodialysis in China
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Background: In May 2010, the first nationwide, web-based prospective renal data registration platform, the Chinese Renal Data System (CRNDS) was launched in China. The purpose of this study was to determine the current status of hemodialysis in China by analyzing the data from CRNDS.

Methods: The data from CNRDS were used for dialysis cases including demographic, clinical, and laboratory data. We analyzed the data from CRNDS by the end of 2014.

Results: (1) There were 4047 domestic hemodialysis centers and 339748 survival patients were registered by the end of 2014. (2) In the 339748 patients, 58.85% were male. The average age was 59.9 years and average dialysis duration was 42.2 months. The three leading causes of ESRD were glomerulonephritis, diabetic nephropathy and hypertensive renal diseases. (3) 14322 patients died in 2014, with an average age of 61.9 years and average leading causes of ESRD were glomerulonephritis, diabetic nephropathy and hypertensive renal diseases.

Conclusions: Hemodialysis (HD) care is routinely assessed by a set of clinical and laboratory parameters, known as Clinical Quality Indicators (CQI). CQI registry and reporting systems constitute an instrument to evaluate the quality of care provided at each HD Unit. The purpose of this study was to determine whether CQI, applied on an individual patient basis, is a predictor of mortality.

FR-PO680
Outcomes and Quality of Care in Rural versus Urban Managed Dialysis Patients
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Background: A proportion of patients are managed in remote satellite units in Manitoba, Canada. Urban nephrologists oversee all dialysis care; however family physicians (FP) co-manage patients. This study examines outcomes and quality of care indicators in rural vs urban managed patients.

Methods: Prospectively collected clinical data from the Manitoba Renal Program and administrative health data housed at the Manitoba Centre for Health Policy were analyzed retrospectively. All adult (>18yo) hemodialysis patients (n=90 days from 1995 to 2010 were included. Individuals dialyzing in rural satellite units (n=510) more than 50% of the time were compared to their urban (n=2629) counterparts. Differences in cohort characteristics were analyzed at baseline as well as differences in primary care quality indicators. Regression analyses examined differences in hospitalizations and days in hospital. Cox proportional hazard models were performed to examine differences in survival.

Results: Patients in rural satellite units vs urban were younger, 58 yrs (p<0.002), but were more likely to have DM 69.4 vs 55.3% (p<0.001), PVD 9.4 vs 4.0% (p<0.001) and HD (MD, Angiogram or PTCA) 42.8 vs 34.2% (p<0.002). More rural patients accessed a FP at least once per year 85.7% vs 67.3% (p<0.001) and 85.3% vs 68% (p<0.001), after controlling for sex, income, charlson, era, age and region at the start of dialysis.

Conclusions: Survival in a cohort of patients dialyzing in remote satellite units was found to be worse compared to their urban counterparts, after controlling for co-morbidities. A potential reason might be increased primary care involvement, although differences were not seen in traditional quality of care indicators.

Funding: Private Foundation Support

FR-PO681
Applying Hemodialysis Clinical Quality Indicators to Individual Patients: A Useful Mortality Prognostic Tool in Clinical Practice?

Background: Hemodialysis (HD) care is routinely assessed by a set of clinical and laboratory parameters, known as Clinical Quality Indicators (CQI). CQI registry and reporting systems constitute an instrument to evaluate the quality of care provided at each HD Unit. The purpose of this study was to determine whether CQI, applied on an individual patient basis, is a predictor of mortality.

Methods: Retrospective study that included 334 patients of a HD Unit from 2011 to 2014. Demographic, clinical and laboratory data were collected. The CQI considered were eleven, which included intended target: spgK/V ≥ 1.4; weekly dialysis time ≥ 720 minutes; Albumin ≥ 3.5 g/dL; Hemoglobin between 10 and 12 g/dL; phosphatemia between 2.5 and 5.5 mg/dL; CaP product < 55 mg²/dL; PTH levels between 150 and 600 pg/mL; Ferritin between 200 and 800 mg/L; Mean arterial pressure < 105 mmHg; interdialytic weight gain (IWG) < 4%; and fistula at vascular access. Single CQI were rated in a binary form (0 = not reached target/1 = reached target) at each monthly evaluation and the average were determined. Ultimately, the eleven parameters were added in a single variable for each patient (CQp).

Results: During follow-up, 33% of patients died. In the Cox regression model, age (HR 1.09; CI 1.07-1.11; p < 0.001), diabetes (HR 2.88; CI 1.92-4.32; p < 0.001), peripheral arterial disease (HR 1.63; CI 1.09-2.44; p = 0.016) and CQp (HR 0.73; CI 0.62-0.87; p < 0.001) were shown to be independent predictors of mortality, after adjustment for other clinical and demographic factors. When CQp was replaced by its constituent variables, albumin (HR 0.06; CI 0.08-0.32; p < 0.001), PTH (HR 2.8; CI 1.10-3.93; p = 0.023), IWG (HR 0.34; CI 0.14-0.83; p = 0.018) and fistulae presence (HR 0.61; CI 0.45-0.90; p = 0.021) presented statistical significance.

Conclusions: A set of parameters, generally applied as a quality care indicators, proved to be an independent predictor of death when applied to individual patients. This should be regarded as an easy and practical prognostic tool to be applied in current practice.

FR-PO682
Association of Estimated Glomerular Filtration Rate at Commencement of Maintenance Dialysis with Mortality Among Patients with Advanced Chronic Kidney Disease in Singapore

Background: Recent evidence suggests that higher estimated glomerular filtration rate (eGFR) at commencement of dialysis may be associated with increased mortality. However, there is scarcity of data on patients of Southeast Asian origin. We analyzed and compared mortality risk in patients with early and late start dialysis as measured by kidney function at dialysis initiation among Southeast Asian population of Singapore.

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

517A
Methods: We performed a retrospective analysis of patients enrolled in the Singapore Renal Data system database from 2008 to 2011. Patients were classified into groups by eGFR at dialysis initiation.

Results: In this total incident population (n=3708), a total of 1510 individuals died during a median follow-up period of 2.8 years. The hazard ratio (HR) and 95% CI associated with different levels of eGFR at commencement of RRT are shown in table below. The main multivariable model (n=3189 without missing information on covariates) associated with the eGFR at dialysis initiation within the groups: age, gender, level of education, smoking, presence of diabetes, ischemic heart disease, cerebrovascular disease, and peripheral vascular disease, malignancy, hepatitis B, hepatitis C, kidney transplant, and prevalence of dialysis. Additional models accounted for serum albumin (n=2657), and serum ferritin (n=2462), and serum calcium (n=1628).

The results were consistent after accounting for serum albumin, serum ferritin, and serum calcium in the multivariable models.

Conclusions: Late initiation of dialysis is associated with a lower risk of mortality in comparison with early dialysis initiation in Southeast Asians in Singapore.

FR-PO683
Predicting Mortality for Patients Who Are on Hemodialysis—A National Cohort Study in Taiwan
Jinn-Yang Chen, Div of Nephrology, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Comorbid conditions and medical history provide prognostic information for dialysis patients. The objective of this study was to develop a prognostic model to predict short-term (6-months and 1-year) and long-term (2.5-years) survival for incident hemodialysis (HD) patients.

Methods: Incident Taiwanese hemodialysis patients from 2006 to 2010 were extracted from National Health Insurance claim records. Prognostic model was developed by using comorbid conditions (summarized as Taiwan index), monthly income and medical history during one year before initiation of dialysis. Somer’s D statistic was used to assess the discrimination ability of our model.

Results: A total of 36,875 incidence HD patients were included in this study and the last follow-up day was December 31, 2011. More comorbid burden, male gender, history of acute kidney injury, dementia, admitting to intensive care unit, staying at nursing home and ever using ventilator were significant prognostic factors. Monthly income only had marginal effects on survival at 2.5 years. For discrimination ability, our model has Somer’s D statistics of 0.76, 0.75, and 0.75 for 6-months, 1-year, and 2.5-years survival, respectively.

Conclusions: Three prognostic models with same covariates for short-term and long-term survival in HD patients were found in this study. The consistency in model performance helps clinicians and patients to make decision.

Funding: Government Support - Non-U.S.

FR-PO684
Twice Weekly Treatment Eligibility for Incident Hemodialysis (HD) Patients
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Background: KDOQI guidelines advise that hemodialysis treatments constitute a patient burden and a risk to native kidney function that can be lowered by reducing HD frequency from 3 to 2/week in patients with substantial residual kidney function. To determine eligibility for twice weekly HD we analyzed 24 hour residual urea clearances (Kru) and volume removal requirements in all incident patients with urine output >100 mL/day in 4 HD centers.

Methods: From the years 2000-2014, 420 out of 734 incident patients who survived ≥6 mos, starting HD 3 week had Kru measurements within 1-3 months after starting HD. The fractional weekly renal clearance (KrT/V) was subtracted from the continuous equivalent minimum goal stdKT/V of 2.0 volumes/week to determine the minimum required standard dialyzer clearance (stdKT/V). With N set as 2 week, stdKT/V was back-calculated from the Leypoldt equation for stdKT/V, KeyT/V from the Tattersall equation for TTV, and KrTu from modeled V and T that was limited to a maximum of 4 hours. Patients were excluded if the ultrafiltration (UF) rate needed to control volume was >10 mL/kg/hr, MAP dropped >10 mmHg, or the patient exhibited symptoms of nausea, vomiting, or cramps.

Results: Patients: N=420, age 57±15 yrs, 58% male, 51% diabetic, 66% TD Catheters. Urine collections: 974±617 mL, Kru 3.0±2 mL/min, KrT/V 7.0±1.5. UF/2±1.1/L/dialysis (3x/week), 2.8±1.6% of dry weight.

In the 225 patients who could achieve the target stdKT/V with 2/week HD, the mean spKT/V required was 0.83±0.36. A total of 105 or 25% of patients with measured Kru met all 4 criteria.

Conclusions: Urine collections disclosed that 225 or approximately 30% of 734 incident patients were eligible for 2/week HD based on solute kinetics alone. Using conservative criteria, half of these were judged ineligible because of UF requirements or HD-induced symptoms. Opportunity exists for incremental HD in a significant number of incident patients.

FR-PO685
The Relationship of Diabetes and Congestive Heart Failure to Costs of Care in End Stage Renal Disease Patients
Sheetal Chaudhuri, Jane Brzozowski, Hao Han, Len A. Usvyat, John W. Larkin, Mahathi Mohali, Terry Ketchersid, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: Many Medicare patients (Pts) with end stage renal disease (ESRD) are known to have co-morbidities of diabetes mellitus (DM) and/or congestive heart failure (CHF). Total costs of care for ESRD Pts are likely to be dependent on patient co-morbidities and likely to vary by geography. We investigated the relationship of DM and CHF based on Pts’ geographic location.

Methods: ESRD Pts with evidence of dialysis at any time during Jan 1, 2010 through Dec 31, 2011 and Medicare as their primary payer were analyzed. Pts were stratified based on Metropolitan Statistical Areas (MSA) and Medicare Part A and B costs were calculated from 100% Medicare data. T-test comparisons were performed for quartiles of total cost of care for eight groups: based on vintage (incident [<90 days on dialysis] or prevalent [≥3 years on dialysis]), as well as, comorbidities (no DM and no CHF, no DM and with CHF, no DM and with both DM and CHF).

Results: Claims for 107,659 Pts were analyzed. Total cost of care increased significantly as the percent (%) of Pts with CHF and DM increased; cost of care declined significantly as the % of Pts with neither DM nor CHF increased by MSA. Cost of care did not change with the increase in % of Pts without DM and with CHF. Yet, costs of care declined as % of Pts with DM and without CHF increased by MSA. These patterns were observed in both incident and prevalent Pts.

Figure 1. Costs of care by MSA (per member per month)

FR-PO686
Long Term Outcomes Over 2 Years following a Dialysis Adequacy Quality Improvement Initiative
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Background: Dialysis adequacy is known to correlate with clinical outcomes such as mortality. Evidence based guidelines recommend that haemodialysis patients should achieve a urea reduction ratio of >65%. UK Renal Registry data shows wide variation in facility attainment of target URR. In 2010 the Salford Renal Network implemented an ambitious programme to uplift attainment of key quality of care indicators to within the top 10% in the UK; dialysis adequacy was a target in 2 phases of improvement in 2010-2012.

Methods: Our network implemented a quality improvement programme using collaborative methodology. We set four teams a different clinical indicator to work on over 12 month cycles for 2 successive years, guided by QI facilitation input. Unit A worked on URR in phase 1 and developed a package of changes using plan-do-study-act (PDSA) testing that was used for improvement by Unit B in phase 2. We analysed the long-term outcomes in these units for a further 2 years until May 2014.

Results: Both units reached their aim of >90% of patients achieving target URR>65% within their improvement year. Both units sustained the improvements for 2 years with no additional resource input after the collaborative. Changes included protocolised nurse-led changes to dialysis prescriptions, multidisciplinary review of vascular access, a nurse-led anticoagulation protocol, blood sampling protocol, and monthly reports.

Conclusions: These results identify differences in association between ESRD related co-morbidities and total costs of care: the % of Pts with both DM and CHF is higher in areas with higher total costs. Surprisingly, costs of care are lower in areas where the % of Pts with DM and without CHF is higher. Risk Adjustments should be considered.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America
Conclusions: Longer term outcomes from QI interventions are underreported with limited evidence on sustainability. We implemented multifaceted interventions to improve dialysis adequacy in our network to within the top 10% in the UK. Implementing evidence-based changes led by frontline staff trained in QI has sustained these improvements for 2 years after a formal QI intervention, improving quality of care for our patients.

FR-PO687
Clinical Effectiveness of Intermittent Infusion Hemodiafiltration (I-HDF) Compared with Conventional Hemodialysis: A Multicenter Clinical Trial
Michio Mineshima, Kei Eguchi. Clinical Engineering, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Intermittent infusion hemodiafiltration (I-HDF) using backfiltration of an ultrapure dialysis fluid has been developed to improve the peripheral circulation of the patient receiving a typical hemodialysis (HD) with repeated intermittent infusion by an automated dialysis machine, GC-110N (JMS Co. Ltd., Tokyo, Japan). In a typical HD treatment, excessive water removal often induces hypotension and muscle spasm. In the I-HDF, some 200-300 mL of ultrapure dialysis fluid was infused into the blood component through the dialysis membrane at a rate of 100 mL/min, every 30 min. I-HDF, namely, means a HDF treatment with small amount of infusion volume, 1.4 to 2.1 L (200-300 mL x 7 times)/session.

Methods: In this paper, clinical effectiveness of I-HDF was evaluated in comparison with conventional HD (CHD) during a multi-center clinical trial that twenty chronic renal disease patients participated.

Results: A significantly lower value for time-averaged blood volume reduction was obtained with I-HDF compared with CHD in spite of there being no difference in the total amount of water removal. It was due to a higher plasma reffilling rate in I-HDF. In addition, increasing peripheral blood flow rate in the patient’s toe was detected by a laser flowmeter for each infusion in many patients. The cleared space value defined as amount of normalized solute removal during a treatment were higher with I-HDF than CHD for inorganic phosphate and α 1-MG. Moderate α 1-MG clearance reduction was found in I-HDF due to the prevention of membrane fouling by intermittent backfiltration of the backfiltration solution. Mean URR, % (SD) Unit A 70.3 ± 8.3 74.5 ± 5.5 74.9 ± 4.9 0.002

Conclusions: Intermittent Infusion HDF using an automated dialysis machine was effective for improvement of the peripheral circulation of patients receiving conventional HD.

FR-PO688
Impact of Post-Hospital Phone and Telehealth Case Management to Reduce Admissions in Hemodialysis Patients
Rebekah L. Wingard,1 Billie Axley,1 Kathryn A. McDougall,1 Andrew D. Howard,1 Joelle Helemann,2 Perry Parlier,1 Sophia Rosen,1 Len A. Usuyvat,1 Alexis Porras,1 Franklin W. Maddux.1 1Fresenius Medical Care, Waltham, MA; 2Metropolitan Nephrology Associates, Clinton, MD.

Background: 2012 30-day readmissions for hemodialysis (HD) patients (pts) were at high 35% in 2012 (USRDS). The Right Trac (RT) Program addressed factors in the complex process of care transitions, with the aim to reduce hospital admissions and readmissions.

Results: 26 HD clinics (3682 pts) were in RT. Interventions deployed in 3 phases (Apr ‘13-Nov ’14). I: Pre- and post-hospital checklists for clinics to manage pt teaching, anemia, nutrition, medications, and dry weight. II: Telephonic case management for 30 days post-discharge. III: Dialysis Link® centralized clinical info exchange among providers. Admission and readmittance rates per pt year (ppy) for “baseline year” (2012) vs. “full intervention year” (2014) were compared to 18 control clinics (2449 pts) matched for clinic size, admission and readmission rate, and urban vs. rural location at baseline. Poisson models with random effects for pt and clinic, adjusted for age, vintage, race, gender, ethnicity, DM, CHF, and COPD were constructed to assess the difference between baseline and intervention and between RT and control clinics.

Conclusions: RT interventions were associated with significant declines in admissions and 30-day readmissions. The difference in the changes between RT vs. controls was significant for admissions, but not significant for 30-day readmissions.

FR-PO690
Predicting Early Mortality Among Hemodialysis Patients Using USRDS Data
Fang Wang,1 2 Zhi He,1 Jennifer L. Bragg-Gresham,1 Yuan Yang,1 Haoyu Gu,1 Yi Li,1 Kamyar Kalantar-Zadeh,1 Elani Streja,1 Rajiv Saran,2 1Div of Nephrology-Dept of Internal Medicine and KeCC, Univ of Michigan, Ann Arbor, MI; 2Renal Div Dept of Medicine, Peking Univ First Hospital, Beijing, China; 3Dept of Biostatistics and KeCC, Univ of Michigan, Ann Arbor, MI; 4Univ of California Irvine, Orange, CA; 5Harold Simmons Center, Orange, CA.

Background: Higher early mortality of hemodialysis (HD) is recognized. We sought to quantify the risk of early mortality and develop a robust prediction model which could potentially guide clinical decision-making.

Methods: The 2007-2012 data from the United States Renal Data System (USRDS) on incident HD patients, age 18-17 years, were randomly split as ‘training’ and ‘validation’ samples. Cox proportional hazards model with piece-wise constant coefficients was used to model all-cause mortality during day 0-90 and day 91-365 of HD. Those transferred to peritoneal dialysis or transplantation were censored. The resulting model was validated by C statistic.

Results: The model mean (n=611,094) was 63.6±14.9 years, with 130,473 deaths during the first year of HD. Mortality rates were 35 per 100 person-years in the first 90 days and 21 per 100 person-years during days 91-365. The model was used to estimate early mortality involving 23 variables including demographics characteristics, pre-ESRD care, laboratory values, co-morbidities as well as institutionalization status. In adjusted analyses, selected variables with significant time-varying effects are listed in the Table.

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

519A
Table: Hazard ratios for death in the first year of HD

<table>
<thead>
<tr>
<th>Measures</th>
<th>Adjusted HR (95%CI)</th>
<th>Interaction between time and individual effect (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD caused by ATN</td>
<td>1.15 (1.08-1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.91 (0.89-0.93)</td>
<td>0.000</td>
</tr>
<tr>
<td>Pre-ESRD care 0-5 months</td>
<td>1.52 (1.40-1.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;6-12 months</td>
<td>1.20 (1.17-1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>1.00 (as ref)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>1.95 (1.85-2.06)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The prediction model reached a C statistic of 0.70 (95% CI, 0.57-0.82).

Conclusions: We have developed a predictive model for early mortality in a national cohort of incident HD patients and identified risk factors with time-varying effects. We intend to further refine and validate this model before recommending in clinical practice.

Funding: NIDDK Support

FR-PO691

Recent Evidence on the Impact of Medicare’s Bundled, Prospective Payment System for Renal Dialysis

Richard Hirth, Tammi A. Nahra, Adam S. Wilk, Marc Turenne, John Wheeler, Kathryn Sleeman, Wei Zhang, Jonathan H. Segal, Univ of Michigan; Arbor Research Collaborative for Health.

Background: Medicare implemented an expanded prospective payment system (PPS) in 2011, including services previously paid by fee-for-service. One intent of the PPS was to incentivize providers to be more efficient in the mix of services provided.

Methods: We used Medicare claims to assess monthly trends from 1/2010-12/2014 for injectable drugs that were previously billed separately. For 2010, we assessed actual payments. For 2011-14, we projected spending based on reported utilization.

Results: ESA use declined in the months immediately pre- and post-PPS, continuing to decline through 2012. In 2013, ESA use leveled off. Use of iron products, often improving efficacy of ESAs, increased through 2011 and then began to decline. Total drug cost, including ESAs, iron, and vitamin D, fell by more than 50%, from a high of $76.16 per session in early 2010 to a low of $37.67 toward the end of 2012. This decline was driven by reduced drug utilization. Since early 2013, total drug costs have risen a bit due to higher drug prices. Beginning in 2013, we assessed actual payments. For 2011-14, we projected spending based on reported utilization.

Conclusions: The expanded bundle dialysis PPS provided incentives for both lower medication utilization overall and the use of lower cost therapies. These incentives seem to have motivated an immediate movement toward lower cost methods of care. Facilities have been able to maintain a lower cost of care over the last two years. CMS continues to monitor facility costs and will continue to make a reduction to the ESRD PPS Market Basket through CY 2018, in accordance with section 217 of PAMA.

Funding: Other U.S. Government Support

FR-PO692

Effect of Medicare’s Payment Adjustment for Low-Volume Dialysis Facilities on Facility Closures

Richard Hirth, Tammi A. Nahra, Adam S. Wilk, Marc Turenne, Jonathan H. Segal, John Wheeler, Kathryn Sleeman, Wei Zhang, Univ of Michigan, Ann Arbor; Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: Small dialysis facilities may face higher per-treatment costs due to economies of scale. Since 2011 a low-volume payment adjustment (LVPA) raised Medicare payments 18% to facilities with <4500 treatments in each of the 3 prior calendar years. A goal of this policy is to preserve access to care by preventing the closure of small facilities.

Methods: We tested the hypothesis that the LVPA prevented closures by examining the year-to-year closure rates of U.S. dialysis facilities during 2007-2013, before and after the policy, comparing facilities providing <4000 and >4000 annual treatments. Analyses with linear regression relate facility outcomes to prior year size, ownership, for-profit status, hospital affiliation, patient mix, rural location, modality mix and county characteristics, to examine the effect of the LVPA on 8 of treatments provided by facilities.

Results: Among low-volume facilities, year-to-year closure rates fell from 3.8%, 4.9% and 4.0% pre-LVPA, falling to 1.1%, 0.5% and 0.8% post-LVPA. Among facilities with >4000 treatments, closure rates also decreased, but to a much smaller extent (from 1.0%, 1.2% and 0.8% pre-LVPA to 0.6%, 0.2% and 0.3% post-LVPA).

Conclusions: In Medicare’s bundled payment system, closure rates decreased overall, with a much larger absolute reduction among small facilities. The gap in closure rates between small and large facilities fell from about 3% points before the policy to about 0.5% points after. LVPA appears to have helped prevent small dialysis facility closures, but it may also motivate some small facilities to avoid growing in order to retain the LVPA. Emphasizing a dialysis facility’s importance for patient access rather than size alone may help inform payment policy modifications.

Funding: Other U.S. Government Support

FR-PO693

Delayed Thrombectomy Increases Risk for Dialysis Catheter Placement

Scott Reule, Sunil Akkina, Andrew J. Esten, Paul E. Drawz, Dept of Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Arteriovenous dialysis accesses (fistulas or grafts) are associated with significant rates of thrombosis. Though timely thrombectomy may have a significant impact on immediate and long-term access survival, it is not always readily available. The goal of this study was to evaluate whether delayed thrombectomy increases risk for loss of dialysis access and subsequent placement of a dialysis catheter.

Methods: All patients at the Fairview Health System with thrombectomy as the primary reason for admission between January 2008 and April 2015 were included in this retrospective observational study. The electronic medical record was reviewed to evaluate type of access, timing of admission and declot, and access on discharge and 6 and 12 months after discharge. Baseline characteristics and proportions were determined for the overall population as well as stratified by tertile of time to thrombectomy, defined as the time from admission to the declot procedure. The outcomes of interest included need for dialysis catheter at discharge and 6 and 12 months after discharge. Logistic regression was used to evaluate the risk for dialysis catheter use adjusting for prior intervention, access type, and time to thrombectomy.

Results: Among 444 patients identified using procedural codes, 122 were admitted primarily for thrombectomy. The mean age was 60.4 years, 65% were male, and 44.3% utilized arteriovenous fistula for access. Mean time to thrombectomy was 0.45 days (range: 0.05-1.13 days). Fifteen patients utilized a catheter for hemodialysis on discharge. Delayed thrombectomy was associated with a two-fold increase in requirement for catheter at discharge (OR 2.02; CI 1.19-3.43) and at 6 months (OR 2.04; CI 1.20-3.48). This association remained present at 12 months (OR 1.75; CI 1.02-3.00).

Conclusions: In this study of patients cared for within a large academic health system, a one day delay in thrombectomy doubled the risk for need for a dialysis catheter at discharge and 6 and 12 months after discharge. These results indicate that a clotted dialysis access should be considered a medical emergency.

Funding: Other U.S. Government Support

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

520A

Hemodialysis: Clinical Science Potpourri

Poster/Friday
FR-PO694

Intradialytic Body Weight Reduction and Outcome of Vascular Access: Analyses of Data from the Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS)

Manabu Asano,1 Kenichi Oguchi,2 Akira Saito,1 Yoshishiro Onishii,1 Yusuke Yamamoto,1 Shinichi Fukuhara,1 Takashi Akiba,1 Tadao Akizawa,1 Tosei Hospital, Saitama, Japan; 2J-DOPPS Research Group, Japan; 1Hope International, Kyoto, Japan; 1Inst for Advancement of Clinical and Translational Science, Kyoto Univ Hospital, Kyoto, Japan.

Background: There is no doubt that large-volume ultrafiltration is one of the important risk factors for vascular access (VA) thrombus in hemodialysis patients. However, the relationships between intradialytic body weight reduction and VA patency are still in the middle of being discussed. We tried to determine whether large-volume ultrafiltration was practically associated with VA failure by means of the results obtained from the phase 3 and 4 J-DOPPS.

Methods: Referring data from the phase 3 and 4 J-DOPPS, the current analyses were limited to 2736 patients who were evaluable for VA patency and body weight change during dialysis. They were assigned to one of the following three groups according to the tertiles (T1-T3) of intradialytic fluid removal per body weight: T1, -0.5% to 3.8%; T2, 3.8% to 5.1%; and T3, 5.1% to 13.7%. The hazard ratio of VA failure was compared across these tertile groups using Cox regression models. The models were adjusted for the following risk factors: age, gender, BMI, diabetes, hemoglobin, phosphorus, Kt/V, ESA use, and antplatelets use. Primary VA survival was defined as the days until the first VA intervention. Secondary VA survival was defined as the days until new VA creation.

Results: The incidence rates (events/100 person-years) of primary and secondary VA events were 4.7 and 1.3 for T1, 5.6 and 1.6 for T2, and 6.7 and 1.7 for T3, respectively. The adjusted hazard ratios versus T1 for primary VA patency were 1.16 (95% confidence interval [CI], 0.88 to 1.52) for T2 and 1.41 (95% CI, 1.07 to 1.87) for T3. The hazard ratios versus T1 for secondary VA patency were 1.29 (95% CI, 0.78 to 2.13) for T2 and 1.45 (95% CI, 0.86 to 2.45) for T3.

Conclusions: This study shows that large-volume ultrafiltration during dialysis tends to increase VA failure in hemodialysis patients.

FR-PO695

Post-Endovascular Intervention Venous Access Pressure Ratio (VAPR) Predicts Access Survival

Lalathaksha Kumbar1,2, Gerard Zasuwa1,3, Matthew E. Bennett1, Francis E. Loh1, Eric K. Peden1, Eugene J. Nuccio1, Alfred K. Cheung1,4, Tom Greene, Michel Charonch1,2 Denver VA Medical Center; University of Colorado Denver; VA Salt Lake City; Univ of Utah.

Background: There is no doubt that large-volume ultrafiltration is one of the important risk factors for vascular access (VA) thrombus in hemodialysis patients. However, the relationships between intradialytic body weight reduction and VA patency are still in the middle of being discussed. We tried to determine whether large-volume ultrafiltration was practically associated with VA failure by means of the results obtained from the phase 3 and 4 J-DOPPS.

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Conclusions: This study shows that large-volume ultrafiltration during dialysis tends to increase VA failure in hemodialysis patients.

FR-PO696

Abnormalities in Mineral Metabolism and Dialysis Arteriovenous Fistula Thrombosis in the HEMO Study

Anna Jeanette Jovanovich,1 Eugene J. Nuccio,1 Alfred K. Cheung,1 Tom Greene, Michel Charonch1,2 Denver VA Medical Center; University of Colorado Denver; VA Salt Lake City; Univ of Utah.

Background: Vitamin D deficiency and fibroblast growth factor 23 (FGF23) excess are highly prevalent among patients requiring chronic hemodialysis. This study aims to determine the association of 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D), and FGF23 serum levels with arteriovenous fistula (AVF) thrombosis in hemodialysis patients.

Methods: The HEMO Study was a randomized multicenter study evaluating the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum 25(OH)D, 1,25(OH)2D, and intact FGF23 levels were measured in stored serum samples obtained at baseline in 881 patients in this cohort. Cox proportional-hazards models were used to examine the association of 25(OH)D, 1,25(OH)2D, and FGF23 serum levels with time to first AVF clotting event after controlling for important clinical covariates in the HEMO Study.

Results: Patients had a mean age of 57±14 years, 55% were females, and 46% were white. During a median follow-up of 3.0 years, 111 AVF clotted. Median (IQR) serum 25(OH)D, 1,25(OH)2D, and FGF23 levels were 19.1 [14.2, 26.6] ng/ml, 6.3 [2.9, 14.5] pg/ml, and 3118 [726, 12928] pg/ml. Among patients with levels in the highest tertile compared to the lowest tertile, both 1,25(OH)2D and FGF23 were significantly associated with an increased risk of clotting in adjusted analyses, hazard ratio (HR) 2.70 (95% CI, 1.21-6.46) and HR 1.35 (95% CI, 1.002-1.83), respectively. No statistically significant associations were observed between 25(OH)D serum levels and AVF thrombosis.

Conclusions: Calcitriol and FGF23 excess were associated with an increased risk of AVF thrombosis among chronic hemodialysis patients.

Funding: NIDDK Support, Veterans Administration Support

FR-PO697

Ultrasound-Guided Evaluation of New A V Fistulas Safely Decreases Time to First Cannulation

Farzin Fanpour,1 Roshan A. Patel1, George N. Cortisid,1 2Nephrology, Elmhurst Hospital, Icahn School of Medicine at Mount Sinai, Elmhurst, NY; 2Nephrology, Broadway Atlantic Dialysis Center, Elmhurst, NY.

Background: The use of bedside ultrasonography (USG) in various medical specialties has exploded over the last decade. For the past year, we have been using bedside USG for earlier AV fistula utilization and for diagnosing potential problems. Prior to the use of USG, cannulation was based on physical exam. We were interested to see whether use of bedside USG helps in early cannulation of AVF.

Methods: USG procedures from February 2014 to February 2015 were reviewed. Time to cannulation in the year prior to the introduction of USG (2013 - 2014) was calculated and compared to similar data with USG use. By week 4 all new fistulas underwent the first USG exam. Examinations were performed by the renal attendings and fellows each exam lasting about 5 minutes. SonoSite M-Toro ultrasound machine was used.

Results: Total of 44 USG examinations were performed on 14 patients while monitoring new AVF maturation. In 10 patients USG-guided cannulation occurred at an average of 6.2 ± 0.9 weeks compared to 10.2 ± 0.9 weeks prior to USG use (P=0.006). There were no complications seen with the earlier USG-guided cannulations. Subsequent cannulations by the nursing staff were successful without USG. In 4 patients failure of maturation was diagnosed by USG at an average of 3.8 ± 0.9 weeks vs 9.6 ± 1.2 weeks prior to USG (P=0.08). Antibiotic dosing occurred 21 times prior to USG compared to 11 times with USG, despite the similar catheter rates for both years.

Conclusions: USG use facilitates early AVF cannulation with decreased time to first use. Identification of potential AVF issues and their referral are accomplished earlier. This may translate to earlier catheter removal and fewer infections.

FR-PO698

Arteriovenous Grafts Reduce CatherDependence in the Elderly

Thomas M. Loh, Matthew E. Bennett, Francis E. Loh, Eric K. Peden. Vascular Surgery, Houston Methodist, Houston, TX.

Background: Arteriovenous fistulas (AVF) are the permanent access of choice. The benefits of AVF, durability and longevity, are minimized in the elderly where more than 40% of patients will die within their first year of initiating hemodialysis. We investigate an expanded role for primary arteriovenous grafts (AVG) in this population.

Conclusions: USG use facilitates earlier AVF cannulation with decreased time to first use. Identification of potential AVF issues and their referral are accomplished earlier. This may translate to earlier catheter removal and fewer infections.
Methods: We retrospectively review consecutive patients over the age of 70 who underwent upper extremity access creation from January 2008 to July 2014. Data collection included demographics, past medical histories, subsequent interventions, volume flows, access usage, and patient survival.

Results: We performed 366 AVF and 124 AVG creations in 442 patients over the age of 70 (197 women, 245 men). There were no significant differences in the comorbidities between the two access types. The AVG group was significantly older and more likely to be female, 79.2 yo vs. 77.2 yo (p<0.001) and 60% vs. 41% (p<0.001) respectively. Patients with AVF were significantly more likely to never use their permanent access, 25% vs. 11% (odd ratio p=0.002) and if utilized, cannulated significantly later, 3.6 ± 0.2 months vs. 1.3 ± 0.1 months (p<0.001). Catheter dependence at 6 months was 40% for AVG and 28% for AVG. (Figure 1) Secondary patency at 18 months was 64% for AVF and 63% for AVG.

Conclusions: Prosthetic grafts should be considered as the preferred permanent access type in the elderly. Better predictors of mortality, including frailty scores, should be investigated for determining the best choice of permanent access in elderly patients.

FR-PO699

Background: Conventional outpatient hemodialysis utilizes various forms of anticoagulation to prevent access and extracorporeal circuit clotting. In contrast, to reduce the risk of bleeding events, inpatient dialysis units do not frequently use anticoagulation. We aimed to investigate the consequences of anticoagulation-free dialysis and the factors associated with failure to achieve ultrafiltration target (UFT) in our inpatient unit.

Methods: We performed a retrospective analysis of 250 consecutive hemodialysis treatments in 125 chronic patients. Patients were excluded if they were admitted for initiation of dialysis or required systemic anticoagulation. We looked at both instances of successful achievement and failure of UFT. We looked at the following factors: type of access, episode of intradialytic hypotension (IDH), episode of access clotting, and episode of extracorporeal circuit clotting. No anticoagulation was used in the HD treatments. Correlation analyses were performed and categorical data was analyzed using chi-square test. STATA, version 11, was used for statistical analyses.

Results: Overall the incidence of failure to meet UFT was 35%. Association of failure to meet UFT and episode of IDH was noted (p=0.001, Pearson chi2(1) = 13.5). There was no correlation between meeting UFT and type of access (graft r=-0.09, fistula r=0.13, and catheter r=-0.07), access clotting (r=-0.07), and extracorporeal circuit clotting (r=0.08).

Conclusions: Our study of 250 anticoagulation-free hemodialysis treatments suggests that access and extracorporeal circuit clotting was not associated with failure to meet ultrafiltration target. However, the failure to achieve ultrafiltration target was significantly associated with intradialytic hypotension. Larger cohort, multi-center prospective trials should be performed to look at causality of failure to meet ultrafiltration targets in the hospitalized patients.

FR-PO700
Evaluation of the Ability of Transonic Monitoring to Predict Dialysis Access Stenoses Jerard Zaki Kneefati-Hayeck,1 Gaurav Ghosh,2 Stephen Kruger,3 Jeffrey I. Silberzweig,2,3 1Dept of Medicine, New York-Presbyterian Hospital, New York, NY; 2Weill Cornell Medical College, New York, NY; 3The Rogosin Inst, New York, NY.

Background: Patency of vascular access is critical to successful maintenance hemodialysis. It is well established that lesions are easier to treat if they can be identified prior to thrombosis. Non-invasive evaluation of access blood flow with the Transonic device is established for this purpose. We previously analyzed its performance after two years and demonstrated >99% sensitivity and specificity. We now seek to extend that work by looking at performance over a fifteen-year period.

Methods: Transonic studies are performed on approximately 1500 maintenance dialysis patients with AV grafts or fistulae in our 7 clinics in New York City. Transonic flow rates <600 cc/min or decreases by >10% from prior readings prompt referral to Interventional Radiology or Vascular Surgery. We report on the sensitivity, specificity and predictive values for patients treated between 1998 and 2012.

Results: Sensitivity was 42%; specificity 72%. Positive predictive value (PPV) was 20%; negative predictive value (NPV) was 85%.

We evaluated our ability to predict stenosis based on decreased dialysis clearance: for Kt/V, PPV was less than 10% and NPV less than 80% for different cutoff points; for URR, PPV was less than 10% and NPV less than 80%.

Conclusions: We hypothesize that the large numbers of false positive and false negative results were caused by scheduled referrals to Interventional Radiology, which have become routine. This study suggests that routine Transonic studies may no longer be as important as they were in 2000; however, Transonic studies provide better predictive ability than reductions in urea-based dialysis clearance.

FR-PO701
Hemodialysis Vessel Mapping in Women and Men Rita L. McGill, Robin Ruthazer, Dana Miskulin, Klemens B. Meyer, Daniel E. Weiner. Tufts Medical Center, Boston, MA.

Background: Men initiate hemodialysis (HD) with fistulas (AVF) more often than women, and this gap widens following initiation. Angiography and Doppler vessel mapping may promote AVF creation by detecting vessels not found by physical examination. Women may benefit more from imaging, as they are less likely to have veins that are visible upon inspection, even when suitable for AVF construction. We hypothesized that the sex disparity in AVF use may in part reflect a disparity in vessel mapping rates.

Methods: After restricting to patients with pre-dialysis Medicare claims, we used CPT codes to ascertain all vascular imaging during the 2 years before starting HD and up to 12/31/2012, in the subset of adult HD patients entering USRDS in 2010 or 2011 with central venous catheters (CVC) as sole vascular access. Doppler studies performed on the same day as an angiogram were excluded. Angiograms and Dopplers per 100,000 patients-months were calculated. Incidence rate ratios (IRR) between women and men were estimated for age, BMI, diabetes, and vascular disease using Poisson regression.

Results: Among women with preHD claims, 62% had CVC-only and 14% AVF; men had 57% CVC-only and 20% AVF. 18494 men and 16686 women with CVC-only contributed 615257 and 558647 patient-months of data. No imaging was performed in 57% of men and 54% of women. The distribution of studies in men and women showed:

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18494</td>
<td>16686</td>
</tr>
<tr>
<td>ANGIOGRAPHY (# studies performed)</td>
<td>5705</td>
<td>5851</td>
</tr>
<tr>
<td># individuals with Angiography</td>
<td>4058 (22%)</td>
<td>3986 (24%)</td>
</tr>
<tr>
<td>Crude IRR Angiography</td>
<td>1.13 [1.09, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Adjusted IRR Angiography</td>
<td>1.10 [1.07, 1.15]</td>
<td></td>
</tr>
<tr>
<td>DOPPLER VEIN MAPPING (#studies performed)</td>
<td>5815</td>
<td>5746</td>
</tr>
<tr>
<td># individuals with Doppler</td>
<td>4953 (27%)</td>
<td>4743 (28%)</td>
</tr>
<tr>
<td>Crude IRR Doppler</td>
<td>1.09 [1.05, 1.13]</td>
<td></td>
</tr>
<tr>
<td>Adjusted IRR Doppler</td>
<td>1.07 [1.05, 1.11]</td>
<td></td>
</tr>
<tr>
<td># individuals with ANY imaging studies</td>
<td>8011 (43%)</td>
<td>7654 (46%)</td>
</tr>
</tbody>
</table>

Conclusions: Vascular imaging was performed in fewer than 50% of individuals starting hemodialysis with CVC. Higher rates of vascular imaging in women were statistically but not clinically significant. Promotion of vein mapping and angiography in women merits exploration as a means to decrease the disparity in fistula rates between women and men.

Funding: Other NIH Support - NIH/NIDDK T32 DK007777 “Epidemiology, Clinical Trials and Outcomes Research In Nephrology” Tufts CTSI Grant [UL1 TR001064]
FR-PO702
Association of Bacteremia with Arteriovenous Access Failure in Hemodialysis Patients

Seyed Mustafa Ahmed, Laura Plantinga, Rachel E. Patzer, Jason Cobb, William M. McClellan. Emory Univ, Atlanta, GA.

Background: Obesity, female sex, diabetes, peripheral vascular disease, and pacemakers are known risk factors for arteriovenous fistula (AVF) and arteriovenous graft (AVG) failure. We examined whether bacteremia in hemodialysis (HD) patients with AVF/AVG represents an additional, independent risk factor for subsequent AVF and AVG failure.

Methods: We conducted a retrospective observational study among 29,571 U.S. patients from the United States Renal Data System who started HD with AVF and AVG between 1/1/2009 and 9/30/2010. We used inpatient ICD-9 codes after dialysis start to define bacteremia and AVF/AVG failure. We then used a multivariable Cox proportional hazards model to assess relationship between exposure to bacteremia and time to access failure.

Results: Overall, 12.2% of patients with bacteremia experienced an access failure, compared to 4.0% of patients without bacteremia (P<0.001). This difference persisted over a median follow-up of 582 days. With adjustment for known confounders, patients who had bacteremia after dialysis start were at 3-fold greater risk of subsequent access failure, relative to those who did not (HR=3.18, 95% CI: 1.71 – 5.95).

Conclusions: This observational study indicates that decreased AVF and AVG survival may be associated with exposure to bacteremia among HD patients.

FR-PO703
Comparison of Loss of Vascular Access Patency in Hemodialysis Patients with End-Stage Renal Disease due to Systemic Lupus Erythematosus versus Other Causes

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Background: Previously we found that U.S. patients with systemic lupus erythematosus (SLE) and end-stage renal disease (ESRD) were 40% less likely than other ESRD patients to have a permanent vascular access in place at the start of dialysis. Here, we examine whether subsequent loss of patency differs in SLE vs. other ESRD patients who have a permanent vascular access.

Methods: A cohort of 106,993 U.S. patients starting hemodialysis with an arteriovenous fistula or graft (705/9/11) was identified from a national registry of treated ESRD (United States Renal Data System). Kaplan-Meier analyses and multivariable Cox proportional hazards models were used to estimate the association between SLE vs. other ESRD (by provider-reported attributed cause at start of dialysis) and the time to first inpatient ICD-9 code for loss of vascular access patency, with censoring for death or the end of follow-up.

Results: Among 597 (0.6%) incident hemodialysis patients with a permanent vascular access, those with SLE are not more likely than other patients to experience a loss of vascular access patency requiring hospitalization. Further analyses will examine whether these patterns persist when outpatient procedures are included; however, confounding by indication would remain a potential bias.

Conclusions: These results suggest that, among those patients who do start dialysis with a permanent vascular access, those with SLE are not more likely than other patients to experience a loss of vascular access patency requiring hospitalization. Further analyses will examine whether these patterns persist when outpatient procedures are included; however, confounding by indication would remain a potential bias.

FR-PO704
The Placement of Tunneled Central Venous Catheters Through Percutaneous Puncture of Superior Vena Cava in Hemodialysis Patients

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Background: After the exhaustion of traditional insertion sites of tunneled central venous catheters (ICVCs), it can be challenging to place the ICVCs in exotic locations. A retrospective case series in West China Hospital was studied to assess the placement of ICVCs through percutaneous puncture of superior vena cava (SVC) in patients with innominate veins occlusion.

Methods: Sixteen patients (male: 62.5%; mean age: 64.7 years; mean duration of HD: 5 years) who underwent placement of ICVCs through percutaneous puncture of SVC were retrospectively analyzed. They had either exhausted AV access sites or chosen not to undergo other vascular access placement. All of the patients had occlusion in innominate veins on both sides. The outcomes were function measurements of ICVCs, and safety parameters.

Results: The procedure succeeded in all of the patients. During the follow-up (mean: 12 months, range: 3-36 months), access failure due to thrombosis was observed in one patient, and the failure was treated by aspirin and Clopidogrel. The remaining continued to function well until the end of the follow-up or until the death of the patients (n=3). The procedure was generally safe. No pneumothorax occurred. The most common complication was mediastinal hematoma after the failure of SVC puncture. The fluoroscopy could reveal the hematoma during the procedure. The largest hematoma was 2cm in diameter in the current series and it resolved spontaneously.

Conclusions: In patients with innominate veins occlusion and exhaustion of the conventional insertion sites, the ICVCs can be safely placed through SVC puncture using percutaneous route.

FR-PO705
Analysis of Survival of Cardiac Function in Maintained Hemodialysis Patients with Arteriovenous Fistula and Tunneled Cuffed Catheter

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Background: Until now, there is little data of cardiovascular regarding to different type of vascular access. This study was to investigate survival of patients with arteriovenous fistula and tunneled cathered group.

Methods: A total of 219 patients who received maintained hemodialysis were included in this study. Patients were divided into two groups: arteriovenous fistula group and tunneled catheter group. The baseline anthropometric and laboratory parameters were measured. The time and cause of mortality were documented.

Results: There were significant difference of left ventricular hypertrophy (P=6.645, P=0.001), left ventricular systolic dysfunction (P=0.045), between two groups. But there was no significant difference of left ventricular diastolic dysfunction between two groups. Kaplan-Meier survival curves showed that the mortality was enhanced among tunneled catheter group.

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Patients with left ventricular hypertrophy, left ventricular systolic dysfunction, left ventricular diastolic dysfunction in arteriovenous fistula group have a high survival rate compared with tunneled catheter group. Furthermore, IPCH, calcium, systolic blood pressure and diastolic blood pressure were independent risk factors of mortality for patients on maintained hemodialysis by COX regression model.

Conclusions: Different factors of vascular access may have influence on mortality in patients on maintained hemodialysis. Those with tunneled catheters have lower survival rate when left ventricular dysfunction occurred.

FR-PO706
A Retrospective Study of Preferable Alternative Sites to Right Internal Jugular Vein for Tunneled Hemodialysis Catheters Insertion: Right External Jugular Vein versus Left Internal Jugular Vein
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Background: It has been recommended by the KDOQI guidelines that right internal jugular vein (RJIV) is a preferred insertion site for hemodialysis (HD) catheters, and both right external jugular vein (REJV) and left internal jugular vein (LIJV) are alternative sites for those who have encountered severe thrombosis and/or occlusion of RJIV. The retrospective study aimed to determine if superiority exists in the two alternative sites by comparing the outcomes of tunneled (cuffed) dialysis catheters (TDCs) through REJVs versus LIVs in HD patients who had failed RJIV.

Methods: From January 1, 2013 to December 31, 2014, 24 LIV-TDCs and 21 REJV-TDCs were inserted in our hospital. All the events were recorded from patient charts until May 31, 2015. Using SPSS 22.0 software, data were analyzed by the Fisher exact test or chi-square test. Event free catheter survival time was estimated by the Kaplan-Meier method. Multivariable Cox hazards analysis was fitted to detect the independent risk factors of events. A p-value of <0.05 was considered statistically significant.

Results: A total of 20924 (LIVs, 11782; REJVs, 9141) catheter-days were evaluated and the mean was 427.02 days. Most of the patients (53.1%) were older than 65 years with an average dialysis time of 25.3 months. The event free catheter survival time was (516.20±55.60) in REJ-VDs and (343.91±40.63) in LIV-TDCs (P=0.038). Mean effective blood flow was higher in REJV-TDCs than that in LIV-TDCs (270.95±24.93 vs 244.82±30.35 ml/min, P<0.002). A substantial trend towards statistical significance was found between two groups in incidence of all events, including death, death related to catheter complication and catheter removal. The total historic catheters indwelling time was identified as an independent risk factor for severe TDCs events by Cox regression hazards test (P<0.01).

Conclusions: REJV might be superior to LIJV as an alternative insertion site for TDC placement in HD patients who had failed RJIV.

FR-PO707
Haemodialysis Recirculation in Patients with Catheter Access: Damien Ashby, Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom.

Background: Recirculation is a well described impairment of the haemodialysis circuit which reduces dialysis dose and electrolyte clearance. Catheter tips are designed to minimise recirculation based on in vitro experiment, with most designs having a tip separation of 25mm, but clinical studies of catheter-related recirculation have not been published.

Methods: In a group of stable adult patients receiving haemodialysis by tunneled catheters, recirculation was calculated by 3-sample urea measurement, and analysed in terms of excessive bleeding, hematoma or infection. At an average follow-up of 6 months, one death had occurred that was unrelated to the procedure or arrhythmia. Subcutaneous ICD is a minimally invasive procedure when compared with an epicardial device. By leaving the venous system untouched, this approach offers the advantage of reduced risk of infection, sternal wound dehiscence, skin infections, and hematomas.

Results: 54 haemodialysis patients (aged 28-90, 61% male) received successful SICD. While the use of these devices is expanding, their insertion in advanced renal failure and hemodialysis patients is somewhat limited. In this analysis, we present 9/13 patients had high recirculation and hemodialysis catheters treated successfully with an SICD. Demographic characteristics revealed; male=8, diabetes=8, hypertension=13, coronary artery disease=10, peripheral vascular disease=8. Two of the four hemodialysis patients had an AVF while two were dialyzing with a tunneled dialysis catheter. Mean GFR for the CKD patients was 40.3 ml/min. Patients received the SICD device for primary prevention of sudden cardiac death (cardiomyopathy with low ejection fraction). 3/13 patients had non-ischemic cardiomyopathy (CMP) with an ejection fraction of <25% while 10/13 suffered from ischemic CMP with an EF of <30%. There were no procedure-related complications in terms of excessive bleeding, hematoma or infection. At an average follow-up of 6 months, one death occurred that was unrelated to the procedure or arrhythmia. Subcutaneous ICD is a minimally invasive procedure when compared with an epicardial device. By leaving the venous system untouched, this approach offers the advantage of reduced risk of infection, sternal wound dehiscence, skin infections, and hematomas.

Conclusions: SICD can be successfully used in patients on hemodialysis and CKD.
BCAVF groups. All participants were followed for 12-months after surgery. The main outcome measures were blood flow velocities and volumes, vessel diameters, primary unassisted fistula patency rate (PUFPR), the cumulative fistula survival rate (CFSR) and complications.

**Results:** The baseline demographic and clinical characteristics were well matched between mNT-BBAVF and BCAVF groups. Blood flow velocities and flow volumes of the corresponding fistula segments increased significantly in both groups. Compared to BCAVF, where only proximal cephalic vein increased in size, the proximal cephalic vein, distal cephalic vein and distal basilic vein in mNT-BBAVF all increased significantly compared to baseline over the 12-month period (p<0.01). Therefore, in addition to the proximal cephalic vein, the distal cephalic vein and distal basilic vein were available for cannulation in mNT-BBAVF. At 12 months, the PUFPR of mNT-BBAVF was significantly better than that of BCAVF (73.0% vs. 45.9%, HR: 2.60; 95%CI: 1.21 to 5.59; p=0.01). Although, the CFSR did not differ between the two groups (91.9% vs 78.4%, HR: 1.18; 95%CI: 0.55 to 2.17; p=0.37). Finally, there were no significant differences in complications between the two intervention groups at 1 and 12 month follow-ups, other than severe arm pain which was much less reported among patients with mNT-BBAVF at 1 month (vs. BCAVF, p=0.03).

**Conclusions:** mNT-BBAVF is an effective alternative for the construction of upper arm vascular access.

**FR-PO711**

Management of Catheter Related Bacteraemias: New Insights into an Old Problem

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**Background:** Catheter related bacteraemias (CRB) pose a significant risk for those dialysis patients using such devices. Strategies are needed to minimise this risk as much as possible, especially in light of growing concerns over antibiotic resistance. Our unit routinely uses citrate to lock catheters. We sought to audit our CRB rate and long term complication rate. We believe this contemporary data will be useful to all involved in caring for patients with catheters.

**Methods:** We retrospectively reviewed all blood cultures taken from our institution’s dialysis patients for 1 year (October 2013 and September 2014). The records of patients with positive cultures were reviewed to ascertain if the infection was related to their access. Data was then collected on the type of organism grown, management of the episode, recurrence rate, and any long term complications.

**Results:** 1014 cultures were taken from approximately 930 haemodialysis patients. 45% of these were dialyzing via a catheter. There were 52 instances of CRB giving a CRB rate of 0.34 per 1000 catheter days. 65% were due to gram-positive organisms, 29% were due to gram-negative organisms and 6% were fungal related. The overall recurrence rate was 26%. Catheter removal was performed in 32 instances (62%). Infective complications occurred in 5 (16%) patients with gram-positive infections and 6 (54%) of those with gram-negative infections; a statistically significant difference. The majority of these were endocarditis. CRB accounted for a total of 583 hospital in-patient days.

**Conclusions:** We observed significantly more infective complications with gram-negative organisms compared with gram-positive. This probably reflects the underlying characteristics of these patients rather than the pathogenicity of the organisms per se (19% of patients with gram-negative infections were intravascular drug users). Never the less our data suggests that gram negative infections are a risk factor for complications and clinicians should consider further investigations in these cases. Our CRB rate was low compared to quoted rates in the literature; this may reflect routine the use of citrate lock in our catheters.

**FR-PO712**

Assessment of Arteriovenous Fistula Access Flow Using Video Image Processing Technology

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**Background:** Vascular stenotic lesions are the main cause of failure in arteriovenous fistula (AVF). Routine measurement of access flow (AF) is important in the timely detection of changes and planning interventions. The aim of this pilot study was to investigate whether video image processing (VIP) techniques could be used to detect AVF motion and explore the relationship between motion patterns and AF.

**Methods:** Skin above the AVF was imaged for 1 minute using a digital single lens reflex camera prior to HD. The video was processed using Eulerian video magnification (Wu et al, ACM Trans. Graph. 31(4), 2012) to amplify AVF motions. Thereafter the motion-amplified video was converted to quantitative waveform data using an algorithm based on change in color of each image (Matlab Image Processing Toolbox). Monthly AF measurements were recorded and correlated with the post-processed AVF waveform pattern.

**Results:** We studied 12 hemodialysis patients (51.5±11.3 years, 50% male) with a mean±SD AF 1501±392/ml/min (N=9; AF was unavailable in 1 subject). Amplitude of skin displacement was 0.069±0.044mm (N=9; technical issues occurred in 2 subjects). While amplitudes of that size are hardly visible to the naked eye, they were clearly discernible in post-processed amplified video. Amplitude was notably smaller in subjects with lower AF (Fig 1). Amplitude analysis of the amplified video indicates a relationship with AF (R²=0.73, p<0.01; N=9).

**Conclusions:** Our proof-of-concept study demonstrates this video imaging and analysis technique has potential to provide a quick, noninvasive, low cost way to obtain quantitative information related to AF. Research is underway to assess the impact of clinical interventions on the amplitude pattern.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

**FR-PO713**

Pre-Emptive Correction of Arteriovenous Access Stenosis: Systematic Review and Meta-analysis of Randomized Controlled Trials

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**Background:** Selective stenosis correction in an arteriovenous (AV) access that is suitable for hemodialysis may prolong its survival, as compared to salvage procedures postponed to when the AV access becomes dysfunctional.

**Methods:** We did a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating pre-emptive correction of an AV access stenosis vs. stenosis correction in a dysfunctional access (deferred correction) in adults treated with hemodialysis therapy. We searched the Cochrane Kidney and Transplant Specialized Register (which includes MEDLINE and EMBASE) to 29 October 2014. Outcomes of interest were access loss (primary outcome), access thrombosis, infection, mortality, hospitalization, and access-related procedures. We did sub-group analyses of access outcomes by access type. We summarized the evidence using the Grading of Recommendations Assessment, Development, and Evaluation criteria.

**Results:** We included 16 studies (including 1,390 participants; follow-up 6-38 months; N=58-189 participants). Nine studies enrolled adults without access stenosis (primary prophylaxis; three studies including people using fistulas) and five enrolled adults with a highly suspected or documented stenosis in a functioning access (secondary prophylaxis; three studies in people using fistulas). Relative to deferred salvage, access surveillance with pre-emptive correction of an AV stenosis did not reduce the risk of thrombosis (RR 0.95; 95% CI 0.8-1.12) or access loss (RR 0.9; 95% CI 0.71-1.15) in grafts (moderate-grade evidence), but reduced the risk of thrombosis (RR 0.5; 95% CI 0.35-0.71) and access loss (RR 0.5; 95% CI 0.29 to 0.86) in fistulas (low-grade evidence). Results were either heterogeneous or imprecise for mortality, rates of infection, procedures and hospitalization. There was unclear or high risk of bias in most studies.

**Conclusions:** Pre-emptive correction of a new or documented stenosis may not improve graft outcomes, but may prevent fistula thrombosis or loss.

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

**FR-PO714**

Real-Time Kt/V Tracking Profile as a Predictor of Dialysis Access Recirculation

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**Background:** On-line monitoring of ultraviolet absorption of spent dialysate in routine hemodialysis allows continuous measure of removed solutes from spent dialysate. We studied whether real-time Kt/V tracking profile could be a predictor of dialysis access recirculation.

**Methods:** End-stage renal disease patients undergoing maintenance dialysis with Dialog (B Braun AG) dialysis machine with a built-in UV-Spectrophotometer (Option Adimea, B Braun AG), high-flux polysulfone dialyzers, and at blood flow rate (Qb) 400-450 ml/min and dialysate flow rate (Qd) 800 ml/min were included in all recording sessions. Real-time Kt/V tracking profile and venous (Pv) and arterial pressures (Pa) were recorded and hemodialysis access recirculation values were biochemically measured using standard protocol.

**Results:** Distinct real-time Kt/V profiles were identified in patients with significant access recirculation (>5%) vs. none (Control).

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

Underline represents presenting author.
In the control profile, real-time Kt/V (Fig 1a, solid line) closely followed the target line (Fig 1a, dashed line) and was associated with normal P<sub>k</sub> and P<sub>r</sub>. In patients with high access recirculation, real-time Kt/V tracking line deviated widely from the target line (High Recirc Kt/V Profile; Fig 1b, c, d) and remained deviant throughout the treatment session. Fig 1d demonstrates a case wherein the initial low Q<sub>r</sub> provided false impression of normal access function, however increasing Qb resulted in unmasking of high access recirculation, i.e., appearance of High Recirc Kt/V Profile. High access recirculation was confirmed by biochemical methods. Interestingly, all High Recirc Kt/V Profile events were associated with abnormal recirculation values, but not all were associated with elevated P<sub>r</sub>.

Conclusions: Real-time Kt/V tracking profile provides a non-invasive, inexpensive and quick assessment of access recirculation in hemodialysis patients.

FR-PO715

Recurrent Vascular Access Stenosis as a Novel Marker for Cardiovascular Outcome in Hemodialysis Patients Hwo Jin Kim, Hajeong Lee, Dong Ki Kim, Kook-Hwan Oh, Yon Si Um, Curie Ahm, Kwon Wook Joo. Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.

Background: Vascular access (VA) is essential component and its stenosis is a major complication in hemodialysis (HD) patients. Nevertheless, there are few data for outcomes on patients who had recurrent VA stenosis. We have explored the influence of recurrent VA stenosis on cardiovascular (CV) event, patient death, and VA failure.

Methods: This is a single-center, retrospective study. Patients who had VA operation at Seoul National University Hospital between January 2009 and March 2014 were enrolled. Patients who had two or more instances of percutaneous angioplasty or revision operation within 180 days were categorized recurrent group. The primary outcome was CV events, as coronary artery or heart failure or cerebrovascular, and or peripheral vascular events. The secondary outcomes were all-cause mortality (ACM), composite of ACM or CV events, and VA failure. The two groups were compared before and after matching with propensity scores (PSM).

Results: A total of 766 patients (59.7% male, age 59.6 ± 14.3 years) were analyzed. Recurrent group patients (n = 77, 10.1%) were older and had higher underlying CV disease and dyslipidemia. A total 213 patients (14.2% in non-recurrent, 71 in recurrent group) were selected by PSM. During 28.7±15.8 months follow-up, 46 patients (21.6%) had CV outcomes, 30 patients (14.1%) died, and 14 patients (6.6%) experienced vascular access failure. After adjustment, recurrent group was an independent risk factor for CV events (adjusted hazard ratio [HR] 2.66, 95% confidence interval [CI] 1.46–4.86, P < 0.001) and composite of ACM or CV events (adjusted HR 1.99, 95% CI 1.21–3.27, P < 0.007). However, it was not associated with increased ACM and VA failure.

Conclusions: Recurrent VA stenosis was a novel independent risk factor for CV event in HD patients, rather than VA failure. For patients suffered from recurrent vascular stenosis, diligent monitoring should be warranted not only for VA patency but also for CV events.

FR-PO716

Stent Insertion Is an Important Tool in Maintaining Arteriovenous Access Patency Stephen G. Johns,1 Kumar Abayasekara,2 Peter M. Bungay,3 Mario De Nunzio, James E. Kirk,1 John Graham Pollock,3 Peter D. Thurley,3 Paul J. Owen,1 Richard J. Fluck,1 Lindsay J. Chesterton.1 1Nephrology, Royal Derby Hospital; 2Vascular Surgery, Royal Derby Hospital; 3Radiology, Royal Derby Hospital, Derby, United Kingdom.

Background: Definitive access for haemodialysis (HD) remains the cornerstone of optimal dialysis. However, HD patients are becoming older, access attempts more problematic and vein preservation remains critical. Clinical examination and access monitoring enable appropriate, timely, endovascular intervention. Stents may be inserted for recurrent stenosis or after endovascular rupture, but their role remains debatable. We report on our single-centre experience of access surveillance and endovascular intervention, highlighting the role of stent insertion.

Methods: Electronic hospital records were retrospectively analysed in all access-related stents inserted from 2006-2014 by 5 vascular radiologists.

Results: 49 stents were inserted during 45 procedures in 39 patients. 12 had diabetes. Mean age was 64.5±25.5 yrs, median dialysis vintage was 1162±1504 days (range 5-5027). Median time from access creation (82% arteriovenous fistula) to stent insertion was 318±926 days (range 31-3752). 34 stents were inserted peripherally (cephalic arch and distally), the majority in the cephalic arch. Equal numbers of covered and bare-metal stents were inserted. 4 stents were placed in thrombosed access. 7 procedures were due to surveillance alone, a further 8 due to surveillance and pressure/flow problems. 12 stents were inserted for rupture or dissection (overall access procedure complication rate 1%). Median time from first stent to access failure/ceased HD was 333±653 days, assisted by median 2 (range 0-11) further procedures. Treatment for rupture was not associated with significantly shorter access longevity. Only 10 patients’ access failed following follow-up. Our overall HD definitive access prevalence rate was 86-90%.

Conclusions: Appropriate HD access is essential in minimising HD morbidity. We recommend stent insertion for newly-occurring stenosis or rupture during endovascular procedures. Our data suggest that appropriate, judicious stent insertion in an appropriately structured pathway results in access durability and longevity.

FR-PO717

Association of Vascular Access Flow and Volume Status on Fistula Arm by Bio-impedance Analysis in Hemodialysis Patients Joon Jeong,1 Hun Jong Kim,1 Eun jung Ko,1 Younhee Lee.1 1Internal Medicine, CHA Bundang Medical Center, CHA Univ, Seongnam, Korea; 2Internal Medicine, Seoul Buchub Hospital, Seoul, Korea.

Background: Multi-frequency bioimpedance is a tool of body composition measure and can monitor changes in extracellular volume during dialysis. Arterio-venous fistulae(AVF) could potentially affect fluid retention in the arm. We investigated whether multi-frequency bioimpedance could detect AVF stenosis or association of AVF with fluid retention in the AVF arm.

Methods: We measured the extracellular water(ECW) and total body water(TBW) in AVF arm following hemodialysis by multi-frequency bioimpedance(bioxy S10) using an eight-electrode contact technique. We measured AVF flow by transonic ultrasonography using an ultrasound dilution technology (HD 03+) in hemodialysis.

Results: Total 28 patients (male 13 patients) were enrolled and the mean age of patients was 54.89 ± 13.21 years. ECW/TBW ratio of fistula arm was a significantly higher than ECW/TBW ratio of non-fistula arm(0.389 ± 0.01 vs 0.382 ± 0.001, p<0.05). ECW/TBW ratio of fistula arm was a significantly negative correlation with access flow level (mL/min) on fistula(< 0.05). The 5kHz reactance of fistula arm was a significantly positive correlation with access flow level (mL/min) on fistula<0.05).

Conclusions: Absolute and also relative extracellular fluid volumes are increased in the fistula arm of hemodialysis. We thought that extracellular fluid volumes in the fistula arm were associated with access flow level (mL/min) and/or relative fistula stenosis. We suggest that multi-frequency bioimpedance can be a useful assistant tool of vascular access flow measure.

FR-PO718


Background: KDIGO Guidelines recommend post-angioplasty (PTA) lesion should have <30% residual stenosis (RS) and hemodynamic parameters should improve. Access blood flow (ABF) is one of the most used. Primary end point: how post-PTA ABF improvement could predict vascular access (VA) outcome. Secondary: compare doppler ultrasound (DU) and angiography diagnostic accuracy; determine how other factors could predict outcome.

Methods: Prospective study in 80 patients with dysfunctional VA. DU evaluation was performed pre and post-PTA. Several parameters were recorded. Secondary patency verified during first 6 months.

Results: Initial DU in 80 patients; 26 excluded due to abnormalities absence or impossible endovascular approach - final 54. Two thirds male; age 68±15y; VA time 36±29months; initial ABF 537±153ml/min; final ABF 1013±345ml/min. Number and location of stenosis was highly correlated between DU and angiography (Pearson 0.828, p < 0.000). Matching in central vessels. Overall survival 83% at first trimester and 63% at semester; significantly better for fistulas (76%) than grafts (51.7%), p = 0.044. Final angiographic RS > 30% occurred in 14.8% patients, who had significantly better survival, p = 0.038. Initial ABF>500 ml/min and multiple stenosis didn’t affect the outcome (p = 0.189 and p = 0.811). A ~2-fold ABF increase had no significant impact on fistulas survival (p = 0.339) but it was highly significantly associated with worst outcomes in grafts (23.1% versus 73.5%, p = 0.009). VA failure HR was 3.3 for grafts (p = 0.034).

Conclusions: DU diagnostic accuracy is highly correlated with angiography. Although less accurate for central lesions, has a key role due to morphologic and hemodynamic assessment. PTA is a powerful therapy with immediate benefit; however final angiographic RS is not predictive of outcome. Grafts have worst patency, demanding more interventions. PTA is associated with mechanical endolethal injury. Higher ABF induce more turbulent flow that is likely to cause more intraluminal hyperplasia, which could explain the shorter patency, especially in grafts where inflammation is higher.
The degree of OH% was 20.2 ± 7.3% among the MEGA vs. 14.4 ± 7.1% in the CONTR group (Student p: 0.01), representing 4.2 ± 3.2 vs. 2.8 ± 1.6 L of excess fluid (p: 0.03). MEGA patients took an average of 1.7 ± 1.4 vs. 0.8 ± 0.8 (p: 0.002) antihypertensive medications compared to the CONTR patients yet their blood pressure was 156/91 vs 141/78 mmHg (p: 0.03–0.0001). We found no difference in fistula vintage, body mass index, age, inflammatory markers, diabetes status or diuretic use. The odds ratio of overhydration being associated with a megafistula is 5.3 (p: 0.01).

**Conclusions:** There is an association of BCM-measured overhydrated clinical state with the presence of megafistulas; either as an increased volume capacitance or as a potential cause.

FR-PO721

The Observation of the Tunneled Cuffed Catheter Insertion Through Right Innominate Vein in Hemodialysis Patient

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**Background:** The routine vascular access for hemodialysis is often available due to thrombosis and occlusion after frequent cannulation, which leads to an increase in cost and difficulty of catheterization or recanalization. Further catheterization may accelerate the development of occlusion of vascular resources. We inserted cuff catheter through right innominate vein in patients with thrombosis or occlusion of right internal jugular vein and subclavian vein so as to preserve precious vascular access at other parts of body. Here we report our observation of right innominate vein catheterization.

**Methods:** We enrolled patients who had been receiving regular HD in our center and to whom catheter cannot be inserted due to thrombosis or occlusion of internal jugular vein and subclavian vein. We performed cuff catheter insertion by puncturing right innominate vein in 8 patients and recorded their clinical features, lesion position, and efficacy of the treatment.

**Results:** Among the 8 cases, where mean age is 67.6 years (range from 54-78), 3 of them are male and 5 are female. All the patients received central venous catheterization for more than 2 times, with median time of having a catheter for 36 months. The vascular ultrasound and CTA reveals that all of them suffered thrombosis or occlusion of right internal jugular vein and subclavian vein. By puncturing right innominate vein, all the patients’ vascular accesses have been successfully established, with the end of cuff catheter located in the right atrium, superior vena cava(SVC) or SVC/ right atrial junction. No obvious discomfort has been reported, nor did complications such as hematoma and pneumothorax recorded. The mean follow-up period lasts for 12 months, all vascular access of these cases are patency.

**Conclusions:** For HD patients with limited vascular resources such as thrombosis or occlusion of right internal jugular vein and subclavian vein, the application of tunneled cuffed venous catheter through innominate vein has been proved to be safe and effective. It could preserve vascular access by bypassing the stenotic lesion internal jugular vein or subclavian vein, and reduce the incidence of vascular access exhaustion.

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

FR-PO722

Tunneled Hemodialysis Catheter and Hemodialysis Outcomes

Vutran Pasara, Mdlen Knotek. Dept of Medicine, Renal Div, Univ of Zagreb, Merkur Hospital, Zagreb, Croatia.

**Background:** Studies have reported that tunneled dialysis catheter (TDC) is associated with inferior hemodialysis (HD) patient (pt) survival, as compared to arteriovenous fistula (AVF). Since many cofactors may also affect survival of HD pts, it is unclear whether the risk for the worse survival arises from TDC per se, or from associated conditions. Therefore, the aim of this study was to determine the long-term outcome of HD patients, with respect to vascular access (VA).

**Methods:** This retrospective case-control study included all 156 TDC pts with TDC placed from 2010 to 2012 at Clinical Hospital Merkur. Control group consisted of 97 pts dialyzed through AVF. The groups were matched according to dialysis unit and time of VA placement. The site of choice for the placement of TDC was right jugular vein. Kaplan-Meier analysis with logrank test was used to assess pt survival. A multivariate Cox regression analysis was used to determine independent variables associated with the pt survival.

**Results:** Cumulative one-year survival of pts who were dialyzed exclusively through TDC was 86.4 % and of those who were dialyzed exclusively through AVF the survival was 97.1 % (p=0.002). In a multivariate Cox regression analysis, male sex and older age were independently negatively associated with the survival of HD pts, while shorter duration of HD before the creation of the observed VA, hypertensive renal disease and glomerulonephritis were positively associated with survival. TDC turned to be an independent negative risk factor for survival of HD pts (HR 23.037, 95% CI 6.221-85.308).

<table>
<thead>
<tr>
<th>TDC</th>
<th>AVF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age at the initiation of HD (yrs)*</td>
<td>62.08±14.39</td>
<td>63.85±13.23</td>
</tr>
<tr>
<td>Patient age at current VA creation (yrs)*</td>
<td>63.69±14.20</td>
<td>64.01±13.39</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>88/68</td>
<td>64/33</td>
</tr>
<tr>
<td>HD vintage (days)**</td>
<td>658 (154, 1114)</td>
<td>536 (320, 1399)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44.2%</td>
<td>40.2%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>20.5%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>16.7%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>19.9%</td>
<td>20.6%</td>
</tr>
</tbody>
</table>

**mean ± SD; ** median with IQR

**Conclusions:** TDC is an independent negative risk factor for the survival of patients on HD.

**Funding:** Government Support - Non-U.S.
FR-PO723

Carpal Tunnel Syndrome Is Associated with Arteriovenous Fistula in Hemodialysis Patients

Il Young Kim, Min Jung Kim, Joo Hui Kim, Dong Won Lee, Soo Bong Lee, Su Min Park, Jong Man Park, Woo Jin Jung, Sang Heon Song, Eun Young Seong, Harin Rhee, Il Soo Kwak.

Background: Carpal tunnel syndrome (CTS) is associated with various systemic diseases such as rheumatoid arthritis, hypothyroidism, peripheral neuropathy and diabetes mellitus (DM). In hemodialysis patients, several factors can contribute to CTS, including amyloid deposition, generalized fluid retention, increased synovial volume, edema around the nerve, and an ischemic or ‘steal’ effect distal to a dialysis access. This study aimed to evaluate the influence of arteriovenous fistula (AVF) dysfunction on the development of CTS.

Methods: The study included 43 patients (23 male & 20 female) on maintenance hemodialysis via AVF and 97 healthy controls. The median nerves of study population were examined by ultrasonography. Cross-sectional area (CSA) of the median nerve was measured at the distal wrist (CSA-D), and proximal forearm (CSA-P), and wrist-to-forearm ratio (WFR; CSA-P/CSA-D) was calculated for each hand. We also investigated the history of percutaneous transluminal angioplasty (PTA) in them.

Results: The mean age of hemodialysis patients was 60.4 ± 16.0 years. The mean duration on hemodialysis was 48.3 ± 39.6 months. The WFRs in hemodialysis patients were higher than those in healthy controls (1.35 ± 0.47 vs. 1.25 ± 0.26, P < 0.05). The WFRs in patients with a history of PTA were higher than those in patients without a history of PTA (1.46 ± 0.56 vs. 1.23 ± 0.32, P < 0.05).

Conclusions: In maintenance hemodialysis patients, WFR of median nerve was significantly increased in the hand with AVF. Moreover, development of CTS was related not only to AVF itself, but also to AVF function.

FR-PO724

Factors Affecting Patency of Haemodialysis Arterio-Venous Fistulae and Grafts


Background: Arterio-venous fistulae (AVF) are the preferred access for haemodialysis (HD), and where these cannot be created, arterio-venous grafts (AVGs) are the next best option. AVFs/AVGs however, not uncommonly fail to mature. The causes of this are varied, but loss of patency due to thrombosis and/or significant stenoses are major causes. We investigated the factors affecting patency of AVFs/AVGs in order to identify whether there were any characteristics which were predictive of this.

Methods: All AVFs/AVGs created in our unit between 2006 and 2014 were reviewed. Reasons for loss of primary patency were obtained from the dialysis access database. Characteristics reviewed were age, gender, co-morbidity score, diabetes status and site of AVF. Patients were grouped as follows: patency <30 days, patency <90 days, patency >90 days and patency >365 days.

Results: There were 1897 (66.8%) AVFs and 251 (34.2%) AVGs created. 649 (32.2%) of AVFs were lower arm, all the AVGs were upper arm, or lower limb. 1346 (62%) were male. The main reasons for AVF loss were clotting/stenosed vessels in 78% of cases. There was no association between ethnicity or gender with regard to patency rates. Other variables are shown in table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;30 days</th>
<th>&lt;90 days</th>
<th>&gt;90 days</th>
<th>&gt;365 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVF % pat</td>
<td>88%</td>
<td>70%</td>
<td>78%</td>
<td>71%</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>72 years</td>
<td>72 years</td>
<td>78 years</td>
<td>71 years</td>
</tr>
<tr>
<td>AVG % pat</td>
<td>88%</td>
<td>75%</td>
<td>62%</td>
<td>35%</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>70.5 years</td>
<td>70.5 years</td>
<td>66.8 years</td>
<td>67.1 years</td>
</tr>
<tr>
<td>Diabetic</td>
<td>31%</td>
<td>36%</td>
<td>35%</td>
<td>34%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Davies Co-morbidity score</th>
<th>0 (no co-morbidities)</th>
<th>1 (1-2 co-morbidities)</th>
<th>2 (3 or more co-morbidities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.3%</td>
<td>13.1%</td>
<td>14.4%</td>
<td>14.3%</td>
</tr>
<tr>
<td>60.3%</td>
<td>62.3%</td>
<td>60.9%</td>
<td>64.2%</td>
</tr>
<tr>
<td>11%</td>
<td>13.1%</td>
<td>13.8%</td>
<td>13.0%</td>
</tr>
</tbody>
</table>

Conclusions: We did not find any definite predictive factors for loss of primary patency in the variables we studied. In particular, co-morbidity score, age and diabetes showed no association with poorer outcomes. There is quite a significant ‘drop off’ in primary patency at 12 months. In the majority of cases, this was due to thrombosis of the HD access. This highlights the importance of close surveillance, as measures to maintain patency (surgical or radiological) are more likely to be required in this period.

FR-PO725

Drug-Eluting Stents versus Bare-Metal Stents During Percutaneous Coronary Intervention in Patients on Dialysis

Tara I. Chang, Maria E. Montez-Rath, Mark A. Hlatky, Wolfgang C. Winkelmayer.

Background: In patients undergoing percutaneous coronary intervention (PCI), drug-eluting stents (DES) reduce the need for repeat revascularization (RR) compared with bare-metal stents (BMS). The effects on death and MI are more controversial, with mixed results from observational studies and generally null results from clinical trials. However, few previous studies have focused patients with end-stage renal disease (ESRD). We compared the effectiveness of DES with BMS in a representative cohort of US patients on dialysis.

Methods: Using the US Renal Data System, we identified 36,117 patients on dialysis with Medicare Parts A+B who had PCI with stenting after DES became available in the US (4/23/03 – 12/31/10). We used propensity-score matching (PSM) and inverse probability of treatment weighting (IPTW) with Cox regression to examine the association of DES versus BMS on the following 1-year outcomes: death, death or MI, and death, MI or RR. Due to concerns about residual indication bias, we conducted a second, temporal analysis that leveraged the large changes in the prevalence of DES use during three distinct eras: Transitional (4/23/03 – 6/30/04); Liberal (7/1/04 – 12/31/06); and Selective (1/1/07 – 12/31/10).

Results: In the PSM and IPTW analyses, DES was associated with lower risks of all three outcomes compared with BMS.

Table: Hazard ratios (95% CI) for DES vs BMS

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Death/MI</th>
<th>Death/MI/RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSM</td>
<td>0.82 (0.78-0.86)</td>
<td>0.84 (0.91-0.87)</td>
<td>0.87 (0.84-0.91)</td>
</tr>
<tr>
<td>IPTW</td>
<td>0.82 (0.79-0.85)</td>
<td>0.85 (0.82-0.87)</td>
<td>0.88 (0.85-0.90)</td>
</tr>
</tbody>
</table>

DEU var used by era: Transitional=56%, Liberal=85%, and Selective=62%. In the temporal analysis, outcomes in the Liberal DES era were significantly better than in the Transitional Era, but not consistently better than in the Selective Era.

Conclusions: Adoption of DES for PCI was associated with improved outcomes in US patients with ESRD on dialysis.
FR-PO726

Eleven Year Trends in Myocardial Infarction and Stroke in the Incident and Prevalent Dialysis Population

Len A. Usvyat,1 Len A. Usvyat,1 Ann Mooney,1
1Medicaturated Medical Office, Fresenius Medical Care North America, Waltham, MA; 2Div of Nephrology, Massachusetts General Hospital, Boston, MA.

Background: Myocardial infarction (MI) and cerebrovascular (CVA) events are highly prevalent in the chronic dialysis population. We aimed to quantify the annual incidence and trends of MI and CVA events from 2004 to 2014 in a large dialysis population.

Methods: We analyzed >600,000 patients receiving chronic dialysis from a large dialysis provider from January 2004 to December 2014. For each calendar year, we calculated the incidence of MI and CVA (event per 100 patient years) identified by ICD9 code for the population in the first 120 days of chronic dialysis (incident period) and in the subsequent period after the first 120 days (prevalent period). Linear regression was used to quantify statistically significant trends in MI and CVA rate of the eleven year period.

Results: Over an eleven year period in the incident population, the mean incidence of MI and CVA was 3.3 and 3.2 events per 100 patient years respectively. Among the prevalent population, the mean incidence of MI and CVA was 1.9 and 1.8 events per 100 patient years respectively. Using linear regression models, the incidence of MI and CVA was found to decrease by 0.14 (p=0.05) and 0.11 (p=0.0009) per year among incident patients. Similarly, the incidence of MI and CVA was found to decrease by 0.06 (p=0.0007) and 0.10 (p=0.0001) per year among prevalent patients. See Figure 1.

Conclusions: Both MI and CVA rates are decreasing among incident and prevalent dialysis populations over the past eleven years.

FR-PO727

Relationship of Ticagrelor Dose and Platelet Reactivity in Patients with End Stage Renal Disease on Hemodialysis

Jin sue Kim,1 Taec won Lee,2 Chun-Gyoo Ihm,1 Sang ho Lee,3 Se yun Lee,4 Shin yeong Lee,5 Yu ho Lee,6 Kyung-hwan Jeong.
1Internal Medicine, KyungHee Univ School of Medicine, Seoul, Korea.

Background: In our previous study, ticagrelor has superiority on platelet inhibition than clopidogrel in patients with end stage renal disease (ESRD) on hemodialysis (HD). One study compared two doses of ticagrelor (90 or 60mg) and placebo, reported that ticagrelor significantly reduced the risk of cardiovascular death, MI, or stroke and increased the risk of bleeding. The rate of bleeding is more frequent in 90mg group. We hypothesized there was some relationship between ticagrelor dose and platelet inhibition. We investigated efficacy and safety of standard and low dose ticagrelor, and clopidogrel in ESRD patients on HD.

Methods: In a single-center, prospective, randomized study, 50 ESRD patients were enrolled in the study: mean age 67.5 years old, 56% male, 47% had diabetes and 28% had pre-existing coronary artery disease. There were 236 patients were enrolled in the study: mean age 67.5 years old, 56% male, 47% had diabetes and 28% had pre-existing coronary artery disease. There were 88 enrolled Td levels (13% of all measured) in 52 patients. In univariate analysis, high UFR and dialysis vintage, but not IDH or IDWG, were associated with TnI variability. In multivariate analysis, both high UFR (p=0.02) and dialysis vintage (p=0.01) explained TnI variability. The intraclass correlation coefficient was found to be 1%, suggesting that the observed variability is within and not between subjects, with session related parameters being more important than inter-individual differences.

Conclusions: Low dose ticagrelor may result in greater platelet inhibition than clopidogrel in ESRD patients on HD. Further studies with large number and various doses of medicine are needed.

FR-PO728

Prognostic Accuracy of Serial versus Single Troponin Measurements in Hemodialysis Patients

Table/Divasovs,1 Allan Snidersman,1 Ahsan Alam.1
1Div of Nephrology, McGill Univ Health Center, Montreal, QC, Canada; 2Div of General Internal Medicine, Geneva Univ Hospitals, Geneva, GE, Switzerland; 3Div of Cardiology, McGill Univ Health Center, Montreal, QC, Canada.

Background: Cardiac troponin I (Tnl) elevation in stable patients receiving chronic hemodialysis (HD) is associated with increased mortality. The frequency of measuring Tnl to determine risk is not yet known. This study aimed to assess whether using serial Tnl measurements improves the predictive accuracy for mortality compared with a single measurement.

Methods: Pre-treatment Tnl levels were measured in 130 stable HD patients monthly for 3 consecutive months. A value above the laboratory reference range (>0.06 mg/L) was considered to be elevated. To assess the prognostic accuracy of Tnl measurement, three different approaches were used to determine high risk: i) only the first month’s value was elevated; ii) at least one of three monthly Tnl values were elevated; iii) at least two of the three monthly Tnl values were elevated. All the patients were followed-up for 12 months. Multivariate Cox proportional hazard analysis was used to examine the association of Tnl elevation with the outcomes of mortality or a composite of mortality with major cardiovascular events. The performance of each Tnl classification method was compared using net reclassification index (NRI).

Results: Of 130 patients, 36 had an elevated Tnl in the first month, 44 had at least one elevated Tnl value, and 26 had 2-3 elevated Tnl values. The composite outcome was significantly higher in patients with an elevated Tnl compared with patients who had normal Tnl levels, regardless of the method used [HR (1.36 (1.76-6.3) ii) 3.55 (95% CI 1.68-7.52) iii) 3.81 (95% CI 1.83-7.94)]. Similar associations were seen with the outcome of mortality alone. Patients classified as high risk using at least one elevated serial Tnl measure were associated with a NRI of 0.035, as compared with a single Tnl measurement. If patients were classified as high risk using at least two elevated Tnl values, the NRI was -0.072.

Conclusions: Serial Tnl measurements are associated with only marginal improvement in predicting mortality or MACES as compared with a single Tnl measurement.

Funding: Government Support - Non-U.S.

FR-PO729

High Ultrafiltration Rates Are Associated with Increased Troponin Levels in Stable Hemodialysis Patients

Table/Avasovs,1 Allan Snidersman,2 Murray L. Vasilevsky,1 Ahsan Alam.1
1Div of Nephrology, McGill Univ Health Center, Montreal, QC, Canada; 2Div of General Internal Medicine, Geneva Univ Hospitals, Geneva, GE, Switzerland; 3Div of Cardiology, McGill Univ Health Center, Montreal, QC, Canada.

Background: An elevated troponin level in asymptomatic patients on hemodialysis is associated with a higher risk of mortality and cardiovascular events. The underlying mechanisms for this association has not been elucidated. The objective of this study was to assess whether intra- and inter-dialytic parameters are associated with higher troponin I (Tnl) levels.

Methods: Stable chronic hemodialysis patients at 2 tertiary care centers were enrolled in this observational study. Td levels were measured with monthly bloods for three consecutive months. Tnl was measured by immunoassay and was considered to be elevated if it exceeded the laboratory reference range (>0.06 mg/L). We examined the association of the dialysis vintage, session duration, intradialytic hypertension (IDH), high ultrafiltration rate (UFR), defined as a UFR ≥ 12.4 ml/kg/h, and interdialytic weight gain (IDWG) using a mixed linear fixed effects model for repeated measures.

Results: 236 patients were enrolled in the study: mean age 67.5 years old, 56% male, 47% had diabetes and 28% had pre-existing coronary artery disease. There were 88 enrolled Td levels (13% of all measured) in 52 patients. In univariate analysis, high UFR and dialysis vintage, but not IDH or IDWG, were associated with Tnl variability. In multivariate analysis, both high UFR (p=0.02) and dialysis vintage (p=0.01) explained Tnl variability. The intraclass correlation coefficient was found to be 1%, suggesting that the observed variability is within and not between subjects, with session related parameters being more important than inter-individual differences.

Conclusions: In this observational study we identify potentially modifiable factors associated with Tnl elevation. Strategies to prevent hemodialysis-induced myocardial injury may include efforts to avoid excessive ultrafiltration, minimize IDWG, or offer more frequent dialysis, but these need to be validated by interventional studies.

Funding: Government Support - Non-U.S.

FR-PO730

Prognostic Value of High-Sensitivity Troponin T in Stable Dialysis Patients

Titi Chen, Angela Makris. Dept of Nephrology, Liverpool Hospital, Liverpool, New South Wales, Australia.

Background: We evaluated the prognostic value of high-sensitivity cardiac troponin T (hs-TNT) in predicting myocardial infarction (MI) and death in dialysis patients after 4 years.

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

529A
Methods: A retrospective review of a cohort of 354 hemodialysis (HD, 254) and peritoneal dialysis (PD, 109) patients was followed up to 4 years after baseline hs-cTNT. All-cause mortality, cardiac mortality and new MI were assessed.

Results: The median hs-cTNT was 60 ng/L (interquartile range IQR 38-105 ng/L) with no observed difference between HD and PD patients (P=0.18). Patients dying (n=148) had a higher baseline hs-cTNT (median 90 vs 50 ng/L, P<0.001). Similar trends were observed for both HD and PD subgroups. Patients with cardiac mortality (n=25) had a higher baseline hs-cTNT compared with non-cardiac mortality (121 vs 75.5 ng/L, P=0.013). These trends were only observed in the HD subgroup. Patients with a new MI (n=65) had no difference in their baseline hs-cTNT (66 vs 59 ng/L, P=0.064) compared to controls. The group was divided into quartiles based on hs-cTNT. Incremental increase in mortality (P<0.001), cardiac mortality (P=0.001) and MI (P=0.033) were observed with increasing hs-cTNT quartiles. Similar trends were observed for both HD and PD subgroups except MI in the PD subgroup. For every increase of 25 ng/L in hs-cTNT, the unadjusted hazard ratio (HR) was 1.094 for cardiac mortality (P=0.043, 95%CI 1.001-1.192), 1.123 for MI (P=0.000, 95%CI 1.053-1.198). The adjusted HR for MI was 1.107 (P=0.018, 95%CI 1.101-1.205). Kaplan-Meier curves demonstrated increasing hs-cTNT quartiles was associated with an increase in the incidence of cardiac mortality (P=0.014) and MI (P=0.013) but not overall mortality. 178 patients had hs-cTNT repeated at 4 years. There was a significant increase in hs-cTNT from a baseline of 60 ng/L (IQR, 38-105 ng/L) to a 4-year concentration of 64 ng/L (IQR, 42-104 ng/L) (P=0.000). This was true for both patients with (P=0.008) or without (P=0.001) new MI. Similar trends were observed for both HD and PD subgroup analysis.

Conclusions: hs-cTNT has a useful role in predicting all-cause mortality, cardiac mortality and MI in stable dialysis population. There was an increase in hs-cTNT level over a 4-year period.

FR-PO731
Temporal Trends in Myocardial Infarction Incidence and 30-Day Mortality in U.S. Dialysis Patients Charles A. Herzog,1 Keri L. Monda,2 Anne C. Beaubrun,2 Wolfgang C. Winkelmayer,3 Til Stürmer,3 Allan J. Collins,1 Akhtar Ashfaq,4 Kenneth J. Rothman,5 David T. Gilbertson.1

Background: Acute myocardial infarction (MI) is a catastrophic event in dialysis pts. Few data exist on current MI hospitalization rates. We assessed trends in type of MI (ST elevation MI [STEMI], non-ST-elevation MI [NSTEMI], and unclassifiable MI [other]), and death rates by type of MI in 2005-2011.

Methods: Using Medicare claims data, we created yearly cohorts of dialysis pts point prevalent on January 1 of each year 2005-2011. We assessed STEMI, NSTEMI, and other MI hospitalization rates, and calculated annualized 30-day death rates following MI.

Results: In 2005 there were 10,275 NSTEMI, 1,892 STEMI, and 1,918 other MI vs 2011, 16,235 NSTEMI, 2,169 STEMI, and 1,634 other MI. Demographics: mean age 67; 5% < 45, and 6% > 84 yrs; 47% female; 48% white, 32% black; 55% ESRD from DM. While overall MI rate increased slightly from 2005-2011 (80.1/1,000 PY in 2005 vs 91.2 in 2011), STEMI and other MI decreased by 44% and 29% respectively, while NSTEMI increased by 31%. Short term mortality was relatively unchanged for NSTEMI (295 deaths/1000 PY), increased slightly for STEMI (495/1000 PY in 2005 to 565/1000 PY in 2011), and was highest following other MI (881/1000 PY in 2005 and 915/1000 PY in 2011).

Conclusions: In the recent treatment era there has been little change in either rates of overall MI hospitalization or 30-day mortality. The increase in NSTEMI rates may be due to greater utilization of more sensitive cardiac biomarkers (cardiac troponins) for MI diagnosis. MI remains a catastrophic event for dialysis pts. Aggressive interventions to reduce the burden of ischemic heart disease and to improve its prognosis in dialysis pts are warranted.

FR-PO732
Risk of Acute Coronary Events and Coronary Interventions for Overweight and Obese Patients versus Normal Weight Patients Undergoing Dialysis – A National Study Austin G. Stock,1,2 Mohamed Elsayed,1,2 Muhammad Umar Sharif,1,2 John P. Ferguson.2

Background: Although elevated body mass index (BMI) is associated with increased risk of cardiovascular events in the general population, it is suggested that the converse may hold true for patients on dialysis.

Methods: We tested this hypothesis in a national cohort of 1,072,737 incident Medicare-eligible US patients, who began dialysis between 5/1995 and 12/2008. Hospitalizations attributed to first myocardial infarction (MI) [ICD 9 codes; 410] and major coronary interventions (coronary angioplasty, stent, and coronary bypass surgery) following first MI were obtained from the US Renal Data System. Multivariable Cox regression compared hazard ratios [HR] of MI and subsequent coronary interventions among BMI categories.

Results: The adjusted HR of MI was highest for overweight patients and lowest for morbidly obese patients, decreasing significantly with increasing BMI category. Overweight patients were significantly more likely to receive a coronary intervention post-MI compared to normal weight individuals but this benefit did not extend to morbidly obese or underweight patients.

Conclusions: In contrast to the general population, higher BMI is associated with lower risk of major coronary events in US dialysis patients suggesting a protective effect. Furthermore, access to coronary interventions following a major coronary event is not equal across BMI categories.

FR-PO733
Propensity-Based Comparison of Haemodialysis and Peritoneal Dialysis with Risk of Haemorrhagic and Ischaemic Stroke Among New Dialysis Patients Austin G. Stock,1,2 Mohamed Elsayed,1,2 Muhammad Umar Sharif,1,2 John P. Ferguson.2

Background: The risk of stroke is between 6-10 fold higher in dialysis patients compared to the general population. It is hypothesised that the choice of dialysis modality at initiation may influence the risk of stroke.

Methods: We tested this hypothesis in a national cohort of 1,097,747 US patients (n=86,168 on PD) who were Medicare eligible and began dialysis between 5/1995 to 12/2010 and followed until 9/2011. Hospitalizations attributed to first Haemorrhagic Stroke (H-CVA) and Ischaemic stroke (I-CVA) were obtained from the US Renal Data System files and merged with data from the medical evidence, treatment history and mortality files. Multivariable Cox regression compared the hazards ratio [HR] of H-CVA and I-CVA for PD versus HD with a propensity-matched intent-to-treat (ITT) approach and as-treated analysis. Patients were censored at transplantation, death, recovery of kidney function, or end of study (Sept 2011). Approval was received from University Hospitals Ethics Committee.

Results: The adjusted PD/HD HRs for first hospitalized H-CVA using the intent-to-treat model was 0.89 (0.83,0.95) and this decreased from 0.73 (0.61,0.87) in the period 1995-1998 to 0.64 (0.51,0.80) in the period 2007-2010. In contrast, overall HRs for I-CVA were 1.15 (1.12-1.18) and this decreased from 1.20 (1.13-1.27) in the period 1995-1998 to 1.06 (0.97-1.15) in the period 2007-2010. The as-treated model suggested more favourable outcomes for H-CVA with overall HR of 0.61 (0.57,0.67) and for I-CVA with a HR 0.96 (0.90-1.02) in 2007-2010 period. Patients who switched from PD to HD or HD to PD had significantly higher HR of H-CVA, while patients who switched from PD to HD had higher HR of I-CVA.

Conclusions: PD and HD contribute differentially to the overall risk of I-CVA and H-CVA among new dialysis patients. While PD is similar to HD with regard to hazards of I-CVA, it appears to protect against the hazard of H-CVA. These associations should be taken into consideration when choosing treatment options for new dialysis patients.

Funding: Other NIH Support - Health Research Board & Irish Heart Foundation
FR-P0734

Predictors of Sudden Cardiac Death in Hemodialysis Patients with and without Previous Arrhythmia – Results from a Multinational Cohort

Viviane Calice-Silva, 1 Stephan Thijsse, 2 Xiaoliang Ye, 2 Aileen Grassmann, 3 Daniele Marcelli, 2 Bernard J. Canuda, 2 Peter Kotanko, 1 Roberto Pecotis-Filho, 1
1Pontifícia Unv Católica do Paraná, Brazil; 2Renal Research Inst; 3Fresenius Medical Care, Germany.

Background: Cardiac dysfunction, rapid electrolyte shifts and high ultrafiltration rates during hemodialysis (HD) are associated with increased vulnerability to arrhythmogenic events. Patients with previous arrhythmia (ARR) are at a higher risk of sudden cardiac death (SCD – Herzog et al, 2011). Our aim was to analyze predictors of SCD in HD patients with and without previous ARR.

Methods: Incident HD patients from the Monitoring Dialysis Outcomes (MONDO) cohort who received in-center treatment between 1/2006-12/2011 and survived at least 90 days on HD were included and followed until 12/2012. Causes of death were classified as SCD according ICD-10/ICD-9. Patients with comorbidity or prior hospitalization due to ARR and/or ARR predisposition were identified. Cox proportional hazards models were constructed to explore associations between baseline parameters and SCD.

Results: We studied 19,129 patients (16 countries), 7,538 patients with complete data were included in the models, 613 died of SCD. Mean age 62.7±15.5 years, 58.1% male, 48.4% diabetics. Age, ischemic heart disease, albumin, serum sodium, interdialytic weight gain in % of post-HD weight and pre-HD-systolic blood pressure were identified as predictors of death in both subgroups. Distinct predictors are shown below. The complete table is not provided in the document.

Table 1: Predictors of SCD in patients with (N=158) and without ARR history and/or predisposition (N=455).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCD with ARR</th>
<th>Hazard Ratio(±SE) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bicarbonate [mmol/L]</td>
<td>0.07 (0.04)</td>
<td>0.04</td>
</tr>
<tr>
<td>Leukocytes [1000/mm 3 ]</td>
<td>0.02 (0.005)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin [g/dl]</td>
<td>0.11 (0.04)</td>
<td>0.005</td>
</tr>
<tr>
<td>Dialysate sodium [mmol/L]</td>
<td>0.095 (0.03)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Catechol as vascular access</td>
<td>0.41 (0.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: Despite the small sample size, some predictors of SCD seem to differ depending on the presence or absence of arrhythmia history or predisposition. These findings may assist the identification of patients at high risk for SCD. Further studies have to be done to corroborate these results.

FR-P0735

The Risks of Acute Health Events After Incident Atrial Fibrillation in Older Hemodialysis Patients

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Background: Limited data exist about whether incident atrial fibrillation/flutter (AF) impacts the risks of major acute health events in patients with ESRD undergoing hemodialysis (HD).

Methods: From the US Renal Data System, we studied older (≥67 years) adults with ≥2 years of uninterrupted Medicare A&F coverage before starting HD (2006-11) and no known AF prior to ESRD. Incident AF was ascertained from ICD-9 diagnosis codes (427.3x) in inpatient claims. We used extended Cox regression to adjust for sociodemographic characteristics and key comorbidities to estimate hazard ratios (HR [95% confidence intervals]) for death, ischemic stroke, myocardial infarction (MI), and hip fracture (as a negative control outcome). AF was treated as a time-varying covariate, with time since first AF diagnosis further categorized as ≤30, 31-90, and >90 days. Patients were censored at time of kidney transplant or end of data (12/31/2011).

Results: We identified 85,377 eligible HD patients; 16.7% developed incident AF and 58.2% died during follow-up. Incident AF was associated with higher adjusted mortality: 8-fold higher during the first 30 days (HR=8.2 [7.9-8.6]), 4-fold higher between 31-90 days (HR=4.2 [4.0-4.4]), and 2-fold higher beyond 90 days after AF diagnosis (HR=2.2 [2.1-2.2]). Incident AF also increased the adjusted rate of ischemic stroke 1.5-2.5-fold during the first 30 days (HR=2.1 [1.6-2.7]), 31-90 days (HR=2.5 [2.0-3.0]), and beyond 90 days (HR=1.5 [1.3-1.7]). Quantitatively similar findings were obtained for MI. However, the adjusted rate of hip fracture was only marginally increased following AF diagnosis (~30 days: 1.0 [0.7-1.6], 31-90 days: 1.4 [1.0-1.8], >90 days: 1.2 [1.1-1.4]). All associations were attenuated when requiring incident AF to be indicated as principal discharge diagnosis.

Conclusions: While AF was independently associated with higher risks of ischemic stroke, MI, and hip fracture in older ESRD patients on HD, it was more strongly associated with excess all-cause mortality.

Funding: NIDDK Support.

FR-P0736

The CRASH-ILR Study: Half a Million Hours of Continuous ECG Monitoring in a Hemodialysis Population

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Background: Sudden cardiac death (SCD) may cause ≥5% of all hemodialysis (HD) patient deaths. Multiple potential mechanisms may contribute to the risk of life-threatening arrhythmias in this population. The CardioRenal Arrhythmia Study in Hemodialysis has continuously monitored patients using an Implantable Loop Recorder (ILR) for more than 350,000 hours.

Methods: A total of 158 patients (60% male) aged 67±12 years on established HD for 39±44 months with various etiologies of CKD (diabetes 37%, hypertension 23%) were included. A total of 568±8 events were ascertained from the CRASH-ILR database (Medtronic, MN, USA). Patients were monitored for a minimum of 2 years after enrollment. Mortality was due to SCD in 50% of patients.

Results: Patients were monitored for a minimum of 2 years after enrollment. Mortality was due to SCD in half of the study population. Mortality was high, but this was due to SCD as an expected end-of-life event in 5 out of 6 patients.

Funding: Pharmaceutical Company Support - Medtronic, MN, USA

FR-P0737

Revisiting Ultrafiltration Rate (UFR), Treatment Time (TT) and Mortality in Thrice Weekly Hemodialysis

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Background: UFR and TT are two potentially modifiable practices for improving outcomes in HD. UFR > 13 ml/kg/hr has been associated with higher mortality. We re-examined this association, focusing on the effect of higher UFR at TT ≥ 4 hours, as longer TT has been claimed to be ‘protective’, even though TT > 4 hours is logistically difficult to implement in the prevailing US practice setting.

Methods: Using recently available national data from CROWNWeb (CW), we analyzed 233,759 adults on thrice-weekly, in-center HD. Baseline CW data was extracted from June 2012. Patients were followed through December 31, 2013. Cox regression was used to examine the association between UFR (calculated as the intradialytic weight loss / TT and expressed in ml/kg post HD-weight/hr) and mortality, adjusting for demographics, co-morbidities, dialysis vintage, interdialytic weight gain (IDWG) and dialysis dose (Kt/V), stratified by TT. Average follow-up was approx 1 year.

Results: Individuals receiving TT ≥ 240 were younger, more likely to be black and male, and had larger BMI. In both strata of TT (< 240 and ≥ 240) those patients with UFR > 13 tended to be younger, non-black race, have a lower BMI, longer HD vintage, higher Kt/V, and higher IDWG than patients with UFR < 13. Congestive heart failure was more prevalent in patients with UFR ≤ 13 regardless of TT. In both strata of TT, patients with a UFR >13 had higher hazard of mortality, with a larger risk found in those with TT ≥ 240.

Conclusions: A higher UFR (>13) was associated with higher mortality irrespective of TT category. The association was surprisingly strong among those receiving longer TT. In the US, longer TT is prescribed in order to achieve small solute targets (confounding-by-indication) and not necessarily to lower the UFR, as high UFR is a consequence of high IDWG and the average shorter TT.

Funding: NIDDK Support.

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

531A
FR-PO738
Sudden Death and Dialysate Potassium in Hemodialysis: Results from the Dialysis Outcomes and Practices Patterns Study (DOPPS)

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Background: Sudden death (SD) is common in hemodialysis (HD) patients. We investigated trends in dialysate (DK) and pre-dialysis serum (SK) potassium across the Dialysis Outcomes and Practices Patterns Study (DOPPS) phases 1-5 (1996-2015) and evaluated whether the risk of SD is higher with lower DK.

Methods: 67,263 patients in 21 countries were studied. Instrumental variable methods were used to model the effect of DK on SK. Adjusted Cox regression was used to test the associations of baseline DK and SK with all-cause death, and an arrhythmia composite (AC) of SD or arrhythmia-related hospitalization.

Results: In the US, DK and SK (mEq/L) have been stable over time (70% DK=2, 25% DK=3; mean±StdDev SK=4.7±0.7). In Europe, DK has increased (currently 15% DK=1, 1.5, 45% DK=2, 33% DK=3) while mean SK has decreased from 5.2 to 4.9. SK was only 0.08 mEq/L higher per 1 mEq/L higher DK. SK ≥ 6 (ref 4.9-5.4) was associated with death (HR=1.12, 95% CI: 1.05-1.19) and AC (HR=1.17, 1.04-1.33). Compared to DK=2, DK=3 was not associated with death or AC, overall or at any level of SK (Fig).

Conclusions: In this large international cohort, SK was associated with elevated risk of SD, but risk of SD was similar for DK=2 or DK=3 across SK levels. Because DK had minimal influence on pre-dialysis SK, efforts to limit dietary K intake may be a more effective strategy to lessen the risks associated with high SK.

FR-PO739
Acute Health Events and the Risk of Incident Atrial Fibrillation in Older Patients Undergoing Maintenance Hemodialysis

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Background: Acute health events might increase the risk of developing atrial fibrillation (AF). We examined the incidence of new onset AF relative to several acute events in patients with end-stage renal disease (ESRD) initiating hemodialysis (HD).

Methods: From the USRDS, we studied older (67+ years) patients with 2 years of Medicare A&B coverage prior to initiating HD (2006-11) who had no documented diagnosis of AF, or claims indicating ischemic stroke, myocardial infarction (MI), or hip fracture prior to ESRD. We used time-varying Cox regression to estimate adjusted hazard ratios for incident AF relative to the acute events of interest, adjusted for socio-demographics and baseline comorbidities. The incidence of AF after either an acute MI, or hip fracture was modeled in time-varying fashion, during the periods of <30, 30-90, and >90 days after the acute event. Patients were censored at kidney transplantation or end of database (12/31/2011).

Results: 85,377 older HD patients met the inclusion criteria. The risk of AF was approximately doubled in the 90 days after an ischemic stroke, and remained elevated thereafter (Table). The risk of AF after an acute MI followed a similar pattern, with highest risk in the 30 days after the MI. The risk of AF after hip fracture followed a slightly different pattern, peaking between 30 and 90 days after the event, with no significant late hazard after 90 days. These associations were essentially unchanged when requiring that the acute health event be reported as principal diagnosis.

Conclusions: The risk of incident AF among patients on HD is increased after a stroke, MI, or hip fracture. Risks were highest in the first 90 days after the event, and remained elevated >90 days after an ischemic stroke or MI, but not after a hip fracture.

FR-PO740
Arrhythmias as a Potential Cause of Dizziness and Syncope in Patients with End-Stage Renal Disease

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Background: It is unknown how often arrhythmias underlie dizziness and syncope in end-stage renal disease. We launched a study to implant subcutaneous loop recorders for their estimation.

Methods: Data is shown for 40 patients (62.4±8.2 years [mean±SD]), range 39 to 78 y, 26 M with stage 4 or 5 renal failure and F of >2 months. Main kidney diseases were diabetic (18), polycystic disease (8) and chronic glomerulonephritis (6). One patient was pre-dialytic, five had peritoneal dialysis, and rest were on hemodialysis. Median time since the start of dialysis was 1.6 years. Seven patients (18%) had either chronic or paroxysmal atrial fibrillation (AF) prior to the implantation of the recorder, being in line with published data.

Results: During the F of 14±7 months, recorder revealed bradycardia in six (15%) patients with an R-R arrest of >5.0 sec with a max. of 9.0 sec; two patients with symptoms thus far received a pacemaker. AF occurred in 21 (53%) patients. The median time to detect new AF was 235 days. Four patients (10%) had non-sustained ventricular tachycardia unknown before the recorder data.

Conclusions: Arrhythmias are more typical than estimated in patients with severe kidney disease. Particularly, symptomatic bradycardia is relatively common and can be easily treated with a pacemaker. AF is three times more common than known before. These findings may change diagnostics and treatment of dizziness in these patients.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO741
Blood Pressure and Risk of Cardiovascular Events Among Hemodialysis Patients: The CRIC Study

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Background: Among hemodialysis (HD) patients, previous studies have reported a U-shaped association between systolic blood pressure (SBP) and risk of mortality. However, the shape of the association between SBP and risk of cardiovascular events (CVD) is not well characterized.

Methods: We studied participants on HD in the Chronic Renal Insufficiency Study (CRIC). SBP was measured at the dialysis unit (“dialysis-unit SBP”, N=803) and at the CRIC study visit (“out-of-dialysis-unit SBP”, N=326). We studied the association of SBP
with time to adjudicated CVD (defined as heart failure, myocardial infarction, peripheral vascular disease and stroke), adjusting for demographics, diabetes, smoking, BMI, prior CVD, k/τ, serum albumin and hemoglobin.

**Results:** Mean age was 60 (±11) years, 42% were women and 64% were Black. There were a total of 121 CVD events over a median time of 1.15 years. The association between dialysis-unit-SBP was U-shaped, with the greatest risk of CVD at the highest and lowest quartiles of dialysis-unit-SBP.

Conversely, the association between out-of-dialysis-unit-SBP was linear, with the highest quartile having greater than 2-fold risk of CVD than the lowest quartile.

**Conclusions:** Among HD patients, the association of SBP measured in the dialysis unit with CVD is U-shaped, while the association of SBP measured outside the dialysis unit with CVD is linear, similar to what has been reported for mortality ( Bansal et al., Hypertension 2015). Targeting SBP measured outside the dialysis unit may improve CVD outcomes in HD patients.

**Funding:** NIDDK Support

**FR-PO742**

**Intradialytic Dynamics of Systolic Blood Pressure in Hemodialysis Patients Based on Survival Status**

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**Background:** Low systolic blood pressure (SBP) before dialysis has been reported to be associated with worsened outcomes in hemodialysis (HD) patients (Maddux et al.,ASN 2014). However, the dynamics of intradialytic SBP and patient outcomes have not been well characterized in this population. We aimed to understand the dynamics of SBP during dialysis in patients based on their survival status.

**Methods:** We studied HD patients treated at FMCNA facilities in 2014 with recorded intradialytic SBP. The intradialytic mean intradialytic SBP was computed in 20 minute intervals during dialysis per patient per treatment; all treatments were then averaged per patient and thereafter for the entire cohort. Patient survival was recorded in 2014 (i.e. "alive" or "died").

**Results:** 31,053 and 2,835 patients (338,771 and 20,380 measurements respectively) were used for calculation of the mean SBP at each 20 minute time point in “alive” and “died” groups, respectively. The results show that the mean intradialytic SBP declines to a similar extent in both patients who died and survived, but patients that died exhibited a lower initial predialysis SBP and greater overall intradialytic variability.

**Conclusions:** These investigations of the dynamics of intradialytic SBP identify increased variability during dialysis and lower starting levels in patients who died. In both patients who were alive and died, SBP declines to a similar extent throughout dialysis. These findings suggest that lower predialysis SBP and intradialytic variability may be associated with mortality in the HD population.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

**FR-PO743**

Choosing the Right Analysis of Repeated Events for Clinical Trials in Dialysis

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**Background:** Cardiovascular (CV) events are a leading cause of morbidity and mortality in hemodialysis (HD) patients. There is a paucity of randomized clinical trials (RCT) in nephrology and fewer positive ones, perhaps due to incorrect choice of endpoints or inadequate power. We simulated RCTs with repeated CV events and competing non-CV death to determine how different analytic methods affected study power (sample size).

**Methods:** We simulated 1000 RCTs of 1100 patients, with frequency and timing of CV events (CV death, MI, stroke, PVD, CV revascularization, and leg amputations) based on real observations in an Ontario HD administrative cohort (n=9647) from 2004-2011. In simulations, patients were randomized to placebo or a treatment with a known effect and censored at 4 years or non-CV death. We analyzed this data with 1) a Cox model for time to first event, 2) a model with non-CV death as a competing risk, 3) a negative binomial (NB) model and 4) several adaptations of the Cox model for repeated events (e.g., Wei, Lin and Weisfeldt, WLW). To check for 2 potential problems (finding a difference when there was none and missing a true difference), we ran simulations in 2 scenarios: 1) with zero treatment effect, we calculated the false positive rate; 2) when the treatment delayed CV events by 33%, we calculated the true positive rate (power) based on the 1000 simulations.

**Results:** In the source (real) data, 45% of patients had >2 CV events; the overall CV event rate was 0.26/yr. When there was no effect of treatment, the NB model had a false positive rate of 11%; for all other models, it was the expected 5%. For the time to first event, competing risk and the WLW marginal Cox model, power was similar (72%) and notably higher than for the remaining Cox-type models (52%-61%).

**Conclusions:** The WLW Cox model for repeated events was as powerful as models for time to first event but has the advantage of assessing the impact on all (repeated) events a patient experiences. This highlights the importance of choosing the appropriate analytic method when designing a clinical trial in HD patients to maximize the likelihood of both a positive and a meaningful result.

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

**FR-PO744**

Routine Predialysis Measurements of Systolic Blood Pressure Are Higher Than Predialysis Standardized Measurements of Systolic Blood Pressure

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**Background:** Measurement of blood pressure (BP) in the dialysis unit does not follow American Heart Association recommendations. We determined the differences between systolic BP (SBP) measured in routine practice versus a standardized procedure.

**Methods:** The Blood Pressure in Dialysis Study is a pilot, multicenter, randomized clinical trial that assesses treatment of hypertensive HD patients to two BP targets. Measurement of predialysis SBP is done after 5 minutes rest, 3 readings 1 minute apart, with attention to cuff size, placement and patient positioning. We compared the 2-week averaged routine predialysis SBP (RDUSBP) taken immediately prior to enrollment with the 2-week averaged predialysis standardized SBP (SDUSBP) in the first 2 weeks of baseline. The within subject variability in SBP, (s^2) was estimated by mixed linear regression.

**Results:** We studied 186 patients. The two week averaged RDUSBP was a mean (SD) 10.3 (16.6) mm Hg higher than 2 week averaged SDUSBP (p<0.001).

**Conclusions:** RDUSBP was ± 5 mm Hg of the SDUSBP in 20% of patients, 6-15 mm Hg higher in 30%, 15-25 mm Hg higher in 17%, >25 mm Hg higher in 17% and >5 lower in 16%. Estimating s^2 for RDUSBP (15.7^2) and SDUSBP (19.6^2) were not significantly different, (p=0.99). Differences between RDUSBP and SDUSBP tended to be greatest among those with a high body mass index.

**Conclusions:** SDUSBP were, on average, 10 mm Hg lower than RDUSBP measured in the dialysis unit. Reliance on routine BP measurements may lead to over-treating hypertensive HD patients. More attention to the measurement of BP in dialysis unit is needed.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc.
Comparison of Central and Peripheral Blood Pressure in Predicting Cardiovascular Surrogates in Patients with End-Stage Renal Disease

Younkyung Kee, Shin, Elaine-1,2

Patients with ESRD. These values did not provide additional information beyond pBP in predicting CV risk in (cSBP) and central pulse pressure (cPP) was 140.2 ±28.9 and 57.1±22.8 mmHg. Mean intima-media thickness, pulse wave velocity (PWV) and left ventricular mass index (LVMI).

We investigated the association between cBP and CV surrogates compared with peripheral blood pressure (pBP) in patients with ESRD.

Methods: A cohort of 92 ESRD patients from the Cardiovascular and Metabolic Disease Etiology Research Center between November 2013 and February 2015 was selected. cBP was measured by SphygmoCor noninvasively. CV surrogates were determined by carotid Etiology Research Center between November 2013 and February 2015 was selected. cBP and pSBP were independently associated with PWV ( ß=0.381, P<0.001; ß=0.353, P<0.001) and LVMI (adj ß=0.411; P<0.001; ß=0.497, P=0.001) after adjustment for confounding factors. However, there were no significant differences in the predictive value of cSBP and pSBP for estimating PWV (adjusted R², 0.494 vs. 0.431, P=0.07) and LVMI (adj R², 0.215 vs. 0.220, P=0.885). No significant difference was found for cPP and pPP for predicting PWV (adj R², 0.451 vs. 0.429, P=0.546) and LVMI (adj R², 0.220 vs. 0.265, P=0.320).

Conclusions: Although cBP values were closely associated with CV surrogates, these values did not provide additional information beyond pBP in predicting CV risk in patients with ESRD.

FR-PO746

Early Mortality in Hemodialysis Patients Anticoagulated for Atrial Fibrillation

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Background: Atrial fibrillation (AF) is prevalent in the Hemodialysis (HD) population and portends a high mortality rate. AF also causes embolic stroke and is treated with lifelong oral anticoagulation (OAT). We have previously shown early increased mortality in HD patients receiving OAT without significant stroke reduction (JASN, 25:690A, 2014). It is unclear why OAT increased early mortality in these patients. To address this question, we queried the USRDS for unique risk factors for mortality in this cohort.

Methods: All incident adult HD cases from the USRDS for 2005-2008 were queried for demographics, access type, risk factors before dialysis, and mortality. Data were derived from ICD9 and CPT codes, or Form 2728. Proportional hazards models were used to estimate the hazard ratio (HR) for death within 90 days.

Results: 34,522 incident HD patients with AF were identified, 6,664 (19.3%) of whom died within 90 days of the initiation of dialysis. For the entire group, demographics showed: 83.1% Caucasian, mean age 57.4 years (SD=9.0), and 41.5% female. When controlling for diabetes, cardiomyopathy TIA, pulmonary hypertension, aortic stenosis, CHF, MI, congestive heart failure, obesity, cardiac device, age and access type the HR for death in the OAT group was 1.10 (95% CI 1.04 - 1.16). The 1-, 2- and 3-month mortality rates were 6%, 15% and 22% in OAT and 5%, 12% and 19% in non-OAT, respectively. Major bleeding episodes were not significantly associated with mortality (p=0.59).

Conclusions: OAT therapy in HD patients with AF may contribute to the increased death rate observed during the first 90 days of dialysis, but not apparently due to bleeding. We speculate that OAT use may be associated with non-hemorrhagic complications that may lead to increased mortality in the HD population. Defining this level of clinical detail is beyond the scope of an administrative dataset like the USRDS. Future studies addressing non-hemorrhagic effects of OAT may provide new insights on possible causes of early mortality in these patients.

Funding: Private Foundation Support

FR-PO747

Reduced Temperature Hemodialysis Augments Dialysis Induced Improvement of Cardiac High Energy Phosphate Levels

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Background: 31P magnetic resonance spectroscopy (31P-MRS) measures levels of high-energy phosphate compounds, including phosphocreatine (PCr) and adenosine triphosphate (ATP). PCr/ATP ratios which evaluates cardiac metabolic activity. PCr/βATP is significantly reduced in end stage renal disease (ESRD) patients. Reducing hemodialysate temperature by 1°C improves intradialytic hypotension and cardiac function. The effects of reduced temperature dialysis on cardiac metabolism have not been evaluated. We compared myocardial function and PCr/βATP ratios levels before and after normothermic and reduced temperature dialysis.

Methods: Twelve hemodialysis patients underwent cardiac MRI and 31P-MRS of their left ventricle (LV) within 30 minutes before (pre) and after (post) three normothermic (36.5°C) and three reduced temperature (35.0°C) maintenance dialysis sessions. Left ventricular dimensions were measured by an observer blinded to intervention. PCr/β ATP were calculated from 31P-MR spectra.

Results: Reduced temperature hemodialysis was significantly associated with increased predialysis LV ejection fraction (36.5°C:64.5%±6.5 vs 35.0°C:69.0%±6.1, p=0.03). At both temperatures, hemodialysis was significantly associated with increased mean LV ejection fraction (36.5°C:Pre 64.5%±6.7 Post 70.9%±6.8, p=0.002;35.0°C: Pre 69.0%±6.1, post 74.2%±6.3, p=0.01). PCr/βATP was significantly higher after normothermic (p=0.01) and reduced temperature hemodialysis (p=0.003). Mean increase in PCr/βATP was higher after reduced temperature compared to normothermic hemodialysis (+51.5% vs +74.1%, respectively).

Conclusions: Hemodialysis is associated with improved myocardial metabolic activity and this effect may be amplified by reducing the dialysate temperature even in patients with no intradialytic hypotension.
Conclusions: CHA2DS2-Vasc score is useful for predicting the risk of outcomes in non-dialysis subjects with AF and dialysis subjects without AF. Dialysis patients with AF already had very high scores and the risk grading by CHA2DS2-Vasc score is not useful.

Funding: Government Support - Non-U.S.

FR-PO749

Post Stroke In-Hospital Disability Deterioration and Mortality of Community-Onset Stroke in Patients with and without End-Stage Renal Disease

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Background: Increasing evidence suggests that end-stage renal disease is associated with higher risk and severity of cerebrovascular disease. However, the risk factors for post stroke disability and mortality is not clear. We examined the association between risk factors including dialysis treatment and disability deterioration and mortality during hospital stay of community-onset stroke.

Methods: The Japanese Diagnosis Procedure Combination database includes administrative claims and discharge abstract data of about 50% of all acute-care inpatients in Japan. Using this database, we extracted data of inpatients age ≥20 years old, admitted within 3 days after community-onset stroke between July 2010 and March 2013. Disability level was divided into modified Rankin Scale (mRS) 0-1, 2-3, 4-5, and 6 (death). Disability deterioration was defined as an increase in disability level. The odds ratio (OR) for in-hospital disability deterioration and mortality was calculated using a logistic regression model.

Results: Out of 438,569 patients, 7,633 (1.7%) had dialysis therapy. The median length of stay was 21 and 20 days for patients with and without dialysis, respectively. During the hospital stay, there were 101,924 (23.0%) disability deterioration and 46,029 (10.5%) death. The patients with dialysis had higher rate of disability deterioration (26.7%) and mortality (13.0%) compared to those without. After adjustment with age, gender, BMI, mRS, Activities of Daily Living, smoking habits, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, heart failure, peripheral arterial disease, cerebrovascular complications, antipatelet, anticoagulant, and thrombolytic medications, multivariate-adjusted ORs of dialysis for deterioration of disability was 1.57 (95%CI 1.48-1.66) and in-hospital mortality was 1.72 (95%CI 1.59-1.86).

Conclusions: Dialysis treatment was an independent risk factor for in-hospital disability deterioration and mortality of community-onset stroke.

FR-PO750

Proportion of Treatments with Low Systolic Blood Pressure and Short Term Mortality in Incident Hemodialysis Patients

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Background: Prior studies have associated low mean predialysis systolic blood pressures (preSBP) with increased 120 day risk for mortality in incident hemodialysis (iHD) patients (Maddux et al., ASN 2014). This study aimed to investigate how the percent (%) of low mean preSBP during the prior weeks’ hemodialysis treatments affects the risk of mortality in iHD patients (Maddux et al., ASN 2014). This study aimed to investigate how the percent (%) of low mean preSBP during the prior weeks’ hemodialysis (HD) treatments affects the mortality of incident hemodialysis (iHD) patients. In the present study, we compared it among PD, HD, and ND patients.

Methods: For this study, 56,525 iHD patients at Fresenius Medical Care North America (FMCNA) clinics were investigated from 1/1/2004 to 12/31/2010. From the first date of outpatient chronic dialysis (FDD), the % of the prior weeks’ mean preSBP <110 mmHg was calculated for the first 4 months of HD. Mortality risk in the following week (7 days) was analyzed by the % of the prior week’s mean preSBP <110 mmHg at weeks 2, 4, 6, 12, and 16 from FDD.

Results: We observed that the short term risk for mortality in the following week increases in iHD patients as the % of the prior week’s mean preSBP <110 mmHg increases at weeks 2, 4, and 6 from the FDD; the risk for mortality was found to be the greatest at week 2 and was slightly reduced by week 6. Conversely, by week 12 and 16 from the FDD, the % of the prior week’s mean preSBP <110 mmHg was not found to be related with the risk of mortality in the next week.

Conclusions: This study demonstrates that increases in the % of low mean preSBP during the prior weeks’ hemodialysis (HD) treatments is associated with heightened short term risks of mortality during the first 6 weeks of iHD, but not during weeks 12 and 16 from the FDD.

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FR-PO751

The Possibility of Faster Progression of Brain Atrophy in Patients on Peritoneal Dialysis Compared with Hemodialysis

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Background: Brain atrophy has been reported in chronic kidney disease (CKD) patients, especially in hemodialysis (HD) patients. Recently, we reported faster decline in normalized gray matter volume (GMV) in peritoneal dialysis (PD) patients compared with non-dialysis-dependent CKD (ND) patients (Tsuruya, et al. Am J Kidney Dis, 2015). However, it has not been reported on the comparison of the progression rate of brain atrophy between PD and HD patients. In the present study, we compared it among HD, PD, and ND patients.

Methods: A total of 151 patients of 38 PD patients aged 60 ± 12 years (men 23, diabetes 11), 24 HD patients aged 64 ± 6 years (men 18, diabetes 9), and 89 ND patients (CKD stage 3a, 34; stage 3b, 31; stages 4-5, 24) were recruited and underwent MRI scanning at baseline and after two years. T1-weighted MRI images were analyzed with statistical parametric mapping software. Total gray matter, total white matter, and cerebrospinal fluid were segmented and each volume was quantified. Normalized GMV was calculated as percentage of intracranial volume to normalize for head size variability. We compared the annual change in normalized GMV among CKD stages.

Results: Annual change in normalized GMV was significantly higher in PD patients than other CKD patients. This finding remained significant even after adjustment for potential confounding factors.

Conclusions: Progression of brain atrophy is significantly higher in PD patients than other CKD patients including HD patients, independent of age, gender, diabetes, and blood pressure level.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
535A
FR-PO752

In Centre Nocturnal Haemodialysis: Improving Outcomes and Experience for Patients Matthew P.M. Graham-Brown,1,2 Darren Robert Churchward,1,2 Alice C. Smith,1,2 Richard J. Baines,1,2 James O. Burton.1,2

Background: Extended periods of haemodialysis (HD) improve patient outcomes. Home HD schedules can deliver extended dialysis, but there are patient and physician related barriers that make home therapies impossible for many. We explored in centre nocturnal HD (INHD) as a method of offering extended periods of HD to patients unsuitable for home therapy.

Methods: Ten prevalent HD patients switched from standard HD (3x4 hours) to INHD (3x5 hours) for four months. Mean ultrafiltration (UF) volumes (L), relative UF rates (mL/kg/hour) and absolute UF rates (mL/hour) were calculated. Additional, biochemical and haematological data, data on dialysis adequacy and blood pressure control were collected. Changes in quality of life (QoL) were assessed using SF12, EQ-5D and the Hospital Anxiety and Depression Score (HADS) questionnaires.

Results: Seven patients completed four months of INHD. Mean dialysis time per session was 355 minutes (SD±43.92). Mean total UF volume increased from 2.0±5.1L to 2.6±3.4L (p=0.02), but there was a reduction in absolute mean UF rates from 513±121 mL/hour on standard dialysis, to 356±66 mL/hour on INHD (p=0.03) and a decrease in mean relative UF rates from 6.5±1.7mL/kg/hr to 4.6±1.6mL/kg/hr (p=0.03). Adequacy measured by urea reduction ratio improved from 72±2% to 80±3% (p=0.001), with a trend towards improved phosphate control to within therapeutic targets, from 7±3±0mmol/L to 1.2±0.2mmol/L (p=0.08). In addition, there were improvements in all QoL scores. Mean EQ-5D-5L analogue score improved from 48±16.9 to 72±13.2 (p<0.001), with a trend towards improved SF12 physical component score from 31±1.3 to 48±10.1 (p=0.05).

Conclusions: Despite an increase in total UF volume, extended INHD led to an overall reduction in UF rate that has been shown to abrogate HD induced cardiac injury. Other physiological benefits included improved urea clearance and better phosphate control. There were also significant improvements in patient QoL measures over four months.

FR-PO753

Association of Multiple Strokes in Mortality in Incident Hemodialysis Patients: An Application of Multistate Model to Determine Transition Probabilities James W. Wetmore,1 Jonathan D. Mahnken,2 Milind A. Phadnis.3

1Medicine, Div of Nephrology, Hennepin County Medical Center, Minneapolis, MN; 2Biostatistics, Univ of Kansas Medical Center, Kansas City, KS.

Background: Little is known about the effect of multiple, or subsequent, ischemic strokes in patients receiving dialysis.

Methods: A retrospective cohort study of incident hemodialysis patients with Medicare Parts A and B coverage who had experienced a first ischemic stroke was performed. A multistate model with Cox proportional hazards was used to predict transition probabilities from first ischemic stroke to subsequent stroke or to death. Demographic and clinical factors associated with the respective transition probabilities were determined.

Results: Overall, 12,054 individuals (mean age 69.7 years, 41.3% male, 53.0% Caucasian and 34.0% African-American) experienced a first stroke. Female sex was associated with an increased risk of having a subsequent stroke (adjusted hazard ratio 1.37, 95% confidence intervals 1.20 – 1.56, P = 0.0001), African-Americans, as compared to Caucasians, had lower likelihood of dying after a first stroke (0.87, 0.77 – 0.98, P = 0.0001). A subsequent stroke trended towards having a higher likelihood of transitioning to death compared to a first new stroke on dialysis (1.72, 0.96 – 3.09, P = 0.071). The probability of transitioning to a subsequent stroke increased over the first 6 months, peaked at approximately 12 months, then declined steadily over time (Figure). When a subsequent stroke occurs at 24 months, probability of survival dropped >15%, in absolute terms, from 0.254 to 0.196, with substantial drops observed at subsequent time points such that the probability of survival was more than halved.

Conclusions: Likelihood of subsequent ischemic stroke and of survival in dialysis patients appears to vary by sex and race.
FR-PO755
The Relation Between Sclerostin, Peripheral Vascular Calcification, and Cardiovascular Events in ESRD Patients
Young Jo Ju, Sang Yoon Lim, Myung-gyu Kim, Sang-Kyung Jo, Won-Yong Cho. Nephrology, Korea Univ Hospital, Seoul.

Background: Sclerostin, a negative regulator of Wnt signaling pathway produced by osteocyte, is a potent regulator of bone metabolism and a novel candidate for the bone vascular axis in chronic kidney disease patients. Although sclerostin is known as an inhibitor of vascular calcification, recent studies demonstrated conflicting results about the association between sclerostin and cardiovascular events or mortality. In this study we tested the association between sclerostin, peripheral vascular calcification, and cardiovascular events in end stage renal disease (ESRD) patient starting peritoneal dialysis.

Methods: In this prospective study, we included 45 ESRD patients admitted to Korea University Anam Hospital for starting peritoneal dialysis. Circulating sclerostin level was measured in all patients before the start of peritoneal dialysis. Simple vascular calcification score (SVCS) was measured using plain radiographic films of both hands and the pelvis. Median follow up period was 36 months.

Results: Higher sclerostin level was associated with male sex, diabetes mellitus, higher left ventricle (LV) mass index, and lower LV fractional shortening in univariate analysis. ESRD patients with severe vascular calcification (SVCS ≥3) had significantly higher prevalence of diabetes mellitus. They had lower peak wave velocity, alkaline phosphatase, and lower cholesterol levels, LV fractional shortening and in multivariate analysis, the presence of diabetes mellitus (OR, 4.59, p=0.023), lower cholesterol levels (OR, 0.94, p=0.032) were independent risk factors predicting severe vascular calcifications. In multivariate Cox regression model, higher pulse wave velocity (HR 1.3, p=0.028) was a significant predictor for cardiovascular events. In addition higher sclerostin group (HR 9.82, p=0.094) and lower albumin levels (HR 0.23, p=0.081) display a strong tendency of increased cardiovascular events.

Conclusions: This study showed the important role of sclerostin in the development of vascular calcification and cardiovascular events in PD patients. Longer term follow up with larger sample size will be needed to clarify this issue.

FR-PO756
Use of Anticoagulants in Patients with Atrial Fibrillation and End Stage Renal Disease: A Study of Real World Data
Lloyd P. Haskell,1 Chris Knoll,2 Patrick Ryan,1 Zhong Yuan,3 1Cardiovascular, Janssen R and D, Raritan, NJ; 2Epidemiology, Janssen R and D, Titusville, NJ.

Background: End stage renal disease (ESRD) in patients with atrial fibrillation (AF) is a significant cause of morbidity and mortality. While these patients are at high risk for stroke, there are limited data with respect to use of anticoagulants in clinical practice and current guidelines are not clear on how to manage them.

Methods: US-based, four large healthcare databases (Truven MarketScan Commercial Claims/Encounters [CCAE], Medicare Supplemental [MDCR], Medicaid [MDCD]) and Optum Clinformatics [Optum]) were used to establish cohorts of patients with AF and ESRD, who were identified using ICD-9 codes. The first encounter with evidence of both conditions during the inception period of 2010-2012 was the index date; patients must have had at least 1 year enrolment prior to and after the index date to be eligible for the study. The use of anticoagulants was examined during the follow-up period.

Results: Table 1 shows patient demographics and use of anticoagulants by data source. As expected, the privately-insured patient populations (CCAE and Optum) as well as the Medicaid population (MDCD) were younger as compared with the Medicare eligible population (MDCR). Across study cohorts, approximately 37% to 40% of patients with AF and ESRD received at least one dispensing of warfarin, with the exception of the Medicaid population [MDCD].

Conclusion: Mortality rates decrease substantially once patients initiate HD. After approximately one year on HD, mortality remains consistent in all groups, but remains lower for those with higher albumin, younger age and black race. Diabetes appears to not affect mortality. Since only patients starting in an outpatient setting were included, selection bias may apply differently to the patient groups.

Table 1: Use of Anticoagulants in Patients with AF and ESRD

<table>
<thead>
<tr>
<th>Datasource</th>
<th>N</th>
<th>Mean Age [S.D.]</th>
<th>Male, %</th>
<th>Novel Oral Anticoagulants</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>3650</td>
<td>56 [7.7]</td>
<td>66.2%</td>
<td>2.5%</td>
<td>37.7%</td>
</tr>
<tr>
<td>Medicare</td>
<td>9866</td>
<td>77 [7.7]</td>
<td>59.7%</td>
<td>3.4%</td>
<td>40.1%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>5663</td>
<td>64 [3.7]</td>
<td>41.6%</td>
<td>0.6%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Optum</td>
<td>2825</td>
<td>65 [12.4]</td>
<td>66.8%</td>
<td>4.1%</td>
<td>37.5%</td>
</tr>
</tbody>
</table>

Conclusions: Less than 40% of patients with AF and ESRD received anticoagulant therapy. As these are high risk patients, anticoagulant therapy may be underutilized. Further research is necessary to investigate clinical outcomes associated with anticoagulation in these patients.
FR-PO759
Survival in Elderly on Dialysis and Impact of Institutionalization
Amarpali Brar, David Kau, Moro O. Sallifu, Mary C. Mallapallil. Renal, SUNY Downstate, Brooklyn, NY.

Background: We hypothesized that in the very elderly dialysis patients in the United States, institutionalization in nursing homes would increase mortality in addition to age alone.

Methods: Data was obtained from the U.S. Renal Data System. Incident dialysis patients from 2001 to 2008 above the age of 70 were included. Follow-up period was from incident dialysis date to either death or last follow up on September 30, 2009. Patients above 70 were categorized into four groups according to age as 70-75 years, 76-80 years, 81-85 years, greater than 85 years and further divided into institutionalized and non-institutionalized.

Results: A total of 349,440 patients were identified above the age of 70 years at the time of initiation of dialysis. Major causes of end stage renal disease were diabetes, hypertension, glomerulonephritis, cystic kidney disease, and urological mean cause. Mean survival for non institutionalised patients was 3.15 ± 0.01 years for those between 70-75 years of age, 2.55±0.01 years for 76-80 years of age, 2.12±0.01 years for 81-85 years of age and 1.64±0.01 years for those above 85 years at the time of initiation of dialysis respectively. For institutionalized patients, mean survival was significantly lower, 1.71±0.03 years for 70-75 years old, 1.44±0.02 years for 75-80 years old, 1.25±0.02 years for 81-85 years old and more than 85 years and 1.04±0.02 years for > 85 years age group, p<0.0001. The oldest group in non-institutionalized over the age of 85 years had a similar survival as the institutionalized ESRD patients 70-75 years old.

Conclusions: There was increased mortality in institutionalized elderly patients as compared to non institutionalised elderly patients in the same age group. Keeping with the increased frailty and decreased benefits of therapies in the very elderly especially in those with additional co-morbidities besides age, palliative and end of life care should be considered.

FR-PO760
Geriatric Nutritional Risk Index Is a Simple Predictor of Mortality in Chronic Hemodialysis Patients
Kosaku Nitta, Ken Tsuchiya. Dept of Medicine, Kidney Center, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan.

Background: Malnutrition is common in hemodialysis (HD) patients, and is associated with increasing risk of mortality. The geriatric nutritional risk index (GNRI) has been developed as a tool to assess the nutritional risk. The aim of the present study was to examine the reliability of the GNRI as a mortality predictor in a Japanese HD cohort.

Methods: We prospectively examined the GNRI of 332 maintenance HD patients aged 65.4 ± 13.2 years, 213 males, and followed up them for 36 months. The patients were divided into quartiles (Q) according to GNRI values (Q1: <91.6, Q2: 91.7-97.0, Q3: 97.1-102.2, Q4: >102.3). Predictors for all-cause mortality were examined using Kaplan-Meier and Cox proportional-hazards analyses.

Results: The GNRI presented a normal distribution. During the follow-up period of 36 months, a total of 76 patients died. The overall mortality at the end of the 3-year observational period was 22.3%. At the 3-year follow-up period, Kaplan-Meier survival rates for all-cause mortality were 72.3%, 79.3%, 84.9%, and 92.6% in Q1, Q2, Q3, and Q4, respectively (p = 0.0067). Multivariate Cox proportional-hazards analysis demonstrated that the GNRI was a significant predictor of adjusted all-cause mortality (HR 0.958; CI 0.929–0.980, p < 0.001).

Conclusions: The results of the present study demonstrate that the GNRI is a strong predictor of overall mortality in HD patients. However, cardiovascular mortality was not associated with GNRI values, and did not differ among the GNRI quartiles. The GNRI score can be considered a simple and reliable marker of predictor for mortality risk in Japanese HD patients.

FR-PO761
Frailty and Clinical Outcomes in Chronic Dialysis Patients
Eun jung Ko,1 Hyen Jeong.1 1Internal Medicine, CHA Bundang Medical Center; Seongnam, Republic of Korea; 2Internal Medicine, CHA Gumi Medical Center; Gumi, Republic of Korea.

Background: Frailty is a biological syndrome of decreased reserve and resistance to stressors and is independently associated with mortality and hospitalization in the general population. We investigated the relationship between frailty and clinical outcomes in chronic dialysis patients.

Methods: In this prospective study, 1,658 patients receiving chronic dialysis were enrolled. Chronic dialysis was defined as dialysis for more than 6 months. Of the 1,658 patients, 1,255 received hemodialysis. The remainder received peritoneal dialysis. Frayed’s criteria for frailty as modified by Woods et al. was used. A trained interviewer asked study participants about 5 frailty stereotypes (slowness, weakness, exhaustion, shrinking, and physical inactivity) using the RAND 36-item Short Form.

Results: The mean age was 55.2±11.9, and 55.2% were male. Overall, 577 (34.8 %) patients met the study definition of frailty. Another 757 (45.7%) patients were pre-frail.

Table 1 shows the prevalence of frailty and its components by age group. During the 30-month follow-up period, 607 patients (79 non-frail, 249 pre-frail, and 279 frail) were hospitalized; and 87 patients (10 non-frail, 24 pre-frail, and 53 frail) died (p<0.0001). Frailty was strongly associated with hospitalization (adjusted hazard ratio [HR] 1.30, 95% CI 1.4 to 2.3) and mortality (HR 2.37, 95% CI 1.11 to 5.02) in multivariate analysis. The relationship between frailty and hospitalization was strongest among patients age 40 to 49, with a HR of 3.02 (95% CI 1.48 to 6.20).

Table 1. The prevalence of frailty and its components by age.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Frail, %</th>
<th>Pre-frail, %</th>
<th>Sloowness/Weakness, %</th>
<th>Exhaustion, %</th>
<th>Inactivity, %</th>
<th>Shrinking, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>21.1</td>
<td>57.9</td>
<td>33.0</td>
<td>60.8</td>
<td>58.3</td>
<td>13.7</td>
</tr>
<tr>
<td>40-49</td>
<td>20.6</td>
<td>55.9</td>
<td>40.9</td>
<td>60.7</td>
<td>45.6</td>
<td>12.9</td>
</tr>
<tr>
<td>50-59</td>
<td>32.8</td>
<td>47.2</td>
<td>35.2</td>
<td>53.4</td>
<td>34.2</td>
<td>8.9</td>
</tr>
<tr>
<td>60-69</td>
<td>38.0</td>
<td>41.0</td>
<td>35.6</td>
<td>34.0</td>
<td>35.6</td>
<td>10.1</td>
</tr>
<tr>
<td>≥ 70</td>
<td>63.8</td>
<td>26.5</td>
<td>30.6</td>
<td>26.0</td>
<td>50.6</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Conclusions: We found a high prevalence of frailty in chronic dialysis patients across all age groups. The risk of hospitalization and mortality in the 30-month follow-up period significantly increased in frail chronic dialysis patients.

FR-PO762
Outcomes of Early Initiation of Dialysis in Elderly Patients with End Stage Renal Disease: A Propensity-Matched Analysis of a Prospective Cohort Study
Jae Yoon Park,1 Kyung Don Yoo,1 Jeonghwae Lee,2 Dong Ki Kim,1 Kwon Wook Joo,1 Shin-Wook Kang,1 Chul Woo Yang,1 Yong-Lim Kim,1 Chun Soo Lim,1 Yon Su Kim,1 Jung Pyo Lee.1 1Seoul National Univ College of Medicine, Seoul, Korea; 2Hallym Univ Hanyang Sacred Heart Hospital, Seoul, Korea; Yongdusan College of Medicine, Seoul, Korea; The Catholic Univ of Korea College of Medicine, Seoul, Korea; Kyungpook Univ National School of Medicine, Daegu, Korea.

Background: The optimal timing for initiating dialysis in end-stage renal disease (ESRD) remains controversial, especially in elderly patients. We therefore investigated the effect of dialysis initiation timing on clinical outcomes in elderly patients with ESRD.

Methods: A total of 665 patients aged equal or over 65 years who started dialysis from August 2008 to February 2015 were enrolled in Clinical Research Center for End Stage Renal Disease cohort study in Korea. They were divided into 2 groups based on the median estimated glomerular filtration rate, which was 8.85 mL/min/1.73m². The primary outcome was patient survival and the secondary outcomes were cardiovascular events and Kidney Disease Quality of Life Short Form 36 (KDQOL-36) score.

Results: Overall cumulative survival rates were lower in early initiation group (Log-rank P<0.001). However, the survival rates showed no significant difference after matching propensity score. Additionally, early initiation of dialysis was not associated with survival rates after adjustment for age, sex, Charlson comorbidity index, hemoglobin, serum albumin, serum calcium and phosphorus level. Although the early initiation group showed lower physical component summary in KDQOL-36 at 3 months after dialysis, the difference of the scores was not significant at 12 months after dialysis.

Conclusions: Early initiation of dialysis was not associated with prognosis in elderly patients with ESRD. The physical functioning was worse for 3 months after dialysis but it became similar to late initiation of dialysis at 1 year after dialysis.
FR-PO763

1- and 2-Year Mortality Prediction Models for Patients Starting Chronic Dialysis
Mikko Haapio,1 Jaakko Helve,1 Carola Gronhagen-Riska,1,2 Patrik Finne,1,2 1Nephrology, Univ of Helsinki and Helsinki Univ Hospital, Helsinki, Finland; 2Finnish Registry for Kidney Diseases, Helsinki, Finland.

Background: Mortality risk of patients with end-stage renal disease (ESRD) is highly elevated compared to patients without ESRD. Taking into account our limited nephrological care resources and the simultaneously increasing number of ESRD patients there is a great need for means of mortality risk estimation to assist both in individualized patient care as well as in sound use of resources. Some mortality prediction models already exist, but many have shown a lack of comprehensiveness in data or in patient recruitment in their development.

Methods: Our objective was to design a prediction model for 1- and 2-year all-cause mortality in patients starting chronic renal replacement therapy. In addition, we aimed to build an easy-to-apply model consisting of only a few variables. We used the comprehensive data of the Finnish Registry for Kidney Diseases with complete coverage of Finnish ESRD patients. Model training group included all incident adult patients who started chronic dialysis in Finland from 1 January 2000 to 31 December 2008 (n=4335). The external validation cohort consisted of all those who started dialysis from 1 January 2009 to 31 December 2012 (n=1706). Prediction algorithms for 1- and 2-year mortality were developed using multivariate logistic regression with stepwise selection of variables. Our primary analyses included 32 variables, from which the most important ones were selected.

Results: Both final prognostic models, including only 6-7 variables, showed adequate discrimination (c-statistic 0.77 and 0.74 for 1- and 2-year mortality, respectively). Because of a significantly lower mortality in the newer (validation) cohort, both models somewhat overestimated mortality risk.

Conclusions: Mortality prediction algorithms could be more widely implemented into clinical treatment-planning of ESRD patients. Our prediction models perform sufficiently and are convenient to use, and could assist in individualized risk-stratification and, furthermore, in equal and fair sharing of limited health care resources.

FR-PO764

Comorbid Burden at Dialysis Initiation and Mortality: A Retrospective Cohort Study
Alvyn Titus Gomez,1 Bryce A. Kibert,1 Talal A. Alfaahdhel,2 Brenda Hennemlagn,3 Karthik T. Tunnenkore,1 1Medicine, Dalhousie Univ, Halifax, NS, Canada; 2Medicine, Univ of Toronto, Toronto, ON, Canada; 3Medicine, Univ of Calgary, Calgary, AB, Canada.

Background: Contemporary assessments of the validity and prognostic value of comorbidity indices in dialysis are lacking. We sought to assess the validity of two comorbidity indices used for dialysis patients and to determine if a high degree of comorbidity was associated with mortality.

Methods: We conducted a retrospective cohort study of incident chronic dialysis patients in a tertiary care institute from 2006-2013. The Charlson Comorbidity Index (CCI) and End-Stage Renal Disease Comorbidity Index (ESRD-CI) were calculated in all patients at dialysis initiation. These indices combine individual medical conditions into an overall score. Comorbid conditions were ascertained using electronic records. The primary outcome was all-cause mortality.

Results: The cohort consisted of 771 patients. Most were male (62%) and Caucasian (91%). Patients had a high prevalence of diabetes (48%) and history of myocardial infarction (31%). The c-index was 0.61 for the CCI, and 0.63 for the ESRD-CI. In an adjusted analysis, ESRD-CI scores of 4, 5 and ≥6 were associated with a similar mortality risk (Table 1). There was a small increased mortality risk for CCI scores of 4, 5 and ≥6.

Conclusions: The CCI and ESRD-CI had a limited ability to discriminate risk of death for incident dialysis patients. Although a higher comorbidity burden was associated with an increased mortality risk compared to the absence of both.

Table 1. Multivariable Cox survival analysis for the ESRD-CI and CCI

<table>
<thead>
<tr>
<th>End-Stage Renal Disease Comorbidity Index</th>
<th>Score</th>
<th>Relative Hazard [95% Confidence Interval]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/1 Reference</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>2</td>
<td>1.63</td>
<td>[1.12 to 2.36]</td>
</tr>
<tr>
<td>3</td>
<td>1.28</td>
<td>[0.84 to 1.91]</td>
</tr>
<tr>
<td>4</td>
<td>1.95</td>
<td>[1.34 to 2.85]</td>
</tr>
<tr>
<td>5</td>
<td>1.89</td>
<td>[1.25 to 2.36]</td>
</tr>
<tr>
<td>≥6</td>
<td>1.99</td>
<td>[1.41 to 2.81]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Charlson Comorbidity Index</th>
<th>Score</th>
<th>Relative Hazard [95% Confidence Interval]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Reference</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>3</td>
<td>1.76</td>
<td>[1.10 to 2.82]</td>
</tr>
<tr>
<td>4</td>
<td>1.86</td>
<td>[1.22 to 2.83]</td>
</tr>
<tr>
<td>5</td>
<td>2.38</td>
<td>[1.53 to 3.72]</td>
</tr>
<tr>
<td>≥6</td>
<td>2.71</td>
<td>[1.81 to 4.06]</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, cause of end-stage renal disease, type of dialysis (hemodialysis or peritoneal dialysis), estimated GFR, albumin, phosphate and hemoglobin.

FR-PO765

Cumulative Risk of Death in Propensity-Matched Incident Dialysis Patients: A Nationwide Prospective Multicenter Cohort Study in Korea
Hee-Yeon Jung,1 Sukyung Lee,1 Ji-Young Choi,1 Se-Hee Yoon,2 Jung-Hee Cho,1 Sun-Hee Park,1 Chan-Duck Kim,1 Yong-Lim Kim.1 1Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; 2Internal Medicine, Konyang Univ, Daejeon, Republic of Korea.

Background: Our previous study reported the superior outcome of peritoneal dialysis (PD) than hemodialysis (HD) in the early dialysis period. This study investigated the impact of dialysis modality after the early period of incident dialysis patients.

Methods: Incident dialysis patients were enrolled from Korean nationwide prospective cohort from September 2008 to December 2013. The patients were stratified by modality at day 90 after the first dialysis or the modality at dialysis initiation if death occurred prior. The survival of PD and HD patients were compared by propensity score matching analysis. Relative risk of death was estimated using the cumulative hazard ratio from the stratified Cox proportional hazard model adjusted for residual confounding.

Results: A total of 1348 patients were matched from 2658 incident dialysis patients with mean follow-up of 29.9 ± 14.1 months. All clinical parameters including baseline residual renal function were comparable between PD and HD patients. The cumulative risk of death was significantly lower in PD than HD from 6 months after dialysis initiation. The cumulative hazard ratio for death was 0.70 (95% confidence interval [CI] 0.41-0.98) at one year for PD compared with matched HD and 0.68 (95% CI 0.46-0.90) at two years. The cumulative survival probability was higher in PD patients for up to 3.5 years on dialysis, with no difference after the period.

Conclusions: Overall survival in maintenance dialysis patients favored PD in the early period of dialysis and the survival advantage lasted to 3.5 years after initiation of dialysis. However, PD and HD patients had similar survival outcomes thereafter.

FR-PO766

Inflammation and Fluid Overload a Complex Interaction: Results from the International MONDO Initiative
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Background: In hemodialysis (HD) patients, the presence of inflammation or fluid overload (FO) is associated with increased mortality. The combined presence of these two is associated with even a greater risk of death. This study aims to unravel the temporal relationship between fluid status alterations and inflammation.

Methods: We conducted a longitudinal study (baseline and follow-up 3 months each) in a European subset of the MONDO-Initiative. Fluid status was assessed by multifrequency bioimpedance and inflammation by C-reactive protein (CRP). We divided patients into 4 groups based on fluid- and inflammation status. FO was defined as overhydration above ≥2.5L. Inflammation was defined as CRP >10mg/L.

Results: We included 5954 patients (56.1% male, age 63 years, v1.5 years). At baseline inflammation and FO were jointly present in 1092 (18.3%) patients. 141 (11.8%) developed inflammation during follow up. Of the 1192 (20%) patients with inflammation but without normal fluid status at baseline, 111 (10.2%) had FO during follow up. Inflammation at baseline predicted FO during follow up (odds ratio(OR) 1.2095% CI 1.05-1.37). Likewise, FO during baseline predicted inflammation during follow up (OR 1.30 [95% CI 1.15-1.47]). However, in a minority of patients the presence of FO and/or inflammation appears to a relatively stable condition. The presence of both inflammation and FO during baseline was associated with an increased mortality risk compared to the absence of both.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Blood Volume Analysis as a Guide for Dry Weight Determination in Chronic Hemodialysis Patients

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**Background:** Volume overload and depletion both lead to high morbidity and mortality. Achieving euvolemia is a challenge in patients with end stage kidney disease (ESKD) on hemodialysis (HD). Blood volume analysis (BVA) uses radiolabeled albumin to determine intravascular blood volume (BV). The measured BV is compared to an ideal BV (validated in healthy controls). We hypothesized that BVA could be used in HD to evaluate the adequacy of the fluid status of a patient to an estimated dry weight (EDW) and to titrate EDW in order to improve overall volume status. We were also interested in the reproducibility of BVA results in ESKD. This is the first longitudinal study of BVA in HD patients.

**Methods:** 12 adults on chronic HD were recruited; 10 completed the study. BVA (Daxor, New York, NY; USA) was used to measure BV at baseline. EDW was kept the same if the patient was deemed to be euvolic by BVA otherwise, the prescribed EDW was changed with the aim that measured BV would match ideal BV. A second BV measurement was done 1-3 months later in order to measure BV again.

**Results:** Based on BVA, 6/10 patients were euvalacmic at baseline and 5/10 were euvalacmic at the second measurement. When comparing patients who had their prescribed EDW changed after the initial BVA to those who did not, both groups had similar differences between measured and ideal BV (P=0.75). BV values were unchanged at the time of the euvolemic at the second measurement. When comparing patients who had their prescribed EDW was changed with the aim that measured BV would match ideal BV. A second BV measurement was done 1-3 months later in order to measure BV again.

**Conclusions:** This pilot study is the first longitudinal measurement of BVA in HD patients. It revealed that changing weight did not proportionally change intravascular BV. BV remained stable for 1-3 months. BVA may not be reliable in clinically stable HD patients but studies on hemodynamic instability and uncertain volume status are needed.

**Funding:** Pharmaceutical Company Support - Daxor provided BVA equipment and supplies but was not involved in study design or execution and did not participate in the analysis of data or preparation of the manuscript

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**Effects of Physician Payment Reform on Provision of Home Dialysis**

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**Background:** Patients with end-stage renal disease can receive dialysis at home or in-center. In 2004 the Centers for Medicare and Medicaid Services reform physician payment for in-center hemodialysis care from a capitated to a tiered fee-for-service model, augmenting physician payment for frequent in-center visits. We evaluated whether payment reform influenced dialysis modality assignment.

**Methods:** Using a national cohort of patients starting dialysis in the US in the three years before and after payment reform, we conducted difference-in-difference analyses comparing patients with Traditional Medicare coverage (who were affected by the policy) to others with Medicare Advantage (who were unaffected by the policy). We also examined whether the policy had a more pronounced influence on dialysis modality assignment in areas with lower costs of traveling to dialysis centers.

**Results:** Patients with Traditional Medicare coverage experienced a 12% (95% CI, 2% to 21%) reduction in home dialysis use following payment reform compared to patients with Medicare Advantage. Patients living in areas with larger dialysis facilities (where payments were linked to travel costs made in-center hemodialysis comparatively more lucrative for physicians) experienced a 16% (95% CI, 8% to 23%) reduction in home dialysis use following payment reform compared to patients living in areas with smaller facilities (where payment reform made in-center hemodialysis comparatively less lucrative for physicians).

**Conclusions:** National physician payment reform intended to improve the quality of dialysis care resulted in fewer patients receiving home dialysis. This highlights a major failure of the policy and the importance of considering unintended consequences of future physician payment reform efforts.

**FR-PO768**

**Effects of Sildenafil on Erectile Dysfunction in Hemodialysis Patients**

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**Background:** Erectile dysfunction (ED) is prevalent in dialysis patients. Sildenafil, a PDE-5 inhibitor, has been shown to be very effective against ED in general population. However, there is some evidence that dialysis patients are resistant to sildenafil treatment. We performed this meta-analysis to evaluate efficacy of sildenafil in dialysis patients with ED compared with control.

**Methods:** We comprehensively searched the databases of MEDLINE, EMBASE, and Cochrane Databases. The inclusion criteria were published RCT comparing sildenafil therapy to placebo or controls on ED in patients with dialysis. The primary outcome was change in International Index of Erectile Function (IIEF) score. The diagnostic ED was confirmed with a score of 21 or less in IIEF.

**Results:** From 153 full-text articles, 3 studies involving 153 dialysis patients were included in the meta-analysis. All included studies were RCT comparing sildenafil with active control in either hemodialysis or peritoneal dialysis patients. A meta-analysis using fixed-effects model was performed. Those who received sildenafil had a significant improvement in IIEF score compared to a change in IIEF score with a mean difference of 10.48 (95% CI: 9.96 to 11.00, p-value<0.01).

**Conclusions:** This is the first meta-analysis to show that sildenafil is effective in dialysis patients with erectile dysfunction compared with control. Further study considering other benefits and side effects of PDE-5 inhibitor in dialysis patients should be conducted.

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**Validation of Screening Questionnaires for Sleep Apnea in Hemodialysis Population**


**Background:** Sleep apnea hypopnea syndrome (SAHS) is common in end stage renal disease (ESRD). We investigated the validity of Berlin and STOP-BANG questionnaires against nocturnal oximetry in identifying high risk hemodialysis patients for SAHS.

**Methods:** After obtaining local IRB approval, adult hemodialysis patients who were undergoing regular chronic hemodialysis for at least 3 months were consented and asked to complete Berlin and STOP-BANG questionnaires. Nocturnal oximetry from hemodialysis night using Pulsox 300i wristwatch was also completed. The saturation recordings were downloaded and analyzed using Profox software. The first hour of recording was deleted in effect saturation oximetry reading from sleep time on dialysis patients were also excluded from analysis. Oxygen desaturation index (ODI) was defined as the number of desaturations ≥ 3% from baseline lasting ≥ 10 seconds, per hour. Sensitivity, specificity, positive and negative predictive values were calculated for the Berlin and STOP-BANG questionnaires.

**Results:** Twenty HD patients (11 males and 9 females) aged 54 ± 13 years with a mean body mass index of 25.5 ± 4.6 kg/m^2 and neck circumference of 38.4 ± 5.8 cm were analyzed. Oxygen saturation index was ≥ 90% in 30% of patients, ≥ 94% in 20% of patients, ≥ 95% in 15% of patients, and ≥ 96% in 10% of patients. Oxygen saturation index ≥ 90% and ≥ 94% was 67% and 67% for Berlin questionnaire, respectively. STOP-BANG questionnaire had a positive predictive value of 85% and a negative predictive value of 29%.

**Conclusions:** Reliable screening tools for SAHS in ESRD population are limited. Both Berlin and STOP-BANG questionnaires lack specificity to be utilized in this setting. Additional studies are warranted to elaborate the role of screening questionnaires for SAHS in end stage renal disease population.
Moderate to Severe Nocturnal Hypoxemia and Executive Dysfunction in Patients Undergoing Maintenance Hemodialysis

Background: Nocturnal hypoxemia and executive dysfunction is common in end stage renal disease. We investigated the impact of moderate to severe nocturnal hypoxemia on executive function in patients undergoing maintenance hemodialysis.

Methods: Following local IRB approval, adult hemodialysis patients were consented to complete 1 night of nocturnal oximetry using Pulsox 3060 wristwatch. The first hour of recording was deleted in efforts to capture oximetry reading from sleep time only. Oxygen desaturation index (ODI) was defined as the number of desaturations ≥ 3% from baseline lasting ≥ 10 seconds per hour. Trail making tests A and B were also completed during dialysis session. Trail making test A and B performance was compared using t-test in patients with ODI <15 versus those with ODI ≥ 15. Executive dysfunction was defined as trail making A and B completion time > 75 seconds and 180 seconds, respectively.

Results: Nine of 20 patients aged 45 ± 12 years with a mean body mass index (BMI) of 23 ± 3 kg/m² and neck circumference of 35.4 ±4 cm had ODI < 15. The remaining eleven patients aged 60 ± 12 years with a mean BMI of 28 ± 5 kg/m² and neck circumference of 41 ± 16 cm had ODI ≥ 15. Patients with ODI ≥ 15 took significantly longer (77 ± 34 seconds) to complete trail making test A compared to only 1 patient out of 9 (11%) with ODI < 15. Mean duration for completion of trail making B test was also longer in patients with ODI ≥ 15 (157 ± 87 seconds) compared to ODI < 15 (117 ± 67 seconds) [p<0.05]. Two of 11 patients with ODI ≥ 15 and 2 of 9 patients with ODI < 15 required > 180 seconds to complete trail making test B.

Conclusions: Patients with ODI <15 performed better on trail making test A, were younger with a smaller BMI and neck circumference, compared to those with ODI ≥ 15. Additional research is warranted to confirm these findings. Whether treatment of moderate to severe nocturnal hypoxemia may slow or prevent executive function decline in patients undergoing maintenance hemodialysis remains to be determined.

Indoxyl Sulfate (Indican) and Sleep Disorders in Hemodialysis Patients: The Retained Otolaryngic Solutes and Clinical Outcomes (ROSCO) Study
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Background: Although sleep disorders are common in dialysis patients, the pathophysiology of sleep disturbance is unclear. Protein-bound solutes inadequately removed during dialysis may contribute to sleep disorders.

Methods: We examined the association of total and free levels of IS with sleep disorder in 1,241 prevalent dialysis patients from the HEMO study. IS levels were measured using mass spectrometry and modeled as tertiles. Sleep disorder was assessed using a 5-level categorical question in the Short Form (36) Health Survey. We used ordinal logistic regression to assess the relation of IS with sleep disorder, adjusting for confounders including age, race, gender, ICED score, body mass index, diabetes, congestive heart failure, serum albumin, creatinine, and phosphate levels. The lowest tertile of IS was the reference group. Effect modification was tested for IS levels with Kt/V and gastrointestinal (GI) disease (due to IS's GI origin).

Results: Patients were on average 57.5 years old, 62.8% were black, and 43.2% were male. There was a significant association between increasing tertiles of free IS and more impaired sleep disorders [OR 1.68 (1.09-2.58)]. There was effect modification by Kt/V (p=0.03) but none by GI disease (p=0.17). Similar results were observed with total IS and sleep disorder [2.09 (1.37-3.19)]. Stratified analyses by race did not show an association between higher tertiles of free IS and sleep disorder in the high Kt/V group [0.72 (0.45-1.14)]. However greater odds of sleep disorder with highest tertile of IS were noted in the low Kt/V group. This relation was also present for total IS; those with low Kt/V had greater odds of sleep disorder with the highest total IS tertile [2.11 (1.29-3.45)] but not with the high Kt/V group [0.91 (0.61-1.35)].

Conclusions: Higher levels of IS are significantly associated with sleep disorder. Patients with a lower dialysis dose may be more susceptible. Further research on whether removal of IS improves sleep outcomes is needed.

Quantifying Physical Activity Levels and Sleep in Hemodialysis Patients Using a Commericially-Available Activity Tracker
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Background: Hemodialysis (HD) patients frequently develop functional impairment. The study used decision tree analysis to identify risk factors for functional impairment in HD patients.

Methods: A total 1166 maintenance HD patients were enrolled in one hospital-based HD center. The observational period was from 2009 to 2013. Karnofsky Performance Status Scale (KPS) was used to quantify functional status. KPS assessment was based on HD patients’ self report yearly for consecutive five years. High KPS score was defined as ≥ 80 and low score as < 80. Decision tree analysis was used to analyze odds ratio (OR) of functional impairment from variables in demographics, laboratory test and primary renal disease classification.

Results: Subjects (853) with high KPS scores demonstrated significantly younger age (58.2 vs 71.3 years), longer HD duration (7.2 vs 4.7 years), higher nutritional indices, higher HD duration (1.65 vs 1.59) and lower cardiothoracic (CT) ratio compared to subjects (313) in low KPS scores. A total 3509 KPS values were collected. 2697 (76.9%) values belonged to high functional scores, 812 (23.1%) values in low functional scores. The first variable chosen by decision tree analysis to split the data was age (67.5 years). There were six leaf nodes and twenty-eight subgroups. In age > 67.5 years group, the odds of consecutive chosen were serum albumin level (≤ 3.75 g/dL, OR 25.78, p = 1.77E-199), Cr level (≤ 8.93 mg/dL, OR 39.40, p = 0.019), HD duration (≤ 0.95 year, OR 39.40, p = 0.019), ferritin (>664.5 mg/dL, OR 26.26, p = 2.06E-13), P level (>5.35 mg/dL, OR 9.28, p = 8.88E-24), HD level (>10.85 g/dL, OR 0.89, p = 0.10). In age ≤ 67.5 group, the odds of consecutive chosen were renal disease classification, Cr level (10.43 mg/dL, OR 11.23, p = 2.03E-72), age (≤58.5 years, OR 0.89, p = 0.06), PTH level (≥ 356.4 mg/pL, OR 0.44, p = 0.072), CT ratio (≥ 0.44, OR 11.16, p = 9.17E-35).

Conclusions: By decision tree analysis, age was the main risk factor for functional impairment in HD patients. Overall, the weight contribution of different risk factors for functional impairment in HD patients were identified by classification tree analysis.

FR-PO775 Using Decision Tree Analysis to Identify Risk Factors for Functional Impairment in Hemodialysis Patients J. B. Chen. Div of Nephrology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung Univ College of Medicine, Kaohsiung, Taiwan.

Background: Hemodialysis (HD) patients frequently developed functional impairment. Unemployment rates are high among dialysis patients; a 2011 study found approximately 71% of working-age dialysis patients are unemployed. Another study found that dialysis negatively impacts employment status and has the largest effect between dialysis years 1 and 2. We examined whether prolonged dialysis (dialysis vintage) affects employment status.

Methods: Dialysis vintage data and mean age were obtained from a sample of 16,069 employed patients from a large dialysis organization (Nov 2014-April 2015). Employment status was defined as regular full-time (30 hrs/wk), regular part-time (<30 hrs/wk), and part-time (<24 hrs/wk).

Results: Regular full-time employed patients were older (52.6 yrs) than part-time (49.1 yrs) and part-time (49.0 yrs) patients. Employment status was highest among all patients for all categories of employment during year 1 of dialysis (35.7%) and dropped significantly by year 2 (14.4%) [Table]. Employment status continued to drop as vintage increased.
Conclusions: Our study found that dialysis vintage negatively impacts employment status and has the largest effect between years 1 and 2. Further study is needed to reveal if a decrease in face-to-face visits due to the COVID-19 pandemic. These results should alert dialysis staff that support and intervention may be needed to help patients stay employed. References: 1) Muehrer RJ et al. Clin J Am Soc Nephrol. 2011;6(3):489-496. 2) van Manen

FR-PO779

Provider Visit Frequency During Hemodialysis and Its Effect on End Stage Renal Disease Comorbidities

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Background: In the United States, patients with End Stage Renal Disease (ESRD) on dialysis visit their Nephrologist one to four times per month during their dialysis sessions. Medicare reimbursement policy encourages frequent provider visits for patients on ESRD on hemodialysis. We believe that increasing the number of face-to-face provider visits improves the care and clinical outcomes of comorbidities related to ESRD (hypertension, hyperphosphatemia, and hyperkalemia).

Methods: We used a Pre and Post-test pilot study design to evaluate the effect on laboratory measurements and blood pressure by increasing the frequency of Nephrologist face-to-face visits at the Miami VA Medical Center. Seventeen patients that were evaluated during a period of six months were included in the analysis. In the initial three months, the patients were evaluated four times per month (usual care). The number of face-to-face visits was increased to eight times per month (or twice weekly) for the following three months. Results: A paired-sample t-test was conducted to compare the mean systolic blood pressure measure before and after the intervention. Additional provider face-to-face visits per month were associated with a significant difference in the systolic blood pressure before and after the intervention (p=0.004, t=3.303, Mean=8.235, and Standard Deviation=16). In addition, we found improvement of the phosphorus levels with a difference that was statistically significant (p=0.028, t=2.419, Mean=0.512, and Standard Deviation=16). Patients reported increased perceived quality of care when they had the opportunity of seeing the Nephrologist more frequently.

Conclusions: Hypertension and electrolyte abnormalities are known risk factors that increase morbidity and mortality in patients with End Stage Renal Disease. Adherence to medication is a major concern for patients on Hemodialysis therapy. Increasing the number of visits per month with the Nephrologist during Hemodialysis sessions increases adherence to a renal diet, medication use and patient satisfaction.

FR-PO778

Response Rate of Hepatitis B Virus Vaccination in Various Stages of Chronic Kidney Disease

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Background: Although hepatitis B virus (HBV) vaccination is recommended for all dialysis patients, the response rate of HBV vaccination in dialysis patients is very low. Therefore, we tried to investigate the necessity of early HBV vaccination in pre-dialysis patients analyzing the response rate of vaccination in various stages of chronic kidney disease (CKD).

Methods: A total of 87 patients in 3 different stages of CKD was enrolled in this study. Patients in stage 3 (n=30) and 4 (n=28) were received the HBV vaccine as standardized schedule, consisting of 1 mL of the recombinant vaccine, Hepavac-gene TF at 0, 1, and 6 months. And then, the patients with stage 5 (n=29) were received the same vaccine for doubling doses at 0, 1, 2, 6 months. And then, the patients with stage 5 (n=29) were received the same vaccine for doubling doses at 0, 1, 2, 6 months. Three months after each of the last vaccination, serum levels of HBsAg were measured in all patients.

Results: There was no significant difference in baseline characteristics including age, sex, presence of DM among the 3 groups. The overall seroconversion rate after vaccination was 79.4%. The seroconversion rate was significantly higher in patients with stage 3 than other patients (stage 3: 94%, stage 4: 79%, stage 5: 66%, p=0.031). Analyzing based on dialysis, seroconversion rate was also significantly higher in pre-dialysis patients than in dialysis patients (pre-dialysis group: 86%, dialysis group: 63%, p=0.02). There was no significant factor to contribute seroconversion in multivariate analysis.

Conclusions: Our study showed the high seroconversion rate after HBV vaccination in CKD patients with stage 3 and pre-dialysis. Therefore, the HBV vaccination should be considered in early CKD stages.
medication handling (3), separation of clean and contaminated workspaces (2), and vascular access care (1). Multiple lapses were identified in 7 outbreaks. No specific infection control lapses were identified at the time of the investigation in 2 outbreaks.

Conclusions: Outpatient hemodialysis clinics remain a common setting for healthcare-related HCV outbreaks. Infection control lapses were frequently identified in reported outbreaks. Rigorous adherence to recommended infection control practices is needed to protect patients and prevent future outbreaks in this setting.

Funding: Other U.S. Government Support

FR-PO781

Influenza and Outcomes in ESRD Patients  

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Background: Yearly influenza vaccination is recommended for all ESRD patients, due to a high risk of influenza-related complications. Through the CDC’s Outpatient Illness Surveillance, information on patient visits to health care providers for influenza-like illness (ILI) is collected. These data give estimates of the percent of all OP visits that are for presumed influenza, and give national information on timing and severity of each influenza season. We assessed the association between CDC ILI data and outcomes in ESRD patients.

Methods: We aggregated weekly ILI data from 2000-2012 to monthly, and calculated the monthly number of deaths and hospitalizations among US ESRD patients during the same time period. Using time series decomposition, we subtracted out seasonal and trend effects from the overall ILI metric. We used all-cause hospitalization as a potential confounder of outcomes.

Results: The overall rate is still below 70%, suggesting room for further improvement. While influenza vaccination rates among ESRD patients have improved over the last decade, we still observed gaps. Other peaks and valleys of the ILI data did not parallel the beginning of the next calendar year. Similar “early” peaks are seen in deaths among ESRD patients. There is also correlation between other peaks and valleys of the ILI data and periods of increased contacts in the community, such as holiday seasons and prior to vaccine administration.

Conclusions: There is an opportunity for increased influenza vaccination rates and improved infection control practices to reduce the burden of influenza among ESRD patients.

Funding: The National Institute on Aging, the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Mental Health, the National Institute of Minority Health and Health Disparities, the National Institute of Nursing Research, the National Library of Medicine, the National Institute of Dental and Craniofacial Research, the National Institute of Biomedical Imaging and Bioengineering, the National Center for Advancing Translational Sciences, and the National Center for Research Resources.

FR-PO782

The Burden of Pneumonia in Patients Receiving Dialysis: Incidence, Case Fatality, and Costs to Medicare  

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Background: End-stage renal disease patients receiving dialysis are at particular risk for infection. We assessed the clinical and economic burden of pneumonia in a population of Medicare-enrolled ESRD patients with respect to incidence and case fatality rates, rates of all-cause hospitalization, and costs.

Methods: Patients included in the analysis received dialysis between 01 Jan 2009 and 31 Dec 2011, and were enrolled in Medicare Parts A and B. Pneumonia episodes were identified from institutional and supplier claims. Patients were considered at-risk from the first date of Medicare coverage and were censored from the analysis upon transplant, withdrawal from dialysis, recovery of renal function or death. Linear mixed effects models were used to assess hospitalization rates and costs over the 3 months prior to and 12 months following a pneumonia diagnosis.

Results: The pneumonia incidence rate for the study period was 21.4 events/100 patient-years with the majority of episodes (90.1%) requiring inpatient treatment. The 30-day case fatality rate was 10.7%; case fatality rates were higher for older patients and for pneumonia requiring inpatient treatment (11.2%). All-cause hospitalization rates were greater in the month of the pneumonia episode vs month -3 prior to diagnosis (IRR, 4.61; 95%CI: 4.46, 4.76) and remained higher than baseline over the 1-year follow-up period. Mean per patient per month costs were $10,976 (95% CI: $10,717, $11,275) higher in the month of the index episode compared to month -3, largely driven by increased inpatient costs, and remained elevated through end of follow-up.

Conclusions: Pneumonia episodes are frequent among ESRD patients and result in hospital admissions and greater overall costs to Medicare (~$20,000 incremental) over the following year.

Funding: Pharmaceutical Company Support - Pfizer Inc

FR-PO783

Opioid Use Associates with Infection Related Morbidity and Mortality in Hemodialysis Patients  

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Background: Opiates are frequently prescribed for pain in the US hemodialysis (HD) population but have intrinsic properties that increase risk of infection, a common cause of morbidity and mortality for patients. Data regarding the association of opioids with infection are lacking.

Methods: We conducted a retrospective cohort study using data from a large national dialysis provider linked with the United States Renal Data System and Medicare Part D (2006-2010). We used a new user design – comparing only new users of opioids to new users of prescription non-steroidal anti-inflammatory drugs (NSAIDS) to address confounding, as well as excluding patients with cancer, use of hospice services, or use of ≥ 1 opiate. We assessed treatment effects on infection-related morbidity and mortality using inverse probability of treatment weighted Kaplan-Meier methods, adjusting for many comorbid, lab, and clinical variables.

Results: 5,113 patients met entry requirements, of which 3,439 (67.3%) received an opioid. Relative to new NSAID users, new opioid users had similar baseline laboratory values, but were slightly younger, and had a higher prevalence of comorbidities, including recent infections (8.7% vs 6.8%), diabetes (52.3% vs 49.3%), and chronic obstructive pulmonary disease (COPD), 17% vs 12.2%. After multivariable adjustment, we observed an elevated risk of 90-day infection-related hospitalization, (Risk Difference (RD) 2.5/100 patients, 95% CI 0.6-4.5) (Figure 1), and 90-day risk of infection-related mortality (RD 0.6%, 95% CI 0.3-0.9), no figure. For subgroups, infection-related hospitalizations were elevated among females and patients with diabetes, COPD, and lower dialysis vintage.

Funding: Other U.S. Government Support

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

Underline represents presenting author.

543A
Conclusions: Our results suggest that opioid initiation increases the short-term risk of infection-related morbidity and mortality among HD patients.

Funding: Clinical Revenue Support

FR-PO784

A Retrospective Review of the Two-Step Tuberculin Skin Test in Manitoba’s Dialysis Population

Rukhsana A. Foster,1,2 Thomas W. Ferguson,1 Claudio Rigatto,1 Navdeep Tangri, Blake R. Lerner, Whit Reid,1 Paul Komenda.1,2

Background: Reactivation of latent Mycobacterium Tuberculosis (LTBI) is a health concern for patients on dialysis due to their immunosuppressed state. The most frequently used test for LTBI screening in this population is the Tuberculin Skin Test (TST). The diagnostic accuracy (sensitivity and specificity) and clinical utility of the TST in a contemporary North American dialysis population is unknown.

Methods: We performed a retrospective cohort study of 483 hemodialysis and peritoneal dialysis patients across 4 dialysis units. All patients received a two-step TST and full TB risk assessment between February 2008 and December 2008. We then linked the cohort with the Manitoba Health TB Registry to ascertain if treatment was received for LTBI.

Results: At an induration cut-off of 5mm, 62 (13%) patients had a positive two-step TST. Patients with a BCG vaccination were more likely to test positive (50 vs. 34%, p = 0.006). Using a diagnostic gold standard of an abnormal chest X-ray as a proxy for LTBI, the sensitivity of the TST was only 13.9%, and the specificity was 87.7%. Only 8 of 62 patients (13%) were prescribed treatment for LTBI. None of the patients who tested negative were treated.

Conclusions: The TST has limited diagnostic and clinical utility for LTBI screening in patients on dialysis. Further research into the diagnostic accuracy of interferon-gamma release assays, and a revision of TST screening guidelines in patients on dialysis should be considered.

FR-PO785

Reliability and Construct Validity of the Coping Strategy Inventory-Short Form in Hemodialysis (HD) Patients in 13 Countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Elodie Speyer,1 Hal Morgenstern,2 Yasuki Hayashino,1 Peter G. Kerr,1 Hugh C. Rayner,1 Robert L. Pisoni.1

Background: In international studies, questionnaires are often translated into several languages without consideration of cultural and linguistic differences that may compromise the reliability and validity of survey instruments, especially those measuring psychosocial factors. The Coping Strategies Inventory-Short Form (CSI-SF) is a 16-item questionnaire, developed in English, and previously validated in US-Canadian failure patients. It is scored by computing 4 scales (each with 4 items) to measure 4 different coping strategies. The aim was to assess reliability and construct validity of the CSI-SF in HD patients across 13 countries.

Methods: The CSI-SF was self-administered to HD patients across 13 countries in 9 languages in DOPPS 4 (2009-11). Cronbach’s alpha was used to assess internal consistency. Exploratory and confirmatory factor analyses were used to assess the factor structure of the CSI-SF by country and language.

Results: 6,656 HD patients completed the CSI-SF and were included in this analysis (55% male; median age=63, range: 18-96 yrs). Using the English version in 4 countries and the Swedish version, we found good internal consistency (α=0.63-0.77) for 3 of the 4 scales; the 4th scale was internally consistent if two items were dropped. In these countries, both types of factor analyses indicated a factor structure perfectly consistent with these same 4 scales. In the 8 other non-English versions, results were very different: internal consistency was lower for the 4 scales; no country showed an exploratory factor structure similar to that found previously, nor was the 4-factor structure confirmed with factor analysis.

Conclusions: The CSI-SF is reliable for measuring coping in HD patients in English and some non-English versions. As tested in the DOPPS, the importance of coping in predicting outcomes in HD patients can now be described in these countries. More research is needed for measuring coping strategies in other countries and languages.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi, Novo Nordisk, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHIC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGIN, Sire, WIne Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support

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

FR-PO786

Associations Among Psychosocial/Medical Factors and Quality of Life in Hemodialysis Patients with End-Stage Renal Disease

Gum woo Kang

Background: Patients with end-stage renal disease (ESRD) have a significant impairment in quality of life (QoL). Most previous studies have focused on medical factors mainly. However, quality of life can also be affected by psychosocial problems in the circumstances of chronic illness. The aim of this study was to identify the associations among psychosocial factors, medical factors and QoL in hemodialysis (HD) patients.

Methods: The study included 101 patients with ESRD who were undergoing HD (mean age 57.1 ± 2.1 years). Psychosocial factors were measured using the Hospital Anxiety Depression Scale (HADS), Multidimensional Scale of Perceived Social Support (MSPSS), Montreal Cognitive Assessment and Pittsburgh Sleep Quality Index. In addition, for evaluating caregivers’ burden in part of psychosocial factors, HADS and Zarit Burden Interview of main caregivers were administered. We also assessed medical factors (Kt/V and urea reduction ratio, etc.) with laboratory results (body mass index, albumin, hemoglobin, etc.). The QoL was evaluated using WHO Quality of Life-BREF (WHOQOL-BREF). The canonical correlation analysis was used to investigate the patterns of associations.

Results: The canonical correlation between psychosocial factor and QoL was significant. The first canonical correlation was 0.673 (proportion = 60.6%, p = 0.001) and the second was 0.519 (proportion = 26.9%, p = 0.006). However, the canonical correlation between medical factor and QoL was not significant (the first: p = 0.586, the second: p = 0.713).

Conclusions: The QoL of patients with ESRD was not associated with medical factor, but psychosocial factor in canonical correlation analysis. This finding may suggest that medical workers should recognize and treat psychosocial problems as well as medical problems. We also would like to emphasize the comprehensive approach with cooperation between psychiatrists and nephrologists for improvement of QoL in ESRD patients.

FR-PO787

Longitudinal Associations of Dietary Protein and Energy Intake with Protein-Energy Wasting Syndrome in Hemodialysis Patients

Xiaorui Chen,1 Xiaoru Xia,1 G. Wei,1 Robert E. Boucher,1 Dominique Ferranti,1 Kalani L. Raphael,1,2 Tom Greene,1 Michel Chonchol,1 U of Utah; VA SLIC,UC Denver.

Background: Low dietary protein intake (DPI) (<0.6 g/kg/d) and low dietary energy intake (DEI) (<25 kcal/kg/day) are included in the definition of protein-energy wasting (PEW) syndrome. Therefore, we examined the longitudinal associations of baseline DPI and DEI with PEW syndrome (defined by modified criteria that excludes dietary variables) at 1 year of follow-up in 1480 MHD pts in the HEMO Study.

Methods: DPI and DEI were obtained by 24-h dietary recall. PEW syndrome at month 12 was defined as the presence of 2 out of the 3 criteria: serum chemistry (albumin by BCP method < 3.5 g/dl or cholesterol < 100 mg/dl), body weight (BMI < 23 kg/m2 or wt loss > 10% over 1 yr), and muscle mass (mid-arm muscle circumference 10% or more less than the 50th percentile of reference population). PEW syndrome at month 12 was related to baseline DPI and DEI in logistic regression models.

Results: 17.4% had PEW at month 12. The prevalence of PEW syndrome at month 12 by baseline DPI and DEI quartiles are summarized in the figure.
FR-PO788

PEW Syndrome, Inflammation and Mortality in Hemodialysis Patients Srimi Beddu,1 Xiaorui Chen,2 G. Wei,1 Robert E. Boucher,1 Dominique Ferrari,1 Kalani L. Raphael,1 Tom Greene,1 Michel Chonchol,3 1U of Utah; 2VA SLC; 3UC Denver

Background: The term ‘malnutrition-inflammation complex syndrome’ implies that malnutrition and inflammation are tightly interlinked. Therefore, we examined whether the mortality associations of markers of inflammation and protein-energy wasting syndrome (PEW) are attenuated by each in 906 maintenance hemodialysis (MHD) patients in the HEMO Study, a multi-center RCT that examined the effects of dialysis dose and dialiser flux on mortality.

Methods: High sensitivity Creative Protein (hsCRP), tumor necrosis factor (TNF)-α and interleukin (IL)-6 were measured in the month 12 stored samples. Weight loss was estimated from baseline and month 12 post-dialysis weights and hence, PEW syndrome at month 12 was defined as the presence of 2 out of 3 criteria: serum chemistry (albumin by nephelometry < 3.5 g/dl or cholesterol < 100 mg/dl), body weight (BMI < 23 kg/m² or wt loss > 10% from baseline), and muscle mass (mid-arm muscle circumference 10% or more than the 50th percentile of reference population). Cox models were used to relate month 12 PEW syndrome and hsCRP, TNF-α and IL-6 with subsequent mortality.

Results: Mean age was 57 ± 14 yrs. 45% were women. 67% were black. PEW syndrome was present in 17.4% at month 12. Median (IQR) serum hsCRP was 6.3 (2.6-16.4) mg/L, IL-6 3.3 (2.0-7.6) pg/ml, and TNF-α 31.2 (21.3-46.1) pg/ml. There were 388 deaths over 2189 years of follow-up. PEW syndrome had 2 fold higher risk of mortality which was only marginally attenuated by adjustment for markers of inflammation (table). CRP and IL-6 were associated with higher mortality risk independent of PEW. TNF-α was not associated with mortality.

<table>
<thead>
<tr>
<th>Model 1*</th>
<th>Model 2*</th>
<th>Model 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEW syndrome</td>
<td>2.22 (1.78, 2.76)</td>
<td>2.09 (1.68, 2.61)</td>
</tr>
<tr>
<td>Each doubling of CRP</td>
<td>1.10 (1.04, 1.17)</td>
<td>1.10 (1.03, 1.17)</td>
</tr>
<tr>
<td>Each doubling of TNF-α</td>
<td>1.04 (0.90, 1.19)</td>
<td>1.03 (0.90, 1.17)</td>
</tr>
<tr>
<td>Each doubling of IL-6</td>
<td>1.13 (1.08, 1.19)</td>
<td>1.12 (1.07, 1.18)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, race, duration of ESRD, Kt/V group, smoking, alcohol use, DM, IHD, CVD, PVD, CHF and arrhythmia.

Conclusions: PEW and inflammation are independent predictors of mortality. These results suggest PEW and inflammation might not be tightly interlinked.

Funding: NIDDK Support

FR-PO790


Background: Patients who undergo dialysis prior to renal transplant have overall worse outcomes than patients who receive a preemptive transplant. However, individual studies give conflicting results regarding whether post-transplant outcomes differ based on pre-transplant dialysis modality (peritoneal dialysis (PD) versus hemodialysis (HD)).

Methods: We searched English-language literature from January 1, 1980 through August 31, 2014, national conference proceedings and reference lists of all included studies. We used combinations of terms related to dialysis (hemodialysis, peritoneal dialysis, or renal replacement therapy), kidney transplant and outcomes. Studies were included if they measured post-transplant patient mortality for both pre-transplant HD and PD. Studies were excluded if they were not in English or if they included pediatric patients.

Results: A total of 15 studies reported five-year patient mortality. These included 166,531 patients on HD and 51,980 patients on PD pre-transplant. The pooled hazard ratio for five-year patient mortality after renal transplant was 0.91 (CI 0.85-0.97) in favor of pre-transplant PD over HD (p=0.006).

Conclusions: Distance is an important factor in patient decision-making when initiating PD, particularly for those living farther away from commonly offered HD services. Analyses of treatment selection must appropriately model distance to reflect logistics of treatment options and service availability to patients.

Funding: NIDDK Support, Other U.S. Government Support
Impact of Poverty and Health Care Insurance on Pre-End Stage Renal Disease Care in Dialysis Patients  
Robert Nee,1 Lawrence Agodoa,2 Kevin C. Abbott,1  
1Nephrology, Walter Reed National Military Medical Center; Bethesda, MD; 2NIDDK, National Insts of Health, Bethesda, MD.  

Background: Access to nephrology care prior to end-stage renal disease (ESRD) is significantly associated with lower rates of morbidity and mortality. We assessed the association of area and individual-level indicators of poverty and types of health care insurance on pre-ESRD care provided by nephrologists.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 739,537 patients initiated on maintenance dialysis from January 1, 2007 through December 31, 2012. We assessed the Medicare-Medicaid dual-eligibility status as an indicator of individual-level poverty and ZIP code-level median household income (MHI) data obtained from the 2010 United States Census. We conducted multivariable logistic regression of pre-ESRD care as the outcome variable, as reported on the Centers for Medicare and Medicaid Services Form 2728.

Results: The proportions of dual-eligible and non-dual-eligible patients who had pre-ESRD care were 53.06% and 61.82%, respectively (p<0.001). Dual-eligibility was associated with significantly lower likelihood of pre-ESRD care (adjusted odds ratio (aOR) 0.83, 95% confidence interval [CI] 0.82-0.84). Patients in the lowest area-level MHI quintile had an aOR 0.89 (95% CI 0.88-0.90) compared to those in higher quintile levels. Both African American (AA) and Hispanic patients were significantly less likely to have received pre-ESRD care (aOR 0.85, 95% CI 0.84-0.86 and aOR 0.71, 95% CI 0.70-0.72, respectively). Interaction terms for dual eligibility and AA race and Hispanic ethnicity were significant (p=0.001 and p=0.002, respectively).

Conclusions: Individual and area level measures of poverty were independently associated with lower likelihood of pre-ESRD care. Efforts to improve pre-ESRD nephrology care may require focusing on the poor and minority groups. [Disclaimer: The United States government nor its employees assume any liability or responsibility for the contents of this presentation.]

FR-P0794  
Does Race Affect the Cause of Mortality in End Stage Kidney Disease?  
Luxme Nadarajah, Kieran McCafferty, Muhammad M. Yaqoob.  

Background: Cardiovascular disease accounts for 50% of mortality in end-stage kidney disease (ESKD). Caucasians (C) are more likely to die from cardiovascular disease, infection and withdrawal compared to Afro-Caribbean’s (AC). Little is known about the causes of mortality for Indo-Asian (IA) patients; with the rise in diabetes mellitus (DM) it is inevitable that more patients from IA backgrounds will get ESKD. We aim to investigate whether there are any differences in causes of mortality based on race.

Methods: We performed a single center, prospective, observational study. Electronic case notes were used to extract data to include cause of death, age of initiation of RRT, age of death, dialysis vintage (DV), gender and presence of DM. Patients were excluded if RRT was less than 90 days, or if they were transplanted.

Results: In total 3431 patients commenced RRT during the study period, 802 patients died, 364 were C, 259 IA and 179 were AC. There were no significant differences between the groups for age at initiation, DV, and age of death. Significantly fewer IA died during the follow up period compared to C (p<0.0001) and AC (p<0.0001). More IA and AC were diabetic (p<0.0001). Cardiovascular deaths were more common in C and AC patients compared to those of IA race (p<0.0001). IA’s had higher sepsis related deaths when compared C or AC (p<0.0001).

<table>
<thead>
<tr>
<th></th>
<th>Caucasian</th>
<th>Indo-Asian</th>
<th>Afro-Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of patients</td>
<td>1055</td>
<td>1616</td>
<td>760</td>
</tr>
<tr>
<td>Number of deaths (%)</td>
<td>365 (34%)</td>
<td>259 (16)</td>
<td>179(23)</td>
</tr>
<tr>
<td>Cardiovascular (%)</td>
<td>101 (28)</td>
<td>48 (19)</td>
<td>54 (30)</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>79 (22)</td>
<td>97 (37)</td>
<td>36 (20)</td>
</tr>
<tr>
<td>Withdrawal (%)</td>
<td>68 (19)</td>
<td>49 (19)</td>
<td>34 (19)</td>
</tr>
<tr>
<td>Malnourish (%)</td>
<td>43 (12)</td>
<td>42 (16)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>CVA (%)</td>
<td>14 (4)</td>
<td>8 (3)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>59 (16)</td>
<td>16 (6)</td>
<td>27 (15)</td>
</tr>
</tbody>
</table>

Conclusions: Despite the increased prevalence in DM, IA patients do not have worse survival outcomes or cardiovascular deaths compared to C and AC. We believe that the elevated sepsis related mortality in IA patients is secondary to the higher prevalence of diabetes. This data enables stratifying management therapies dependent on race and may help in designing cardiovascular end points trials in racially diverse group of patients.

Funding: Other NIH Support - William Harvey Research Institute

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author.  
546A
FR-PO795

Association of Dialysis Provider Assignment with Early Dialysis Mortality in U.S. Veterans: A Transition of Care in CKD Study

Melissa Han, Ling Sun, Kamyar Kalantar, Keith C. Norris, Alison J. Yu

Note: most of these HRs were significant at p<0.05.

Methods: We examined all-cause mortality during the 3, 6, 12 and 24 month period after transition in a cohort of 52,158 US veterans who transitioned to ESRD over 4 years (10/2007-9/2011) and the association of dialysis provider assignment. Baseline provider was determined by facility information and divided into five categories: DaVita(DV), Fresenius(FR), Other Chain(OC), Non-Chain(NC), and VA. Associations were examined in Cox proportional hazard models and adjusted for age, gender, race, ethnicity, initial vascular access and primary cause of ESRD.

Results: Upon dialysis transition, patients were 70±12 yrs old, 6% female, 25% African-American, 19% initially used AV fistula and 42% had diabetes as the cause of ESRD. At baseline, 24%, 28%, 13%, 21%, and 10% of veterans received treatment at DV, FR, OC, NC, and VA facilities, respectively. Over the first 3, 6, 12 and 24 mos after transition, 5480(1%), 9283(18%), 14339(27%) and 21607(42%) veterans died, respectively (Figure left). Compared to patients initiating treatment at the VA, all patients receiving treatment at other facilities had higher risk of mortality through all periods of follow-up, after adjusting for case mix covariates (Figure right).

Conclusions: Veterans transitioning to dialysis treatment in a VA based dialysis center have the best survival over the first 2 years of follow up. Whether the better survival of VA dialysis care is from selection bias versus true superior care in the VA system warrants additional studies.

Funding: NIDDK Support

FR-PO796

Time-Varying Racial/Ethnic Differences in Mortality After Initiation of Dialysis in U.S. Dialysis Patients

Guofen Yan, Keith C. Norris, Alison J. Yu, Tom Greene, Jennie Z. Ma, Wei Yu, Alfred K. Cheung

Background: While survival advantage for African Americans (AAs) and Hispanics, compared to Whites, has been observed for decades, our understanding of the mechanism is still incomplete. Using national dialysis patients, we examined whether this survival advantage exists across the entire course of ESRD or just within a certain time interval after initiation of dialysis.

Methods: The study included 1,255,640 adult incident dialysis patients between 1995 and 2010 in the USRDS. We calculated age-specific hazard ratios (HRs) of death for AAs and Hispanics vs. Whites, adjusted for covariates, for every 6-month interval in the first 4 years of dialysis and for the period thereafter.

Results: For each age group above 40 years (Table), lower risk of death for AAs than Whites (HR<1) did not vary greatly across these time intervals. In contrast, in each age group under 40 years, the HR for AAs vs. Whites evolved over time, which was highest in the first year, declined in the second year, and reached stable over time. Hispanics exhibited lower mortality risks in all age groups that remained relatively constant over time (not shown).

Table. Adjusted HRs for AAs vs. Whites

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Months after Initiation of Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>1.72</td>
</tr>
<tr>
<td>31-40</td>
<td>1.34</td>
</tr>
<tr>
<td>41-50</td>
<td>0.89</td>
</tr>
<tr>
<td>51-60</td>
<td>0.76</td>
</tr>
<tr>
<td>61-70</td>
<td>0.72</td>
</tr>
<tr>
<td>71-80</td>
<td>0.76</td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Note: most of these HRs were significant at p<0.05.

Conclusions: AAs over 40 years old and Hispanics of all ages have uniformly lower risks of death than Whites across the course of ESRD. For younger AAs, conversely, their higher-mortality risk period is limited to the first two years of dialysis. Further studies to delineate the factors responsible for excessive mortality associated with racial subgroups will improve care for all dialysis patients.

Funding: NIDDK Support

FR-PO797

An Evaluation of Completeness of Monthly Clinical Data in CROWNWeb, a New Data Source for the United States Renal Data System (USRDS)

Valarie B. Ashley, Lingqiu Liu, Xizhao Li, Tempie H. Shearon, Bruce M. Robinson, Douglas E. Schaubel, Yi Li, Rajiv Saran

Background: CROWNWeb (CW) is a web-based system which collects administrative and clinical data from all Medicare-certified dialysis facilities in the US. It includes patient admission, tracking, and discharge information, CMS forms, and clinical data elements, and is not limited to Medicare patients. Monthly clinical data submission began in May 2012. Previously, monthly clinical data were only available to the USRDS through administrative claims for Medicare patients.

Methods: CW data were used to analyze 355,846 and 370,610 dialysis patients in 2013 and 2014, respectively, who remained on dialysis the entire year (those who were incident, died, or lost to follow-up were excluded). The percentages of patients with any and high-level reporting of selected CW clinical data were calculated, with 'high-level' defined as 10+ months (except 3+ months for peritoneal dialysis (PD) Kv/v). The percentage of high-level reporting for patient subgroups was also calculated.

Results: The percentages of patients with CW data (any, high) are shown below. All measures had an increase in reporting from 2013 to 2014. High-level reporting in 2014 ranged from 75% (Hemodialysis (HD) Kv/v) to 90% (vascular access type). For all measures, reporting was higher for HD than PD patients, for adults than children, and for patients with diabetes (versus without) diabetes as cause of ESRD. 72% of HD patients had high-level reporting for all 6 HD measures. 70% of PD patients had high-level reporting for all 5 PD measures.

Table. Clinical Data:

<table>
<thead>
<tr>
<th>Year</th>
<th>Any</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>95.4%</td>
<td>95.8%</td>
</tr>
<tr>
<td>2014</td>
<td>95.8%</td>
<td>96.2%</td>
</tr>
</tbody>
</table>

Note: most of these HRs were significant at p<0.05.

Conclusions: AAs over 40 years old and Hispanics of all ages have uniformly lower risks of death than Whites across the course of ESRD. For younger AAs, conversely, their higher-mortality risk period is limited to the first two years of dialysis. Further studies to delineate the factors responsible for excessive mortality associated with racial subgroups will improve care for all dialysis patients.

Funding: NIDDK Support
Epidemiology and Cost Center, Univ of Michigan, Ann Arbor, MI; 2Centers for Medicare and Medicaid Services.

Background: In 2015 CMS implemented star ratings for dialysis facilities to make it easier for consumers to compare dialysis facilities by providing a summary of each facility’s performance on a set of 9 DFC quality measures. Our study compares two scoring approaches to the star rating to assess the impact of each on controlling outlying measure values with regard to facility size.

Methods: Fixed percentiles are applied to assign 10% of facilities 1-star or 5-stars based on performance. 2015 data were extracted from the 2015 January DFC file. Probit ranking and z-score transformation were applied to the DFC measures to develop an overall score and final star rating. We compared the final distribution of star ratings for each approach and assessed impact on smaller facilities. We represent the rating by number of patients in each facility contributing to the hospitalization measure, and split –6000 facilities into groups of ~100 and calculated percentage of each star rating in each group.

Results: Use of original measure values and z-scores allowed skewed measures to highly influence the ratings, but preserved original measure distributions. Probit ranking resulted in giving more 5-star ratings to smaller facilities and a z-scored approach resulted in assigning more 1-star and 5-star ratings to smaller facilities (Figure 1).

Conclusions: Small facilities have more variation in measures and be over represented in the 1 or 2 star categories. Probit ranking (current DFC Star Rating method) controlled impact of outlier measure values. Z-score methods appeared to allow greater impact of undetermined mechanisms.

FR-PO801
Efficacy of Loop Diuretics in the Management of Undocumented End Stage Renal Disease Patients Receiving Emergency Hemodialysis
Salman Ahmed, Biruh Workeneh.

Background: Nearly eleven million undocumented immigrants reside in the United States. An estimated six thousand undocumented patients suffer from End Stage Renal Disease (ESRD). These patients routinely present to public hospitals for life-saving emergent dialysis treatments. Since these patients lack a dialysis unit, they often do not have medication management by a nephrologist. This can result in poorer outcomes.

Methods: We reviewed charts of 93 undocumented patients who presented for at least three emergent hemodialysis (HD) treatments during three consecutive months to the Ben Taub General Hospital, a centrally located county facility in Houston, TX. We abstracted prescription data for furosemide and several commonly prescribed medications. We also abstracted data regarding the number of ER visits, number of HD sessions, and mean, median, and peak potassium values.

Results: On average, the diuretic group had 3.1 (SE=1.8) fewer ER visits during the three-month period for emergency dialysis, compared with subjects not on diuretics (p=0.10). There was no significant relationship between furosemide total daily dose (TDD) and potassium levels. Patients on diuretics were more likely to also be taking ESAs and sevelamer (p<0.05). In a multiple regression model, the diuretic group had significantly fewer ER visits after adjusting for use of ESAs and sevelamer use (p=0.007). The association between diuretic use and ER visits is significantly associated with concomitant ESA use (p=0.04). Among subjects using ESAs, patients on diuretics have about 7.7 (95% CI: 1.9, 13.6) fewer ER visits compared with the non-diuretic group.

Conclusions: There was no significant independent association between loop diuretic dosage and number of ER visits, although there was a strong trend. The subset of patients on ESAs and loop diuretics had decreased ER utilization, and this may be explained by increased doctor-patient time, less symptomatology while on ESAs, or other, as-yet-undetermined mechanisms.

FR-PO802
Unfractionated Heparin May Contribute More to Dialysis-Associated Bleeding Risk Than Low-Molecular Weight Heparin
Suzanne H. Forbes,1 Sean Platton,2 Michael K. Almond,1 Laura Green,2 Neil Ashman.1

Background: Haemodialysis (HD) patient are well recognised to be at increased risk for major bleeding. The contribution of circuit anticoagulation to this risk is unknown. The use of unfractionated heparin (UFH) vs low-molecular weight heparin (LMWH) is debated.

Methods: We studied 127 patients; 60 LMWH, 61 UFH, 6 heparin-free. Blood was taken at t0=pre-anticoagulation, t1=1hr, t2=2hrs, t3=end. TG was performed on platelet count, prothrombin time, and partial thromboplastin time. Results are shown in table 1. With LMWH 42% failed to generate thrombin (p=0.06) and peak thrombin (p=0.05). In a multiple regression model, the diuretic group had significantly fewer ER visits after adjusting for use of ESAs and sevelamer use (p=0.007). The association between diuretic use and ER visits is significantly associated with concomitant ESA use (p=0.04). Among subjects using ESAs, patients on diuretics have about 7.7 (95% CI: 1.9, 13.6) fewer ER visits compared with the non-diuretic group.

Conclusions: There was no significant independent association between loop diuretic dosage and number of ER visits, although there was a strong trend. The subset of patients on ESAs and loop diuretics had decreased ER utilization, and this may be explained by increased doctor-patient time, less symptomatology while on ESAs, or other, as-yet-undetermined mechanisms.
FR-PO803

Anti-Platelet Factor 4 Antibodies: A One HIT Wonder
Suzanne H. Forbes, ‘1, Sean Platon, ‘2, Michael K. Almond, ‘1, Neil Ashman, ‘1, Laura Green, ‘1, Nephrology, Royal London Hospital; ‘2Haematology, Royal London Hospital; ‘3Nephrology, Southend Hospital.

Background: Hemodialysis (HD) patients are exposed to regular anticoagulation, usually unfractionated heparin (UFH) or low-molecular weight heparin (LMWH). For standard HD (4 hrs, 3 days/week) this equates 26 full days exposure/yr. Recently there was publication suggesting the presence of the antibody, without the clinical syndrome of HIT, is present in up to 25% HD patients, may be an important risk factor for cardiovascular and vascular access morbidity.

Methods: We looked for HIT antibodies in 2 prevalent HD cohorts, one with UFH, one LMWH (time lock sodium citrate). We tested for anti-PF4 antibodies using several established tests; STic Expert® (IgG-specific exclusion test), Diamed (particle gel immuno-assy), poly-specific IgG/AM ELISA, IgG-specific ELISA.

Results: We included 127 patients: 60 receiving tinzaparin, 61 receiving UFH and 6 heparin-free. Serum samples were taken at the start of a standard HD session. The average duration on dialysis was 3.4 years. Results of the various tests are shown.

<table>
<thead>
<tr>
<th>Test</th>
<th>UFH</th>
<th>LMWH</th>
<th>Heparin-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>226</td>
<td>190</td>
<td>248</td>
</tr>
<tr>
<td>STic Expert</td>
<td>positive -52% negative-48%</td>
<td>positive -40% negative-60%</td>
<td>positive -0% negative -100%</td>
</tr>
<tr>
<td>DiaMed</td>
<td>positive -1% negative-99%</td>
<td>positive -1% negative-99%</td>
<td>negative -0% positive -100%</td>
</tr>
<tr>
<td>Poly-specific ELISA</td>
<td>median OD -0.2 (positive&gt;0.4)</td>
<td>median OD -0.15 (positive&gt;0.4)</td>
<td>median OD -0.05 (positive&gt;0.4)</td>
</tr>
<tr>
<td>IgG specific ELISA</td>
<td>median OD -0.13 (positive&gt;0.4)</td>
<td>median OD -0.07 (positive&gt;0.4)</td>
<td>median OD -0.05 (positive&gt;0.4)</td>
</tr>
</tbody>
</table>

Only 1 patient tested antibody positive (OD 0.5) in the LMWH group. Platelet count and reactivity (sticking and epinephrine, collagen) did not differ between the STic positive/negative groups, the UFH/LMWH groups, or those with higher or lower tertiles of ELISA OD.

Conclusions: Despite the previously reported concern over the presence of HIT antibodies in HD patients, we comprehensively show here no evidence of antibody positivity in HD patients. Exclusion tests such as STic expert are not useful in these patients.

FR-PO804

Upper Gastrointestinal Bleeding Among Dialysis Patients in an Endemic Area for Chronic Liver Disease: Taiwan National Cohort Study
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Background: End-stage renal disease (ESRD) and chronic liver disease (CLD) both increase the risk for upper gastrointestinal (UGI) bleeding. The prevalence of ESRD and CLD are high in Taiwan. The aim of this study was to evaluate the incidence, risk factors, and categories of UGI bleeding in ESRD CLD dialysis patients.

Methods: Using Taiwan’s National Health Insurance research database, we enrolled 42,457 incident ESRD dialysis patients who began dialysis between 1999 and 2004. The patients were followed until death, dialysis cessation, or 31 December 2008. Cumulative incidence of UGI bleeding after initiation of dialysis was calculated using Kaplan-Meier methods. Predictors for UGI bleeding were determined using Cox models.

Results: During the follow-up period, 5,528 patients had a UGI bleeding. Male, elderly, receiving hemodialysis (HD) and patient with comorbidities had a higher rate of UGI bleeding. The 1-, 3-, 5- and 7-year cumulative incidence rate of UGI bleeding were 9.8%, 21%, 25.3% and 28% in patients with liver cirrhosis (LC) on HD, 5.8%, 16.2%, 22.2% and 24.4% in patients with LC on PD, 3.7%, 9.2%, 13.2% and 16.4% in patients without LC on HD, and 2.1%, 5.5%, 8.2% and 10.4% in patients without LC on PD (log-rank: p <0.001). After multivariate adjustment, prior gastrointestinal bleeding (HR 1.731, 95% CI, 1.651-1.834), LC (1.682, 95% CI, 1.524-1.856), alcoholism liver disease (1.536, 95% CI, 1.635-1.834), and receiving HD (1.316, 95% CI, 1.153-1.502) were independently risk factors for UGI bleeding in ESRD dialysis patient. Gastric ulcers were found to be the most common source of bleeding (50.3%), while bleeding resulting from a gastrojejunal ulcer was least frequent.

Conclusions: ESRD dialysis patients had a higher risk for UGI bleeding, especially those with prior gastrointestinal bleeding, LC, and alcoholism liver disease. In addition, receiving HD is a strong predictor for UGI bleeding. More attention should be paid to select dialysis modality, especially in high risk patients.

FR-PO805

Palmitoylthiopanamidine Is A Promising Potential Therapeutic Target For Increasing High Density Lipoprotein Cholesterol Levels

Background: End stage renal disease (ESRD) is associated with significant increased risk of cardiovascular (CV) mortality. High density lipoprotein (HDL) deficiency and dysfunction is a major contributor to CV disease in ESRD. Strategies aimed at improving HDL function are crucial in improving CV outcomes. Palmitoylated panamidine (PEA) is an anti-inflammatory lipid derived mediator that activates PPARalpha nuclear transcription factor. We hypothesized that serum PEA will correlate with HDL and PEA can increase HDL via activation of apoA1/ApoAl expression.

Methods: Serum PEA concentration was determined in 50 patients on maintenance hemodialysis (MHD) using LC/MS technology and correlated with clinical laboratory indices including a lipid panel. Liver cells (Hepatoma cell line HepG2) were exposed to various concentrations of PEA in-vitro for 24 hours and subsequently mRNA expression of ApoAI, the major protein component of HDL, was measured using real-time PCR.

Results: Serum PEA concentrations strongly correlated with serum HDL levels in MHD patients (r=0.57, p <0.001). PEA also correlates with total cholesterol (r=0.36, p=0.009) however not with LDL or triglycerides. In the in-vitro studies, PEA at a concentration of 60 micromolar and 120 micromolar was increased ApoAI expression significantly in HepG2 cells after 24 hours.

Conclusions: For the first time we report that serum PEA concentrations strongly correlate with serum HDL concentrations in MHD patients. Involvement of PEA in HDL production is confirmed in in-vitro studies where incubation of liver cell in PEA resulted in increased ApoAI expression. These novel findings indicate that PEA may be a promising therapeutic target in HDL deficiency treatment associated with not just ESRD but any proatherosclerotic condition.

Funding: NIDDK Support

FR-PO806

Arachidonoylglycerol, a Major Activator of the Endocannabinoid System, Is Significantly Increased in Patients with Kidney Disease

Background: Chronic kidney disease (CKD) is associated with oxidative stress and inflammation. There is evidence that cannabinoid 1 receptor activation leads to increased oxidative stress and inflammation. We previously showed that 2-arachidonoylglycerol (2-AG), one of the main activators of the endocannabinoid system, is significantly increased in the kidney of animals with ischemia-reperfusion (IR) injury. We hypothesized that serum 2-AG levels will be significantly elevated in CKD patients.

Methods: Serum concentrations of AG were determined in 21 healthy controls, 50 randomly assigned age and gender matched patients on maintenance hemodialysis (MHD), 13 patients on peritoneal dialysis (PD) and 6 patients with CKD stage IV using LC/MS technology. In MHD patients, serum levels of AG were correlated with various laboratory indices.

Results: Serum levels of 1-AG and 2-AG were significantly and incrementally increased with CKD compared to healthy controls. MHD patients had the highest AG levels which positively and significantly correlated with number of treatments per week (r=0.47, p=0.008), AST/ALT (r=0.5, p=0.001), platelet count (r=0.40, p=0.008), ferritin (r=0.36, p=0.016) and negatively with HDL cholesterol (r= -0.43, p=0.04).
Conclusions: For the first time we report that serum AG concentrations are significantly increased in CKD patients. These novel findings are in line with our report on IR acute kidney injury and with a recent study which showed that in an oxidative stress setting, monoacylglycerol lipase, an enzyme responsible for AG breakdown is inhibited leading to increased levels. Moreover, the substantial increase in MHD patients is intriguing given association of MHD with increased oxidative stress, inflammation and platelet activation. Funding: NIDDK Support

FR-PO807
Newly Launched Cellulose Tri-Acetate Membrane with Asymmetric Structure Dramatically Improves Peripheral Circulation and Hemodynamic Stability During Hemodialysis.

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Background: The most important concern about the biocompatibility of dialysis membrane is the activation of platelets and it would lead hemodynamic instability during dialysis session. The newly launched CTA with asymmetric thick structure (ATA) was produced in order to reduce stimulant property to platelets and the rapid reduction of the serum levels of small urmic solutes by thickening the membrane. We evaluated the solute removal performance and biocompatibility of ATA.

Methods: Seven chronic hemodialysis patients were enrolled to the current study. The conventional CTA was used for the first 4 months and ATA was used for the next 4 months.

We evaluated the solute removal property by the clearance of urea, beta-2 microglobulin (B2MG) and removed amount of alpha-1 microglobulin (A1MG) and albumin loss in spent dialysate. The biocompatibility was evaluated by changes in WBC and platelet count, IL-6, Pentorexine-3 (PTX-3) and high sensitive CRP (hsCRP). The peripheral circulation was estimated by the Skin Perfusion Pressure (SPP) by PAD-3000® (Kaneka Medix, Osaka, Japan). Intra-dialytic hemodynamic stability was evaluated by arterial blood pressure and subjective feelings of the patients.

Results: The clearance of Urea was significantly reduced through dialysis session in both groups but the B2MG clearance was maintained only in ATA. The total removed amount of A1MG and the albumin leakage were not different between two groups. The removal of A1MG was significantly higher in ATA than in CTA. The platelet count didn’t change in ATA during dialysis session but significantly decreased in CTA. WBC counts, IL-6, PTX-3, hsCRP in both groups didn’t change. The systolic blood pressure and frequency of intradialytic hypotension were not different in both groups whereas some of the patients felt post-dialytic fatigue improved in ATA. SPP was maintained during dialysis session in ATA but deteriorated in CTA.

Conclusions: The new ATA membrane could reduce the activation of platelets and maintain the peripheral circulation during a dialysis sessions and the time-dependent deterioration of solute removal. The new ATA membrane may improve the QOL and prognosis of chronic dialysis patients.

FR-PO808
Mathematical Modeling of Fluid Transport in Peritoneal Cavity

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Background: The current standard method (peritoneal equilibration test (PET)) is used to obtain transport characteristics of the peritoneal membrane for creatinine, urea and electrolytes, but not for fluid volume. Consequently, ultrafiltration profiles are difficult to obtain because the difference between the inlet and outlet dialysate concentration is not different between two groups. The removal of A1MG was significantly higher in ATA than in CTA.

Methods: Segmental bioimpedance was continuously monitored in ten PD patients to provide VPC during standard PET in the clinical unit (Zhu, et al. Am J Kidney Dis, 2003). VPC was measured with whole body bioimpedance technique (Hydra 4200). A two compartment model of VPC and Vf (Fig. 1a) was established (Eq 1-4). Two transport coefficients: k1 and k2 represent the rate of fluid shift from VPC to Vf by reabsorption and from Vf to VPC , driven by the glucose gradient. k1 and k2 were estimated by best fitting with the actual measurements based on the Marquardt-Levenberg algorithm.

Results: Parameter estimation was successful (residuals<0.01) in all but one patient, who experienced technical problems during the measurements. Fig. 1 (B) shows change in VPC during standard PET in a patient. k2 correlated inversely with the initial tissue fluid volume VPC(k2=−0.0002* Vf +0.0024, R2=0.46, p<0.05).

Conclusions: This model describes dynamics of fluid transport during PD treatment. K1 and k2 reflect the characteristics of peritoneal membrane in individual patient. The relationship of k2 and Vf suggests that fluid status could be a factor in ultrafiltration, which could be helpful in clinical practice.

FR-PO809
Linagliptin Ameliorated Methylglyoxal-Induced Peritoneal Fibrosis in Mice

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Background: Recent studies have reported that methylglyoxal (MGO) was increased in peritoneal dialysis patients, playing an important role in the development of peritoneal fibrosis. On the other hand, linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, exhibits beneficial effects in diabetes patients independent of blood glucose concentration. In this study, we examined whether linagliptin suppressed MGO-induced peritoneal fibrosis in mice.

Methods: Male C57/BL6 mice were divided into three groups: a vehicle group, an MGO injection group, or an MGO injection plus linagliptin group (n=6 per group). Peritoneal fibrosis was induced by a daily intraperitoneal injection of saline containing 40 mmol/L MGO for 21 days. Saline was given in the vehicle group. Linagliptin was administered at a dose of 10 mg/kg by oral gavage once a day.

Results: Immunohistochemical staining revealed that linagliptin suppressed the expression of α-smooth muscle actin and fibroblast-specific protein-1, the deposition of collagen 1 and collagen 3 and infiltration of macrophages (F4/80). In addition, linagliptin reduced TGF-β1 concentration in peritoneal fluid of MGO-treated mice. Peritoneal fibrosis tests showed improvement of peritoneal function in mice receiving linagliptin treatment.

Conclusions: These results suggest that oral administration of linagliptin ameliorated MGO-induced peritoneal fibrosis.

Funding: Private Foundation Support

FR-PO810
Addition of Alanyl-Glutamine to Dialysis Fluid Restores Peritoneal Cellular Stress Responses – A Randomized Controlled First-in-Man Trial

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Background: Peritoneal dialysis (PD) fluid cytotoxicity and intermittent bacterial infections contribute to membrane failure and peritonitis in PD patients. Recent meta-analyses revealed no significant influence of newer biocompatible PD fluids on peritonitis rate or peritoneal membrane function, but glutamine addition to standard PD fluids has shown cytoprotective effects both in vitro and in vivo.

Methods: In this open-label randomized controlled cross-over phase I/II trial (NCT01353638), 20 stable PD patients each underwent two 4 hour equilibration tests with glucose-based PD fluids supplemented with or lacking 8 mM alanyl-glutamine dipeptide (AlaGln), and separated by a 4 week washout phase. Effects of AlaGln on peritoneal inflammation and stimulated cytokine release were also tested in a mouse model of PD-associated peritonitis.

Results: Intraperitoneal (IP) exposure to AlaGln-supplemented PD fluid increased dialysate [glutamine] more rapidly (at 2 h mean 0.55-0.71 mM, p<0.05) and increased heat shock protein expression in peritoneal effluent cells (median 2.12-3.20, p<0.05), but did not alter peritoneal ultrafiltration, small solute transport, cell counts, or biomarkers. AlaGln increased ex vivo LPS-stimulated TNF-α release (effect CI 60-100 pg/mL, p<0.001) and, in patients with previous peritonitis, decreased dialysate [IL-8] (effect CI 0.1-4.3, p<0.05). IP AlaGln also reduced inflammation and enhanced cytokine release in the mouse model. No adverse effects of AlaGln were noted.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 550A
Conclusions: Ala-Gln administration to standard PD acutely attenuated PD-related pathological changes in peritoneum and in mice. These data encourage our ongoing phase I/II testing IP Ala-Gln supplementation as a routine therapeutic intervention in clinical PD. 

Funding: Pharmaceutical Company Support - Zyprotec GmbH

FR-PO811
Dipeptide Alanyl-Glutamine Protects from Peritoneal Fibrosis and Attenuates IL-17 Dependent Pathways During Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) is complicated by chronic inflammation and progressive peritoneal membrane damage. Alanyl-Glutamine (Ala-Gln), a stable dipeptide commonly used in parenteral nutrition, has immunomodulatory effects and improved resistance of mesothelial cells to PD fluids. Recently, IL-17 was identified as novel player in PD induced peritoneal damage. In this study we investigated if intraperitoneal Ala-Gln administration confers protection against peritoneal damage by modulating IL-17 expression in uremic rodent PD models.

Methods: Uremia was obtained by performing 5/6 nephrectomy and animals were daily instilled with PD fluid enriched or not with Ala-Gln during a period of 5 and 8 weeks respectively for rats and mice. Mice were injected weekly with recombinant IL-17 or with saline. Histological analysis was carried out in parietal peritoneum. Gene expression in the parietal peritoneum biopsies was evaluated by real-time quantitative PCR. Protein levels were determined by ELISA in peritoneal effluents.

Results: Supplementation of PD fluid with Ala-Gln resulted in reduced peritoneal thickness (70.90 ±13.45 vs 16.23 ± 0.70, P<0.001), ASMA expression and angiogenesis. Addition of Ala-Gln also showed attenuation of PD induced IL-17 mediated pathways, reflected by substantial reduction/normalisation of peritoneal levels of IL-17 (32.55 ± 7.99 ± 1.59, P<0.001), TGFI-3, IL-6 and BOR(γ). Moreover, repeated exposure of the Ala-Gln treated group to recombinant IL-17 increased peritoneal fibrosis which was however restored upon IL-17 neutralization.

Conclusions: These results suggest that intraperitoneal administration of Ala-Gln ameliorates PD induced peritoneal damage at least in part by modulating IL-17 expression. Therefore, this evidence paves into investigations whether Ala-Gln could be a potential strategy to ameliorate peritoneal deterioration during PD.

FR-PO812
JAK1/2 Inhibitor Preserves Peritoneal Membrane Function in a Non-Uremic Peritoneal Dialysis Rat Model

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Background: We previously showed JAK/STAT pathway activation in the peritoneal membrane (PM) of rats receiving PD with 4.25% Dianel for 10 days; concomitant treatment with a JAK1/2 inhibitor (JAKi) attenuated PM inflammation, fibrosis, and hypervascularity. We also showed that the mean concentration of MCP-1 was higher in the PD fluid of patients on long-term PD (>6mos) vs new patients (<2wks), demonstrating the potential for clinical relevance (KI.2014). These experiments were performed to determine if a JAKi could prevent deterioration of peritoneal membrane function after longer-term exposure to PD fluid.

Methods: Tunnelled PD catheters were placed in rats who received BID infusions of normal saline (n=3), 4.25% Dianel (n=3), or 4.25% Dianel + JAKi (n=3) for 12 weeks. Peritoneal equilibration testing (PET) was performed at baseline and again after 12 weeks of fluid instillation. For PET calculations, d lysate glucose was measured enzymatically at time 0 and at 90 minutes after fluid instillation. Plasma and dialysate total protein were measured at 90 minutes after dialysate instillation. D/D glucose and D/P total protein were calculated as [D/D glucose (at 12 wks)] / [D/P total protein (12 weeks – Baseline)/Baseline] for each rat. Results are expressed as mean ± SD for each group.

Results: Both D/D glucose and D/P total protein functional measurements demonstrate that JAKi protects the peritoneal membrane from the damaging effects of 4.25% Dianel.

Figure 1

Conclusions: Membrane failure limits the use of PD long-term. Strategies that preserve PD function are critically needed. Together with our prior results, these studies demonstrate the capacity of JAKi to preserve rat PD membrane structure and function during PD fluid exposure.

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FR-PO813
MicroRNA Expression Profiling in Peritoneal Fibrosis

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Background: Peritoneal fibrosis (PF) is an intractable complication leading to peritoneal membrane failure in peritoneal dialysis (PD). The aim of this study was to identify the microRNAs (miRNAs) involved in PF.

Methods: miRNA screen was performed using microarray analysis in peritoneal tissue of PF patients. Results were validated by qPCR in PF and control groups. Results were validated by qPCR in PF and control groups.

Results: The initial profiling study identified 6 miRNAs (miRNA-21-5p, miRNA-221-3p, miRNA-223-3p, miRNA-142-3p, miRNA-327 and miRNA-34a-5p) increased more than twofold. All miRNA decreased less than half in peritoneum tissue of PF rats compared with control rats. Among them, serum level of miRNA-21-5p (D/P Cr =0.44, p=0.01; D/D glucose r=−0.43, p=0.01), miRNA-327 (D/P Cr =r=0.48, p=0.01, D/D glucose r=0.50, p=0.01) and miRNA-221-3p (D/P Cr =r=0.50, p=0.01, D/D glucose r=0.50, p=0.01) and drained dialysate level of miRNA-221-3p (D/P Cr =r=0.52, p=0.01) and D/D glucose r=0.46, p=0.01) and miRNA-34a-5p (D/P Cr =r=0.44, p=0.01, D/D glucose r=0.48, p=0.01) were significantly correlated with peritoneal membrane functions in PD patients. Anti-miRNA-21-5p significantly inhibited miRNA-21-5p expression in peritoneum of PF mice. It also inhibited peritoneal fibrosis thickening and maintained better peritoneal membrane functions.

Conclusions: The results of present study suggested several miRNAs involved in PF, and they may be used as the novel diagnosis biomarkers and therapeutic targets for PF.

Funding: Government Support - Non-U.S.

FR-PO814
Nanoparticles of Lipids Associated with Paclitaxel as an Alternative Strategy to Block Peritoneal Fibrosis

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Background: Peritoneal fibrosis (PF) and loss of ultrafiltration represent important complications of long term peritoneal dialysis, with limited options of treatment. Advances in nanotechnology enabled drug release systems that can provide the release of an active drug in the target tissue. Nanoparticles similar to LDL were developed, linked to Paclitaxel (NanoPACL), an antiproliferative drug. NanoPACL have the ability to bind to LDL receptors present on the cell surface, particularly in immune-inflammatory sites. The aim of this study was to analyze the effect of NanoPACL administration in an experimental model of PF.

Methods: PF was induced in Wistar rats by daily IP injections of chlorhexidine gluconate (CG) at 0.1% during 15 days. Animals (n=20) were divided into 4 groups: Control, normal rats, PF treated with CG, NanoF, PF treated with NanoPACL (4mg/kg every 3 days, via IP). Euthanasia was performed on day 30. Peritoneal thickness and function, immunohistochemistry and qPCR were analyzed.

Results: NanoPACL significantly reduced peritoneal thickness, α-SMA expression and cell proliferation compared with control groups. Treatment with NanoPACL decreased TGF-β and Smad 3 mRNA expression and preserved peritoneal function characterized by preservation of UF and reduced mass transfer of glucose (MTG).

*p<0.05 vs Control; **p<0.05 vs Nano.

Conclusions: NanoPACL administration was effective in preventing PF and preserving peritoneal function, possibly by local effect of Paclitaxel.

Funding: Government Support - Non-U.S.

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Underline represents presenting author.

551A
FR-PO815

Background: EMT is known as a key mechanism of peritoneal fibrosis in peritoneal dialysis. Oxidative stress induced by NOX and mitochondrial dysfunction is one of the mechanisms responsible for EMT. Paricalcitol, a selective VDRA, is known to exert anti-fibrotic effect organ fibrosis, however there are no studies about the role of paricalcitol on peritoneal fibrosis. We investigated whether paricalcitol imposed any effect on TGFB1-induced EMT of HPMC with an exploration of mechanism of anti-fibrotic effect of paricalcitol in terms of modulation of oxidative stress.

Methods: EMT was evaluated by morphological changes of HPMCs and the expressions of E-cadherin and α-smooth muscle actin. Intracellular ROS was analyzed by measurements of NOX activity, NOX mRNA expressions with DCF-DA and MitoSox staining. Activation of Erk1/2, p38 MAPK, nuclear translocation of β-catenin and snail expression were assessed by western blotting and immunocytochemistry. Effect of paricalcitol on ROS generation and EMT was analyzed in HPMC exposed to TGFB1.

Results: TGFB1 (1ng/ml) induced EMT of HPMCs with an increase in ROS generation and NOX activity from 30 minutes, and mitochondrial ROS production from 6 hours. TGFB1 also increased the phosphorylation of Erk and p38 MAPK from 1hour, which was followed by nuclear translocation of β-catenin and snail up-regulation in HPMC. Paricalcitol (50nM) ameliorated TGFB1-induced EMT in HPMC, which was associated with a decrease in both NOX- and mitochondria-mediated ROS production. TGFB1-induced EMT was partially alleviated by N-acetyl cysteine (5mM) or apocynin (100µM), which was further inhibited by an addition of rotenone (1µM) or paricalcitol.

Conclusions: One of the VDRAs, paricalcitol, ameliorated TGFB1-induced EMT of HPMCs by a decrease in ROS generation in HPMCs. Anti-oxidant effect of paricalcitol seems to be related to the direct inhibition of NOX and mitochondria-mediated ROS production.

Funding: Government Support - Non-U.S.

FR-PO816
Adenosine Monophosphate-Activated Protein Kinase (AMPK) Agonist Attenuated Epithelial-to-Mesenchymal Transition (EMT) of Mesothelium and Peritoneal Fibrosis via an Amelioration of Oxidative Stress. Duk-Hee Kang, Juyeon Ko, Eun-sun Ryu, Hyun-yon Jung, Shina Lee, Dong-Ryeol Ryu, Seung-Jung Kim, Kyu Bok Choi, Sun-Hee Park, Yong-Lim Kim. Dept. of Internal Medicine, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea; Kyungpook National Univ School of Medicine, Daegu, Republic of Korea.

Background: Phenotype transition of peritoneum has been regarded as an early mechanism of peritoneal fibrosis. Metformin, one of the AMPK agonists, has recently received a new attention due to an inhibitory effect on EMT of cancer cells. We investigated whether metformin imposed any effect on EMT of HPMC with an exploration of cellular mechanism for anti-fibrotic effect of metformin.

Methods: EMT was evaluated by morphological changes and the expressions of E-cadherin and α-SMA after stimulation of TGFB1 (1ng/ml). ROS generation was analyzed by measurements of NOX activity, NOX mRNA expressions, and MitoSox staining. Activation of Smad2/3, MAPK, nuclear translocation of β-catenin and snail expression were also assessed. Animal model of peritoneal dialysis (PD) was established by daily infusion of H2O2 (100mM), peritoneal NOX- and mitochondria-mediated ROS production. TGFB1-induced EMT was partially alleviated by N-acetyl cysteine (5mM) or apocynin (100µM), which was further inhibited by an addition of rotenone (1µM) or paricalcitol.

Conclusions: One of the VDRAs, paricalcitol, ameliorated TGFB1-induced EMT of HPMCs by a decrease in ROS generation in HPMCs. Anti-oxidant effect of paricalcitol seems to be related to the direct inhibition of NOX and mitochondria-mediated ROS production.

Funding: Government Support - Non-U.S.

FR-PO817
Twist Accelerates Human Peritoneal Mesothelial Cells Proliferation and Fibrosis by Regulating YB-1. Liijie He. Dept of Nephrology, Xijing Hospital, Xi’an, China.

Background: We have previously shown that E-box-binding transcription factor Twist is overexpressed in high glucose damage of human peritoneal mesothelial cells (HPMCs) and is involved in peritoneal membrane (PM) fibrosis in vitro. Here, we further identify its precise function related to peritoneal membranes (PM) fibrosis.

Methods: We have previously shown that E-box-binding transcription factor Twist is overexpressed in high glucose damage of human peritoneal mesothelial cells (HPMCs) and is involved in peritoneal membrane (PM) fibrosis in vitro. Here, we further identify its precise function related to peritoneal membranes (PM) fibrosis.

Results: Here, up-regulated expression and activation of Twist and YB-1 were found in HPMCs under extensive periods of PM fibrosis ex vivo. In immortal HPMCs and in HG-induced PD animal model, Twist and YB-1 were also up-regulated and a transformed fibroblastic phenotype of HPMCs was found stimulated by high glucose (HG, 60mM/L).

Conclusions: Our data suggested that activation of Twist/YB-1 pathway might contribute to the growth retardation of HPMCs and the progressive PM fibrosis during PD.

Funding: Government Support - Non-U.S.

FR-PO818

Background: Peritoneal fibrosis (PF) is an almost invariable consequence of peritoneal dialysis (PD), which is an established alternative for the replacement therapy of end-stage renal disease. We know that miR-200a belong to miR-200 family, which is closely related to a variety of fibrotic diseases.However, the role of miR-200a in peritoneal fibrosis is largely unknown.

Methods: The peritoneal fibrosis mouse model associated with PD was established by intraperitoneal injection of lipopolysaccharide + 4.25% peritoneal dialysate. The expression of miRNA was detected by microarray. The expression of miRNA profiles between fibrotic and normal peritoneal tissues was compared (n=3 in each group). The differentially expressed miRNA (miR-200a) was validated by real-time PCR in larger sample size cohorts (n=15). The expressions of miR-200a were also detected in the epithelial-mesenchymal transition (EMT) process of peritoneal mesothelial cells.

Results: In mice model of PD, peritoneal tissue was markedly thickened and with a massive extracellular matrix accumulation. By microRNA microarray analysis, miR-200a was significantly down regulated (3.31 folds change, P<0.05) in fibrotic peritoneal tissues. The down-regulated expression level of miR-200a was also validated by real-time PCR in larger cohorts (P<0.05). Then, the expression level of miR-200a was detected in the EMT process of human peritoneal mesothelial cells. During the process of TGFB1 induced EMT, miR-200a was significantly down-regulated compared with the control (P<0.05)

Conclusions: Our data suggested that activation of Twist/YB-1 pathway might contribute to the growth retardation of HPMCs and the progressive PM fibrosis during PD.

Funding: Government Support - Non-U.S.

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Peritoneal Dialysis - II

FR-PO820
Effects of Astragaloside IV against the TGF-β-Induced Epithelial-to-Mesenchymal Transition in Peritoneal Mesothelial Cells by Promoting Smad7 Expression

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Background: To investigate the effect of Astragaloside IV (AS-IV) on the regulation of the TGF-β1-Smad signaling pathway in peritoneal mesothelial cells with an epithelial-to-mesenchymal transition (EMT).

Methods: EMT of human peritoneal mesothelial cells (HMrSV5) was induced using 2 ng/ml TGF-β1. Cells were randomly divided into a vehicle group, a vehicle group with AS-IV, a TGF-β1-treated group, and a TGF-β1-treated group receiving varied doses of AS-IV or NAC. Real-time quantitative PCR and western blot were used to detect the expression of genes and proteins associated with the TGF-β1-Smad signaling pathway and EMT. DCFH-DA was used to detect the generation of ROS in HMrSV5 cells, and a transwell migration assay was used to verify the capacity of AS-IV to inhibit EMT in HMrSV5 cells. Lentiviruses were used as carriers for the overexpression or knockdown of the Smad7 gene.

Results: Expression levels of E-cadherin (epithelial marker) were decreased and vimentin, α-SMA (EMT markers) and collagen I (extracellular matrix protein) phosphorylated Smad-2/3, Snail1 and Snail2 increased significantly in the TGF-β1-treated HMrSV5 cells. AS-IV was associated with downregulated expression of vimentin and phosphorylated Smad-2/3 in a dose-dependent manner, while the expression of Smad7 increased. Silenced or forced expression of Smad7 verified its role in the inhibitory effect of AS-IV on TGF-β1-induced EMT in HMrSV5 cells.

Conclusions: AS-IV effectively promotes the upregulation of Smad7 in the TGF-β1-Smad signaling pathway during the EMT of HMrSV5 cells, indicating its potential therapeutic effect for the control of peritoneal dialysis associated fibrosis (PD-FA). Funding: Government Support - Non-U.S.

FR-PO821
Extracellular Vesicles in Peritoneal Effluent

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Background: Continuous and long-term exposure to peritoneal dialysis (PD) solutions induces constant low-grade inflammation and remodeling of peritoneal membrane morphology. Although the biochemical composition of peritoneal effluent offers the opportunity to explore the peritoneal membrane status in a simple and non-invasive manner, to date no clinically useful effluent biomarker has been identified that reflects the peritoneal membrane integrity sufficiently. As human body fluids contain extracellular vesicles (EVs), which are now believed to provide novel biomarkers for diseases, we investigated the presence of EVs in peritoneal effluent.

Methods: Peritoneal effluent of a short-term PD patient was collected from a regular dialysis dwell. After centrifugation, aliquots of cell-free effluent were frozen in liquid nitrogen and stored at -80°C until analysis. EVs were isolated by size exclusion chromatography. Thereafter, transmission electron microscopy (TEM) and flow cytometry (comprising markers for epithelial and mesothelial cells, leukocytes, platelets and erythrocytes) were used to detect the presence of single EVs.

Results: EVs and liposomes were identified by TEM and flow cytometry. EVs exhibited their characteristic cup shape. The majority of EVs had a mean diameter <100nm, and were present in similar amounts as in human plasma. Most EVs originate from epithelial and mesothelial cells. Moreover, EVs stained positive for leucocyte antigens, mesothelin and cancer antigen 125.

Conclusions: This is the first study to demonstrate the presence of EVs in human peritoneal effluent. Furthermore, the cellular origin of most peritoneal EVs is established.

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FR-PO819
Peritonitis Induces Native and EDA+ Fibronectin Synthesis in Human Peritoneal Mesothelial Cells Through PI3K and MAPK Activation

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Background: Peritonitis is a severe complication of peritoneal dialysis (PD), which could lead to progressive structural and functional deterioration of the peritoneum and PD failure. EDA+ fibronectin (FN) is induced during disease states, but its expression in PD associated peritonitis has not been investigated. We examined peritoneal expression of native and EDA+ FN, collagen and SNAIL synthesis.

Methods: Male C57BL/6 mice were challenged with PBS or lipopolysaccharide (LPS, 500mg) by intraperitoneal injection for 2, 3 and 6 times (n=6), after which time the peritoul peritonitis was excised for further studies. Confluent, growth arrested human peritoneal mesothelial cells (HPMC) were stimulated with peritonitis PD fluid, LPS, or exogenous TGF-β1 or CTGF (growth factors that are increased during peritonitis) either alone or in combination, for periods up to 72h to investigate their effect on cell morphology, and FN, collagen and SNAIL synthesis.

Results: Mice exposed to six, but not fewer, challenges of LPS exhibited mesothelial denudation, influx of infiltrating cells and substantial submesothelial thickening attributed to increased collagen and native and EDA+ FN deposition. Peritonitis PD fluid induced phenotypic changes, and SNAIL, collagen I, and native and EDA+ FN synthesis in HPMC. Exogenous TGF-β1, but not CTGF, significantly increased native and EDA+ FN by 4.3-fold and 6.2-fold respectively (P<0.05 for both). Cells co-stimulated with TGF-β1 and CTGF showed synergistic increase of native and EDA+ FN. This was mediated in part through PI3K, ERK and p38 MAPK activation. TGF-β1 and CTGF neutralizing antibody significantly decreased native and EDA+ FN synthesis, but had no effect on collagen I or SNAIL expression in HPMC.

Conclusions: Our data demonstrated that peritonitis, especially when recurrent, induced progressive peritoneal deposition of collagen, and native and EDA+ FN, TGF-β1 and CTGF synergistically induced native and EDA+ FN synthesis in HPMC, and play important roles in peritoneal fibrosis induced by bacterial peritonitis.

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We postulate that the presence and composition of such EVs in peritoneal effluent will closely mirror the peritoneal membrane morphology. Future studies will be necessary to investigate the clinical relevance for the detection of peritoneal membrane damage and potential use of these peritoneal EVs in PD patient care.

FR-PO822

miR-200a Negatively Regulates TGF-β1-Induced Peritoneal Mesothelial Cell Epithelial-Mesenchymal Transition by Targeting ZEB1 and ZEB2 Expression Xin Wei, Guojun Hao, Qinkai Chen. Nephrology Dept, The First Affiliated Hospital of Nanchang Univ, Nan Chang, China.

Background: Peritoneal fibrosis (PF) is an almost invariable consequence of peritoneal dialysis (PD), which is an established alternative for the replacement therapy of end-stage renal disease. In our previous study, we found that the expression level of miR-200a were down-regulated in fibrotic peritoneum and the epithelial-mesenchymal transition (EMT) process of peritoneal mesothelial cell. However, the role of miR-200a in EMT of peritoneal mesothelial cell and peritoneal fibrosis is largely unknown.

Methods: Human peritoneal mesothelial cell line (HMMSV5) was cultured in the presence or absence of TGF-β1. The protein expression levels of EMT index and E-box-binding homeobox (ZEB) 1/2 were determined by western blot. The level of miR-200a was determined by real-time PCR. miR-200a mimic or inhibitor and negative control RNA was transfected into HMMSV5 cells using Lipofectamine 2000.

Results: We found that miR-200a mimic can attenuated TGF-β1 induced peritoneal mesothelial cell EMT and synthesis of extracellular matrix. It was also demonstrated that the miR-200a was responsible for protecting peritoneal mesothelial cells from mesenchymal transition by targeting suppression of ZEB1/2.

Conclusions: The results suggested that miR-200a may not only be a useful biomarker of EMT in ovarian cancer, but also of potential therapeutic value in peritoneal fibrosis.

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FR-PO823

Identification and Functional Characterization of Human Peritoneal Fibroblast Subsets According to the Expression of CD90/Thy-1 Edyta Kawka,1 Andras Rudolf,2 Maria Bartosova,2 Rusan Catar,1 Janusz Witowski,2 Duska Dragun,1 Achim Joerres,1 Claus P. Schmitt.1 1Dept of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany; 2Dept of Pathophysiology and Clinical Immunology, Poznan Univ of Medical Sciences, Poznan, Poland; 1Center for Pediatric and Adolescent Medicine, Universitätsklinikum Heidelberg, Heidelberg, Germany.

Background: The exact origin of myofibroblasts in PD-associated peritoneal fibrosis is unknown. Lineage tracing studies suggest that resident submesothelial fibroblasts may be their major precursors. Here, we set out to identify HPFB subsets in human peritoneum and examined co-expression of CD90/Thy-1 with markers of the myofibroblastic phenotype.

Methods: HPFB were isolated from omentum, purified and then separated (MACS) into CD90/Thy-1+ and CD90/Thy-1− populations for assessment of myofibroblastic markers.

Conclusions: The role of miR-200a in EMT of peritoneal mesothelial cell and peritoneal fibrosis is largely unknown.

Funding: Cell-free DNA is present in the peritoneal effluent of stable PD patients, but there is no data on cDNA in case of peritonitis. We investigated the variation of peritoneal cDNA (pcDNA) levels in PD-related peritonitis.

Methods: We enrolled 53 PD patients: 30 without any history of systemic inflammation and peritonitis in the last 3 months (group A) and 23 with acute peritonitis (group B). pcDNA were quantified by Real-Time PCR. Peritoneal samples on day 1-3-10 and until the 120th from the start of peritonitis were collected for WBC counts and pcDNA evaluation in group B.

Results: Quantitative analysis of pcDNA showed significantly higher levels in group B compared with group A (p<0.01), similarly as WBC. pcDNA showed significantly higher levels in group B on day 1-3-10 and 30 compared with group A (p<0.05). A significant positive correlation was observed between pcDNA level and WBC on day1 (rho=0.89) and day3 (rho=0.5) both p<0.05. No statistically significant correlation was observed on day10 and 30. In group B, pcDNA tends to progressively decrease. From this decreasing curve, we estimated that 49 days are necessary to reach the value of 51 GE/ml (75 percentile in group A) and 63 days to reach 31 GE/ml (median). We observed a new rapid increase of pcDNA level (consistent with WBC) in 5 relapsing patients, at the first day of relapsing peritonitis.

Conclusions: pcDNA increased in peritoneal effluent in PD-related peritonitis and tended to progressively decrease in relation with membrane repair process. Peritoneal cDNA could be a new method to determine acute damage and an inverse index of repair process. PefDNA could help to evaluate functional and structural integrity of peritoneal membrane and to follow the evolution of infections during peritonitis.

FR-PO825

The Role of Cell-Free DNA for Management in PD-Related Peritonitis Grazia Maria Virzì, Sabrina Milan manani, Alessandra Brocca, Massimo de Cal, Ilaria Tantillo, Carlo Crepaldi, Claudio Ronco. Nephrology, San Bortolo Hospital-IRRI

Background: Peritonitis and exit site infections are the major complications of PD and remains the major cause of switch from HD. In this study, we investigated the role of peritoneal cell-free DNA (cDNA) and its association with peritonitis.

Methods: We enrolled 23 PD patients with peritonitis and without any history of systemic inflammation (14 male, mean age: 68±16yrs). cDNA was extracted and quantified in peritoneal effluent by Real Time PCR for β-globin gene.

Results: All patients were treated and clinically recovered from peritonitis in 13.5±4 Days. 18/23 patients had a first episode of peritonitis and responded to first-line antibiotics (65% Gram+, 22% Gram- and 13% sterile), whereas 5/23 had a relapsing episode of peritonitis (responded to other course of intra-peritoneal antibiotics). There were 1.2-fold greater reduction in collagen gel contraction assays (n=3).

Conclusions: The results suggested that miR-200a may not only be a useful biomarker of EMT in ovarian cancer, but also of potential therapeutic value in peritoneal fibrosis.

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no was difference in cDNA levels between Gram- (+Gram-peritonitis; patients with single episode and relapsing peritonitis, but there was a significantly difference in cDNA between PD patients with positive and negative outcomes (n=4), defined as death (p<0.05). cDNA shown significantly higher 1 level in 3 patients required catheter removal(p<0.05). There was no difference in cDNA levels between PD patients with a negative history of previous peritonitis (n=3) and PD patients with a positive history (n=20)(p=0.48). there was no statistically significant correlation between cDNA and number of previous peritonitis (r=0.13, p=0.55).

Conclusions: This pilot study provided substantial basis for further investigations of molecular mechanisms of peritoneal injury and potential clinical application of cDNA. cDNA could provide some additional information about patient’s outcome and management. These results can be considered hypothesis generating, and stimulate further exploration of a prognostic and predictive role of cDNA in PD-related peritonitis.

FR-PO826

Epimorphin Expressions in Mice Model of Peritoneal Fibrosis Munchuan Yamada, Takashi Oda, Shuuhei Komatsu, Taito Oshima 1,2 Kimio Watanabe, 1 Hiroyuki Terawaki, 1 Yoshimitsu Hayashi, 1" 1Dept of Nephrology, Hachioji Medical Center of Tokyo Medical Univ, Hachioji, Tokyo, Japan.

Background: Long-term peritoneal dialysis induces peritoneal fibrosis in submucosal area. Epimorphin is a mesenchymal protein that regulates epithelial morphogenesis through epithelial-mesenchymal transition, has recently attracted attention as an important modulator of tissue repair. We previously reported that epimorphin was involved in the repair of fibrosis in mice (Lab Invest 2010). In this study, we evaluated the epimorphin expressions in the peritoneal fibrosis mice model.

Methods: Peritoneal fibrosis was induced by the injection of 0.1% chlorhexidine gluconate in 15% ethanol and 85% normal saline (CG-injected mice) into peritoneal cavity of 10-week-old male C57B16 mice every other day. Control mice received intraperitoneal injection of normal saline. The mice were sacrificed 3 weeks after the first CG injection and peritoneal tissues were dissected out. Morphologic peritoneal changes were assessed by Masson’s Trichrome staining. Epimorphin expressions were assessed by immunohistochemically and real-time RT-PCR.

Results: In CG-injected mice, the marked thickening of the submesothelial compact zone was shown in Masson’s trichrome staining. IF staining for epimorphin was positive in the submucosal area corresponding to the fibrotic area. Epimorphin staining was significantly stronger than that in control mice. Such an increase in epimorphin expression was confirmed by and real-time RT-PCR (n=5, p<0.05 vs control).

Conclusions: These findings suggest that epimorphin expression may have pivotal role in the repair of peritoneal fibrosis similar to that of UUO release model in mice.

FR-PO827

Peritoneal Mesothelial Cells (PMCs) Injury Induced by Neutral Peritoneal Dialysis Solution (NPDS) and Its Amelioration by Molecular Hydrogen (H2) Wai-lun Zhu,1 Kinue Watanabe,2 Hirokuni Terawaki,1 Yoshimitsu Hayashi,1 Naoki Nakamichi,1 Shigeru Kabayama,2 Masaaki Nakayama,2 1Dept of Pediatrics, Japan, Pediatrics, 2Medical School, Fukushima Medical University, Fukushima, Japan.

Background: PMCs play pivotal roles in suppression of peritoneal fibrosis, adhesion, and bacterial infection in PD therapy. It is reported that histological changes of peritoneum and incidence of encapsulating peritoneal sclerosis, have been decreased by NPDS introduction. However, meta-analysis did not show superiority of NPDS in incidence of bacterial peritonitis, suggesting bio-incompatibility of current NPDS. H2 has anti-oxidative effects in biological way, and its clinical application has been studied. The present study aims to examine PMC injury by NPDS, and its ameliorating effect of H2.

Methods: Male SD rats (n=24) were divided into three groups: control (Con), 2.5% glucose lactate-based NPDS (PD), and the same NPDS with dissolved H2 (400 ppb) (HPD). The latter two groups were given NPDS or H2-NPDS intraperitoneally for 20 ml once a day. Peritoneal tissues were subjected to morphological analysis including immunohistochemistry (cytokeratin, vimentin, proliferation: Ki67 and apoptosis: M30 cytodeath), and PMCs obtained to gene analysis by real time PCR, and microarray assay.

Results: The collagen thickness increased in PD and HPD, however, there were significant changes in stainings of vimentin, M30 cytodeath, and Ki67 in PD as compared to control, with no change in HPD. In gene cluster analysis, there were changes by 8.7% in whole gene expression between PD and Con, and 3.7% changes between PD and HPD. In PCR, no difference was found in Epithelial-Mesenchymal Transition (Snail, TGF-β, αSMA) among the groups, while wound healing (MMP9, CTGF, Fibronectin, FAK), cytokines (IL1β, TNFα, FAK) were decreased in PD as compared to Con, but no changes in HPD.

Conclusions: The current lactate-based NPDS may disturb wound healing and local immunity of PMCs, and H2 dissolved dialysate correct them. H2 could increase biocompatibility of PDS in preserving physiological function of PMCs in PD therapy.

FR-PO828


Background: Long-term peritoneal dialysis is associated with functional and structural alterations of the peritoneal membrane. Lactate-buffered peritoneal dialysis fluid (L-PDF) has impaired biocompatibility due to the presence of supra-physiological levels of lactate. Although bicarbonate-buffered PDF (B-PDF) has been developed, its biocompatibility remains unclear. Here, we investigated the effects of L- or B-PDF on cell to cell apoptosis in cultured human peritoneal mesothelial cells (HPMCs), focusing on monocarboxylate transporters (MCT).

Methods: HPMCs were cultured in media containing 10% fetal bovine serum and L-PDF with 1.5% glucose (L1) or 2.5% glucose (L2), B-PDF with 1.5% glucose (B1) or 2.5% glucose (B2), or no PDF (control). Cell viability and apoptosis were measured with the WST-1 and TUNEL assays, respectively. The roles of MCT-1 and -4 on lactate-induced apoptosis were evaluated by siRNA transfection for MCT-1 and -4.

Results: Cell viability was significantly decreased in cells incubated with L1 (12.2% vs. control-100%) and L2 (21.1%), compared with B1 (74.2%) and B2 (72.2%) after 72 h incubation. Apoptotic cells were also increased in L1 (69±16%), L2 (73±8%) compared with B1 (3±0%) and B2 (±1%). MCT-1 and -4 protein and mRNA expression levels, examined by Western blotting and real-time-PCR, respectively, were similar in all cells. Protein expression levels of MCT-1 and -4 were almost completely diminished after transfection of siRNA's for MCT-1 and -4, respectively. MCT-1 siRNA increased the levels of cell viability by 3.2–3.7-fold and decreased the amount of apoptotic cells from 64±8% to 47±4% in cells treated with L1 for 72 h. Interestingly, MCT-4 siRNA had no effect on cell viability and apoptosis.

Conclusions: Our results showed that L-PDF induced apoptosis by importing lactate via MCT-1 in HPMCs, and suggest that B-PDF improved biocompatibility by inhibiting mesothelial cell apoptosis.

FR-PO829

MiRNA-143/145 Gene Cluster Enhances Cell Deformation and Fibrosis of Human Peritoneal Mesothelial Cells via Modulating TPM4 Li-Jie He, Shiren Sun. Dept of Nephrology, Xijing Hospital, Xi’an, Shaanxi, China.

Background: In this study, we worked for the function and mechanism of miR-143-145 gene cluster in human peritoneal mesothelial cells (HPMC), who were as possible triggers for peritoneal membrane fibrosis.

Methods: To investigate if miR-143/145 gene cluster could promote PM fibrosis, all these immortal HPMCs were characterized by fibrosis related markers and tested the expression of miRNA-143/145 cluster and tropomyosin4 (TPM4) by real time PCR or Western blot. We also used PD dialysis rat model to observe the response of PM to miR-143/145 gene cluster and their possible target.

Results: Here, we found that miR-143/145 gene cluster, which are examined to be highly expressed in HG-induced HPMCs (HG, 60 mmol/L) and in PD animal model. TPM4 were found significantly lower expression in HG-induced HPMCs. So our study was based on high glucose for human peritoneal fibrosis, and we found that miR-143/145 of HPMCs and reduce the expression of TPM4, compared with normal glucose-cultured HPMCs. Reporter assays further supported that TPM4 were post-transcriptionally regulated together by miR-143-145 gene cluster. Collectively, these data suggested that TPM4 was a key target gene for miR-143/145 gene cluster. Re-expression of miR-143/145 gene cluster by miR-143 or miR-145 mimic led to cell deformation, and reduced cell adhesion, following the down-regulating expression of TPM4 and E-cadherin, but up-regulating expression of α-SMA, CTGF, collagens and fibronectin which might increase PM fibrosis.

Conclusions: Our data suggested that miR-143/145-TPM4 pathway might contribute to the cell deformation of HPMCs and the progressive PM fibrosis during PD.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only.
Mitochondrial DNA Copy Number Is Associated with Peritoneal Dialysis Failure in Younger and Metabolically Healthier Peritoneal Dialysis Patients


**Background:** Insulin resistance and inflammation are known to be closely related to adverse outcomes in peritoneal dialysis (PD) patients. Recently, mitochondrial function has been reported to play a key role in glucose metabolism as well as systemic inflammation in various populations. However, the clinical consequences of mitochondrial function in PD patients are not well known. Therefore, this study aimed to investigate the relationship of mitochondrial DNA (mtDNA) copy number and clinical outcome in PD patients.

**Methods:** A total of 120 prevalent PD patients were recruited. mtDNA copy number was counted by a PCR based method. Primary outcome was PD catheter removal due to ultrafiltration failure. Metabolic syndrome was defined using the Modified National Cholesterol Education Program (Adult Treatment Panel III) criteria. Cox proportional hazard analysis was performed to determine the independent association of mtDNA copy number with primary outcome.

**Results:** The mean age was 52.3 years and 52 patients (42.5%) were male. The mean mtDNA copy number was 29.1±14.9. During a mean follow-up duration of 59.4±39.3 months, primary outcome was observed in 54 patients (45.0%). There were no significant differences in baseline characteristics between non-PD and PD failure group except for serum adiponectin levels (20.5±7.3 vs. 17.5±7.3 mg/mL, P=0.028). mtDNA copy number was significantly associated with PD failure in multivariate Cox analysis (hazard ratio (HR)=0.995, 95% confidence interval (CI)=0.976-1.015, P=0.634). However, a subgroup analysis revealed that mtDNA copy number was an independent predictor of PD failure in patients younger than 55 years without metabolic syndrome (HR=0.819, 95% CI=0.692-0.970, P=0.020) after adjustment for confounding factors.

**Conclusions:** mtDNA copy number may be associated with ultrafiltration failure in younger and metabolically healthier patients treated with PD.

**FR-P0830**

IL-6 Induces VEGF Production by Human Peritoneal Mesothelial Cells During Peritonitis Through SP4-Mediated Trans-Signaling with sIL-6R


**Background:** Vascular endothelial growth factor (VEGF) has been implicated in peritoneal angiogenesis and membrane remodelling in peritoneal dialysis (PD). Human peritoneal mesothelial cells (HPMC) have been identified as a major source of VEGF in the peritoneum. However, the exact mechanism of VEGF induction in HPMC is unclear. Since IL-6 concentrations in the drained dialysate correlate with VEGF levels, the link between the two has been suggested. While HPMC do not bear classical IL-6 receptor, they can respond to IL-6 trans-signaling that involves soluble IL-6 receptor (sIL-6R). Here, we have examined whether this mechanism can underlie VEGF synthesis by HPMC. By transfection of HPMC with SP4, a transcriptional factor that binds to the VEGF promoter, we have shown that SP4 is required for IL-6 induction of VEGF.

**Methods:** HPMC were isolated from normal omentum. Dialysate effluent was obtained from stable PD patients and during peritonitis. VEGF mRNA and protein levels were measured by RT-qPCR and ELISA, respectively. The involvement of transcriptional factors was assessed by EMSA, transient transfections with VEGF promoter constructs, and siRNA silencing.

**Results:** IL-6 and sIL-6R alone had no effect on VEGF release by HPMC. However, the exposure to IL-6+sIL-6R resulted in a time- and dose-dependent induction of VEGF mRNA and protein. The combination of IL-6+sIL-6R activated the VEGF promoter region that contained high affinity binding sites for the transcription factor SP4. Specific mutation of the SP4 binding site eliminated VEGF promoter activation. In turn, the induction of SP4 was controlled by STAT3. Exposure of HPMC to dialysate effluent obtained during acute peritonitis and containing increased levels of IL-6 and sIL-6R resulted in a dose-dependent VEGF induction. This effect was significantly attenuated in cells treated with siRNAs for either SP4 or STAT3.

**Conclusions:** Dialysate IL-6 and sIL-6R act through the trans-signalling pathway controlled by the STAT3-SP4 axis to up-regulate mesothelial VEGF production during peritonitis.

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

**FR-P0832**

'H NMR Based Metabolome Can Predict Relapsing Peritonitis and Differentiate Bacterial and Fungal Peritonitis as Well

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**Background:** Metabolomics is a powerful but resource-intensive approach for the study of metabolic changes in human disease. In the past few years, metabolomics has gained increasing attention in different diseases of human origin, including cardiovascular diseases, diabetes, cancer, and infections. In the present study, we aimed to develop a metabolomic-based approach for predicting relapsing peritonitis and differentiating bacterial from fungal peritonitis.

**Methods:** Five unused PD fluid, 13 effluent from normal PD and 45 effluents from 15 patients (at baseline, 1 week and 2 weeks of therapy) with BP including 3 who relapsed and 3 FP were included. Half of each was subjected to total and differential WBC count and culture; and half was frozen at -80 °C for NMR analysis. BP and FP was diagnosed based on identification of organism. RP was defined as per standard definition. High Resolution NMR spectra were recorded at 29V K on a Bruker Avance III 800 MHz spectrometer. Standard 1D 1H NMR spectra were acquired using the Carr–Purcell–Meiboom–Gill (CPMG) pulse sequence. To confirm the assignment of marker peak, two-dimensional (2D) HH-1H TOCSY and 1H-13C HSQC spectra were also acquired.

**Results:** Five unused and 15 normal PD effluents after 6 hours of dwell did not show any marker peak at NMR spectra at 0.67 ppm while 15 cases of BP showed marker peak; however marker peak disappeared after resolution of peritonitis at 1 week and 2 weeks of antibiotic therapy except for 3 cases which relapsed in whom marker peak was persisting despite absence of clinical peritonitis. In the 3 cases of FP did not show any such marker peak differentiating it from BP. Marker signal represent trans-methylene protons of cyclopropene ring moiety as reported earlier and depicted in Figure 1.

**Conclusions:** The cyclopropene signal at 0.67 ppm can be marker signal to differentiate BP and FP and persistence of this signal at 2 weeks after clinical resolution of peritonitis predicts RP.

**FR-P0833**

Peritoneal Mesothelial Cell Sodium Glucose Co-Transporter 1 (SGLT1) Regulates VEGF Production: Potential Target in Ultrafiltration Failure


**Background:** D-glucose and vascular endothelial growth factor (VEGF) are important in the development of ultrafiltration failure (UFF) in peritoneal dialysis (PD). The role of glucose transport in peritoneal mesothelial cells (PMC) in UFF is unknown. Herein we hypothesize that the glucose transporter SGLT1 is increased in response to high glucose and regulates VEGF production.

**Methods:** PMC, obtained from omental digestion of non-PD patients and from spent PD dialysates, were incubated for 48 hrs under 200mM D-glucose or L-glucose, 200mM mannitol, 200mM 3OMG a non-metabolizable glucose analog transported by SGLT1, 7.5% icodextrin, with and without 50μg/ml phlorizin (Ph), an SGLT1 inhibitor. VEGF was measured by ELISA. mRNA for VEGF and SGLT1 was measured by RT-PCR. Immunofluorescence microscopy for cytokeratin and SGLT1 was performed on human peritoneal biopsies obtained at PD catheter insertion (CI) and at catheter revision (CR) after 6 months of PD. Results: SGLT1 expression was minimal in PMC in biopsies at CI, but abundantly present in PMC in biopsies at CR. PMC’s cultured under 200 mM D-glucose had a 6 fold increase in SGLT1 mRNA vs 5mM D-glucose and an increase in VEGF: 70 ±9.9 pg/mg to 2,456 ±189 pg/mg (p<0.05). D-glucose stimulation of VEGF was partially inhibited by 50 μM Ph: 6,988 ± 405 pg/mg to 3,991 ±289 pg/mg (p<0.003). 3OMG also stimulated VEGF: 71 ± 1.9 pg/mg to 1,474 ±160 pg/mg (p<0.01) that was inhibited by Ph 623 ± 74 pg/mg, suggesting Ph inhibition of VEGF is partly independent of glucose metabolism (p<0.05). 200mM L-glucose stimulated VEGF less than D-glucose (543 ± 35pg/mg, p<0.01). This stimulation was inhibited by Ph (123 ± 12 pg/mg). 7.5% icodextrin vs 5mM Glucose did not stimulate VEGF production (47 ± 5.1 pg/mg, p<0.005).

**Conclusions:** SGLT1 expression in PMC is upregulated in response to high D-glucose in vivo and in vitro. Glucose transport regulates VEGF production under high D-glucose conditions, which may provide a therapeutic target for UFF.

**Funding:** Pharmaceutical Company Support - Baxter Healthcare Corp
CVD. Increased intact parathyroid hormone and FGF-23 levels are associated with the progression of peritoneal dialysis (PD) in chronic PD patients. N-acetylcysteine (NAC) acts on atherosclerosis and also improves the endothelial functions. This study was designed to evaluate the correlation between FGF-23, endothelial dysfunction and markers of inflammation in chronic PD patients and to evaluate the effect of three months of NAC on these parameters.

**Methods:** All patients underwent Doppler studies to assess endothelial function by the flow-mediated dilatation (FMD) of the brachial artery and carotid arterial intima media thickness (CIMT). Brachial artery was imaged during reactive hyperemia (endothelium-dependent dilatation, FMD) and during the brachial artery with acetylcholine (endothelium-independent dilatation, nitroglycerine-mediated dilatation, NMD, endothelium-independent) in all PD patients. NAC was given in the dose of 1200 mg in two divided doses for a period of three months. The associations between different parameter were analyzed using Spearman correlation. All the parameters were repeated after three months of therapy with NAC.

**Results:** A total of 73 chronic PD patients were enrolled in this study. FGF-23 showed strong positive correlation with serum homocysteine level (r = 0.10, P < 0.001), hsCRP (R = 0.977, P < 0.001), Endothelium Dependent Dilatation (EED) (r = 0.968, P < 0.001) and CIMT (r = 0.994, P < 0.001), but negatively correlated with Endothelium Independent Dilatation (EID) and Vitamin D level. All these parameters including FGF-23, hsCRP, homocysteine, CEMT and EDD were significantly reduced after three months of therapy with NAC.

**Conclusion:** FGF-23 correlated well with inflammatory markers and endothelial function. With three months of therapy, NAC significantly reduces the CIMT, inflammatory markers and improves the endothelial function in chronic PD patients.

**FR-PO835**

**SRF Enhances Cell Adhesion, Migration and Peritoneal Fibrosis via Modulating miRNA-199a-214 Cluster in Human Peritoneal Mesothelial Cells**

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**Background:** Our previous work showed that serum response factor (SRF) was involved in fibrosis of peritoneal membrane, but the exact underlying mechanism were still unclear. Here we further study the role of miR-199a-214 cluster and the relationship of SRF in peritoneal fibrosis.

**Methods:** We isolated HPMCs from the effluents of end-stage renal disease (ESRD) patients with peritoneal dialysis (PD), and also used PD dialysate rats model to observe the response of PM to miR-199a/214 cluster and the predicted target CDH1 and CLDN2.

**Results:** In this study, we found that miR-199a-5p/214 cluster, which was examined to be highly expressed in HG-induced HPMCs by real time PCR, was directly regulated by SRF after HG stimulation. All these HG induced immortal HPMCs became scatter, to be highly expressed in HG-induced HPMCs by real time PCR, was directly regulated by SRF after HG stimulation. All these HG induced immortal HPMCs became scatter. We also found that SRF acted on atherosclerosis and also improved the endothelial functions. This study was designed to evaluate the correlation between FGF-23, endothelial dysfunction and markers of inflammation in chronic PD patients and to evaluate the effect of three months of NAC on these parameters.

**Conclusion:** FGF-23 correlated well with inflammatory markers and endothelial function. With three months of therapy, NAC significantly reduces the CIMT, inflammatory markers and improves the endothelial function in chronic PD patients.

**Choice of Dialysis Modality for Children with End Stage Renal Disease**

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**Background:** Despite many studies that aim to assess the best modality of dialysis, results remain conflicting both in adults and in children. This lack of medical evidence leads commentators to emphasize the importance of patients' choice in the decision process. Thus, we try to assess factors that impact the choice of the dialysis modality in children and to determine which from medical factors, center practices or patients' wishes plays the major role.

**Methods:** All incident patients <20 years old at start of dialysis, recorded in the French ESRD registry between 2002 and 2013 were included. We used multivariate hierarchical logistic regression models to study patients and centers characteristics associated with the probability of starting with peritoneal dialysis (PD). The effect of centers was assessed by including centers as a random effect.

**Results:** Among 806 patients treated in 177 centers, 601 (74.6%) started with PD, 121 (14.9%) with hemodialysis (HD) and 20 (25.4%) with PD. A higher probability of PD was found in patients younger than 1 year and in centers with an annual emergency associated with a low use of PD. Low and high educational level of the town of residence were both associated with less probability of PD when compared with average educational level. There was a significant variability between centers, that was not explained by patients' case-mix. Being treated in specialized pediatric centers was associated with less probability of PD, while the probability of PD was proportional to the rate of PD in the center.

**Conclusions:** Although little evidence exists to favor a dialysis modality over the other in children, PD remains the predominant modality in France. PD is still mostly offered to treatment-naive children while it remains understudied in patients starting RRT in emergency. However, we found that besides medical factors, centers practices play a major role in the choice of dialysis modality. This raise concerns about the place left to patients' and families' choices and to what extend doctors may influence the final decision. Further pediatric studies focusing on children and parents' wishes are needed in order to provide cares as close as possible to there expectations.
Clinical Course of Children Born with Chronic Kidney Disease – A Single Centre Experience
Christina Taylan, 1 Bernd Hoppe, 2 Eva Maria Haffner, 2 Lutz Thorsten Weber. 1 Pediatric Nephrology, Univ Hospital of Cologne, Cologne, Germany; 2 Pediatric Nephrology, Univ Hospital of Bonn, Bonn, Germany.

Background: The number of babies born alive suffering from chronic kidney disease (CKD) is constantly increasing.

Methods: We analyzed the outcome of infants with CKD and renal replacement therapy (RRT) that were treated within their first year of life. Between 2007 and 2013 17 infants (11 male; 6 female) developed end-stage renal disease resulting in RRT in our department.

Results: All of them received peritoneal dialysis (PD) initially at a median age of 34 [1-334] d. During follow-up 10 children underwent renal transplantation (RTx), 1 child was still on PD at last follow-up, 1 child had to go back to hemodialysis after graft loss and 2 had a recovery of renal function. 3 out of 17 children died during the PD period. Causes of death were severe sepsis twice and one cerebral bleeding. The mean GFR at last follow-up (2.2±6.37 years) of patients who underwent RTx was 105±22.8 ml/min/1.73 m². Mean time on dialysis was 11.1±14.3 months before RTx, mean age at transplantation was 29.2±14.2 months. Mental development was measured by Mental Development Index (Bayley Scales of infant development BSID-II) at an average age of 12 [9-16] months and showed developmental delay at the motor, mental and behaviour rating scale. At time of transplantation 6/10 infants had tube feeding, 9/10 were <3 percentile of height, 3/10 were <3 percentile of body weight.

Conclusions: RRT started in the first year of life was associated with reasonable outcome and should be offered to all infants with end stage renal disease. It is, however, associated with a high risk of developmental delay. This work emphasizes the great needs for research on this interdisciplinary field of pediatric nephrologists, psychologists and social workers.

FR-PO840
Altered Myogenesis and Oxidative Stress in a Rat Model of Chronic Kidney Disease
Keith Ayin, 1 Neal X. Chen, 2 Jason M. Organ, 3 Kaliala O’Neill, 4 Sharon M. Moe. 1 Dept Physical Therapy, Indiana Univ, Indianapolis, IN; 2 Div of Nephrology, Indiana Univ, Indianapolis, IN; 3 Dept of Anatomy, Indiana Univ, Indianapolis, IN; 4 VAMC, Indianapolis, IN.

Background: Skeletal muscle atrophy and impaired muscle function are associated with lower quality of life, and greater disability and mortality risk in those with chronic kidney disease (CKD). However, the pathogenesis of atrophy is unknown.

Methods: We used a slowly, progressively, naturally occurring, CKD rat model (Cy/ rat) and its normal littermate (NL). At 35 weeks, we tested muscle strength, sacrificed and collected tissues and blood. RNA and protein were isolated from skeletal muscle and real time PCR and western blot were performed.

Results: CKD rats developed sarcopenia evident by reduced cross sectional area (p<0.05), increased connective tissue deposition on histology (p<0.05), and impaired strength (p<0.05). Strength was defined as the maximal amount of force produced during maximal, electrically stimulated dorsiflexion. These findings of atrophy can be explained by reduced regeneration, increased catabolism, or differentiation of muscle stem cells toward myofibroblasts. By PCR, there was increased activation and differentiation of muscle stem cells (reduced Pax-7, increased MyoD and myogenin (p<0.05)) and increased proteolytic markers (increased Atrogin-1 and MuRF-1 (p<0.05). Fibrosis may be enhanced via decreased miR-29b (p<0.05) and increased Wnt5a (p<0.01). Finally myostatin was increased in blood and muscle RNA expression yet no difference in the activin type IIB. The long term consequences of the impaired balance of increased proteolysis and inadequate regeneration is further supported by mitochondrial derangement (electron microscopy) and increased mitochondrial complex I (p<0.05) despite decreased expression of the antioxidant nuclear erythroid 2-related factor 2 (p<0.05).

Conclusions: In a rat model of CKD, sarcopenia was present despite the activation of myogenic factors. The atrophy is due to a combination of factors including increased myostatin, increased expression of atrogenes, and the presence of oxidative damage. Augmentation of the myogenic and antioxidant responses through treatments may prevent progressive sarcopenia in CKD.

Funding: Other NIH Support - NIH R01AR058005

FR-PO841
Can Calcitriol and Calcidiol to Regulate Toll Like Receptors 7, 9 and IL-6 in HD Patients?
Marina Dalboni, 1,3 Marion Schneider, 1 Lilian Cuppari, 1 Caren Cristina Grabulosa, 1 Silvia Regina Manfredi, 1 Edgar Maquigussa, 1 Danilo Takashi Aoki, 1 Miguel Cendoroglo Neto, 1 Jose Tarcisio Giffoni. 1 Nephrology Div, Univ Federal de Sao Paulo, Sao Paulo, Brazil; 2 Div of Nephrology, Univ Federal de Sao Paulo, Sao Paulo, Brazil; 3 Medicine, Tufts-New England Medical Center, Boston; 4 Medicine, Univ Nove de Julio, Sao Paulo, Brazil.

Background: Toll-like receptors (TLR) are involved in immunologic response. The TLR4 is related with cytokines and counter-regulators and therefore these vitamins alone to induce a degradation of 1,25 (OH)2D3, we did a CYP24 silencing, and observed an additional reduction in IL6, IFNγ, TLR7 and TLR9 expression on B and T lymphocytes for both treatment when compared to effect of 25(OH)D3 alone (p<0.05). In the same condition, we also observed an increase VDR expression.

Conclusions: Our results suggests that both 25(OH)D3, and 1,25 (OH)2D3, had immunomodulatory effects in B and T lymphocytes. This in vitro model confirm the antiinflammatory role of Vitamin D in uremia environment. However, these effects of Vitamin D were enhanced after CYP24 silencing. So, this data support that CYP24 inhibitors may also be a target of treatment in association with vitamin D supplementation to improve inflammatory response mechanisms.

FR-PO843
Effect of Cholecalciferol Supplementation on Toll Like Receptors 7, 9 Expression and IL-6 and IFN-γ Intraacellular on B and T Lymphocytes on Chronic Dialysis Patients
Maria Dalboni, 1,3 Marion Schneider, 1 Lilian Cuppari, 1 Caren Cristina Grabulosa, 1 Silvia Regina Manfredi, 1 Edgar Maquigussa, 1 Danilo Takashi Aoki, 1 Miguel Cendoroglo Neto, 1 Jose Tarcisio Giffoni. 1 Div of Nephrology, Univ Federal de Sao Paulo, Sao Paulo, Brazil; 2 Div of Nephrology, Univ Federal de Sao Paulo, Sao Paulo, Brazil; 3 Medicine, Tufts-New England Medical Center, Boston; 4 Medicine, Univ Nove de Julio, Sao Paulo, Brazil.

Background: Vitamin D deficiency is highly prevalent among patients in all stages of CKD. Studies have reported that the Vitamin D deficiency is associated with mortality and morbidity in CKD patients and may modulate TLRs that are involved in inflammatory responses. Thus, the purpose was evaluate the effect of cholecalciferol on IL-6, IFN-γ TLR-7 and TLR-9 expression in lymphocytes B and T in patients on dialysis with vitamin D hypominhemia.

Methods: In a randomized, placebo-controlled, double-blind study, we investigated the effect of cholecalciferol (100,000 UI once per week) for 3 months, in patients on chronic dialysis, who had nutritional vitamin D deficiency. The 25(OH)D3 detection was performed by immunoassay and the 25(OH)D3 levels were compared by Student t-test (p<0.05).

Results: TLR-7 and TLR-9 expression in lymphocytes B and T on patients on dialysis with vitamin D hypominhemia. The 25(OH)D3 detection was performed by immunoassay and the 25(OH)D3 levels were compared by Student t-test (p<0.05).

Conclusions: It is possible that the deregulation of TLR2 and TLR4 expression on lymphocytes may be caused by uremic toxins in CKD population. Besides, the high expression of TLR2 and TLR4 in these cells resulted in an increase of TLR-9 and IL-6 levels, suggesting that TLRs are associated with inflammatory mechanisms in uremic patients.

FR-PO847
Can Calciotropic and Calcidiol to Regulate Toll Like Receptors 7, 9 and IL-6 and IFN-γ Expression on Lymphocytes Incubated with Uremic Serum?
Marina Dalboni, 1,3 Marion Schneider, 1 Lilian Cuppari, 1 Caren Cristina Grabulosa, 1 Silvia Regina Manfredi, 1 Edgar Maquigussa, 1 Danilo Takashi Aoki, 1 Miguel Cendoroglo Neto, 1 Jose Tarcisio Giffoni.

Background: Vitamin D deficiency is highly prevalent among patients in all stages of CKD. Studies have reported that the Vitamin D deficiency is associated with mortality and morbidity in CKD patients and may modulate TLRs that are involved in inflammatory responses. Thus, the purpose was evaluate the effect of cholecalciferol on IL-6, IFN-γ TLR-7 and TLR-9 expression in lymphocytes B and T in patients on dialysis with vitamin D hypominhemia.

Methods: In a randomized, placebo-controlled, double-blind study, we investigated the effect of cholecalciferol (100,000 UI once per week) for 3 months, in patients on chronic dialysis, who had nutritional vitamin D deficiency. The 25(OH)D3 detection was performed by immunoassay and the 25(OH)D3 levels were compared by Student t-test (p<0.05).

Results: TLR-7 and TLR-9 expression in lymphocytes B and T on patients on dialysis with vitamin D hypominhemia. The 25(OH)D3 detection was performed by immunoassay and the 25(OH)D3 levels were compared by Student t-test (p<0.05).

Conclusions: It is possible that the deregulation of TLR2 and TLR4 expression on lymphocytes may be caused by uremic toxins in CKD population. Besides, the high expression of TLR2 and TLR4 in these cells resulted in an increase of TLR-9 and IL-6 levels, suggesting that TLRs are associated with inflammatory mechanisms in uremic patients.

FR-PO848
Nutrition, Inflammation, and Metabolism Poster/Friday

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

558A
associated with intracellular production of vitamin D on lymphocytes from CKD patients. These results suggest that vitamin D may affect heart disease, associating with thyroid hormone impairment. Therefore, we tried to investigate the effect of selenium deficiency on thyroid hormone and cardiovascular diseases in HD patients.

**Methods:** This cross-sectional study enrolled 83 HD patients. They were divided into two groups based on serum selenium levels: 62 patients were normal level and 22 patients were selenium deficient. Thyroid hormones such as TSH, free T4 were measured. And cardiovascular diseases, including IHD, heart failure or cardiomyopathy, were evaluated.

**Results:** Thyroid hormone impairment, including hypothyroidism and subclinical hyperthyroidism, showed higher tendency in selenium deficient group than that in non-selenium deficient group. (27% vs 10% P=0.06) The prevalence of IHD was significantly higher in selenium deficient group than that in the non-selenium deficient group. (59% vs 21%, p=0.04) But there was no difference in heart failure and cardiomyopathy. Patients with thyroid hormone impairment showed high prevalence of IHD, and the coincidence of thyroid hormone impairment and IHD was also significantly higher than that in selenium deficient group than that in non-selenium deficient group. (18% vs 4%, p=0.014).

**Conclusions:** This study showed the significant high prevalence of thyroid hormone impairment and IHD in HD patients with selenium deficiency. Selenium deficiency may be affect heart disease, associating with thyroid hormone impairment.

**FR-PO845**

Associations of Prelude (Pre-ESRD) BMI and Weight Change with Early Dialysis Mortality Among U.S. Veterans: A Transition of Care in CKD Study

**Elani Sheppard,1 Melissa Soohoo,1 Joline L.T. Chen,1 Amanda R. Tortorici,1 Jennie Jing,1 Danh V. Nguyen,1 Csaba P. Kovessy,1 Kamyar Kalantar-Zadeh,2 1UC Irvine; 2UHSC.

**Background:** In end stage renal disease (ESRD) lower body mass index (BMI) portends a higher risk of mortality while obesity is protective, the so-called obesity paradox. However, the association of BMI and change in BMI over time in the pre-ESRD period and early post-ESRD mortality is unknown. We hypothesized that lower and decreasing BMI prior to transition to ESRD may be associated with higher early dialysis deaths.

**Methods:** In a cohort of 22,716 US veterans who transitioned to dialysis between 10/2007 and 9/2011 with available BMI values within the last 2 year prelude period (prior to ESRD transition), we examined the association of 6 month average BMI and 2 year BMI slope as continuous predictors of all-cause mortality in the first 3 months after transition, using restricted cubic spline analyses and Cox models adjusted for age, sex, race, ethnicity, cause of ESRD, and region. In the models of BMI slope, we also adjusted for BMI level at the time of transition.

**Results:** The mean SD age was 69±11 yrs, 27% were African-American, 7% Hispanic, and 49% diabetic. There was a reverse J-shaped association between BMI and mortality, where patients with BMI <27 kg/m² were at higher risk of death (Figure A). When examining changes in weight over the 2-year prelude there was a U-shaped association where patients with little to no-change in BMI (-1 to +1 kg/m² per year) exhibited the best survival (Figure B).

**Conclusions:** Among veterans transitioning to dialysis, obese patients and those patients with little to no weight change in the last 2 years prior to ESRD have the greatest survival in the first 3 months post transition. Weight change in late stages of pre-dialysis CKD, possibly due to uremic wasting and fluid gain, portend poor outcomes, and could be used to identify at-risk patients.

**Funding:** NIDDK Support

**FR-PO846**

Nutritional Assessment for Incident Elder Dialysis Patients

**Suzette Thompson,2 Laura Rosales,3 Nathan W. Levin,1 Peter Kotanko,1 Fansan Zhu,1 1Renal Research Inst, New York, NY; 2Presbyterian Vascular Care, New York, NY.

**Background:** Electrolyte balance between the intracellular (ICV) and extracellular (ECV) fluid compartment is essential in the control of normal physiological functions. Nutritional status is mainly reflected by ICV. In hemodialysis (HD) patients the relationship between control of electrolyte and management of fluid balance is not completely understood. We aimed to evaluated whether the degree of reduction of fluid overload affects the measurement of ICV, and concentrations of serum albumin (Alb), sodium, potassium, and calcium.

**Methods:** Fifty six HD patients were studied. At baseline (BL), the fluid status was evaluated by calf biimpedance spectroscopy (cBiS). If patient’s dry weight (DW) was not reached by criteria of cBiS DW, the post target weight was gradually reduced (Zhu et al, 2015).
Physiol Meas, 29:S530-S516, 2008). At six months follow up, the patients either reached DW or did not (NDW) due to difficulty in prolonging treatment time. ECV and ICV, weight, and systolic blood pressure (SBP) were measured pre and post HD. Comparison of all parameters between BL and follow up were made using student t test.

**Results:** Thirty one patients reached DW and 25 did not. Weight and ECV were significantly reduced during follow up. However, ICV, electrolytes and Alb concentrations did not change between different fluid statuses. Post HD SBP significantly decreased from BL to the end of the study in DW but not in NDW groups.

**Conclusions:** Although extracellular fluid (ECV) was largely reduced, the ICV and serum concentrations of sodium, potassium, and calcium did not differ significantly. This implies that there is no fluid or mass shift from ICV to ECV, suggesting over all isotonic removal of sodium and that nutritional status is not changed by attainment of dry weight.

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BL (n=31)</th>
<th>DW</th>
<th>NDW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>138.2±3.8</td>
<td>137.0±7.9</td>
<td>140.5±3.1</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>4.7±0.8</td>
<td>4.7±0.8</td>
<td>4.5±0.7</td>
</tr>
<tr>
<td>Ca⁺⁺ (mEq/L)</td>
<td>9.1±0.6</td>
<td>9.0±0.6</td>
<td>9.1±0.3</td>
</tr>
<tr>
<td>Alb (mg/dL)</td>
<td>3.9±0.4</td>
<td>3.9±0.3</td>
<td>3.8±0.3</td>
</tr>
<tr>
<td>albumin (g/L)</td>
<td>16.3±0.3</td>
<td>15.8±0.3</td>
<td>15.3±0.3</td>
</tr>
<tr>
<td>HD ECV (l)</td>
<td>18.5±3.6</td>
<td>18.1±3.0</td>
<td>19.3±2.4</td>
</tr>
<tr>
<td>HD ICV (l)</td>
<td>18.5±4.9</td>
<td>18.5±4.9</td>
<td>18.9±4.9</td>
</tr>
</tbody>
</table>

*NDW or did not (NDW) due to difficulty in prolonging treatment time. ECV and ICV, weight, and systolic blood pressure (SBP) were measured pre and post HD. Comparison of all parameters between BL and follow up were made using student t test.*

FR-PO849

**Trends in Weight Change During the First Two Years of Transition to Hemodialysis Treatment**

**Vivian Ngo,1 Elani Streja,1 Anna Mathew,2 Tae Hee Kim,1 Yoshitsugu Obi,1 Connie Rhee,1 Csaba P. Kovessy,1 Kamyar Kalantar-Zadeh1.1 UC Irvine; 2Hofstra North Shore LIJ Health System; 1UTHSC.**

**Background:** Some hemodialysis patients may undergo rapid weight loss in the first few months of starting dialysis, but the nature of this trend has not yet been characterized in large nationally representative studies. We hypothesized the trajectory of weight change during the first 24 months of hemodialysis therapy may differ by baseline body mass index (BMI).

**Methods:** We examined percent post-dialysis weight (kg) change from baseline in 37,759 incident hemodialysis patients who initiated dialysis in a large US dialysis organization in calendar years 2007-2011 and who survived the first 2 years of hemodialysis. Trends of percent weight change over time were analyzed using crude and case-mix adjusted mixed effects models. Baseline BMI was categorized into 8 categories (~18.5, 18.5~20, 20~23, 23~25, 25~30, 30~35, 35~40, 40+ kg/m²).

**Results:** Patients were 60±14 years old, 64% diabetics, 44% female, and had an average starting weight of 82±22 kilograms. Patients reached a nadir of weight at the 5th month of dialysis with an average 2% weight loss from baseline. At 14 months, patients’ weight stabilized at an average of 1% drop from baseline. However, trends differed across groups of baseline BMI groups. Underweight (BMI <18.5) did not experience weight loss but stabilized at an average of 1% drop from baseline. However, trends differed across groups starting weight of 82±22 kilograms. Patients reached a nadir of weight at the 5th month of starting dialysis, but the nature of this trend has not yet been characterized in large nationally representative studies. We hypothesized the trajectory of weight change during the first 2 years in hemodialysis patients. Further studies are needed to better understand the cause of these differences and their impact on clinical outcomes.

**Funding:** NIDDK Support

FR-PO850

**Significance of Renal Autonomic Nerves in the Reduction of Body Weight by SGLT2 Inhibitors**

**Aika Hagiyawara, Kazutoshi Miyashita, Masaaki Sato, Hiroyuki Uinoue, Kentaro Fujii, Masanori Tamaki, Hiroshi Itoh. Nephrology, Endocrinology and Metabolism, School of Medicine, Keio Univ, Shinjuku, Tokyo, Japan.**

**Background:** Sodium-glucose co-transporter (SGLT) 2 inhibitors decrease not only serum glucose level but also body weight significantly. Similarly, it is reported that renal denervation (RDN) decreases body weight, in addition to blood pressure. The urinary glucose might have a relationship with sympathetic activation that controls body weight, however, the relationship has not been elucidated.

**Methods:** The present study examined the roles for renal autonomic nerves in the weight reduction by SGLT2 inhibitors through performing RDN on mice fed on a high-fat diet. The C57BL/6 mice fed on a high-fat diet were divided into 4 groups; control group, RDN group, SGLT2 inhibitor group and SGLT2 inhibitor with RDN group. The body weight, glucose tolerance, tissue weights, tissue hormone sensitive lipase (HSL) activity and noradrenalin concentration were examined. The SGLT2 inhibitor (tofogliflozin 50 mg/kg pellet) was administered to mice from 8 weeks old mixing it in the high-fat diet (60 Kcal% fat). RDN was performed at 7 weeks old by surgically stripping the renal arteries and coating the vessels with a solution of 10% phenol in ethanol.

**Results:** The body weight at 16 weeks old significantly decreased in the SGLT2 inhibitor group. In that group, the catecholamine levels in subcutaneous fat and the activity of HSL which was measured by the phosphorylation level were increased. On the other hand, RDN with SGLT2 inhibitor group significantly weakened the degree of the reduction of body weight by the SGLT2 inhibitor associated with suppression of the catecholamine levels and the activity of HSL in the adipose tissue. In RDN without SGLT2 inhibitor group, the body weight significantly decreased; however, HSL in the adipose tissue was not activated.

**Conclusions:** These results indicate that HSL activation in the adipose tissue mediated by the renal autonomic nerves was involved in the mechanism of weight-reduction by SGLT2 inhibitors. The renal autonomic nerves were suggested to have a role in the control of tissue HSL activity and body weight.

FR-PO851

**The Combination of Walking Exercise and Branched Chain Amino Acid Recovered Response of Protein Synthesis in Low Protein Diet Fed Chronic Kidney Disease Model Rats**

**Takuya Yoshida, Hiromichi Kumagai. Nephrology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy.**

**Background:** Low protein diet (LPD) protects progression of renal injury in patients with chronic kidney disease (CKD). However, LPD may accelerate muscle wasting in these patients. The exercise and branched chain amino acid (BCAA) are known to increase the muscle synthesis by activating mTOR signaling pathway. The aim of this study is to investigate whether walking exercise and BCAA would increase muscle protein synthesis in LPD fed CKD (5/6 nephrectomized) rats.

**Methods:** CKD rats were fed LPD or LPD fortified with BCAA diet (BD), and about half of the each group were loaded with the walking exercise (7 weeks of treadmill, 15 m/min, 1 hour/day, 5 days/week). After 7 weeks, the kidney and the soleus muscle were collected to evaluate the renal fibrosis and the muscle protein synthesis, respectively.

**Results:** The renal function and fibrosis were not different between LPD and BD fed CKD rats, and the walking exercise did not accelerate renal damage in both LPD and BD fed CKD groups. The walking exercise increased the phosphorylation of p70s6kinase, a biomarker of mammalian target of rapamycin complex 1 activity, in soleus muscle of LPD and BD fed CKD rats. However, the phosphorylation of p70s6kinase was lower in RDN without SGLT2 inhibitor group, the body weight significantly decreased; however, HSL in the adipose tissue was not activated.

**Conclusions:** These results indicate that HSL activation in the adipose tissue mediated by the renal autonomic nerves was involved in the mechanism of weight-reduction by SGLT2 inhibitors. The renal autonomic nerves were suggested to have a role in the control of tissue HSL activity and body weight.

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

FR-PO852

**Unacyl-Ghrelin: A Key Molecule in Uraemic Cachexia in Children and Adolescents**

**Alice Monzani1, Michella Perrone1, Sara Testa,2 Fabio Paulliafano2, Silvia Consolo,2 Gianluigi Ardissino,1 Francesca Tel2, Marta Lepore2, Stefano Rotondo,2 Antonietta Biasuzzi,2 Luciana Ghio,1 Gianni bona,1 Alberto Edefonti.2 Div of Pediatrics, Univ del Piemonte Orientale, Novara, Italy; 1Pediatric Nephrology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy.**

**Background:** Cachexia and poor growth are common in children with chronic kidney disease (CKD). Several mechanisms are involved, including loss of appetite and poor food intake. Unacyl-ghrelin (UAG) is known to produce an inhibitory effect on feeding. We measured UAG levels in children and adolescents with CKD stage II-IV on conservative treatment (CKD-CT), on haemodialysis (CKD-HD) and after transplantation (Tx), compared to healthy controls, in relation to biochemical and anthropometric parameters.

**Methods:** Plasma UAG levels were measured by ELISA in 43 CKD-CT, 20 CKD-HD, 48 Tx and 43 healthy children. Urea and creatinine levels were measured in all subjects and GFR was calculated by Schwartz formula. Weight, height and bicipital, tricipital, subcapacular and suprailliac folds were measured, and BMI z-score, fat-mass and fat-free mass pro body weight (FM/WW and FFM/WW, respectively) were calculated.

**Conclusions:** Baseline BMI can affect the trajectory of weight change over the first two years in hemodialysis patients. Further studies are needed to better understand the cause of these differences and their impact on clinical outcomes.

**Funding:** NIDDK Support

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.**
Visceral Fat Area Is Associated with Renal and Cardiac Function in a Population with Normal and Cardiac Diseases.

**Methods:**
This cross-sectional study included 719 middle-aged adults who underwent a voluntary health check-up program. Participants with estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m² were excluded. VFA was measured using bioimpedance analysis. Subjects were divided into tertiles according to their VFA.

**Results:**
- Across the tertiles of VFA, there was a significant trend for decline in eGFR (P < 0.001), increase in baPWV (P < 0.001) and left ventricular mass index (LVMI, P < 0.001).
- VFA was linearly associated with eGFR (β = -0.06, 95% confidence interval [CI] -0.08 to -0.04, P < 0.001), and E/E’ (β = 0.01, 95% CI 0.006 – 0.019, P<0.001), after adjustments for cardiovascular risk factors.

**Conclusions:**
VFA is associated with renal and cardiac function in middle-aged adults with normal or mildly impaired renal function.

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

**FR-PO855**
Chronic Inflammation Is Associated with Poor Clinical Outcomes Independent of Mineral Metabolism Abnormalities in the HEMO Study

**Background:**
Epidemiological studies show a high prevalence of chronic inflammation, vitamin D deficiency, and fibroblast growth factor 23 (FGF23) excess in hemodialysis patients. Whether the relationships of high circulating C-reactive protein (CRP) and interleukin-6 (IL-6) with all-cause mortality and cardiac and infectious events are attenuated in the presence of circulating markers of mineral metabolism is unknown.

**Methods:**
We studied the association of inflammatory markers (CRP and IL-6) with all-cause mortality, and cardiac and infectious hospitalizations and deaths among 1340 subjects from the Effect of Dialysis and Membrane Flux in Maintenance Hemodialysis (HEMO) trial. Cox regression models adjusted for important confounding variables: demographics, comorbidities, Kt/V, dialyzer, smoking, albumin, and mineral metabolism markers including serum calcium, phosphorus, intact parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and FGF23.

**Results:**
Mean age was 58±14 years, 56% were female, and 63% were black. Median (IQR) CRP and IL-6 levels were 6.1 (2.6-15.2) mg/L and 3.2 (1.7-6.9) pg/mL, respectively. Over mean 2.84 years follow-up, there were 582 deaths, 514 cardiovascular events, and 499 infectious events. Among subjects with levels in the highest quartile compared to the lowest quartile, both CRP and IL-6 were significantly associated with all-cause mortality in adjusted analyses, odds ratio (OR) 1.96 (95% CI, 1.27-3.02) and OR 1.51 (95% CI, 1.02-2.23), respectively. However, only CRP was associated with cardiovascular disease events (OR 1.90, 95% CI, 1.04-3.44) and infectious events (OR 3.84; 95% CI, 1.37-10.74) among subjects with levels in the highest quartile compared to the lowest quartile.

**Conclusions:**
CRP and IL-6, were significantly associated with all-cause mortality independent of mineral metabolism abnormalities. Only CRP was significantly associated with cardiovascular disease and infectious disease events independent of mineral metabolism abnormalities among subjects in the HEMO trial.

**Funding:**
NIDDK Support, Veterans Administration Support

**FR-PO856**
Assessment of Protein-Energy Wasting: Comparing a New PEW Score and the MIS in Chronic HD Patients

**Background:**
The assessment of protein-energy wasting, a syndrome of decreased bodily protein and energy fuels, remains debated. Recently, a French group introduced a new PEW score, encompassing BMI, serum creatinine, nPNA and serum albumin. In a cohort of chronic hemodialysis patients, we compared the predictive value of this score with the Malnutrition Inflammation Score (MIS) using all-cause mortality as end point. Furthermore, we investigated which of these scores correlates best with quality of life (QOL).

**Methods:**
Data from the CONvective TRAnsport Study (CONTRAST), the new PEW score and the MIS were determined at baseline. QOL was measured with the Kidney Disease QOL-Short Form 36, which results in 2 general and 12 kidney-disease specific domains of QOL. Discrimination and calibration for mortality were tested by Harrell’s C Statistics. Calibration and the Hosmer-Lemeshow Goodness-of-Fit test, respectively. Spearman’s rank correlation coefficient p was used to determine correlations between a test and the various QOL domains.

**Results:**
489 out of 714 patients were analyzed. 183 died during follow-up (mean 3.15±1.78 years). Discrimination was better for the MIS than for the new PEW score (Harrell’s C statistic 68.0% [95% CI 65.7-69.8] and 61.0% [95%CI 59.0-63.3], respectively). Furthermore, mortality calibration was adequate for MIS (p=0.65), but not for the new PEW score (p=0.03). Lastly, MIS correlated with 15 domains of QOL (p’ is between -0.47 and 0.12), whereas the new PEW score only correlated with the physical component score (p=0.18).

**Conclusions:**
Both the MIS and the new PEW discriminate for mortality, but the MIS performs better. Furthermore, only the MIS is properly calibrated. Third, the MIS correlates with more QOL domains with higher correlation coefficients. Therefore, we conclude that MIS is preferred over the new PEW score in assessing PEW.
association between ΔMIS and mortality was not linear; patients were divided into quartiles of ΔMIS. Cox proportional hazards models, crude and adjusted for potential confounders, were used to calculate hazard ratios (HRs) of patients with severe deteriorating MIS (increase >2 points), mild deteriorating MIS (increase of 1 or 2 points), stable MIS versus patients with an improving MIS.

Results: 404 patients were available for analysis. Mean age was 63.0±13.5 and 62.4% were male. During follow-up (median 3.1 years), 135 patients died. Median ΔMIS was 1.0 (IQR -1.0 to 3.0). Survival curves are shown in fig. 1. HR of patients with a mild deteriorating or stable MIS versus patients with an improving ΔMIS was 0.85 (95%CI 0.53-1.39) and 0.97 (95% CI 0.56-1.67), respectively; for patients with a severe deteriorating MIS, HR was 1.63 (95%CI 1.02-2.51). After correction for age, sex, dialysis vintage and dialysis modality, this association did not remain significant (p=0.1).

Conclusions: a change in ΔMIS over 1 year is not associated with mortality in a multivariable survival analysis.

FR-PO858

Soluble CD14, a Marker of Endotoxia, Associates with Survival and Cardiovascular Disease in CKD Patients Ruben Poesen, Ian Barrows, Ali Ramezani, Pieter Evenepoel, Kathleen Claes, Bjorn Meijers, Dominic S. Raj.

Background: CKD goes along with gut microbial dysbiosis and gut barrier dysfunction, possibly contributing to endotoxin translocation. Subsequent binding of endotoxin to toll-like receptor-4 and its co-receptor CD14 activates the innate immune system. As half-life of systemic endotoxin is very short, soluble CD14 (sCD14) has been proposed as better marker of endotoxin exposure. Whether sCD14 relates to adverse outcome in CKD patients not yet on dialysis is unknown.

Methods: We performed a single-center prospective study in patients with CKD stage 1-5. Baseline serum levels of TMAO were determined using LC-MS. Correlation between eGFR and serum TMAO was explored using Spearman’s rank correlation analysis. The relationship between TMAO, survival and cardiovascular disease was examined using Cox proportional hazard analysis.

Results: 488 CKD patients were followed from November 2005 until December 2010. Median serum level of TMAO was 11.6 µM (IQR 5.7 – 21.8). We observed a highly significant inverse correlation between eGFR and serum TMAO (rho 0.71, P < 0.0001). During follow-up, we noted a total of 51 deaths and 75 cardiovascular events. In univariate cox proportional hazard analysis, TMAO was a significant predictor of mortality (HR 1.521 (1.183 – 1.956), P=0.001) and cardiovascular disease (HR 1.570 (1.283 – 1.921), P < 0.0001). However, significance was lost after adjustment for eGFR for overall mortality (HR 1.126 (0.795 – 1.595), P=0.50), as well as for cardiovascular events (HR 1.256 (0.958 – 1.647), P=0.10).

Conclusions: Serum levels of TMAO rise in parallel to a declining renal function and further analysis of 24h urine samples is ongoing to elucidate its renal handling. In this European cohort of CKD patients, we were not able to find an association between TMAO and adverse outcome that is beyond renal function, which is in contrast to previous observations in US populations, both general and CKD. This may question the validity of TMAO as a universal biomarker for cardiovascular disease, possibly due to population-specific differences in diet and/or microbial metabolism.

FR-PO860

Microbiota Derived Phenylacetylglutamine Associates with Survival and Cardiovascular Disease in CKD Patients Ruben Poesen, Pieter Evenepoel, Bjorn Meijers.

Background: Lately, there is increasing interest in gut microbiota derived uremic retention solutes as driving force behind adverse outcome in CKD. Both p-cresyl sulfate and indoxyl sulfate are considered representatives of this group, also commonly referred to as protein-bound solutes due to their high protein binding and dependence on active tubular secretion for renal clearance. Phenylacetylglutamine is another microbial metabolite subjected to high tubular secretion, although protein binding is rather low. We questioned whether this solute also relates to adverse outcome in CKD patients not yet on dialysis.

Methods: We performed a prospective study in CKD patients stage 1-5. Serum levels of phenylacetylglutamine were determined using LC-MS. Correlation between eGFR and serum phenylacetylglutamine was explored using Spearman’s rank correlation analysis. The relationship between phenylacetylglutamine, survival and cardiovascular disease (CVD) was examined using Kaplan Meier and Cox PH analysis.

Results: 488 CKD patients were followed from November 2005 until December 2010. Median serum level of phenylacetylglutamine was 6.2 µM (IQR 3.0-13.2). We observed a highly significant inverse correlation between eGFR and serum phenylacetylglutamine (rho -0.76, P<0.0001). During follow-up, we noted a total of 51 deaths and 75 cardiovascular events with a gradual and significant increase with higher tertiles of phenylacetylglutamine (both log rank P<0.0001). In univariate Cox PH analysis, phenylacetylglutamine was a significant predictor of mortality (HR 1.997 (1.590-2.508), P<0.0001), even after adjustment for renal function, Framingham risk factors, calcium-phosphorus-PTH, CRP and albumin (HR 1.611 (1.140-2.275), P=0.007 for mortality and HR 1.668 (1.295-2.149), P<0.0001 for CVD).

Conclusions: Serum levels of microbiota derived phenylacetylglutamine are elevated in patients with more advanced CKD. Serum phenylacetylglutamine is also a strong and independent risk factor for mortality and CVD. Further analysis of 24h urine samples is ongoing to differentiate between impact of higher urinary excretion as surrogate of intestinal generation vs. impact of lower tubular secretion.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.
FR-PO861
Sarcopenia Among Prevalent Hemodialysis Patients: Weighing the Evidence
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Background: There is no consensus on the best way to define sarcopenia in ESRD. Use of muscle/height² (Ht²) is suggested by geriatric societies but may underestimate sarcopenia, particularly in the setting of excess adiposity. We compared three definitions of sarcopenia in a prevalent HD cohort.

Methods: ACTIVE/ADIPOSE enrolled HD patients from San Francisco and Atlanta from 6/09 to 8/11. Biomechanical impedance spectroscopy was performed before a midweek dialysis session (n=645), and total-body muscle mass was estimated using an equation containing age, sex, body weight (BW), and intracellular water. We defined sarcopenia as muscle mass ≥2SD below sex-specific means for adults 18-49 y from NHANES data indexed to Ht², %BW, and body surface area (BSA) by DuBois formula. We compared the prevalence of low muscle mass among the three methods and assessed their correlation with handgrip strength.

Results: Mean age was 57±14 years, 41% were women, 61% black. The prevalence of sarcopenia was 8% by muscle/Ht², 25% by muscle/%BW and 32% by muscle/BSA. Most sarcopenic patients by muscle/BSA method had normal BMI, while >50% of sarcopenic patients by %BW were obese. Almost none of the overweight or obese patients were identified as sarcopenic by muscle/Ht².

Conclusions: Skeletal muscle mass normalized to Ht² may underestimate the prevalence of sarcopenia, particularly in overweight HD patients. Detection of sarcopenia among overweight/obese patients requires adjustment for body size or adiposity. Funding: NIDDK Support

FR-PO862
Does a Probiotic Supplementation Alter the Indoxyl Sulfate Levels in Non-Dialysis Chronic Kidney Disease Patients? A Randomized Placebo-Controlled Clinical Trial
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Background: Gut microbiota is known to function in producing uremic toxins in chronic kidney disease (CKD) patients. Therapeutic strategies like probiotic supplementation may modulate the gut microbiota and reduce the toxins levels. To determine the effect of probiotics supplementation on indoxyl sulfate (IS) plasma levels in non-dialysis CKD patients.

Methods: In this double-blind, placebo-controlled trial, 29 non-dialysis CKD patients were recruited. Patients were randomized to receive probiotic (1 capsule, containing 30 billion of colony forming units - S. thermophilus, L. acidophilus, and B. longum, n=17) or placebo (n=12) for 3 months. IS plasma levels were quantified by HPLC, calprotectin and protein C reactive were analyzed by immunoensymatic assay. Five patients in probiotic group and three in placebo were lost to follow-up.

Results: Plasma IS increased significantly in patients who received probiotics whereas the other parameters did not change.

Patients who were classified as sarcopenic by muscle mass/BSA but not Ht² had significantly higher BMI and %body fat than those who were sarcopenic by both methods (25.2 vs 21.3 kg/m², p=0.001 and 31.1 vs 24.4%, p=0.001, respectively). Handgrip strength was moderately correlated with muscle/BSA (r=0.6) but weakly correlated with muscle/Ht² (r=0.3) and %BW (r=0.4).

Conclusions: Skeletal muscle mass normalized to Ht² may underestimate the prevalence of sarcopenia, particularly in overweight HD patients. Detection of sarcopenia among overweight/obese patients requires adjustment for body size or adiposity. Funding: NIDDK Support

FR-PO863
Prevention of the Progression of Both Renal Dysfunction and the Atherosclerotic Change in Chronic Kidney Disease (CKD) Stage 3–4 Patients due to Benign Nephrosclerosis
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Background: Effect of EPA for CKD patients is not fully known. We studied the efficacy of EPA to prevent the progression of both renal impairment and atherosclerosis in CKD stage 3-4 patients due to benign nephrosclerosis (BNS).

Methods: 31 CKD stage 3-4 patients due to BNS with dyslipidemia were followed for 3 years after the start of EPA treatment. The dosage of 1800 mg/day of EPA was newly prescribed. T-cho, LDL-cho, Triglycerides (TG), eGFR, the amount of proteinuria, EPA, arachidonic acid (AA), Dihomo-gamma-linolenic acid (DGLA) and docosahexaenoic acid (DHA) were studied. Both right and left (RL) brachial-ankle pulse wave velocity (baPWV), RL maximum carotid intima-media thickness (max IMT), RL maximum carotid plaque thickness and RL ankle-brachial index (ABI) were evaluated at before treatment (baseline), after 1-year and at the end of the study (3-year).

Results: EPA, EPA/AA ratio, TG, RL bPWV, RL max IMT and eGFR showed significant improvement at 3-year (table 1).

Furthermore, both EPA and DHA levels were significantly low in eGFR exacerbation patients group (n=9) compared with the improvement group (n=22) at both baseline and 3-year. Patients showing the highest EPA levels at baseline (EPA: 124.6±18.8 mg/ml, n=8) showed significant improvement in both eGFR and baPWV compared with those with the lowest EPA levels (30.1±8.1 mg/ml, n=6). There was no difference on both plaque thickness and ABI between baseline and 3-year.

Conclusions: EPA powerfully prevents the progression of both renal dysfunction and the atherosclerotic change in CKD stage 3-4 patients due to BNS.

FR-PO864
Relationships Between Composition of Gut Microbiota and Uremic Toxins
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Background: Gut microbiota is known to function in producing uremic toxins (UTs) and their precursors, such as indox, phenols and so on. However the relationships between specific bacteria and UTs are not clear. To elucidate the production of UTs by gut microbiota, we collected blood, urine and feces samples in normal rats, rats subjected to 5/6 renal removal. AST-120, a spherical carbon adsorbent of intestinal small-molecular-weight UTs and/or their precursors, was used to evaluate the effects of UTs on gut microbiota.

Methods: Serum and urine levels of UTs were quantified by SRM of LC/ESI-MS/MS. Gut microbiota from feces were analyzed using 454-pyrosequencing of a hypervariable V1-V2 region of the 16S rRNA gene in combination with barcode sequences. We used the GLSEARCH program and self-build 16S sequences database and genome database to determine the closest species. We identified the indole and/or phenol producing species using BLASTX.

Results: In CKD rats, urinary excretion and serum concentrations of UTs, such as indoxyl sulfate and phenyl sulfate, were higerthan control rats. In AST-120-administered CKD rats, urinary excretion and serum concentrations of UTs decreased compared to CKD
rats. The overall bacterial community composition was compared according to the UniFrac distance metric among control rats, CKD rats, and CKD + AST-120 rats. A principal coordinate analysis plot revealed clustering of each group. We identified the intestinal microbiome containing tryptophanase and/or tyrosine phenol-lyase gene in the genome sequences from NCBI bacterial genome. These enzymes metabolize tryptophan to indole and tyrosine to phenol, respectively.

Conclusions: Our data suggest that UT production is not only the cause of uremic symptoms but also correlated with a subset of indigenous gut microbes and affects the composition of gut microbiota.

FR-PO865

Association of Urine Volume at the Start of Dialysis and Subsequent Changes in Serum Albumin Level in Incident Hemodialysis Patients

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Background: Previous studies have shown that low serum albumin (Alb) levels are associated with higher mortality in hemodialysis (HD) patients. While serum Alb is a critical inflammatory and nutritional marker, low Alb may also result from albuminuria. It is unknown if a change in serum Alb over time is due to the loss of residual kidney function. While data on urine Alb was unavailable, we hypothesized that higher urine volume (UV) (U) is associated with a decrease in Alb.

Methods: Among 38,504 incident HD patients receiving care from a large dialysis organization from 2007-2011, we examined serum albumin level trajectory over 5 years (divided into 20 patient quarters) across five strata of baseline UV: <300, 300-<600, 600-<900, 900-<1200, ≥1200 mL/d. The association between baseline UV and serum albumin trend was examined using mixed effects models with adjustment for age, gender, race, diabetes, and insurance type.

Results: Patients were 62±15 years old, 38% female, 28% black, and 46% diabetic. Higher baseline UV was incrementally associated with higher Alb levels across strata: 3.4±0.48g/dL, 3.5±0.46g/dL, 3.57±0.44g/dL, 3.59±0.45g/dL, and 3.65±0.46g/dL, respectively. [Figure] Serum Alb increased over the first 6 patient quarters (18 months) on dialysis and then stabilized. Patients with higher UV not only had a higher baseline serum Alb level, but also maintained a higher serum Alb level over follow-up.

Conclusions: Higher baseline UV appears to be associated with sustained higher serum Alb levels over time. Improvement in hypoalbuminemia as a result of transition to dialysis therapy appears to be independent of residual kidney function and may suggest an inherent advantage of dialysis initiation.

Funding: NIDDK Support

FR-PO866

Individual Variation of Hippuric Acid and P-Cresyl Sulfate Plasma Levels Correlate with Variation of Intestinal Microbial Phylotypes in Hemodialysis Patients

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Background: In chronic kidney disease (CKD), a myriad of metabolites accumulate with the maximum intrapatient variability of metabolite levels and the corresponding time-points of feal microbial phylotypes was assessed. In addition, cross-sectional correlations at 0 were evaluated. Statistical analyses were performed with R package phylloseq using Spearman correlation, with multiple testing correction (FDR) per metabolite for the number of genus-level phylotypes.

Results: Within this patient group, we observed a strong positive correlation between an increase in total hippuric acid and unclassified Peptostreptococcaceae (r=0.83; corrected p-value=0.012). We also found a positive trend for total p-cresyl sulfate and unclassified Clostridiales and unclassified Ruminococcaceae (r=0.77 and 0.74; corrected p-value=0.074 and 0.028, respectively). Cross-sectionally at 0, strong negative correlations between indoxyl sulfate, indole acetic acid and specific unclassified bacterial phylotypes (<p=0.79 and <p=0.84; corrected p-value=0.028 and 0.004) were observed.

Conclusions: There is a link between plasma levels of specific uremic metabolites and fecal bacterial phylotypes, suggesting that these microbiota might be a target for reducing uremic metabolite levels in patients with CKD. Data needs validation on larger patient groups.

Funding: Government Support - Non-U.S.

FR-PO867

Decreased Vitamin K Intake in Italian Hemodialysis Patients

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Background: Vitamin K is involved in the production of Bone and Matrix Gla Proteins (BGP and MGP, respectively), regulating bone and vascular health. We carried out a pilot study to evaluate vitamin K intake in hemodialysis (HD) patients.

Methods: We measured vitamin K1 intake (7-day food record) in 78 Italian hemodialysis patients (48 M, 30 F) compared to intake in 39 healthy adults (28 M, 11 F).

Results: HD patients had a mean (± SD) age of 62.8±13.9 years, mean dialytic age of 97 months, mean BMI of 25.4±4.5 Kg/m2. Mean serum levels of interest for CKD-MBD were: Ca 9 mg/dL, P 4.3 mg/dL, PTH 231.5 pg/mL, ALP 81.5 U/l. Control group mean age was 54.6±13.9 years. HD patients had a significantly lower intake of vitamin K1 compared to controls (see Table). We also evaluated and compared between HD patients and controls the intake of the other fat soluble vitamins and of nutrients commonly associated with bone and mineral disorders in KD patients (see table). All were decreased in HD patients.

Conclusions: This Vitamin K intake study is the first carried out on Italian diet. We found a decreased intake of Vitamin K1 in HD patients. This finding supports the hypothesis of supplementing vitamin K for the prevention of vascular calcifications and bone disorders in HD patients. Benefits of vitamin K supplementation should be proved by a randomized trial.

FR-PO868

Association of Geriatric Nutrition Risk Index with Body Fluid Composition, Renal Adverse Outcomes and Mortality in Patients with Chronic Kidney Disease

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Background: Decreased body stores of protein and energy fuels may express by the geriatric nutritional risk index (GNRI) consisting of body mass index (BMI) and serum albumin levels. We studied the association of the GNRI with body fluid composition, renal adverse outcomes and all-cause mortality in patients with chronic kidney disease (CKD).

Methods: Body fluid composition was measured in 306 patients with CKD from 2005 to 2014 and was separated into three components – (a) free water mass consisting of muscle, fat, and minerals, (b) intracellular water (ICW) content, and (c) extracellular water (ECW) content. Patients were categorized according to tertiles of GNRI levels. Of those, 275 patients were followed until March 2015. The adverse renal outcomes were defined by a decline of 50% or more from baseline glomerular filtration rate or initiation of renal replacement therapy.

Results: Patients with the lower tertiles of the GNRI levels were more likely to be higher age, have a lower BMI, diastolic blood pressure, serum albumin, hemoglobin, glomerular filtration rate, and proteinuria (P < 0.05). In the body fluid composition, those tended to have lower free water mass (r = 0.73, P < 0.001) and the ratio of extracellular water to total body water mass (r = 0.87, P < 0.001) were significantly increased in the lower tertiles of GNRI levels.

Conclusions: We showed a significant correlation between the geriatric nutritional risk index (GNRI) and body fluid composition, renal adverse outcomes and all-cause mortality. The association of GNRI and body fluid composition can be a useful predictor for renal adverse outcomes and all-cause mortality in patients with chronic kidney disease.
intracellular water ($r = 0.37, P < 0.001$). Compared with patients with the middle tertile of the GNRI levels during a median 2.5-year follow-up, the lowest tertile of the GNRI levels had higher mortality (6.8 vs. 1.7 per 100 patient-years, $P < 0.001$), but had no worse adverse renal outcomes (16.5 vs. 9.0 per 100 patient-years, $P = 0.08$). In multivariate analysis, the lower GNRI levels independently remained as a risk factor for all-cause mortality (hazard ratio, 3.16, 95% CI, 1.30–8.84, $P < 0.001$).

**Conclusions:** The GNRI may be a simple and useful tool for predicting the risk of mortality even in CKD population including patients with massive proteinuria. These findings emphasize the importance of adequate body stores of protein and energy fuels in patients with CKD.

**FR-PO869**

A Novel Index for Estimation of Muscle Mass Using Biomarkers of Kidney Function: Sarcopenia Index

**Kijanoosh Banati-Kashani,1,2 Lucie Kukralova,3 Erin N. Frazee,4 Rahul Kashyap.2**

Background: Sarcopenia is associated with poor patients’ outcomes in Intensive Care Unit (ICU). Tools to evaluate sarcopenia are DXA scan, CT and MRI, which may not be feasible for critically ill patients. We hypothesize a novel index which can be used as a surrogate for sarcopenia among ICU patients.

**Methods:** This is a secondary analysis of prospectively enrolled critically ill patients. Adult ICU patients ($\geq 18$ years) with shock, sepsis, use of IV antibiotics and contrast media exposure, in 24 hours of enrollment, intra-abdominal hypertension or severe Trauma were included. We excluded patients with pre-existing acute kidney injury, pregnancy, and kidney transplant, or those who were on dialysis or were moribund. We measures paraspinal muscle surface area at L3 level, using Slice-O-Matic software (TomoVision®, Magog, Canada). Sarcopenia Index (SI) was calculated as [Serum Creatinine (Scr) Cystatin C (CysC)] X 100.

**Results:** A total of 226 patients met the inclusion criteria. Among these enrollees, 110 patients who had abdominal CT within $\pm 4$ weeks of their index ICU admission were included in the final analysis. The median age (IQR) was 67 (57–77) years and 59.5% (91.9%) were female. The median DNI levels were 91.7 (91.7–97.8) and H: >97.8, and GNRI were 95.9±7.6, 94.9±5.8, 87.1±11.0 in A, B and C of tertiles according to the ADL defined by the Renal Data Registry of Japanese Society for Internal Medicine, Mayo Clinic, Rochester, MN; 4Faculty of Medicine in Hradec Kralove, Charles Univ, Prague, Czech Republic; 4Dept of Pharmacy, Mayo Clinic, Rochester, MN.

**Conclusion:** ADL and GNRI could strongly predict the mortality, and combination of both setting also improved the prediction of mortality with ESRD patient on HD.

**FR-PO871**

Delta Neutrophil Index Is a Predictive Marker of Disease Severity in Patients with Acute Pyelonephritis

**Sul A Lee,1 Jong Hyun Jhee,1 Jae Eun Um,2 Meiyan Wu,2 Hyung Jung Oh,1 Jung Tak Park,1 Seung Hyekol Han,1 Shin-Wook Kang,21,2,3 Hyun Yoo.1**

**Background:** Delta neutrophil index (DNI) is the fraction of immature granulocytes provided by a complete blood count (CBC) count. Previous studies demonstrated that DNI was a novel marker to predict clinical outcomes in sepsis patients. Therefore, this study was aimed to evaluate DNI as a predictive marker of disease severity in patients with acute pyelonephritis (APN).

**Methods:** Patients who were diagnosed with APN at Severance Hospital from December 2009 to July 2012 were retrospectively investigated. DNI levels were measured at the time of admission. Patients were classified into two groups according to the median value of DNI. Severe APN was defined as one or more of following conditions: bacteremia, acute kidney injury, hypotension requiring use of vasopressors, and admission of intensive care unit. Independent risk factors for severe APN were determined by multivariate logistic regression analysis. Area under the receiver operating characteristic curves (AUC) was compared among DNI, white blood cell (WBC) count, and C-reactive protein (CRP).

**Results:** A total of 258 patients were included in this study. The median age was 61.0 (19.0 – 87.0) years, and 237 patients (91.9% ) were female. The median DNI levels were 7.25%. Severe APN was significantly more prevalent in the high DNI group. Multivariate analysis showed that DNI independently predicted severe APN (per 1% increase, odds ratio=1.287, 95% confidence interval=1.131-1.458, P=0.001). Furthermore, DNI was a better predictive marker of severe APN than WBC count [AUC (95% confidence interval); 0.697 (0.637-0.753) vs. 0.562 (0.499-0.624), P=0.001] and not inferior to CRP levels [0.697 (0.637-0.753) vs. 0.633 (0.571-0.692), P=0.118].

**Conclusions:** DNI at admission could be a valuable predictor of disease severity in patients with APN.

**FR-PO872**

An Improved Magnesium Formulation for Mitigating Cisplatin-Induced Renal Epithelial Cell Injury

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**Background:** Cisplatin is a potent chemotherapy for treating cancer. It causes nephrotoxicity in ~25% and hypomagnesemia in ~90% patients. This hypomagnesemia is treated with oral magnesium (Mg) chloride (MgCl2) and/or i.v. Mg sulfate (MgSO4). Poor Mg intake and Mg deficiency are not uncommon in the US. Our previous studies revealed the beneficial effects of MgSO4 in reducing cisplatin-induced acute kidney injury (AKI) (Solanki et al., AIP Renal 2014). This study compared the efficacy of various Mg formulations in reducing cisplatin-induced renal epithelial cell injury.

**Methods:** LLC-PK1, renal epithelial cells were maintained in media containing 100% Mg (i.e. the amount of Mg found in growth media) or 10%Mg (Mg-deficient) for 3 days. To mimic Mg replacement, the 10%Mg cells were restocked to 100%Mg using: MgSO4, Mg-L-threonate (MgT), MgCl2, and Mg gluconate (MgG) (keeping elemental Mg equal) and then treated with vehicle or cisplatin. Oxidative stress, cytotoxicity and inflammation were measured by DCF-DA assay, MTT assay and TNFα production, respectively. ERK activation was measured by in-cell western.

**Results:** Cisplatin-induced oxidative stress, cytotoxicity, and inflammation were exacerbated by Mg deficiency, while Mg supplementation with all formulations consistently prevented these effects. MgT was the most effective Mg-formulation in reducing cisplatin-induced oxidative stress and inflammation. Mechanistic studies revealed that cisplatin-induced ERK activation was modulated by Mg status and MgT was most protective.

**Conclusions:** Mg supplementation protected against cisplatin-induced oxidative stress, cytotoxicity and inflammation in renal epithelial cells. This is the first study to reveal the effectiveness of MgT over other Mg-formulations in reducing cisplatin-induced renal
epithelial cytotoxicity. Note: MgT has significantly lower GI-effects (bloating and diarrhea) than other Mg formulations. These results warrant further in vivo and clinical studies to investigate the beneficial role of MgT in protecting against cisplatin-AKI.

**Funding:** Private Foundation Support

**FR-PO873**

Impact of Uremic Serum on the Barrier Function and Inflammation in Human Colonocytes

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**Background:** In chronic kidney disease (CKD) it has been suggested that alterations of the gut are associated with inflammatory state and uremic toxicity. Studies suggest that uremia may impair the intestinal barrier function, by promoting increased intestinal permeability. In this study we aimed to evaluate the in vitro effect of uremic serum on the transepithelial electrical resistance (TER), inflammation and apoptosis in the intestinal epithelial cells.

**Methods:** Pools of serum were prepared from blood samples from patients maintained on hemodialysis (Pre-HD and Post-HD), and of patients with CKD stage 4 (NND-CKD). A pool of serum form healthy individuals served as control (CTL). When the TER exceeded 1,000 Ω cm² was reached, the T84 cells were incubated for 24 h in medium containing 10% pool of serum from each group. At the conclusion of the incubation period, the TER was measured again and the following parameters were determined by flow cytometry: expression of toll-like receptor (TLR), production of reactive oxygen species (ROS) and apoptosis. TNF-α and IL-6 in the culture supernatant was determined by ELISA. A total of nine experiments were performed.

**Results:** No differences among groups were found regarding TER (p=0.443), apoptosis (p=0.751), ROS (p=0.999), expression of TLR-2 (p=0.493), TLR-4 (p=0.418) and TLR-9 (p=0.937) and secretion of TNF-α (p=0.438). IL-6 secretion was higher (p=0.001) by cells incubated with post-HD pool (2.07±0.93pg/ml) when compared with cells incubated with CTL pool (0.67±0.35), NND-CKD (0.61±0.53) and pre-HD (0.11±0.45).

**Conclusions:** The results obtained from this model suggest that uremic serum protects colonocytes from the detrimental effects of inflammation and apoptosis. Serum uremia may break the intestinal barrier, which could be a consequence of pro-inflammatory stimuli of the dialysis process.

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

**FR-PO874**

Prediction of One-Year Mortality and Hospitalization Risk Using Nutritional Indicators and Their Trajectories in a Large Prevalent Hemodialysis Cohort

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**Background:** Existing nutritional scores developed in the hemodialysis (HD) population do not consider temporal trajectories of nutritional parameters. We aimed to develop predictive models for mortality and hospitalization using readily available nutritional indicators and their rates of change.

**Methods:** Using retrospective data from a large US HD provider, a cohort with HD vintage ≥1 year (N=21,082 and N=23,384 in mortality and hospitalization analyses, respectively) was randomly split 2:1 for model development, testing and validation. Parameters included demographics, nutritional/inflammation parameters, and slopes of all continuous variables over 6 months. Follow-up period was January-December 2012. Performance of generalized linear models and generalized additive models (GAM) was evaluated with area-under-the-curve (AUC), sensitivity and specificity.

**Results:** For both mortality and hospitalization prediction, GAM performed best. The best mortality model included neutrophil:lymphocyte ratio (NLR) slope, serum bicarbonate slope, albumin, creatinine, age, sex and vintage (AUC 0.85, 95% CI 0.83-0.86; sensitivity 0.70; specificity 0.83). The best hospitalization model included NLR slope, albumin, congestive heart failure, serum bicarbonate slope, creatinine, serum phosphate slope, vintage, diabetes, serum phosphate, volume of urea distribution, age and enPCR (AUC 0.70, 95% CI 0.62-0.79; sensitivity 0.41; specificity 0.88).

**Conclusions:** We developed novel and accurate predictive models for mortality and hospitalization using nutritional indicators and their slopes over time. Future studies are needed to assess if its application can improve nutritional intervention allocation and outcomes in HD patients.

**Funding:** Pharmaceutical Company Support - Renal Research Institute

**FR-PO875**

Extracellular Fluid/Intracellular Fluid (ECF/ICF) Volume Ratio Is A Novel Risk Indicator of Death and Highly Related to Malnutrition-Inflammation-Arteriosclerosis (MIA) Complex in Hemodialysis (HD) Patients

Fumijung Kim, Soyon Rhee, Jiwon Ryu, Hee Jung Jeon, Jungs-woo Noh, Ja-Ryong Koo. Nephrology, Hallym Univ Hospital, Dongtan/Seoul, Korea.

**Background:** Fluid overload and malnutrition are well recognized risk factors contributing to the high mortality in HD patients. Recent studies suggest pathophysiological link between fluid overload and malnutrition as a part of MIA complex. Because the ECF and ICF volume can represent fluid volume and nutritional status respectively, ECF/ICF ratio could be defined as a novel integrated marker reflecting both fluid overload and malnutrition. Accordingly we investigated the relationship of ECF/ICF ratio to survival in the context of MIA complex in chronic HD patients.

**Methods:** 77 HD patients (age 53±13 year, diabetes 38%) were prospectively enrolled. ECF/ICF volume was measured by multi-frequency bioimpedance analysis. Nutrition, inflammation, arteriosclerosis and volume status were measured by serum albumin, C-reactive protein (CRP), pulse wave velocity (PWV) and serum B-type natriuretic peptide (BNP) respectively.

**Results:** Mean ECF/ICF ratio was 0.56±0.06 and cut-off value for maximum discrimination of survival was 0.57 by ROC curve. As compared with low ECF/ICF group (ratio<0.57, 58%), high ECF/ICF group (ratio>0.57, 42%) had higher all-cause mortality, CRP, PWV, BNP and lower serum albumin level. During the 5-year follow-up, 24 all-cause death occurred (18 in high ECF/ICF group versus 6 in low ECF/ICF group, log rank P<0.001). In Cox analysis adjusted for age, diabetes, BP and cardiac function, the ECF/ICF ratio was an independent predictors of all-cause death (HR=1.25, 95% CI=1.01-1.54, per 0.01 in ECF/ICF ratio) and nullify the effect of MIA component and volume marker on survival. The degree of malnutrition (albumin), inflammation (CRP), arteriosclerosis (PWV) and fluid overload (BNP) were correlated well with ECF/ICF ratio.

**Conclusions:** Chronic HD patient with high ECF/ICF ratio is not only fluid overloaded but malnourished and have stiff artery with more inflammation. As a novel integrated marker of fluid overload and malnutrition, ECF/ICF ratio is highly related to MIA complex and a major risk indicator of death in chronic HD patients.

**FR-PO876**

Weight Gain After Listing Independently Predicts Pre-Transplant Sensitization Status

Pritika Shrivastava,1 Krista L. Lentine,2 Ankit Sakhuja,2 Fidel Barrantes,3 Diane M. Cibrik,1 Yihung Huang,1 Abhijit S. Naik.1 1Univ of Michigan; 2Saint Louis Univ; 3Renal Medical Associates, NM.

**Background:** Non-alloimmune stimuli such as infections, vaccinations and pro-inflammatory events cause sensitization to HLA antibodies and increased panel reactive antibodies. Obesity is recognized as an inflammatory state. Given relationship between obesity and inflammation we speculated that weight gain on the waitlist may increase sensitization status at the time of transplantation.

**Methods:** Using national data from the Organ Procurement and Transplantation Network we identified first time kidney only transplant recipients, aged 18-70, transplanted between January 1,2009 and June 30,2013. Previous non-renal transplants were excluded. A calculated panel reactive antibody of 20% or more at the time of transplant was considered to be “sensitized”. Using a priori chosen variables we performed a logistic regression model with sensitized status at time of transplantation as the dependent variable and change in BMI from listing to transplantation, BMI at transplant, recipient age, prior sensitization status, prior pregnancy, dialysis time and race as independent variables.
Results: Among 55,894 patients transplant recipients. 39.45 % were female of which 67.31 % were previously pregnant. Overall 15.12 % had received prior blood transfusions. Mean BMI at listing and transplantation was similar at 28.4± 5.5 kg/m². Greater than 50 % patients with BMI ≥ 30 kg/m² at listing had an increased their BMI by time of transplantation, while <50 % patients in BMI< 30 kg/m² had lost weight. A 1-unit increase in BMI at listing in female patients was associated with an increased risk of being sensitized. aOR:1.01 (1.01-1.02). Other independent predictors included prior transplantation aOR:1.25 (1.18-1.33), AA race aOR:1.26 (1.19-1.32), pregnancy aOR:3.32 (3.04-3.63), dialysis time aOR:1.23 (1.11-1.14).

Conclusion: The majority of obese patients gain weight on the waitlist. We identified weight gain on the waiting list to be associated with a small but statistically significant increase in odds of being sensitized. Further studies are needed to determine the impact of malnutrition-inflammation complex on pretransplant sensitization.

FR-PO877

High Salt Diet Impairs the Immune Defense against Uropathogenic Escherichia coli in Murine Pyelonephritis

Katarzyna Jobin, Katharina Hochheiser, Maike Giesen, Christian Kurts. Inst of Experimental Immunology, Univ of Bonn, Bonn, Germany.

Background: Recent studies demonstrated that NaCl stimulates immune responses, for example by promoting Th17 cells differentiation, macrophage recruitment into tissues and pro-inflammatory cytokine release from epithelial cell lines. Specifically, high salt diet (HSD) exacerbated experimental autoimmune encephalomyelitis and improved immune defense against L. major infection. Little is known about the influence of HSD on anti-microbial responses in the kidney – an organ with extremely high sodium chloride concentration.

Methods: Wild type female mice were given normal salt diet (NSD) or HSD one week prior to infection with uropathogenic E. coli into the bladder resulting in pyelonephritis development. 20 h after the infection, kidneys were harvested and analyzed for CFU and immune cell subsets by flow cytometry.

Results: HSD exacerbated pyelonephritis as measured by CFU. Additionally, in kidney medullas of mice fed HSD the number of PMNs, Ly6c⁺ macrophages and NK cells was significantly decreased in comparison with NSD fed mice. Although PMNs from mice given HSD produced more ROS than PMNs from mice on NSD, in vitro studies demonstrated that less medullary PMNs from mice fed HSD than NSD were able to perform phagocytosis.

Conclusions: Contrary to the expectations, HSD worsened experimental pyelonephritis, possibly through affecting immune cell activation and/or migration into the kidney medulla. This finding may be of clinical significance and, if confirmed in human studies, decreasing salt intake during bladder infection or pyelonephritis could support antibiotic therapy. Further studies are needed to elucidate the immune mechanisms underlying the negative effect of HSD on pyelonephritis.

Funding: Government Support - Non-U.S.

FR-PO878

Gut Microbiota Lactobacillus Protects against the Progression of Renal Impairment Through the Modulation of TLR2-Mediated Gut Barrier Stability in Rats

Ayumi Yoshifuji, Shu Wakino, Junichiro Irie, Takaya Tajima, Katsuyuki Inokuma, Hirotsugu Hiro, Toshiro Sekiya. Keio Univ, Japan.

Background: Gut microbiota has been shown to have some role in the pathogenesis of various diseases and previous study demonstrated that Lactobacillus (Lact) decreased in number in CKD. In this study, we elucidated the significance of Lact in the pathogenesis of CKD.

Methods: Six-week-old spontaneously hypertensive rats (SHR) were rendered CKD by 5/6th nephrectomy (Nx). The SHR were divided into three groups; sham-operated SHR (SHR), SHR with Nx (Nx), and Shr given Lact (Nx+Lact). After 12 weeks, biochemical parameters, urinary protein excretion, IL-6, histological changes in the kidney, and molecular changes of tight junctions and TLR2 expression were explored. Furthermore, concentrations of fecal uroic acid were measured. To confirm the effect of Lact, rats are administered with broad antibiotics as pseudogerm-free condition and kept for 8 weeks with Lact. Human colon cell line, Caco-2 cells were treated with uremic toxin precursor, indole in the presence or absence of Lact or OxPACP, an inhibitor of toll-like receptor, putative receptor recognizing Lact. The expressions of colon tight junction proteins were examined by immunoblotting.

Results: The gut flora analysis revealed that the decrease in Lact in Nx, which was restored in Nx+Lact. However, fecal uroic acid contents did not show significant changes. Both serum indoxylsulfate and IL-6 increased in Nx. These increases were ameliorated inNx+Lact. The decreases in the tight junction protein Occludin and ZO-1 as well as in TLR2 in Nx were mitigated by Lact. In the pseudogerm-free condition, Lact decreased the urinary protein excretion. In Caco-2 cells, the downregulations of Occludin and ZO-1 by indole were ameliorated by Lact. OxPACP inhibited the Lact-induced restoration of these tight junctions.

Conclusions: The supplementation of Lact improves the gut environment through the activation of TLR2 pathway. This improvement would contribute to the decrease in systemic uremic toxin levels, systemic inflammation and urine protein excretion. This probiotic therapy can provide novel therapeutic strategy against the progression of CKD.

Funding: Government Support - Non-U.S.

FR-PO879

Relationship Between Serum Uric Acid Change and Renal Injuries: An Observational Cohort Research from Pinggu District, Beijing

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Background: Hyperuricemia is thought to be a risk factor of CKD and ESRD. This research aims to demonstrate the relationship between serum uric acid change (dUA) based upon baseline from general population and indexes of renal injuries.

Methods: This cohort research was based on 5 years’ follow up of an epidemiological study in 2008 in Pinggu District, Beijing. Baseline population was 7086, and 5364 subjects were followed up in 2014. All subjects were interviewed with questionnaires, tests of antiproreopulmonary indicators, blood and urine sample collection. Serum creatinine, cystatin C, eGFR were tested. Serum uric acid was applied to evaluate differences of indexes among all groups. Risk factors of CKD (CRIC≥3.9mg/ mmol & eGFR<60ml/min/1.73²)were evaluated with Multiple Logistic regression analysis.

Results: 1. 5364 patients(M:F:1:1.1) were included. In 2008 prevalence of hyperuricemia was 5.9%(7.0% for men, 5.0% for women), and Prevalence of hyperuricemia was 5.9%(7.0% for men, 5.0% for women) in 2014. 2. CRIC≥3.9mg/ mmol & eGFR<60ml/min/1.73² were evaluated with Multiple Logistic regression analysis.

Results: 1. 5364 patients(M:F:1:1.1) were included. In 2008 prevalence of hyperuricemia was 5.9%(7.0% for men, 5.0% for women), and Prevalence of hyperuricemia was 5.9%(7.0% for men, 5.0% for women) in 2014. 2. aOR of group N/N were significantly higher than that of group N/H/N, indicating that GFR of hyperuricemia patients following up in 2014 declined more than that of patients without hyperuricemia; serum cystatin C in 2014 increased significantly from group 1 to group 4; there was no significant difference among all groups inlnIMGAG/Cr. 3. AUA, age, BMI, hypertension, DM were independent risk factors of CKD. HR of CKD in group N/H/N was 1.38 times(95%CI 1.30-2.68, P<0.001) and 4.2 (95%CI 1.26-6.70, P=0.001) times of group N/N.

Conclusions: In general population, elevation of serum uric acid is the independent risk factor of GFR decline and serum cystatin C ascent. It is also the independent risk factor of the development of CKD, and the decline of uric acid in the blood may reduce the risk of renal injuries.

Funding: Government Support - Non-U.S.

FR-PO880

Leucine Disposal Rate for Assessment of Amino Acid Metabolism in Maintenance Dialysis Patients

Evelyn Herring, Serpal Muge Deger, Feng Sha, Cindy Booker, Charles D. Ellis, Talat Alp Ikizler, Nephrology, Vanderbilt Univ, TN; Veteran Affairs, TN.

Background: Protein energy wasting (PEW) is common in patients undergoing maintenance hemodialysis (MHD) and is closely associated with poor outcomes. Insulin resistance and associated alterations in amino acid metabolism is a potential pathway leading to PEW. In this study we hypothesized that measurement of leucine disposal rate (LDR) during a hyperinsulinemic-euglycemic-enauxaminocidic clamp (HEAC) procedure would accurately measure the sensitivity of insulin for its actions on concomitant carbohydrate and protein metabolism in MHD patients.

Methods: We examined 15 MHD (aged 52±13 years, BMI 29.5±kg/m²; patients and 16 control subjects (aged 46±10 years and BMI 28±7 kg/m²) by hyperinsulinemic euglycemic clamp (HEAC) procedure followed by HEAC clamp procedure to obtain glucose disposal rate (GDR) and LDR, respectively.

Results: The GDR by HEAC was 4.9±1.9 mg/kg/min in the MHD subjects compared to 6.3±1.4 mg/kg/min in the controls (P<0.047). The LDR during HEAC was 0.99±0.03 mg/ kg/min for MHD patients vs 0.12±0.05 mg/kg/min for control (P<0.11). The GDR derived by HEAC and LDR correlated well in the control population (r=0.793, P=0.001), but less so in the MHD subjects (r=0.346, P=0.25).

Funding: Government Support - Non-U.S.
Conclusions: Leucine disposal rate reliably measures amino acid utilization in MHD patients. The lack of correlation between GDR versus LDR in MHD subjects requires further investigation for understanding the effects of insulin signaling on protein metabolism in MHD patients.

FR-PO881
Age and Dependence on Dialysis Are More Important Predictors of Immune Response to Influenza Vaccine Than Inflammation and Iron Status

Jaromír Eiselt,¹ Lukas Kielberger,¹ Daniel Rajdl,2 Jaroslav Racek.2 Internal Dept 1, Charles Univ, Plzen, Czech Republic; 2Dept of Biochemistry, Charles Univ, Plzen, Czech Republic.

Background: The immune response to influenza vaccine is not uniform and may be influenced by many factors, e.g. comorbidities, age, inflammation or iron metabolism. The aim of our study was to identify factors associated with low production of hemagglutination-inhibition antibodies (HIA) after vaccination in hemodialysis (HD) patients and controls.

Methods: We evaluated the immune response to the influenza vaccine in a total of 122 stable HD patients and in 37 subjects without renal dysfunction. To identify factors associated with immune response, a stepwise backward and forward algorithm for a linear regression model was used with postvaccination increase in HIA titre against H1N1 vaccine strain as dependent variable and following independent variables: age, dependence on dialysis, diabetes, iron, transferrin, transferrin saturation, ferritin, hepaticin, interleukin-6, C-reactive protein, albumin, prealbumin and pre-vaccination HIA protective titre.

Results: The rate of HIA production was lower in HD patients than in controls. Factor increases in geometric mean titer for the H1N1 strain were 2.9 in HD and 6.6 in controls (p<0.001), with the respective figures being 2.8 and 3.1 (p=ns) for the H3N2 strain, and 2.4 and 4.7 (p=0.05) for the B strain. Also, post-vaccination seroconversion rates were lower in the HD group than in controls (43% versus 73% against the H1N1 strain; p<0.005; 43% versus 53% against the H3N2 strain; p=ns; and 36% versus 62% against the strain B; p<0.05). According to the regression model (adjusted R² 0.298, p<0.00001), the predictors of low HIA production against H1N1 strain were high age (p<0.0001), dependence on dialysis (p=0.011) and high transferrin saturation (p=0.03).

Conclusions: The immune response to the influenza vaccine was lower in HD patients than in controls. Besides dependence on dialysis, the most significant predictors of low antibody production were high age of vaccinated subjects and high transferrin saturation. Immune response was independent of other markers of iron metabolism and inflammation.

Funding: Government Support - Non-U.S.

FR-PO882
Intravenous Administration of L-Carnitine (LC) May Maintain the Muscle Volume in Hemodialysis (HD) Patients

Jyunichiro Hashiguchi,¹ Takuhisa Uchino,¹ Miki Yano,¹ Satoshi Funakoshi,¹ Osamu Sasaki,¹ Hiroshi Ichinose,¹ Kenji Sawase,¹ Yoko Obata,¹ Tomoyo Nishino,¹ Yutaka Mori,¹ Kazunori Utsunomiya,¹ Takashi Harada.¹ ¹Nagasaki Kidney Center, Nagasaki, Japan; ²Nagasaki Univ Graduate School of Medicine, Nagasaki, Japan; ³Jikei Univ, Tokyo, Japan.

Background: Patients on maintenance HD usually suffer from dialysis-related carnitine deficiency, causing various clinical symptoms. At Carnitine Consensus Conference in 2003 convened by The National Kidney Foundation, the level of evidence was strongest for the treatment of anemia, and weakest for the response of muscle weakness. We hereby investigated whether intravenous administration of LC can maintain the muscle volume in HD patients as assessed by % creatinine generation rate (%CGR).

Methods: Thirty-eight HD patients were enrolled in this study after appropriate informed consent. Subjects were treated with intravenous administration of 1000mg / body of LC at the end of every HD session for 12 months, then assessed by %CGR. Normalized protein catabolic rate (nPCR), geriatric nutritional risk index (GNRI) as well as serum albumin or hemoglobin levels were measured at the three points: 1 year prior to the treatment, the start of LC administration and 1 year after the treatment.

Results: As shown in Figure 1, average %CGR significantly declined during 1 year before the start of LC, and then stabilized 1 year after the treatment, suggesting LC administration might prevent the loss of muscle volume. Serum albumin, hemoglobin, nPCR and GNRI stayed the same level during observation period.

Conclusions: Intravenous LC administration may potentially maintain the muscle volume in patients undergoing HD.

Funding: Private Foundation Support

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

568A
FR-PO883
Nutrition Application Mobile Application in Patients with Chronic Kidney Disease
Kumar Sharma, 1 Sakkarin Chirapongsathorn, 2 Zhen Wang, 3 Haun Jenny Lu. 1
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Background: While mobile phone applications have become increasingly important in the last decade, few eating healthy mobile applications exist for patients. Yet in their daily lives, patients on a restricted diet often lack instant access to health information with regards to the food that is in front of them. It is therefore an objective of this pilot project to introduce a device that patients can utilize to overcome such problems.

Methods: The nutrition analysis application is named “GoFoody Project” and primarily consists of two functions: a scanning system and a recommendation system.

Results: The first major component of this invention is the food scanning and recognition process, which is comprised of two sub-processes: a photo recognition and a barcode scanning. In the photo recognition, the user can take a picture of food and send it to the cloud database for further processing, regardless of their location. Second, the recommendation system compares the patient’s medical profile with their consumptions records in order to make health and dietary suggestions.

Conclusions: Over the next few years, we anticipated that this invention will be popular in grocery stores such as Walmart, Target, etc. We plan to demonstrate our invention to the healthcare industry by using the example of computer vision technology and cloud database.

FR-PO884
Lipoxin A4, Attenuates Obesity-Induced Adipose Inflammation and Associated Liver and Kidney Disease
Emma Borjeson, 1 Kumar Sharma, 1 Catherine Godson, 2 1 Center for Renal Translational Medicine, Inst for Metabolomic Medicine, UC San Diego, San Diego, CA; 2 Diabetes Complications Research Centre, Convay Inst, Univ College Dublin, Dublin, Ireland.

Background: Visceral obesity and adipose inflammation is considered a driving force of systemic disease, e.g. chronic kidney disease (CKD). Inflammatory resolution is actively regulated by specialized pro-resolving mediators (SPMs), including the lipid LX4A. Impairment of SPMs may underlie development of obesity-related pathology. Here we explored the therapeutic potential of LXA4 in experimental obesity-induced systemic disease, e.g. liver cirrhosis and CKD.

Methods: C57BL/6 or Adiponectin-/- mice were fed a standard (10% fat) or high fat (60% fat) diet for 12 wks. LXA4 (1 nM) and benzo-LXA4 analogue (1.7 ng/g) were given via attenuation of visceral inflammation and associated liver and renal disease.

Results: Obesity caused distinct pathologies, including impaired glucose-tolerance, adipose inflammation, fatty liver and CKD. Lipoxins attenuated obesity-induced CKD; reducing glomerular expansion, mesangial matrix and urinary H2O2. Furthermore, LXA4 reduced liver weight, serum alanine-aminotransferase and hepatic triglycerides. LXA4 is actively regulated by specialized pro-resolving mediators (SPMs), including the lipid LX4A. Impairment of SPMs may underlie development of obesity-related pathology. Here we explored the therapeutic potential of LXA4 in experimental obesity-induced systemic disease, e.g. liver cirrhosis and CKD.

Conclusions: In conclusion, Lipoxins protect against obesity-induced systemic disease and these data support a novel therapeutic paradigm for treating obesity and associated CKD.

FR-PO885
Prevalence of Protein-Energy Wasting Syndrome and Its Association with Anemia, Erythropoietin Resistance, Overhydration and Body Composition in Hemodialysis Patients
Carlos Adrian Chavez-Mendoza, Jose Luis Ortega vargas, Jorge Osvaldo Montes rivera, Ricardo Correa-Roter, Olynka Vega-Vega.

Background: The prevalence of protein-energy wasting syndrome (PEW) in Mexican hemodialysis (HD) patients is unknown. Accordingly, there is no information on which clinical, biochemical, quality of life (QL), and body composition (BC) variables are associated or predictive of PEW in this population.

Methods: Observational comparative study that included 191 prevalent HD patients. PEW was determined by BIS employing (BCM,Fresenius®), QL was measured with KDQOL-36 and presence of PEW according to ISRNM criteria.

Results: General characteristics are shown in Figure 1, prevalence of PEW was 22%(n=41). No differences between groups (with or without PEW) were present in: age, Charlson index, number and type of drugs employed, time on dialysis, vascular access, history of PD or kidney transplant and hospitalization days in the last year. PEW patients had a higher prevalence of DM(p=0.04), lower Hb(p=0.006) and higher EPO requirements(p<0.04) despite similar iron reserves. In terms of BC, PEW patients had more overhydration (OH) and higher extracellular water (ECW), and lower lean and fat tissue indexes (TLT,FTI). Surprisingly, QL indicators were not different between groups. In a Cox multivariate logistic regression model analysis, predictors of PEW were:degree OH (OR 3.2, 95%CI 1.2-8.3; p=0.001), and ECW (OR 0.51, 95%CI 0.22-0.89; p=0.01).

Conclusions: Prevalence of PEW in the studied population was lower compared to other series. PEW patients exhibit a state of overhydration which is given by increased ECW, and accompanied by loss of LTI and FTI. No PEW impact on QL was observed. PEW pathways have increased anemia and higher requirements of EPO possibly associated to chronic inflammation.

FR-PO884
Lipoxin A4, Attenuates Obesity-Induced Adipose Inflammation and Associated Liver and Kidney Disease
Emma Borjeson, 1 Kumar Sharma, 1 Catherine Godson, 2 1 Center for Renal Translational Medicine, Inst for Metabolomic Medicine, UC San Diego, San Diego, CA; 2 Diabetes Complications Research Centre, Convay Inst, Univ College Dublin, Dublin, Ireland.

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Methods: C57BL/6 or Adiponectin-/- mice were fed a standard (10% fat) or high fat (60% fat) diet for 12 wks. LXA4 (1 nM) and benzo-LXA4 analogue (1.7 ng/g) were given via attenuation of visceral inflammation and associated liver and renal disease.

Results: Obesity caused distinct pathologies, including impaired glucose-tolerance, adipose inflammation, fatty liver and CKD. Lipoxins attenuated obesity-induced CKD; reducing glomerular expansion, mesangial matrix and urinary H2O2. Furthermore, LXA4 reduced liver weight, serum alanine-aminotransferase and hepatic triglycerides. LXA4 is actively regulated by specialized pro-resolving mediators (SPMs), including the lipid LX4A. Impairment of SPMs may underlie development of obesity-related pathology. Here we explored the therapeutic potential of LXA4 in experimental obesity-induced systemic disease, e.g. liver cirrhosis and CKD.

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Conclusions: In conclusion, Lipoxins protect against obesity-induced systemic disease and these data support a novel therapeutic paradigm for treating obesity and associated CKD.

Funding: Other NIH Support - NIH DP3 award (DK94935-01), Veterans Administration Support, Government Support - Non-U.S.
Efficacy of Nutrition Counseling on Protein Intake Restriction in Chronic Kidney Disease Patients – Niigata Part of SOFT-J (Study on Regional Variation of FROM-J Intervention by JSN) 

**Methods:** 47 patients with CKD stage 3 (eGFR 30-59 mL/min/1.73m^2), age 48-85 years were recruited. Nutrition counseling was conducted once for 30 min by national registered dieticians using iPad and textbook used in FROM-J (Frontier of Renal Outcome Modification in Japan) study, aiming at promoting relationship between home doctor and nephrologist.

**Results:** All patients recorded their daily diets, 26/47 provided 24 hours urine collections. Counseling significantly decreased protein intake (record p<0.01, 1.00±0.23 g/kg/day post 1.00±0.26 g/kg/day, p<0.01, urine p<0.01 0.29±0.29 post 0.91±0.22 p<0.04). Although energy intake slightly decreased (record p<0.01, from 319±6.4 kcal/kg/day post 301±5.2 p=0.03), this was not below the prescribed optimal calories. Salt intake decreased in recorded data but not in urine data (record p<0.01, 7.6±1.2 p<0.03, urine p=0.42 post 9.1±4.4 p=0.36, respectively). There was no significant difference in body mass index, eGFR, and renal ischemic score.

**Conclusions:** iPad and textbook counseling by dieticians is effective in reducing protein intake without compromising necessary caloric requirements, even in clinics without regular nephrologist or dietary staff. Informational technology may be an effective method of delivering in-demand nutritional counseling that can directly benefit patient care.

**FR-P0887**

**Actinib Has a Functional Role in Hepcidin Induction by Inflammation**

**Background:** Hepcidin is a negative iron regulatory hormone. Hepcidin contributes to the anemia of chronic kidney disease by restricting iron availability. Bone morphogenetic protein 6 (BMP6) signaling is a central transcriptional regulator of hepcidin. Recently, the transforming growth factor-β (TGF-β) BMP superfamily member Actinib was implicated in hepcidin induction by inflammation via noncanonical SMAD1/5/8 signaling, but its mechanism of action and functional significance in vivo remain uncertain.

**Methods:** Hep3B cells and primary hepatocytes were treated with Actinib B, BMP6, or Actinib A, without or with siRNA knockdown of Actinib/BMP pathway components, and were tested for SMAD2/3 versus SMAD1/5/8 phosphorylation and hepcidin expression. Liver Actinib B expression was measured and the effect of the Actinib inhibitor follistatin-315 was examined in multiple rodent models of anemia of inflammation.

**Results:** Actinib B, but not Actinib A, stimulated SMAD1/5/8 signaling and hepcidin expression in liver cells to a similar degree as canonical SMAD2/3 signaling, and with similar potency and kinetics. Liver Actinib B-induced hepcidin expression was selective, in hepatocyte-derived cells and was not induced by HIV in other cell types. Liver Actinib B mRNA expression was increased in multiple rodent models of inflammation associated with increased hepcidin and hypoferritermia. Follistatin-315 had no effect on basal hepcidin expression, but blunted hepatic induction by inflammation in mice.

**Conclusions:** This study establishes a novel mechanism for noncanonical SMAD activation by BMP/TGF-β superfamily members, and supports a functional role for Actinib B in hepatic induction by inflammation in vivo. Targeting the Actinib B-hepcidin pathway may lead to new therapies for anemia of inflammation including the anemia of chronic kidney disease.

**Funding:** NIDDK Support

**FR-P088**

**Effects of a Very Low Protein Diet Supplemented with Amino and Keto Acids on Skeletal Muscle Protein Synthesis and Degradation in Patients with Chronic Kidney Disease**

**Background:** Inulin, a non-digestible polysaccharide, was used to estimate protein synthesis and degradation in 6 healthy volunteers with healthy kidney function. Amino and keto acids were added to a VLPD period. Studies were performed after an overnight fast (post-absorptive state) and results express basal rates of protein turnover.

**Results:** After supplemented VLPD, as compared to a standard LPD: a) whole body protein turnover declined only slightly (0.51±2 vs. 0.55±2 µmol/kg/min, VLPD vs. LDP, p=NS); b) forearm protein net balance, i.e. the difference between protein synthesis and degradation, was less negative by 18% (from 113±3 to -9.3±2 nmol/min/100 ml, p<0.02); c) the efficiency by which amino acids are cyclic back from protein degradation into protein synthesis was increased by 12% (from 44±4 to 46±5 ±nmol/min/100 ml , p<0.02); d) Protein synthesis increased by 17% (from 33±1 to 38±4 nmol/min/100 ml, p<0.05).

**Conclusions:** Our data show that in patients with CKD stage 5 the response of muscle protein turnover to a AA/KA supplemented VLPD, as compared to a standard LDP, is characterized by similar reduced rates of protein degradation, but an increase in muscle protein synthesis, with enhanced recycling of amino acid derived from catabolism. Net protein balance is less negative, which suggests that the use of AA/KA-supplemented VLPD may be nutritionally safer than a standard LDP.

**Funding:** National Kidney Foundation, Phnixial and Company Support - Fresenius-Kabi Kestoril Award 2012, Government Support - Non-U.S.
FR-PO891

Chronic Kidney Disease Is Associated with Altered Muscle Mitochondrial Energetics by Functional MR Spectroscopy and Optical Spectroscopy

Baback Roshanravan,1 Bryan R. Kestenbaum,2 Jorge Gamboa,2 Jonathan Himmelfarb,1 Ian H. De Boer,1 Kevin Conley.1 1Medicine, Kidney Research Inst - Univ Washington, Seattle, WA; 2Vanderbilt Univ, Nashville, TN.

Background: Exercise intolerance and muscle weakness are frequent clinical complications of CKD associated with adverse health outcomes, yet the pathophysiology underlying these conditions is poorly understood.

Methods: Cross-sectional study of in vivo muscle mitochondrial energetics using 31P Magnetic Resonance Spectroscopy and optical spectroscopy (MRS/OS) in 12 subjects with non-diabetic CKD (eGFR<60) and 26 controls. 13MRS and OS were performed on the hand muscle under controlled ischemia. ATP/ADP (ATPase rate) was measured from phosphocreatine breakdown. Hemoglobin and myoglobin desaturation rates were assessed by OS to measure muscle oxygen uptake (O2 uptake). The primary outcome was the coupling efficiency of mitochondrial oxidative phosphorylation ATP production (ATPflux) per unit of oxygen consumed (O2 uptake) or O2/P ratio. Grip strength and timed up and go were assessed. Pearson's correlation coefficient was calculated for univariable associations. We used multivariable linear regression adjusting for age.

Results: Mean age of CKD patients was 53±13yrs. Physical performance of the CKD group was significantly decreased compared to controls (p=0.002). Mitochondrial ATP/ADP (ATPase rate) was significantly decreased in the CKD group vs. healthy controls (p=0.004). Mitochondrial coupling efficiency (ATPflux) was decreased (p=0.008). Mitochondrial respiratory chain efficiency was decreased (p=0.013). Previous studies have shown that the mitochondrial ATP/ADP ratio is inversely related to muscle strength. In the current study, the ATP/ADP ratio was also inversely related to grip strength (r=-0.52, p=0.006) and time to get up and go (r=-0.43, p=0.003). We also observed a decrease in hemoglobin and myoglobin desaturation rates in the CKD group compared to controls (p=0.001). The coupling efficiency of the mitochondrial respiratory chain (ATPflux) was significantly lower in the CKD group compared to controls (p=0.004). We also observed a decrease in hemoglobin and myoglobin desaturation rates in the CKD group compared to controls (p=0.001).

Conclusions: Application of non-invasive tools reveals that CKD is associated with greater muscle O2 uptake reflecting uncoupling of oxidative phosphorylation. These results suggest altered mitochondrial respiration in skeletal muscle of patients with CKD prior to dialysis.

Funding: NIDDK Support

FR-PO892

Improving Outcomes with Nutrition in Older People with Advanced Chronic Kidney Disease – Baseline Data from a Pilot Randomised Controlled Trial

Lina Johansson,1 Mary Hickson,1 Edwina A. Brown,2 1Nutrition and Dietetics, Imperial College Healthcare NHS Trust, London, United Kingdom; 2Imperial Kidney and Transplant Centre, Imperial College Healthcare NHS Trust, London, United Kingdom.

Background: It is difficult to determine when to start dialysis in older people as creatinine and eGFR can be misleading. Dialysis start is often determined by weight loss, symptoms, potassium and fluid overload, all of which are potentially modifiable with nutrition. This pilot RCT aims to determine whether dietary interventions can result in improved patient outcomes, including time to dialysis, in older people with advanced chronic kidney disease (CKD).

Methods: Patients >65 years, with eGFR 10-20mls/min were randomised to an observational or intervention group (greater dietetic input). Data will be collected every 6 months for up to 2 years: nutritional status (Subjective Global Assessment), symptoms (Palliative Outcome Scale – Symptoms Renal), function (6 metre walk gas test speed and Jamar handgrip dynamometer) and fluid overload using Body Composition Monitor (Fresenius).

Results: 80 patients were recruited, baseline data presented. The 2 groups have statistically similar baseline demographic and clinical characteristics. Overall, 30% have malnutrition of which 58% are overweight/obese. 28% have nutritionally relevant potentially uraemic symptoms (nausea, vomiting and/or poor appetite). Fluid overload (>2L) was observed in 22% of those that were assessed (n=58).

Demographics

Control (n=40) Intervention (n=40)

Male n (%) 27 (67.5) 26 (65.0)
Age years, mean (SD) 74.5 (6.8) 76.0 (7.4)
Diabetes n (%) 19 (47.5) 18 (45.0)
EgFR mls/min, mean (SD) 16 (4) 16 (3)
Potassium >5.5mmol/l % 10 5
Subjective nutritional assessments, %
Malnourished 38 23
Nausea, vomiting and/or poor appetite 25 30
Physical function
Handgrip strength ≤20kg women or ≤ 30kg men, indicative of weakness % 50 58

Conclusions: There is a high prevalence of indications for dietetic interventions within older people with advanced CKD at baseline which may positively affect outcomes within two years.

Funding: Government Support - Non-U.S.

FR-PO893

Retention of Acetylcarnitine in Chronic Kidney Disease Causes Insulin Resistance in Skeletal Muscle

Yasunori Miyamoto,1 Teruo Miyazaki,2 Akira Honda,3 Homare Shimohta,1 Kouichi Hirayama,1 Masaki Kobayashi.1 1Nephrology, Tokyo Medical Univ Ibaraki Medical Center, Ami, Ibaraki, Japan; 2Joint Research Center, Tokyo Medical Univ Ibaraki Medical Center, Ami, Ibaraki, Japan.

Background: Insulin resistance occurs frequently in patients with chronic kidney disease (CKD) and ameliorates after introduction of hemodialysis (HD). However, the mechanisms of insulin resistance associated with CKD are unclear. An increased mitochondrial acetyl-CoA/carnitine ratio causes insulin resistance in skeletal muscle, and this ratio is regulated by carnitine acetyltransferase (CAT), which transfers excess acetyl moieties to carnitine (CT). Because the resulting acetylcarnitine (AcCT) is excreted in urine, we hypothesized that retention of AcCT might be a cause of insulin resistance in patients with CKD.

Methods: Serum samples were collected from 64 patients with CKD (including 14 HD patients) and 31 control subjects who underwent a medical examination. CT and AcCT concentrations in sera were measured by HPLC-ESI-MS/MS. The effects of exogenous AcCT (0-300 µM) on insulin-dependent 2-deoxyglucose (2DG) uptake, mitochondrial CT and AcCT levels, and the mitochondrial acetyl-CoA/carnitine ratio were examined in a cultured skeletal muscle cell line (C2C12 myotubes).

Results: The serum concentration of AcCT, but not that of CT, significantly increased with reduction of renal function, as classified by eGFR (stage I 2.7 ± 0.6 µM, stage 3a 6.1 ± 1.1 µM, stage 3b 10.9 ± 1.9 µM, stage 4 46.3 ± 2.1 µM, stage 5 28.2 ± 5.9 µM, mean ± SEM). After introduction of HD, the increased AcCT levels were significantly reduced (pre 16.3±2.5 µM, post 6.3 ± 0.7 µM). In vitro experiments in skeletal muscle cell lines showed that uptake of 2DG was significantly and dose-dependently inhibited by addition of...
High Protein Intake in Relation to Incident End-Stage Renal Disease (ESRD) Among Blacks and Whites in the Southern Community Cohort Study (SCCS) - Rakesh Malhotra, Edmond Kato Kabagambe, Kerri L. Cavanaugh, William J. Blot, Talat Alp Ikizler, Loreen Lipworth. Vanderbilt U Med Center.

Background: Dietary composition could contribute in part to observed racial disparities in ESRD incidence. Diabetes, a major risk factor for ESRD, may lead to differences in dietary intake and metabolism. We examined whether protein intake is associated with ESRD risk and whether the association varies by race and diabetes.

Methods: We conducted a nested case-control study of ESRD within the SCCS, a prospective study of low income blacks and whites in the southeastern U.S. (2002-2009). Through 2012, 1,074 incident ESRD cases were ascertained by linkage with the USRDS, and matched to 3,230 controls on age, sex, and race. A validated food frequency questionnaire was administered at baseline. Odds ratios (OR) and 95% confidence intervals (CI) for ESRD were computed in relation to protein intake, expressed as daily % of total energy intake and modeled in 1 standard deviation (SD) increments in unconditional logistic regression models stratified by race and diabetes. ORs were adjusted for age, sex, BMI, education, income, hypertension, total energy intake and % energy from saturated and polyunsaturated fat.

Results: Median daily % energy intakes from protein were higher among whites than blacks and those with vs. without diabetes, but differences between ESRD cases and controls were small (15.9 and 15.7%, respectively, for blacks with diabetes, 14.6 and 14.6% for blacks without diabetes, 16.6 and 16.4% for whites with diabetes, and 15.1 and 15.1% for whites without diabetes). For a 1 SD (3.17%) increase in daily % energy intake from protein, adjusted ORs (95% CI) for ESRD were 1.18 (1.05-1.34) for blacks with diabetes, 1.06 (0.93-1.21) for blacks without diabetes, 0.89 (0.61-1.30) for whites with diabetes and 1.00 (0.74-1.33) for whites without diabetes.

Conclusions: Our results raise the possibility that among blacks with diabetes, a diet higher in protein is associated with increased incidence of ESRD. If confirmed, future studies might examine contributors leading to adverse outcomes associated with high protein intake in this subpopulation.

Funding: Other NIH Support - Grant R01 CA92447 from the National Cancer Institute (NCI), including American Recovery and Reinvestment Act funding (3R01 CA024478-08S1)

FR-PO896
High-Fat Diet Induces the Production of IKKε by Macrophages to Promote Nephrotoxicity - Xin Wan, Binbin Pan, Changchun Cao. 1 Nanjing Hospital Affiliated to Nanjing Medical Univ (Nanjing First Hospital).

Background: The NF-κB activation may participate in lipid nephrotoxicity which may be regulated by inhibitor kappa B kinase epsilon (IKKε). To investigate the role of IKKε in this process, mice experiment was performed.

Methods: Mice were grouped into wild-type with normal fat diet (WN), 2 wild-type with high fat diet (WH), 3 IKKε knock-out with normal fat diet (KN), and 4 IKKε knock-out with high fat diet (KH). Renal function, lipid, histological changes and tubular proliferation were analyzed. IL-1β, TNF-β, p50 and p65 were determined by western blot. NF-κB level was tested by EMSA. Expression of IKKε was evaluated through immunohistochemistry and immunofluorescence.

Results: Cystatin C levels were significantly higher in WH group than others. Staining with hematoxylin-eosin revealed that tubular lesions in WH group (3.53±0.21) were more severe than in WN group (0.32±0.11). By Immunohistochemistry, WH group exhibited marked macrophages infiltration than WN, KN and KH groups. Western blot showed significant increase of IL-1β, TNF-β and marked increment in the expression of NF-κB pathway components consists of p50 and p65 in WH group, while these increases were blocked in KN and KH groups. Furthermore, NF-κB level in WH group was higher than other groups. WH group exhibited remarkable macrophages infiltration than other groups by Immunofluorescence. Immunohistochemistry showed remarkable increases in the expression of IKKε in the WH group compared with other groups. Immunofluorescence analysis demonstrated that the expression of IKKε was located around macrophages.

Funding: Government Support - Non-U.S.
There was no relationship between muscle logTLR4 and age, BMI, muscle area, nPNA, calorie intake, albumin, CRP, BUN, bicarbonate, triglycerides, fibrinogen, and phosphate levels. At multivariate analysis SGA and eGFR only contributed significantly to the prediction of TLR4 expression in muscle (p=0.003).

Conclusions: Both low SGA score (which indicates an overall concept of nutritional status) and eGFR (an index of residual renal function) play an independent role to predict TLR4 content in muscle of CKD patients. TLR4 content in muscle rises progressively along with progressive decline of residual renal function, with a 2-fold increase in TLR4 as eGFR declines from 12 to 5 ml/min. Both wasting and progressive loss of residual renal function are predictive of muscle deterioration.

Funding: Government Support - Non-U.S.

FR-PO998

Randomized, Double-Blind, Crossover Clinical Trial on Oral Rice Endosperm Protein Supplementation to Patients on Maintenance Hemodialysis

Background: Protein-energy wasting, a state of metabolic and nutritional derangements, is an important risk factor that affects outcomes of patients with CKD, particularly in ones with ESRD and on maintenance dialysis. Purified rice endosperm protein (REP) contains less phosphorus (150 mg/100g) compared with soybean (787 mg/100g) and casein (737 mg/100g) proteins, and may improve nutritional status without imposing further metabolic derangements.

Methods: We carried out a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effect of REP supplementation (5 g per day x 4 weeks) on nutritional and metabolic status in 50 MHD patients (UMIN000010876). The primary outcome was the change in urea kinetic-based normalized protein nitrogen appearance (nPNA), an indicator of protein intake in MHD patients. The inclusion criteria were: (1) nPNA < 1.2 g/kg/day, (2) serum albumin concentration ≤ 3.0mg/dl, (3) body mass index ≥ 19 kg/m² and < 23 kg/m², (4) 5% variation in dry weight during the period of preceding 6 months, and (5) duration of MHD ≥ 2 years.

Results: By intention-to-treat analyses, REP increased nPNA by 0.07 (95%CI, 0.03-0.11) g/kg/day compared with placebo, whereas Dserum phosphorus concentration was not significantly different between the groups (0.18 (95%CI, -0.23-0.58) mg/dL). REP did not show significant effects on other nutritional parameters. Per-protocol analyses yielded similar results. There were no specific complications associated with the REP supplementation.

Conclusions: REP may be useful for dietary supplementation in MHD patients. Further studies are warranted to evaluate its long-term or high-dose efficacy.

Funding: Government Support - Non-U.S.

FR-PO999

Association of Serum Phosphate Levels and Mortality Risk in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis

Background: Abnormalities of serum phosphate are associated with increased risk for mortality in end stage renal disease (ESRD) or dialysis patients. Use of phosphate binders is an important risk factor that affects outcomes of patients with CKD, particularly in ones with ESRD and on maintenance dialysis. Purified rice endosperm protein (REP) may be useful for dietary supplementation in MHD patients.

Methods: We comprehensively searched the databases of MEDLINE, EMBASE, and Cochrane Databases. The inclusion criteria were published RCT and prospective cohort studies assessing effects of high serum phosphate (compared to normal range) and a 1-mg/dL increase in phosphorus level in patients with CKD (eGFR < 60 ml/min/1.73 m²). We excluded ESRD, dialysis, or renal transplant patients. The primary outcome was risk of all-cause mortality. We used hazard ratio (HR) or risk ratio (RR) in the multivariate model as an effect estimate.

Results: From 15 full-text articles, five studies involving 6,536 patients were included in the meta-analysis. All were prospective cohort studies of CKD stage 3 or 4 patients. There was an increase all-cause mortality risk in higher phosphorus levels (HR = 1.36, 95% CI: 1.24 to 1.0, p=0.01, I²=0%) compared with normal phosphorus levels. A 1-mg/dL (0.1 mmol/L) elevation in serum phosphate also increases mortality risk with HR=1.23 (95% CI: 1.14-1.34, p<0.01, I²=0%).

Conclusions: Elevated serum phosphate levels were independently associated with increased mortality risk among patients with CKD. Randomized controlled trials are needed to assess the benefits of using phosphate lowering therapy in patients with CKD before developing ESRD or dialysis.

Funding: NIDDK Support
FR-PO901
The Comparison of Serum Calcium, Phosphorus and Intact Parathyroid Hormone Between Peritoneal Dialysis Patients and Hemodialysis Patients
Guisén Li, Li Wang.
Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: In this study, we compared the serum calcium, phosphorus and intact parathyroid hormone between peritoneal dialysis patients and hemodialysis patients to study the difference in MBD biochemical variables between PD and HD.

Methods: 907 patients were enrolled from July 1, 2014 to December 31, 2014, including 148 patients received peritoneal dialysis and 359 patients received hemodialysis patients (HD) more than 3 months. Basic clinical information, data of dialysis, serum calcium, phosphorus and iPTH levels were collected in all patients, and comparative analysis was carried out based on those information.

Results: The age and the dialysis vintage was significantly higher in HD group than in the PD group (P <0.001). Serum phosphorus was lower, percentage of phosphorus in target was higher and percentage of calcium in target was lower (P =0.271) in PD group than in HD group (P<0.001). The serum phosphorus levels of PD patients with peritoneal high transport characteristics or high average transport were much lower than those with low transport or low average transport (P = 0.017). The levels of serum phosphorus (P <0.001), iPTH (P<0.01) and alkaline phosphatase(P=0.001) were much lower in patients with RRF<2ml/min than those with RRF≥2ml/min. The levels of serum calcium (P <0.01), corrected calcium(P<0.01), phosphorus (P = 0.025), iPTH (P<0.001) and alkaline phosphatase(P<0.01) were much lower in patients with urine volume ³100ml/d than those <100ml/d. There was a negative correlation between RRF and serum phosphorus (r=−0.291, P<0.01) and iPTH(r=−0.271, <0.01) in PD group. The weekly total KT/V(−0.201,P = 0.019) and weekly total creatinine clearance(Ccr) (r=−0.407, P<0.001) negatively related to serum phosphorus. The Cor(r=−0.241,P <0.01) negatively correlated with serum iPTH.

Conclusions: The serum levels of phosphorus is lower and the percentage of achieving targets of serum phosphorus is higher in PD patients than HD patients. The peritoneal high transport characteristics, RRF<2ml/min, urine volume ³100ml/d and the nutrition status have obvious influence on the serum phosphorus and iPTH levels in PD patients.

FR-PO902
Increased Risk of Cerebral Hemorrhage in Hemodialysis Patients with Hyperphosphatemia: The Q-Cohort Study
Shunsuke Yamada,1 Masanori Tokumoto,1 Masatomo Taniguchi,1 Takanari Kitazono,1 Kazuhiko Tsuryu,1 2 Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; 1Integrated Therapy for Chronic Kidney Disease, Kyushu Univ, Fukuoka, Japan; 1Internal Medicine, Fukuoka Dental College, Fukuoka, Japan.

Background: Mounting evidences have shown that hyperphosphatemia, an established component of CKD-MBD, accelerates cardiovascular disorders in dialysis patients. However, previous studies did not separately determine the effects of hyperphosphatemia on the onset of cerebrovascular disorders and cardiovascular disorders in dialysis patients.

Methods: The present study is an observational study consisting of 3431 outpatients undergoing hemodialysis. The associations between the baseline serum phosphate (Pi) level and the onset of cerebral bleeding and infarction were examined. Individual variable was serum Pi level. Dependent variable was the onset of cerebral hemorrhage and infarction. Age, sex, diabetes mellitus, history of cardiovascular events, dialysis vintage, Kt/V, etc. were adjusted. The regression coefficients for Pi level were analyzed using multiple linear regression analysis.

Results: The serum levels of phosphorus is lower and the percentage of achieving targets of serum phosphorus is higher in PD patients than HD patients. The peritoneal high transport characteristics, RRF<2ml/min, urine volume ³100ml/d and the nutrition status have obvious influence on the serum phosphorus and iPTH levels in PD patients.

Conclusions: Novel correction equations for iCa show better association with iCa and hypercalcemia evaluated by iCa. Its clinical usefulness needs to be evaluated in further studies.

Funding: NIDDK Support

FR-PO904
Relationship Between Dietary Phosphorus Intake and Protein and Energy Intakes in Hemodialysis Patients
David F. Seigles,1 David S. Goldfarb,2,3 Mary Lou Pompeii,1 Kathleen Woolf,1 Kamyar Kalantar-Zadeh,2 Mary A. Sevick.1 1NYU School of Medicine; 2NY Harbor VA Medical Center; 3NYU Langone Medical Center; 2NYU Steinhardt; 3UCLA School of Public Health.

Background: Excess dietary phosphorus may contribute to mineral and bone disorders in hemodialysis (HD) patients. However, many high phosphorus foods are also important sources of dietary protein, which raises concerns that phosphorus restriction may compromise protein status.

Methods: We conducted a cross-sectional study of 190 African American and white men and women on intermittent HD for >3 months. Dietary data were collected by three 24-hour recalls, which were analyzed using NDSR®. Only participants who completed all three recalls and reported intakes >500 kcal/d were included (n=137).

Results: Dietary phosphorus and protein were highly correlated (R=0.73). Based on linear regression, a 1,000 mg/d phosphorus restriction would provide about 78 g protein/d (or 1.1 g protein/kg/d for a 70-kg person). When adjusting for energy intake, the association of dietary phosphorus and protein was far less apparent (R=0.42). Further, the highest phosphorus intake was about two times greater than the lowest phosphorus intake for each energy and protein intake level (500 kcal and 5% of kcal increments), reaching 600 mg/d for some groups.

FR-PO903
Development and Evaluation of Novel Correction Equations for Serum Calcium Concentrations in Hemodialysis Patients
Yoshitsugu Ohji,1 Wei Ling Lau,1 Elani Streja,1 Connie Rhee,1 Steven M. Brunelli,2 Csaba P. Kovesdy,1 Kamyar Kalantar-Zadeh,2 1UC Irvine; 2DaVita Clinical Research; *UTHSC.

Background: Ionized calcium (iCa) but not total calcium (tCa) is the physiologically relevant component of blood calcium. However, these measurements correlate poorly in hemodialysis patients even after correction for serum albumin, which may be partly explained by electrolyte and acid-base derangements in this population.

Methods: In 1,366 patients who initiated conventional HD over four years (1/2007-12/2010), we identified 6,830 iCa measurements where serum albumin, iCa, sodium, chloride, phosphorus, and bicarbonate were measured simultaneously. We randomly divided patients into a derivation set (n=681) or a validation set (n=685) to develop and evaluate new correction equations for serum iCa concentrations by comparing correlation r and Bayesian information criterion (BIC) in linear regression analysis as well as receiver operating characteristic (ROC) curves for hypercalcemia determined by iCa (≥5.28 mg/dL).

Results: Albumin was associated with iCa, but its coefficient was -0.15, not -0.8 as shown in the conventional correction equation. Furthermore, albumin-corrected iCa showed lower correlation than uncorrected iCa with iCa (r=0.69 and 0.76, respectively). Two equations were developed from the derivation set as follows; [EQ1] 1.1*iCa – 0.12*(phosphorus+1) and [EQ2] 1.1*iCa – 0.08*(anion gap – 2). In the validation set, EQ1 and EQ2, compared to the conventional correction by albumin, showed better correction with iCa (r=0.78 and 0.80, respectively), lower BIC (96% and 92%, respectively), and higher area under the ROC curve for Ca-defined hypercalcemia (P<0.01 for both).

Conclusions: Novel correction equations for iCa show better association with iCa and hypercalcemia evaluated by iCa. Its clinical usefulness needs to be evaluated in further studies.

Funding: NIDDK Support
FR-PO907

Recruitment and Retention to a Randomised Trial of Low versus High Serum Phosphate Levels in Hemodialysis Patients

Ranveer Bhattarava, 1 Paul E. Brenchley, 1 Philip A. Kalra, 2 Alastair J. Hutchinson. 1 Manchester Royal Infirmary, United Kingdom; 2 Salford Royal Hospital, United Kingdom.

Background: High phosphate is linked with increased mortality in dialysis patients in retrospective observational studies but cause and effect is unproven. A large scale RCT of high versus low serum phosphate would be required to determine whether serum phosphate reduction improves length or quality of life of dialysis patients. We performed a feasibility study to investigate whether such a large scale RCT might be possible in the future.

Methods: After consent, 104 HD patients were randomized to low (2.5-4.4 mg/dL) or high phosphate (5.6-7.5 mg/dL) groups. Non-calcium binders, and an adherence self-help program were used to titrate to target PO4 over 8 weeks. A 10 month maintenance period followed. Primary endpoint; % patient months within target range over 10 months. Secondary end points: % nephrologists agreeing to enrol patients, % eligible patients willing to participate, drop-out rate over 12 months, pill burden per subject.

Funding: 768 HD patients screened, 263 suitable, 228 treated, 207 randomized (13.5% of screened), 21 of 24 nephrologists (87.5%) agreed to enrol patients after assessing the protocol.

<table>
<thead>
<tr>
<th>PO4 Group</th>
<th>Patient Months</th>
<th>% Patients within PO4 range</th>
</tr>
</thead>
<tbody>
<tr>
<td>High PO4</td>
<td>36</td>
<td>49.5 (35.7)</td>
</tr>
<tr>
<td>Low PO4</td>
<td>38</td>
<td>53.5 (38.7)</td>
</tr>
</tbody>
</table>

Results: Conclusions: Less than 50% of PO4 levels were within target range over 10 months, and this will be analyzed as time-averaged results. More patients withdrew consent in the low PO4 group, with GI side-effects plus high pill burden being possible contributory factors. 65% patients completed the study with a drop-out rate of 35%. Drop-out due to death was substantially greater in the high PO4 group, but randomization was not stratified for other risk factors, and the overall mortality rate of 10% is lower than the expected dialysis rate of 13-17% per annum.

Activities: Research buy-in, 24 nephrologists agreed, 13.5% screened, 263 suitable, 228 randomized, 104 randomized (13.5% of screened), 21 of 24 nephrologists (87.5%) agreed to enrol patients after assessing the protocol.

FR-PO908

Randomization to High or Low Phosphate Control in Hemodialysis: Is Such a Study Feasible? Ranveer Bhattarava, 1 Paul E. Brenchley, 1 Philip A. Kalra, 2 Alastair J. Hutchinson. 1 Manchester Royal Infirmary, United Kingdom; 2 Salford Royal Hospital, United Kingdom.

Background: High phosphate is linked with increased mortality in dialysis patients in retrospective observational studies but cause and effect is unproven. A large scale RCT of high versus low serum phosphate would be required to determine whether serum phosphate reduction improves length or quality of life of dialysis patients. We performed a feasibility study to investigate whether such a large scale RCT might be possible in the future.

Methods: From a pool of 768 HD patients, 104 were suitable and consented to a binder washout period, and were randomized to low phosphate (2.5 to 4.4 mg/dL) or high phosphate (5.6 to 7.5 mg/dL) groups. Subjects were titrated to target over 8 weeks with lanthanum or sevelamer binders only, then followed for 10 months. The pill burden in each group and secondary hyperparathyroidism were assessed. Serum albumin as a measure of nutritional status was recorded.

Results:

<table>
<thead>
<tr>
<th>Number randomised</th>
<th>HRG</th>
<th>LRG</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation PO4 (mg/dL)</td>
<td>51</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Week 8 PO4 (mg/dL)</td>
<td>2.1 +/- 0.1</td>
<td>2.2 +/- 0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Randomisation PTH(pg/ml)</td>
<td>436 +/- 62</td>
<td>424 +/- 54</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 8 PTH(pg/ml)</td>
<td>362 +/- 258</td>
<td>472 +/- 380</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Randomization Albumin(g/L)</td>
<td>32 +/- 0.8</td>
<td>32 +/- 0.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 8 Albumin(L/g)</td>
<td>34 +/- 0.6</td>
<td>34 +/- 0.7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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

575A

FR-P0905

Assessment of Barriers to Phosphorus Control in Dialysis Patients

Rashmi Bisla, Jasmin Sandhu, Vinod K. Bansal, Stephanie Kliethermes, Anuradha Wadhwa. Loyola Univ Medical Center, Maywood, IL.

Background: High phosphate levels are associated with increased cardiovascular and all-cause mortality but phosphate control continues to be a challenge amongst dialysis patients. In this study, we conducted a survey to assess phosphate control and identify barriers to phosphate control in patients receiving dialysis at Loyola outpatient dialysis unit.

Methods: The study consisted of 17 question survey evaluating patients knowledge and understanding of phosphate control, self care practices and social support as potential barriers to phosphate control. Patients were approached during dialysis to participate. Objective patient data and laboratory data was collected from electronic medical records. Study was approved by Loyola IRB.

Results: Of the 99 eligible subjects, 57 completed the survey. Mean age of the participants was 62 years, 52% were males and 75% were African Americans. Patients were categorized into uncontrolled (phosphate >5.5 mg/dL) and controlled phosphate group. The two groups had similar demographics, co-morbidities, dialysis adequacy and medication pill burden. Approximately 80% of patients with uncontrolled phosphate were aware of normal phosphate levels in dialysis patients, complications associated with high phosphorus and identified majority of foods with high phosphorus compared to 53% in the controlled phosphate group. There were no differences among the two groups related to social support or self-care practices. 75% patients in the controlled and 55% in the uncontrolled group were interested in learning more about phosphate control.

Conclusions: Patients with uncontrolled phosphate had significantly greater knowledge and understanding of phosphate control. While continued education of patients regarding phosphate control is important, qualitative research to study patients’ behavioral aspects is needed to better understand barriers to phosphate control.

FR-P0906

Use of a Simple, Widely Available Laboratory Test to Quantify and Explain Variation in Phosphorus Levels in Beverages

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Background: Restriction of dietary phosphorus (P) is essential in the management of hyperphosphataemia in CKD. Beers and wines contain inorganic P that is readily absorbed but data on these beverages, and less well-known soft drinks, is difficult to obtain. An assay used routinely in hospital laboratories has been validated for measurement of P in a range of beverages (Lindley et al. 2014) enabling renal unit staff to compile information on locally sourced products and investigate variation between brands.

Methods: Beverages were processed as if they were urine samples and tested using inorganic P analysers in different countries.

Coca-Cola, which is strictly regulated world-wide, was used to check agreement between laboratories in the Saarland selection, with similar PO4 results. Yeast nutrient (a widely-used yeast nutrient) were compared with 8 Australian wines from UK supermarkets. Classic New South Wales containing little or no di-ammonium phosphate (DAP, a widely-used yeast nutrient) were compared with 8 Australian wines from UK supermarkets. Classic New South Wales containing little or no di-ammonium phosphate (DAP, a widely-used yeast nutrient) were compared with 8 Australian wines from UK supermarkets.

Results: The P content of alcoholic beers in the Saarland selection varied from 12 to 27 mg/dL, while reds contained 14 to 20 mg/dL. DAP increased the P level by about 2 mg/dL for every 100 mg/L added to the wine must. Much higher P levels in the supermarket wines were processed as if they were urine samples and tested using inorganic P analysers in different countries.

Conclusion: Restriction of dietary phosphorus (P) is essential in the management of hyperphosphataemia in CKD. Beers and wines contain inorganic P that is readily absorbed but data on these beverages, and less well-known soft drinks, is difficult to obtain. An assay used routinely in hospital laboratories has been validated for measurement of P in a range of beverages (Lindley et al. 2014) enabling renal unit staff to compile information on locally sourced products and investigate variation between brands.

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Serum phosphate in the two groups

Conclusion: 1. Statistically significant separation in serum phosphate was achieved between the two groups (fig 1) with no apparent increase in secondary hyperparathyroidism. 3 patients in the HRG commenced Cinacalcet during the course of the study because serum PTH > 1200 mg/dL. 2. As expected, LRG had a significantly larger pill burden than the HRG, with 2 patients in the LRG taking 9 or more binder pills. 3. Despite increased pill burden, albumin levels were not different between groups. 4. Crude mortality 4 times higher in the HRG.

Funding: Pharmaceutical Company Support - Shire pharmaceuticals provided an unrestricted educational grant towards the research fellow’s salary for 12 months.

FR-PO909

Efficacy and Safety of PT20: A Novel Iron-Based Phosphate Binder

Methods: Patients were on hemodialysis with serum phosphate (P) levels between 4.0 and 8.0 mg/dL plus serum ferritin levels <1000 ng/mL at their screening visit. All patients were then washed out of previous P-binders and required to have an increase in serum P of at least 1.0 mg/dL to enter study. 153 subjects were randomized to either 400 mg, 800 mg, 1600 mg, 3200 mg PT20 or placebo, each taken TID with meals for 28 days. Doses were not modified during the treatment period. Primary end point was change in serum P from Baseline to Day 29. Secondary endpoints assessed safety as well as haematological parameters.

Results: PT20 treatment significantly reduced serum P levels and demonstrated a dose response effect (ITT population; p<0.001). All dose groups showed a reduction in mean P levels greater than placebo. Mean reduction in P over the 28 days was (mg/dL) 1.36 /3200mg; 1.29 /1600mg; 0.59 /800mg; 0.40 /400mg and 0.17 /Placebo dose.

Conclusions: Use of adapatte-modified iron oxide (PT20) resulted in a statistically significant and dose-dependent reduction in serum phosphate over a 28 day period. The safety profile and tolerability were acceptable with AE's being mostly GI in nature, with no pattern of serious adverse events related to treatment. Limited iron absorption from PT20 was observed.

Funding: Pharmaceutical Company Support - Phosphate Therapeutics Ltd

FR-PO911

Phase III Study to Investigate the Long-Term Efficacy, Safety, and Tolerability of PA21 (Sucroferric Oxydroxide) in Japanese Hemodialysis Patients with Hyperphosphatemia

Conclusions:

Results:

Methods: In total, 213 patients were randomized to SFOH (750–3000 mg/day; starting dose 750 mg/day; available as 250 mg and 500 mg tablets). SFOH was administered at Week 0, after treatment with any prior phosphate binders had been discontinued. Doses of SFOH were titrated to maintain predefined serum phosphorus (sP) concentrations of 3.5–6.0 mg/dL.

Results: Mean sP concentrations decreased from 5.46 mg/dL at Week 0 to 5.00 mg/dL at the last evaluation. Mean sP concentrations were maintained within the target range of 3.5–6.0 mg/dL throughout the 52-weeks treatment period. The average number of SFOH tablets was 3.3 tablets/day, and the average dose of SFOH was 1.141 mg/day. Overall, the incidence of adverse events and adverse drug reactions was 93.6% and 32.9%, respectively. Frequently observed adverse drug reactions were diarrhea (22.4%) and constipation (2.5%), no severe diarrhea or constipation was reported. In spite of slight increases in serum ferritin and transferrin saturation, no clinical signs of iron accumulation or overload were observed at 52 weeks.

Conclusions: SFOH demonstrated a sustained sP-lowering effect 52-weeks of treatment in Japanese HD patients, and was associated with a low pill burden and good tolerability.

Funding: Pharmaceutical Company Support - Kissey pharmaceutical Co, Ltd

FR-PO912

Improved Serum Phosphorus Control and Decreased Phosphate Binder Pill Burden Amongst African American Hemodialysis Patients

Conclusions:

Methods:

Results:

Conclusions: 1. Statistically significant separation in serum phosphate was achieved between the two groups (fig 1) with no apparent increase in secondary hyperparathyroidism. 3 patients in the HRG commenced Cinacalcet during the course of the study because serum PTH > 1200 mg/dL. 2. As expected, LRG had a significantly larger pill burden than the HRG, with 2 patients in the LRG taking 9 or more binder pills. 3. Despite increased pill burden, albumin levels were not different between groups. 4. Crude mortality 4 times higher in the HRG.

Funding: Pharmaceutical Company Support - Kissey pharmaceutical Co, Ltd

FR-PO911

Phase III Study to Investigate the Long-Term Efficacy, Safety, and Tolerability of PA21 (Sucroferric Oxydroxide) in Japanese Hemodialysis Patients with Hyperphosphatemia

Funding:

Background: A retrospective database study was conducted on the real-world effectiveness of sucroferric oxydroxide (SO) in controlling serum phosphorus (sP) among hemodialysis (HD) patients (pts). This analysis focuses on the subset of patients who self-reported race as Black or African American.

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

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In a cohort of African American hemodialysis patients prescribed sucroferric oxyhydroxide, a 57% increase in patients with in-range (3.5-5.5 mg/dl) serum phosphorus (p<0.001) along with a decrease in pill burden (4.8 fewer pills, p<0.001) was observed.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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**FR-PO913**

Real-World Use of Sucroferric Oxyhydroxide in Hemodialysis Patients: Changes in Serum Phosphorus Control and Phosphate Binder Pill Burden

**Linda H. Ficociello, Lin Ma, Vidhya Parameswaran, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. Fresenius Medical Care North America (FMCNA), Waltham, MA.**

**Background:** Approximately 40% of US dialysis patients (pts) do not achieve serum phosphorus (sPhos) goals (US-DOPPS Practice Monitor, 4/2015). This retrospective database analysis assessed the real-world effectiveness of sucroferric oxyhydroxide (SO) to control sPhos in hemodialysis (HD) pts.

**Methods:** In-center HD pts prescribed SO as part of routine clinical practice at FMCNA clinics with ≥1 sPhos during SO use were included. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and phosphate binder (PB) pills per day (PPD) were assessed 3-months before (baseline) and 3-months during SO treatment (follow-up).

**Results:** On average, pts (n=3151) were 54 years old with 4.3 years dialysis vintage (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and phosphate binder (PB) pills per day (PPD) were assessed 3-months before (baseline) and 3-months during SO treatment (follow-up).

**Conclusions:** In a large HD patient cohort prescribed sucroferric oxyhydroxide as part of routine clinical care, in-range serum phosphorus increased by 57% (13 to 20.4%, p<0.001) and mean pills per day decreased by 4.7 pills (8.4 to 3.7 pills, p<0.001).

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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**FR-PO914**

Serum Phosphorus Control and Phosphate Binder Pill Burden Among Hemodialysis Patients Who Switched from Calcium Based Phosphate Binders to Sucroferric Oxyhydroxide

**Vidhya Parameswaran, Lin Ma, Linda H. Ficociello, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. Fresenius Medical Care North America, Waltham, MA.**

**Background:** A retrospective database analysis of in-center hemodialysis (HD) patients (pts) who switched from calcium-based phosphate binders (PB) to sucroferric oxyhydroxide (SO) was conducted to study the real-world effectiveness of SO in controlling serum phosphorus (sPhos).

**Methods:** In-center HD pts who had ≥ 1 sPhos measured during SO treatment and switched from calcium-based PB were included. Comparisons were made between baseline (3 months prior to SO) and follow-up (3 months during SO) levels of sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and PB pills per day (PPD).

**Results:** Analyzed pts (n=1011) were, on average, 54 years old with dialysis vintage of 4.5 years and hyperphosphatemia (baseline sPhos=6.98 mg/dl). Prior therapy included 81.7% calcium acetate and 18.3% calcium carbonate. There was a significant decrease in sPhos (6.98 to 6.77 mg/dl, p<0.001) and PB PPD (8.2 to 3.7 pills, p<0.001). A 47% increase (13.5% to 19.8%, p<0.001) in the number of pts with in-range sPhos (3.5-5.5 mg/dl) was observed. Levels of iPTH (559.3 to 552.9 ng/ml) and sCa (9.2 to 9.1 mg/dl) did not change significantly. Significant differences in TSAT (34.0 to 34.8%, p-value=0.007) and FER (931.7 to 973.1 ng/ml, p<0.001) were observed. In pts not receiving IV iron (n=103), there were no significant changes in TSAT (34.5% to 33.4%) and FER (1039 to 1003.4 ng/ml).

**Conclusions:** In a HD cohort switched from calcium-based binders to sucroferric oxyhydroxide as part of routine clinical care, a 47% increase (p<0.001) in the number of patients with in-range serum phosphorus and reduction of serum phosphorus (0.21 mg/ dl, p<0.001) was observed. Pill burden decreased significantly (4.6 fewer pills, p<0.001).

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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**FR-PO915**

Phosphate Binder VS-505 Prevents Hyperphosphatemia from Altering Aortic Gene Expression in 5/6 Nephronecrotic Uremic Rats

**J. Ruth Wu-Wong, Xiaoxuan Ruan, Yung-wu Chen, Jeery Wessell, Vidasym, Jackson Lab.**

**Background:** Chronic kidney disease (CKD) patients are known to have impaired vascular function. Clinical studies have linked hyperphosphatemia to a higher cardiovascular mortality in CKD.

**Methods:** We compared gene expression profiles in aorta isolated from 5/6 nephrectomized (NX) uremic Sprague Dawley rats fed a normal diet vs. a high phosphate (Pi) diet. Real-time RT-PCR analysis was conducted on selected genes in aorta prepared from 5/6 NX uremic rats on a high Pi diet for 4 weeks treated with or without the phosphate binder VS-505, a non-absorbable, calcium- and aluminum-free, chemically-modified, plant-derived polymer currently being evaluated in hemodialysis patients.

**Results:** An increase in serum Pi was observed in uremic rats on the special diet (3.92 ± 0.42 vs. 3.29 ± 0.55 mmol/L on normal diet). A total of 135 target genes were affected (out of 15923 genes; 2-fold change, p<0.01) by increased serum Pi, with 122 up-regulated and 13 down-regulated. Target genes fell into various categories including carboxylic acid metabolism, lipid metabolism, mitochondrion, and oxidoreductase activity. In a separate study, VS-505 (0.2 - 5% by weight in food) prevented the increase in serum Pi (3.06 ± 0.30 mmol/L in the 5% VS-505 group vs. 3.74 ± 0.68 mmol/L in the vehicle-treated group, p=0.01), and it increased fecal Pi in a dose-dependent manner in the uremic rats on high-Pi diet (2.48 ± 0.60 mmol/24 hr in the 5% VS-505 group at Week 4 vs. 0.84 ± 0.55 mmol/24 hr at pre-dosing, p<0.001). VS-505 did not affect food/water consumption, feces appearance, dietary intake, histomorphology and NPT2b gene expression. VS-505 treatment prevented the effects of hyperphosphatemia on altering the expression of aortic genes related to oxidative stress and inflammation such as activin A receptor-type 1C, glycogen synthase 2, heat shock 70KD protein 1A, steroyl coenzyme A desaturase 1, and uncoupling protein 1.

**Conclusions:** In a HD cohort switched from calcium-based binders to sucroferric oxyhydroxide as part of routine clinical care, a 47% increase (p<0.001) in the number of patients with in-range serum phosphorus and reduction of serum phosphorus (0.21 mg/dl, p<0.001) was observed. Pill burden decreased significantly (4.6 fewer pills, p<0.001).

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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Conclusions: These results suggest that hyperphosphatemia affects aortic gene expression to oxidative stress and inflammation, and that the adverse cardiovascular effects of high serum Pi may be prevented by oral treatment with the phosphate binder VS-505.

Funding: NIDDK Support

FR-PO916

Fractional Excretion of Phosphorus Misrepresents Hormonal Effects on Phosphate Reabsorption in Chronic Kidney Disease

Keneith R. Phelps,1,2 Darius Mason,1,2 Sun J. Kang,1 (Stratton VAMC, Albany, NY; Albany Medical College, Albany, NY; ‘Albany College of Pharmacy and Health Sciences, Albany, NY.

Background: The serum P concentration ([P]) – E P/Cr + TR P/Cr, where E P/Cr and TR P/Cr are rates of urinary excretion and tubular reabsorption of P per volume of filtrate. E P/Cr is proportional to filtrate [P] in the cortical distal nephron ([P]); we have argued that [PTH] correlates with E P/Cr, for this reason in CKD. Fractional excretion of FE P was calculated as ([P]u/[P]s)u/[P]s and [FGF23] correlated directly with E P/Cr. TR P/Cr was not associated with [PTH] and [FGF23] did not result from effects of the hormones on TR P/Cr, and therefore did not reflect quantitative relationships between hormone concentrations and P reabsorption.

Methods: We measured fasting [cr], [P], [P], [PTH], and [FGF23] in 30 patients with stages 3-4 CKD. We calculated E P/Cr as ([P]u/[P]s)u/[P]s and FE P as ([P]u/[P]s)u/[P]s. We performed simple linear regressions as in the table and a multilinear regression of E P/Cr on TR P/Cr, E P/Cr, and TR P/Cr.

Results: FE P correlated directly with [PTH], [FGF23], and E P/Cr, and inversely with TR P/Cr, [PTH] and [FGF23] correlated directly with E P/Cr, TR P/Cr was not associated with [PTH] or [FGF23]. In the multilinear regression, E P/Cr and TR P/Cr caused > 90% of variation in FE P, [PTH] and [FGF23] did not contribute significantly.

Conclusions: TR P/Cr was unrelated to [PTH] and [FGF23] even though both hormones reduce P reabsorption. Although FE P varied inversely with TR P/Cr, correlations of FE P with [PTH] and [FGF23] did not reflect quantitative relationships between hormone concentrations and P reabsorption. The correlations occurred because FE P, [PTH], and [FGF23] were associated with E P/Cr. FE P should not be used to relate P reabsorption to hormones in CKD.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation

FR-PO917

Attributes of the Walton-Bijvoet Nomogram at Normal and Reduced Glomerular Filtration Rate

Keneth R. Phelps,1,2 Darius Mason,1,2 Sun J. Kang,1 (Stratton VAMC, Albany, NY; Albany Medical College, Albany, NY; ‘Albany College of Pharmacy and Health Sciences, Albany, NY.

Background: The serum P concentration ([P]) is the sum of E P/Cr and TR P/Cr (urinary excretion and tubular reabsorption of P per volume of filtrate). In Bizoil’s infusion studies, observed TR P/Cr equaled maximum TR P/Cr (Tm P/GFR) at fasting fractional P excretion (FE P) > 20%; as FE P fell, (Tm P/GFR) – (TR P/Cr) rose. These observations were incorporated into a nomogram that derives Tm P/GFR from [P]u/[P]s, TR P/Cr, and FE P. We performed simple linear regressions as in the table and a multilinear regression of E P/Cr on TR P/Cr, E P/Cr, and TR P/Cr.

Conclusions: TR P/Cr was unrelated to [PTH] and [FGF23] even though both hormones reduce P reabsorption. Although FE P varied inversely with TR P/Cr, correlations of FE P with [PTH] and [FGF23] did not reflect quantitative relationships between hormone concentrations and P reabsorption. The correlations occurred because FE P, [PTH], and [FGF23] were associated with E P/Cr. TR P/Cr, [PTH] and [FGF23] did not contribute significantly.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation

FR-PO918

Role of KHSRP and Pin1 in Mediating the Parathyroid Hormone Response in the Proximal Tubule

Rebecca Murray,1,2 Michael Merchant,2 Syed J. Khundmiri,1,2,3 Barbara Clark,4 Eleanor D. Lederer.1,2,3

Background: Parathyroid hormone (PTH) regulates the type IIa sodium-phosphate cotransporter (Npt2a), the major proximal tubule phosphate transporter at both the protein and mRNA level. We previously identified KHSRP as a PTH-responsive phospho-protein that binds Npt2a mRNA and may mediate its degradation. Pin1, a pep-tidyl phosphoserine isomerase, is the upstream regulator of KHSRP function and localization. Pin1 phosphorylated Pin1 binds KHSRP, promoting KHSRP dephosphorylation and maintaining its cytosolic localization. We hypothesize that PTH stimulates Npt2a mRNA destabilization through PAKa-mediated phosphorylation of Pin1.

Methods: To address this hypothesis, we treated opossum kidney (OK) cells, a proximal tubule cell line, with 100mM PTH or 10mM branes-acMPA (b-Br [to directly activate PAKa] in the presence or absence of 1mM H-89 (a PAKa inhibitor).

Results: 2h PTH induced a 2.5-fold increase in Pin1 phosphorylation. IP of KHSRP followed by immunoblot for Pin1 showed that Pin1 associates with KHSRP under basal conditions, but not following 2h PTH or 8-h treatment. Pre-treatment with H-89 blocked the PTH/8-Bt-induced dissociation. 2h PTH did not alter total expression of KHSRP, but stimulated its translocation to the nucleus.

Conclusions: We conclude that PTH-mediated destabilization of Npt2a mRNA likely involves PAKa-mediated regulation of Pin1 and KHSRP activity. Funding provided by VA to EDL.

Funding: Veterans Administration Support

FR-PO919

Phosphate Depletion-Induced Metabolic Acidosis and Alkalai Urine May Be Caused by Inappropriate Stimulation of Apical Cl/HCO3− Exchanger (Pendrin) in Mouse Kidney Type B Intercalated Cells (IC-B)


Background: Mice treated with a low phosphate (P) diet can maintain normal levels of plasma Pi concentration via stimulation of bone reabsorption, but show hypercalciemia, hypercalcuria, and hypophosphaturia. Recently, the Ca-sensing receptor (CaSR) was found to be localized in the basolateral membrane of IC-B as well as in the thick ascending limb of Henle’s loop (Yasuoka et al., 2014). This study was aimed to determine whether hypercalciemia and/or hypercalcuria affect urine pH as expected in mice treated with either dietary Pi depletion or CaCl2-loading.

Methods: C57Bl/6j mice (10 wks, male) were divided into three groups: (1) normal diet (1% P, n=6), (2) low-P (LP) diet (0.02% P, n=4), (3) CaCl2-loading (1% P, +1% CaCl2, n=6). All diets contain 1% Ca (CaCl2). On day 7, a 24-h urine, blood, and kidney samples were collected.

Results: Serum and urinary Ca were markedly and significantly increased in the LP and CaCl2 groups [serum, 9.1 and 8.9 mg/dL and urine, 2,400 and 2,140 µg/day, respectively] compared with control (serum, 7.6 mg/dl; urine, 105 µg/day). Although serum pH decreased similarly to 7.25 and 7.20 in both groups, pH of the urine decreased to 5.6 (P < 0.05) in the CaCl2 group and, surprisingly, increased to 7.4 (P < 0.05) in the LP group (control, serum pH 7.35; urine, pH 6.3). Kidney histology and immunohistochemistry showed that

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the IC-A cell height and basolateral Cl−/HCO3− exchanger type 1 (AE1) staining significantly increased in the CaCl2 group, whereas the IC-B cell height and apical Pendrin and basolateral AE4 staining significantly increased in the LP group.

**Conclusions:** P-depletion induced metabolic acidosis may be due to imbalanced urinary acidification and acidosis caused by inappropriate stimulation of Pendrin and AE4 through the hypercalcemia-induced activation of the basolateral CaSR in IC-B.

**FR-PO920**

MUC1 Increases Renal Calcium Channel TRPV5 Activity to Enhance Calcium Reabsorption in a Galectin-3 Dependent Fashion

**Background:** MUC1 (MUC1) mutations cause autosomal dominant tubulointerstitial kidney disease (ADTKD-MUC1), a condition similar to a nephropathy caused by Uromodulin (UMOD) mutations (ADTKD-UMOD). We previously showed that UOMOD may protect against calcium-containing kidney stones by increasing TRPV5 cell surface abundance and tubular calcium reabsorption, which may decrease the risk of urinary supersaturation. The role of MUC1 in kidney is unclear. As UOMOD and MUC1 share characteristics regarding disease phenotype, protein function, and structure, we examined the hypothesis that MUC1 enhances TRPV5 channel activity.

**Methods:** We expressed TRPV5 and MUC1 variants in HEK293 cells and studied TRPV5 current density by whole-cell patch-clamp recording.

**Results:** MUC1 coexpressed with TRPV5 resulted in a higher TRPV5 current density compared to mutant MUC1-C or control. MUC1 increased TRPV5 current density when applied extracellularly and required TRPV5 N-glycan for upregulation. Immunofluorescence imaging showed apical MUC1 expression along the distal nephron which is compatible with TRPV5 regulation in DCT. To test if MUC1 affects TRPV5 endocytosis, we tested if MUC1 upregulates TRPV5 in a Ca2+-deficient fibroblasts, as TRPV5 undergoing endocytosis by caveolin-1. While MUC1 alone had no effect, cotransfection of reconstituting caveolin-1 with MUC1 restored TRPV5 upregulation by MUC1. The extracellular domain of MUC1 contains variable number tandem repeats (VNTRs) which bind galectin-3, a lectin involved in lattice formation of channels. Using galectin-3 siRNA, we identified galectin-3 as a prerequisite for TRPV5 upregulation by MUC1. This was confirmed by the inability of MUC1 lacking VNTR to upregulate TRPV5. In urine samples of patients with calcium-containing kidney stones we found less urinary MUC1 compared to control individuals.

**Conclusions:** MUC1 upregulates TRPV5 by extracellular lattice formation with TRPV5 N-glycan via galectin-3 which impairs TRPV5 channel endocytosis. These data are consistent with MUC1 contributing to protection against calcium-containing kidney stones.

**Funding:** NIDDK Support

**FR-PO921**

NCC Activity Modulation as a Mechanism for PTH Regulation of DCT Calcium Transport

**Background:** The distal convoluted tubule (DCT) is a major site of both calcium and sodium transport. While altered DCT calcium handling is not required for thiazide-induced hypocalciuria, studies have documented increased DCT calcium reabsorption in response to thiazide administration. This suggests that DCT sodium transport does affect DCT calcium transport, and while thiazide induced hypocalciuria is due to a proximal effect, modulation of NCC activity may affect DCT calcium transport by TRPV5. Since parathyroid hormone (PTH) is known to increase TRPV5 activity and decrease NCC activity, we theorized that decreased NCC-mediated sodium reabsorption may contribute to the enhanced TRPV5 calcium reabsorption seen with PTH administration.

**Methods:** Radioactive uptake and biotinylation in mDCT15 cells were used to measure sodium and calcium uptake as well as surface expression of NCC and TRPV5.

**Results:** mDCT15 cells expressed rhesus monkey sensitive “Ca2+-influx via 5.9±0.2 mmol/mg/min and surface expressed TRPV5. PTH increased “Ca2+-uptake to 8.8±0.7 mmol/mg/min (n=4, p<0.01 compared to control) and decreased NCC activity from 75.4±2.7 to 20.3±1.3 mmol/min (n=4, p<0.01 compared to control). Knockdown of RasGRP1, the pathway by which PTH affects NCC, had no baseline effect on “Ca2+-influx but significantly attenuated the increased “Ca2+-uptake response to PTH from a 55% increase (6.0±1.0 vs 7.3±0.2 mmol/mg/min, p<0.01) of non-targeting groups). Inhibition of PKC and PKA, the known pathways by which PTH acts upon TRPV5, resulted in further attenuation of the PTH effect.

**Conclusions:** Here, through the use of a cell model with native NCC and TRPV5 activity, we report that modulation of NCC activity does indeed contribute to the TRPV5 response to PTH, implying a role for hormonal modulation of NCC activity in distal calcium handling. Further study is needed to determine the mechanism for these findings.

**Funding:** NIDDK Support, Veterans Administration Support

**FR-PO922**

How Disruption of Distal Nephron Salt Reabsorption Causes Calcium Wasting, Tubule Calcification and Skeletal Changes

**Background:** Sharon L. Barone, 1,2 Jie Xu, 1,2 Manoocher Soleimani. 1,2 1Internal Medicine, Univ of Cincinnati, Cincinnati, OH; 2Research Services, Veterans Affairs Medical Center, Cincinnati, OH.

**Background:** Carbonic anhydrase II/sodium chloride co-transporter (NCC) and pendrin/AE4 double knockout mice (dKO) develop salt wasting and are growth retarded. We propose that the disruption of sodium and chloride reabsorption in these mice causes phosphate and calcium wasting and leads to bone and skeletal anomalies.

**Methods:** Renal alterations that lead to distorted calcium and phosphate reabsorption and contribute to tubular calcification and growth retardation in the dKO mice were examined.

**Results:** dKO mice are volume depleted, exhibit kidney hyperperfusion, and have increased urinary calcium and phosphate excretion. These mice also exhibit skeletal anomalies and osteopenia and develop tubular calcium phosphate deposits. Parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) levels are increased in dKO mice.

The urinary content of prostatic luteinizing hormone (PGE2) is significantly elevated, along with the expression of microsomal prostaglandin E synthase 1, while the sodium phosphate transporter IIa (NaP-IIa) is downregulated in the kidneys of dKO mice. qRT-PCR analyses revealed that the expression levels of NCC2 variants A and B were reduced while NCC2-B levels are increased in dKO animals. The latter changes lead to decreased NCC2 Ca2+ activity in the medullary thick limb and increased calcium excretion, while NaPi-IIa downregulation reduces the reabsorption of phosphate in the proximal tubules. Placement of dKO mice on a high calcium diet and insufflation increased the above parameters. These results show an important role for salt wasting and dehydration-induced PGE2 synthesis in renal calcium and phosphate excretion as well as in bone calcium mobilization.

**Conclusions:** Our studies suggest the presence of PGE2-mediated pathways, which are involved in the response to PTH, dehydration and volume contraction and independent of sodium and chloride transport. PGE2 and FGF-23 activity can lead to amorpholisation and mobilization of calcium and phosphate, and ultimately lead to skeletal abnormalities and growth retardation.

**Funding:** NIDDK Support, Veterans Administration Support

**FR-PO923**

Hypercalcemia-Induced Natriuresis Induced by Endothelin-1 (ET-1)

**Background:** Hypercalcemia commonly increases urinary sodium and water excretions. We previously showed that targeting the calcium receptor CaSR does not affect sodium transport in the renal tubule (Lopuy et al., JCI, 2012), suggesting that the natriuretic effect of hypercalcemia does not involve CaSR. Since hypercalcemia increases the renal expression of ET-1, we tested if ET-1 mediates the natriuretic effect of hypercalcemia.

**Methods:** Forty-two 8 week-old, male C57Bl/6 mice were studied. Osmostat minipumps were implanted to infuse PTH1-34 and maintain the concentration of PTH to normal range throughout the experiment. Hypercalcemia was induced by the oral administration of diltiazem (DHT: 7.5mg/kg food/day). Eighteen mice were treated with an ET-1 receptor antagonist, macitentan (Maci, 27mg/kg BW/day), with or without DHT. Mice were treated for 3 days of treatment. On 3rd day of treatment mice developed hypercalcemia (5.0±1 vs 2.4±0.1 mmol/L control mice) and exhibited increased water and sodium excretion as compared to control mice (2.0±1 vs 1.4±0.1 mL/day and 46±4 vs 36±2 mmol Na+/mL creatinine, respectively, p<0.01 for both). Mice treated with DHT had similar levels of hypercalcemia and polyuria as mice treated with DHT only. However, mice treated with Maci+DHT showed no increase in urinary sodium excretion. Mice treated with Maci only were similar to control mice. A 3-4 fold increase in the renal level of ET-1 mRNA was observed in mice treated with DHT and Maci+DHT.

**Conclusions:** Hypercalcemia increases the renal production of ET-1, which is likely responsible for the increase of urinary sodium excretion. In contrast, ET-1 is not involved in hypercalcemia-induced polyuria.

**Funding:** Government Support - Non-U.S.
Methods: Primary human umbilical vein endothelial cells (HUVECs) were serum starved for 24 hours and stimulated with a physiological buffer and preincubated with reverse-mode (Ca2+ influx) Ncx inhibitors Sn-6 or SEAP504 and the general Ncx inhibitor ORM-1013. Ncx1 protein was knockdown using siRNA. ERK1/2 activation was determined by western blot. [Ca2+]i was measured in ECs loaded with the fluorescent Ca2+ indicator Fluo-4NW.

Conclusions: We propose that Ca2+ influx through reverse-mode Ncx is required for IS-induced ERK1/2 activation. Given the known role of ERK1/2 activation in the expression of pro-inflammatory molecules such as COX-2 and VCAM-1 in ECs, reverse-mode Ncx could be a novel target for improving endothelial function in CKD.

FR-PO925
Chronic Kidney Disease Impairs Myocardial Perfusion and Disturbs Cardiac Calcium Handling
Maarten Oranje,1 Desiree Ling Yang,1,2 Joost Hoenderop,2 René J. Bindels,2 David H. Ellison.

Background: The molecular and microcirculatory changes that may underlie the increased prevalence of heart failure and cardiac mortality in CKD are ill-defined. We hypothesized that IS directly impairs both myocardial perfusion and disturbed cardiac diastolic and systolic function due to disturbed calcium fluxes across the myocardial sarcoplasmic reticulum.

Methods: Eight-week old C57Bl/6 mice were subjected to partial nephrectomy (5/6 nephrectomy or sham surgery) and after 6 weeks mice were subjected to myocardial contrast echocardiography (MCE) to test myocardial perfusion. Cardiac function was assessed using Cine MRI. In single intact cardiomyocytes diastolic and systolic function, as well as intracellular Ca2+ transients were measured by fura-2 loaded cardiomyocytes.

Results: No difference was found between groups for heart weights over tibia length, neither for ejection fraction, cardiac output, end diastolic and systolic volume, and E/A ratio.

Conclusions: CKD compromises both myocardial microvascular perfusion reserve, and systolic and diastolic function in cardiomyocytes. Calcium fluxes across the sarcoplasmic membrane are disturbed, due to a reduced amount of phosphorylated phospholamban, which activates the sarcoplasmic reticulum Ca2+ channel SERCA.

FR-PO926
Recessive Mutations in SLC34A1 (NaPi-IIa) as a Cause of Idiopathic Infantile Hypercalcemia
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Background: Idiopathic infantile hypercalcemia (IIH) is characterized by severe hypercalcemia with failure to thrive, vomiting, dehydration, and nephrocalcinosis. Initially mutations in CYP24A1 encoding the vitamin D catabolizing enzyme 25-hydroxyvitamin D2-24-hydroxylase were discovered that lead to accumulation of active 1,25(OH)2D3 with subsequent hypercalcemia and hypercalciuria.

Methods: In a subgroup of IIH patients without mutations in CYP24A1 we now performed a positional candidate gene approach in order to identify a second IIH gene locus. Results: We identified a shared homozygous interval on chromosome 5q35 with a maximum LOD score of 6.91. The sequence analysis of SLC34A1 encoding proximal-tubular sodium-phosphate co-transporter NaPi-IIa revealed recessive mutations in the 4 index cases as well as in 18 additional sporadic IIH patients. The clinical reevaluation revealed renal phosphate wasting but no signs of rickets. Functional studies of mutated NaPi-IIa in Xenopus oocytes and OK cells demonstrated a disturbed membrane trafficking as well as a loss of phosphate transport activity. The reexamination of SLc34A1 knockout mice highlighted the critical role of phosphate depletion and FGF-23 suppression. In affected patients, clinical and laboratory findings persist after omitting vitamin D prophylaxis but highlight the critical role of phosphate depletion and FGF-23 suppression.

Conclusions: Therefore, an early differentiation between CYP24A1 (24-hydroxylase) and SLC34A1 (NaPi-IIa) defects appears crucial for a effective therapy in children with IIH.

FR-PO927
Identification of SLC4A13 as a Novel Player in Renal Magnesium Homeostasis
Jeroen H.F. De Baati,1 Anke Lameris,2 René J. Bindels, Joost Hoenderop.2

Background: Hypomagnesemia is a common clinical cause of muscle cramps, epilepsy and cardiac arrhythmias. In the distal convoluted tubule (DCT) of the kidney, transcellular reabsorption of Mg2+ regulates the body Mg2+ balance by determining the final urinary Mg2+ excretion. In the DCT, Mg2+ is reabsorbed from the pro-urine via the apical Mg2+ channel TRPM6. Until now, the basolateral Mg2+ exclusion mechanism in DCT is still unknown, but recent findings suggest that proteins of the SLC4A1 family may contribute to cellular Mg2+ exclusion. The aim of this study was, therefore, to investigate the role of SLC4A13 in Mg2+ homeostasis using the SLC4A13 knockout mouse.

Methods: The SLC4A13 knockout mice were used for serum and urinary electrolyte analysis. To determine the effect of SLC4A13 on intestinal Mg2+ absorption, the Mg2+ absorption capacity was measured using the stable [25Mg] isotopomer.

Results: Tissue expression screening was performed by RT-PCR, showing that SLC4A13 is the only SLC4A1 isoform with enriched expression in DCT compared to other segments in the kidney. Interestingly, serum and urinary electrolyte determinations demonstrated that SLC4A13 knockout mice suffer from hypomagnesemia due to renal Mg2+ wasting. Serum magnesium Na+, K+ and Ca2+ levels were not affected. "Mg2+ uptake was similar in wild type and knockout mouse, although Slc4a13 knockout animals exhibited increased intestinal expression of Mg2+ transporters Trpm6 and Slc4a14. Remarkably, 10% of the Slc4a13 knockout mice developed severe unilateral hydronephrosis, as demonstrated by the presence of transitional epithelium lining the fluid cavity. Feeding the Slc4a13 knockout mice a low Mg2+ diet may have instigated the formation of hydronephrosis.

Conclusions: In conclusion, SLC4A13 was established as a new important factor for renal Mg2+ handling, suggesting that SLC4A13 is the basolateral Mg2+ exclusion mechanism in DCT. Slc4a13 mice provide the first mouse model with isolated hypomagnesemia, without concomitant electrolyte disturbances. In the future, SLC4A13 mutations should be considered in patients with unilateral hydronephrosis and/or hypomagnesemia. Funding: Government Support - Non-U.S.

FR-PO928
Dietary Inulin Supplementation Stimulates Magnesium Absorption in Patients with Proton Pump Induced Hypomagnesemia
Jeroen H.F. De Baati,1 Mark Wilhelm Hess,2 Joost Hoenderop,2 Joost P.H. Drenth,2 René J. Bindels,2

Background: Hypomagnesemia is a common and severe side effect of patients using proton pump inhibitors (PPI), causing severe muscle cramps and depression. Given that PPI users are dependent on PPIs for gastric acid protection, drug withdrawal or antacid switching is often not possible to prevent hypomagnesemia. This study, therefore, aimed to restore serum Mg2+ levels during PPI use by the dietary application of fructose-oligo-saccharide-enriched inulin fibers.

Methods: This clinical trial prospectively determined serum Mg2+ concentrations in 133 patients using PPIs. Under maintenance of PPIs, eleven identified cases of PPI-induced hypomagnesemia were exposed to 2 repetitive dietary suplementations with inulin for 4 weeks each, followed by 14 days washout and compared to 10 healthy non-PPI users. The primary endpoint was serum Mg2+. Secondary endpoints were serum Ca2+, K+, and Na+ levels.

Results: Hypomagnesemia is present in 13% of the study population. Dietary supplementation with inulin significantly enhanced mean serum Mg2+ levels by + 0.1 mEq/L in the PPI users and + 0.2 mEq/L in healthy controls. Moreover, in patients with PPIH concomitant treatment effects were observed for serum Ca2+ (+ 0.9 mmol/L) and serum K+ (+ 0.07 mmol/L), no effects were seen on serum Na+. Patients with PPIH had adequately reestablished serum Ca2+ and Mg2+, which increased due to inulin following increases in serum levels. Additionally, two SNPs in TRPM6 (rs3779025 and rs2274024) were identified that cause a 4.75 times higher risk to develop hypomagnesemia.

Conclusions: Inulin fibers are a new promising probiotic treatment strategy to treat intestinal- and renal-caused hypomagnesemia. For the first time we provide a successful alternative for oral Mg2+ supplementation. Funding: Government Support - Non-U.S.

FR-PO929
The Distal Convoluted Tubule Plays a Key Role in Tacrolimus-Induced Hypomagnesemia and Hypercalciuria
Rebecca A. LaRocce,1 Sabina K. Jelen,2 Chao-Ling Yang,2 Joost Hoenderop,2 René J. Bindels,2 David H. Ellison.2

Background: The immunosuppressive drug tacrolimus, used to prevent graft rejection, often leads to hypomagnesemia and can also cause hypercalciuria. A decrease in renal Mg2+ and Ca2+ reabsorption is thought to be involved, but the molecular mechanisms are unclear. Tacrolimus requires a binding partner, FKBP12, to inhibit its canonical target, calcineurin. We generated a mouse model in which FKBP12 can be deleted along the intestinal expression of Mg2+ transporters Slc34a1 and Slc41a3 -/-. The molecular and microcirculatory changes that may underlie the formation of hydronephrosis.

Methods: We propose that Ca2+ influx through reverse-mode Ncx is required for IS-induced ERK1/2 activation. Given the known role of ERK1/2 activation in the expression of pro-inflammatory molecules such as COX-2 and VCAM-1 in ECs, reverse-mode Ncx could be a novel target for improving endothelial function in CKD.
nephron (KS-FKBP12+). We then tested if either FKBP12 disruption or calcineurin inhibition altered the nephron along the mRNA abundance of renal ion transport proteins leading to hypomagnesemia and hypercalciuria.

Methods: KS-FKBP12+ mice were generated using an inducible CRE/LOX system driven by the Pax8 promoter. Mice were treated with doxycycline (KS-FKBP12+) or vehicle (control). The abundance of mRNA encoding Claudin 16 and 19, thick ascending limb (TAL) proteins involved in Mg2+ and Ca2+ transport by the distal convoluted tubule (DCT) including, TRPM6, calbindin-28K and the Sodium Calcium Exchanger-1. In contrast, tacrolimus had no effect in KS-FKBP12+ mice (p > 0.05 by 2-way ANOVA). The abundance of mRNA encoding Claudin 16 and 19, thick ascending limb (TAL) proteins involved in Mg2+ and Ca2+ handling, were not affected by tacrolimus treatment in either group.

Conclusions: Tacrolimus reduces the abundance of mRNA encoding proteins involved in Mg2+ and Ca2+ transport by the DCT. These effects require FKBP12, suggesting that calcineurin inhibition is essential. The results show that the DCT plays a key role in these troubling side effects.

Funding: NIDDK Support, Private Foundation Support

FR-PO930

Regulation of Magnesium Reabsorption and Transient Receptor Potential M6 Channel Activity by Protein Kinase A Signaling

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Background: The transient receptor potential melastatin type 6 (TRPM6) epithelial magnesium (Mg2+) channel participates in Mg2+ transport in kidney and intestine. Previous reports have suggested a hormonal cAMP-dependent regulation of Mg2+ reabsorption in the kidney. The molecular details of this process are, however, unknown. Adenylyl cyclase type 3 (Adcy3) has been shown to colocalize with the Na+Cl- cotransporter (NCC), a marker of the distal convoluted tubule, the principal site of TRPM6 expression.

Methods: Given the critical role of TRPM6 in Mg2+ reabsorption, an inducible kidney-specific Adcy3 deletion mouse model was characterised for blood and urinary electrolyte disturbances under normal and low Mg2+ diet. Using patch clamp, cell surface biotinylation and Total Internal Reflection Fluorescence (TIRF) live cell imaging of transfected HEK293 cells, TRPM6 channel activity was measured.

Results: Urinary Mg2+ excretion was increased (~1.7-fold) in AC3 deleted mice compared to controls where as serum Mg2+ concentrations were not different. Renal TRPM6 mRNA levels were increased by ~2-fold in AC3 deleted mice. Serum Mg2+ was significantly lower in AC3 deleted animals for 7 days on the low Mg2+ diet compared to the control animals. In HEK293 cells, it was demonstrated that cAMP signaling rapidly potentiates the activity of TRPM6 by promoting its accumulation at the plasma membrane and by increasing its single channel conductance.

Comparison of electrophysiological data between the phosphorylation-deficient SI252A and phosphonemic SI252D mutants suggests that phosphorylation at this intracellular residue participates in the observed stimulation of channel activity.

Conclusions: These data support a physiologically relevant magnesiumotropic role of cAMP signaling in the direct stimulation of action of protein kinase A on the plasma membrane trafficking and function of TRPM6 ion channels in the distal convoluted tubule.

Funding: Government Support - Non-U.S.

FR-PO931

Renal Handling of Magnesium in Individuals on Long Term Proton Pump Inhibitor Therapy

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Background: Proton Pump Inhibitors (PPI) are a group of very commonly used medication.Recently the US–FDA has warned of increased levels of hypomagnesemia in patients receiving low dose PPI therapy. The present study was conducted to determine the effect of long term PPI therapy on serum magnesium and renal handling of magnesium in long term PPI patients.

Methods: The study was designed as a case control study consisting of adult patients on long term PPI therapy (Omeprazole; Rabeprozole; Pantoprazole etc) for more than 1 year. Patients on PPI with diabetes, chronic kidney disease or on diuretics were excluded. Age and sex matched healthy controls not on any medication were included as controls. Serum Magnesium and Urinary Fractional Excretion of Magnesium (FE-Mg) were measured using an automated clinical chemistry autoanalyser. The study was conducted for one year following standardized analysis of data with Graphpad software.

Results: The mean age of the long term PPI group was 47.5 years and 45.9 years in the control group. The mean FAMg of the PPI group was significantly lower in AC3 deleted animals for 7 days on the low Mg2+ diet compared to the control animals. In HEK293 cells, it was demonstrated that cAMP signaling rapidly potentiates the activity of TRPM6 by promoting its accumulation at the plasma membrane and by increasing its single channel conductance.

Conclusions: These data support a physiologically relevant magnesiumotropic role of cAMP signaling in the direct stimulation of action of protein kinase A on the plasma membrane trafficking and function of TRPM6 ion channels in the distal convoluted tubule.

Funding: Government Support - Non-U.S.
FR-PO934
Oral Magnesium Supplementation Improves Serum Calcification Propensity in Chronic Kidney Disease Stage 3-4

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Background: In previous experimental studies of chronic kidney disease (CKD) magnesium has been shown to improve vascular calcification. Serum calcification propensity measured using the T50 analysis has been shown to predict all-cause mortality among patients with chronic kidney disease (CKD) stage 3-4.

Methods: In a proof-of-concept randomized placebo-controlled double-blinded trial of placebo versus slow-release magnesium oxide at two different doses (360 mg daily or 360 mg twice daily) for eight weeks in 34 subjects with CKD stage 3-4 and plasma magnesium <0.82 mmol/L, T50 was measured to examine whether magnesium supplementation affects serum calcification propensity.

Results: In subjects randomized to magnesium 360 mg twice daily (n = 11) plasma magnesium increased by 0.11 mmol/L (confidence interval; 0.05 - 0.17, p = 0.003) and T50 increased by 40 minutes (confidence interval; 18 - 63, p = 0.003) after eight weeks of treatment (Figure 1), while there were no changes in plasma phosphate, calcium or parathyroid hormone. There were no significant changes in T50 in the placebo (n = 12) or magnesium 360 mg once daily (n = 11) groups.

Conclusions: Oral magnesium oxide 360 mg twice daily improves serum calcification propensity in CKD stage 3-4 after eight weeks of treatment. Larger, long-term trials are needed to assess whether this translates into reductions in vascular calcification (e.g. coronary artery calcium score or pulse wave velocity) and cardiovascular endpoints.

FR-PO935
The Novel NaPi-IIb Inhibitor ASP3325 Does Not Mitigate Hyperphosphatemia in Chronic Kidney Disease Patients on Hemodialysis

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Background: The sodium-dependent phosphate co-transporter type 2b (NaPi-IIb) is considered an important mediator of intestinal inorganic phosphate (Pi) absorption and therefore recognized as a target molecule for treatment of hyperphosphatemia. We evaluated the pharmacological characteristics of ASP3325, a novel NaPi-IIb inhibitor being developed to treat hyperphosphatemia in chronic kidney disease (CKD).

Methods: The inhibition ratio of 32P-Pi uptake during ASP3325 (0.03-1000 nmol/L) treatment was measured in HEK293 cells stably expressing rat or human NaPi-IIb. To assess the contribution of NaPi-IIb to intestinal Pi absorption, ASP3325 and 45Pi were orally administered in sequence, and then serum 45Pi levels were measured. For normal rats, an ASP3325 containing-diet was provided for three days and the rate of Pi excretion in urine was measured on the final day. For rats with adenine-induced renal failure, an ASP3325 containing-diet was provided for two weeks after which plasma levels of phosphorus were measured.

Results: ASP3325 inhibited 32P-Pi uptake with an IC50 value of 7.0 mmol/L in HEK293 cells expressing human NaPi-IIb and an IC50 value of 88 nmol/L in HEK293 cells expressing rat NaPi-IIb. In normal rats, oral administration of ASP3325 at 1 and 3 mg/kg significantly reduced the area under the concentration curve of serum 45Pi from 0 to 30 min post 45Pi administration. ASP3325 (0.001%-0.01%) reduced urinary Pi excretion dose-proportionally, and treated with 0.01% ASP3325 reduced excretion by 31.2% compared to vehicle (P<0.01). In rats with adenine-induced renal failure, ASP3325 (0.001%-0.01%) exhibited a dose-related reduction in plasma levels of phosphorus. Following two weeks of treatment, plasma level of phosphorus in the vehicle-treated group was 11.43 ± 0.66 mg/dL and in the 0.01% ASP3325-treated group was 6.61 ± 0.47 mg/dL (P<0.01).

Conclusions: ASP3325 inhibited NaPi-IIb-mediated Pi transport and decreased plasma levels of phosphorus in rats with renal failure as well as urinary Pi excretion in normal rats. ASP3325 might therefore be a novel candidate for the treatment of hyperphosphatemia in humans.

FR-PO936
Novel NaPi-IIb Inhibitor ASP3325 Inhibits Phosphate Absorption in Intestine and Reduces Plasma Phosphorus Level in Rats with Renal Failure

Keichi Taniguchi, Kazuhiro Terai, Yoh Terada, Yuichi Tomura.

Background: The sodium-dependent phosphate co-transporter type 2b (NaPi-IIb) is considered to be an important mediator of intestinal inorganic phosphate (Pi) absorption and therefore recognized as a target molecule for treatment of hyperphosphatemia. We developed a novel NaPi-IIb inhibitor ASP3325.

Methods: In a proof-of-concept study 2b (NaPi-IIb) inhibition was measured in HEK293 cells stably expressing rat NaPi-IIb. To assess the contribution of NaPi-IIb to intestinal Pi absorption, ASP3325 and 45Pi were orally administered in sequence, and then serum 45Pi levels were measured. For normal rats, an ASP3325 containing-diet was provided for three days and the rate of Pi excretion in urine was measured on the final day. For rats with adenine-induced renal failure, an ASP3325 containing-diet was provided for two weeks after which plasma levels of phosphorus were measured.

Results: ASP3325 inhibited 32P-Pi uptake with an IC50 value of 7.0 mmol/L in HEK293 cells expressing human NaPi-IIb and an IC50 value of 88 nmol/L in HEK293 cells expressing rat NaPi-IIb. In normal rats, oral administration of ASP3325 at 1 and 3 mg/kg significantly reduced the area under the concentration curve of serum 45Pi from 0 to 30 min post 45Pi administration. ASP3325 (0.001%-0.01%) reduced urinary Pi excretion dose-proportionally, and treated with 0.01% ASP3325 reduced excretion by 31.2% compared to vehicle (P<0.01). In rats with adenine-induced renal failure, ASP3325 (0.001%-0.01%) exhibited a dose-related reduction in plasma levels of phosphorus. Following two weeks of treatment, plasma level of phosphorus in the vehicle-treated group was 11.43 ± 0.66 mg/dL and in the 0.01% ASP3325-treated group was 6.61 ± 0.47 mg/dL (P<0.01).

Conclusions: ASP3325 inhibited NaPi-IIb-mediated Pi transport and decreased plasma levels of phosphorus in rats with renal failure as well as urinary Pi excretion in normal rats. ASP3325 might therefore be a novel candidate for the treatment of hyperphosphatemia in humans.

FR-PO937
Statin Therapy Reduces Phosphate Levels in Dialysis Patients: Results from the Epidemiological Vitamin K Italian Study (VIKI Study)

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Background: Statin therapy is the mainstay approach to reduce VC and prevent CV events in patients with dyslipidemia. The aim of this study was to investigate an association between statin therapy and phosphate levels in patients on hemodialysis recruited in the VIKI Study.

Methods: The VIKI Study is a multicenter, cross-sectional study in 387 CKD patients on hemodialysis from 18 hospitals in Italy. We determined plasma levels of vitamin 25(OH)D, vitamin K, osteocalcin (bone-Gla-Protein or BGP), matrix-Gla-protein (MGP) and routine biochemistry. Assessment of VC was centralized (Witteman’s method: by measuring the length of calcific deposits along the anterior and posterior wall of the aorta). Plasma phosphate levels were dichotomized according to the median value (>4.6 vs ≤4.6 mg/dL).

Results: 33% of the VIKI Study population (n=126) was on statin therapy. Patients on statin had significantly lower HDL cholesterol (mean:SD: 40.4±11.1 vs 43.5±13.4 mg/dL, p=0.0473) and higher plasma triglyceride levels (median: 164.0 vs 142.0 mg/dL, p=0.0041) than those not on statin. Plasma phosphate levels were significantly lower in patients on statin therapy (4.57±1.12 vs 4.8±1.33 mg/dL, p=0.035). The analysis of the vitamin K components showed that patients on statin therapy had higher plasma MK7 levels (median: 1.16 vs 0.84 ng/ml, p=0.0241), while concentrations of vitamin K25(OH)D were significantly reduced (median: 26.0 vs 30.7 ng/ml, p=0.0198). In a multivariate analysis adjusted for BMI, angina, LDL, BGP and antibiotics, statin therapy was significantly associated with lower plasma phosphate levels (OR 0.61, 95%CI 0.38-0.98, p=0.0411), while BMI (OR 1.06, 95%CI 1.01-1.12, p=0.0250) and serum BGP levels ≥182 mcg/L (OR 1.58, 95%CI 1.01-2.48, p=0.0472) were associated with higher phosphate concentrations.

Conclusions: To our knowledge this is the first evidence of an association between statins and reduced plasma phosphate levels in CKD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
582A
Epidemiology of Kidney Stone Disease in Icelandic Children 1985-2013
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Background: The aim of the study was to examine time trends in the prevalence and incidence of kidney stone disease in Icelandic children and adolescents over the past 3 decades.

Methods: Computerized databases of all major hospitals and medical imaging centers in Iceland covering the years 1985 to 2013, were searched for ICD, radiology and surgical procedures indicating of kidney stones for subjects <18 years of age. Incidence was calculated for the time periods 1985-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009 and 2010-2013, based on population information for Icelandic children in these years. Prevalence was calculated for the years 1999-2013.

Results: From 1985 to 2013, there were 186 incident patients, 110 (59%) of whom were female. Median (range) age at diagnosis was 15.0 (2.1-17.9) years. The annual incidence increased from a mean of 3.7/100,000 in the first 5 years to 11.0/100,000 in the years 1995-2004, but decreased thereafter and was 7.8/100,000 in 2010-2013. This trend was more pronounced in boys, for whom the incidence was 4.7/100,000 in the first time period, 11.0/100,000 during 2000-2004 and only 2.4/100,000 in 2010-2013. The incidence for girls increased from 2.7/100,000 in the first time period to 14.2/100,000 in 1995-1999 and has since then leveled off and was 13.6/100,000 in 2010-2013. The largest incidence rise was seen in girls aged 14-17 years, for whom it increased from 9.8/100,000 in 1985-1999 to 39.2/100,000 in 2010-2013. The mean annual prevalence of kidney stone disease in 1999-2013 was 44/100,000 for boys and 51,100,000 for girls.

Conclusions: The incidence rise observed and current incidence of kidney stones in Icelandic children is similar to that recently reported in the USA. A significant incidence increase for girls was observed for the female patients in the late 1980’s and early 1990’s, and has since then trended downwards in boys and remained stable in girls. These trends cannot be adequately explained and warrant further study.

FR-PO938
Kidney Stone Recurrence in Icelandic Children Sólnborg E. Ingvarsdóttir,1 Olafur S. Indridason,2 Runolfur Palsson,1,2 Vidar O. Edvardsson,1,31 Children’s Medical Center, Landspitali – The National Univ Hospital of Iceland;2 Div of Nephrology, Landspitali – The National Univ Hospital of Iceland;1 Faculty of Medicine, Univ of Iceland, Reykjavik, Iceland.

Background: The 5-year recurrence rate of kidney stones in adults is in the range of 30-50%. No population-based data are available on the recurrence of childhood kidney stone disease. The purpose of this study was to examine the recurrence rate of stone disease in Icelandic children.

Methods: Patients were identified by searching computerized databases of all the major hospitals and the only freestanding radiology clinic in Iceland for diagnostic, radiology and surgical codes indicating of kidney stones in 1985-2013. We subsequently examined medical records of patients with kidney stone disease for information on stone recurrence.

Results: We identified 186 children with stone disease during the study period. There were 76 boys with a median (range) age of 14.6 (0.2-17.9) years and 110 girls aged 15.4 (0.8-17.9) years. The follow-up time was 13.0 (0-36) years. A total of 67 children (37%) experienced a second stone event, at a median of 1.9 (0.9-18.9) years after the initial diagnosis. The recurrence rate was 26%, 35%, 41% and 46% after 5, 10, 15 and 20 years of follow-up, respectively. There was no significant difference in recurrence rate between boys and girls (p=0.24) and those aged under and over 13 years at diagnosis (p=0.56), but a significant difference between patients diagnosed in 1985-1994, 1995-2004 and 2005-2013 was observed, with a 5-year recurrence rate of 9%, 24% and 33% respectively (p=0.002).

Conclusions: In our population-based pediatric study, the recurrence rate of kidney stones is similar to that reported in adults. Further, the rate of recurrence appears to be increasing as has recently been reported for the incidence of childhood stone disease. Increased recurrence rate may be related to improved diagnosis and documentation of stone events and/or environmental factors affecting urinary lithogenicity.

FR-PO939
Clinical Stone Events in Patients Diagnosed with Asymptomatic Nephrolithiasis Berlingrí Eik Guðmundsdóttir,1 Rebekka Sigrún Lynch,2 Runolfur Palsson,2,13 Vidar O. Edvardsson,1,31 Children’s Medical Center, Landspitali;1 Faculty of Medicine, Univ of Iceland;2 Div of Nephrology, Landspitali – The National Univ Hospital of Iceland, Reykjavík, Iceland.

Background: Most frequent use of high-resolution medical imaging in recent years has been in increased detection of asymptomatic kidney stones (KS). The purpose of this study was to investigate the frequency of clinical stone events in incident patients with asymptomatic KS.

Methods: We searched databases at all major hospitals and imaging centers in Iceland for radiographic diagnosis of incident KS during 2000-2008. We found 2550 incident cases, review of medical records identified 218 patients with no past history of nephrolithiasis or symptoms consistent with KS, who, therefore, were considered to have asymptomatic KS. The patients’ records were then thoroughly reviewed for the development of a clinical stone event defined as abdominal pain, fever and/or hematuria associated with stone passage and/or a stone removal procedure. End of follow-up was between June 2014 and April 2015 or at patient’s death. Event-free survival was examined by the Kaplan-Meier method.

Results: Of the 218 patients, 54.6% were men, the median (range) age was 65 (11-91) years. The diagnosis of KS was made by computed tomography in 156 (71.6%), ultrasound in 49 (22.5%) and by plain X-ray in 13 patients. The median follow-up time was 6.0 (0.0-14.5) and 6.7 (0.0-14.9) years for men and women, respectively. Twenty patients (9.2%) died during follow-up. A clinical stone event was defined as a renal stone event, with or without need for a stone removal procedure to remove the stone. The mean age at a clinical stone event was 25.8 (2.0-14.4) and 12.1 (0.1-9.3) years following diagnosis for men and women, respectively. When a procedure performed to remove an asymptomatic stone was considered a clinical event, a total of 49 patients experienced a clinical stone event, and the 5 and 10 year-event-free survival was 80% (95% CI, 74-85) and 73% (95% CI, 65-80), respectively.

Conclusions: Approximately 10% of asymptomatic KS were considered clinically significant at diagnosis. In the remaining patients, a clinical stone event was unlikely to occur over a decade following diagnosis of asymptomatic stone disease.
Supplemental Calcium Increases the Growth Rate of Renal Calculi in Stone Formers

**Background:** Though dietary calcium is associated with a decreased risk of stone formation, post-menopausal women supplemented with calcium have an increased risk of urinary tract stones. Prior studies have examined the effect of supplemental calcium on the risk of passing symptomatic stones but its role in the pathogenesis of stone formation is not clear.

**Methods:** We retrospectively identified 6059 patients with a history of urolithiasis. Eligible patients had 2 unenhanced CT scans greater than 30 days but less than 2 years apart during the time of supplementation. For those on no supplementation, the most recent data were used. Of these, 426 patients met the criteria: 195 on calcium, 127 on vitamin D only, and 104 on none. Patients on calcium received 439mg/dL 2793IU vitamin D3 or 560IU D2/d and patients on vitamin D only received 3085 IU D3/d or 6296 IU D2/d. Stone burden was calculated as the sum of the maximum diameters of all stones on CT and rate of stone growth was calculated by the change in consecutive stone burdens divided by the elapsed time between scans.

**Results:** Stone composition was similar among all groups: 65.5% calcium oxalate, 20.0% calcium phosphate, and 11.8% uric acid. Stone formation rate in mm/year: standard deviation was 7.8±2.0 for calcium group, 3.3±1.14 for vitamin D, and 4.49±13.8 for none. Those supplemented with calcium had a higher rate of stone formation than those supplemented with vitamin D, p=0.015. Stone group was statistically significant when controlling for serum PTH and calcium on multiple logistic regression. BMI, gender, age and dose of calcium were not significantly associated with stone formation rate while dose of vitamin D had an inverse association, p=0.049.

**Conclusions:** Between supplemented groups for any urinary excretion values.

**FR-P0944**

Effects of Calcium and Vitamin D Supplementation on Known Stone Formers

**Background:** While high dietary calcium has protective effects against kidney stone formation, the effect of supplementation with calcium and vitamin D on the risk of kidney stone formation remains unclear. Post-menopausal women supplemented with calcium have an increased risk of urinary tract stones; however, there is conflicting evidence for the effects of supplementation on urinary excretion of calcium.

**Methods:** We identified 6059 patients with a history of urolithiasis by CT scan, 2061 of which had 24-hour urine collections before and after starting supplementation. For patients on no supplementation, the most recent data were used. A total of 1,486 patients were supplemented with calcium, 417 with vitamin D only, and 158 with no supplementation. Patients on calcium received an average of 460mg/d 2720IU vitamin D3 or 5678IU D2/d and patients on vitamin D only received 3005IU D3/d or 6307IU D2/d.

**Results:** Stone composition did not differ among groups: 70.0% calcium oxalate, 16.6% calcium phosphate, and 10.8% uric acid stones. There was a significant decrease in urinary calcium excretion in patients supplemented with calcium (p=0.021) and vitamin D (p=0.011) and significant decreases in urinary oxalate in those supplemented with calcium (p=0.0001) and vitamin D (p=0.0001). No differences were seen in the amount of change between supplemented groups for any urinary excretion values.

**Conclusions:** Both calcium and vitamin D supplementation decreased urinary calcium excretion, and high serum calcium and vitamin D was associated with higher urinary calcium excretion in both men and women.

**Funding:** Private Foundation Support

**FR-P0945**

Tolvaptan Therapy Effectively Decreases Urinary Calcium Oxalate, Calcium Phosphate, and Uric Acid Supersaturations in Stone Formers

**Background:** Drinking large amounts of fluids is universally recommended for urinary stone prevention but can be difficult to do for many stone formers. Tolvaptan, a V2 receptor antagonist, blocks water reabsorption in the collecting duct. This in turn should increase serum osmolality and stimulate thirst. The net effect should be lower supersaturation of stone forming salts, but this has not been proven.

**Methods:** This double blind, randomized, placebo-controlled, crossover study was conducted in 21 adult calcium urinary stone formers, stratified as majority calcium oxalate (CaOx, n=10) or calcium phosphate (CaP, n=11). Patients were randomized to receive tolvaptan 45 mg/day or placebo for week 1, followed by washout week 2, and then crossover to drug or placebo for week 3. The 24 hr urine volume and chemistries were assessed at the end of week 1 and week 3.

**Results:** Tolvaptan versus placebo decreased urinary osmolality (204±96 vs 529±213 mOsm/kg, P=0.001) and increased urinary volume (4.8±12.9 vs 1.8±0.9 L, P<0.001). However, the majority of urinary salt excretion rates (mg/24 hrs) including sodium and calcium did not significantly change. Thus, urinary CaOx SS (-0.01±1.1 vs 0.95±0.87, P=0.001) and CaP SS (-1.66±1.7 vs -0.1±1.02, P=0.001) both decreased. Urinary Uric Acid (UA) SS also fell (-2.05±4.05 vs -5.2±3.12, P=0.03). The tolvaptan treatment effect on urinary supersaturation did not differ between CaOx and CaP stone types (P=0.05 for all interactions). Serum sodium increased slightly while on tolvaptan (142±3 vs 141±2 mEq/L, P=0.01).

**Conclusions:** Use of tolvaptan increased urinary volume but did not appreciably change daily excretion of urinary constituents. The net effect was thus a fall in CaOx, CaP and UA SS. This study highlights the dramatic benefit increased free water ingestion alone can have on urinary supersaturation. Use of tolvaptan or other V2 receptor antagonists could be a useful strategy for selected stone formers not responsive to intensive dietary and/or behavioral counseling.

**Funding:** Other NIH Support - The investigators acknowledge support from the Rare Kidney Stone Consortium (U54KD083908), a member of the NIH Rare Diseases Clinical Research Network (RDCRN), funded by the NIDDK and the National Center for Advancing Translational Sciences (NCATS), and the Mayo Clinic O’Brien Urology Research Center (U54 DK100227), Pharmaceutical Company Support - Research work for this review was supported by Onsuka America Pharmaceutical, Inc.
Conclusions: Prescribing doses of CBTDs greater than 1 gm did not improve lithogenicity significantly. Higher doses may not have clinical benefit. Prescribing the minimum effective dose based on CysCap can potentially decrease the adverse effects often associated with CBTDs.

Funding: NIDDK Support, Other NIH Support - Rare Diseases Clinical Research Network - Rare Kidney Stone Consortium

FR-P0947

Claudin-14 Gene Polymorphisms May Regulate Urine Calcium Excretion Teresa Arcidiacono, Marco Simontini, Lorenza Macrina, Paolo Manunta, Donatella Spotti, Giuseppe Vezzoli. Nephrology and Dialysis Unit, San Raffaele Scientific Inst, Milan, Italy.

Background: Claudins are a family of proteins that form paracellular calcium channels in tight-junctions and may thus regulate tubular permeability to divalent cations. Claudin-14 is expressed in the ascending limb of Henle’s loop and inhibits calcium reabsorption. A previous GWA showed that two polymorphisms (SNPs) of CLDN14 (rs219778 and rs219781) were associated with kidney stones and calcium excretion in an Iceland population. The present study aims to evaluate the effect of CLDN14 SNPs on calcium excretion.

Methods: We performed a retrospective study on 380 hypertensive patients never treated with antihypertensive drugs. These patients underwent a saline load test (i.v. infusion of NaCl 0.9% 2 litres in 2 hours) to evaluate sodium sensitivity. Kidney stones in their clinical history was ascertained by interview. Calcium was measured in 24-h urine and clinical history was ascertained by interview. Calcium was measured in 24-h urine and clinical history was ascertained by interview.

Conclusions: CLDN14 genotype is associated with calcium excretion. This association was observed even after saline load test, a well-known stimulus to urinary calcium excretion. Minor alleles of these SNPs could cause a reduction of calcium excretion and could be protective against kidney stones and hypercalcuria. The lack of association among stones and CLDN14 SNPs could be due to the method used to identify stone formers.

FR-P0948

Independent Effect of Blood Glucose Level on Urinary Citrate and pH Majuran Perinpan,1 Erin Bakhis Ware,1,2 Jennifer Smith,1 Stephen T. Turner,1 Sharon R. Kardia,3 John C. Lieske,1,2 1Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Laboratory Medicine, Mayo Clinic, Rochester, MN; 3Dept of Epidemiology, School of Public Health, Univ of Michigan, Ann Arbor, MI; 4Inst for Social Research, Univ of Michigan, Ann Arbor, MI.

Background: Urinary citrate is an important kidney stone inhibitor and its excretion is influenced by systemic acid base status and diet. However, the effects of demographics and other factors on urinary citrate excretion are not well defined, including the independent influence of blood glucose.

Methods: Twenty-four hour urine samples were collected from non-Hispanic white sibships in Rochester, MN. Height, weight, blood pressure, blood glucose, serum creatinine and cystatin C were measured. Diet was assessed using the Viocare food frequency questionnaire. The effects of blood glucose, demographics and diet on urinary citrate excretion, urine pH and net gastrointestinal (GI) alkali absorption were evaluated in binvariate and multivariable models, plus interaction models that included age, sex, and weight.

Results: Samples were available from 709 individuals (mean age 66±9 years). In general urine citrate and urine pH correlated positively with higher net alkali absorption (p=0.0001). Urine pH was higher in women for any given net alkali absorption value, but not after adjustment for covariates. In multivariable models urinary pH decreased with higher serum creatinine, blood glucose, dietary protein and increased with dietary potassium. Meanwhile, in multivariable models urinary citrate increased with age, weight, eGFR, blood glucose and decreased with loop diuretic and thiazide use. Association of urinary citrate and age was influenced by blood glucose (p=0.01).

Conclusions: In our study urinary citrate and pH correlated positively with net GI alkali absorption. Blood glucose had independent effects on urine pH and urinary citrate. This study provides the first evidence that blood glucose could influence stone risk independent of urinary pH and uric acid crystallization. These observations could provide new insights into the association of obesity and urinary stone disease.

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FR-P0949


Background: Primary Hyperoxaluria (PH) is a rare genetic disease causing high hepatic production of oxalate. Renal excretion of oxalate keeps plasma oxalate (Pox) controlled but leads to stones and often ESRD. Systemic oxalosis occurs when GFR is reduced and Pox rises above the supersaturation threshold (approximately 45 mmol/L). Renal handling of oxalate in relation to GFR is poorly understood.

Methods: PH patients ≥ 12 years without ESRD were identified from the Rare Kidney Stone Consortium registry. We used the recent simultaneous Pox, serum creatinine and 24 hour urine oxalate (Uox). Net oxalate secretion (Sox) equals Uox-GFR×Pox. Proximal tubular oxalate (PTox) is Uox corrected for creatinine and estimated proximal tubule water absorption. eGFR is by CKD-EPI (adults) or modified Schwarz (adolescents). We grouped patients by CKD stage and balanced eGFR groups. Analysis was by Fischer exact test and ANOVA.

Results: 55 patients were identified (33 PH-1; 5 PH-2; 7 PH-3). Median age was 23.2 (IQR: 16.7, 32.9) and eGFR was 66.1 mL/min/BSA (54.8, 80.8). Pox, Sox and Uox strongly when eGFR fell below 45 mL/min. Similar results were seen in eGFR groups. PTox and Pox increased proportionally (p<0.001).

Conclusions: Pox rises above the supersaturation threshold (approximately 45 mmol/L). Renal handling of oxalate in relation to GFR is poorly understood. Minor alleles of these SNPs could cause a reduction of calcium excretion and could be protective against kidney stones and hypercalcuria. The lack of association among stones and CLDN14 SNPs could be due to the method used to identify stone formers.

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Underline represents presenting author.

585A
FR-PO950

Effect of Antibiotic Treatment on Oxalobacter formigenes Colonization


Methods: We followed 64 healthy subjects tested for Helicobacter pylori (HP), who were treated with antibiotics (Amoxicillin and clarithromycin for 2 weeks) for HP eradication. Using species-specific PCR, we tested for colonization at baseline and at follow-up.

Results: Of the 64 subjects (MF: 24/40; mean age 25.0 ± 5.5 years) tested for HP, 25 (39%) were positive at baseline. Subject to HP elimination, 6 became HP-negative at 6 weeks, only 2 reverted to positive at week 24, and 4 patients remained negative at follow up (Mean 21.0 ± 6wks). Of 16 untreated positive people, 12 (75%) remained positive at follow up (Mean 18.8 ± 7.7wks), but of 26 untreated negative subjects, only 6 (23%) were positive at follow up (mean 19.7 ± 6wks), significantly fewer than the untreated positives (p = 0.001 by Fisher exact test).

Conclusions: We conclude that HP status remains stable over a follow-up period of several months, with antibiotics suppressing colonization in the majority of people in the short term. The differential long-term effect of antibiotics on HP colonization and its effect on urinary oxalate excretion, will be important to evaluate.

FR-PO951

Identification of Calcium-Oxalate Binding Proteins in Human Urine That Prevent Crystal Adhesion: An In Vitro Model of Kidney Stone Formation

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Background: There are limited therapeutic options for the treatment of stone disease and about 50% of patients experience at least one recurrence. Existing treatment protocols focus on altering urine concentrations, which presents challenges due to the idiosyncratic nature of many stones and the variety of underlying factors. In this study, we examine the hypothesis that there are naturally occurring urinary proteins capable of binding calcium oxalate crystals, promoting their clearance, and preventing stone formation. Elucidating these interactions may provide novel therapies.

Methods: Calcium oxalate monohydrate (COM) crystals and fluorescently-labeled derivatives (COM-FITC) were synthesized in vitro. Stone formation was modeled in vitro by assessing the adhesion of COM-FITC crystals to confluent monolayers of inner medullary collecting duct (IMCD) epithelial cells. Affinity chromatography was used to isolate COM-binding proteins from human urine.

Results: COM and COM-FITC crystals synthesized in vitro exhibited the typical prismatic morphology of urinary crystals. Incubation of IMCD cells with COM-FITC crystals resulted in rapid binding to the cell surface with high affinity. The addition of urinary proteins purified from human urine inhibited COM-FITC binding by 76.2%. Furthermore, urinary proteins inhibited the growth of COM crystals in free solution by 63.7%. In using affinity chromatography to isolate COM-binding proteins, we found that this technique was highly specific as only 17.2% of urinary proteins exhibited binding activity. The bound fraction was eluted, purified by electrophoresis, and four prominent proteins were identified (97 KD, 69 KD, 56 KD, 45 KD).

Conclusions: This study demonstrates that urinary proteins bind to COM crystals and inhibit their adhesion to the renal epithelium. Further characterization of these proteins may facilitate the design of peptide-based therapies that prevent crystal adhesion and stone formation as well as the development of diagnostic biomarkers that stratify patients and guide treatment decisions in at-risk populations.

FR-PO952

Hydroxyapatite Induces Tolerance in Primary Human Monocytes Exposed to Calcium Oxalate Crystals

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Background: Although most crystal deposits within tissue produce inflammation, renal interstitial hydroxyapatite deposits do not, accumulating as Randall’s plaque. To further explore this lack of response, we investigated the effect of oxalate, hydroxyapatite, and combination of both on time dependent, immunological responses in human THP-1 (monocyte) cells, the precursors to tissue macrophages.

Methods: Using 1 ug/ml LPS and untreated as positive and negative controls, THP-1 cells were exposed to varying concentrations of soluble potassium oxalate (KOs) or CaOx and treated with or without 100 and 1000 mg/ml. In addition, a group of primary human monocytes were pre-treated with 100 mg of HA or CaOx followed by secondary treatment with 100 ug/ml HA, 100 mg/ml CaOx, and 1 ug/ml LPS. THP cells were collected at 2, 4, and 8 hours after various treatments, and RNA was analyzed by quantitative real time PCR.

Results: THP cells at baseline responded strongly to TNFa (baseline), while a dose dependent inhibition to this cytokine was observed. When THP cells were exposed to hydroxyapatite, a dose dependent inhibition to TNFa, IL-1β, IL-8, and IL-10 was observed. No response to KOs and HA. Prevent exposure of human monocytes to HA had little effect on cytokine response to subsequent CaOx and LPS exposure; however, pre-exposure to CaOx followed by HA negated all further cytokine production.

Conclusions: In our human monocyte model, the order of CaOx and HA exposure affects monocyte response. HA neither stimulates cytokine production nor inhibits demonstrated production when pre-exposing monocytes to prior CaOx exposure. Pre-exposed CaOx monocytes, however, had decreased cytokine and chemokine expression when subsequently treated with HA. This tolerance mechanism may partially explain the lack of papillary inflammation in the pathogenesis of Randall’s plaque.

FR-PO953

A Low Sodium Diet Inhibits Stone Formation in Genetic Hypercalciuric Stone-Forming Rats

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Background: Increasing dietary (D) sodium (Na) intake results in greater urine (u) calcium (Ca) excretion, leading to the recommendation that D Na be restricted in hypercalciuric stone formers to decrease stone recurrence. However, there is no direct clinical evidence that reduction in D Na intake alone will reduce recurrent stone formation.

Methods: To determine if D Na restriction reduces kidney stone formation, we utilized 1O generation genetic hypercalciuric stone-forming (GHS) rats fed either a low (LNa, 0.05%) or normal (NNa, 0.4%) Na diet for 18 wks. Urine was collected at 6 wks at a mean was determined for each analyte and then an overall 18 wks mean calculated. Radiographic analysis for stone formation was done at 18 wks.

Results: As anticipated, rats decreased mean uCa (LNa=2.48±0.3 mEq/24h; NNa=3.9±0.2, p<0.001) and uCl (NNa=2.6±0.13 mEq/24h; LNa=1.9±0.16, p<0.001). Overall mean uCa was lower with LNa than NNa (NNa=17.3±3.5 mEq/24h; LNa=15.2±0.5, p<0.01) as was a phosphate (P) (NNa=16.5±0.6 mg/24h; LNa=13.8±0.4, p<0.001). Urine oxalate (Ox), pH, NH4, Ca, CL, citrate and volume did not differ with diet Na. There were no significant differences in u supersaturation with respect to CaOx or CaOx. Serum Ca was slightly increased with LNa (NNa=10.9±1.0 mg/dl; LNa=11.4±1.0, p<0.01) though there were no differences in urine P, PTH or FGF23. Radiographic analysis of kidneys demonstrated a significant decrease in calcification with LNa (calcification scores with a range of 0-3; NNa=1.4±0.15; LNa=0.3±0.12, p<0.001).

Conclusions: Thus a low Na diet reduced uCa and stone formation in GHS rats even though urine supersaturation was not altered. These data, in a genetic model of hypercalciuria and stone formation, lend support to the use of dietary Na restriction to prevent recurrent Ca nephrolithiasis.

FR-PO954

Ethylene Glycol Induced Hyperoxaluria in Rats: A Translational Study

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Background: Hyperoxaluria, if remains undiagnosed, can cause renal injury and inflammation leading to a number of diseases including advanced stages of renal failure. In order to look into the different pathways and molecular mechanisms involved in the kidneys of hyperoxaluric rats, we performed genome wide analysis of differentially expressed genes in the kidneys of rats fed ethylene glycol (EG).

Methods: Male rats were divided into two groups. Rats in one group were fed normal diet and the other group diet supplemented with 1.25% EG. Urinary assays were done at different time intervals and after 14 and 28 days rats were euthanized, kidneys explanted and total RNA extracted for micro array analysis using Agilent 8 x 60K single color arrays. Data was analyzed using bio-conductor Limma (Linear models for micro array analysis) package using R. Gene ontology (GO) and KEGG pathway analyses was also performed. Immunohistochemical (IHC) and Eosin and Hematoxylin (E &H) staining was also done for highly significant genes.

Results: All rats became hyperoxaluric from day 7 and had crystal deposition at different time intervals. Urinary LDH, sodium and creatinine were significantly different in the EG group as compared to the control. There was significant expression of different genes encoding for macromolecular modulators such as osteopontin (OPN), monocyte chemoattractant protein-1 (MCP-1), lipocalin 2 (Lcn-2), fibronectin (Fn-1), clusterin (CLU) and kidney injury molecule-1 (KIM-1) along with nicotine amide dinucleotide phosphate (NADPH) oxidase-4 (NOX-4) and glutathione peroxidase (Gpx-2). Gene analysis showed that 17 and 33 differentially expressed pathways for day 14 and day 28 respectively.

Conclusions: Results highlight that the EG treated rats showed heavy deposition of crystals and there were 15 pathways that were common between day 14 and day 28 giving a deep insight into the molecular mechanisms and pathways activated in hyperoxaluric rats.

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Sulfate and Thiosulfate Competitively Inhibit Oxalate Transport via a Drosophila Prestin (dPrestin, dSlc26a6)-Dependent Mechanism Greg M. Landry,1,2,3 Taku Hira,1 Jacob B. Anderson,1 Christopher Joseph roel Gallo,1 Michael F. Romero,1,2,3 Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN; 2Nephropathy and Hypertension, Mayo Clinic College of Medicine, Rochester, MN; 3Brien Urology Research Center, Mayo Clinic College of Medicine, Rochester, MN.

Background: Nephrolithiasis affects approximately 12% of men and 6% of women in indiavidualized countries with the majority of stones being composed of calcium oxalate (CaOx). Our findings suggest that pharmacological agents can be used to inhibit CaOx crystallization.

Methods: Using Drosophila melanogaster as a robust and translatable model of CaOx nephrolithiasis, we studied the effects of sulfate and thiosulfate on oxalate transport, and subsequent CaOx crystal formation, as a proof of principle in providing a nida to identify new therapeutic interventions.

Results: Results indicate that dPrestin transports thioulate with a much higher affinity than sulfate (dPrestin sulfate Kᵩₒ = 8.65 ± 3.87 mM compared to dPrestin thioulate Kᵩₒ = 0.23 ± 0.03 mM). Additionally, both sulfate (48 h) and thioulate (24 and 48 h) were effective at decreasing Malpighian tubule CaOx crystallization with the opposite results observed at 48 h in Malpighian tubules where dPrestin was not expressed indicating a role on cell type-specific dPrestin in luminal oxalate transport.

Conclusions: Given the higher affinity of thioulate for dPrestin when compared to those which are reported for oxalate (dPrestin average Kᵩₒ for oxalate = 0.87 ± 0.16 mM and for thioulate = 0.22 ± 0.03 mM), we have confirmed that the ability of thioulate to act as a competitive inhibitor of oxalate at the transporter level, specifically dPrestin, may explain the inhibitory effect on CaOx crystallization seen in human tissue sections of thioulate uptake. Overall, our findings predict that thioulate or oxalate-mimics may be effective as therapeutic competitive inhibitors of CaOx crystallization.

Funding: NIDDK Support

FR-PO956

Background: C3 glomerulopathy (C3G) is a progressive form of glomerulonephritis (GN) that is frequently associated with abnormalities in regulation of the alternative pathway (AP) of complement. Mice with deficiency of factor H (Cfh/–), a negative AP regulator, are an established experimental model of C3G in which abundant complement C3 accumulates along the glomerular basement membrane.

Methods: We examined the spontaneous renal phenotype in Cfh/– mice with and without accompanying deficiency of complement receptor 3 (CR3), the main receptor for iC3b. We performed accelerated serum nephrotoxic nephritis (ANTN) in Cfh/– deficient mice to assess the role of CR3 in glomerular injury outside the setting of FH deficiency. The effect of iC3b ligation of CR3 on macrophages and other leukocytes during inflammation was assessed in vitro.

Results: In 8-month old Cfh/– mice, accompanying CR3 deficiency was associated with significantly increased albuminuria, glomerular hypercellularity and macrophage influx, and mortality. In ANTN mice, transplantation experiments in Cfh/– recipients indicated that the protective effect of CR3 was dependent on BM-derived cells. ANTN produced severe crescentic nephritis in CR3-deficient mice (but not wild-type mice). In vitro ligation of CR3 using iC3b-coated particles down-regulated the proinflammatory cytokine response of both murine and human macrophages to lipopolysaccharide stimulation in vitro. These cytokine-modulating effects were cell-type specific, an observation that may reconcile some of the conflicting reports concerning the immune role of CR3 in the literature.

Conclusions: Deficiency of CR3 unexpectedly enhanced the severity of both experimental C3G and immune complex GN. Our findings suggest that pharmacological potentiation of the CR3-iC3b interaction could be therapeutically useful in patients with chronic GN.

FR-PO957
Two Autoimmune Forms of C3-Glomerulopathy Are Defined by Complement Convertases Deregulating Autoantibodies Christine Skerka,1 Fei Zhao,1 Giuseppe Remuzzi,2 Rossella Piras,2 Peter F. Zipfel,1,3 Dept of Infectious Biology, Leibniz Inst for Natural Product Research and Infection Biology, Jena, Germany; 2Laboratory of Immunology and Genetics of Transplantation and Rare Diseases, IRCCS- Istituto di Ricerche Farmacologiche, 24020- Ranica (Bergamo), Italy; 3Friedrich Schiller Univ, Jena, Germany.

Background: In C3G glomerulopathy (C3G) deficient complement activation on level of the C3 convertase is caused by mutations in genes coding for complement components or regulatory proteins as well as by autoantibodies. C3 nephritic factor (C3NeF) has been reported in 50-80% of C3G patients. Notably also autoantibodies to C3b and Factor B were identified in C3G patients, which do not score in the standard C3NeF assay. Here we compare how the new C3 convertase reacting antibodies and also C3NeF affect complement regulation on the level of the C3- and the C5 convertases.

Methods: The autoantibodies were isolated from the serum of C3G patients (n=34), assayed for binding to the C3 convertase by ELISA and further characterized by using a number of functional complement assays.

Results: Among the 34 C3G patients, 19 patients were identified with autoantibodies which bind to the C3 convertase, but lack C3NeF. 15 patients were identified C3NeF positive according to the binding to the C3 convertase, high titer (HT) and low titer (LT) autoantibodies were identified among isolated autoantibodies from all 34 C3G patients. HT as well as LT antibodies strongly activated the C5 convertase and enhanced C5a generation. Interestingly all antibodies bound to the C3 convertase, but only HT and not LT antibodies enhanced C5 convertase activity. The HT but not the LT antibodies increased C3 convertase assembly, stabilized the convertase and increased C3a generation.

Conclusions: Two classes, HT and LT, of complement C3 convertase binding autoantibodies were identified in C3NeF- positive and negative C3G patients. These antibodies deregulate complement by two different mechanisms: HT antibodies activate complement on the C3- and C5 convertase levels, while LT antibodies activate only on C5 convertase level. We speculate that these functional different autoimmune forms explain responder and non-responder types to therapeutic C5 inhibitors.

Funding: Government Support - Non-U.S.

FR-PO958
Autoimmune C3 Glomerulopathy: Can Complement Inhibiting Drugs Reduce Complement Activation by C3 Convertase Autoantibodies? Friederike Sophie Schulze,1 Fei Zhao,1 Giuseppe Remuzzi,2 Marina Noris,2 Christine Skerka,1 Peter F. Zipfel,1,3 Hans Knoll Inst, Jena; 2Mario Negri Inst for Pharmacological Research, Bergamo; 3Friedrich Schiller Univ, Jena.

Background: C3 glomerulopathy is a severe kidney disorder that is caused by deregulation of the alternative complement pathway due to autoantibodies that bind to the C3 convertase, but lack C3NeF. 15 patients were identified C3NeF- among all 34 C3G patients. HT antibodies were found to increase C3 convertase activity, whereas LT antibodies only increased C5 convertase activity. We aim at characterizing the clinical features of these new autoantibodies cause complement deregulation and how complement inhibitors affect the action of these autoantibodies.

Methods: IgGs were purified from patients with C3 convertase antibody lacking C3NeF (n=19) and also from C3NeF patients (n=15). These purified IgGs were tested for their impact on complement activity and the effect of soluble CR1 (scCR1) and Eculizumab was examined by ELISA, Western blot and complement activation assays.

Results: C3 convertase antibodies from patients lacking C3NeF deregulated complement in some antibody groups stabilized the C3 convertase and all activated the terminal complement pathway. C3NeFs activated complement in a related manner. In probes with C3 convertase antibodies scCR1 did inhibit excessive complement activity. Also Eculizumab prevented antibody mediated complement activation. Both inhibitors blocked C3NeF-mediated complement deregulation in a related manner. For some probes from either C3NeF- or C3NeF+ patients a higher dose of scCR1 was necessary to affect C3 convertase activity.

Conclusions: A subgroup of C3G patients present with C3 convertase-binding antibodies but lack C3NeF. Some C3 convertase antibodies deregulate the C3 convertase and all stabilize the C5 convertase. The complement inhibitors scCR1 and Eculizumab reduced complement activity. Patients with antibodies causing only excessive C5 convertase activity may benefit from Eculizumab, whereas patients with excessive C3 convertase may require additional C3 convertase inhibitors.

Funding: Government Support - Non-U.S.

FR-PO959
Respiratory Syncytial Virus May Exacerbate Kidney Damage in IgA Nephropathy Through Csa/CsaR and Csa/CsAR Signaling Amplifying the Effects of Th17 Cells Xiaozhao Li,1 Xinuye Hu,2 Ting Meng,2 Juntao Feng,2 Qiaoling Zhou,1 1Dept of Nephrology, Xiangya Hospital of Central South Univ, Changsha, Hunan, China; 2Dept of Clinical Laboratory, Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: The exacerbation of IgA nephropathy (IgAN) is related to respiratory tract infection with respiratory syncytial virus (RSV), but the mechanism is unknown. In this study we investigated the role of complement activation products C3a/C5a and CsAR/CsAR signaling responses to the effect of T helper 17 (Th17) cells in the pathogenesis of IgAN associated with RSV.

Methods: IgA nephropathy was induced in BALB/c mice with lipopolysaccharide, carbon tetrachloride and bovine serum albumin. Then the mice were sensitized with respiratory syncytial virus (RSV) in sequence. Urine Albumin-Creatinine ratio and sediments were measured. The pathological changes in kidney and lung tissues were observed under microscopy. C3aR and CsAR proteins in kidney tissue were examined by immunohistochemical staining. C17 chemical staining and CsAR antibodies were tested by flow cytometry. C3a/C5a, IL-17A, IL-6 and IL-21 were in the kidneys were detected by ELISA.

Results: The IgAN mice had albuminuria and microscopic hematuria, renal mesangial proliferation, IgA deposition, high electron dense deposition in glomerular mesangial region, increased frequency of Tregs, increased frequency of Th17 and Th17-Treg ratio. Furthermore, C3a, C5a, C3AR, CsAR and Th17-related cytokines IL-17A, IL-6 and IL-21 were all increased in the kidneys of IgAN mice. Compared with IgAN mice, the manifestations in RSV-IgAN mice were more severe, but alleviated in CsAR-treated groups and CsAR-treated groups respectively.

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

Underline represents presenting author.
Functional Glomerular Decay Accelerating Factor Induction by Heme: Role of HO-1  

Giouli Makri, 1  Vasileios Atsaves, 1  Pu Duann, 2  Elias A. Lianos, 1, 2 Medicine, Univ of Athens, Greece; 3 Medicine, Rutgers Biomedical and Health Sciences, NJ.

Background: In hemolytic disorders and glomerular injury associated with hematuria intraglomerular free heme increases and may activate the alternative complement (C)-pathway. Rat glomeruli express decay accelerating factor DAF in glomerular epithelial cells (GEC). We assessed whether heme upregulates glomerular DAF to minimize C activation and explored underlying mechanisms.

Methods: hmox1-/- and hmo1-/- rats were generated by Zinc Finger Nuclease (ZNF)-mediated HO-1 gene disruption and rats with GEC targeted HO-1 overexpression (GEC ho1+) by Sleeping Beauty Transposon mediated transgenesis using a nephron promoter. Wild-type (WT) or hmo1-/-, hmo2-/- or GEC ho1+/+ glomeruli were treated for 18 h with heme (hemin, FePP) or non-iron porphyrins with opposite effects on HO activity: 1) HO inducers, Cobalt (CoPP) and the non-metal protoporphyrin IX (PPIX) and 2) HO inhibitors: Zinc (ZnPp), Tin (SnPP) protoporphyrin, Tin (SnMP) and Chromium (CrMP) mesoporphyrins. C3b deposition in glomeruli was triggered by exposure to 10% rat serum. DAF, HO-1 and C3b levels were assessed by western blotting or Real-time PCR. HO enzyme activity was measured by standard methods.

Results: Constitutive DAF (mRNA and protein) decreased in both hmo1-/- and hmo2-/- and increased in GEC ho1+. Heme, at concentrations encountered in HD patients, increased DAF expression in WT glomeruli. This effect was attenuated in both hmo1-/- and hmo2-/- and augmented in GEC ho1+. HO-mediated DAF induction in hmo1-/- glomeruli persisted despite complete HO-1 absence. Of the non-Fe porphyrins, CoPP and CrMP increased DAF and HO-1. SnnP induced DAF but not hmo1-/- or CrMP and CrMP had no effect on either protein. Hemin or SnPP-mediated DAF induction reduced C3b deposition. This was reversed by PI-PLC which removed membrane bound DAF.

Conclusions: HO-1 regulates constitutive DAF expression and heme-mediated DAF induction. The latter is independent of metal moiety and HO enzyme activity, requires the porphyrin ring and may also occur via a HO-1 independent mechanism. DAF induction by heme is functional and attenuates C-activation.

Funding: Government Support - Non-U.S.

FR-PO961  
Complement Activation Impairs Endothelial Cell Migration – Possible Role in TMA Pathogenesis  

Background: Cell migration is a key requirement in multiple physiological scenarios including angiogenesis and endothelial cell repair. Thrombogenic microangiopathy (TMA) is characterized by endothelial cell (EC) activation and injury, in atypical hemolytic urticarial syndrome caused by complement activation on ECs. We hypothesized that EC injury in aHUS was at least in part – caused by complement-mediated inhibition of cell migration. Methods: To test this hypothesis blood outgrowth ECs were exposed to complement by blocking EC surface regulators (CD46, CD55, CD59) and incubating ECs with 50% normal human serum (NHS; complement active). Heat inactivated serum (HS; complement inactive), C5-depleted serum (terminal pathway inactive) and media served as controls. Results: Wound healing assay in fluidic conditions (wound infection by trypan/ EDTA) showed within 1.5 h a wound area decrease to 62.5±1% when perfused with media. Subsequent (1.5 h) HS perfusion allowed for further wound area reduction to 38±6%, similar to C5-depleted serum (46±5%). In contrast, exposure to complement (NHS) inhibited further wound closure (wound area 63±7%, p<0.05). The proliferation rate (%BrdU positive cells after 2 h) was similar between controls and complement-treated ECs (20±2 vs. 21±3%), and no apoptosis or necrosis was detected within a 20 min - 4 h observation period (Annexin V, live dead aqua dye). However, we demonstrated an instantaneous but transient cell membrane retraction (perforated cell) after perfusion with NHS or complement. Consequences of this sublytic C5b-9 deposition caused immediate and sustained (2h) cyto-skeletal (live cell imaging of F-actin, Rho-GTPases), cell-cell contact (decreased VE-Cadherin expression, decreased transendothelial resistance) and cell motility abnormalities (live cell imaging) in complement-exposed ECs, all leading to defective cell migration.

Conclusions: Our data suggest that sublytic EC complement exposure results in impaired cell migration leading to EC injury and defective EC repair – findings extending our current concept of TMA pathogenesis.

Funding: Government Support - Non-U.S.

FR-PO962  
Uncommon Features in Antigen Binding Sites of Human Anti-Glomerular Basement Membrane Autoantibodies  
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Background: Detection of pathogenic anti-α3(IV)NC1 collagen autoAb in the serum or kidneys is required for diagnosis of anti-GBM nephritis and Goodpasture Syndrome. Yet little is known about the origin and structure of human autoAb in these diseases. The heterogeneity of serum Ig, lack of ready access to kidney disease tissue, and inability to reproduce complex immunological microenvironments in vitro present formidable barriers. Humanized models provide a novel platform to circumvent these obstacles.

Methods: We generated Hu-Hsc mice by injection of human CD34+ hematopoietic stem cells into immunodeficient NOD-scid-gamma hosts. Mice with an established human immune system (mean blood chimerism 15.0±15.9% at 3 mos post-injection) were immunized twice with α3(IV)NC1 collagen prior to tissue harvest. Human B cells from both donors were transformed using CpG oligos and kinase inhibitors, screened for antigen binding, electrofused with a human heterohybridoma, and subcloned. The mAb sequences were determined using PCR of cDNA with published primer panels and analyzed using IMGT/V-QUEST.

Results: Sequence analysis of 6 non-clonally related human anti-α3(IV)NC1 mAbs revealed skewed gene use and unusual motifs in the critical HCDR3 that is predominantly responsible for antigen binding. 4 of 6 (67%) human mAbs are encoded by an IgH J6 allele, the extended sequence of which enriches for aromatic tyrosine residues in HCDR3. The HCDR3 are exceptionally long, with mean length 26.4 amino acids (a.a.) compared to average human HCDR3 of 15.2 a.a., and include hydrophobic motifs, an autoimmune signature uncommon in Ig repertoires of healthy individuals and of unimmunized Hu-Hsc mice. Similar motifs were observed in murine anti-α3(IV)NC1 mAb but, despite substantial species differences in Ig gene loci and a.a. composition.

Conclusions: Our results suggest that binding of α3(IV)NC1 collagen by human anti-GBM autoAb requires unusual structural motifs that can access recessed hydrophobic epitopes and that are normally excluded from the healthy human immune repertoire. Similar motifs in man and mouse suggest origins by convergent selection.

Funding: NIDDK Support, Veterans Administration Support

FR-PO963  
Antigenicity Alteration of Deglycosylated Myeloperoxidase  
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Background: Myeloperoxidase (MPO) is a kind of enzyme located in the azurophilic granules of neutrophils, which is the most common target antigen of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) in Chinese patients. Native MPO possesses five N-glycans at positions 323, 355, 381, 483 and 729. The alteration of MPO antigenicity after deglycosylation of these glycans is not elucidated.

Methods: We prepared deglycosylated MPOs via glycosidases based on commercial human-derived intact MPO, and then detected the antigenicity of deglycosylated MPOs in 40 patients with anti-glomerular basement membrane (GBM) disease without MPO-ANCAs.

Results: We found antibodies against deglycosylated MPOs existed in patients with anti-GBM disease. 12/40 (30%) patients were positive for MPO treated with PNGase F naked MPO without hydrocarbon side-chain. 12 (30%) patients were positive for MPO treated with Endo H (MPO with one GluNAc only). Antibody against the intact native MPO was not detectable in all these patients. Furthermore, clinical analysis presented that the levels of antibodies against deglycosylated MPOs were positively associated with renal dysfunction. The plasma levels of antibodies against naked MPO without glycan were positively correlated with the concentrations of serum creatinine (r=0.006, R²=0.178). The plasma levels of antibodies against MPO with one GluNAc only were also positively correlated with the concentrations of serum creatinine (P=0.002, R²=0.234).

Conclusions: The existence of patients’ antibodies towards deglycosylated MPO first discovered the new epitope exposure of MPO after the loss of hydrocarbon side-chain, explicating the possible reasons for antigenicity alteration, and then prompting some clinical significance of these antibodies.

Funding: Government Support - Non-U.S.

FR-PO964  
Autoantibodies to a Cryptic Myeloperoxidase-Specific Immunodominant Epitope Correlate with Disease Activity in Patients with MPO-ANCA Vasculitis  
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Background: ANCA vasculitis is commonly characterized by polyclonal autoantibody reactivity to one of two autoantigens, proteinase 3 (PR3) and/or myeloperoxidase (MPO). ANCA positivity has been observed in patients with active and quiescent disease. A subset of MPO-ANCA in many patients recognizes a cryptic epitope in the N terminal region of the MPO molecule. This peptide is buried within MPO suggesting that this epitope may be exposed by mechanisms that are not yet understood. We assessed human anti-KIV reactivity longitudinally in a large cohort of patients with MPO-ANCA vasculitis to better understand the temporal association of the autoimmune response.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Serum, plasma, and extensive clinical data from patients with ANCA vasculitis were prospectively collected every 3 months. A highly sensitive and specific indirect ELISA using KIV peptide was developed to longitudinally screen patient samples for reactivity over their disease course. To minimize non-specific antibody signal, reactivity to a scrambled peptide of the same amino acid composition was also measured. A positive signal was defined as two standard deviations above the healthy control mean (HC n=85).

Results: Of 67 patients with MPO-ANCA vasculitis, 28 were positive for human anti-KIV autoantibodies at least once during their disease course spanning an average follow-up of 3.3 years. The majority of these patients displayed positivity during initial stages of disease, whereas other patients exhibited recurrence of reactivity. Further structural analysis of autoantibody-binding native MPO confirmed this peptide to be a cryptic epitope.

Conclusions: These findings suggest that conformational changes in MPO that expose this cryptic epitope may be important in the pathogenesis of MPO-ANCA vasculitis and may provide insight into the etiology of this disease. Further, this assay could help to more clearly define temporal disease activity.

Funding: NIDDK Support

FR-PO965
An Anti-GBM Autoantibody Gene Contributes Risk to Distinct Anti-Collagen Responses
Amy G. Clark, Inge M. Worni-Schudel, Mary H. Foster.

Background: The mechanism by which anti-GBM nephritis is initiated and regulated remains an enigma. Recent studies indicate that anti-GBM patients’ serum IgG react with multiple collagen chains and with atypical alpha3(V)NC1 epitopes, and that diverse murine anti-GBM autoantibodies are serologically linked. We examined these relationships in a novel autoAb transgenic (IgG) model expressing an IgKV gene used at low frequency in adult mice but enriched in anti-GBM Ig and arthritogenic anti-collagen II IgG.

Methods: Mice expressing an IgKV3-encoded Ig kappa light chain Tg were bred with C57BL/6J mice. All sera from 3-9 month old mice were tested for alloreactivity by western blot, dot blot, and immunoprecipitation. Reactivity with single domains or several multiple constructs composed of 1 to 4 adjacent domains, and could be detected by western blot, such as IgKV serially truncated from the N- or C-termini, was stronger than that against non-B cells expressing the major autoantibody. In vivo, a subset of primary membranous nephropathy patients. Its extracellular domain consists of 1 transmembrane glycoprotein expressed by the podocyte. It serves as the antigen in situ that impairs podocyte biology resulting in foot process effacement and subsequently extracellular region. Further analysis of additional anti-THSD7A positive sera will help to define the epitope within the molecule, underlie the pathogenesis of this autoimmune disease, and identify potential targets for novel therapeutic agents.

Funding: NIDDK Support

FR-PO967
Intramembranous Epitope Spreading in Phospholipase A, Receptor in IMN
Quan Sheng Zhu, Hong Tang, Phat H. Duong, Meryl A. Waldman, Mary H. Foster.

Background: Idiopathic membranous nephropathy (IMN) is an organ specific autoimmune disease. The major antigen responsible for developing IMN in patients has been identified to be the phospholipase A receptor (PLAR) expressed in the glomerular visceral epithelial cells. Clinical studies demonstrated that over 70% of circulating autoantibodies that target PLAR triggers immune complexes formation in situ and deposition in the glomerular subepithelial spaces. The immunodominant epitope in PLAR was recently located to the extreme N-terminus of the receptor encompassing the CysR-FnIII-CTLD1 region. In the rat model of MN, epitope spreading was detected in the antigenic peptide, megalin that is correlated with the disease progresses. Whether epitope spreading occurs in human IMN and its relationship to disease progresses is unclear.

Methods: Serum samples from biopsy-proven IMN patients were collected and screened for anti-PLAR antibodies using Western-blot and epitope-specific ELISA assays. The reactions of autoantibody and PLAR epiteope protein was further analyzed using immunoprecipitation and immunoblotting assays.

Results: Western-blot analysis using patient sera against full-length PLAR or the dominant epitope region indicated that, 3 of the 12 serum samples that were positive with non-B PLAR autoantibodies failed to recognize the dominant epitope protein. Further test of these 3 samples against a series of truncated PLAR extracellular domains on Western-blot demonstrated that the autoantibodies bind strongly to the CysR-FnIII-CTLD1-3 region of PLAR. Interestingly, serial analysis of sera from a patient with worsening proteinuria showed that, the autoantibodies first recognized the CysR-FnIII-CTLD1-3 region and then spread to the CysR-FnIII-CTLD1 region, suggesting epitope spreading is associated with the disease progresses.

Conclusions: Our results demonstrate for the first time that intramembranous epitope spreading occurs in PLAR in IMN. This finding supports the important role of the dominant epitope in IMN pathogenesis and disease progresses.

FR-PO968
Demonstration of a High Titer Low Affinity Anti-PLAR Autoantibody in an IMN Patient En Route to End-Stage Renal Disease
Michael Shye, Theresa L. Nilson, Ritu Vahi, Miguel Fernandez Palma Diaz, PC. Pham, Phat H. Duong, Liyo Kao, Douglas Yao, Ira Kurz, Quan Sheng Zhu.

Background: Clinical studies have established that over 70% of patients with idiopathic membranous nephropathy (IMN) possess high levels of circulating autoantibodies targeting phospholipase A receptor (PLAR) in the glomerular visceral epithelial cells (podocyte). Binding of autoantibodies to PLAR triggers immune complex formation in situ that impairs podocyte biology resulting in foot process effacement and subsequently proteinuria in patients. In this study, we monitored the fluctuation of autoantibody level in a patient progressing to the end-stage renal disease (ESRD) under the supportive treatments.

Methods: Serum samples from biopsy-proven IMN patient monitored between ESRD and supportive treatments over a period of 6 month were collected (5 clinical visits) and tested for the level of anti-PLAR antibodies using Western-blot, indirect immunofluorescence staining and epitope-specific ELISA assays. The reaction of autoantibodies toward the dominant epitope occurs in PLAR was further analyzed using immunoprecipitation under the non-denaturing and denaturing conditions.

Results: A sharp decline of autoantibody reactivity toward PLAR in sera from the last two visits was detected on Western-blot as the patient approaching ESRD. In contrast, an epitope-specific ELISA assay indicated that the autoantibodies were remained at high levels in these two serum samples, and this observation is further confirmed by the immunofluorescence staining analysis. Test of epitope-antibody reaction under the non-denaturing and denaturing conditions revealed that, the properties of the autoantibodies in the last two visits differ significantly from that in the first three visits, which have low affinity toward PLAR and only bind to the non-denatured form of the epitope.

Conclusions: Our results demonstrate that a high titer low affinity anti-PLAR autoantibody presents in an IMN patient at the late stages of IMN approaching ESRD under the supportive treatments. This autoantibody has altered reactivity toward PLAR that only binds to the non-denatured immunodominant epitope of the receptor.

FR-PO969
Immune Complex Binding to Renal Endothelial Cells Induces TRAIL and Promotes Apoptosis
Scott E. Wenderfer, Adisak Suwanichkul. Pediatrics, Baylor College of Medicine, Houston, TX.

Background: Circulating immune complexes (IC) deposit in the glomeruli of the kidney in many autoimmune diseases, leading to proliferative glomerulonephritis. IC binding can promote proliferation or induce apoptosis in human macrovascular EnCs.
Tumor necrosis family (TNF) superfamily members regulate proliferation and apoptosis, and both are strongly upregulated by immune complex (IC). Quantitative RT-PCR was used to measure mRNA levels of TNF superfamily members. A cellular ELISA was used to assess TRAIL protein expression on EnC surfaces. Apoptosis was assessed using flow cytometry and caspase 3 activity assays, as well as TUNEL staining. In vitro findings were validated in a rodent model of acute IC kidney injury.

**Results:** TRAIL mRNA expression is up-regulated by renal endothelial cells in vitro in the presence of IC binding and in vivo. Membrane TRAIL expression on EnCs also increases after treatment with IC in a dose dependent manner. Receptors for TRAIL, DR5, DR4, A2aR and A2bR are expressed by EnC at RNA and protein level. Using XTT cell proliferation assays, there is a modest decrease in EnC metabolism or proliferation after treatment with IC. Caspase 3 activity and DNA double strand breaks were both increased in cultured EnCs after treatment with IC in a dose dependent manner. Results were similar for both murine and human glomerular EnCs.

**Conclusions:** Our findings indicate that IC binding to glomerular EnCs in vitro is pro-apoptotic. Several TNF superfamily members known to promote apoptosis and their receptors are also up-regulated on EnCs treated with IC. Targeting TRAIL binding to glomerular EnCs by vaccination or antibody treatment may reduce IC binding and disease.

**Funding:** NIDDK Support

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**FR-PO970**

**Paired Immunoglobulin-Like Type2 Receptor (a PILRα) Negatively Regulates Immune Complex-Mediated Glomerulonephritis**

Yutaka Suzuki, Akiko Takahata, Seiichi Matsuo. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

**Background:** PILRα expressed mainly on macrophages, dendritic cells and granulocytes, has been described for its regulatory functions for leukocyte β2 integrin activation in acute inflammation including LPS-induced endothox shock model. Here, we investigated roles of PILRα in immune complex (IC)-mediated glomerulonephritis.

**Methods:** IC-mediated glomerulonephritis was induced by intravenous administration of nephrotoxic serum (NTS) after pre-infection with rabbit IgG in C57BL/6 (WT) and PILRα-/- mice. Functional analysis for renal injury was performed by urine albumin and serum creatinine (SCr) concentrations at day 7, 14 and 21. Diseased kidneys from both mouse strains were harvested for histology, renal leukocyte infiltrates by flow cytometry and renal cytokine profiles by ELISA after induction of NTS glomerulonephritis. In vitro, αIC3 integrin-dependent neutrophil adhesion on IC was evaluated in both mouse strains. Results: BUN and Cr concentrations were significantly elevated in PILRα-/- mice compared to wild type mice at day 14 and day 21 and those were highly associated with deteriorated proteinuria. In histological analysis, glomerular damages, corroborated with both glomerular PAS deposits and glomerular crescent formation, were more severe in PILRα-/- mice at day 21 (p<0.05). Moreover, glomerular neutrophil accumulation was remarkably observed in PILRα-/- mice compared to WT mice at day 21. In addition, total infiltration of Ly6G+ neutrophils, F4/80+ macrophages and CD3+CD4+ T cells in whole kidneys were increased in PILRα-/- mice than WT mice at day 14 and day 21. Renal proliferation rate and patent kidney from IL-10 receptor-deficient mice also demonstrated severe renal infiltration in PILRα-/- mice. In vitro, PILRα deficient neutrophils showed enhanced adhesion and spreading on IC compared to WT.

**Conclusions:** PILRα deficiency resulted in deteriorated renal damage in mouse IC-mediated glomerulonephritis compared to WT mice, indicating that PILRα negatively regulates IC-mediated leukocyte recruitment by inhibition of αIC3 integrin activation.

**Funding:** NIDDK Support

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**FR-PO971**

**Role of Interferon Regulatory Factor 5 and Toll-Like Receptor 7 in Intra-Capillary Glomerulonephritis**

Naotake Tsuibo, Yutaka Kamimura, Shoichi Maruyama, Seichi Matsu. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

**Background:** Interferon regulatory factor 5 (IRF5) and toll-like receptor 7 (TLR7) signaling is required for the development of glomerular inflammation during the heterologous phase of ICGN. However, proteinuria was only significantly increased in IRF5-/-KO, but not in the IRF7-/-KO mice. Therefore, IRF7-independent pathway downstream of TLR7 is responsible for the pathogenesis of TLR7/IRF5 mice.

**Conclusions:** IRF7 and TLR7 signaling is required for the development of glomerular inflammation during the heterologous phase of ICGN. However, proteinuria was only significantly increased in IRF5-/-KO, but not in the IRF7-/-KO mice. Therefore, IRF7-independent pathway downstream of TLR7 is responsible for the pathogenesis of TLR7/IRF5 mice.

**Funding:** NIDDK Support, Other NIH Support - NIAIMS

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**FR-PO972**

**Therapeutic TLR9 Inhibition Prevents the Establishment of Anti-Myeloperoxidase Autoimmunity and the Development of Glomerulonephritis in Mice with Established Autoimmunity**

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**Background:** We have shown TLR9 ligands enhance anti-myeloperoxidase (MPO) autoantibody (AI) and glomerulonephritis (GN) through dendritic cell (DC) activation. We assessed therapeutic TLR9 inhibition on both the development of anti-MPO AI induced through DC vaccination and subsequent development of GN by TLR9 responsive innate effector cells.

**Methods:** Injection of MPO/Freud’s Adjuvant or transfer of MPO/CpG (TLR9 ligand) pulsed bone marrow derived DCs established anti-MPO AI. To stimulate effector cells, intraperitoneal (IP) CpG or MPO/Freud’s Adjuvant was injected after inducing anti-MPO AI, triggering renal injury and antimicrobial activity and glomerular inflammation.

**Results:** In vivo TLR9 signaling was inhibited with an inhibitory oligodeoxynucleotide before both induction of AI and triggering renal injury.

**Conclusions:** Mice receiving MPO/CpG/Ds + IP CpG compared to MPO/CpG/Ds + IP CpG (Control) developed heightened immune responses (cells/spleen: 5.4±6 vs 3.6±1x10^5, p<0.05) and renal injury (area:3.1±7 vs 11±3µmol/L, p<0.05, abnormal glomeruli:93±3 vs 15±3%, p<0.001) confirming effector cell TLR9 ligand is required for disease induction and a target for therapeutic inhibition. TLR9 inhibition prevented MPO/CA induced systemic AI and MPO autoimmunity measured by MPO specific dextral DTH swelling (2.6±1.1 vs 18.6±3Dmm, p<0.05) and decreased frequency of MPO stimulated IL-17A producing cells (6.1±vs 21±3cells, p<0.01) compared to control. TLR9 inhibition prevented MPO/CA driven in mice receiving MPO/CpG-ODNs (DTH:3.1± vs 18±3Dmm, p<0.01, IL-17A:21± vs 13±3Dmm, p<0.02) and decreased frequency of MPO stimulated IL-17A producing cells when given to mice with established anti-MPO AI compared to control (DTH:3.1± vs 13±1mm footpad swelling, p<0.05, urea:26±1 vs 34±1µmol/L, p<0.05, abnormal glomeruli:43±9 vs 79±5%, p<0.01).

**Conclusions:** Therapeutic TLR9 inhibition prevents the development of anti-MPO AI and is a therapeutic option to prevent the development of renal injury once anti-MPO AI is established.

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

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**FR-PO973**

**TLR9 Activation Aggravates Murine IgA Nephropathy? Possible Role of BAFF Mediated Pathway**

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**Background:** Contribution of Toll like receptors (TLRs) which play a key role in the innate immune system has been discussed in the pathogenesis of IgAN. We recently demonstrated that TLR9 is importantly involved in progression of kidney injuries in IgAN prone mice. On the other hand, role of B cell activating factor (BAFF) is discussed in the pathogenesis of human IgAN. Present study examined the contribution of BAFF in the TLR9 mediated progression of IgAN using IgAN prone mice.

**Methods:** Commercially available quiescent IgAN prone mice (ddY mice) at 4 weeks of age were used for this study. They were divided into two groups with (n=8) or without (n=8) TLR9 ligand (CpG-ODN) for 12 weeks. Renal histological lesions and serum levels of IgA, IgG and C3. Moreover albuminuria and renal histological scores based on mesangial proliferation and mesangial matrix expansion in CpG-ODN treated mice were significantly higher than those in non-treated mice. The expressions of MyD88, BAFF and TACI were determined by RT-PCR in renal tissues from both groups.

**Results:** TLR9 activation led to increase of mesangial proliferation and mesangial matrix expansion in CpG-ODN treated mice significantly higher than those in non-treated mice. The expressions of MyD88, BAFF and TACI were also significantly increased by treatment with CpG-ODN. Interestingly there were significant correlations between BAFF expression and serum levels of aberrantly glycosylated IgA and IgA-IgG IC.

**Conclusions:** Present study indicated that TLR9 activation exacerbates murine IgAN via increase of aberrantly glycosylated IgA and nephriticic IgG. In addition, present findings also suggested that TLR9 BAFF expression may be involved in the nephritogenic IgA and IC production.
Key Role of Apoptosis Inhibitor of Macrophage in Phlogenic Action of Glomerular Nephritic IgA in IgA Nephropathy

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Background: Apoptosis inhibitor of macrophage (AIM), a protein mainly produced by macrophages, has been reported to be related to autoimmune diseases as well as arteriosclerosis.

Methods: We evaluated the role of AIM in IgA nephropathy (IgAN) using IgAN prone mice, grouped ddY (gddY) (J Am Soc Nephrol:2012;3:1364-74). Serum of gddY mice was injected to AIM-deficient (AIMKO) and wild-type (WT) mice, and proteinuria and glomerular depositions were evaluated over time. In addition, nephritogenic IgA, produced by gddY splenic B cells hybridomas, was injected to AIMKO and WT to perform the experiments.

Results: We found excessive expression of AIM in gddY, which were co-localized with glomerular IgA. Glomerular IgA deposition were observed in AIMKO and WT 2h after the injections of gddY serum and purified nephritogenic IgA. The depositions were cleared soon thereafter in WT but later in KO after being accumulated. However, proteinuria as in non-depleted WT. The depletion of macrophages did not change the degree of glomerular depositions in WT, as in non-depleted WT.

Conclusions: These findings suggest that AIM is a critical molecule in the glomerular IgA on IgAN prone mice which may be a contributor to such inflammatory responses by glomerular resident cells such as mesangial cells.

Funding: Government Support - Non-U.S.

FR-PO976

Characterization of a Signaling Network That Enhances Production of Galactose-Deficient IgA1 in IgA1-Secreting Cells from Patients with IgA Nephropathy

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Background: Interleukin (IL)-6, leukemia inhibitory factor (LIF), and oncostatin M (OSM) cytokines are likely involved in the pathogenesis of IgA nephropathy (IgAN). IL-6/LIF/OSM cytokines activate B cells through similar receptors and the downstream JAK/STAT pathways. We identified key roles of STAT transcription factors in IL-6/LIF/OSM-mediated enhancement of production of IgA1 with galactose-deficient O-glycans (Gd-IgA1) secreted by IgA1-secretory cells from IgAN patients. Our study defines how these signaling pathways influence IgA1 glycosylation.

Methods: IgA1-secretory cells from IgAN patients and healthy controls (HC) were stimulated with IL-6/LIF/OSM with or without JAK/STAT inhibitors. Gd-IgA1 levels were determined by lectin ELISA. Cell lysates from IgAN and HC were analyzed by global tyrosine kinase profiling using PanPhospho®12 platform and Western blotting. The role of STAT3 and STAT1 in mediating IL-6/LIF/OSM, signaling was confirmed by siRNA knock-down (kd).

Results: siRNA kd of STAT3 and STAT1 reduced production of Gd-IgA1 in IgAN cells induced by IL-6 and LIF/OSM, respectively. A specific inhibitor of JAK/STAT signaling reduced IL-6/LIF-enhanced production of Gd-IgA1, but only in IgAN cells. Global tyrosine kinase profiling identified nine target peptides that were selectively inhibited by the tested JAK/STAT inhibitor in the IgAN cell lysates. Bioinformatics analyses and pathway mapping identified abnormal signaling in JAK/STAT and MAPK cascades as the highest ranked pathway.

Conclusions: IL-6/LIF/OSM cytokines enhanced production of Gd-IgA1 via overactivation of JAK/STAT pathways in IgAN cells. Global tyrosine kinase profiling validated this finding and also indicated participation of MAPK. Elucidating the mechanisms of abnormal signaling associated with Gd-IgA1 production in IgAN-secretory cells may provide new targets for treatment of IgAN.

Funding: NIDDK Support.
Endothelial NF-κB Induction by ANCA-Activated Neutrophils

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Background: The activation of the NF-κB/Rel family and subsequent transcriptional activity of NF-κB may help limiting the ANCA-mediated damage.

Methods: ANCA Disease Patients Demonstrate a Higher Frequency of CD33+ Myeloid Cells with Variable Suppressive Abilities

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Background: Myeloid-derived suppressor cells (MDSCs), or CD33+ myeloid cells, have been extensively studied in cancer as potent suppressors of T cell activation. Regulatory T cells develop in the control T cell cytoplasm of anti-neutrophil cytoplasmic antibody (ANCA) disease, so we sought to determine the role of CD33+ myeloid cells in ANCA disease as an alternative suppressive mechanism.

Methods: Analyses were performed using flow cytometry on peripheral blood mononuclear cells (PBMCs) from 63 patients stained with relevant antibodies. Suppressive potential of CD33+ myeloid cells was assessed with a standard T cell suppression assay.

Results: Flow cytometric analysis of PBMCs revealed an increased population of lineage negative, CD11b+ and CD33+ myeloid cells in patients with ANCA disease compared to healthy controls (mean 2.72% versus 0.18% of PBMCs). This CD33+ myeloid cell population also contained MPO and PR3. Suppression assays utilizing patient CD33+ myeloid cells and autologous T cells have demonstrated variable suppressive capacities with the majority of patients exhibiting modest (30-60%) suppression. Conclusions: CD33+ myeloid cells are increased in patients with ANCA disease and represent a potential source of T cell suppression not previously investigated. Intriguingly, the patients demonstrated the highest frequency of CD33+ myeloid cells were those who had sequentially received rituximab and cyclophosphamide.

Funding: NIDDK Support

FR-PO981

Ubiquitin C-Terminal Hydrolase-L1 Controls Dendritic Cell Cross Priming of the CD4+ T Cell Response

Anne Reinecke,1 Malte Mühlig,1 Pina Schmucker,1 Timo Lischke,2 Elisabeth Mettke,1 Christian Kunts,1 Hans-willli Mittrücker,2 Catherine Meyer-Schwenninger.1
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Background: Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) is a central deubiquitinating enzyme of the ubiquitin proteasomal system. UCH-L1 is thought to regulate the pool of ubiquitin. Within the kidney, UCH-L1 is de novo expressed in glomerular and tubulo-interstitial cells.

Methods: Constitutive knockdown of UCH-L1 in dendritic cells (DCs) using shRNA and Cre-lox technology demonstrated that the ubiquitin proteasomal system with ANCA disease compared to healthy controls (mean 2.72% versus 0.18% of PBMCs). We confirmed this with analyses utilizing patient CD33+ myeloid cells and autologous T cells have demonstrated variable suppressive capacities with the majority of patients exhibiting modest (30-60%) suppression. Suppression assays utilizing patient CD33+ myeloid cells and autologous T cells have demonstrated variable suppressive capacities with the majority of patients exhibiting modest (30-60%) suppression. Conclusions: CD33+ myeloid cells are increased in patients with ANCA disease and represent a potential source of T cell suppression not previously investigated. Intriguingly, the patients demonstrated the highest frequency of CD33+ myeloid cells were those who had sequentially received rituximab and cyclophosphamide.

Funding: NIDDK Support

FR-PO979

CD33+ dendritic cells (DCs) in non-lymphoid organs exhibit two main types of function, namely maintaining tolerance by induction of regulatory T cells and protecting against tissue injury through activation of CD8 T cells. However, the characteristics and functions of CD103+ DCs in kidney cortex but not medulla. The number of kidney CD103+ DCs was significantly reduced in vitro and in vivo when co-culture of CD4+ T cell response is unaffected. Finally, exposure to L. monocytogenes results in a significantly decreased generation of antigen-specific CD8+ T cells.

Conclusions: We describe a hitherto unrecognized role for UCH-L1 in controlling CD4+ T cell activation by DCs.

Funding: Government Support - Non-U.S.

FR-PO982

CD103+ Dendritic Cells Elicit CD8+ T Cell Responses to Accelerate Kidney Injury in Adiramycin Nephropathy

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Background: CD103+ dendritic cells (DCs) in non-lymphoid organs exhibit two main types of function, namely maintaining tolerance by induction of regulatory T cells and protecting against tissue injury through activation of CD8 T cells. However, the characteristics and functions of CD103+ DCs in kidney cortex but not medulla. The number of kidney CD103+ DCs was significantly reduced in vitro and in vivo when co-culture of CD4+ T cell response is unaffected. Finally, exposure to L. monocytogenes results in a significantly decreased generation of antigen-specific CD8+ T cells.

Conclusions: We describe a hitherto unrecognized role for UCH-L1 in controlling CD4+ T cell activation by DCs.

Funding: Government Support - Non-U.S.

FR-PO983

Advanced Glycation End Products Induced the Imbalance between Th17 and Treg Cells via RAGE Pathway in Diabetic Nephropathy

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Background: The imbalance of Th17/Treg cells has been involved in diabetic nephropathy, but the mechanism is still unclear. Advanced glycation products (AGEs) increase in the patients with diabetic nephropathy, The main purpose of this experiment is to explore whether AGEs can cause the imbalance of Th17/Treg cells through RAGE signaling pathway.

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

Underline represents presenting author.
Methods: (1) Recruitment of 20 healthy adults and 40 diabetic nephropathy patients of C57/BL6 and 12-week-old non-obese diabetic (NOD) mice. (2) Intraperitoneal injection of AGEs containing CD4+ T cells to assess the correlation. (2) Prepared AGE-HSA in vitro and isolated and cultured the initial CD4+ T cells from healthy volunteers peripheral blood to explore the effect of AGE-HSA on the differentiation of initial CD4+ T cell: AGE-HSA with different dose and time stimulated initial CD4+ T cells, compared with RAGE neutralizing antibodies and blocking RAGE to detect the ratio of Th17 cell and Treg cells by flow cytometry and determine the expression mRNA of RORgt and Foxp3, and the expression of mRNA and protein of STAT3 and IFN-1. 3 Patients with diabetic nephropathy, there is accumulation of AGES and increasing of Th17 and the reduction of Treg cells. The ratio of Th17 cells and Treg cell is imbalance (increase in the proportion). There was a positive correlation between the concentration of AGES and the proportion of Th17 cells and Treg cells; (2) The AGES-HSA in a dose dependent manner can differentiate Th17 cells, to differentiate Th17 cells and blocking RAGE could mitigate this effect; (3) AGES-HSA increased the expression of RORgt in the initial CD4+ T cells, but had no effect on Foxp3. After blocking RAGE, it could inhibit the expression of RORgt induced by AGE-HSA; (4) the expression of STAT3 and IFN-1 was reduced in the initial CD4+ T induced by AGE-HSA, while blocking RAGE, expression of STAT3 and IFN-1, induced by AGES-HSA was inhibited.

Conclusions: In the patients with diabetic nephropathy, there was a positively correlated between the content of AGES and the proportion of Th17 cells and Treg cells, and AGES-HSA can induce the initial CD4+ T cells to generate Th17 cells by RAGE-RORgt signaling.

FR-PO984

RORgt Activation in biTregs Promotes Lupus Nephritis Malte A. Kluger, Anna Nosko, Paul Derenhardt, Boeren Goerke, Matthias C. Meyer, Michael Luig, Rolf A. Stahl, Oliver M. Steinmetz.

Background: We recently characterized Foxp3+ regulatory T cells, co-expressing the Th17 characteristic transcription factor RORgt, as an independent and bi-functional T cell lineage (biTregs). biTregs secrete both, anti-inflammatory (IL-10, IL-35), but also pro-inflammatory (IL-17) cytokines. Studies in a model of acute crescentic glomerulonephritis suggest that pro-inflammatory biTreg functions are mediated by RORgt. This is of high clinical relevance, since multiple RORgt blocking agents are currently under development.

Methods: Systemic lupus erythematosus (SLE) Pristane in biTregRORgt mice did not. In order to assess effects of biTreg expressed RORgt on development of renal injury. Our data therefore favor RORgt directed interventions as role for generation of humoral auto-immunity.

Conclusions: Five (38%) of the patients responded to rituximab treatment. Plasma cytokine profiling was performed on each of these patients utilizing multiplexed Lumines® Cytokine Human 27-Plex assay pre- and post-rituximab therapy. Statistical analysis was performed using Wilcoxon signed-rank test with a p-value of less than 0.05 considered as statistically significant.

Results: Five (38%) of the patients responded to rituximab, defined as having achieved complete resolution of proteinuria accompanied by cessation of prednisolone and calcineurin inhibitors within 3 months. All patients in the study demonstrated an increase in plasma interferon-gamma-inducible protein (IP)-10 levels post-rituximab treatment (554.3±62.4 pg/ml (pre) vs 793.4±125.5 pg/ml (post), p<0.008). Comparing the cytokine profile between responders and non-responders, responders demonstrated a positive mean-fold change in mean inflammatory protein (MIP)-1α, in contrast to non-responders which demonstrated a negative mean fold change (0.23±0.16 vs -0.17 ±0.08, p=0.04). There were, otherwise, no noted significant differences in the other cytokines i) pre- (post-rituximab) and ii) between responders and non-responders.

Conclusion: Our study results suggest the development of a pro-inflammatory state in our patients post-rituximab therapy. The increase in plasma IP-10 in patient post-rituximab may account for the phenomenon of rituximab-associated colitis. The finding of increased plasma MIP-1α in responders compared to non-responders is novel. Further mechanistic studies are required to ascertain the role of MIP-1α in the mechanism of action of rituximab.

FR-PO987

Cytokine Profiling in Ritusimab-Treated Pediatric Focal Segmental Glomerulosclerotic Nephrotic Patients Wee Song Yeo, Chang-Yien Chan, Hui Kim Yap. Pediatrics, Yong Loo Lin School of Medicine, National Univ of Singapore, Singapore, Singapore.

Background: Focal segmental glomerulosclerosis (FSGS) is the most common histological pattern seen in pediatric steroid-dependent and steroid-resistant nephritic patients. In recent years, rituximab is increasingly used in nephrotic patients who have failed therapy with conventional immunosuppressants. This study aimed to examine the cytokine profile in rituximab-treated pediatric FSGS nephritic patients and elucidate the cytokine profile differences between responders and non-responders.

Methods: Our study population consisted of 13 pediatric FSGS patients who underwent rituximab therapy. Plasma cytokine profiling was performed on each of these patients utilizing multiplexed Lumines® Cytokine Human 27-Plex assay pre- and post-rituximab therapy. Statistical analysis was performed using Wilcoxon signed-rank test with a p-value of less than 0.05 considered as statistically significant.

Results: Five (38%) of the patients responded to rituximab, defined as having achieved complete resolution of proteinuria accompanied by cessation of prednisolone and calcineurin inhibitors within 3 months. All patients in the study demonstrated an increase in plasma interferon-gamma-inducible protein (IP)-10 levels post-rituximab treatment (554.3±62.4 pg/ml (pre) vs 793.4±125.5 pg/ml (post), p<0.008). Comparing the cytokine profile between responders and non-responders, responders demonstrated a positive mean-fold change in mean inflammatory protein (MIP)-1α, in contrast to non-responders which demonstrated a negative mean fold change (0.23±0.16 vs -0.17 ±0.08, p=0.04). There were, otherwise, no noted significant differences in the other cytokines i) pre- (post-rituximab) and ii) between responders and non-responders.

Conclusion: Our study results suggest the development of a pro-inflammatory state in our patients post-rituximab therapy. The increase in plasma IP-10 in patient post-rituximab may account for the phenomenon of rituximab-associated colitis. The finding of increased plasma MIP-1α in responders compared to non-responders is novel. Further mechanistic studies are required to ascertain the role of MIP-1α in the mechanism of action of rituximab.

FR-PO988

Hyporesponsive T-Cell Phenotype Predicts a Subset of Focal Segmental Glomerulosclerosis (FSGS) Patients Responsive to Rituximab Changle-Yien Chan, Isaac Liu, Lourdes Paula Real Resontoc, Kar Hui Ng, Thong Thien, Yew Wong Perry Lau, Stanley C. Jordan, Kong Peng Lam, Wee Song Yeo, Hui Kim Yap.

Poster/Friday

Background: Rituximab has been used with variable success in difficult FSGS, but the immunological basis of its efficacy is poorly characterized. This study aimed at identifying T-cell subsets in pediatric FSGS patients in order to define an immunological signature predictive of a favorable response to rituximab.

Methods: 22 FSGS patients (median age 14.4 years, range 6.2-25.0 years) were recruited prospectively to receive rituximab (375mg/m2 fortnightly to a maximum of 4 doses). Median duration of follow-up was 26.7 months (range 6.5-66.6 months). Baseline immunological subsets were compared with 30 healthy controls, and subsequently examined for association with response to rituximab. Good response was defined as complete resolution of proteinuria accompanied by cessation of prednisolone and calcineurin inhibitors within 3 months.

Results: Of the 22 patients, 12 (54.5%) responded to rituximab therapy. Activated CD4+ CD3+ CD43+ subsets significantly lower in responders (54.9±8.10%) compared to non-responders (78.9±5.18%) (p=0.03) and controls (75.7±2.49%) (p<0.001). IFN-γ+ CD3+ subsets were similarly decreased in responders (0.35±0.24%) compared to non-responders (7.2±1.21%) (p<0.005) and controls (4.1±2.15%) (p<0.001). IL-2+CD3− subsets were also lower in responders (0.24±0.14%) compared to non-responders (4.4±2.19%) (p<0.001) and controls (6.6±1.31%) (p<0.003). Significant recovery of all 3 activation subsets occurred 3 months post-rituximab treatment. Using ROC curve analysis, activatedCD54+ CD43+ (AUC 0.82, 95% CI 0.63-1.00), IFN-γ+CD3+ (AUC 0.86, 95% CI 0.67-1.00) and IL-2−CD3− (AUC 0.82, 95% CI 0.63-1.00) were good predictors of response to rituximab.

Conclusion: We have identified prognostic markers which define a subset of FSGS patients bearing an immunological signature representing hyporesponsiveness to T-cell stimulation, with good response to rituximab therapy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO988

Gut-Kidney Axis in the Pathogenesis of IgA Nephropathy
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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. It is characterized by deposition of deglycosylated IgA1 and IgA antibodies in the glomeruli and its pathogenesis is only partially defined. Intestinal microbiota could be involved in IgAN, as suggested by the observation that B-cell activation factor (BAFF) transgenic mice had high levels of aberrantly glycosylated serum polymeric IgA, the presence of commensal flora and the circulation of corresponding specific IgA antibodies being essential for the development of IgA deposits. BAFF is an important regulator of B cell maturation, survival and function. The aim of the study was to analyze the role played by gut-kidney axis in the pathogenesis of IgAN.

Methods: 16 healthy controls (HC) and 32 IgAN patients (16 non-progressors - NP and 16 progressors - P) were included in the study. Serum creatinine, estimated Glomerular Filtration Rate, 24-hour proteinuria and histological lesions following Oxford Classification (MEST score) were analyzed. Gut microbiota, urinary and fecal metabolome of all subjects were characterized by 16S sequencing, Biochorm 30 series amino acid analyzer and gas- chromatography mass spectrometry/solid-phase microextraction (GC-MS/SPME). Galactose-deficient IgA1 (Gd-IgA1) were measured by helix aspersa agglutinin binding assay. BAFF serum levels were quantified by ELISA.

Results: Some traits of the gut microbiota and urinary and fecal metabolome profiles showed significant differences between P, NP and HC. Gd-IgA1 and BAFF were significantly higher in IgAN patients, particularly in P, compared to HC (Gd-IgA1: p=0.01; P<0.05 NP vs HC; BAFF: p<0.01 P vs HC). IgAN patients with histological grade at diagnosis M1, E1, S1 and T1 had significantly higher levels of serum BAFF than HC. Moreover, serum BAFF levels were positively correlated with 24-hour proteinuria (r=0.47, p=0.0069) and with the levels of fecal phenolic metabolites (r=0.61, p=0.0003).

Conclusions: Gut-kidney axis might play an important role in the pathogenesis of IgAN.

FR-PO989

Intestinal Macrophages Polarized to Activation of Pro-Inflammatory and Had Dysfunction of Phagocytosis Leading to Aggravate Microinflammation and Asstis Bacterial Translocation as Carrier in Uremia Rats
Hongli Jiang, Hua Liu, Meng Wei. Dialysis Dept of Nephrology Hospital, First Affiliated Hospital of medicine school.

Background: This study investigated whether intestinal macrophages are related to low-grade inflammation and bacterial translocation (BT) during uremia, and whether probiotics can alter the macrophage activity.

Methods: Male Sprague-Dawley rats were randomly divided into 3 treatment groups: sham, uremia (untreated), and uremia + probiotic. The expression of cell surface antigen CD11a (a.k.a., lymphocyte function-associated antigen 1 [LFA1]), inducible nitric oxide synthase (iNOS), ICAM1, and TGF-β were analyzed by immunohistochemistry. Gene and protein expression of early growth response protein 1 (EGR1) and TLR4 in intestinal specimens were determined. Density of labeled macrophages and tracer bacteria in intestinal and extraintestinal tissues were examined by immunofluorescent microscopy, and macrophage morphomorphy were examined by transmission electron microscopy. Intestinal macrophages from uremic rats showed a highly injured and altered phenotype characterized by CD11a expression, iNOS, ICAM1, and TGF-β staining. Gene and protein expression levels of intestinal TLR4 and EGR1 were also highest in this group. Intestinal segments of uremic rats exhibited high iNOS, ICAM1, and TGF-β staining. Gene and protein expression levels of intestinal TLR4 and macrophage micromorphology were examined by transmission electron microscopy. Intestinal and extraintestinal tissues were examined by immunofluorescent microscopy, and protein expression of early growth response protein 1 (EGR1) and TLR4 in intestinal synthase (iNOS), ICAM1, and TGF-β were analyzed by immunohistochemistry. Gene expression of intestinal TLR4 and macrophage micromorphology were examined by transmission electron microscopy. Gene expression of EGR1 and TLR4 in intestinal tissues were examined by immunofluorescent microscopy. Gene and protein expression of EGR1 and TLR4 in intestinal tissues were examined by immunofluorescent microscopy.

Results: The expression of cell surface antigen CD11a and iNOS were higher in P compared to NP and HC. CD11a and iNOS expression was abolished with wort, confirming PI3K/AKT involvement in BT production. Media from probiotic treated HC suppressed UCUG production compared to media from HC pretreated with wort or vehicle control, suggesting that PI3K/AKT and R7 is involved in BT pathogenesis. Urinary R7 levels were significantly higher in P compared to NP (r=0.66, P<0.01). R7 levels were increased in P compared to NP (r=0.66, P<0.01). R7 levels were increased in P compared to NP (r=0.66, P<0.01).

Conclusions: PI3K/AKT activation is required for R7 induction. R7 induction suppresses UCUG expression. Diabetics, with decreased PI3K activity, have lower urinary R7 levels, therefore data may indicate why UTIs are more prevalent with DM and may provide new regulatory targets for BT treatment.

Funding: NIDDK Support

FR-PO991

Serum Acetate and Lipopolysaccharide Levels Correlate with Disease Activity in Patients With Lupus Nephritis
Daniel Tak Mao Chang, Ping Lung Chan, Qing Zhang, Kin Yi Au, Desmond Y.H. Yap, Mel Chau, Susan Yung. Dept of Medicine, The Univ of Hong Kong, Hong Kong.

Background: Lupus nephritis is a severe manifestation of systemic lupus erythematosus and is associated with poor prognosis. The gut microbiota has been implicated in the etiology of autoimmune diseases. Bacterial products from the gut may enter the circulation and influence local and systemic responses. Acetate is a short chain fatty acid (SCFA) produced by gut microbiota and lipopolysaccharide (LPS) is a component of the outer wall of Gram-negative bacteria. We measured serum acetate and LPS levels and intra-renal expression of their cell surface receptors in lupus nephritis patients to investigate the potential relationship between gut microbiota and lupus nephritis pathogenesis.

Methods: Serum acetate and LPS levels were measured in patients with biopsy-proven severe proliferative lupus nephritis, patients with non-lupus glomerular diseases and healthy controls (n=50 for each group). Intra-renal expression of LPS-binding protein (LBP) and GPR-41 and GPR-43 (SCFA receptors) was also examined.

Results: Serum acetate and LPS levels were significantly higher in patients with lupus nephritis compared to levels in patients with non-lupus renal diseases (P=0.05, for both) and healthy subjects (P=0.01, for both). In lupus nephritis patients, serum acetate and LPS levels were significantly higher during disease flare (P=0.04 and P=0.0015 respectively compared to levels during remission). Serum LPS level correlated with acetate level (r=0.52, P<0.001), and inversely correlated with that of IgG (r=0.61, P<0.01). Renal LBP, GPR-41 and GPR-43 expression showed markedly increased in lupus nephritis patients compared to healthy controls, and was predominantly detected in the tubulo-interstitialis, associated with urinary cell infiltration, fibrosis and tubular atrophy. LBP, GPR-41 and GPR-43 expression showed similar staining intensities and localization in patients with lupus nephritis and those with non-lupus renal diseases.

Conclusions: Our data suggest that acetate and LPS may be involved in the pathogenesis of lupus nephritis and non-lupus glomerular diseases.

Funding: Government Support - Non-U.S.

FR-PO992

Noninvasive Assessment of Macrophage Activation in Experimental Glomerulonephritis Using Optical Imaging with Near-Infrared Light Serves as a Surrogate of Disease Activity
Sebastian Braehler, Dongyue Huang, Matthew David Cheung, Walter J. Akers, Alfred Hyoungji Kim. Washington Univ School of Medicine, St. Louis, MO.

Background: Glomerulonephritis (GN) represents a major cause of morbidity & mortality. The standard for diagnosing GN is through renal biopsy, but this is not performed uniformly across many centers. There is an unmet need to identify a noninvasive approach for assessing GN. Recent advances in deep tissue imaging using probes detected by near-infrared (NIR) wavelengths have enabled the noninvasive probing of biologic activity. Macrophage infiltration of the kidney is observed in early GN and once activated, express the cytokine protease cathepsin B. Thus, renal macrophage activation can be assessed using an NIR probe that becomes fluorescent upon cleavage by cathepsin B. We tested the ability of using NIR optical imaging to assess renal macrophage activation as a noninvasive marker for early-stage GN.

Methods: GN was induced in 129 mice by nephrotoxic serum (NTS) delivered intravenously (IV). Proteins were assessed using albumin ELISA & chromogenic assay reagent. H&E & PAS stained slides of mouse kidneys were observed using light microscopy. Presence of renal macrophages was confirmed using FACS. NIR optical imaging of anesthetized mice was performed following IV administration of a cleavable fluorophore and a FITC fluorochrome. Kidney fluorescence intensity was determined using H&E & PAS stained slides of mouse kidneys were observed using light microscopy. Presence of renal macrophages was confirmed using FACS. NIR optical imaging of anesthetized mice was performed following IV administration of a cleavable fluorophore and a FITC fluorochrome. Kidney fluorescence intensity was determined using NIR imaging. Kidney fluorescence intensity was determined using NIR imaging. Kidney fluorescence intensity was determined using NIR imaging. Kidney fluorescence intensity was determined using NIR imaging.

Results: In mice with uninflamed kidneys, we confirmed the paucity of renal macrophages. Accordingly, there was minimal renal fluorescence signal as determined by fluorescent molecular imaging of cathepsin B activity. 3 days post-NTS administration, we observed a massive influx of macrophages into the kidney, along with necrotic range proteinuria. This correlated with significant increase in renal fluorescence intensity signal in NTS mice compared to control mice.

Funding: NIH

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Underline represents presenting author.
Conclusions: Induction of GN by NTS caused significant macrophage infiltration, which was detected noninvasively by a cathespin B-activatable probe and NIR optical imaging. These data establish the proof-of-principle that NIR optical imaging may represent a translatable approach to establishing early stages of GN.

Funding: Private Foundation Support

FR-PO093

Improved Tissue Clearing and 2-Photon Imaging of Mouse Kidneys Reveals Immune Cell Architecture in Nephrotic Nephritis Matthew David Cheung, Dongyue Huang, Alfred Hyoungju Kim. Rheumatology, Washington Univ School of Medicine, St. Louis, MO.

Background: Tissue clearing approaches such as CLARITY renders tissue transparent, and in combination with two-photon microscopy, enables microscopic visualization deep internal structures within unaltered tissues. These cutting edge approaches have drastically improved the understanding of cellular circuits in the brain. However, application of this approach has only recently been described for the kidney. Here, we clear mouse kidneys to better understand the immune cell architecture following induction of nephrotic nephritis (NTN) using a modified lipid removal approach that also worked for human kidney fragments.

Methods: 129 mice were injected intravenously with nephrotic serum to induce NTN. Mice were perfused with an acrylamide monomer solution to form the basis of the hydrogel. Lipid removal was accomplished using 8% sodium dodecyl sulfate (SDS). An aminoalcohol solution was used to quench light absorbing heme in red blood cells trapped within the tissue. Cleared mouse kidneys were stained with antibodies specific for B cells, T cells, macrophages, and dendritic cells (DCs). Human kidney fragments were incubated in acrylamide monomer solution, then cleared as mentioned above. Cleared tissue was imaged using two-photon microscopy.

Results: Compared to previously published protocols, perfusion of acrylamide monomers into mice significantly accelerated the tissue clearing process. Enhanced tissue clearing was observed when we incubated kidneys in aminoalcohols. We observed vast networks of lymphocytes, lymphocytes, and DCs cleared NTN kidneys compared to DCs cleared control kidneys. Human kidneys also were cleared using this approach, and we noted DC networks in healthy donor controls.

Conclusions: We identified a new protocol that enhanced and accelerated tissue clearing in mouse and human kidneys. Using this approach, we found elaborate networks of lymphocytes and monocyte-derived cells in NTN mouse kidneys. We also observed DC networks in healthy human donor fragments. These data demonstrate the utility of tissue clearing in evaluating cellular architecture in mouse and human kidneys.

Funding: Private Foundation Support

FR-PO094

Natural IgM Mediates Ischemic AKI Lindsey R. Goetz, Jennifer Laskowski, Brandon Renner, Rachel A. Woolaver, Ludivila Kulik, Kazue Takahashi, Matthew C. Pickering, Joshua M. Thurman. 1Dept of Medicine, Univ of Colorado Denver School of Medicine, Aurora, CO; 2Dept of Radiology, Massachusetts General Hospital, Boston, MA; 3Centre for Complement and Inflammation Research, Imperial College London, London, United Kingdom.

Background: Glomerular IgM deposition occurs in numerous “non-immunologic” kidney diseases and has been shown in chemical and inflammatory models of injury. We recently demonstrated that complement activation within the kidney leads to neo-epitope formation. Because the alternative complement pathway is activated in renal ischemia-reperfusion (I/R) injury, we hypothesized that co-expressed complement and DC neo-epitopes within I/R generates neo-epitopes recognized by natural IgM antibodies that then exacerbate inflammatory injury.

Methods: To investigate this hypothesis, we used a 24 minute I/R model. Results: We first subjected soluble IgM deficient (sIgM-) mice to renal I/R and found a trend toward less severe injury in these mice vs. wild type (wt) controls (mean BUN of 135 ± 39 [SD] and 152 ± 26 mg/dL, respectively; n ≥ 26, p < 0.01). To accentuate complement activation in this model, we then exposed mice heterozygous for complement regulatory protein factor H (H+) to the same I/R protocol and found that the H+ mice sustained worse renal injury and had greater glomerular IgM deposition than wt controls (mean BUN of 114 ± 46 and 63 ± 48 mg/dL, respectively; n ≥ 14, p = 0.009 and mean glomerular IgM RFUs of 44 ± 7 and 22 ± 7, respectively; n ≥ 8, p = 0.0002). To further evaluate IgM pathogenicity, we induced I/R injury in mice deficient in both factor H and IgM (H-+/sIgM-) and noted a trend toward attenuation of renal injury in the H-+/sIgM- vs. H-+/sIgM+ mice (mean BUN of 106 ± 69 and 127 ± 52 mg/dL, respectively; n ≥ 7, p = 0.09) with data collection ongoing.

Conclusions: These data suggest that natural IgM contributes to ischemic renal injury by binding neo-epitopes generated during complement activation in this kidney. This adds to a growing body of evidence suggesting a common final pathway of IgM-mediated glomerular injury in a variety of “non-immunologic” renal disorders and offers a novel therapeutic target for the treatment of these diseases.

Funding: NIDDK Support

FR-PO095

Activation of Toll-Like Receptor 2 in the Pathogenesis of Contrast-Induced Nephropathy Kristina Angela Rathmell, Altuf-M Khan, Federico Jose Teran, Kathleen S. Hering-Smith, Eric E. Simon, Vecchi Batuman. 1 Medicine, Nephrology & Hypertension, Tulane Unv, School of Medicine, New Orleans, LA; 2VA, SLVHCS, New Orleans, LA.

Background: Innate immunity mediated by Toll-like receptors (TLRs) is involved in the pathophysiology of contrast-induced nephropathy (CIN). We studied the expression of TLRs and associated molecules in CIN using human renal proximal tubule epithelial cells (RPTECs) and aged diabetic (db/db) mice.

Methods: We cultured RPTECs in normal (5 mM) or high (35 mM) glucose media for 24 h and then exposed them to nonionic (iodixanol or iohexol) and ionic (Urografin) contrast agents (CM) at a dose of 25–100 mg iodine/ml for another 24 h in the same media. 24-wk-old male db/db mice were given nonionic CM i.v. (3 g of iodine/kg bw) after 24 h water deprivation. All mice were sacrificed 24 h after CM injection.

Results: The mRNA expression of TLR2 increased by 2.5 fold (p < 0.05), TICAM-1 by 1.7 fold (p < 0.05) in RPTECs exposed to iodixanol compared to untreated RPTECs in a dose-dependent fashion. RPTECs in high glucose for 48 h and exposed to iodixanol showed significantly increased apoptosis compared to RPTECs in normal glucose, 24-wk-old db/db mice became obese, polyuric, glucosuric, ketogenic, and had increased GFR, systolic blood pressure, urine NGAL, and renal tubular damage compared to nondiabetic (db/m) control mice. 24 h after iodexhol injection, db/db mice showed a significant decrease in GFR, metabolic acidosis and significant increases in serum creatinine, urine and kidney KIM-1 levels and kidney damage histologically compared to control db/db mice. After iodexhol administration, the mRNA level of TLR2 was significantly increased by 2.4 fold (p < 0.01) in kidney compared to control mice but there was no change in TLR4 expression. The expression of CD11b and CD68 were also significantly upregulated in kidney.

Conclusions: High glucose RPTECs and diabetic (db/db) mice are vulnerable to CIN. Innate immune mediated by TLR2 plays a major role in the pathogenesis of CIN as demonstrated by in vitro and in vivo studies. TLR2 may prove to be a promising drug target for the development of new therapeutics against CIN.

Funding: Private Foundation Support

FR-PO096

Heparanase Deficiency Improves Renal Function During Experimental Glomerulonephritis Marileine Garson, Marlien Benner, Henk Dijkman, Jin-ping Li, Ton J. Rabeklink, Idsray Slodovskv, Jin-ping Li, Henk Dijkman, Michael Elkin, Rodney May, Michael Elkin. 1Pathology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2Pathology, Radboud Univer Medical Center, Nijmegen, Netherlands; 3Medical Biochemistry and Microbiology, Uppsala Univ, Uppsala, Sweden; 4Nephrology, Leiden Univer Medical Center, Leiden, Netherlands; 5Cancer and Vasculat Biology Research Center, Bruce Rappaport Faculty of Medicine, Haifa, Israel; 6Sharet Inst, Hadassah-Hebrew Univ Medical Center, Jerusalem, Israel.

Background: Heparanase (HPSE), a heparan sulfate (HS)-specific endoglucohydrolase, mediates the onset of proteinuria and renal damage during experimental diabetic glomerulonephritis. Glomerular HPSE expression is increased in the majority of proteinuric diseases. The exact role of HPSE in the development of other inflammatory glomerular diseases is still unknown.

Methods: Here, we evaluated the role of HPSE in two models of experimental glomerulonephritis, being an acute glomerular basement membrane and lipopolysaccharide (LPS)-induced glomerulonephritis, in wild type (WT) and HPSE-deficient mice.

Results: Induction of experimental glomerulonephritis led to an increased HPSE expression in WT mice, which was associated with a decreased glomerular HS expression and albuminuria. Albuminuria was reduced in the HPSE-deficient mice in both models, which was accompanied by a better renal function and less renal damage. Notably, glomerular HS expression was preserved in the HPSE-deficient mice. Glomerular leukocyte and macrophage influx was reduced in the HPSE-deficient mice, which was accompanied by a reduced expression of both Tk1 and Tk2 cytokines. In vitro, tumor necrosis factor (TNF)-α and LPS directly induced HPSE expression and increased transendothelial albumin passage in a HPSE-dependent manner.

Conclusions: Our study shows that HPSE deficiency ameliorates proteinuria and renal damage in experimental glomerulonephritis by preserving glomerular HS expression, and reducing leukocyte and macrophage influx, and by affecting the local cytokine milieu.

FR-PO097

Iron Chelation as a Novel Renoprotective Strategy in Lupus Nephritis Erik L. Bossem, Cellular & Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE.

Background: Poorly liganded iron damages tissue via several mechanisms. Multiple iron homeostasis proteins have been proposed as urinary biomarkers of lupus nephritis, and we have previously found that renal tissue iron levels are increased in the NZB/NZW/F1 mouse model of lupus nephritis. Anemia is also common in lupus patients. Together, these data suggest that dysregulation of body iron homeostasis may occur in lupus. This pilot study aimed whether (i) iron chelation in the NZB/NZW/F1 model of lupus nephritis, and (ii) whether this therapy adversely affects hematological parameters.

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Methods: Female (NZBxNZW)F1 mice were treated with the iron chelator deferiprone from 20 weeks of age onwards. Albuminuria was monitored in 24h urine samples collected weekly, and mice were sacrificed at 25-40 weeks (100mg/d by dipstick) or 40 weeks of age, whichever was sooner. Hematocrit, red cell hemoglobin, plasma non-heme iron concentration as well as kidney and liver iron concentrations were measured at sacrifice.

Results: As shown in Figure 1, there was a trend towards later onset of albuminuria in deferiprone-treated mice compared with vehicle treated mice (median onset of albuminuria from 20 weeks of age onwards. Albuminuria was monitored in 24h urine samples relevant situations, because it also impairs Treg and thereby unleashes pre-existing nephritogenic immune responses in vivo, it may aggravate such responses in clinically relevant to protect against renal injury in murine nephrotoxic serum (NTS) nephritis.

Conclusion: Administration of M2 M6 may have therapeutic potency for glomerular injury by further M2 cell conversion and induction of regulatory T cells.

FR-PO1000
A Randomized Multicomponent Intervention to Reduce Disparities in Transplant Referral: Results from the RaDIAnt Community Study

Background: The reducing disparities in access to kidney transplantation is a dialysis facility-level randomized clinical trial to test the effectiveness of a multicomponent intervention in improving kidney transplant (KTx) referral and reducing racial disparities in referral in Georgia.

Methods: In 2013, 134 dialysis facilities were randomized to receive either usual KTx education (+7.8% vs. -2.5%) and decrease mortality rate. Thus, it is reasonable to suggest that EA and MO could be an additional strategy to be employed in CKD.

Funding: Government Support - Non-U.S.

FR-PO998
IKK2 Inhibition Inhibits the Initiation, but Aggravates the Progression of Crescentic Glomerulonephritis
Janine Goerlitz,1 Gisela Piotrowski,2 Gisa Tieg,3 Ulf Panzer,3 Christian Kuris,3 Friedrich Thaiss,1 1Rheinische Friedrich-Wilhelms-Universit, 2Inst of Experimental Immunology, Bonn, Germany; 3Universitssklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: The NFkB transcription factor family facilitates the activation of dendritic cells (DC) and CD4+ T helper (Th) cells, which are important for protective adaptive immunity. Inappropriate activation of these immune cells may cause inflammatory disease, and NFkB inhibitors are promising candidate drugs.

Methods: Here, we investigated whether inhibiting the NFkB component IKK2 can attenuate crescentic glomerulonephritis, a severe DC- and Th-cell-dependent kidney disease by induction of the pausive and the accelerated NTN mouse model.

Results: Prophylactic pharmacological IKK2 inhibition reduced DC activation, Th cell activation and ameliorated glomerulonephritis in mice. However, therapeutic IKK2 inhibition during ongoing disease, which is relevant for clinical situations, unexpectedly aggravated the nephritogenic immune response and disease symptoms. This resulted from systemic loss of regulatory T cells (Tregs) which have been previously shown to protect against crescentic glomerulonephritis and which require IKK2 as well.

Conclusions: In conclusion, although IKK2 inhibition can suppress the induction of nephritogenic immune responses in vivo, it may aggravate such responses in clinically relevant situations, because it also impairs Tregs and thereby unleashes pre-existing nephritogenic responses. Our findings argue against using IKK2 inhibitors in chronic glomerulonephritis, and perhaps also in other immune-mediated diseases.

Funding: Government Support - Non-U.S.

FR-PO999
Transfused M2 Macrophages Ameliorate Renal Injury in Murine Nephototoxic Serum Nephritis
Oshima Du, Naotake Tsuobi, Yuta Sugiya, Seichi Matsuo, Shoichi Maruyama. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

Background: Glomerular leukocyte infiltration is a hallmark of glomerulonephritis. In addition to the effector roles of glomerular macrophages (MΦ) for tissue injury, recent studies found involvement of alternatively activated macrophages (M2 MΦ) in resolution of kidney inflammation. The aim of this study is to directly assess the potential of M2 MΦ to protect against renal injury in murine nephototoxic serum (NTS) nephritis.

Methods: Bone marrow (BM)-derived M6 and mouse iPS-derived M6 were obtained under the approval of the Animal Use Committee of CD260. FACs and RT-PCR were performed to assess efficient M6 differentiation. 0.6 x 10^6 of M2 MΦ were intravenously transferred 4 days after NTS nephritis induction. Immunostaining was used to detect M6, T cell and neutrophil infiltration. Renal cytokines were determined by ELISA. BM-derived M2a Mjs from EGFp transgenic mice (EGFP+M2a MΦ) was exploited to investigate the cell distribution. To investigate in vitro function of M2a MΦ on other leukocyte subsets, BM-derived M6 MΦ and splenic CD4+CD25+ T cell were co-cultured with EGFP+M2a MΦ.

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FR-PO1003
Deceased Donor Renal Transplant eGFR at Six Months Has Improved in the Last 13 Years in Spite of Declining Donor Quality
Douglas Scott Keith, Gayle M. Vranic, Angie G. Nishio-Lucar. Medicine, Univ of Virginia, Charlottesville, VA.

Background: Deceased donor quality has declined in the last decade but long-term graft outcomes are improving. We sought to analyze the trend in graft function at six months post-transplant in relation to this improvement.

Methods: All adult deceased donor kidney transplant recipients with at least six months graft survival recorded in the SRTR database between 2000 and 2012 were analyzed. The CKD EPI eGFR was determined based on the patient characteristics and serum creatinine at six months post-transplant. KDPI of the donors was also calculated. Linear regression was used to determine the effect of covariates on eGFR.

Results: 111,678 deceased donor recipients were identified. 4918 (4.4%) recipients with no six month creatinine were excluded. The median eGFR improved from 54.5 ml/min/1.72m2 in 2000 to 58.9 in 2012 (p=0.001) while the median KDPI increased from 41% to 46% (p=0.001). The use of tacrolimus/mycophenolate derivative also increased from 33.1% to 89.8%. Every 10 unit increase in KDPI resulted in a 3 ml/min/1.72m2 decline in eGFR.

Linear Regression Analysis

<table>
<thead>
<tr>
<th>B ml/min/1.72m2</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>73.87</td>
</tr>
<tr>
<td>KDPI</td>
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</tr>
<tr>
<td>Acute Rejection in First Six Months</td>
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<tr>
<td>En Bloc Pediatric Kidney</td>
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<tr>
<td>Dialysis in the First Week Post-Transplant</td>
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<tr>
<td>Tacrolimus/Mycophenolate Derivative</td>
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</tr>
<tr>
<td>CNI/Azathioprine</td>
<td>-2.93</td>
</tr>
<tr>
<td>Other combination</td>
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</tbody>
</table>

KDPI adjusted median eGFR increased 13%.

Conclusions: Graft function improved significantly over the 13 year period in spite of declining donor quality and appears to be an important factor in the improvement in long-term graft survival. The transition to tacrolimus/mycophenolate derivative as the dominant maintenance immunosuppression appeared to be an important factor in this improvement.

FR-PO1004
Recipient Age and KDPI Are the Most Potent Predictors of Early Acute Rejection in Deceased Donor Kidney Transplantation
Douglas Scott Keith, Gayle M. Vranic, Angie G. Nishio-Lucar. Medicine, Univ of Virginia, Charlottesville, VA.

Background: The rate of acute rejection in the first six months after deceased donor kidney transplant is now under 10% in the modern era of immunosuppression. We sought to determine the factors predictive of acute rejection in this era.

Methods: All recipients transplanted between 2001 and 2012 in the SRTR database were included in the analysis. Logistic regression was performed to determine the odds ratio of acute rejection in the first six months adjusting for multiple covariates.

Results: The acute rejection rate was 7.1% during the study period. KDPI and recipient age were the most important factors influencing rejection rates with recipients under 30 years old having a rate of rejection more than double that of recipients 60 years or older and recipients receiving donor kidneys with a KDPI over 90% having a 2 fold increase in rejection rate over those receiving a kidney with a KDPI less than 30%.

Conclusions: Graft function improved significantly over the 13 year period in spite of declining donor quality and appears to be an important factor in the improvement in long-term graft survival. The transition to tacrolimus/mycophenolate derivative as the dominant maintenance immunosuppression appeared to be an important factor in this improvement.

FR-PO1002
Association of Neighborhood Poverty and Living Donor Kidney Transplant Rates by Race
Douglas Scott Keith, Angie G. Nishio-Lucar, Gayle M. Vranic. Medicine, Univ of Virginia, Charlottesville, VA.

Background: Despite a growing shortage of deceased donor kidneys in the US, living donation (LD) rates have declined steadily since 2004. We sought to understand the impact of candidate socioeconomic environment on living donation rates.

Methods: We identified all candidates listed for kidney or kidney pancreas transplant in the SRTR database from 2000-2010. Data was linked to US census data on median income by zip code. Candidate zip code of residence was used as a surrogate for neighborhood socioeconomic environment on living donation rates.

Results: A total of 51 of the 67 (76.1%) intervention facilities improved their percentage of patients referred for KTxs over the 9 month study period. Intervention vs. control facilities had a greater increase in referral among AA (+7.3% vs. -2.5%) than white (+0.4% vs. -1.2%) patients over 9 months. Among the 26 dialysis facilities that had an AA vs. white racial disparity in referral at baseline, 69.2% no longer had a racial disparity in referral by 9 months.

Conclusions: Data from Radiant Community Study intervention facilities suggest that a large, randomized, quality improvement program among dialysis facilities in GA may improve KTxs access. Availability of data after 12 months of the intervention will allow final assessment of the effectiveness of the intervention.

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The only factors in the KDPI determination associated with rejection were donor age, donor hypertension, HCV seropositivity, and black donor race, with age accounting for most of the effect.

Conclusions: KDPI and recipient age are the most important factors associated with rejection. Risk stratification for donor recipient pairs based on age and KDPI should be considered when determining induction and maintenance immunosuppression needs.

FR-PO1005

Transplantation of Cadaveric Kidneys from Infants and Toddlers into Adults in the Era of Extreme Donor Shortage

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Background: Kidney transplantation is the treatment of choice for patients with ESRD. The number of patients in the waiting list for a deceased donor kidney transplant continues to increase. In this era of extreme donor shortage we present our experience with transplantation of cadaveric kidneys from infant and toddler into adult recipients.

Methods: This was a retrospective study of twelve adult deceased donor kidney transplant recipients from pediatric donors ages 0-5 years. Medical records were reviewed from visits previous to transplantation to the most recent follow up after transplant.

Results: Twelve consecutive adult patients were transplanted with pediatric en bloc kidneys from donors 0-5 years between February 2014 to February 2015. Ten of the donors were standard criteria brain death (DBD) and two were donors with cardiac dead (DCD). KDPI scores ranged from 47 to 87%, donor age from 6 months to 5 years, weight 6 to 15 Kg. Recipients were equally distributed by gender, average age 56 years, mean BMI 22. KDPI scores ranged from 47 to 87%, donor age from 6 months to 5 years, weight 6 to 15 Kg. Recipients were equally distributed by gender, average age 56 years, mean BMI 22.

Acknowledgment: This work was supported by a research grant from the Cleveland Clinic Foundation Research Institute and the Eye Bank Association of America.

FR-PO1006

The Role of Dobutamine Stress Echo in Identifying Cardiac Ischaemia, Cardiovascular Events and Role of Subsequent Cardiac Angiography

Maria Ventura, Robin Ramphul, Sami Firoozi, Juan Carlos Kaski, Rajan Sharma, Debasish Banerjee, Renal and Cardiology Depts, St. George’s Univ Hospitals NHS Foundation Trust.

Background: Dobutamine Stress Echo (DSE) is an established method of identifying cardiovascular (CV) risk in patients undergoing kidney transplantation, however the role of coronary angiography (CA) is not clear. The aim of this study was to investigate the role of DSE and CA in predicting cardiac ischaemia and CV events in this population.
Survival of Elderly Incident Home Hemodialysis and Kidney Transplant Patients
Miklos Zsolt Molnar,1 Vanessa A. Ravel,2 Elani Streja,2 Csaba P. Kovessy,1 Danh V. Nguyen,2 Rajnish Mehrotra,1 Kamyar Kalantar-Zadeh,2 1Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of California, Irvine, CA; 3Univ of Washington, WA.

Background: The proportion of elderly (≥65 years) patients with kidney failure is increasing. Previous data suggest that the projected increases in the life spans of kidney transplant (KTx) patients compared to conventional dialysis were 2.8 and 1.1 years for patients aged 65-69 and 70-74 years, respectively. However, no studies have compared mortality of elderly patients using alternative dialysis modalities such as home hemodialysis (HD) with KTx recipients.

Methods: Comparing elderly patients, who started home HD with those who received KTx in the US between 2007-2011, we created a 1:1 propensity score (PS) matched cohort of 960 elderly patients (480 KTx and 480 HD) and examined the association between treatment modality and all-cause mortality using Cox proportional hazard models.

Results: The mean±SD age of the PS matched home HD and KTx patients at baseline were 71±6 years and 71±5 years, 69% were male (both groups), and 81% and 79% of patients were whites in home HD and KTx group, respectively. Median follow-up time was 205 days (IQR: 78-364 days) for home HD patients and 795 days (IQR: 366-1,221 days) for KTx recipients. There were 97 deaths (20%, mortality rate 253 [297-309]/1000 PY) in the home HD group, and 48 deaths (10%, 45 [34-60]/1000 PY) in the KTx group. Over 5 years of follow-up, home HD patients had almost 5 times higher mortality risk compared to KTx recipients in the entire patient population (HR: 4.74, 95%CI:3.25-6.91).

These results were consistent across different types of kidney donors and recipients characteristics.

Conclusions: Elderly home HD patients appear to have almost 5 times higher mortality compared to KTx recipients regardless of the type of kidney donor.

Funding: Other NIH Support - R21AG047306 and R01DK95668

FR-PO1009
Beyond the Bones – The Association Between Vitamin D, Graft Outcomes and Vascular Disease
Aravind Cherukuri,1 Santanarakrishnan Balasubramanian,2 Rebekah Molyneux,2 Richard J. Baker.2 1Univ of Pittsburgh; 2Univ of Leeds.

Background: Vitamin D deficiency in KTRs is an emerging theme. The purported associations between Vitamin D deficiency and various metabolic, cardiovascular and non-metabolic adverse events have not been thoroughly studied in kidney transplant recipients (KTRs).

Methods: Here, we examined the association between Vitamin D deficiency and graft loss, mortality, NODAT, cardiovascular events and development of cancers.

Results: 504 KTRs had their vitamin D checked in 2008 and were followed up for 6 years. Vitamin D deficiency was defined as a level<50nmol/L. In this population, the prevalence of vitamin D deficiency was high at 66.5% with a significantly higher prevalence in older (71.9% vs. 60.9%, P=0.006) and female recipients (62.1% vs. female 73.2%, P=0.006) and in relatively new transplants (recent transplants 72.3% vs. old transplants 66.6%, P=0.003). KTRs who were vitamin D deficient had significantly worse overall (77% vs. 82.1%, P=0.001), death censored graft survival (89% vs. 96%, P=0.009), development of NODAT (19.8% vs. 10%, P=0.005) and cardiovascular events (9.9% vs. 2.9%, P=0.002) when compared to those with normal levels. In a stratified analysis, this was noted to be worse in KTRs on maintenance steroids, with relatively worse baseline renal function and proteinuria, with secondary hyperparathyroidism, deceased donor transplants and earlier vs. late transplants. Although vitamin D deficiency is not associated with a higher incidence of malignancy, it is associated with higher mortality in those with cancer (33.3% vs. 12.9%, p=0.005). In a multivariate Cox model, vitamin D deficiency was associated with significantly worse overall graft (HR 2.7, P=0.001) and death censored graft survival (HR 2.4, P=0.04), NODAT (HR 2.3, P=0.03) and cardiovascular events (HR 4.0, P=0.004) independent of age, PTH levels, gender, graft number, type of transplant, time since transplantation, graft type and renal function measured by both proteinuria and eGFR.

Conclusions: Vitamin D deficiency is an important modifiable risk factor for graft loss, mortality and cardiovascular events in KTRs.

Funding: Other NIH Support - R21AG047306 and R01DK95668

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: In conclusion, vitamin D deficiency which is highly prevalent in KTRs is associated with adverse outcomes. Our study stresses the need for a prospective trial of vitamin D replacement in KTRs.

Funding: Private Foundation Support

FR-PO1010
Acute Tubular Necrosis Changes in Living Kidney Donor Implant Biopsy

Associates with Higher Rejection Rates Post-Transplant

Chunping Yu, Nissreen Elafawdy, Andres G. Chiesa-votto, Leal C. Herltz, Emilio D. Poggio, Dept of Nephrology and Hypertension, Glickman Urological and Kidney Inst, Cleveland Clinic, Cleveland, OH.

Background: Ischemic injury may occur during organ retrieval. In deceased kidney donor transplants, delayed graft function, a form of acute tubular necrosis (ATN), associates with acute graft rejection. Histological changes consistent with ATN can also be seen in implant biopsies of living donor (LD), however, the influence of ATN-like changes at time on donation from LD on recipient graft outcomes is unclear, especially its impact on graft rejection.

Methods: We retrospectively studied all LD kidney transplants at our center from Jan 2005 to Dec 2014 who had an implant biopsy. We perform protocol biopsies at 3, 6, 24 months post-transplant and for cause biopsies in all our patients. Post-transplant biopsy results were reviewed, and patients with subclinical and clinical borderline and/or BANFP scored graft rejection were captured.

Results: The study included 350 LD kidney transplant recipients, the mean age was 47.8±13.7 years (range 10-75) and 224(64%) were male. The incidence of ATN in implant biopsies was 16% (n=56). Patients with ATN had a trend toward higher risk of graft rejection in post-transplant biopsy compared with those without ATN (32.1% vs. 21.7%, p=0.09). When the study population was stratified by time from transplant to post-transplant biopsy, there was a statistically significant higher incidence of graft rejection in those biopsies performed between 1 and 24 months post-transplant (31.0% in the ATN group vs. 17.8% in the non-ATN group, respectively, p=0.02). No statistical correlation was found between ATN and graft rejection after 24 months post-transplant. Importantly, implant ATN has no impact on GFR at 3, 6, 12, 24 months post-transplant.

Conclusions: Histological changes consistent with ATN in LD kidney implant biopsies are associated with higher rates of graft rejection between 1 and 24 months post-transplant. However, ATN does not affect graft function at 3, 6, 12, or 24 months.

FR-PO1011
Impact of Pre-Transplant Cardiovascular Risks on Renal Allograft Survival: A Multi-Center Prospective Study

Jung Nam An, 1,2 Song Vogue Ahn, 1 Chun Soo Lim, 1,2 Non Su Kim, 1,2; Hoomin Kim, 1,2, Junhong Park1,4 1Seoul National Univ Boramae Medical Center; 2Seoul National Univ College of Medicine; 3Yonsei Univ Wonju College of Medicine; 4Asan Medical Center and Univ of Ulsan College of Medicine, Republic of Korea

Background: Cardiovascular (CV) disease is a leading cause of mortality in patients with end-stage renal disease. Even after successful renal transplantation, CV risks can induce CV morbidity and mortality in renal transplant recipients. However, the impact of pre-transplant CV risks on renal allograft outcomes has not been reported.

Methods: We analyzed the graft outcomes of 2902 renal transplant recipients who were enrolled in a multi-center cohort from 1997 to 2012. We calculated pre-transplant CV risk scores by the Framingham risk model using age, sex, total cholesterol levels, smoking and a history of hypertension. Cox proportional hazard models were used to assess hazard ratios (HRs) with and without competing risks of post-transplant CV deaths, adjusting for risk factors of allograft failure including recurrence of glomerulonephritis and acute rejection.

Results: Hypertension and vascular disease (a composite of ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) were noted in 84.1% and 6.5% of the patients, respectively. During a median 6.4 years of follow-up, 122 (4.2%) patients died and 286 (9.9%) patients developed allograft failure. In multivariable-adjusted models, pre-transplant vascular disease was associated with increased risk of renal allograft failure (HR 2.43; 95% confidence interval [CI] 1.58-3.71). The HR for renal allograft failure comparing the highest with the lowest tertiles of pre-transplant CV risk scores was 1.49 (95% CI 1.11-2.00). In competing risk models, the HR of pre-transplant vascular disease was 2.01 (95% CI 1.0-3.36) and the HR for renal allograft failure comparing the highest with the lowest tertiles of pre-transplant CV risk scores was 1.44 (95% CI 1.05-1.98).

Conclusions: Both pre-transplant CV risk and vascular disease are independently associated with renal allograft failure in this multi-center prospective study. Pre-transplant CV risk assessment could be useful to predict renal allograft failure.

FR-PO1012
Blood Pressure (BP) Control in Kidney Transplant Recipients: A Single Centre Experience

Kristin Vibeke Vejheg, Jacqueline C. Nevols, Panagiotis Chondrogiannis, Amanda Jane Laird, Irene Synodinou, Doreen Zhu, Katherine A. Alington, Nichola Dawn Pugh, Chun ying Ung, Gopalakrishnan Venkat-Raman, Wexsex Kidney Unit, Portsmouth Hospitals NHS Trust, Portsmouth, United Kingdom.

Background: Cardiovascular disease is the leading cause of death among kidney transplant recipients (KTRs), however there remains uncertainty regarding optimal BP targets. Current UKRA, KDIGO and KDQI guidelines advocate BP control to 130/80 in KTRs. UKRA/KDIGO advocate tighter control (125/70) in proteinuric KTRs. We examined BP control and proteinuria in all KTRs under longterm follow up at one centre, and adherence to these recommendations.

Methods: As of 1 March 2015, 839 KTRs were attending for regular clinical review (excluding recent KTRs<1yr). We performed a retrospective database review of BP, proteinuria, renal function and antihypertensive use.

Results: The cohort was 60% male with mean allograft age 10±0.28 years. Mean decline in eGFR was 0.83ml/min/m² per year (p<0.0004). Mean SBP was 134±5.65, DBP 79±1.37. 48% had SBP<130, 62% DBP<80, 39% both. 76% received at least 1 antihypertensive, 42% 2-3, 4% 4-24 agents. Only 9% had PCR measured. In those with PCR, 50%, 19% had treated to 125/75. Dipstick proteinuria was recorded in 58% and showed a significant association with SBP (p=0.01). There were significant correlations between reducing eGFR and increasing PCR (R²=0.11, p<0.0001), and between PCR and ACE/ARB use (p=0.0002). There was no correlation between CNI level and BP (CyA p=0.88, FK506 p=0.49). There was a significant stepwise decrease in renal function (scGFR p=0.005, eGFR p=0.01) and increase in dipstick proteinuria (p=0.03) when data were analysed in groups <70, 70-140 and >140. In terms of DBP, the stepwise decrease in renal function remained (scGFR p=0.01, eGFR p=0.0001) when data were analysed in groups >70, 70-90 and >90. DBP>90 had the most significant impact on eGFR. DBP was not associated with proteinuria.

Conclusions: The optimal BP target remains uncertain. Adherence to current guidelines is reasonable in our unit but could be improved. This study again demonstrates that SBP is the key risk factor for proteinuria, however increases in DBP >90 were most strongly associated with graft dysfunction.

FR-PO1013
Dobutamine Stress Echocardiography (DSE) Significantly Reduces the Need for Coronary Angiography in Renal Transplant Recipients

Robin Raman, Maria Ventura, Sami Firoozy, Juan Carlos Kaski, Rajan Sharma, Debashis Banerjee. Renal and Cardiology Unit, St. Georges Univ Hospitals NHS Foundation Trust, United Kingdom.

Background: There is significant controversy regarding optimal cardiac workup strategy for kidney transplantation. Some centres perform coronary angiograms (CA) in all patients whereas others have adopted a tailored approach using non-invasive techniques such as Exercise Tolerance Testing (ETT) and ischaemia assessment with cardiac imaging. This study examines the role risk stratification and DSE for cardiac workup in this patient group.

Methods: We analysed data on patients referred between 1/2/2012 and 31/12/2014 who were risk stratified and investigated according to the protocol (figure 1).

Results: Of 233 patients referred 92 were high risk and went on to have DSE. All other patients underwent echocardiography with/without ETT (35 ETT, 122 echocardiography and 33 CA). 16 patients had CV events, but none were perioperative. Overall event rate was 4% per year. 11 of 92 patients who had DSE had events. 11 of 33 patients who had CA event. 28 of 92 patients had a positive DSE (i.e. suggestive of myocardial ischemia) and of these 23 went on to CA. 6 of 28 patients with a positive DSE and 5 of 64 with a negative DSE had an event (figure 2, log rank p=0.1). 25 of 33 patients had evidence of coronary artery disease (CAD) at CA of which 13 received coronary artery stents. There was no significant difference between those with significant (>50% stenosis) CAD on CA who had events (8 of 21 patients) compared to those without significant (<50% stenosis) CAD who had events (3 of 12) (log rank p = 0.7). 6 patients with significant CAD who had PCI had events. 35 patients underwent ETT, 4 had CA following positive ETT. One patient with negative ETT had an event.

Conclusions: A careful risk stratification and using DSE decreases the need for CA and achieves very low event rates.

FR-PO1014
Levels of Indoxyl Sulfate in Kidney Transplant Patients, and the Relationship with Hard Outcomes

Sophie Liabeuf, 1 Lucie Desjardins, 1 Ziad Massy, 1 François Brazier, 1 Dimitri Titeca Beauport, 1 Monar Diosa, 1 Griet Lriel, 1 Raymond C. Chen, 1 Caroli, 1 Maite Jaureguy, 1 Gabriel Choukroun, 1 1Nephrology, Amiens; 2Nephrology, Ambrose Pare; 3Nephrology, Gent.

Background: Kidney transplant recipients are at greater risk of cardiovascular disease (CVD). Indoxyl sulfate (IS) is a protein-bound uremic toxin that is known to be associated with the risk of CVD and mortality in both pre-dialysis and dialysis patients. Data on levels of protein-bound uremic toxins in kidney transplant patients are scarce. The objective
of the present study was to evaluate the levels of IS in kidney transplant patients and their relationship with biochemical parameters and hard outcomes (including mortality, cardiovascular (CV) events and graft loss).

Methods: In 311 consecutive kidney transplant patients, total and free IS levels were measured immediately before transplantation (T0) and then 1 month (M1) and 12 months (M12) afterwards. In a case-controlled sub-study (n=90), IS levels in transplant patients were compared with those in non-transplant patients with chronic kidney disease matched for age, and estimated glomerular filtration rate (eGFR). Over a mean ± standard deviation follow-up period of 113 ± 29 months, 55 deaths, 70 CV events and 71 graft losses were recorded.

Results: We observed a rapid, consistent, significant decrease in IS levels after kidney transplantation. Majority of IS levels were below or near the normal value at M1 and M12. We did not observe a correlation between IS levels and eGFR at M1 and M12. Total and free IS levels at T0 were significantly higher in non-transplant patients (0.34±0.23 mg/dl and 0.04±0.07 mg/dl, respectively) than in transplant patients (0.21±0.17 mg/dl and 0.01±0.01 mg/dl; p=0.003 and <0.0001 respectively), despite having similar eGFRs. Lastly, IS levels were not associated with overall mortality, CV events or graft loss at T0, M1 or M12.

Conclusions: Total and free IS levels were significantly lower in transplant recipients than in non-recipients matched for age, gender and renal function - suggesting that kidney transplantation protects against an increase in IS levels. Importantly, serum IS levels were not associated with hard outcomes at any of the three time points.

FR-PO1015
Identification of Metabolic and Cardiovascular Risk in Pediatric Kidney Transplant Recipients: Body Mass Index, Waist Circumference, or Waist-to-Height ratio?


Background: In the general population, abdominal obesity is more closely associated with metabolic and cardiovascular (CV) risk than BMI. The ideal measure of obesity to identify risk in pediatric kidney transplant (Tx) recipients, who have improved growth and altered body composition, has not been established. In this prospective study we compared ability of BMI, Waist Circumference (WC), and Waist-to-Height ratio (WHtR) to identify metabolic and CV risk in pediatric kidney Tx recipients.

Methods: Kidney Tx recipients 3-20 years old and 0-30 months post-Tx had WC, BMI, WHtR, blood pressure (BP), fasting lipids, leptin, HbA1c%, standard and speckle echocardiogram and carotid intima-media thickness (CIMT) measured. Patients were classified as obese or lean by 3 methods: WC (ATP cut-point males=94th%ile females=84 th%ile), WHtR (CDC cut-point=0.539), and BMI (295th%). Logistic regression determined associations of groups with metabolic and CV factors.

Results: The study group comprised of 33 Tx recipients, age 13.6±0.3 years. Prevalence of obesity by BMI, WC, and WHtR was 21.2%, 33.3%, and 48.5%. Prevalence of hyperglycemia (HbA1c) was 24.2%, high LDL 15.2%, low HDL 57.5%, high leptin 39.3%, high BMI 12.1%, left ventricular hypertrophy (LVH) 30.3%, hypertension (HTN) 69.6%, and high CIMT 44.8%. In all groups (WHtR, WC, and BMI), obese children were more likely than lean to have HTN (OR 4.5, 95% CI: 2.2, 9.4, p<0.001), LVH (OR 5.4, 95% CI: 7.4, 8.8, p<0.001), and high leptin (OR 19.1, 9.3, 7.3, p<0.001). Obese children in WHtR and WC groups, but not BMI group, had greater chance of high TG (OR 4.3, 9.2, p<0.001), high CIMT (OR 2.0, 9.2, p<0.05), and impaired myocardial strain (OR 1.2, 1.1, p=0.01). Five patients with short stature (height z-score 2.56) and CV risk factors (3.01±0.5 factors/patient) were not identified as obese by WC criteria (height z-score -2.08, p<0.003).

Conclusions: WC and WHtR are more effective than BMI for detecting metabolic and CV risk amongst pediatric Tx recipients. WC may underestimate prevalence of obesity in children of short stature, and therefore WHtR may be a more sensitive method for CV risk amongst pediatric Tx recipients. WC may underestimate prevalence of obesity were not identified as obese by WC criteria (height z-0.08, p=0.003).

FR-PO1016
Knowledge About Benefits of Kidney Transplant: A Survey of Dialysis Patients

Naman Trivedi, Fareeha Khalil, Ming Wang, Eric Chang, Nasrollah Ghahramani. Pennsylvania State Univ College of Medicine.

Background: Kidney transplant (KT) is the treatment of choice for end stage renal disease (ESRD). Knowledge of dialysis patients about the benefits of KT is an important determinant of their active engagement in the decision making process. We studied factors associated with patients’ knowledge about benefits of KT.

Methods: We sent flyers to 1,283 dialysis units. Of 2536 interested participants fulfilling inclusion criteria, we randomly selected and invited 1400 to complete the questionnaire. Independent predictors of knowledge about KT were age, gender, education, years on dialysis, the number of years on the transplant waiting list, and religion. We performed logistic regression to estimate the odds ratios and 95% confidence intervals of factors for predicting KT knowledge. Multivariate analysis was performed to determine factors associated with KT knowledge after adjusting for confounders.

Results: 673 participants responded to questions about overall survival benefit of KT (correct response: 92%), benefits of KT for diabetes patients (correct: 46%), for patients > 60 (correct: 29%) and for patients transplanted pre-emptively (correct: 17%). Receiving 3 or more modes of education about KT was associated with higher likelihood of correct response to questions about overall survival benefit of KT (OR: 2.19; CI: 1.50 to 3.20), survival benefit of KT for diabetics (OR: 2.08; CI: 1.39 to 3.01) and patients transplanted pre-emptively (OR: 1.67; CI: 1.06 to 2.64). White race was associated with higher likelihood of correct response to questions about overall survival benefit of KT (OR: 1.59; CI: 1.11 to 2.28) and the benefit of KT for patients > 60 (OR: 1.54; CI: 1.07 to 2.21). Age > 60 was associated with lower likelihood of correct response to the question about overall survival benefit of KT (OR:0.65; CI:0.45 to 0.94), benefits of KT for diabetics (OR:0.54; CI:0.38 to 0.77), and for patients > 60 (OR:0.64; CI:0.44 to 0.93). Patients on dialysis > 5 years were less likely to be aware of the benefit of KT for diabetics (OR:0.68; CI:0.48 to 0.98).

Conclusions: Dialysis patients’ knowledge about survival benefits of KT is rather limited. The most significant modifiable contributor to improvement in knowledge is diversity of modes of education about KT. Other factors include race, age and number of years on dialysis.

FR-PO1017
Pretransplant HbA1c Predicts New-Onset Diabetes After Transplantation Among Renal Transplant Recipients

Jung-Im Shin, Mari Palta, Arjag Djamali, Brad C. Astor. Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: New-onset diabetes after transplantation (NODAT) is a common complication among renal transplant recipients and is associated with a higher risk of cardiovascular events and poorer graft and patient survival. The association of pretransplant HbA1c with NODAT remains unclear. Identifying recipients at greatest risk of NODAT may help guide monitoring and treatment strategies to prevent or delay the onset of NODAT.

Methods: We assessed the association between pretransplant HbA1c and NODAT in 1522 non-diabetic recipients using data from the United States Renal Data System (USRDS) from 2004-2011. Cox proportional hazards models adjusted for demographics, cause of ESRD, year of transplantation, number of prior transplants, duration of pretransplant dialysis, comorbidities, lipid levels, hemoglobin level, body mass index, HCV and CMV serostatus, donor type and age, HLA mismatch, and posttransplant steroid and tacrolimus usage.

Results: Median HbA1c was 5.4% and 531 (34.9%) patients had HbA1c ≥ 5.7% (i.e., prediabetes) A total of 404 (26.5%) patients developed NODAT during a median follow-up of 1.7 years. Pretransplant HbA1c was associated with the risk of NODAT in a non-linear fashion. The adjusted hazard ratio (HR) associated with 1% higher pretransplant HbA1c was 0.94 (95% confidence interval [CI]: 0.62, 1.42) for HbA1c lower than 5.4% and 1.87 (95% CI: 1.30, 2.68) for HbA1c higher than 5.4%.

Conclusions: Pretransplant HbA1c is independently associated with the risk of NODAT among renal transplant recipients. A continuous relationship between pretransplant HbA1c and the risk of NODAT suggests that greater risk starts at levels below the standard threshold for prediabetes.
Results: Mathematically (assuming average weights), the Cockcroft-Gault equation always yields higher numeric values compared with the MDRD and CKD-EPI equations. When applied to the three actual patient cohorts, Cockcroft-Gault consistently disadvantaged patients, delaying average time to waitlist qualification by 1 to 2 years.

Conclusions: This study identified a potential source of significant inequity (on the order of 1-2 years) in wait-time accrual for kidney transplantation that stems from imprecise rules for waitlist qualification. The OPTN may need to revise the language in their kidney transplantation policies so that consistent methods to assess renal function are adopted and patients are not inadvertently disadvantaged.

Funding: NIDDK Support

FR-PO1019

New Onset Diabetes Has Unfavorable Effect on Patient but Not on Allograft Survival Thomas Diehnemann,1,2 Naohiko Fujii,1,2 Roy D. Bloom,1,2 Harold I. Feldman,1,2 Yimei Li.2

Background: New onset diabetes after transplantation (NODAT) has been linked to higher rates of graft loss and shorter patient survival. More recent awareness, recent awareness, and changes in immunosuppression may have modified this association.

Methods: Retrospective single center analysis of 1427 (age=18) first time renal transplant recipients (KTR) without pre-transplant (Txp) diabetes. Patients with <1 year of follow up and those with allograft failure in the first year post-Txp were excluded. NODAT was defined as prescription of a glucose lowering medication 1 year after Txp. Cox models adjusted for mult. potential confounders were used to examine the relationship of NODAT with allograft and patient survival.

Results: The incidence of NODAT was 16.1%. Median follow up was 5.9 years (IQR3.5-9.2) for allograft and 6.3 (IQR3.8-9.8) for patient survival. Age, BMI, non-white race and HCV were independently associated with NODAT (all p<0.01). Compared with KTRs without DM NODAT was associated with an increased risk of overall graft failure (aHR1.59, CI1.00–2.41 p=0.49), but not for death censored graft survival (DCGS) (aHR1.12, CI0.86–1.46 p=0.49). Compared to those with NODAT, outcomes were not detectably different over time (p=0.25 for DCGS).

Conclusions: In this cohort of KTRs NODAT had no impact on graft survival but was independently associated with reduced overall survival.

FR-PO1020

Frequency of Hospital Readmission Post Kidney Transplantation Essy Mozaffari,1 Jay Lin,2 Melissa Linghour-Smith.2 ‘Chimerix Inc., Mendham, NJ; ‘Novosys Health, Green Brook, NJ.

Background: Early hospital readmission following kidney transplantation has been identified to be a strong predictor of adverse sequelae that can have significant clinical and economic implications. Our goal was to quantify the frequency of hospital readmissions post kidney transplantation, as well as the reasons for the readmissions.

Methods: Patients who received a kidney transplant between Jan 2009 and Sept 2013 were identified from the Premier Hospital database by ICD-9-CM code. The first year post-transplant was excluded. NODAT was defined as prescription of a glucose lowering medication 1 year after Txp. Cox models adjusted for mult. potential confounders were used to examine the relationship of NODAT with allograft and patient survival.

Results: Among the readmissions related to vital infections, the majority were related to CMV (79%). Readmission of patients with high severity APR-DRG levels of 3 (major) and 4 (extreme) at 30% and 9%, respectively (severity of illness level rated 1-4: minor, moderate, major, and extreme).

Conclusions: Over 4 in 10 of the kidney transplant recipients in this study were rehospitalized post transplantation. A significant number of the readmissions occurred in the first month post-transplant and the majority were within the first three months; almost 4 in 10 readmissions were classified as major or extreme severity level. Among hospital readmissions, more than half of them were related to an opportunistic or viral infection, underscoring unmet needs for the prevention of these infections.

Funding: Pharmaceutical Company Support - Chimerix Inc.

FR-PO1021

Role of Non-Invasive Cardiac Stress Studies During Assessment for Kidney Transplantation in Pre-Dialysis Recipients Talvinder S. Bhoegal, Simon James Gray, Patrick Hamilton, Durga A.K. Kamigichlera. Manchester Inst of Nephrology & Transplantation, United Kingdom.

Background: Non-invasive cardiac stress studies (NISS) are routinely undertaken during listing of patients for kidney transplantation. Although guidelines recommend NISS in high risk patients based on studies reported on patients on RRT. However role of NISS in pre-dialysis population is unknown. We analysed the role of NISS in listing process and impact on longer term outcomes.

Methods: Retrospective study of all patients undergoing assessment for kidney transplantation at our centre between 2009 and 2014. 695 patients were assessed, including 397 who were pre-dialysis (naïve to RRT).

Results: 306 (77.1%) patients underwent NISS (98% were myocardial perfusion studies). Baseline and outcomes during follow-up are below.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>No NISS</th>
<th>Normal NISS</th>
<th>Abnormal NISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>225</td>
<td>81</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline % or Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Any vascular disease</td>
</tr>
</tbody>
</table>

Follow up

<table>
<thead>
<tr>
<th>Follow up (in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

Death

| 14       | 11 |

Conclusions: In this cohort of KTRs NODAT had no impact on graft survival but was independently associated with reduced overall survival.

Only 3 patients with abnormal NISS (1% of all who had NISS) had flow limiting lesions, needing interventions (2CABG and 1PCI). At last follow up, compared to those with normal NISS, patients with abnormal studies a) were less likely to be listed for kidney transplantation, b) had increased cardiovascular events (p=0.01). But there was no significant difference in patient survival.
Conclusions: Our study illustrates lack of benefit of non-invasive myocardial perfusion studies in kidney transplant candidates in identifying early disease during pre-transplant assessment in pre-diabetes patients. Better risk stratification strategies are needed to inform assessment of kidney transplantation.

FR-PO1022
Longitudinal Association of Recipient Nonmuscle Myosin IIA Gene rs5756168 with Transplanted Kidney Doppler Ultrasound Blood Flow Indices
Joanna Pazik,1 Ewa Nowacka-Cieciera,2 Zbigniew Lewandowski,2 Monika Oldak,2 Dominika Ozzi7to,2 Magdalena Durlik.1 1Transplantation Medicine and Nephrology, Medical Univ of Warsaw, Warsaw, Poland; 2Pathology, Medical Univ of Warsaw, Warsaw, Poland; 3Histology and Embryology, Medical Univ of Warsaw, Warsaw, Poland; 4Inst of Physiology and Pathology of Hearing, Warsaw, Poland.

Background: MYH9 gene polymorphisms associate with nephron injury in hypertensive nephrosclerosis and FSGS. We have shown the association of rs5756168 with transplanted kidney eGFR (ATC 2015). MYH9 polymorphisms correlate with cerebrovascular blood flows. In transplanted kidneys resistance and pulsatility indices predict graft function.

Methods: The study aims at evaluating the association of donor/recipient MYH9 SNPs (rs3752462, rs11089788, rs5756168, rs136211 rs2397784) and transplanted kidney pulsatility (PI) and resistive (RI) indices. Recipients enrolled 2007–2012 with available donor/recipient DNA, kidney and transplanted kidney Doppler ultrasound (US) were included. For genotyping custom TaqMan genotyping assays were used. Mixed models were used to assess relations of SNPs and PI, RI values.

Results: Genotyping was performed in 295 kidney recipients and their donors, in 202 at least one US was done. In the longitudinal observation between first day and 2 years after engraftment, recipients carrying two T alleles in rs5756168 showed significantly different PI indices in opposite to allele C carriers, p = 0.04, for RI the differences did not reach statistical significance (p = 0.14). In two-factor analyses the effects of rs5756168 was maintained in first transplants for RI (p = 0.02) and PI (p = 0.02), in recipients with TTI >2 (p = 0.03 and 0.07, respectively), with grafts from donors >55 years old (p = 0.05 for PI only), with panel reactive antibodies <20% (p = 0.01 and 0.04 for PI and RI), patients on immunosuppression without induction (p = 0.07 for PI only) and on tacrolimus treatment (p = 0.05 for PI only).

Conclusions: Identified association of transplanted kidney blood flow parameters and MYH9 polymorphism additionally confirms MYH9 effect on graft functioning shown in our previous study cited above. The study supported by grant from National Science Center NN4022668/40.

Funding: Government Support - Non-U.S.

FR-PO1023
Determinants of Hepcidin, the Key Regulator of Iron Homeostasis, in Renal Transplant Recipients
Michele F. Pisenga,1 Stefan P. Berger,1 Robin P.F. Dullaart,2 Aiko P.J. De Vries,2 Stephan J.L. Bakker,1 Carlo A. Gaillard.1 1Internal Medicine, UMC; 2Internal Medicine, UMC.

Background: Hepcidin is synthesized in the liver and secreted into the circulation. Circulating concentrations may be influenced by body iron availability, inflammation, insulin resistance and tissue hypoxia. Moreover, hepcidin is a small 2.8 kD molecule. Therefore, renal clearance may be an important additional determinant of circulating hepcidin. We aimed to investigate whether markers of iron availability (ferritin), inflammation (C-reactive protein (CRP)), insulin sensitivity (fasting insulin), tissue hypoxia (erythropoietin) and renal clearance may be an important additional determinant of circulating hepcidin. We aimed to investigate whether markers of iron availability (ferritin), inflammation (C-reactive protein (CRP)), insulin sensitivity (fasting insulin), tissue hypoxia (erythropoietin) and renal clearance may be an important additional determinant of circulating hepcidin.

Methods: We included 561 RTR (age 51±12 years; 55% males at 7.8±6.4 years after Tx). Mean hemoglobin (Hb) was 8.6 ±1.0 mmol/l. Median [IQR] serum hepcidin was 3.2 ng/ml (1.3–6.6 ng/ml). Univariable associations between serum hepcidin concentrations and donors or recipients sex, recipients body mass index (BMI), estimated glomerular filtration rate (eGFR) were determined. P-values for inclusion and exclusion were determined when adding variables to the model. To assess independent determinants of serum hepcidin, we used a multivariable linear regression model.

Results: We included 561 RTR (age 51±12 years; 55% males at 7.8±6.4 years after Tx). Mean hemoglobin (Hb) was 8.6 ±1.0 mmol/l. Median [IQR] serum hepcidin was 3.2 ng/ml (1.3–6.6 ng/ml). We found that donors or recipients sex, recipients BMI, eGFR were determinants of serum hepcidin in a total model R2 = 0.69. After adjusting for BMI and eGFR, significant independent determinants of serum hepcidin were donors or recipients BMI (β = 0.09, p = 0.001), donors or recipients eGFR (β = −0.12, p = 0.001), recipients BMI (β = 0.16, p = 0.001), recipients BMI (β = 0.16, p = 0.001), recipients BMI (β = 0.16, p = 0.001), and recipients BMI (β = 0.16, p = 0.001). The association of serum hepcidin concentrations in RTR can be attributed to variation in iron status, inflammation, insulin sensitivity and tissue hypoxia reflected by erythropoietin, rather than to variation in renal clearance.

Conclusions: Despite large variation in eGFR, fifty-three percent of the variation in serum hepcidin concentrations in RTR can be attributed to variation in iron status, inflammation, insulin sensitivity and tissue hypoxia reflected by erythropoietin, rather than to variation in renal clearance.

FR-PO1024
Associations of Serum Soluble α-Klotho, Fibroblast Growth Factor 23, and 25 (OH) Vitamin D with Kidney Function and Left Ventricular Hypertrophy in Japanese Kidney Transplant Recipients
Makoto Tsujita,1 Shoichi Matuyama,1 1Transplant Surgery, Nagoya Daini Red Cross Hospital, Japan; 2Nephrology, Nagoya Univ School of Medicine, Japan.

Background: Determination of kidney function and left ventricular hypertrophy (LVH) is crucial for kidney transplant recipients. Any marker for predicting kidney function and LVH is needed to prevent complications.

Methods: This was a retrospective cohort study. Forty-seven consecutive patients were enrolled in this study at Nagoya Daini Red Cross Hospital in 2011.

Table 1. Study population characteristics (n = 47)

<table>
<thead>
<tr>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Gender (%)</td>
</tr>
<tr>
<td>D/O/N</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
</tr>
<tr>
<td>Phosphate, mg/dl</td>
</tr>
<tr>
<td>Intact parathyroid hormones, pg/ml</td>
</tr>
<tr>
<td>T3Urine, mg/dl</td>
</tr>
<tr>
<td>Low density Lipoprotein Cholesterol, mg/dl</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
</tr>
<tr>
<td>C-reactive protein, µg/dl</td>
</tr>
<tr>
<td>Soluble eKlotho, pg/ml</td>
</tr>
<tr>
<td>Fibroblast growth factor, pg/ml</td>
</tr>
<tr>
<td>25(OH)D vitamin D, ng/ml</td>
</tr>
<tr>
<td>eFGF23, pg/ml</td>
</tr>
<tr>
<td>FGF23, pg/ml</td>
</tr>
<tr>
<td>LVMI 1 year, g/m²</td>
</tr>
<tr>
<td>LVMI 5 year, g/m²</td>
</tr>
<tr>
<td>Use of Copeptine, %</td>
</tr>
<tr>
<td>Use of acetylsalicylic acid, %</td>
</tr>
<tr>
<td>Use of ARB, %</td>
</tr>
<tr>
<td>Use of statin, %</td>
</tr>
</tbody>
</table>

Conclusions: Serum soluble α-Klotho may be a good marker for kidney function and intact FGF23 for LVH in Japanese kidney transplant recipients.

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

Underline represents presenting author.
Conclusion: Most study participants who received a KT were non-frait, but the proportion of black KT recipients was small despite blacks' lower observed risk for frailty compared with whites. Closer alignment of frailty status with support for KT access may have implications for reducing racial disparity in KT rates.

Funding: NIDDK Support

FR-PO1026
Circulating Inflammatory Cell Subsets Are Associated with Cardiac Function in Renal Transplant Recipients Jill Neale,1 Danielle Richelh-Potts,1 Maurice Dungey,1 Patrick Highton,1 N. Martin,2 Nicollette C. Bishop,2 Alice C. Smith,1 'Leicester Kidney Exercise Team, Univ of Leicester, United Kingdom; 2School of Sport, Health and Exercise Sciences, Loughborough Univ, United Kingdom.

Background: Cardiovascular (CV) disease is a major cause of mortality and morbidity in renal transplant recipients (RTRs). Systemic and vascular inflammation is paradoxically common despite immunosuppression and is an important non-traditional CV risk factor. Monocytes are heterogenous: the intermediate phenotype (CD14++CD16+) is particularly pro-atherogenic and pro-inflammatory compared to the classical phenotype (CD14++CD16-). Regulatory T-cells (TRegs) maintain peripheral tolerance and minimise tissue damage. This study aimed to explore the association of circulating inflammatory cell subsets with cardiac function in RTRs.

Methods: 18 stable RTRs (Mean age 55 years, 61% male) and 5 healthy controls participated. Blood monocytes and T cells were analysed by flow cytometry, and cardiac hemodynamic function measured by bioimpedance (NICOM).

Results: Circulating pro-anti-inflammatory cell subsets differed significantly in RTRs and controls. Mean % (SEM) intermediate monocytes was higher in RTRs (7.2±8.8) vs controls (3.2±8.5), p=0.01, while classical monocytes and TRegs were lower in RTRs (83.2±13) vs (88.9±1.6), p=0.03 and 28.0±2 vs 5.0±1, p=0.001 respectively. In RTRs, % intermediate monocytes was inversely correlated with stroke volume (SV: r=-0.48, p=0.05) and cardiac output (CO: r=-0.52, p=0.03) and positively correlated with total peripheral resistance (TPR: r=0.50, p=0.04), while the opposite was seen with % classical monocytes (SV: r=0.56, p=0.02; CO r=0.62, p=0.006; TPR r=-0.54, p=0.02).

Conclusions: Our results reveal a significant bias towards pro-inflammatory circulating leucocyte subsets in RTRs (increased intermediate monocytes, reduced classical monocytes and TRegs), which likely promotes an atherogenic environment. Furthermore, the observed significant correlations between pro- and anti-inflammatory monocyte subsets and indices of cardiac function strongly support an important pathogenic role for these cell subsets, which represent a potential therapeutic target in this vulnerable population.

Funding: Private Foundation Support

FR-PO1027
Iron Deficiency Is Associated with Mortality Independent of Anemia in Renal Transplant Recipients Michele F. Eisenberg,1 Stefan P. Berger,2 Jenny E. Kootstra-Ros,2 Else van den Berg,1 Jer gan Navis,3 Peter Van der meer,3 Stephan J.L. Bakker,1 Carlo A. Gaillard,1 'Nephrology, 'Clinical Chemistry, 'Cardiology, UMCG.

Background: Anemia and iron deficiency (ID) are highly prevalent in renal transplant patients (RTR). Anemia is associated with poor outcome, but the role of ID is unknown. Therefore, we aimed to investigate the association of ID, irrespective of anemia, with all-cause mortality in RTR.

Methods: In a previously defined cohort of RTR, with hemoglobin data available, we additionally assessed serum iron, transferrin and ferritin. ID was defined as transferrin saturation (TSAT)=20% and ferritin <300 ng/mL. Anemia was defined as Hb<13 g/dL (M) or <12 g/dL (F). Cox regression analyses were used to investigate prospective associations with all-cause mortality.

Results: We included 701 RTR (age 51±12 yrs; 56% men, 6.0 [2.6-11.6] yrs post-transplant). Baseline concentration of serum KYN was 1.8 [1.4-2.2] μmol/L, that of TRP was 40.0 [34.5-46.0] μmol/L, and KYN/TRP was 44.3 [35.0-57.9] μmol/mol. In multivariable linear regression analyses, KYN/TRP was positively associated with proteinuria (β=0.17, P<0.001) and waist circumference (β=0.12, P<0.001), and inversely with eGFR (β=0.54, P<0.001) and HDL-c (β=-0.14, P<0.001). During follow-up for 6.9 [6.1-7.4] years, 51 (9.2%) RTR developed GF. In multivariable Cox-regression analyses, KYN/TRP was positively associated with GF (age, sex, eGFR, and proteinuria adjusted HR 3.6 [95% CI 1.3-9.9], P=0.01). Further adjustment for waist circumference and HDL-c did not materially change this association (HR 3.1 [95% CI 1.3-8.9], P=0.02).

Conclusions: IDO activity, as measured by KYN/trypophan (TRP) were measured with LC-MS/MS; KYN/TRP is a widely accepted measure of IDO activity.

Funding: NIDDK Support

FR-PO1028
Indoleamine 2,3-Dioxygenase Activity and Late Graft Failure After Kidney Transplantation Laura V. de Vries,1 Claude P. Van der Ley,2 Casper F.M. Franssen,1 Gerjan Navis,2 Stephan J.L. Bakker,2 Id o Peter Kema,2 'Dept of Nephrology, UMCG, Netherlands; 'Dept of Laboratory Medicine, UMCG, Netherlands.

Background: Long-term graft survival after kidney transplantation remains a major clinical problem. Therefore, markers that allow for early identification of patients at risk for late graft failure (LGF) are urgently needed. Indoleamine 2,3-dioxygenase (IDO) catalyzes tryptophan along the kynurenine pathway. Recent studies found IDO activity associated with occurrence of acute rejection and renal function decline shortly post-transplant. We hypothesized that IDO activity could also be a marker for LGF after kidney transplantation.

Methods: We prospectively included outpatient renal transplant recipients (RTR) with a functioning graft >1 yr, between 2001-2003. Follow-up was recorded until May 2009. Death-censored GF was defined as return to dialysis or re-transplantation. Serum kynurene (KYN) and tryptophan (TRP) were measured with LC-MS/MS; KYN/TRP is a widely accepted measure of IDO activity.

Results: We studied 562 RTR (age 51±12 yrs, 56% men, 6.0 [2.6-11.6] yrs post-transplant). Baseline concentration of serum KYN was 1.8 [1.4-2.2] μmol/L, that of TRP was 40.0 [34.5-46.0] μmol/L, and KYN/TRP was 44.3 [35.0-57.9] μmol/mol. In multivariable linear regression analyses, KYN/TRP was positively associated with proteinuria (β=0.17, P<0.001) and waist circumference (β=0.12, P<0.001), and inversely with eGFR (β=0.54, P<0.001) and HDL-c (β=-0.14, P<0.001). During follow-up for 6.9 [6.1-7.4] years, 51 (9.2%) RTR developed GF. In multivariable Cox-regression analyses, KYN/TRP was positively associated with GF (age, sex, eGFR, and proteinuria adjusted HR 3.6 [95% CI 1.3-9.9], P=0.01). Further adjustment for waist circumference and HDL-c did not materially change this association (HR 3.1 [95% CI 1.3-8.9], P=0.02).

Conclusions: IDO activity, as measured by KYN/TRP, is cross-sectionally associated with eGFR, proteinuria, waist circumference, and HDL-c. Prospectively, it is associated with increased risk for LGF after kidney transplantation. Increased IDO activity may not only be a marker for LGF, but also an interesting target for intervention to prevent decline of renal transplant function leading to LGF.

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FR-PO1029
The Significance of Preoperative Left Ventricular Diastolic Dysfunction and Left Atrial Enlargement on Clinical Outcomes in Kidney Transplantation Jin Ho Hwang,1 Jung Nam An,2 Jae Seok Yang,2 Curie Ahn,3 Chun Soo Lim,2 Yon Su Kim,2 Young hoon Kim,2 Jung Pyo Lee,3 'Internal Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea; 'Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Republic of Korea; 'Transplantation Center, Seoul National Univ Hospital, Seoul, Republic of Korea; 'Internal Medicine, Seoul National Univ College of Medicine, Seoul, Republic of Korea; 'Surgery, Asan Medical Center and Univ of Ulsan College of Medicine, Seoul, Republic of Korea.

Background: In spite of improved survival of kidney transplant (KT) recipients, cardiovascular mortality is the leading cause of death following KT. Echocardiography is commonly performed as a screening test to evaluate cardiac function before KT. However, there are only limited data on echocardiographic parameters to evaluate the effect of left ventricular diastolic dysfunction (LVDD) and left atrial enlargement (LAE) on the long term outcome in KT recipients.

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Methods: A total of 2,779 adult recipients who underwent pretransplant echocardiography from 1997 to 2012 were evaluated. We divided the patients into two groups by two different categories: LVDD grade 0-1 vs. 2-3, and LA size=38 mm vs. >38 mm. Post-KT fatal/non-fatal acute coronary syndrome (ACS), graft failure (GF), and all-cause mortality was evaluated.

Results: During a mean follow-up of 4.5 years, fatal/non-fatal ACS was occurred in 49 (1.8%) patients. A total of 231 (12.4%) patients experienced GF and 116 (6.2%) died. The recipients with LVDD grade 2-3 (P=0.005) and LAE (P=0.001) showed higher occurrence of fatal/non-fatal ACS after KT. Graft failure and all-cause mortality was not significantly different between the groups depending on both the LVVD grades and LAE. In a multivariate analysis, increased age (P<0.001), previous history of CV event (P=0.01) and LVDD of grade 2-3 (hazard ratio[HR]:2.98, 95% confidence interval[Ci]:1.535-5.787;P=0.001), and LAE (HR:1.052, 95% Ci:1.006-1.101;P=0.025) were associated with ACS. However, none of LVDD and LAE was significantly associated with mortality and GF in a multivariate analysis.

Conclusions: In patients of KT candidate, pretransplant LVDD and LAE were independently associated with high occurrence of ACS after KT.

FR-PO1030 Effect of Dietary Sodium Restriction on Blood Pressure and Urinary Protein Excretion in Renal Transplant Recipients on RAAS-Blockade Laura V. de Vries,1 Linn Charlotte Dobrowolski,2 C.T.P. (Paul) Krediet,2 Frederik J. Bemelman,3 Stephan J.L. Bakker,4 Gerjan Navis,1 1Dept of Nephrology, UMCU, Netherlands; 2Renal Transplant Unit, AMC, Netherlands.

Background: In CKD patients on RAAS-blockade, it is well established that dietary sodium restriction exerts renoprotection by reduction of blood pressure (BP) and by reduction of urinary protein excretion (UPE), which is partly independent of BP. In renal transplant recipients (RTR), the effect of sodium restriction is not well-documented. We therefore studied the effects of dietary sodium restriction on BP and UPE in RTR.

Methods: We performed a randomized, cross-over trial in stable outpatient RTR with creatinine clearance >30 ml/min, BP>120/80 mmHg, 24-hour UPE <1.5 g/day, and use of RAAS-blockade. Exposure consisted of a 6-week regular sodium (RS) diet (target: 150 mmol/24h) and 6-week low sodium (LS) diet (target 50 mmol/24h). End points were BP, UPE, urinary albumin excretion (UAE), and eGFR at the end of each diet period. Dietary compliance was assessed by 24h urinary sodium excretion.

Results: We randomized 23 RTR, of which 22 RTR (age 58±1 years, 50% men, eGFR 51±21 ml/min) completed the study. One patient dropped out, due to orthostatic complaints on the LS diet. Sodium intake was 156 [130-193] vs. 68 [55-86] mmol/24h on RS vs. LS respectively. One patient was excluded from BP analysis because of severe hypotension. At 1st and 12th mth, femoral Dual X-ray absorptiometry and vertebral column X-ray for assessment of bone mineral density were performed. Results showed a significant reduction of urinary protein excretion (UPE) and BP (SBP:140±14 vs. 129±12, P<0.0001, DBP:86±8 vs. 79±8, P=0.0001).

Conclusions: Dietary sodium restriction effectively reduces BP in stable RTR on RAAS-blockade, but, at variance with findings in CKD, has no material change in UPE, UAE and eGFR.

FR-PO1031 Individual Blood Calcification Propensity in a Cohort of Renal Transplant Patients Carlo M. Alfieri,1 Andreas Pasch,1 Anna Regalia,1 Maria Meneghini,1 Maria Teresa Gandolfo,1 Valentina Binda,1 Deborah Mattinzoli,1 Masami Ikehata,1 Piergiorgio Messa. 11Dept of Nephrology, UMCU, Netherlands; 2Renal Transplant Unit, AMC, Netherlands.

Background: Vascular calcifications and related cardiovascular disease have a strong impact in kidney transplant recipients (KTx). Calciprotein partitioning/maturating time (T50) is a new measure of individual blood calcification propensity. Our aim is to explore in a cohort of 410 KT recipients: 1) the levels of T50 and their modifications during the first year of KTx; 2) the relationship between T50 and routine clinical and biochemical parameters, 3) the relationship between T50 and mineral density (BMD) and aortic calcification (AC).

Methods: 70 KTx pts(M=38, Age:48±12 yrs), transplanted between 2005 and 2009 were recruited. Along with T50 evaluation, routine clinical and biochemical parameters and FGF-23,OPG, SHBG, acetate and 25(OH)-Vitamin D were tested at 1st, 6th and 12th mth after KTx. At 1st mth, serum intact PTH, serum Ca, P, albumin, creatinine, ionic Ca and phosphate and by dual energy X-ray absorptiometry and vertebral column X-ray for BMD(cm2/m) and AC (Kaputriala) evaluation were performed. T50 (min.) was determined using a Nephelometric nephelometer(BMG Labtech, Offenburg, Germany) in the laboratory of one of the authors.

T50 at 1st and 12th mth were of 243[72–283], 218[79-275] and 227[79-279] resp., with a reduction of T50 at the 12th mth of KTx(p=0.04). In a multivariate analysis, T50 was influenced by uric acid and fetuin-A (14th mth=0.02 and 0.001), by alkaline phosphatase, fetuin-A and 25-(OH)-Vitamin D (6th mth=p<0.01, p=0.001 and p=0.03 resp.), and by estimated glomerular filtration rate,body mass index and 25-(OH)-Vitamin D(12th mth=p<0.01, p=0.03 and 0.01 resp.). Both at baseline and at 12 mth of KTx a direct correlation between BMD and T50 was demonstrated (p=0.002-p=0.04 respectively).

Conclusions: The main results of our study are that 1)during the 1st year of KTx T50 does decrease significantly, and 2) has a strong and direct relation with Fetuin-A and 25OH vitamin-D both implicated in bone-vascular axis, T50 is associated with BMD but not of AC status.

FR-PO1032 Prediction of Acute Rejection in Kidney Transplant Recipients Using a Multicenter Cohort Kyung Don Yoo,1 Junhyug Noh,1 Junhong Lee,1 Dong Ki Kim,1 Chun Soo Lim,1 Young hoon Kim,1 Yon Su Kim,1 Gunhee Kim,2 Jung Pyo Lee.1 1Seoul National Univ College of Medicine; 2Seoul National Unives College of Engineering; 3Ulsan Unive College of Medicine.

Background: More than 20% of kidney transplant recipients (KTR) are likely to have rejection episode, which is associated with graft loss. However, the impact of risk factors on acute rejection has not been well clarified. Here, we aimed to build new prediction models through considering variables related to immunologic and non-immunologic factors using machine learning methods.

Methods: This multicenter cohort study included adult KTR admitted to 2 major experienced tertiary hospitals in Korea between 1997 and 2014. A total of 3,117 KTRs were enrolled. Biopsy-proven acute rejection (BPAR) of these recipients were investigated by the individual learners such as decision tree, logistic regression, and ensemble learners such as random forest.

Results: We analyzed 2,045 recipients’ records, with more than 50 attributes. Among them, we identified 39 independent attributes which could account for BPAR incidence for building our models. In the decision tree model for the prediction of BPAR after three years of KTx, HLA DR mismatch was found to be the most important predictor. In the case of HLA DR mismatch, donor specific antibody (+) predicted in 66.6% of BPAR incidence at three year after transplantation, and also posttransplant infection episode showed significant association with BPAR. In the case of HLA full matched, old age with heavy weighted recipient showed high probability of BPAR (71.4%). The final modeling represent AUC performance 0.670 (logistic regression) and 0.665 (random forest) in the BPAR prediction.

Conclusions: In this study, machine learning modeling could present an accurate and versatile tool for forecasting probability of having BPAR episode during the early years following the transplant.

FR-PO1033 Prediction of Long-Term Prognosis of the Kidney Transplantation Using Comorbidity Score Jae Yoon Park,1 Eunjin Bae,2 Soejoong Kim, Dong Ki Kim,1 Chun Soo Lim,1 Kwon Wook Joo,1 Yon Su Kim,1 Jung Pyo Lee.1 1Seoul National Univ College of Medicine; 2Seoul National Univ College of Engineering.

Background: Comorbidity assessment is important to the informed interpretation of kidney allograft outcomes. Weights assigned to comorbidities to predict survival may vary based on the type of index disease and advances in the management of the comorbidities. We developed a modified Charlson comorbidity index (CCI) in renal allograft recipients (mCCI-KT), thereby improving risk stratification for mortality.

Methods: A total of 3,765 recipients in multicenter cohort were included to develop comorbidity score. The weights of comorbidities per the CCI were recalibrated using a Cox proportional hazards model. The modified score was validated in an independent nationwide cohort (n=1,538).

Results: The Cox proportional hazards model revealed that peripheral vascular disease, mild liver disease, and diabetes with end-organ damage in the CCI significantly predicted mortality. Thus, the mCCI-KT included 3 comorbidities with recalibrated severity weights. In the validation cohort, both the CCI and the mCCI-KT were correlated with mortality. The mCCI-KT showed modest increases in C statistics compared with the CCI (0.565 versus 0.534, P=0.002).

Conclusions: The mCCI-KT stratifies the risk better for mortality in renal allograft recipients compared with the CCI, suggesting that it could be a preferred index for use in clinical practice.

FR-PO1034 Patient Uncertainty Regarding Kidney Transplantation Associated with Length of Dialysis prior to Transplant Evaluation Laura J. McPherson,1 Mohua Basu,1 Stephen O. Pastan,1 Sumit Mohan,2 Rachel E. Patzer.1 1Emory Univ, Atlanta, GA; 2Columbia Univ, New York, NY.

Background: End stage renal disease (ESRD) patients’ uncertainty about undergoing kidney transplantation (KTx) —i.e., decisional conflict—may be affected by cumulative time spent on dialysis prior to KTx evaluations. We aimed to investigate the association between time from dialysis start to KTx evaluations and decisional conflict.

Methods: In an ongoing clinical trial of study patients measuring the effectiveness of a shared decision tool at a single KTx center, ESRD patients were asked 10 questions assessing decisional conflict related to KTx, with possible scores ranging from 0 (none)
Haptoglobin and Long-Term Outcomes in Renal Transplant Recipients

Isidor Minovic, Ineke J. Riphagen, Else van den Berg, Jenny E. Kootstra, J.L. Bakker, Andy P. Levy, Johanna M. Geleijnse, Gerjan Navis, Stephan Haptoglobin (Hp) is a hepatocyte-derived protein that protects against oxidation by binding free hemoglobin (Hb). Being an acute-phase protein, Hp is upregulated by inflammation. We hypothesized that both low and high Hp are risk factors for all-cause mortality and graft failure in renal transplant recipients (RTR).

Methods: Hp was measured using a turbidimetric immunoassay in a well-characterized prospective RTR cohort. Cox regression analysis was used to assess the association of Hp with endpoints.

Results: We included 707 RTR (57% male, age 53±13 y, eGFR 49 ±18 ml/min/1.73m2) and 58% used a calcineurin inhibitor. Median Hp was 1.4 [IQR 1.0-1.8] g/L. Hp phenotype 1-1, 1-2, and 2-2 distribution was 18%, 50%, and 33% resp., with Hp levels of 1.7 [1.3-2.1], 1.4 [1.1-1.8] and 1.1 [0.9-1.7] g/L resp. (P<0.001). Among median 38 [32-46] months follow-up, 81 (12%) RTR died and 45 (6%) developed graft failure. Hp showed a U-shaped association with mortality (P=0.01, fig. 1), but not with graft failure (P=0.7). Accordingly, the lowest (<0.9 g/L) and highest (>1.6 g/L) quintiles of Hp levels were associated with mortality (HR 2.65 [95% CI 1.11-6.35] and 3.0 [3.0-1.41-7.72], resp.). Adjustment for sex, age, hsCRP, serum albumin, eGFR, BMI, Hba1C, LDL and Hp polymorphism did not materially influence the association of low Hp with mortality (HR 3.55 [1.42-8.84]). However, adjustment for hsCRP and serum albumin markedly weakened the association of high Hp with mortality (HR 2.06 [0.84-5.08]).

Conclusions: Low Hp is independently associated with mortality, but not graft failure, in RTR. High Hp was also associated with mortality, but this association largely depended on hsCRP and serum albumin.

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Pre-Transplantation Flow-Citometry Crossmatch Can Be a Predictor of Outcome when Donor-Specific Antibodies Are Present

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Background: Clinical relevance of pre-transplant (Tx) donor-specific antibodies (DSA) detected by single antigen beads (SAB) when pre-Tx CDC-AIH crossmatch (XM) is negative is still unclear. The aim of this study was to evaluate the importance of a positive flow-citometry-XM (FCXM) in patients with DSA over patient and graft survival.

Methods: Retrospective study, performed between Jan09 and Dec13 evaluating FCXM influence on antibody-mediated rejection (AMR) incidence, and over graft and patient survival. Biopsies were classified according to Banff’09 criteria and DSA by Luminex SAB.

Results: From 2009-2013, 1002 kidney transplants (Tx) were performed in our center. 261(26%) were sensitized (PRA>0%) and 87 (8.7%) presented pre-Tx DSA. 60 (69%) of them had FCXM performed with serum collected before transplantation: 22 (36%) positive and 38 (64%) negative. There was no difference between the highest DSA-MFI between Tx with positive or negative FCXM [FCXM+ = 5080 (1046-15360) vs FCXM- = 3120 (597-14400)], or between the sums of all DSA-MFI of each patient between these groups [FCXM+ = 2474 (597-51530) vs FCXM- = 2867 (974-89400)]. A significant difference between DSA-MFI was only found when DSA became negative: FCXM had a significantly higher incidence of AMBR than DSA+XFCXM-Tx [FCXM- = 12.54% (95% CI 9.3-23%); p = 0.024]. After a median follow-up of 34 mo, graft survival (GS) between Tx with positive and negative FCXM differed significantly (41% vs 92%; p < 0.001). Among FCXM+ patients, GS was not influenced by ABMR (p=0.256). However, among patients with AMBR, FCXM+ had worse graft survival than FCXM+ (25% vs FCXM- 90%; p 0.011). Patient survival did not differ between FCXM+ (82%) and FCXM- (95%) neither was affected by AMBR.

Conclusions: A positive pre-Tx FCXM is related to a higher incidence of AMBR in the first year after Tx and to worse graft survival, and did not influence patient survival.

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Pre-Transplant Mental Health Disorders and Non-Adherence and Post-Transplant Outcomes in Kidney Transplant Recipients

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Background: Mental health disorders (MH) and non-adherence (NA) have been associated with lower access to kidney transplantation (KT) and poorer clinical outcomes. We examined the relationship between history of MH problems, NA, and post-transplant outcomes (i.e., biopsy proven acute rejection: BPAR; death censored graft failure: DCGF; or loss of graft function: LGF).

Methods: This was a single-centre retrospective cohort study of adult patients transplanted at our KT program from July 1, 2004 and Dec 31, 2012, and followed up until June 30, 2014. Patients with complete information about pre-transplant MH problems or pre-transplant history of NA in their medical record (n=955) were included. We analyzed the contribution of co-morbidities and other covariates to the associations between MH and NA, and time to event (for BPAR, DCGF and DCGF) were explored using log rank analysis and Cox proportional hazards models.

Results: The mean (±SD) age was 50.5 (±13.4) years, 61% of patients were male and 24% had a history of diabetes. Twenty-two percent had a positive history of MH disorders and 11% had a history of NA. Fifteen percent of the patients had BPAR, 5.6% had DCGF and 13% had TGF (death or DCGF). Participants with a history of pre-transplant NA but not with history of MH had higher risk for BPAR (log rank test p = 0.049 and p=0.46 for NA and MH, respectively). This difference, however, was not significant after adjusting for socio-demographic characteristics, donor type and HLAmismatch: adjusted HR (95% CI) 1.36 (0.84-2.23) and 1.16 (0.77-1.75) for NA and MH, respectively. Neither the history of pre-transplant MH nor pre-transplant NA was associated with DCGF or TGF. These results remained qualitatively unchanged after multivariable adjustment : adjusted HR (95% CI) 1.81 (0.96-3.42) and 0.99 (0.58-1.70) for NA and MH, respectively.

Conclusions: A history of pre-transplant mental health disorders or non-adherence are not associated with poor post-transplant outcome in a select group of patients who are cleared for transplantation. Patients with such problems should have equal access to kidney transplantation compared to patients with no MH problems.

Funding: Government Support - Non-U.S.

HILA Profile and Short and Long Term Outcomes in African American Donors and Recipients

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Background: We have previously reported the apparent greater impact of HLA-matching on both early allograft events as well as graft survival in the United Network for Organ Sharing database (UNOS). Here, we specifically studied the influence of HLA-matching and mismatching on allograft outcomes among African American (AA) recipients and AA-donor organs in deceased donor kidney transplantation (DDKT).

Methods: We utilized data from the UNOS database (1995 – 2012), and analyzed 10 year death censored graft survival (DCGS), 1 year clinical acute rejection (1y-AR), and delayed graft function (DGF) using Cox-regression and logistic regression in a combined multivariable model including HLA-matching and mismatching adjusted for key covariates. We performed sensitivity analysis using a subgroup of DDKT patients after 2003 with less heterogeneous HLA nomenclature and employing bootstrap methodology.

Results: We had complete data (outcomes and predictors) for 96236 recipients (Age 49.23±15.13, 60.4% male). AA-recipients constituted 30.2% while AA-donor organs were used in 19% of recipients (n=18201). Only AA-donor organs were associated with DCGF and TGF. These results remained qualitatively unchanged after multivariable adjustment : adjusted HR (95% CI) 1.36 (0.84-2.23) and 1.16 (0.77-1.75) for NA and MH, respectively. The other history of pre-transplant MH nor pre-transplant NA was associated with DCGF or TGF. These results remained qualitatively unchanged after multivariable adjustment : adjusted HR (95% CI) 1.81 (0.96-3.42) and 0.99 (0.58-1.70) for NA and MH, respectively.

Conclusions: A history of pre-transplant mental health disorders or non-adherence are not associated with poor post-transplant outcome in a select group of patients who are cleared for transplantation. Patients with such problems should have equal access to kidney transplantation compared to patients with no MH problems.

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matching, nor mismatching had any effect on the three examined outcomes in either individual or combined multivariable models. Sensitivity analysis in the 2003-2012 cohort showed similar results.

**Conclusions:** Our analysis in this large cohort reports for the first time the absence of any effect from HLA-matching or -mismatching on allograft outcomes among AA-donor kidneys. These findings suggest that the allocation algorithm for AA-donor organs may need to be re-evaluated without including HLA-match status.

**FR-PO1039**

Femoral Bone Mineral Density Is Related With Aortic But Not With Coronary Calcifications in KTx Patients

**Background:** Our study wants to evaluate in a cohort of kidney transplanted(KTx) patients,undergone to femoral DXA:1) the prevalence of bone mineral abnormal;2) the factors related to femoral bone mineral density(f-BMD) 3) the relationship of f-BMD with aortic calcifications(ACI) and coronary calcifications(CAC).Lumbar DXA was not considered to avoid confounders between abdominal vascular calcifications(VC) and BMD.

**Methods:** 293pts(M=170) transplanted in our Unit(2004-2013) were evaluated. Clinical and routine biochemical exams plus PTH,FGF-23,Fetuin and VitD were tested at 1(T0) and 12(T1) mths of KTx. At the same time,DXA,lumbar X-Ray(193pts) and coronary tomography(60pts) for f-BMD;acu(3),ACI(Kauppila) and CAC(Agatson) evaluations were performed.ACI increase(ACI-Prog) any increase in ACI.Presence of CAC(CAC+):Agatson score >400.CAC increase(CAC-Prog) assessed using Sevrukov formula.

**Results:** At T0 and T1,OPN in 55% and 52%,OPR in 15% and 12% of pts resp.F-BMD was associated with age, alkaline phosphatase(ALP) at T0 and T1), fetuin and P at T0). A logistic regression with BAbn(OPN) or P as a whole dependent variable confirmed age and ALP as the only independent associated variables(T0 and T1).ACI were found in 55% and 61% of pts(T0-T1).ACI were higher in BAbn(T0 and T1).ACI-Prog(26%) had lower F-BMD(T0 and T1).F-BMD showed a discriminatory role in ACI-Prog ROC Curve, T0:AUC 0.66, p=0.02;T1:AUC 0.70, p=0.05).CAC was found in 13%,20% and 28% pts at T0,T1 and T2.CAC-Prog was found in 13% at T1 and in 49% of pts at T2.F-BMD didn’t correlated with CAC at T0,T1,T2; and both at T1 and T2 its levels weren’t different between CAC-Prog and CACnot-Prog.

**Conclusions:** High prevalence of BAbn and VC from the beginning of KTx is present. Age and ALP are strongly associated with f-BMD, ACI and CAC progress in a high % of patients, in the early post-KTx period. However, though F-BMD was significantly related with ACI-Prog,no association was observed with CAC worsening,possibly suggesting that different mechanism/s might underlie VC processes at different sites.

**Funding:** Private Foundation Support

**FR-PO1040**

Relationship Between Pre-Transplant Physical Function and Quality of Life following Kidney Transplant

**Background:** Decreased physical function predicts adverse outcomes following non-transplant surgery. The goal of this study was to assess whether pre-transplant physical function predicts impaired quality of life (QOL) following kidney transplant.

**Methods:** We conducted a prospective cohort study involving all recipients of living donor kidney transplants at our center from 2012 until 2014. Physical function was measured using the Short Physical Performance Battery (SPPB), a composite measure of gait speed, balance and chair rise time (score range 0-12, with higher score indicating better physical function). QOL was measured 12-months post-transplant using the Short Form 36 Health Survey (SF36) with standardized scores adjusted for age and gender. Below-average physical and mental QOL was defined as physical (PCS) and mental component summary scores (MCS) < 45, respectively.

**Results:** Among the cohort of 140 patients, mean age was 51 ± 15 years, 61% were male, 91% were Caucasian, 21% had diabetes and 26% had a pre-transplant SPPB score < 12. A pre-transplant SPPB score < 12 was associated with a significantly lower 12-month QOL score (54.2 ± 9.4 vs 55.2 ± 8.4, p=0.04) but not a lower MCS score (54.2 ± 9.4 vs 55.2 ± 8.4, p=0.90).

**Conclusions:** Below-average physical QOL at 12-months was observed in 23% of patients and was associated with pre-transplant BMI (OR 1.12 per 1 kg/m2 increase; CI 1.02-1.23, p=0.02) and a pre-transplant SPPB score < 12 (OR 3.05, CI 1.17-7.97, p=0.02). In contrast, pre-transplant diabetes, dialysis, maintenance steroids and 12-month eGFR were not associated with physical QOL.

**Funding:** Private Foundation Support

**FR-PO1041**

I“t” Report of Korean Organ Transplantation Registry (KOTRY)

**Background:** The Korean Organ Transplantation Registry (KOTRY) were launched in 2014 to construct the nationwide transplant database system which encompasses outcomes of various transplant organs by support of the Korea Centers for Disease Control and Prevention.

**Methods:** In 2014, kidney, liver and heart transplant cohorts were established with participation of 29/58 centers for kidney, 13/35 centers for liver, and 4/8 centers for heart, covering more than 80% of total cases. Lung and pancreas transplant cohorts are also in progress since 2015. A web-based database system and attached biobank system have been developed. Annual data report and related information of database development process are available at http://www.kotry.org. From July 2014 to December 2014, 419 transplants in kidney transplantation (KT), 430 in liver transplantation, and 77 in heart transplantation were registered.

**Results:** Among 419 KT, deceased donor (DD) was performed in 156 patients (37.2%). Mean age was 47.7±11.2 and 56.8% of transplants were males. Diabetic recipients were 23.2%, and 5.5% of transplants were older than 65 years. Their original kidney disease was most often chronic glomerulonephritis (39.6%), followed by diabetic nephropathy (18.6%). Preemptive KT was 29.3% among living donor KT. The high panel-reactive antibody (>50%) accounted for 9.8% of transplants. Positive results of T or B flow cytometric crossmatch were found in 1.9% and 4.5% of transplants, respectively. ABO incompatible KT was performed in 21.7% of living donor KT. Mean age of donors was 45.3±13.2 and 59.9% were males. Among DD, expanded-criteria donor was 23.7%. Mean serum creatinine of living donor before and after KT were 0.81±0.18mg/dl, and 1.16±0.27mg/dl, respectively. In KOTRY, pre-transplant diabetes, dialysis, maintenance steroids and 12-month eGFR were not associated with physical QOL.

**Conclusions:** Decreased pre-transplant physical function predicts impaired physical QOL, one year after kidney transplant. Further studies are needed to determine whether physical rehabilitation interventions can improve post-transplant QOL.

**FR-PO1042**

Pre-Transplant Midodrine Use: A Newly Identified Risk Marker for Complications After Kidney Transplantation

**Background:** Midodrine is increasingly prescribed to decrease the severity and complications of hypotension in dialysis patients. The impacts of midodrine use before kidney transplantation on graft and patient outcomes early after transplantation are not well described.

**Methods:** We analyzed linked national U.S. transplant registry, pharmacy records and Medicare claims data to follow 16,322 kidney transplant recipients (2005-2008), of whom 308 (1.9%) had filled midodrine prescriptions in the year prior to transplantation. We examined associations of midodrine use with DGF, graft survival and death as reported to the registry, and with clinical complications captured in Medicare claims.

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**Funding:** Government Support - Non-U.S.
Burden through novel methods including pharmacy claims, and associated impacts on complications including graft failure and death. As the new KAS is expected to increase need for midodrine before kidney transplantation is a bio-marker for increased risks of stiffness in renal transplant recipients. Impact of proton pump inhibitors on hypomagnesemia and arterial stiffness in renal transplant recipients.

**Results:** At 3mo, patients who used midodrine before transplant had higher rates of DGF, 32% vs. 19%; hypotension, 14% vs. 4%; acute myocardial infarction (AMI), 4% vs. 2%; cardiac arrest, 2% vs. 0.9%; graft failure, 5% vs. 2%; and death, 4% vs. 1% than the non-users (P<0.05). After multivariate adjustment including recipient, and donor factors, as well as for the propensity of midodrine exposure, pretransplant midodrine use was independently associated with risks of DGF (aOR 1.95; CI 1.49-2.56), death-censored graft failure (aHR 1.94; CI 1.14-3.27), death (aHR 3.55; CI 1.99-6.33), as well as many potentially mediating complications. Patterns were similar at 12mo.

**Conclusions:** Although associations may in part reflect underlying conditions, the need for midodrine before kidney transplantation is a bio-marker for increased risks of complications including graft failure and death. As the new KAS is expected to increase ESRD duration at the time of allocation for many patients, monitoring recipient comorbidity burden through novel methods including pharmacy claims, and associated impacts on transplant outcomes, are important priorities.

**Funding:** NIDDK Support

**FR-PO1044**

Comorbidity Burden of Kidney Transplant Recipients Predicts Emergency Usage Despite Increased Family Physician Visits

**Background:** Kidney transplant (KTX) recipients utilize many aspects of the healthcare system, especially emergency (ER) visits. Unterman et al showed that within a four year period, 378 KTX recipients generated 828 ER visits. This study aims to understand factors leading to ER usage by KTX recipients.

**Methods:** This is a single center retrospective study in conjunction with patient questionnaire, collected from March 2012 - 2013. The questionnaire inquired the frequency of the family physician (GP) visits and ER usage within the past year. Patient demographics and comorbidities were collected from chart reviews. Univariate logistic regression was used to define factors that are predictive of ER usage. Significant covariates were then used in multivariate backward stepwise logistic regression model to predict ER visits.

**Results:** Number of GP visits (OR = 1.6, P = 0.003), diabetes (OR = 1.7, P = 0.016), coronary artery disease (OR = 2.5, p = 0.001), below knee amputation (OR = 4.3, p = 0.037), and number of comorbidities (OR = 1.35, p = 0.001) significantly predict ER visits. Number of transplant clinic visits does not significantly decreased ER visits (p = 0.32). By multivariate backward stepwise logistic regression, number of GP visits (OR = 1.5, p = 0.007) and coronary artery disease (OR = 2.1, p = 0.011) remain significantly predictive of ER usage.

**Conclusions:** This single center study showed that KTX recipients with more comorbidities have increased ER usage, particularly coronary artery disease, despite higher frequency of GP visits. However, kidney transplant recipients with more ER usage are not seen more frequently by our transplant clinic. The results suggest that KTX recipients with higher comorbidity burden may need to be followed more closely by transplant clinics, rather than relying on GP’s, to improve effective usage of ER visits.


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

**FR-PO1045**

Stroke Predictors and Outcome in Renal Transplant Recipients

**Background:** End-stage renal disease is associated with a high incidence of cerebrovascular disease. Conventional risk factors do not always apply & established preventive strategies may be ineffective. The incidence, predictors & outcomes following stroke in those with a functioning renal transplant is not well described.

**Methods:** All adult patients with a renal transplant attending Glasgow Renal and Transplant Unit between 1st Jan 2007 and 31st Dec 2012 were identified using the electronic patient record. Clinical, demographic & laboratory data were collected including presence of diabetes, cardio- or cerebrovascular disease (CeVD), atrial fibrillation, deprivation, serum renal and bone chemistry and use of immune suppressants. Stroke was identified via discharge codes, cerebral imaging or death certification. Independent predictors of stroke were identified via multivariable regression analysis. Fatality & causes of death are presented.

**Results:** 636 patients were identified, mean age 38 years (SD 12.9). 60.5% were male and 9.1% had AF. During follow-up 7.1% received a transplant as first RRT modality. 24 patients experienced a stroke during 3455 patient years of follow-up. 83.3% were ischemic. Stroke incidence was 6.9/1000 patient years for all stroke and 3.76/1000 patient years for first stroke. A stepwise backward regression revealed predictors of stroke as older age (HR 1.05, p = 0.025) and previous CeVD (HR 18.16, p = 0.001). Significant independent predictors for first stroke were age, diabetes and AF (p = 0.05). There were no cases of SAH in PCKD. AF associated with time to stroke (p = 0.003), but there was no detectable benefit from use of warfarin. 134 died during follow-up. 62.5% deaths followed stroke with 7, 28 and 365 day fatality of 20.8, 25 and 45.8%. Cardiovascular (75%) or malignancy (13%) were the cause of death in most cases.

**Conclusions:** Renal transplant recipients have a high incidence of stroke and poor outcome following stroke. Risk factors include prior CeVD, age, diabetes and AF. Although AF associated with time to stroke, the role of warfarin in prevention is poorly defined, requiring further study.

**Funding:**

Transplantation: Clinical and Translational - I

Poster/Friday
FR-PO1046
Factors Influencing Racial Disparities in Renal Transplantation Outcomes
Sumit Mohan,1 Barry I. Freedman,2 William Mark Brown,3 Stephen O. Pastan,3 Ajay K. Israni,4 David P. Schlaid,3 Robert S. Gaston,4 R. Bray,3 Amber M. Reeves-Daniels,3 Bruce A. Julian,3 Jasmin Divers,2 Columbia Univ; Wake Forest School of Medicine; Emory Univ; Univ of Minnesota; Minneapolis Medical Research Foundation; Univ of Alabama at Birmingham.

Background: Kidney transplants from African American (AA) deceased donors have worse outcomes than kidneys procured from donors of other ethnic groups; deceased donor kidney transplants (DDKTs) engrafted into AAs fare worse than kidneys placed into recipients of other ethnic groups. The role of biological and environmental factors in these disparities remains unclear. We sought to identify factors contributing to these ethnic differences in AA and European American (EA) recipients of kidneys from AA and EA donors, in a study using donor-matched design to eliminate donor-specific confounding effects.

Methods: We compared allograft survival of DDKTs in 4 types of donor/recipient pairs (TDRP) (AA-AA, AA/EA, EA-AA and EA/EA). Models were fitted using a mixed effect Cox model with particular focus on effect modifiers of the TDRP association with allograft survival.

Results: We identified 669 AA and 3,383 EA donors resulting in 669 AA/AA, 669 AA/EA, 3,383 EA/AA and 3,383 EA/EA DDKTs. In agreement with previous reported trends, AA donors were more likely to be younger, male, hypertensive, and with higher serum creatinine, while EA recipients were more likely to be employed (46% vs. 37% and 33%) and less likely to experience delayed allograft function (DGF) (19% vs. 28% and 23%). Adjusted analyses controlling for donor and recipient characteristics identified strong interaction effects between the TDRP and incidence of DGF (P<0.009) and between the TDRP and employment status (P=0.04). Observed hazard ratios varied from 0.9 for an employed (EA/EA) pair without DGF to 4.3 for an unemployed (AA/AA) pair with DGF.

Conclusions: Ethnic differences in employment status and incidence of DGF were the strongest effect modifiers of the association between the TDRP and allograft survival for DDKTs. These differences partially explained the observed racial disparity in outcomes for DDKTs.

Funding: Other NIH Support - NIH RO1 DK070941 (BIF), NIH RO1 DK084149 (BIF), NIH RO1 MD009055 (JIF, BIF), NIH/NIAD Genomics of Transplantation SU19-AI070119 (AKI)

FR-PO1047
Renal Transplantation in Bardet-Biedl Syndrome
Robert M. Hawks,1 Aditya Joshi,2 Siddharth A. Shah,2 Omar M.A.A. Alkandari,3 Martin A. Turan.1 1Dept of Pediatrics, Marshfield Clinic, Marshfield, WI; 2Dept of Pediatrics, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK; 3Dept of Pediatric Nephrology, Univ of Louisville, Louisville, KY; 4Dept of Pediatrics, Mubarak Al-Kabeer Hospital & Hamid Al-Essa Transplant Center, Safat, Kuwait.

Background: Bardet-Biedl syndrome (BBS) is a rare, multisystemic genetic disorder frequently associated with chronic kidney disease (CKD). Data regarding renal transplantation (RT) in BBS is lacking and reports tend to highlight complications. We report RT outcomes in the largest BBS cohort examined to date.

Methods: An international BBS registry was interrogated to identify individuals that had undergone RT and capture age, gender, body mass index (BMI), transplant and patient survival, donor source, and comorbidities.

Results: RT was performed in 19/171 (11%) registry subjects (mean age 9 y; range 2-25 y). RT patients were younger (9 vs. 17.9 y, p<0.005) and more likely to be female (82% vs. 50%). Deceased donors provided 12/21 kidneys; one patient received a combined liver/renal transplant. Two patients that underwent RT in the 1980s and died <10 y of age were excluded from further analysis. Patient and kidney survival is shown.

Conclusions: Outcomes following RT in patients with BBS is favorable. Female predominance raises questions regarding gender as a potential modifying factor impacting CKD prevalence.

Funding: Private Foundation Support

FR-PO1048
Kidney Transplant Recipient Hospital Readmission: Examination of Discharge-Level Factors
Michelle L. Lubetzky, Maria Ajaimy, Layla Kamal, Graciela De Boccardo, Enver Akalin. Transplantation, Montefiore, Bronx, NY.

Background: Early rehospitalization after kidney transplantation (KTxs) is common and is considered a quality metric. Few studies have examined preventability or discharge factors associated with early rehospitalization.

Methods: We performed a single-center, retrospective cohort study between 2011-2015 of adult KTxs recipients. The primary outcome was at least one readmission within 30 days after discharge. Secondary outcomes were reason for readmission, potential for process improvement to reduce readmission, and all-cause graft failure.

Results: Of 462 KTxs, 31.4% were readmitted within 30 days of discharge. The reason for first readmission was surgical in 20.8% of those with non-surgical reasons, 21.7% were from infection, 20.9% graft dysfunction, 21.7% gastrointestinal, 21.7% metabolic, and 13.9% other. Readmission was significantly associated with all-cause graft failure (p<0.006). The assessment of preventability showed that the reason for readmission was present at the time of discharge in 17.7%, additional hospital resources may have abrogated the readmission in 15.8%, and 12.4% could have been managed as outpatient. On univariate analysis, risk factors for rehospitalization were: presence of comorbidities (p<0.03), complication during hospitalization (p<0.001), discharge electrolyte abnormalities (p<0.001) and kidney function at discharge (p<0.003). Table 1. On multivariate analysis, the presence of 3 comorbidities pre-KTx (OR 2.01 95% CI 1.84-3.86), electrolyte abnormalities at discharge (OR 1.77 CI 1.17-2.69), delayed graft function (OR 1.65 95% CI 1.2-2.17), and post KTxC complications (OR 1.79 95%CI 1.1-2.61) were associated with increased risk of readmission

Table 1: Comparisons of Patients Requiring Readmission versus No Readmission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Readmitted No</th>
<th>Readmitted Yes</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient Age, years</td>
<td>58.2±13.2</td>
<td>53.4±13.5</td>
<td>0.1933</td>
</tr>
<tr>
<td>Recipient, Male</td>
<td>168 (93%)</td>
<td>91 (62%)</td>
<td>0.7375</td>
</tr>
<tr>
<td>Recipient Race</td>
<td>20 (10%)</td>
<td>12 (8%)</td>
<td>0.1011</td>
</tr>
<tr>
<td>Hispanic</td>
<td>115 (63%)</td>
<td>40 (27%)</td>
<td>0.2286</td>
</tr>
<tr>
<td>White</td>
<td>45 (24%)</td>
<td>18 (12%)</td>
<td>0.5391</td>
</tr>
<tr>
<td>Any Recipient Comorbidity</td>
<td>273/505 (54%)</td>
<td>119/274 (43%)</td>
<td>0.0394</td>
</tr>
<tr>
<td>Recipient BMI &gt;50 kg/m²</td>
<td>35 (10%)</td>
<td>13 (8%)</td>
<td>0.1612</td>
</tr>
<tr>
<td>Recipient diabetes mellitus</td>
<td>137 (42%)</td>
<td>63 (44%)</td>
<td>0.1519</td>
</tr>
<tr>
<td>Recipient, prior solid Organ Transplant</td>
<td>35 (10.7)</td>
<td>17 (11.9)</td>
<td>0.9756</td>
</tr>
<tr>
<td>Recipient, Cardiacs Disease</td>
<td>89 (28%)</td>
<td>41 (27%)</td>
<td>0.9045</td>
</tr>
<tr>
<td>Recipient, peripheral vascular disease</td>
<td>35 (10.7)</td>
<td>20 (13.2%)</td>
<td>0.6836</td>
</tr>
<tr>
<td>Recipient, CKD, or HF</td>
<td>35 (10.7)</td>
<td>20 (13.2%)</td>
<td>0.6836</td>
</tr>
<tr>
<td>Recipient, pre-transplant albumin&lt;3.5 g/dL</td>
<td>10 (3.9)</td>
<td>7 (3.8)</td>
<td>0.3982</td>
</tr>
<tr>
<td>Recipient, pre-transplant hemoglobin&lt;10 g/dL</td>
<td>68 (25.1)</td>
<td>27 (18.8)</td>
<td>0.1687</td>
</tr>
<tr>
<td>Recipient QoL on day of discharge</td>
<td>123 (28.5)</td>
<td>72 (29.3%)</td>
<td>0.7728</td>
</tr>
<tr>
<td>Malnutrition, high/low</td>
<td>130 (41.9)</td>
<td>50 (41.4%)</td>
<td>0.5954</td>
</tr>
<tr>
<td>Readmission time on day of discharge</td>
<td>42 (16.7)</td>
<td>6 (0.2%)</td>
<td>0.0106</td>
</tr>
<tr>
<td>Kidney</td>
<td>80 (27.2%)</td>
<td>87 (30.1%)</td>
<td>0.6885</td>
</tr>
<tr>
<td>Graft</td>
<td>80 (27.2%)</td>
<td>87 (30.1%)</td>
<td>0.6885</td>
</tr>
</tbody>
</table>

Conclusions: Early readmission is associated with worse graft survival. Many readmissions may be preventable and review of process improvement may reduce early readmission after KTxs.

Funding: Other NIH Support - NIH RO1 DK070941 (BIF), NIH RO1 DK084149 (BIF), NIH RO1 MD009055 (JIF, BIF), NIH/NIAD Genomics of Transplantation SU19-AI070119 (AKI)
FR-PO1049

Kidney Transplant Outcomes for Patients with Amyloidosis – A United Network for Organ Sharing Database Analysis

Ali Khalil, Tim E. Taber, Muhammad Ahmad Mujtaba, Muhammad S. Yaqub, Asif A. Sharifuddin. Medicine/Neph, Indiana Univ, Indianapolis, IN.

**Background:** Outcomes of patients with Amyloidosis who receive a kidney transplant have not been extensively studied. We examined UNOS database for outcomes of such recipients.

**Methods:** UNOS database was queried for recipients with code “3016” which corresponds to “Amyloidosis”. Duration of study period was Nov 1987 to Dec 2014.

**Results:** A total of 625 recipients were identified as in the table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at time of transplant (yrs) SD</td>
<td>54.8±11.1</td>
</tr>
<tr>
<td>Mean Donor Age</td>
<td>46±15.1</td>
</tr>
<tr>
<td>Median Time On Wait List (days)</td>
<td>2610(0-2706)</td>
</tr>
<tr>
<td>Caucasian/African American/Hispanic/Other (%)</td>
<td>80.5/7.2/9.3/1.2</td>
</tr>
<tr>
<td>Deceased/Living (%)</td>
<td>56.5/43.5</td>
</tr>
<tr>
<td>M/F (%)</td>
<td>62.4/37.6</td>
</tr>
<tr>
<td>On Dialysis at time of transplant (%)</td>
<td>80.2</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>25.7±4.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>6.3</td>
</tr>
<tr>
<td>Repeat Kidney Transplant (%)</td>
<td>3.8</td>
</tr>
<tr>
<td>PRA &gt;80 (%)</td>
<td>3.6</td>
</tr>
<tr>
<td>Zero Mismatch (%)</td>
<td>8.6</td>
</tr>
<tr>
<td>Blood Type A/AB/O (%)</td>
<td>40.7/5.3/12.5/41.6</td>
</tr>
<tr>
<td>ECD Donor/DCD (%)</td>
<td>9.6/29</td>
</tr>
<tr>
<td>Multi-Organ Transplant (%)</td>
<td>6.6</td>
</tr>
<tr>
<td>- Heart(n)</td>
<td>6.6</td>
</tr>
<tr>
<td>- Liver(n)</td>
<td>2.1</td>
</tr>
<tr>
<td>- Pan(n)</td>
<td>2.3</td>
</tr>
<tr>
<td>- Delayed Graft Function (%)</td>
<td>14.6</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL) at discharge (SD)</td>
<td>2.3±2.1</td>
</tr>
<tr>
<td>Treated for Rejection within 6mo (%)</td>
<td>11.2</td>
</tr>
<tr>
<td>Treated for Rejection within 1yr (%)</td>
<td>12.8</td>
</tr>
<tr>
<td>Death With Functioning Graft (%)</td>
<td>28.3</td>
</tr>
<tr>
<td>Unadjusted 1 yr/3yr/5yr/10 yr Graft Survival (%)</td>
<td>87.5/79.3/71.2/58.2</td>
</tr>
<tr>
<td>Actual Patient Survival 1yr/3yr/5yr/10 yr</td>
<td>91.8/83.0/75.8/61.2</td>
</tr>
</tbody>
</table>

After excluding multi-organ transplants, the 1 year unadjusted graft survival was 88.6% and the 1 year patient survival was 92.1 %. Kaplan Meier Survival Curves are in the Figure.

DGF incidence increased from 26.5% pre-KAS to 31.6% post-KAS (p<0.001); in a multilevel (center-level) model, DGF increased 37% (OR=1.21 1.37 1.55 , p<0.001). We also compared CPRAs of DDKT recipients pre vs post-KAS, and incidence of delayed graft function (DGF).

**Conclusions:** After excluding multi-organ transplants, the 1 year unadjusted graft survival was 88.6% and the 1 year patient survival was 92.1 %. Kaplan Meier Survival Curves are in the Figure.

FR-PO1050

Early Experience with the New Kidney Allocation System


**Background:** On December 3, 2014, major changes to deceased donor kidney allocation were implemented under the new Kidney Allocation System (KAS).

**Methods:** Using national registry data, we compared changes in rate of DDKT among adult kidney-only waitlist registrants 1/2011-3/2015 pre vs post-KAS via Poisson regression, adjusting for age, sex, race, ABO blood type, calendar year, calculated panel reactive antibody (CPRA), and wait time. We compared donor service area-level geographic disparity pre vs post-KAS using multilevel Poisson regression and median incidence ratio (MIRR). We also compared CPRA of DDKT recipients pre vs post-KAS, and incidence of delayed graft function (DGF).

**Results:** Pre-KAS, access to DDKT was poorer for women (IRR=0.99 0.99 0.99), African-Americans (AAs) (IRR=0.88 0.88 0.88), and Hispanics (IRR=0.79 0.79 0.79, all p<0.01). Access was best for patients of ABO type AB (IRR vs O=2.29 2.29 2.29 , p<0.01) and worst for ABO type B (IRR vs O=2.29 2.29 2.29 , p<0.01). KAS was associated with no change in overall DDKT access (p=0.7), but with improved access for AAs (IRR=1.16 1.16 1.16, interaction p<0.001) and patients of ABO type AB (IRR=1.29 1.29 1.29, interaction p<0.001). Geographic disparity declined post-KAS (MIRR=1.76 pre-KAS, 1.64 post-KAS). Median CPRA at transplantation was 0 both pre and post-KAS; the proportion of recipients with CPRA 80-99 decreased from 13.6% to 10.1% (p<0.001), but the proportion with CPRA>99 rose from 1.6% to 14.0% (p<0.001, Figure 1).

**Conclusions:** After recent changes to kidney allocation, DDKT access improved for AA patients and geographic disparity declined. Women and Hispanic patients are still disadvantaged, and disparity by ABO type worsened. The proportion of recipients for AA patients and geographic disparity declined. Women and Hispanic patients are still disadvantaged, and disparity by ABO type worsened. The proportion of recipients with CPRA>99 rose dramatically. Increase in DGF may suggest risk of poorer long-term outcomes.

**Funding:** NIDDK Support

FR-PO1051

Kidney Transplantation Tourism: High Risk and Bad Outcome for the Recipients

Amgad E. Elagroudy. Internal Medicine Dept, College of Medicine and Medical Sciences, Arabian Gulf Univ, Manama, Bahrain.

**Background:** While the ethical aspects of transplant tourism have received much attention recently, less has been written about the medical safety of this practice. We retrospectively evaluated the outcomes of patients who purchased organs internationally and presented to our center for follow-up care.

**Methods:** We report the outcome parameters of 270 local recipients of unrelated kidney (URT) vendor transplants presenting to our institute between 1986 and 2014. Their outcome was compared with 123 recipients of living-related donor transplants matched for age, gender and transplant duration done in our center as controls (RT).

**Results:** Age of unrelated recipients was 42.6 ± 13.4 years with Male % of 68. The country of transplant was mainly in Philippines (n = 85), Pakistan (n = 56), India (n = 57), Iran (n = 40) and Egypt (n = 25). Comparison of commercial recipients with controls showed high co morbidities (P = 0.01) with hepatitis-C (n=2 vs. 0) and hepatitis-B (n=2 vs. 0) and cytomegalovirus (n=4 vs. 1). Donor age was 25.9 ± 3.8 vs. 34.6 ± 8.6 years (P = 0.0001) and 90.4% were male. Biologic agents induction in 74 (27.4%) vs. 123 (100%) (P = 0.0001), acute rejections in 65 (24.1%) vs. 26 (21.1%) (P = 0.7), while recurrent rejection in 13 (4.8%) vs. 10 (0.8%) (P=0.04), surgical complications including lymphocoele 16 (5.9%) vs. 0 (0%) (P = 0.0001), ureteral obstruction 7 (2.6%) vs. 0 (0%) (P = 0.007), hematoma 4 (1.5%) vs. 1 (1.1%) (P = 0.06) and recurrent urinary tract infection 18 (6.8%) vs. 6 (6.8%) (P = 0.3). Overall 1- and 10-year for graft survival was 91% and 90.4% were male. Biologic agents induction in 74 (27.4%) vs. 123 (100%) (P = 0.0001), acute rejections in 65 (24.1%) vs. 26 (21.1%) (P = 0.7), while recurrent rejection in 13 (4.8%) vs. 10 (0.8%) (P=0.04), surgical complications including lymphocoele

**Conclusions:** Although 1 year graft and patient survival of kidney transplants in recipients with Amyloidosis is inferior to standard outcomes, long-term outcomes are not remarkably different. Careful selection of this population can lead to satisfactory outcomes. To our knowledge this is the first and largest report on the outcomes of these patients from the US national database.
**FR-PO1052**

**The Negative Effect of First Transplant Nephrectomy for Second Transplant Outcome**

Masaki Muramatsu,1,2 Michael Sheaff,1 Arun Gupta,1 Atsushi Aikawa,2 Carmelo Pulitelli,1 Muhammad M. Yaqoob,1 Nephrology and Transplantation, The Royal London Hospital, London, United Kingdom;
Nephrology, Toho Univ Faculty of Medicine, Tokyo, Japan;1 Cellular Pathology, The Royal London Hospital, London, United Kingdom;2 Clinical Transplant Laboratory, The Royal London Hospital, London, United Kingdom.

**Background:** The impact of failed renal allograft nephrectomy on the outcome of retransplantation is unclear. This single center study was conducted to address this question.

**Methods:** We analyzed 93 patients who received a 2nd transplant at The Royal London Hospital between November 1994 and January 2015. 59 patients did not receive primary transplant nephrectomy (TNx) and had failed allograft in situ at the time of second graft (group A) whilst 34 patients underwent TNx prior to second graft (group B). 2nd transplant survival was the primary end point. Sensitization, waiting time for 2nd graft, graft function and rejections were secondary end points.

**Results:** Group A patients had significant longer graft survival than group B (100.6 months vs 40.2 months, p<0.001). Waiting time from primary graft loss to second transplant in group A was shorter than group B (36.7 months vs 59.1 months, p<0.013). In total, 33 patients had pre-formed anti-HLA antibodies (low titer). Group B had significantly higher rate of pre-formed anti-HLA antibodies than group A (50% vs 29.3%, p=0.047). The rate of HLA class I in group B was also significantly higher than that in group A (47.1% vs 25.7%, p=0.038). Group B had numerically higher rate of acute rejection than group A (32.4% vs 15.3%, p=0.003). GFR between both groups did not differ until 3 years post-transplant. In group A, 2nd graft survival rates at 6 month, 1 and 5 years were 94.9%, 93.0%, 87.0% and 82.3%, and were significantly better group B (73.3%, 70.0%, 60.6% and 46.8%, p<0.001). On multivariate analysis, waiting time for second transplant, TNx, second transplant donor age and delayed graft function were independently associated with second graft survival. TNx had highest hazard ratio (2.83, 95% CI 1.22-6.67, p=0.015).

**Conclusions:** Prior TNx is associated with inferior 2nd renal graft survival in this observational study and calls for an urgent randomized control trial.

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**FR-PO1053**

**Induction Agent Use, Mortality and Acute Rejection in Older KT Recipients**


**Background:** Induction agents are commonly used as an initial intensive immunosuppression after kidney transplantation (KT) to prevent acute organ rejection; this paper aims to quantify their label. Little is known about induction agent use in older KT recipients.

**Methods:** Data on 19,546 older KT recipients (2005-2013) was ascertained from the Scientific Registry of Transplant Recipients. Induction agents were classified as thymoglobin/ATG, IL-2, or other induction agents. The risk of mortality was estimated using a time-varying proportional hazards model (hazard ratio (HR)) adjusting for all HTX factors (age, sex, race, BMI, peak PRA, history of diabetes, years on dialysis) and KT factors (age, sex, race, BMI, peak PRA, history of diabetes, years on dialysis) and KT factors (HCV, HLA mismatches, cold ischemia time, donor type, donor age, and donor sex). The relative risk (RR) of 1 year acute rejection was estimated using modified Poisson regression adjusting for all recipient and KT factors.

**Results:** The mean age was 69 (SD=3.8 years), 36% female, 19% black and 27% live donor recipients. There is an increasing utilization by year of induction agents, with thymoglobulin/ATG, IL-2, or other induction agents. The risk of mortality was estimated using a Cox Proportional Hazards model (hazard ratio (HR)) adjusting for all recipient factors (age, sex, race, BMI, peak PRA, history of diabetes, years on dialysis) and KT factors (age, sex, race, BMI, peak PRA, history of diabetes, years on dialysis) and KT factors (HCV, HLA mismatches, cold ischemia time, donor type, donor age, and donor sex). The relative risk (RR) of 1 year acute rejection was estimated using modified Poisson regression adjusting for all recipient and KT factors.

**Conclusions:** Prior TNx is associated with inferior 2nd renal graft survival in this observational study and calls for an urgent randomized control trial.

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**FR-PO1054**

**Immunosuppression and the Elderly – Can They Take It?**


**Background:** The aging immune system has fewer naïve T cells, more memory T cells, and less T cell receptor variability. Older transplant patients tend to have more comorbidities and less functional reserve. This combination makes them more difficult to immunosuppress with higher risk of infection, and potentially increased mortality from rejection treatment.

**Methods:** In order to determine the impact of rejection treatment on outcomes in our transplant recipients >70 years of age, we reviewed the outcomes of patients transplanted at our center from 1/2009-12/2013. Induction regimens varied; maintenance immunosuppression consisted of tacrolimus, mycophenolate, and rapid steroid withdrawal.

**Results:** During this period time, we transplanted 110 over 70 years of age. Of these, 27 patients had rejection – 24 ACR, 1 combined AMR/ACR, 1 AMR. 1 AMR followed by ACR (see table). 11 of these patients received Tcell depleting agents, the rest received IV steroids +/- IVlg. There was no difference in age, race, donor type, prior transplant, or induction therapy between the two groups. Mean creatinine was higher in the rejection group compared to the ACR group (1.0 mg/dl vs 0.6 mg/dl, p<0.001). GFR at rejection treatment was different no two patients. Within 6 months of rejection treatment, there were 12 infectious complications, only 3 of which required hospitalization (urosepsis-2, CMV-1). There were no differences in rates of BK viremia, CMV viremia, graft survival, or mortality. 7 of the 27 patients died at some point after rejection. only one was related to infection >1 year later and not related to treatment.

**Conclusions:** Among our >70 patients, rejection treatment appeared well tolerated with few complications requiring hospitalizations and no treatment related mortalities. In addition, it appeared that treatment stabilized function in the majority of patients.

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**FR-PO1055**

**Mortality After Kidney Allograft Failure and Return to Dialysis**

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**Background:** Our hypothesis was that kidney allograft failure (KAF) and return to dialysis (RTD) results in greater mortality versus patients with end-stage renal disease (ESRD). We also sought to identify variables associated with mortality after KAF.

**Methods:** We used an incident cohort of patients from the United States Renal Data System who initiated any form of dialysis between Jan 2003 and Dec 2008 after KAF. We followed patients until retransplantation, death or Sept 2009. Multivariable Cox analysis was used for statistical associations.

**Results:** 7,156 patients were followed for a mean of 30.8 ± 22.6 months. 3,622 (50.6%) patients died. The main causes of death were cardiovascular (47.0%), infections (14.5%), other (16.4%) and metabolic/endocrine (7.9%) causes. Predictors of all-cause mortality included age at KAF (hazard ratio (HR)= 1.03, 95% confidence interval (CI) 1.03-1.04), diabetes (DM) as cause of kidney failure (HR=1.52, CI 1.3-1.8), congestive heart failure (CHF) (HR=1.19, CI 1.04-1.36), peripheral arterial disease (PVD) (HR=1.23, CI 1.04-1.55), stroke (HR=1.27, 95% CI 1.08-1.48).

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

**Underline** represents presenting author.
CI 1.05-1.55), employment (HR=0.80, CI 0.67-0.96), BMI (HR = 0.98, CI 0.97-0.99) and serum albumin (HR = 0.82, CI 0.75-0.90). Mortality was higher in those with either DM or CHF, and increased further in those with PAD (P<0.0001).

Figure 1. Adjusted all-cause mortality [Kaplan-Meier curve]

Gender, number of transplants, donor type (deceased, living), ESRD duration prior to transplant, tobacco use, drug or alcohol abuse and erythropoietin use did not predict all-cause mortality.

Conclusions: DM, CHF and PAD are associated with increased mortality after KAF and RTD. Prevention and early management of these conditions may increase survival. Prospective studies are needed to confirm our findings.

Funding: Private Foundation Support

FR-PO1056

Current Trends in Waiting List of Kidney Transplantation and Mortality in Asian: A National Population-Based Cohort Study Using the Korean Network for Organ Sharing (KONOS) Database

Kyung Don Yoo, Sunhwa Lee, Jung Nam An, Yun Kyu Oh, Chun Soo Lim, Yon Su Kim, Jung Pyo Lee. Seoul National Univ College of Medicine.

Background: Kidney transplantation has been increasing, globally. However, the clinical outcome of wait-listed patients for deceased donor kidney transplantation has not been well described in Asian patients with end-stage renal disease (ESRD).

Methods: We reviewed the detailed trends of wait-listed patients and conducted survival analysis in kidney transplant recipients using KONOS (The Korean Network for Organ Sharing) database which is a complete enumeration survey. We compared the outcomes according to the transplant era as followings: 2000–2004, 2005–2009, 2010–2014.

Results: From 2000 to 2014, a total of 34,843 patients registered in the waiting list, and 5,164 patients received transplantation from deceased donor. The proportion of deceased donor kidney transplantation has increased up to 45.9% in 2013 from 4.6% in 2000. The number of waiting list for kidney transplantation has increased continually more than 3,000 ESRD patients per year. The mean waiting time of deceased donor kidney transplantation was 54.9 months and has been getting longer. A total of 18,687 patients were remained on the waiting list until Jan 2015. Recently, diabetic nephropathy was the leading cause of primary disease on the waiting list, and the mean age of new registrants was getting older. The crude annual mortality rate during waiting time was 8.4%. The survival analysis revealed that there was no difference of patient survival according to the transplant era in kidney transplant recipients. However, the cumulative survival rate of the recently registered wait-listed patients was significantly improved even though they were older and had more proportion of diabetes (P<0.001, HR 0.51 95% CI 0.46-0.57).

Conclusions: In Korea, deceased donor kidney transplantation has increased. Donor organ is still seriously insufficient, therefore, it is necessary to encourage organ donation. In addition, more meticulous management needs to be provided to wait-listed patients.

FR-PO1057

Factors Affecting Mortality During Waiting Time for Kidney Transplantation: A Nationwide Population-Based Cohort Study Using the Korean Network for Organ Sharing (KONOS) Database

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Background: Longer waiting times for kidney transplant have been suggested to be more deleterious than shorter waiting times. We analyzed the impact of waiting time on the post-transplant outcome and investigated risk factors for mortality during waiting time based on complete enumeration survey in Korea.

Methods: We analyzed all persons over 18-years-old deceased donor kidney transplant cases enrolled in Korean Network for Organ Sharing (KONOS) data between Jan 2000 to Jan 2015. The primary end point was all cause of death after enrollment.

Results: Of the 24,296 waiting-listed dialysis subjects, 5,255 patients including 588 re-transplant cases received kidney transplantation from deceased donor with median waiting time of 4.5 years. Ten year overall survival was 81.3% in kidney transplant recipients, whereas 68.1% in dialysis patients. Unlike previously known data, the effect of waiting time on mortality after transplantation was insignificant. During waiting time, however, various demographic and clinical factors were associated with increased mortality. Diabetic patients are more likely to die before transplantation (HR 2.25, 95%CI 1.37-3.70, P<0.001). Age was a significant risk factor for mortality. Only 56% of people aged 65 live after 10 year of waiting, whereas 86% of people aged 35. Men are more likely to die than women during waiting time (HR 1.22, 1.13-1.31, P<0.001). Moreover, Patients with Rh negative blood type shows higher mortality rate than those with Rh positive (HR 1.60, 1.06-2.42, P=0.024). Pre-transplant experienced patients, however, showed better survival during waiting time (HR 0.63, 0.46-0.86, P<0.003).

Conclusions: Longer waiting times on dialysis do not affect survival after transplantation although transplant itself shows overall better survival. It should be emphasized at to have more attention to the patients who are diabetic, old, men, or Rh negative with higher risk for mortality during waiting time.

FR-PO1058

Normal Saline versus Lower-Chloride Solutions for Kidney Transplantation

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Background: The ideal intravenous (IV) fluid for kidney transplantation (KTx) has not been defined, despite the common use of normal saline (NS) in the perioperative period. The high chloride content of NS is associated with an increased risk of hyperchloremic metabolic acidosis, which may increase the risk of hyperkalemia and delayed graft function (DGF). Balanced electrolyte solutions (BHS) have a lower chloride content, which may decrease this risk and avoid the need for dialysis due to hyperkalemia. Randomised controlled trials (RCTs) have used biochemical outcomes to compare fluids and have been underpowered to address patient-centred outcomes such as DGF. We systematically reviewed the effect of BES versus NS on DGF, hyperkalemia and acid-base status in KTx recipients.

Methods: We searched the Cochrane Renal Group’s Specialised Register to 24th March 2015. We included RCTs of KTx recipients that compared peroperative IV lower-chloride solutions to NS. Two independent investigators assessed studies for eligibility and risk of bias. Data were extracted using standardised forms and pooled according to a published protocol.

Results: Six studies (477 participants) were included in the review. All participants were aged ≥18 years and 70% received live-donor KTx. The overall risk of bias was low for selection bias and unclear for remaining domains. There was no difference in the risk of DGF (RR 1.03, 95%CI 0.62-1.70, P=0.91) or hyperkalemia (RR 0.48, 95%CI 0.04-6.10, P=0.57) for participants who received BES compared to NS. Compared to NS, BES were associated with higher serum bicarbonate (mean difference ΔHCO3 3.04mEq/L, 95%CI 2.13-3.94mEq/L, P<0.0001), higher serum bicarbonate (mean difference ΔHCO3 -9.93mEq/L, 95%CI -19.96-0.11mEq/L, P=0.05).

Conclusions: Intraoperative balanced electrolyte solutions are associated with less hyperchloremic metabolic acidosis compared to normal saline. However, these data do not support their use to reduce clinical events.

FR-PO1059

Risk Factors for Delayed Graft Function in Kidney Transplantation

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Background: Renal failure persisting after transplantation necessitating dialysis within the first week is called delayed graft function (DGF). Objective: To assess the impact of erythropoietin usage on DGF after renal transplantation.

Methods: A total of 196 maintenance hemodialysis patients who underwent renal transplantation at one center (Hospital do Rim) were prospectively analyzed pre and post-renal transplantation. Data on demographics, ESRD etiology, pre-transplantation hemodialysis, recombinant human erythropoietin (rHuEPO) use, type of donor kidney and immunosuppression regimen were reported. Two-sample t-test were used to compare differences between two groups (DGF versus non-DGF groups) and X2 to analyze categorical variables. Binary logistic regression was used to determine the impact of factors on outcome-DGF.

Results: The mean duration of maintenance hemodialysis was 18±6 months. The main causes of ESRD were diabetes (37%) and hypertension (15%) followed by chronic glomerulonephritis (9%). There were transplants from deceased-donor kidneys (47%), living unrelated kidney donation (43%) and living related donors (10%). 41 patients necessitated dialysis within the first week after renal transplantation (DGF group). We observed that 131 patients (67%) used recombinant human erythropoietin until one week before renal transplantation. We observed that DGF group was older (39±15; p=0.007), higher cold ischemia time (23±10h, 12±10h; p<0.001), longer time on dialysis (4±4, 2±1 yr; p<0.001) and higher rHuEPO dose (40±44, 16±8±44±11; p=0.001). DGF group had higher use of rHuEPO (p<0.001). Cold ischemia time (p=0.001) was an independent predictor of DGF.

Conclusions: This study shows that rHuEPO was not associated with DGF-protection in renal transplant patients. Cold ischemia time is an independent predictor of DGF.
FR-PO1060
Outcomes of Kidney Transplant Recipients from Donations After Circulatory Death Donors without Pre-Agonal Heparin Administration
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Montefiore- Einstein Center for Transplantation.

Background: Protocols of organ donation after circulatory death (DCD) are considerably varied. Heparin administration during the pre-agonal phase has been recommended to improve organ perfusion and prevent blood clots; however some protocols avoid heparin before verification of death based on legal or professional concerns. We assessed outcomes of kidney transplant recipients who received DCD kidneys recovered with and without heparin.

Methods: We retrospectively evaluated recipients of kidney transplants between 2013 and 2014 from controlled DCD donors who received (n=23) or did not receive (n=29) pre-agonal heparin.

Results: All kidneys underwent machine perfusion. No Heparin donors had a similar kidney donor profile index but were more likely to have mild histologic changes, elevated terminal machine perfusion resistive index, and to be imported from non-local donor service areas compared to the Heparin donors. Recipients of No Heparin kidneys were more likely to be female, sensitized, prior solid organ recipients, and to receive thymoglobulin and 2014 from controlled DCD donors who received (n=23) or did not receive (n=29) pre-agonal heparin.

Between group differences were small in terms of delayed graft function, 6-month acute rejection, and estimated GFR at 3, 6, and 12 months.

Table: Transplant Characteristics and Outcomes by Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heparin No</th>
<th>Heparin Yes</th>
<th>P-Value</th>
</tr>
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<tr>
<td>Kidney Donor Profile Index</td>
<td>N=23</td>
<td>N=29</td>
<td>0.63</td>
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<tr>
<td>Warm ischemia time</td>
<td>28.2+5.9</td>
<td>35.3±16.4</td>
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<tr>
<td>11-25 Intrarenal Resistance or 11-25 Intrastitial Resistance</td>
<td>38.5</td>
<td>27.8</td>
<td>0.04</td>
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<tr>
<td>Kidney from non-local Donor Service Area</td>
<td>86.2</td>
<td>69.6</td>
<td>0.78</td>
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<tr>
<td>Machine Perfusion Terminal Resistive Index</td>
<td>0.2-0.3 mm Hg/mL/min</td>
<td>41.7</td>
<td>43.5</td>
</tr>
<tr>
<td>0.21-0.35 mm Hg/mL/min</td>
<td>41.7</td>
<td>43.5</td>
<td></td>
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<tr>
<td>0.35 mm Hg/mL/min</td>
<td>16.7</td>
<td>4.4</td>
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<tr>
<td>Recipient, Black race</td>
<td>51.7</td>
<td>56.5</td>
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<tr>
<td>Recipient, Female</td>
<td>53.7</td>
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<tr>
<td>Recipient Age, years</td>
<td>54.3±16.3</td>
<td>55.4±10.1</td>
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<tr>
<td>Recipient, Diabetes Mellitus</td>
<td>44.8</td>
<td>56.9</td>
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<td>Prior Solid Organ Transplant</td>
<td>10.3</td>
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<td>Thymoglobulin Induction</td>
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<td>Panel Reactive Antibody &gt;0%</td>
<td>27.6</td>
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<td>Human Leukocyte Antigen mismatch&gt;4</td>
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<td>Cold Ischemia Time (hrs)</td>
<td>&lt;30</td>
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<td>30-40</td>
<td>27.6</td>
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<tr>
<td>40-50</td>
<td>34.5</td>
<td>23.3</td>
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<tr>
<td>Delayed Graft Function</td>
<td>65.5</td>
<td>60.9</td>
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<tr>
<td>Cumulative Incidence of acute Rejection at 6 months</td>
<td>12.0</td>
<td>5.0</td>
<td>0.62</td>
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<tr>
<td>Overall death Censored Graft Failure</td>
<td>6.9</td>
<td>4.3</td>
<td>0.10</td>
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<tr>
<td>Estimated Creatinine Clearance</td>
<td>50.4±16.4</td>
<td>58.1±15.2</td>
<td>0.12</td>
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<tr>
<td>6-months</td>
<td>54.2±18.6</td>
<td>61.2±15.7</td>
<td>0.24</td>
</tr>
<tr>
<td>12-months</td>
<td>61.5±19.7</td>
<td>58.6±11.5</td>
<td>0.08</td>
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<tr>
<td>Follow-up duration, days</td>
<td>292.4±95.6</td>
<td>233±50.5</td>
<td>0.45</td>
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</table>

Conclusions: Our findings suggest that DCD kidneys recovered without pre-agonal heparin are not at increased risk for primary non-function or thrombosis.

FR-PO1061
Effects of Dopamine Donor Pretreatment on Graft Function After Kidney Transplantation: Five-Year Follow-Up Of a Randomized Controlled Trial
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Background: [For the study group] A previous multicenter randomized controlled trial reported reduced dialysis requirements after kidney transplantation with dopamine donor pretreatment. Data on long-term outcomes are needed.

Methods: We calculated five-year graft survival from follow-ups at 60 European centers. We analyzed intention-to-treat and on-study medication and proteinuria survival estimates as tertiles of dopamine exposure because infusion times varied by treatment arm (range 0-1,929 min). Recipients with functioning grafts at three months were analyzed separately to differentiate early events from long-term consequences of the trial intervention.

Results: Follow-up was complete in 99.2%. Overall graft survival was 68.7%, (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.61-1.19; p=0.35), and death-censored graft survival was 83.3 vs. 80.4% (HR 0.84, 95%CI 0.54-1.29; p=0.42) in the treatment vs. control arms, respectively. The HR decreased to 0.46 (95%CI 0.23-0.94; p=0.03) in recipients with functioning grafts at three months, whose donor had received dopamine >270 min. It remained significant after adjusting for donor age (HR 1.05, 95%CI 1.02-1.08; p<0.001), delayed graft function (HR 2.05, 95%CI 1.12-3.73; p=0.02), biopsy-proven rejection (HR 2.13, 95%CI 1.16-3.93; p=0.02), and repeat transplants (HR 2.49, 95% CI 1.19-5.26; p=0.02). There were no differences of graft survival on intention-to-treat.

Conclusions: Dopamine administered for >270 min provided a long-term graft survival advantage independent of early events after Transplantation.

FR-PO1062
Does Calcineurin Inhibitor Timing Matter? Single Center Experience with En-Bloc Kidney Transplantation
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Background: En-bloc kidney transplantation (KTx) has excellent outcomes. To minimize vascular complications and nephrotoxicity, calcineurin inhibitor (CNI) therapy is often delayed. The purpose of our study is to investigate the impact of CNI initiation timing on 1-year graft outcomes.

Methods: This is a single-center, retrospective review of adult en-bloc KTx between 2001 and 2013. Timing of CNI initiation was decided by the operating surgeon. Patients were divided into two groups, those that received CNI therapy early (<48 hours) or delayed (>48 hours) posttransplant. The primary objective was to compare one year estimated glomerular filtration rate (eGFR) between the groups. Secondary outcomes included graft and patient survival, CNI levels, incidence of delayed graft function (DGF), rejection and graft failure rates.

Results: Twenty-one en-bloc KTx recipients were included in the analysis. Ten patients received CNI therapy within 48 postoperative hours (Early CNI Group). There was no difference in age, race, gender, PRA, cause of ESRD or BMI between the groups. Only 50% of Early CNI patients received lymphocyte depleting therapy vs. 100% in the Delayed CNI group (p = ns). In the Early CNI Group, 3 patients were on cyclosporine; all other patients received tacrolimus and mycophenolate maintenance. There was no difference in eGFR between groups at one year or at any other time points. Comparable therapeutic tacrolimus trough was observed at 5, 10 and 30 days posttransplant. There was no difference in DGF or graft incidence. In the delayed CNI group, one patient died of sepsis at 6 months.

Conclusions: Timing of CNI initiation had no impact on one year graft function and patient survival.

FR-PO1063
Reduction of Pediatric Renal Transplantation Vascular Thrombosis Rates Utilizing Low Dose Heparin Infusion
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Background: Pediatric renal allograft thrombosis rates are 4-10% and often result in allograft loss. Thrombolytic risk factors are smaller native vessel size, deceased donor source (DD), delayed renal allograft function, acute rejection, and small centre size (<50 transplants/decade). In our pediatric program from 1971 – 1992, 5 of 6 consecutive renal transplants (7.2%) were lost to vascular thrombosis. This study assesses if low dose continuous heparin reduces the risk and outcome of thrombosis in pediatric renal transplants.

Methods: Over 22 years (1993-2015), 44 of 100 consecutive children post renal transplant received low dose continuous heparin (10 units/kg/hour) for 1 week from therapeutic risk (1): age < 6 yrs (n=24); 2) laboratory profile of hypercoagulability (n=10); 3) oliguric delayed function (n=5), 4) surgical complications with venous or arterial anastomosis or double artery (n=4), or 5) patient history of access thrombosis or vasculitis (n=1). Renal scans were obtained on days 1, 3, 5 and when clinical deterioration occurred.

Results: Only 2 thrombotic events were noted which did not cause graft loss: 1) BD RD transplant- venous thrombosis immediately post-op on heparin with successful thrombectomy at 2hr and allograft recovery; 2) 17yr DD double renal artery allograft arterial thrombosis of smaller inferior renal artery on day 10 (heparin stopped day 7). One patient on heparin infusion required laparotomy 3hrs after surgery for thrombosis external to the anastomosis. One patient not on heparin also required laparotomy in the first 24hrs post-op for hemothorax evacuation. One patient in each group had primary non-function/surgical loss with removal of the kidney within the first 3 days post transplant. Graft survival at 1yr was 96% and no allograft was lost due to thrombotic complications.

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Underline represents presenting author.

613A
FR-PO1064

The Influence of Induction Immunosuppressive Therapies and Diabetes on Graft Loss After Kidney Transplant

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Background: Induction therapy plays a significant role to reduce the rate of acute rejection in kidney transplant (KT). Understanding differences in outcomes associated with specific induction agents may lead to improvements in our treatment arm. Our objectives were to examine the influence of various induction therapies and diabetes on graft and patient survival after KT.

Methods: We used the 2000-2013 United Network for Organ Sharing (UNOS) data to evaluate the effectiveness of induction therapies and diabetes on graft and patient survival after KT. The patients were divided into four groups based on induction therapy: Basiliximab (n=24,484), alemtuzumab (n=3,321), rabbit anti-thymocyte globulin (n-ATG) (n=54,974) and daclizumab (n=13,358). Also the patients were divided into four groups based on diabetic status: non-diabetic (n=192,333), type1 diabetes (n=11,863), type 2 diabetes (n=45,543) and new onset of diabetes (n=10,509). The main outcome were the risk of graft loss and death at 1,3,5,10 years. Cox proportional hazards model was used to estimate the hazard ratios.

Results: Graft loss was significantly higher in alemtuzumab group (HR=1.171 ; P< 0.002) and rabbit anti-thymocyte globulin group (HR=1.109 ; P< 0.0001) versus basiliximab group. Daclizumab group showed significantly lower risk for graft loss (HR=0.902; P< 0.0001) than basiliximab group. Death was significantly higher in rabbit anti-thymocyte globulin group (HR=1.075; P< 0.0001) versus basiliximab group. Daclizumab group showed significantly lower risk for death (HR=0.850; P< 0.0001) than basiliximab group. Graft loss was significantly higher in type 2 diabetes (HR=1.451; P< 0.0001).

Conclusions: Induction immunosuppressive therapies and diabetic status play significant role in long-term graft and patient survival. Basiliximab and daclizumab as IL-2 RA receptor antagonists have better long-term graft and patient survival outcomes.

FR-PO1065

Does Induction Type Influence Outcomes in Kidney Transplant Recipients at Different Phases of Hepatitis B Infection?

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Background: Host response to hepatitis B virus (HBV) infection is variable with some patients progressing to chronic liver disease. Immunosuppression associated with kidney transplantation in such patients may increase the risk of disease progression. We aimed to analyze the impact of potent depleting vs. non-depleting antibody induction on the outcomes in our de novo kidney transplant recipients (KTRs) at different serological stages of HBV infection.

Methods: Using UNOS database, we identified adult KTRs from 2001 to 2011 who at the time of transplantation were in one of the 3 serological stages of HBV infection: HBsAg+/HBcAb-(early infection), HBsAg+/HBcAb+ (inactive carrier or immune tolerant) or HBsAg-/HBcAb+ (clearing infection) sero-status. These findings support a practice of choosing induction type based on the immunological risk in such recipients rather than the serological status following HBV infection.

FR-PO1066

Health Economic Analysis of Rabbit Antithymocyte Globulin (Thymoglobulin) versus Basiliximab (Simulect) in Renal Transplantation – A German perspective

Friedrich Thaiss,1 Claudia Sommerer,1 Barbara M. Suvelack,1DSU Dagran,1 Ingeborg A. Hauser,2 Peter Schenker,2 Daniel Baumeier,2 Björn Nashan,3 Athena Study Group; 4Novartis Pharma Germany.

Background: Kidney transplantation is now accepted as a proven therapeutic modality prompting a greater need to understand the cost-effectiveness of different treatment approaches.

Methods: The primary objective of this study was to quantify the economic consequences of acute rejection and adverse events in patients undergoing cadaveric kidney transplantation and receiving ATG (Thymoglobulin - Thymo) compared with those receiving basiliximab (Simulect - Sim). Health economic data were collected according to reimbursement calculations from 3 German sites in an existing database (Brennan et al NEJM, 2006).

Results: Based on the clinical data from the Brennan trial, the study quantified current data and changes in treatment patterns. Results demonstrate that at 12 months the cost of the Thymo-regimen is €5,753 more than that of the Sim-regimen. However, costs of delayed graft function, nonfatal graft failure events and post-graft failure dialysis are lower among Thymo treated patients. Thymo treated patients incurred higher graft maintenance costs, consistent with their longer graft survival. In total the associated cost-offset from lower rejection events with Thymo offset the added cost from drug treatment and therefore Thymo is a more cost-efficient resource vs Sim due to cost avoidance. To further evaluate differences between the two groups we considered quality-adjusted life year differences. The Thymo cohort is projected to enjoy 405,714 QALY after 1 year. After a decade, the Thymo cohort is projected to cost 332,232 Euros less than the Simulect cohort while enjoying 10.8 more QALYs.

Conclusions: This analysis was intended to provide information that should be considered when weighing the costs and benefits of two immunosuppressive regimens and to investigate if treatment changes might result in more cost-effective care.

Funding: Pharmaceutical Company Support - Sanofi and RJM
FR-PO1085

Thymoglobulin Induction Therapy; Results for 5 Years – Improving the Survival of Renal Allograft and Patient
Virginia Barba Pedroza, Benjamin Gomez-Navarro. Nephrology and Transplantation, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, Mexico.

Background: The factor that impacts the survival of renal allograft is the presence of acute rejection. In our city, using Thymoglobulin has offered to patients at high immunological risk, and through the years has sought to reduce adverse events use. The objective is to evaluate the frequency of acute rejection during the last 5 years in patients receiving Thymoglobulin induction.

Methods: An ambispective cohort, patients transplanted in UMAE-CMNO, Jalisco, Mexico is included in the period June 2010 to June 2014 who received induction therapy with Thymoglobulin. Was recorded the frequency of acute rejection, the frequency of infections, use of Filgrastim(G-CSF), graft loss and death at 12 months of transplantation.

Results: A 370 patients were included, which received initial doses of Thymoglobulin 0.6mg/kg-1.5mg/kg. In 2013, by multivariate analysis Thymoglobulin dose that was associated with a lower incidence of acute rejection was analyzed and found that 1mg/kg for 4 days (cumulative dose 4mg/kg) is a protective factor for the occurrence of acute rejection (IC 95%: 0.11-0.60, OR 3.7, p<0.001), for this reason almost patients received this dose. In 2010, the rate of rejection was 10%, and actually is 7.8% (p=0.05).

Conclusions: Interestingly, in our hospital, we observed a lower rate of acute rejection and improved patient survival and allograft. Apparently finding the right dose in our patients has allowed thymoglobulin induction is safe and minor complications.

FR-PO1068

Early Conversion to Everolimus in De Novo Renal Transplant Recipients: 24-Month Results from the ELEVATE Study
Johan W. De Fijter, Hallvard Holdaas, Patricia M. Lopez, Cesar Escrig, Zailong Wang, Josep M. Cruzado, Markus van der Giet. For the ELEVATE Study.

Background: Long-term therapy with calcineurin inhibitors (CNIs) is associated with nephrotoxicity i.e., glomerulosclerosis and interstitial fibrosis (IF). We present the 24 month results from the ELEVATE study (NCT01114529), which compared an early conversion to everolimus (EVR) vs standard CNI in renal transplant recipients (RTxR).

Methods: ELEVATE, a 24M, multicenter, open-label randomized, de novo RtxRs 10–14 weeks post-Tx to convert from CNI to EVR (n=360; CsA 6–10 ng/mL) vs standard CNI (n=357; CsA TAC 5–10 ng/mL, CSA 100–250 ng/mL); all received enteric-coated mycophenolate sodium and steroids. Primary endpoint was change in eGFR (MDRD4) from RND to M12. Main secondary endpoint a composite efficacy of treated biopsy-proven acute rejection (IBPAR, Banff ≥IIb), graft loss, or death and safety.

Results: At M12, the clinical benefit observed in eGFR did not achieve statistical significance (1.70, 95% CI: -0.53, 3.95; p=0.134) whilst eGFR at M24 for EVR was significantly better (p<0.006). The composite efficacy endpoint was comparable at M12 & M24. Overall acute rejection rates were very low with more iIBPAR in EVR, but mild in severity (Banff I/II & III). In both the groups, number of patients with de novo DSA at M12 or M24 was low and unrelated to outcomes. At M24, rate of CAN (IETF/A) was significantly higher in the CNI versus EVR (35.1 vs 26.7%, p=0.029).

Conclusions: Early conversion to EVR at 3 months vs continued CNIs better preserved renal function with comparable overall efficacy and safety up to 2-years.

Table: Outcomes at M12 and M24

<table>
<thead>
<tr>
<th>Outcome</th>
<th>M12</th>
<th>M24</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (%)</td>
<td>8</td>
<td>3.7</td>
</tr>
<tr>
<td>Graft loss (%)</td>
<td>13</td>
<td>2.2</td>
</tr>
<tr>
<td>Use of g-CSF (%)</td>
<td>56</td>
<td>4.5</td>
</tr>
<tr>
<td>Infections (%)</td>
<td>34</td>
<td>32</td>
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</tbody>
</table>

Conclusions: Currently few patients use of rG-CSF because leukopenia- neutropenia, lost the renal graft or die for the first year.

FR-PO1069

Randomized Trial of Tacrolimus/Everolimus versus Tacrolimus/Enteric-Coated Mycophenolate Sodium to Prevent Biopsy-Proven Acute Rejection and Chronic Allograft Injury in Adult, Primary Kidney Transplantation
Gisselle Guerra, Jeffrey J. Gaynor, David Roth, Warren L. Kupin, Dela D. Mattiazzi, Michael J. Goldstein, Linda J. Chen, George William Burke, Gaetano Ciancio. Dept of Medicine, Miami Transplant Inst, Miami, FL; Dept of Surgery, Miami Transplant Inst, Miami, FL.

Background: It was of interest to determine whether everolimus(EVL) might reduce the incidence of biopsy-proven acute rejection(BPAR) during the first 12mo post-kidney transplantation.

Methods: We performed a single-center, open-label randomized trial comparing two maintenance immunosuppression regimens: TAC/EVL (Group A) vs TAC/EC-MPS (enteric coated mycophenolate mofetil)(Group B). In both treatment arms, dual maintenance immunosuppression regimens: TAC/EVL (Group A) vs. TAC/EVR (Group B). In both treatment arms, dual induction therapy (anti-thymocyte globulin plus basiliximab) was given along with planned EC-MPS(enteric coated mycophenolate mofetil)(Group B). In both treatment arms, dual maintenance immunosuppression regimens: TAC(EVL) vs. TAC/EVR, induction therapy (anti-thymocyte globulin plus basiliximab) was given along with planned EC-MPS.

Results: Among 30 eligible adult participants (15 per treatment arm), median follow-up was 11mo(range: 3-20mo). Mean TAC levels were 5-8 ng/ml in both arms; mean EVL level was 110 ng/ml in Group A vs 130 ng/ml in Group B. One patient in Group A vs. 3 patients in Group B experienced BPAR-actual estimates at 12mo were 10%/9% vs. 20%/10%, respectively(P<0.5). All 3 BPAR’s in Group A occurred prior to 6mo vs. the single BPAR in Group B occurring after 6mo (logrank P=0.09 during the first 6mo post-transplant). A slight trend for more favorable renal function(eGFR) was also observed in Group A at 1-3mo post-transplant (P=0.06, 0.19, 0.18, respectively). No graft failures or deaths have been observed. Regarding the incidence of NODAT, a slight trend against Group A was observed (2/15 vs. 0/15 in Group B, P=0.13), and higher mean cholesterol and triglyceride levels also occurred in Group A during 2-12mo(P=0.10 at various times).

Conclusions: Although a relatively favorable performance for the experimental maintenance regimen of TAC/EVL in terms of a low BPAR rate during the first 12mo post-transplantation was observed, it may occur at the expense of possibly higher rates of NODAT and lipidemia.

FR-PO1070

Early Conversion from Cyclosporine to Everolimus following Living-Donor Kidney Transplantation: Outcomes at Five Years Post-Transplant in the Randomized ZEUS Trial: A Post-Hoc Analysis
Ingeborg A. Hauser, Frank Lehner, Wolfgang Arns, Clemens Budde, Ute Eisenberger, Rudolf Wuthrich, Petra Reimke, Rolf A. Stahl, Anja Susanne Mühlfeld, Heiner H. Wolters, Barbara M. Suwelack, Katharina M. Heller, Martina Porstner, Oliver Witzke, Claudia Sommerer. ZEUS Study Group, Germany; ZEUS Study Group, Switzerland; Novartis Pharma, Germany.

Background: To study renal function and patient outcome after 5 years in living-donation subgroup of kidney de novo transplant recipients after conversion to an everolimus (EVR) based regimen and withdrawal of calcineurin inhibitor therapy. Methods: Post hoc subgroup analysis from the prospective, open-label, controlled, multi-center study ZEUS. 300 renal transplant (Tx) patients were randomized at month (mo) 4.5 post Tx to either receive EVR plus enteric coated-mycophenolate sodium (EC-MPS) or cyclosporine (CsA) plus EC-MPS regimen. Of these 80 living donation recipients (EVR group n=42; CsA group n=38). Patients could enter an observational follow-up (FU) period where outcome on patients’ safety and efficacy was recorded until mo 60 post Tx.

Results: Adjusted eGFR (Nankivell) in living-donation subpopulation at mo 60 was 67.2 (95% CI [62.5, 71.9]) ml/min/1.73m² in EVR vs 60.8 (95% CI [56.0, 65.6]) ml/min/1.73m² in CsA patients, resulting in a difference of +6.6ml/min/1.73m² in favor of EVR patients (p=0.031, ANCOVA). Unadjusted mean eGFR after 5 years was 69.5 ml/min for EVR vs 66.0 ml/min for CsA (p=0.006, Wilcoxon). BPARs during FU since mo12 occurred in 4 patients of the EVR and 3 of the CsA group, all BANFF grade IIA except one BANFF grade IIA among EVR patients. From randomization to mo 60 one death occurred in CsA living-donor recipients, two in the EVR living-donation subgroup; one graft loss occurred in the EVR, none in the CsA group. Overall safety profile was similar between both treatment groups.

Conclusions: The presented analysis shows that EVR-based regimen with early elimination of CNI therapy in living-donor kidney transplant recipients is associated with a significant benefit on renal function maintained over 5 years post Tx without compromising safety and efficacy.

Funding: Pharmaceutical Company Support - Novartis Pharma GmbH

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO1072

Co-Expression of RORgt and IFN-Gamma in Regulatory T Cells of Long-Term Sirolimus-Converted Kidney Transplant Recipients

Opas Traithanon, Ekamol Tantattamboon, Mohammed Javeed Ansari, Lorenzo G. Gallon. Medicine - Nephrology, Northwestern Univ, Chicago, IL.

Background: Sirolimus (TAC) and sirolimus (SRL) are commonly used immunosuppressive drugs in kidney transplantation. SRL has been shown to induce the expansion of regulatory T cells in post-transplant recipients converted from TAC to SRL.

Methods: This study included 84 renal transplant recipients from a randomized trial of SRL conversion (~55%) or TAC maintenance (~29%). The conversion started at 12 months post-transplant. PBMC were collected at 0(baseline), 6, 12, 24, 36 and 48 months post-randomization. T cell subpopulations were analyzed by flow cytometry.

Results: At baseline, frequencies of CD4+CD25+Foxp3+ T cells were similar in both groups. The ROC-AUC analysis was applied to define optimal cut-off levels of CD4+CD25+Foxp3+ T cells at 48 months and the differences were not significant compared to the TAC group at 48 months post-conversion (1.41±0.60% (SRL) VS 1.07±0.44% (TAC), p=0.24). Intraacellular staining for interferon (IFN)-γ, interleukin 17 (IL-17) and RAR-related orphan receptor gamma 2 (ROGRT) showed no difference at 24 months. However, at 48 months, we found that PMA-stimulated CD4+CD25+Foxp3+ T cells in SRL-converted group had more percentage of cells that co-expressed IFN-γ and ROGRT which are Th1 and Th17 markers respectively.

Conclusions: Switching from TAC to SRL results in an expansion of CD4+CD25+Foxp3+ T cells which peaked at 12 months post-conversion but no significant frequency differences were observed at 48 months follow-up and we observed more percentage of T cells that co-expressed IFN-γ and ROGRT in the SRL group.

FR-PO1073

Pulmonary Complications in Kidney Transplant Recipients: Role of Everolimus

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Background: Kidney transplant recipients are at higher risk to develop pulmonary complications as drug related side-effects.

Methods: 500 kidney transplanted patients were retrospectively analyzed for pulmonary complications based on chest RX and HRCT, BAL, oximetry and clinical data. Results were classified as parenchymal, interstitial and neoplastic complications.

Results: We found 168 pulmonary complications in 161 pts (32%): 137 parenchymal, 18 interstitial and 3 neoplastic. The higher PFIS score was recorded in patients treated with Sirolimus (R=0.63±0.06% (SRL) VS 0.66±0.12% (TAC), p<0.01). However, we observed a decline of CD4+CD25+Foxp3+ T cells at 24 months and the differences were no longer significant compared to the TAC group at 36 and 48 months post-conversion (1.41±0.60% (SRL) VS 1.07±0.44% (TAC), p=0.24). Intraacellular staining for interferon (IFN)-γ, interleukin 17 (IL-17) and RAR-related orphan receptor gamma 2 (ROGRT) showed no difference at 24 months. However, at 48 months, we found that PMA-stimulated CD4+CD25+Foxp3+ T cells in SRL-converted group had more percentage of cells that co-expressed IFN-γ and ROGRT which are Th1 and Th17 markers respectively.

Conclusions: Switching from TAC to SRL results in an expansion of CD4+CD25+Foxp3+ T cells which peaked at 12 months post-conversion but no significant frequency differences were observed at 48 months follow-up and we observed more percentage of T cells that co-expressed IFN-γ and ROGRT in the SRL group.

FR-PO1074

High Doses of M-TOR Inhibitors May Induce Pulmonary Pro-Fibrotic Effects in Renal Transplant Recipients: Result of a Translational Comparative Research Approach Between Everolimus versus Tacrolimus

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Background: Pulmonary fibrosis is a quite frequent adverse effect occurring in mTOR-I-treated renal transplant (RT) recipients. It has been suggested that epithelial to mesenchymal transition (EMT) in airway cells may determine this condition. However, the exact biological machinery involved is not completely clarified.

Methods: We performed a translational study. First we analyzed the in vivo pulmonary pro-fibrotic potential of Everolimus (EVE) by computing a pulmonary fibrosis index score (PFIS), obtained by using several computerized tomography, hemogasanalytic and spirometric parameters, in 13 RT patients in EVE treatment and 13 patients treated with Tacrolimus (TAC). Subsequently, we carried out an in vitro study in which we assessed whether EVE at low-dose (5, 10 ng/ml) or high-dose (100 ng/ml) or Tacrolimus (5 ng/ml, 500 ng/ml, 5 μM) was able to induce EMT in bronchial epithelial cells (Nuli-1) and human type II pneumocyte-derived A549 cells. Additionally, microarray analysis was performed to identify differentially expressed genes.

Results: In the in vivo part of the study, we found that the PFIS was higher in EVE-treated patients compared to those treated with ADV (mean±SD: 2.58±1.83 versus 1.21±1.25). This effect was positively correlated to the trough levels (TL) in EVE-treated patients (R2=0.35). The higher PFIS score was recorded in patients treated with ADV that reached a TL≥6. Interestingly, in vitro, only very high doses of EVE were able to induce up-regulation of alpha-SMA, Fibronectin and Vimentin at gene and protein level in A549. No effects were seen in Nuli-1. Interestingly, microarray analysis confirmed the above-mentioned results.

Conclusions: All together, our data suggested that only very high doses of EVE may induce pulmonary fibrosis and that this effect could be mediated by EMT in pneumocyte cells.

FR-PO1075

Efficacy and Safety of Three Different Treatment Regimen in De Novo Renal Transplant Patients: 48 Months Follow-Up Results of the HERAKLES Trial

Wolfgang Arns, Volker Klicm, Claudia Sommerer, Johannes Jacobs, Bruno Vogt, Ingeborg A. Hauser, Petra Reinkes, Rolfa Stahl, Thomas Rath, Martina Porstner, Martin G. Zeier, Frank Lehner, Klemens Buddle, Oliver Witzke. 1HERAKLES Study Group, Germany; 2HERAKLES Study Group, Switzerland; 3Novartis Pharma, Germany.

Background: To compare safety and efficacy of 3 different immunosuppressive regimen at month (mo) 48 after kidney transplantation (KTx).

Methods: 802 patients (pts) were included in this 1 year, prospective, open-label, randomized, controlled multi-center study with observational follow-up (FU) to mo 60 post Tx. After induction therapy all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 mo post Tx, 499 pts were randomized 1:1:1 to either a) continue standard CsA(100-180 ng/ml)+EC-MPS(n=166) (STD), b) to a calcineurin inhibitor (CNI)-free regimen with everolimus (EVR) (5-10 ng/ml)+EC-MPS (n=171) or c) to a CNI-reduced regimen with EVR (3-8 ng/ml)+ reduced CsA (50-75 ng/ml; n=162). All pts continued on steroids. At time of mo 48 FU, interim-analysis of the data were available from 1175 (79%) of the ITT population.

Results: At baseline, frequencies of CD4+25 hi Foxp3+ T cells were similar in both groups and the ROC-AUC analysis was applied to define optimal cut-off levels of CD4+25 Foxp3+ T cells at 48 months and the differences were no longer significant compared to the TAC group at 48 months post-conversion (1.41±0.60% (SRL) VS 1.07±0.44% (TAC), p=0.24). Intraacellular staining for interferon (IFN)-γ, interleukin 17 (IL-17) and RAR-related orphan receptor gamma 2 (ROGRT) showed no difference at 24 months. However, at 48 months, we found that PMA-stimulated CD4+CD25+Foxp3+ T cells in SRL-converted group had more percentage of cells that co-expressed IFN-γ and ROGRT which are Th1 and Th17 markers respectively.

Conclusions: For safety and efficacy of 3 different immunosuppressive regimen at month (mo) 48 after kidney transplantation (KTx).

Funding: Pharmaceutical Company Support - Novartis Pharma

FR-PO1076

Spartacus: Multicentre, Prospective Randomised Study Comparing Tacrolimus Hexal® versus Prograf® Based Regimen in De Novo Renal Transplant Recipients

Wolfgang Arns, Thomas Rath, Lars C. Rump, 1Klemens Buddle, Daniel Baueimer, Peter Schenker. 1Spartacus Study Group; 2Novartis Pharma Germany.

Background: In a transplant (Tx) setting, studies evaluating pharmacokinetic (PK) parameters and therapeutic equivalence of generic tacrolimus vs the reference drug are lacking. Spartacus (NCT016149427) study was designed to compare PK profile of tacrolimus hexal® with prograf® in renal Tx recipients (RTxR).

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

Underline represents presenting author.
**Methods:** In this prospective, two-phase open-label study, 76 de novo RTxR were randomized to receive tacrolimus hexal® (n = 35) or prograf® (n = 41), both in combination with enteryi-coated mycophenolate sodium + corticosteroids + basiliximab induction therapy. Starting dose of tacrolimus was 0.15 mg/kg/day, adjusted to target trough levels (C0) of 8–12 ng/mL from Tx to month (M) 1; 5–10 ng/mL up to M3; and 5–8 ng/mL up to M6. Primary objective of the study in Phase 1 was to demonstrate comparable PK (ratio of AUCn0-1 month one period, tac. hexal® vs prograf®). Here we present the PK results of the first month.

**Results:** At M1, the dose-normalised tacrolimus 12-h-AUC of 8/30XLL was comparable between tac. hexal® vs prograf® (adjusted log-transformed LS mean, 2.9 ± 3.0; difference, 0.076; 90% CI: -0.169, 0.321; p = 0.605; adjusted back-transformed LS mean, 19.0 ± 20.5; ratio, 1.079; 90% CI: 0.844, 1.378, p = 0.605). LS mean value for Cmax (1/10^3XLL) and mean 12 h tacrolimus C0 (mg/L) at M1 were comparable between tac. hexal® and prograf® (1.4 ± 0.9, 1.0 ± 0.8; 90% CI: 0.534, 0.737; C0, 12.2 ± 11.1, 11.1, respectively). Of 76 patients, 40 (PK-Sect 40 pts.) to date completed 6-M treatment; tac. hexal®, n = 19; prograf®, n = 21. At M6, tacrolimus hexal® vs prograf® had a comparable incidence of composite events (ITT, n=77; 5.7% vs 9.8%, p = 0.681) and its individual components (BPAR [5.7% vs 7.3%], graft loss [0.0% vs 2.4%], death [0.0% vs 2.4%]). Incidence adverse events (AES, SAFEs) were comparable (AES: 97.1% vs 100%; serious AES: 37.1% and 42.1%).

**Conclusions:** Tacrolimus hexal® has a PK profile similar to that of prograf®, with comparable efficacy and safety in de novo RTxR. **Funding:** Pharmaceutical Company Support - Novartis Pharma Germany

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**FR-PO1079**

**Intensified Dosing of Mycophenolate Mofetil Formulated Is Associated With Slower Progression of Chronic Renal Allograft Injury – Results from a Randomized Controlled Trial**

**Mladen Knotek, 1 Miha Arnol, 2 Jadranka Buturovic, 3 Danica Galesic Lubicanovic, 2 Nika Jocic. 1**

**1Dept of Medicine, Renal Div, Univ of Zagreb Medical School, Merkur Univ Hospital, Zagreb, Croatia; 2Dept of Nephrology, Univ Medical Center Ljubljana, Ljubljana, Slovenia; 3Inst of Pathology, Univ of Ljubljana Medical Faculty, Ljubljana, Slovenia.**

**Background:** Intestinal fibrosis (ci) is a major histological predictor of long-term graft outcome. This randomized controlled trial (NCT01860183) was designed to evaluate the effect of intensified mycophenolate mofetil (MMF) dosing on progression of ci during the first year post kidney transplantation (KT).

**Methods:** Immunologically-low-risk KT recipients were randomized to MMF 3g/d, or 2g/d during the first year post KT. Immunosuppression consisted of basiliximab induction, with tacrolimus, MMF ± steroids. Protocol biopsies were performed at implantation, and at 1, 3, 6, 12 and 24 months post-KT. Progression of ci (Di) was calculated as ci12-ci0. MMF dose was calculated as an average dose at 1, 6, 12 and 24 months. Difference in Di with respect to MMF dose was analyzed in an ITT population using one-way ANOVA.

**Results:** Here we report interim results from patients who completed 12 month follow-up by June 1st 2015. Patient and KT data are similar in MMF 3g and MMF 2g group, except for average MMF dose, which was higher in the 3g group (2967.1±321.6 vs. 1745.3±359.0 g, p<0.001). In an overall study population ci progressed during first 12 months by 0.45±0.51 (ci0) to 1.41±0.87 (ci12) (p<0.001). Di was lowest in the MMF 3 g group (0.06±0.74) as compared with MMF 2 g group (1.36±0.93; p<0.01). Serum creatinine at 1 year was similar in both MMF groups (116.5±25.0 vs. 115.1±33.7; p<0.001). Incidence of acute rejection was similar and no significant differences were seen in common adverse events between both groups.

**Conclusions:** Intensified MMF dosing (3g/d) daily during the first posttransplant year in a tacrolimus-based regimen may be associated with slower progression of chronic allograft injury.

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

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**FR-PO1080**

**Safe Conversion from Tacrolimus to Belatacept in Kidney Transplant Recipients with Allograft Dysfunction**

**Anil Reami, Dhiren Kumar, Hasan Fattah, Anne L. King, Pamela Kimball, Ankur Atal Gupta, Gaurav Gupta. Virginia Commonwealth Univ, Richmond, VA.**

**Background:** Belatacept might be an alternative to Calcineurin Inhibitors (CNI) to avoid short and long-term nephrotoxicity. Prior data on low immunologic risk de-novo kidney transplant recipients (KTxP) with stable graft function switched from a CNI to belatacept demonstrated improved renal function. There is minimal data on the use of belatacept for sensitized patients and those with impaired graft function [estimated glomerular filtration rate (GFR)<50].

**Methods:** EBV seropositive patients were converted to belatacept from tacrolimus for biopsy proven presumed acute CN1 toxicity and/or interstitial fibrosis/tubular atrophy. Belatacept was initiated based upon prior published protocol (Grimyo et al., Transpl Int 2012 Oct). Mycophenolate dose was increased from baseline dose of 1-2g/d to a dose of 2-3g/d to minimize risk of rejections.

**Results:** Seventeen (mean age=46±10 years) patients were switched from tac to belatacept at a median of 4 months post-KTxP. A majority were African-American (13/17; 76%) and received deceased donor KTxP (76%). Seven patients (41%) were sensitized (median PRA=13%; range=0-99%). Renal function improved significantly from a peak mean GFR of 28±12 ml/min/1.73m² to an GFR of 42±16ml/min/1.73m² (p<0.001) at a median follow-up of 15 (range=7-30) months post-conversion. Surveillance biopsies performed in 7/17 patients did not show rejection or worsening of chronicity. No evidence of de-novo donor specific antibody (DSA) was noted in 16/17 (94%) patients. One patient with pre-existing DSA and stable creatinine had rising DSA after a viral infection. A biopsy showed subclinical antibody-mediated rejection. There were no cases of BK viremia, CMV disease or malignancies.

**Conclusions:** In this first study on KTxP patients with significantly reduced GFR we report improved recognition in renal function in patients converted from tacrolimus to belatacept with acute CN1 toxicity and chronic allograft fibrosis without a significant concurrent increase in risk of rejection, worsening chronicity and DSA. Further studies with protocol biopsies are needed to ensure safety and wider applicability of this approach.
FR-PO1081

Infusion of Belatacept in Kidney Transplant Recipients

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1Univ of California, San Francisco; 2Henry Ford Hospital, Detroit; 3Vanderbilt Univ, Nashville; 4Tulane Univ Hospital and Clinic, New Orleans; 5BMS, Lawrenceville; 6Univ of North Carolina, Chapel Hill.

Background: Belatacept (bela) is an IV administered selective T-cell co-stimulation blocker approved for preventing organ rejection in EBV-positive adult kidney transplant recipients. The logistics of IV maintenance therapy are challenging for some pts/clinicians; the safety of home infusion has not been well described. Phase 2/3 study participants had received bela home infusion if the site sought IRB approval and if the pt lived ≥2 hrs from the site and had been exposed to bela for >28 wks in 008 or >16 wks in 010, >6 wks in 034. 008 and 027 compared bela with CsA regimens with basiliximab induction. In 010, pts receiving a stable CNI regimen were switched to a bela regimen. 034 compared bela with tacrolimus steroid-sparing regimens under thymoglobulin induction. Rate and time to pre-specified peri-infusional AEs and peri-infusional serious AEs were recorded in pts who received bela in the home (N=66) or in a facility (N=672).

Results: Pts administered bela in the home received a median of 32.5 (range, 1–61) infusions. No pre-specified or serious peri-infusional AE was reported, including in the 034 study.

Conclusions: No pt (irrespective of steroid use) receiving home infusion of bela had a pre-specified or serious peri-infusional AE. These data suggest that bela was safely administered in the home.

FR-PO1082

Optimizing the Immunosuppression Regimen with Belatacept

David Wojciechowski, 1 Sinhdu Chandran, 2 Flavio Vincenti. 1 MGH; 2UCSF.

Background: Belatacept with basiliximab induction plus maintenance MMF/corticosteroids is associated with a higher 3-year eGFR compared to ciclosporine but a higher 1-year incidence of acute rejection. In an attempt to optimize the belatacept immunosuppression regimen we investigated the safety and efficacy of a novel combination utilizing belatacept with rATG induction (3 mg/kg) and maintenance everolimus ± immunosuppression regimen we investigated the safety and efficacy of a novel combination.

Methods: Retrospective single center analysis of the first 33 patients to receive our belatacept regimen compared to a historical control group of 66 patients matched for donor type, KDPI, ESRD cause, CIT, and corticosteroid protocol who met our belatacept inclusion criteria. We tested archival peripheral blood of 218 kidney recipients for CYP3A5 genotyping with PCR-SSP. The doses and blood concentrations of tacrolimus and CsA for recipients were measured at day7, 1st month , 3rd month,6th month and 12th month after renal transplantation, as well as hepatic and renal function. In addition, we also observed the incident of acute rejection happening on these participants.

Conclusions: 123 patients took tacrolimus treatment and 95 patients took CsA treatment after renal transplantation.In tacrolimus treatment group, genotype CYP3A5*GG was associated with low tacrolimus dose-adjusted concentration after transplantation, showing lower acute rejection rate compared to CYP3A5*AA/AG group but with no significant difference (P=0.154). In CsA treatment group, there was no significant difference in acute rejection rates between CYP3A5*AA/AG and CYP3A5*GG (P=0.494) with no difference in dose-adjusted concentration as well. For CYP3A5*GG patients, tacrolimus treatment cause lower acute rejection rate than CsA treatment (P=0.030), taking shorter time to get a stable immune situation than CsA treatment. For CYP3A5*AA/AG patients, tacrolimus treatment cause similar acute rejection rate with CsA treatment (P=0.982), but took longer time to get a stable immune situation than CsA treatment. What’s more, tacrolimus treatment costs much than CsA treatment.

Conclusions: These results indicate that CYP3A5*AA/AG carriers need higher tacrolimus dose than CYP3A5*GG homozygote to achieve the target blood concentration. And, the treatment selection of tacrolimus and CsA was associated with acute rejection rate. In conclusion, the selection of tacrolimus is recommended in kidney transplant recipients with CYP3A5*GG genotype, while CsA is preferred in patients with CYP3A5*AA/AG genotype.

FR-PO1083

A Change in Insulin Sensitivity and Lipid Profile in Renal Transplant Recipients Converted from Cyclosporine or Standard Release Tacrolimus to Once-Daily Prolonged Release Tacrolimus

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Background: New-onset diabetes after transplantation may be associated with the use of tacrolimus (Tac) causing impaired insulin release or reduced insulin sensitivity. And, dyslipidemia commonly occurred after transplantation. Such effects in insulin sensitivity and lipid profile have not been studied in renal transplant recipients receiving traditional twice-daily tacrolimus (TacBID) or cyclosporine and then compared to the new once-daily prolonged release formulation of tacrolimus (TacOD).

Methods: We performed an observational prospective study of 15 stable non-diabetic renal transplant recipients on change in insulin sensitivity and lipid profile in renal transplant recipients converted from cyclosporine or standard release tacrolimus to once-daily prolonged release tacrolimus. We evaluated the level of HbA1c,total cholesterol, HDL, LDL, TG, apolipoprotein A1, apolipoprotein B, serum creatinine, fasting plasma glucose, fasting insulin and HOMA-IR at baseline, two and four months. To analyze differences in parameter, we performed a t-test in both groups (cyclosporine to TacOD conversion group/TacBID to TacOD conversion group), and GLM-repeated measures ANOVA. HOMA-β = (360 X Fasting insulin)/(Fasting glucose-63) HOMA-IR (insulin resistance) = (Fasting glucose X Fasting insulin)/405.

Results: At baseline, parameters were not different in both groups (cyclosporine to TacOD conversion group/TacBID to TacOD conversion group). In GLM-repeated measures ANOVA, the result did not showed and any change in insulin sensitivity and lipid profile and variation in dose at baseline, two and four months.

Conclusions: Conversion from standard TacBID or cyclosporine to TacOD is safe. In spite of a reduced Tac exposure, there was no change in insulin sensitivity and lipid profile in renal transplant recipients.
FR-PO1085

Intraprotential Tacrolimus Level Variability in Pediatric Kidney Recipients Predicts Allograft Loss After Transfer to Adult Care
Hilda E. Fernandez,1 Sandra Amaral,1 Pamela A. Shaw,2 Roy D. Bloom,2 Alden Michael Doyle,1 Sumit Mohan,1 Susan L. Furth,2 Columbia Univ; CHOP; PENN; Hahnemann Univ.

Results: 74 of 56 subjects had sufficient data for analysis. Median age at transplant was 15.9 yrs (8.5-18.9). The cohort was primarily male (66%), White (77%), had CUKAT (8%), and 46% had LRKT. Median age at transfer was 20y (17.4-22.1). Four patients had allograft loss within 365 days post-transfer. Pre-transfer CV TAC with subjects post-allograft loss post-transfer (n=4) was significantly higher as compared to subjects without allograft loss (n=20) (49.4% vs 26.2%, p = 0.0275).

Conclusions: CV TAC may aid in identifying patients at risk for allograft loss post-transfer. Future analysis will investigate the effect of race, age at transfer, rejection, loss post-transfer (n=4) was significantly higher as compared to subjects without allograft.

Funding: Other NIH Support - NIH Kidney Disease Epidemiology T32 Minority Supplement

FR-PO1086

High Tacrolimus Level Variability in the Early Post-Transplant Period Is Associated with Reduced Patients and Graft Survival After Kidney Transplantation
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Background: The effect of Tacrolimus levels variability in the early period after kidney transplantation has not previously been studied. We sought to evaluate whether increased drug level variability is associated with reduced graft survival and evaluate the relative effect of exposure to high and low drug levels.

Methods: We screened the Rabin Medical Center registry database for adult patients from 2001 to 2013 that were treated with tacrolimus, micophenolate mofetil and corticosteroids and had at least 6 values of drug level during the first six months after the transplantation. Variability was defined as the time average of the absolute value of the difference from the mean and this value was divided by the mean to get the variability index. Univariate and multivariate Cox proportional hazard model was used with the combination of death and graft failure as composite outcome.

Results: We identified 803 patients who met the inclusion criteria, ninety eight (12.2%) of them reached the end point during median follow up time of 3.7 years (range 0.5 to 12.9 years). Increased variability index was associated with increased hazard of death or graft failure by univariate (Hazard Ratio (HR) 1.029 per %, 95% Confidence Interval (CI) 1.006-1.052, p=0.013) and multivariate models (HR 1.036 per %, 95% CI 1.01-1.062, p=0.006). Variability was still significantly associated with reduced graft survival after introducing acute rejection into the model (HR 1.038 per %, 95% CI 1.008-1.06, p=0.006). Introducing exposure to levels above 15 ng/ml into the model didn’t change the association between variability index and the composite outcome while introducing exposure to levels below 5 ng/ml eliminated the association and made it non-significant (p=0.18).

Conclusions: High variability index in the first six month after kidney transplantation is associated with increased mortality and graft loss. This association is, probably, mediated by exposure to low drug levels.

Decision Tree Analysis of Renal Transplantation Recipients Outcomes: A Single Center Data Mining Jingye Zhou, Jianghua Chen. Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, China.

Background: Results from former literature on factors influencing renal transplant outcomes are quite confusion and few include factors influencing outcomes of rejection cases. This study was intended to get the factors in order and to provide reliable predictive models for clinical practice with decision tree analysis, and attempted to discuss about deceased donor integrated into renal transplant database, predict the daily model growth and to serve personal medical care in big data era.

Methods: Renal transplant recipients registering between May 1988 and April 2014 in Kidney Center of the First Affiliated Hospital of Zhejiang University were included. Living state, retransplant, treatment history, renal transplant database, predict the daily model growth and to serve personal medical care in big data era. The results of our study show that the ABOi spousal donor is an important source of living donor in kidney transplantations (KTx). We aimed to compare the clinical outcomes in ABO incompatible KT (ABOi-KT) to those of ABO compatible KT (ABOc-KT) from spousal donors.

Methods: We analyzed 580 KTs from spousal donors among 3043 living donors KTs registered in the Korean Organ Transplantation Registry. Clinical outcome between ABOi-KT and ABOc-KT were compared by episodes of acute rejection (AR), graft function, grafts and patients survival rates.

Results: The proportion of spousal donors in ABOc-KT was higher than that of ABOi-KT (40.9% vs. 21.4%, P = 0.001). The biopsy proven AR-free survival rate in ABOc-KT was comparable to ABOi-KT (79.7% vs. 82.3%, P = 0.188). The renal allograft function showed no difference until 16 months after KT. The 3-year graft survival (92.5% vs. 95.7%), and patient survival (96.4% vs. 98.5%) were not significantly different between ABOi-KT and ABOc-KT groups (P = 0.05, respectively). Multivariate analysis revealed that ABO-KT from spousal donors did not affect the graft, patient survival and BPAR-free survival rate.

Conclusions: The results of our study show that the ABOi spousal donor is an important source of living donor, and can be a good alternative of overcoming donor organ shortage.
FR-PO1090

Three Year Outcome of a Pioneer ABOi Renal Transplant Programme in Malaysia

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Background: ABO incompatible (ABOi) renal transplantation increases organ donor pool and is an option for patients with no blood group compatible donors. We report here results of a pioneer ABOi renal transplant programme in Malaysia which was first established in Prince Court Medical Centre in 2011.

Methods: Ten patients entered into our ABOi programme between July 2011 and December 2013. Data were analyzed to determine the number of therapeutic plasma exchange (TPE) and/or immunoadsorption (IA) with Glycosorb columns to achieve target pretransplant ABO antibody titres of $<1:16$ and ABO titres post transplant. Graft function and rejection rates together with graft and patient survival at 3 years were also determined.

Results: Median baseline ABO titres was 1:128 and all patients achieved target pre transplant ABO titres of $<1:16$ after a median of 4 TPE and/or IA. Median follow up was 32 months with all patients maintaining ABO titres of $<1:16$ at follow up with no protocol post transplant TPE/IA. There was 1 case (10%) of acute cellular rejection at one year which was reversed with steroids but none had antibody mediated rejection. Patient and graft survival was 100% at 3 years with current median serum creatinine 108umol/L.

Conclusions: The results of our pioneer ABOi renal transplant programme with graft and patient survival of 100% at 3 years is extremely encouraging and suggest that graft and patient outcome is similar to ABO compatible renal transplants. The use of ABO incompatible donors may effectively increase organ donor pools especially in countries where both cadaver and living related kidney transplant rates remain poor. Our results also suggest that national ABOi renal transplant programmes may be effectively introduced and led by a private medical centre to complement and support more established renal transplant programmes in government institutions which are now beginning to perform their own ABOi renal transplants in light of our success.

Funding: Clinical Revenue Support

FR-PO1091

Improved Graft Outcome After Blood Transfusion: Still in Effect?

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Dept of Medicine, Southend Univ Hospital, Southend, Essex, United Kingdom; 3Dept of Nephrology and Transplantation, Barts and The Royal London Hospital, London, United Kingdom.

Background: Blood transfusions can lead to sensitisation in potential transplant patients. We previously quantified the risk of sensitisation from transfusion per se by looking at a cohort of male patients on the transplant waiting list and ascertaining the transfusion history from electronic records and questionnaires. Prior to standard triple immunosuppression, transfusions were associated with overall better graft outcome possibly by a tolerogenic effect or by selecting non-sensitisers. The majority of patients who were transfused do not become sensitised, we wanted to characterise graft outcome in this group.

Methods: We obtained graft outcome information on the original cohort of patients. Data was collected prospectively as part of routine surveillance.

Results: 100 out of the initial 126 male patients were transplanted. 10 were excluded from further analysis due to death or graft loss in the immediate post-transplant period. 11 of remaining 90 patients were DSA prior to transplantation, 8 also had a history of previous blood transfusion. 4 of the 8 patients with a previous blood transfusion and DSA had a rejection episode (2 AMR and 2 ACR). Of the remaining 79 patients who were DSA negative prior to transplantation, 26 had a previous transfusion (TR+ DSA-) and 53 did not have a history of transfusion (TR- DSA-). Comparison between the two groups is shown in (table 1).

Conclusions: Lack of sensitisation with a history of leuco-depleted transfusion is associated with a lower risk of rejection post-transplantation. This suggest that previous mechanisms of transfusion tolerance or “non-sensitisers” are still relevant in the modern immunosuppression era.

FR-PO1092

Geriatric Renal Transplantation in Deceased Donor Showed Compatible Clinical Outcomes to Younger Recipients

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Background: According to USA data annual report, while 50.3% of patients who start hemodialysis were aged over 65 years, only 19.3% of patients who underwent renaltransplantation was aged over 65 years. Elderly ESRD patients still are not underwent renal transplantation as much as younger recipients. There were many previous studies about geriatric renal transplantation outcome in white, however data in Asain were limited. The aim of this study is analysis of geriatric kidney transplantation outcome in Korea.

Methods: From May 1993 to December 2013, kidney transplantations performed in Asan medical center were retrospectively reviewed. Recipients younger than 20 years and who underwent other organ transplantation were excluded. Binary logistic regression was used for evaluating risk factors of graft failure before half-life. Half life of kidney allograft was defined as 10 years according to previous study.

Results: Regardless of donor type, there is no statistically significant difference in death censored graft survival between geriatric population and younger recipients.

Conclusions: Renal transplantation in geriatric population can be encouraged in Asain ESRD patients.

Multivariate analysis of deceased donor recipients revealed that recipients aged over 60 years was not a significant risk factor for graft failure before half-life.

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

620A
Long-term Survival and the Associated Risk Factors for Death in Patients (pts) with Kidney Transplantation (Tx)  

Tania Abeling,1  Irina Scheffner,1  Verena Broecker,2  Michael Mengel,1  Hermann G. Haller,1  Anke Schwarz,1  Wilfried Gwinner,1  Hannover Medical School, Germany; 1Cambridge Univ, United Kingdom; 2Univ of Alberta, Canada.

Background: Deaths over a period of up to 10 years (yrs) and the related risk factors were studied in Tx pts with protocol biopsies (Bx) (total observation: 4805 patient-yrs).

Methods: 892 pts with kidney Tx in 2000-2007 were included. Protocol Bx were taken at 6 weeks, 3, and 6 months post-Tx (n=2251). 862 Bx for cause were taken in the 1st year and 262 thereafter. Lost-to-follow up was negligible (n=15). All acute rejections and clinical borderline cases in protocol Bx were treated.

Results: Patient and graft survival was 80% at 5 yrs and 68% at 10 yrs. Patient survival was 92% at 5 yrs and 82% at 10 yrs. 99 deaths occurred, relating to infection (24%), cardiovascular disease (15%), malignancy (16%), other specified causes (8%). Deaths were less in living donor or kidney/pancreas Tx and more frequent for extended donor criteria-Tx. A three-level multivariable Cox regression model was created in a stepwise fashion, using significantly different variables from the pre-Tx, peri-operative, and long-term post-Tx period between survivors and deceased pts. Pre-Tx variables in the final model included recipient age, HLA-DR mismatches, diabetes, coronary heart disease, heart failure, and peripheral arterial disease. A significant peri-operative variable was cold ischemia time. In the long-term course, variables for death included increased loss of graft function, urinary tract infection, and higher PTH levels. Compared to the survivors, deceased pts received more therapies for rejection seen in protocol Bx (0.30 vs. 0.43 per patient) and in Bx for cause (0.29 vs. 0.34 per patient), however, this was not a significant factor in the final model. Also, the proportion of anti-rejection treatments was not higher in pts who died from infections, compared to pts dying from other causes. Concordance of the final model was 0.79; 200-fold bootstrapping confirmed its applicability.

Conclusions: Based on these results a tool is presented that readily allows risk calculation and stratification of individual pts, as a pre-requisite for individualized and optimal pre- and post-Tx care.  

Funding: Government Support - Non-U.S.

Effect of Simultaneous Native Nephrectomy on the Outcome of Kidney Transplant Recipients with Autosomal Dominant Polycystic Kidney Disease  

Jeong Ho Kim, Bun soon Choi, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim, Byung ha Chung. Internal Medicine, Seoul St. Mary's hospital, Seoul, Korea.

Background: End stage renal disease (ESRD) patients with autosomal dominant polycystic kidney disease (ADPKD) required native nephrectomy because of limited space for renal allograft. However, the appropriate timing for nephrectomy and also its effect on allograft patient survival has not been fully investigated.

Methods: We retrospectively analyzed 41 kidney transplant recipients with ADPKD in whom transplantation was done either simultaneously, after or without native nephrectomy at Seoul St. Mary’s hospital between January 1987 and February 2014. We divided patients into 2 groups; simultaneous nephrectomy group (group A, n=13), after or without nephrectomy group (group B, n=28) and compared the perioperative outcome, post-transplant complications, allograft survival rate.

Results: The mean operation time was significantly longer in group A than group B (6.48 ± 1.84 vs. 5.27±0.84 hours; P = .048). The mean intraoperative blood transfusions was also significantly more needed in group A than B (3.66±3.43 vs. 0.75 ±0.26 units; P = .018). However, there were no differences in the incidence of acute rejection and/or complications such as post-operative bleeding, infectious complication between the two groups (P > .05, all). The graft survival rate also did not differ between the two groups (P > .05).

Conclusions: Our study suggests that the complication rates were acceptable and the influence of native nephrectomy was not a significant negative impact on graft survival rate when native nephrectomy was done during kidney transplantation in ADPKD patients with ESRD. Therefore, if native nephrectomy is needed in ADPKD for kidney transplantation it can be done safely during transplantation.

Predictors of Renal Function Change After Kidney Transplantation  

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Background: Several perioperative factors including histological findings of allograft biopsy are known to be associated with graft function. However, little is known about the longitudinal change of renal function (eGFR) in post-KT patients. It is unclear what factors in post-KT period predict the longitudinal change of renal function.

Methods: The data from post-KT patients followed at The University of Tokyo Hospital were collected retrospectively. Patients followed-up less than 6 months after KT were excluded. To identify predictors of the longitudinal change of renal function, we analyzed data including clinical parameters measured at each outpatient visit. The primary outcome was defined as the change of eGFR during 6 months period.

Results: 32 post-KT recipients were analyzed in this study. Age and eGFR at baseline of these patients were 51.3 ± 12.7 years old and 41.2 ± 16.1 ml/min/1.73m² (mean ± SD), respectively. The duration from KT to collection of clinical parameters was 6.8 ± 7.3 years (mean ± SD). Changes of eGFR were evaluated 6 months after. When patients were divided into two groups with (N = 15) and without (N = 17) eGFR decline after 6 months, uL-FABP and urinary protein were significantly higher in the eGFR decline group (uL-FABP; 11.6 ± 14.5 ng/ml/m² and urinary protein; 272.7 ± 97.2 mg/eGFR, respectively). On ROC analysis, uL-FABP and urinary protein predicted eGFR decline after 6 months (AUC [95%CI]) = 0.78 [0.60-0.96] and 0.70 [0.51-0.89], respectively. On multiple regression analysis, uL-FABP and urinary protein were significantly correlated with the absolute and relative eGFR changes during 6 months observation period.

Conclusions: uL-FABP and urinary protein measured at outpatient clinic can predict the change of renal function of post-KT patients.

Plasma Proenkephalin and Poor Long-Term Outcome in Renal Transplant Recipients  

Lynne M. Kienekeng1  Joachim Struck,2  Ron T. Gansevoort,1  Michel M. Joosten,1  Rudolf A. de Boer,2  Oliver Hartmann,2  Stephan J.L. Bakker.1

1Nephrology, UMC Groningen, Netherlands; 2Sphingotec GmbH, Germany; 3Cardiology, UMC Groningen, Netherlands.

Background: Enkephalins are well-known endogenous opioid peptides. Recent evidence indicates that they are not only involved in regulation of pain, but also in homeostasis of the immune system and the circulation. Proenkephalin (pro-ENK) is stable in plasma and has been established as a reliable surrogate marker for unstable opioid receptors. Recent studies found associations of pro-ENK with acute kidney injury and prognosis after myocardial infarction. We aimed to investigate whether pro-ENK could be linked to chronic kidney injury and poor long-term outcome in renal transplant recipients (RTR).

Methods: We included 664 RTR who were 8.1±7.6 years after transplantation. Plasma levels of pro-ENK were measured with a double monoclonal sandwich immunoassay.

Results: Mean age was 53±13 years, 56% was male, estimated glomerular filtration rate (eGFR) 49 ml/min/1.73m² (interquartile range [IQR]: 37-64 ml/min/1.73m²) and
urinary albumin excretion (UAE) 40 mg/24h (IQR: 10-196 mg/24h). Median pro-ENK was 110 pmol/L. (IQR: 85-148 pmol/L). Pro-ENK was correlated with both eGFR (r = 0.73, P<0.001) and UAE (r = 0.35, P<0.001). During a median follow-up of 3.1 years (IQR: 2.7-3.9 years), 45 RTR developed graft failure and 76 died. Pro-ENK was both associated with increased risk of graft failure (hazard ratio per standard deviation increment of the logarithm of pro-ENK, 2.57; 95% confidence interval, 1.69-4.5) and all-cause mortality (1.83; 1.24-2.69), independent of age, sex, eGFR, and UAE. These associations remained materially unchanged after additional adjustment for body mass index, alcohol consumption, smoking, systolic blood pressure, antihypertensive drug use, use of calcinurin inhibitors, and high-density lipoprotein.

Conclusions: High concentrations of pro-ENK are linked to chronic kidney injury as reflected by correlations with eGFR and UAE. In addition, pro-ENK was independently associated with increased risk of graft failure and mortality in RTR. Pro-ENK is an interesting new biomarker which may aid in early identification of RTR at risk for late graft failure and premature mortality.

Funding: Private Foundation Support

FR-PO1098
Serum Albumin Level Has Association with Both Graft Failure and Mortality in Kidney Transplant Recipients
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Background: The studies concerned the association between post-transplant serum albumin concentration and post-transplant outcomes in kidney transplant recipients (KTRs) are scarce.

Methods: To evaluate the impact of serum albumin level on graft and patient survival, we performed a retrospective multi-center cohort study in Seoul National University Hospital, Asan Medical Center, and Kangdong Sacred Heart Hospital. A total of 2815 KTRs who underwent renal transplantation from Jan 1997 to Jan 2012 were classified into two groups according to the level of serum albumin at 1 year after transplantation (higher albumin group, >4.0 g/dL, n=1978 vs. lower albumin group, <4.0 g/dL, n=837). The Cox proportional hazard model was adjusted with age and gender of recipient, donor type, age of donor, diabetes mellitus, and estimated glomerular filtration rate (eGFR) at 1 year after transplantation.

Results: The mean age of the recipients was 41.7±11.3 (range, 18-73) years, and 59.1% were male. The rate of graft failure was higher in lower albumin group compared to higher albumin group (Hazard ratio [HR] 1.840, 95% confidence interval [CI] 1.367-2.477, P<0.001), even though eGFR at 1 year after transplantation was not different between the two groups (61.7±19.8 vs. 62.1±15.8 mL/min, P=0.615). Both all-cause mortality and non-cardiovascular mortality rates were higher in lower albumin group (HR 2.227, 95% CI 1.514-3.347, P=0.001, respectively). Every 1.0 g/dL higher serum albumin concentration was associated with 69.2% lower all-cause mortality (HR 0.308, 95% CI 0.196-0.483, P=0.001).

Conclusions: Serum albumin level at 1 year after transplantation is a prognostic factor for graft failure and patients’ mortality in KTRs. Therefore, evaluation and management for hypoalbuminemia should be considered to improve outcomes in KTRs.

FR-PO1099
Brain Effects of Renal Transplantation: Association Between Cognition and White Matter Integrity
Aditi Gupta, Rebecca J. Lepping, David K. Johnson, Alan S.L. Yu, William M. Brooks, Jeffrey M. Burns.

Background: Cognitive impairment is present in up to 87% patients with end stage renal disease (ESRD). Magnetic resonance imaging (MRI) using diffusion tensor imaging (DTI) shows lower fractional anisotropy (FA) values in these patients. FA values measure structural integrity of white matter and are associated with cognitive impairment. In this study we examine the effect of renal transplantation on cognitive function and determine whether changes in white matter integrity underlie the observed cognitive changes.

Methods: Adults with ESRD were recruited from the renal transplant waiting list. Subjects were evaluated before transplantation and 3 months after transplantation with neuropsychological (NP) tests and brain MRI. Two-tailed paired t-test was used to analyze changes in NP tests and FA values before and after transplantation.Pearson correlation coefficients were calculated.

Results: Two hundred patients were screened and eighteen enrolled. Ten subjects, 57±11 years of age have been transplanted and have completed the study. After transplantation, there was a significant improvement in NP tests for memory and executive function.

There was a significant increase in the FA values in the body of corpus callosum (P=0.017), fornix minor (P=0.058) and left cingulate gyrus (P=0.002). Furthermore, the improvement in NP tests positively correlated with the increase in FA values in these tracts.

Conclusions: Memory and executive function improve after renal transplantation, FA, a DTI metric representing white matter integrity also increases in brain regions important for these functions. This study provides insight into the neural mechanisms underlying cognitive impairment in ESRD and its improvement after transplantation.

FR-PO1100
Pre-Kidney Transplant Left Ventricular Ejection Fraction, Long-Term Allograft Function, and Survival
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Background: End stage kidney disease patients with low left ventricular ejection fraction (LVEF) are considered high risk for poor outcomes following kidney transplantation (KT). No consensus exists on the level of systolic dysfunction below which patients are at increased risk of unfavorable allograft outcomes.

Methods: We studied 387 KT recipients transplanted from 1/02 to 12/09 who underwent pre-transplant invasive and non-invasive cardiac assessment of LVEF. Outcomes included Delayed graft function (DGF), allograft survival, patient survival and allograft function.

<table>
<thead>
<tr>
<th>LVEF</th>
<th>N</th>
<th>DGF</th>
<th>Patient Survival</th>
<th>Graft Survival</th>
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<td>&lt;45%</td>
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<td>45-60%</td>
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<td>(0.56, 2.94)</td>
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<td>(0.43, 1.42)</td>
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<td>&gt;60%</td>
<td>136</td>
<td>Ref</td>
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P-trend: 0.42 0.81 0.80 0.70 0.12 0.86

P: Confidence Interval, Ref: Reference

Data adjusted for age, sex, race, PRA, Duration of RRT, DM, CAD, LVH and Induction Therapy.

Associations between different LVEF values.

Results: A total of 136 (35.1%) patients had LVEF > 60%, 215 (55.5%) had LVEF between 45-60% and 36 (9.3%) had LVEF <45% before KT. Patients with low EF were more likely to receive non-cardiovascular and all cause mortality. During median follow up of 4.4 years there were 122 graft losses including 71 deaths. 73 patients (18.9%) had DGF. There was no significant difference in rate of DGF, serum creatinine, allograft survival and patient survival.

Conclusions: Low LVEF does not appear to significantly effect patient and allograft survival and function, suggesting that patients with low LVEF should not be excluded from transplantation.

FR-PO1101
Progression of Coronary Artery Calcification in Renal Transplant Recipients – A Follow-Up Of 7 Years
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Background: In the general population coronary artery calcification (CAC) and its progression is associated with cardiovascular and all cause mortality. We conducted a study to determine the progression of CAC in renal transplant recipients; we also examined the factors associated with progression and the impact of the analytic methods used to determine CAC progression.

Methods: We used multi-detector computed tomography to examine CAC in 113 prevalent renal transplant recipients, who did not have a documented cardiovascular disease. Measurements were performed and changes in CAC scores were evaluated in each patient individually, to calculate the incidence of CAC progression. Univariate and Multivariate logistic regression analysis was used to evaluate the determinants of CAC progression.

Results: Baseline CAC prevalence was 34.5% and the mean CAC score was 47.08 ± 135.25. At follow-up scan that was performed after an average of 6.9 ± 0.5 years, CAC prevalence increased to 47.6% and the mean CAC score to 140.18 ± 332.11. Progression of individual CAC score was found between 32.7 and 34.5 %, depending on the method used to define progression (Hokanson and Sevrukov). In patients with baseline CAC, median annualized rate of CAC progression was 13.8. Based on univariate analysis, age, presence of baseline CAC, high baseline CAC score, high body mass index were significantly associated with CAC progression defined according to both the Hokanson and Sevrukov methods. Moreover, HDL cholesterol level was significantly associated with CAC progression when progression was defined according to Hokanson’s method and donor type, high triglyceride levels and systolic blood pressure were significantly associated with CAC progression according to Sevrukov’s method. Based on multivariate analysis baseline CAC and high triglyceride were the independent determinants of CAC progression.
**FR-PO1104**

**Association Between Serum Magnesium Level and the Risk of New-Onset Diabetes After Renal Transplantation in Korea**

**Background:** New onset diabetes mellitus after transplantation (NODAT) is a serious complication following renal transplantation. Association between serum magnesium level and new-onset diabetes after renal transplantation is controversial. The aim of this study was to identify the association between serum magnesium level and the development of NODAT in Korea.

**Methods:** The recipients who underwent living donor kidney transplantation between January 2009 and April 2012 were reviewed. Diagnosis of NODAT is defined by American diabetes association criteria. Serum magnesium level were measured at pretransplant, 3 days, 7 days and 3 months posttransplant. Univaried and logistic regression analysis were performed to examine the association between serum magnesium level and NODAT at 1 year posttransplant.

**Results:** Total 419 patients were enrolled. NODAT was diagnosed in 85(20%) patients. Mean magnesium level at 3 and 7 days after transplantation was significantly lower in patients who diagnosed with NODAT. On logistic regression analysis, Age $>$40, Obesity, pretransplant glucose were associated with NODAT. However, there is no association between serum magnesium level and NODAT.

<table>
<thead>
<tr>
<th>Table 1. Risk factors of new-onset diabetes - univariate analysis</th>
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<tbody>
<tr>
<td><strong>Number of patients (%)</strong></td>
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<tr>
<td>Age, years</td>
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<tr>
<td>Sex, male (%)</td>
</tr>
<tr>
<td>Family history of Diabetes (%)</td>
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<tr>
<td>Tacrolimus (%)</td>
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<tr>
<td>Cyclopentolate (%)</td>
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<tr>
<td>Myopencesal tendonitis (%)</td>
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<tr>
<td>Azathioprine (%)</td>
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<td>Corticosteroids (%)</td>
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<tr>
<td>Improved fasting glucose, pretransplant</td>
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<td>Glucose, pretransplant</td>
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<td>Obesity, pretransplant</td>
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<td>Mg, pretransplant</td>
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<td>Mg, 3 days</td>
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<tr>
<td>Mg, 7 days</td>
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**Conclusions:** A lower magnesium level at posttransplant may be associated with NODAT after renal transplantation in Korea.

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**FR-PO1105**

**Is NODAT Really Associated with Acute Rejection in Kidney Only Transplantation?**

**Background:** Previous reports suggest an association with New Onset Diabetes After Transplantation (NODAT) and rejection however it is unclear whether this effect is secondary to hyperglycaemia or a result of previous episodes of treated rejection. This observational study aims to determine the association between acute rejection (AR) and NODAT.

**Methods:** 381 renal transplant recipients (RTR) from the KALIBRE study were analysed. Clinical details and laboratory results were collected in this cohort from 2010-2014. Episodes of AR were identified by renal transplant biopsies;Banff 2009 Categories 2&4 and 3 that were treatment responsive. NODAT was defined as HbA1c$>$6.5% at 3 months post renal transplantation. Cox’s regression proportional hazards was used for survival analysis. diabetes was divided into RTRs (35 female, 64% white, 39% non-white, Age at transplant range: 17-75). 47 patients were diagnosed with NODAT (13.1%) and 93 (24.4%) with AR. 17/47 (36.2%) patients with NODAT had AR. Rejection free survival in NODAT group was significantly lower than patients without NODAT (p=0.036 HR 1.75). Mean tacrolimus...
levels between rejectors and non-rejectors were not significantly different (10.1 and 10.3 mg/dL, respectively). T1DM and T2DM combined did not increase the rates of rejection in the cohort.

**Conclusions:** An association between NODAT and AR has been observed that was independent of tacrolimus levels. RTRs with diabetes mellitus did not have the same effect on AR rates suggesting a different underlying mechanism specific to NODAT rather than just hyperglycaemia.

**Funding:** Other NIH Support -
- Guy’s & St Thomas’ Charity, Gran number R09782 Title: Clinical Validation of non-invasive peripheral biomarkers to predict and diagnose rejection following renal transplantation.
- National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London.
- GSTT Kidney Patient Association
- 4 Quest Diagnostics

**FR-PO1106**

**Insulin Resistance: Is It a Risk Factor for Left Ventricular Hypertrophy in Pediatric Renal Transplant Recipients?**

**Jale Sever, Nur Canpolat, Gulseren Pehlivan, Salim Caliskan. Pediatric Nephrology, Istanbul Univ Cerrahpasa Faculty of Medicine, Istanbul, Turkey.**

**Background:** Renal transplantation reverses uremia-related risk factors for cardiovascular disease; however, immunosuppressive therapy causes metabolic abnormalities such as insulin resistance, hyperglycemia and dyslipidemia. The aim of the present study was to evaluate the effects of these metabolic abnormalities as a risk factor for left ventricular hypertrophy in pediatric renal transplant recipients.

**Methods:** This is a retrospective study involving 31 renal transplanted children and adolescents (19 male; age 4-20 years) and 19 healthy controls. Anthropometric indices, office blood pressure (BP) and laboratory measurements and also left ventricular mass index (LVMI) at the same time were recorded from the patients’ Icc The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. Insulin resistance was defined as a HOMA-IR ≥ 2.5. Dyslipidemia was defined as HDL-C<40 mg/dL, and/or LDL-C >130 mg/dL, and/or TG >150 mg/dL.

**Results:** Age at transplantation was 12.4±4.4 years with a median follow-up of 27 months. One patient received pre-emptive transplantation, 25 were on PD and 5 on HD before transplantation; 25 patients received a kidney from a living donor. Triple immunosuppressive therapy was used in all patients, except two who were not using steroids at the time of the enrolment. Patients had significantly higher BMI-SDS, fasting glucose, fasting insulin, HOMA-IR and TG as well as lower HDL-C levels than controls (p<0.05 for all). Nine patients (29%) had insulin resistance; 11 (42%) were dyslipidemic; and 15 (50%) were hypertensive. LVMI was significantly higher in the patients than the controls (40.0±0.9 vs. 25.8±5.71; p<0.001); left ventricular hypertrophy was noted in 11 patients (48%). LVMI correlated only with indexed diastolic BP (r=0.433, p=0.039), however, not with any of the lipid parameters or HOMA-IR. HOMA-IR was correlated with only BMI (r=0.381, p=0.035). There was no association between HOMA-IR and steroid doses.

**Conclusions:** Although insulin resistance and dyslipidemia are prevalent in pediatric renal transplant recipients, hypertension appears to be the main risk factor for left ventricular hypertrophy.

**FR-PO1107**

**Mediterranean Type Diet Is Associated with Low Risk of New-Onset Diabetes and Mortality After Renal Transplantation**

**Maryse Ostl,1 Eva Corpeleijn,1 Gerjan Navis,1 Charlotte A. Keyzer,1 Sabita Soedamah-muthu,2 Else van den Berg,1 Daan Kromhout,1,2 Stephan J.L. Bakker,1,2 Univ of Groningen;1 Univ of Wageningen, Netherlands.**

**Background:** The incidence of new-onset diabetes after transplantation (NODAT) and cardiovascular events leading to premature mortality is high in renal transplant recipients (RTR). We hypothesized that a Mediterranean type diet protects against development of NODAT and premature mortality in RTR.

**Methods:** In a prospective cohort study consisting of 707 adult stable RTR with a median follow-up of 3.8 (IQR, 3.0-4.6) years, multivariable regression analyses were used to study the association of the Mediterranean type diet with development of NODAT and mortality. Cox multivariable regression analyses were used to study the association of the Mediterranean diet with the development of NODAT and mortality.

**Results:** In total 474 RTR (56.8%) were included with a mean ± SD age of 51.5 ± 13.2 years. At baseline, 256 (54%) had a high resemblance to that of a Mediterranean type diet. During median follow-up of 3.8 (IQR, 3.0-4.6) years, 28 (6%) developed NODAT and 52 (11%) patients died. RTR with ≥ 5 points were both significantly associated with a lower risk of developing NODAT (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.20-0.95; P=0.04) and mortality (HR, 0.54; 95% CI, 0.31-0.98, P=0.03), both adjusted for age and sex. The results of multivariable analyses, in which we adjusted for potential confounders including total energy intake, physical activity and smoking status, did not materially change the results of the analyses adjusted for age and sex.

**Conclusions:** Dietary habits that resemble the Mediterranean type diet may protect against NODAT and mortality after kidney transplantation. More attention should be directed to the nutritional habits of renal transplant recipients.
Intra-Abdominal Hypertension and Renal Dysfunction in Pregnancy

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Introduction: The effects of high intra-abdominal pressure (IAP) on renal function have been known for over a century. However, the diagnosis of peripartum intra-abdominal hypertension (IAH)/abdominal compartment syndrome (ACS) is challenging due to the lack of a single threshold normative values of IAP in pregnancy.

Case Description: A 32-year-old G1P0 at 33 weeks gestation was admitted for intractable nausea and vomiting. She was oliguric and unresponsive to IV fluid. Her blood pressure was normal. Cr increased from a baseline of 0.6 mg/dL to 2.9 mg/dL. She was diagnosed with preeclampsia. A FeNa obtained after fluid resuscitation was 0.02%. Renal ultrasound showed patent renal vessels and no hydrophrenbladder. A diuretic was given with slight improvement in urine output. IAP measured by an intravascular catheter was 35 mmHg, and abdominal perfusion pressure (APP) (difference between mean arterial pressure and IAP) was 46 mmHg (normal ~50-60 mmHg). She was suspected to have IAH/ACS and was closely monitored. 2 days later, she developed hypertension, an increase in liver transaminases, and proteinuria. The decision was made to deliver with delivery due to severe preeclampsia. IAP measured immediately after C-section decreased to 18 mmHg, and it was 7 mmHg prior to delivery. Urine output increased to 2.5 L per day and Cr declined to 0.7 mg/dL after delivery.

Discussion: Animal and human studies indicate that oliguria and acute kidney injury are frequent consequences of IAH/ACS, and can be present at relatively low levels of IAP. In our case, the IAP of 35 mmHg was quite extreme compared to IAP of 4-28 mmHg observed in cohort studies of peripartum patients. We suspected that obesity and twin pregnancy contributed to the extreme IAH. Her APP was significantly low and restoration of renal function was readily observed after reduction of IAP. Our case may support the theory that IAH develops due to increased intra-abdominal pressure caused by respiratory or aortic compression. Restoration of IAP is probably underestimated as IAH is not routinely measured. Further study is needed to elucidate the impact of IAH in pregnancy.

Diabetes, Deafness and Renal Disease – A Case Report


Introduction: Deafness and kidney disease as well as diabetes and kidney disease are associations of which the Nephrologist is well aware. However, the concomitance of the three is not as usual, neither is a family history of these diseases.

Case Description: A 23-yo male with NS due to biopsy proven with non-nephrotic proteinuria, no haematuria, normal renal function, slowly progressive bilateral sensorineural hearing loss and recently diagnosed diabetes and maculopathy and a maternal family history of deafness, diabetes and renal disease. The patient progressed with increasing proteinuria despite antiproteinuric measures and a renal biopsy was performed, revealing Focal and Segmental Glomerulosclerosis (FSGS). Amyloid syndrome and Fabry disease investigation was negative. Facing the personal and maternal family history, the mitochondrial mutation m3243A>G was pursued and identified in heteroplasmy and maternally was negative. Renal function was readily observed after reduction of IAP. Our case may support the theory that IAH develops due to increased intra-abdominal pressure caused by respiratory or aortic compression.

Diabetes, Deafness and Renal Disease – A Case Report

Sonya Godinho, Ian Godinho, Nephrology, Santa Clara Valley Medical Center, San Jose, CA.

Introduction: Chronic denymelinating Polineuropathy Associated with Advanced Focal Segmental Glomerular Sclerosis

Albert Nedzunju, Rada Petrinjac-Neadeic, Lelka K. George, Elvira Gosmanova, Nephrology, UTHSC, Memphis, TN; Neurology, Tri-State Neurology, PLLC, Memphis, TN.

Introduction: Chronic denymelinating polineuropathy (CDP) is rarely reported in patients with nephrotic syndrome (NS). CDP tends to manifest concomitantly with NS. We report a case of CDP developing at a time of focal segmental glomerular sclerosis (FSGS) progression to ESRD and mimicking uremic neuropathy.

Case Description: A 23-yo male with NS due to biopsy proven two years before was diagnosed with focal segmental glomerulosclerosis (FSGS) and serum creatinine (Scr) 1mg/dL was initiated on oral prednisone and lisinopril. He was lost to follow up and returned 1.5 years later complaining on burning pain and numbness in both feet for 4 weeks. Physical exam was normal except for unsteady gait, inability to perform tandem gait, decreased sensation from feet to upper legs, depressed Achilles and ankle flexor reflexes. Laboratory tests showed Scr 44mg/dL, hyperkalemia, metabolic acidosis, normocytic anemia, and normal creatinine phosphokinase. A diagnosis of ESRD due to progression of untreated FSGS was made and dialysis was started. CT head and MRI spine were normal. Cerebrospinal fluid had protein of 74 mg/dL and glucose of 43 mg/dL. Electromyography (EMG) showed absent compound muscle action potential (CMAP) and F-waves in both peroneal and tibial nerves, active denervation in tibialis anterior, gastrocnemius and extensor digitorum brevis muscles, and prolonged distal latencies and reduced action velocity with normal amplitude of CMAP on both arms and sensory nerves action potentials on sural and peroneal nerves were absent with prolongation of peak latencies on other nerves. The constellation of clinical, EMG and normal inflammatory, infectious and autoimmune laboratory markers was consistent with diagnosis of CIDP. Plasmapheresis was performed with partial improvement of neurological symptoms and was followed by intravenous immunoglobulin as an maintenance therapy.

Discussion: CIDP should be considered in patients presenting with peripheral neuropathy and history of FSGS. Correct diagnosis of CDP is critical as untreated CDP leads to inability to walk. Autoimmune mechanisms may be responsible for CDP and glomerular damage in FSGS but remain to be proven.

Silicone Implant Associated Acute Kidney Injury in a Male Transgender Patient

Frank J. O’Brien, Brian Y. Young, Div of Nephrology, Santa Clara Valley Medical Center, San Jose, CA.

Introduction: Obstructive kidney disease secondary to nephrolithiasis is a well-described cause of acute kidney injury. Stone formation is often due to dietary or metabolic factors, often no predisposing factors are found. We describe a rare case of obstructive acute kidney injury associated with hypercalcemia and hypercalciuria in a 32-year-old transgender patient. Patient was found to have granulomatous disease associated with silicone implants.

Case Description: 32-year-old male to female transgender patient presented to our institution with fatigue. Routine labs showed creatinine 11 mg/dL, BUN 140 mg/dL, K 7 mmol/L. She was emergently dialedyzed, and imaging showed obstructing ureteric calculus, requiring bilateral stent insertion. Patient had a history of silicone implants in hips, buttocks and thigh 5 years previous. These were inserted by a non health care professional. There was no history of calculus production or ingestion therapy use. Diagnosis work up for nephrolithiasis revealed, 24 hour urinary calcium 886 mg/24 hours, serum calcium 12.5 mg/dL, phosphorus 8.0 mg/dL. Other 24-hr UFT results were normal. ACE level was 216 units/L. CXR was normal. PTH and malignancy work up was negative. CT abdomen revealed subcutaneous edema in lower back/gluteal area, around the sites of previous silicone implants, and inguinal lymphadenopathy. Subsequent gallium scan showed tracer uptake around silicone implant site and increased activity in left lower quadrant. Blood pressure was 127/67 mmHg. There was minimal peripheral edema. Urinalysis showed small blood, 100 mg/dl protein, 0-2 wbc, 0-2 rbc, and free fat. His serum creatinine was 0.78 mg/dl. He had 1 gram of urine protein per gram of urine creatinine. His proteinuria had ranged from 1.3 to 2.9 gms/gram over the preceding four months. Serological testing showed a negative RPR, negative tests for hepatitis B and C, and an antinuclear antibody of 1:640 titer. A kidney biopsy showed Fabry disease and superimposed membranous nephropathy. Lisinopril 2.5 mg/day was started. Rheumatological evaluation showed no evidence of lupus or rheumatoid arthritis. The most recent urine protein to creatinine ratio was 0.71 gram/gram, with a serum creatinine was 0.8 mg/dl.

His kidney biopsy stained positive for anti-agalsidase, but normal control kidney did not. He had anti-agalsidase antibodies in his serum that did not block agalsidase activity. Immunofluorescence for the phospholipase A2 receptor (PLA2R) was negative within the glomeruli and his serum did not have antibodies to PLA2R.

Discussion: Enzyme replacement therapies may lead to allo-reactivity. Membranous nephropathy has been described in three such patients but not in Fabry disease. Its occurrence may change the therapy of the primary disease and force specific treatment of the nephritis superimposed on the primary disease.

Funding: Veterans Administration Support, Clinical Revenue Support
Isolated Diplopia Caused by Calcineurin Inhibitor Therapy in a Patient with Idiopathic Membranous Nephropathy  
Nader S. Bahri, Ashwani K. Gupta.  
Nephrology and Hypertension, Univ of Florida, Jacksonville, FL.

Introduction: Neurotoxicity is a common side effect of treatment with calcineurin inhibitors. Tremors are frequently reported as the most common manifestation. Variable presentations can include headaches, seizures, visual hallucinations or blindness. Sixth nerve palsy has been reported in previous cases of bone marrow and cardiac transplant patients receiving calcineurin inhibitors. In many of these previously reported cases, the drug was administered intravenously and very high drug levels were found.

Case Description: 42-year-old Caucasian female with biopsy proven idiopathic membranous nephropathy (IMGN) who was being treated with tacrolimus and prednisone for nephrotic syndrome. Her tacrolimus levels were maintained between 6-8 ng/mL. Her urine protein/creatinine ratio of 8 g/gm was successfully reduced to less than 1 g/gm. She continued to be in complete remission but after 3 months of therapy she presented with diplopia. The diplopia was binocular and vertical. The patient was seen for an ophthalmologic evaluation. Her visual acuity was 20/20. Pupils were equal and reactive to light and accommodation. No nystagmus was observed. Visual fields and color vision was also normal in both eyes. Assay for Acetyl-choline receptor antibody was negative.

The patient remained compliant with her medications despite the side effects. At this time she was switched to low dose Cyclosporin (CyA) in anticipation that similar side effects may not be observed. Trough CyA levels were 44 ng/mL and 59 ng/mL on two occasions but her symptoms did not resolve. A consultation with neuro-ophtalmology was sought and the patient was instructed to discontinue CyA. The symptoms completely resolved 4 days after stopping CyA.

Discussion: This is the first reported case of isolated diplopia secondary to calcineurin inhibitors in low doses for treatment of IMGN. Monitoring of serum concentrations of this drugs has not been correlated with toxicity. The mean duration to onset of symptoms can be as much as 70 days suggesting accumulation of the drug in the central nervous system plays a role. Recognition of this condition is important for prompt diagnosis and appropriate management.

Bilateral Renal Artery Stenosis in a Patient Treated with Nilotinib for Chronic Myeloid Leukemia  
Omar M. Shababeet, Milos N. Budisavljevic.  
Medical Univ of South Carolina.

Introduction: The use of tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL oncoprotein has been successful in chronic myeloid leukemia (CML). Nilotinib is a second generation TKI designed and used to overcome deficiencies of imatinib such as resistance or intolerance. Nilotinib also received approval in chronic phase (CP)-CML for superior response rate and less progression to blast crisis compared to imatinib. Reports suggest peripheral artery disease (PAD) as an adverse drug reaction associated with the use of nilotinib. We describe a case of bilateral renal artery stenosis in a patient treated with nilotinib.

Case Description: A 45 year old Caucasian male diagnosed with BCR-ABL positive CML at age 31. He was treated with Hydrea followed by Gleevec and was in complete remission (CR) for 4 years when he developed ALL transformation necessitating therapy. He continued to be in complete remission but after 3 months of therapy she presented with diplopia. The diplopia was binocular and vertical. The patient was seen for an ophthalmologic evaluation. Her visual acuity was 20/20. Pupils were equal and reactive to light and accommodation. No nystagmus was observed. Visual fields and color vision was also normal in both eyes. Assay for Acetyl-choline receptor antibody was negative.

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Eculizumab in Management of Thrombotic Lesions in Kidney Allograft of Patient with Anti-Phospholipid Syndrome  
Anju Yadav, Ravi Sunderkrishnan, Andres Rodrigo Caero.  
Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA.

Introduction: Thrombotic microangiopathy (TMA) is one of the hallmark vascular lesions of anti-phospholipid syndrome (APS). These lesions are at high risk of recurrence after kidney transplantation. The complement pathway is thought to be active in this process by deposition and by presence of apoptotic and vascular cell markers on sequential pathological lesions. Eculizumab is a humanized anti-C5 monoclonal antibody which has been used in atypical hemolytic uremic syndrome. Recently, there have been reports of use of Eculizumab in transplant patients with APS-LTMA. The patient has been treated with Eculizumab and has remained in remission.

Case Description: We present a case of a 58 year old Caucasian man with history of systemic lupus erythematosus, APS on warfarin, hypertension, rheumatoid arthritis, transient ischemic attack, coronary artery disease with triple vessel bypass, chronic kidney disease stage 5 for which he received pre-emptive living unrelated kidney transplant. After an uneventful post-transplant course, he was discharged on warfarin. He presented to the hospital 4 days later, with acute renal failure, pain over the graft and sub-therapeutic INR. A perinephric collection was drained. Cytomegalovirus and BK polyoma viremia were ruled out. Transplant kidney biopsy, revealed TMA with segmental necrosis and small vessel fibrin thrombi and no acute rejection. High dose steroids along with aggressive anticoagulation management were received. Two sessions of plasma exchange. After meningococcal meningitis immunization, Eculizumab 900mg/week was started. After 4 doses, Eculizumab was changed to 1200mg/two weeks. Creatinine trended down from 7.3 to 3.0 mg/dl and dialysis was stopped after 7 sessions. He was positive for IgG anticardiolipin, beta-2 glycoprotein, and lupus anticoagulant and was started on daily aspirin and warfarin with INR goal of 2.5-3.5. The patient continued to respond well and showed rapid and dramatic improvement of graft function in our patient and should be considered in difficult to manage TMA/APS-LTMA in transplant patients. Its use permits a safer approach of controlling the complement final common pathway.

Transient Gestational Diabetes Insipidus in a Patient with Pre-Eclampsia  
Anju Yadav, Ravi Sunderkrishnan, Andres Rodrigo Caero.  
Dept of Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA.

Introduction: Diabetes insipidus (DI) is manifestation of post pituitary insufficiency characterized by polyuria and polydipsia. DI can be neurohypophyseal, nephrogenic, polydipsia related or gestational (GDI). L-deamino-8-D-arginine vasopressin (DDAVP) is a vasopressin analogue which had higher and prolonged anti-diuretic activity with no effects on smooth muscle. An increase in urine osmolality by at least 50% following administration of DDAVP is diagnostic of disorder.

Case Description: We present a case of a 22-year-old African American primigravida woman with no past medical history, in 32nd week of pregnancy, admitted with pre-eclampsia with no liver injury. On admission, blood pressures were between 140-160/60-70. After an uneventful delivery she had urine output ranging 6-9 liters along with polydipsia. Both of these were present all through out her third trimester. On exam there was no evidence of volume overload or dehydration. Labs were sodium 137mEq/L, Potassium 2.8mEq/L, Alb 3.0mg/dl, TSH 4.16, urea nitrogen <0.3, creatinine 0.4, serum osmolality 284, urine osmolality 141, spot urine protein to creatinine ratio of 0.8. With one dose of subcutaneous DDAVP/polydipsia resolved and osmolality to 385 within 24hrs. Oral DDA VP is diagnostic of disorder.
Utility of Hemodialysis in Urea Cycle Disorders

SA-PO011
A Case Report of Baclofen Toxicity in a Hemodialysis Patient
Sweta Carpenter, Sandeep Aggarwal. Nephrology and Hypertension, Drexel Univ.

Introduction: The dangers of baclofen toxicity in patients with advanced kidney disease and in particular patients on dialysis remain underestimated by many physicians.

Case Description: We present a case of a 64 year old male who developed an uncommon case of altered mental status during his hospitalization. His medical history included ESRD for which he was receiving in-center hemodialysis, diabetes and hypertension. He initially presented to the hospital with complaints of shortness of breath and hiccups. His shortness of breath was attributed to volume overload and resolved with two consecutive days of dialysis with fluid removal. For his intractable hiccups, he was started on baclofen. During his hospitalization, he became lethargic and was unable to move his lower extremities. Laboratory data including serum sodium, potassium, glucose, calcium, BUN, phosphorus, liver enzymes, thyroid function tests, troponins, inr and prothrombin work up and ammonia levels were unremarkable. Neuroimaging, including CT head and brain MRI, were unchanged from previous studies and revealed moderate diffuse cerebral atrophy. An EEG was also performed and did not suggest signs of epileptic activity. Further investigation revealed that he had received a total of 20 mg of baclofen over 2 days. After other etiologies were ruled out, we determined that he may have suffered from baclofen induced encephalopathy. His baclofen was stopped and he was prescribed daily sessions of hemodialysis for three days with the intent of clearing baclofen. He was dialyzed for 4 hours during each dialysis session with a high flux dialyzer. After his first session of dialysis, the patient was more alert and would follow simple commands. At 3 days, the patient’s mental status returned to baseline and he was able to move his extremities.

Discussion: Although the kinetics of baclofen elimination during hemodialysis are not well understood, this case demonstrates the resolution of baclofen induced encephalopathy with frequent and consecutive dialysis. Furthermore, we hope this case raises awareness among physicians of the toxic effects that baclofen can cause in dialysis patients.

SA-PO012
Utility of Hemodialysis in Urea Cycle Disorders

Introduction: Urea cycle disorders (UCDs) are rare pediatric diseases but partial enzyme deficiency can persist throughout adulthood. Little has been published about the role of hemodialysis in addressing the acute complications of UCDs in adulthood. Catabolic enzyme deficiency can persist throughout adulthood. Little has been published about the role of hemodialysis in addressing the acute complications of UCDs in adulthood. Catabolic states, he developed a second acute hyperammonemia (270mcg/dl). He was treated with a protein restricted diet of 35 grams per day and Na phenyl butyrate & L-citrulline). This pre-specified protocol (infusion of Na Phenylacetate/benzoate and Arginine HCl, fasting and short term treatment) that led to his ammonia level to 34mcg/dl. Later, patient underwent a procedure and was kept on a conservative approach with a combination of diet and medications. This was continued for 6 months and the patient was stable.

Discussion: The dangers of baclofen toxicity in patients with advanced kidney disease and in particular patients on dialysis remain underestimated by many physicians. We report a case of a 64 year old male who developed an uncommon case of altered mental status during his hospitalization. His medical history included ESRD for which he was receiving in-center hemodialysis, diabetes and hypertension. He initially presented to the hospital with complaints of shortness of breath and hiccups. His shortness of breath was attributed to volume overload and resolved with two consecutive days of dialysis with fluid removal. For his intractable hiccups, he was started on baclofen. During his hospitalization, he became lethargic and was unable to move his lower extremities. Laboratory data including serum sodium, potassium, glucose, calcium, BUN, phosphorus, liver enzymes, thyroid function tests, troponins, inr and prothrombin work up and ammonia levels were unremarkable. Neuroimaging, including CT head and brain MRI, were unchanged from previous studies and revealed moderate diffuse cerebral atrophy. An EEG was also performed and did not suggest signs of epileptic activity. Further investigation revealed that he had received a total of 20 mg of baclofen over 2 days. After other etiologies were ruled out, we determined that he may have suffered from baclofen induced encephalopathy. His baclofen was stopped and he was prescribed daily sessions of hemodialysis for three days with the intent of clearing baclofen. He was dialyzed for 4 hours during each dialysis session with a high flux dialyzer. After his first session of dialysis, the patient was more alert and would follow simple commands. At 3 days, the patient’s mental status returned to baseline and he was able to move his extremities.

Discussion: Although the kinetics of baclofen elimination during hemodialysis are not well understood, this case demonstrates the resolution of baclofen induced encephalopathy with frequent and consecutive dialysis. Furthermore, we hope this case raises awareness among physicians of the toxic effects that baclofen can cause in dialysis patients.

SA-PO013
Treatment of Atypical Hemolytic Uremic Syndrome Early in Pregnancy with Eculizumab
Rahul N. Pawar, Savneek S. Chugh, Amy R. Patel, Prachi Kale. Nephrology, Westchester Medical Center, New York; *Internal Medicine, Westchester Medical Center.

Introduction: Atypical Hemolytic Uremic syndrome (aHUS) is known to cause acute thrombotic microangiopathy (TMA) in pregnancy with adverse maternal and fetal outcomes. A French study showed that aHUS usually occurs postpartum when activity of plasmatic coagulation inhibitor regulatory proteins decreases. We present a case of a young lady early in pregnancy with severe thrombocytopenia and acute renal failure suspicious for TTP, but later diagnosed with aHUS, which improved with eculizumab.

A 30 year old G1P5A5LS 10 weeks pregnant with a past medical history of 5 first trimester miscarriages presented with nausea, vomiting and wasting. Laboratory results which are labs show a hemoglobin (Hgb) 7.8 g/dl, platelet (PLT) count 15k/ul, BUN 65 mg/dL, serum creatinine 2.44 mg/dL along with a LDH of 1,847 U/L, haptoglobin <8 mg/dl, and albumin 3.2 g/dL. Liver function tests (LFTs) and coagulation studies were normal. She was suspected to have TTP and transferred to our tertiary medical center. Urinalysis revealed 3+ protein and 3+ blood. Skin smear showed schistocytes. A diagnosis of TMA was made and plasmapheresis was started. Serologies for lupus and anti-phospholipid antibody syndrome were negative and LFTs remained normal, ruling out HELLP. The ADAMTS-13 activity level was noted to be 129%. Renal function declined requiring the initiation of hemodialysis(HD). On the basis of ongoing hemolytic anemia with thrombocytopenia, renal failure and a negative ADAMTS-13, she was started on Eculizumab. After 2 doses, her renal function and urine output improved and HD was stopped. At discharge, her Hgb was 8.5 g/dL, PLT 150 K/ul, and BUN/creatinine 23/1.84 with the plan to receive monthly eculizumab infusions.

Discussion: aHUS is caused by activation of the complement system due to a genetic deficiency of its regulatory proteins, specifically complement factor H, factor I, and factor IIB. It can lead to TMA causing multi-organ failure and the potential for death if not managed in time. Pregnancy can cause aHUS in any trimester. One should maintain a low suspicion for aHUS in a pregnant patient with prompt initiation of eculizumab to prevent negative outcomes.

SA-PO014
Ashvin Bang, Anam Khan, Celia A. Peña, Rajeev Raghavan. Nephrology, Baylor College of Medicine, Houston, TX.

Introduction: Relatively few renal manifestations have been detected in Familial Mediterranean Fever (FMF). We present a case of biopsy proven pauci-immune glomerulonephritis (GN) in a patient with clinically diagnosed FMF and review past treatments of pauci-immune GN in FMF patients.

Case Description: We present an interesting case of a 22 year old man who had suffered for nearly seven years a constellation of symptoms including fever, nausea, vomiting, abdominal pain, arthralgias, chest pain, and an erythematous rash consistent with a clinical diagnosis of Familial Mediterranean Fever. He had a normal serum creatinine of 1.0 mg/dl which peaked at 2.0 mg/dl. Repeated urinalysis indicated 6-10 RBCs per high powered field (phf) and 6-21 WBCs phf. Laboratory testing revealed only an elevated erythrocytosis. A kidney biopsy was performed which revealed 41% of the glomeruli globally sclerosed and 54 % of the viable glomeruli with active crescents and 25% interstitial fibrosis with tubular atrophy. Immunofluorescence revealed minimal C3 staining. This was consistent with Pauci-Immune Glomerulonephritis or ANCA negative vasculitis treated with Colchicine and pulse steroids, and maintained with mycophenolate mofetil as detection for mutations in the MEFV gene in the diagnosis of FMF is ongoing. He has had no relapse of his FMF with initiation of colchicine and now has had resolution of his hematuria, proteinuria, and acute kidney injury.

Discussion: In the literature, there is minimal knowledge about the renal manifestations of Familial Mediterranean Fever and fewer documented reports on the treatment protocols for ANCA negative vasculitis in FMF. We were able to treat ANCA negative vasculitis in a patient with FMF with only pulse steroids and maintenance immunosuppression with mycophenolate mofetil with great response.

SA-PO015
Stress of Surgery – Is It Just Mental or Can It Be Renal as Well?
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Introduction: Waldenstrom’s macroglobulinemia (WM) is a rare clinicopathological disorder with a reported annual incidence of 3 per million people. It is characterized by Ig M monoclonal gammopathy in the blood and lymphoplasmacytic lymphoma in the bone marrow. Clinical manifestations are non-specific and generally related to Ig M infiltration of hematopoietic tissues. While deposits of Ig M in the glomerular basement membrane may be seen, renal failure per se is unusual. Here, we present a unique case of recurrent acute kidney injury (AKI) post-operatively in a patient with underlying WM with spontaneous recovery each time.

Case Description: 75 year old woman with WM, hypertension, obstructive sleep apnea and paroxysmal atrial fibrillation presented for an elective surgery for lumbar stenosis and spinal decompression. Under post-operative care she developed AKI on postoperative day day 3. She had gradual worsening of lower extremity swelling and shortness of breath and repeat labs showed a serum creatinine of 3.32 mg/dl (0.94 times her baseline).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
mg/dl, 5 days prior) and renal service was consulted for AKI. She had a prior episode of AKI with knee replacement in 2008, dialysis dependent for 3 days, with spontaneous recovery. Further work up revealed fairly active urine sediment with new onset 24 hour urine protein of 3.3 grams. C3 was normal, C4 < 5 mg/dl, cryoglobulin was positive, rheumatoid factor of < 20 ug/dl, serum Ig M were elevated at 646 mg/dl (normal 46-304 mg/dl) and serum immunofixation showed an abnormal restricted band between the beta and gamma regions. Kidney biopsy showed strongly PAS positive hyaline-like precipitates in the glomerular capillaries with immunofluorescence strongly positive (3+) for IgM and lambda light chains. There were abundant, confluent electron dense deposits in the mesangial and subendothelial space. Her symptoms improved with diuresis and she refused any other major intervention. Renal function eventually improved with serum creatinine of 1.2 mg/dl at the time of discharge.

**Discussion:** In conclusion, we believe the stress of surgery precipitated intraglomerular deposition of Ig M leading to AKI with spontaneous resolution thereafter.

**SA-PO016**

**New Causes of Secondary Hyperparathyroidism: Unforeseen Effects of New Drugs on the PTH-Calcium Axis**

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**Introduction:** Calcium homeostasis is a function of the interplay between GI absorption, renal excretion and bone resorption. Although numerous effectors control these processes, PTH is primarily responsible. PTH affects the kidney and bone through PTH receptor 1. In the kidney PTH decreases phosphorus reabsorption, increases calcium reabsorption and stimulates 1-hydroxylation of vitamin D. In the bone PTH up-regulates expression of RANKL and decreases expression of osteoprotegrin. This process increases RANKL binding to RANK on osteoclast precursors stimulating them to become osteoclasts that increase bone resorption. New drugs that inhibit RANK are used to treat osteoporosis and bone metastases. We describe two patients who treated with recently developed chemotherapeutic agents who developed severe hypocalcemia, and secondary hyperparathyroidism with hyperphosphatemia due to renal PO4 wasting. We hypothesized that these drugs inhibit RANK.

**Case Description:** Case 1: A 72 y/o woman with metastatic leiomyosarcoma received Trabactinib, an experimental agent which interacts with DNA. She subsequently complained of weakness. Labs are shown. Case 2: A 73 y/o man with ALL positive for BCR-ABL was torted on the tyrosine kinase inhibitor Dasantabn. He subsequently developed the laboratory abnormalities shown.

<table>
<thead>
<tr>
<th></th>
<th>Initiated calcium</th>
<th>Pi</th>
<th>Urine Co</th>
<th>FePi</th>
<th>25-Vit D</th>
<th>1,25-Vit D</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient 1</td>
<td>0.84 mmol/L</td>
<td>0.9 mg</td>
<td>&lt; 5 mg/dl</td>
<td>44%</td>
<td>33 ug/ml</td>
<td>110 pg/ml</td>
<td>832 pg/ml</td>
</tr>
<tr>
<td>patient 2</td>
<td>0.95 mmol/L</td>
<td>1.3 mg</td>
<td>&lt; 5 mg/dl</td>
<td>46%</td>
<td>32 ug/ml</td>
<td>101 pg/ml</td>
<td>509 pg/ml</td>
</tr>
</tbody>
</table>

Creatinine was 0.7 mg/dl in patient 1 and 0.8 mg/dl in patient 2.

**Discussion:** Both patients developed secondary hyperparathyroidism. The renal effects of PTH appeared to be intact with increased calcium resorption, phosphorus excretion and hydroxylation of 25-Vitamin D. The effects of PTH on bone resorption, however, appeared blunted. Because PTH acts on both kidney and bone through the same receptor, we believe that this represents a post receptor phenomena involving the RANKL osteoprotegrin system. The tyrosine kinase inhibitor, Iminatinib, has been shown to decrease bone resorption through a similar mechanism. As new drugs are developed it is important to recognize potential untoward effects.

**Funding:** Clinical Revenue Support

**SA-PO017**

**Connection or Coincidence: Behçet’s Disease and Focal Segmental Glomerulosclerosis with Nephrotic Syndrome**

*Deanne Leonard, Cherise M. Cortese, Xochiquetzal J. Geiger, Nabeel Aslam. Mayo Clinic, Jacksonville, FL.*

**Introduction:** Behçet’s Disease (BD) often presents with aphthous and genital ulcers, uveitis, and erythema nodosum. Rarely, renal amyloidosis, IgA nephropathy and crescentic glomerulonephritis result. Here we present a case of nephrotic syndrome from focal segmental glomerulosclerosis (FSGS) in a patient with BD evidence to suggest a direct connection.

**Case Description:** 49 y/o female with history of hypertension and BD on enantecpet, colchicine and carvedilol. Following a recent prednisone taper, she developed oral ulcers, uveitis, pathergy reaction and proteinuria. Physical exam: Blood pressure: 170/90, aphthous ulcer, uveitis, and 3+ bilateral leg edema. Laboratory data: serum albumin 3.3 g/dl, total cholesterol 205 mg/dl, triglycerides 1.1 mg/dl. Urinalysis: 3+ proteinuria, 10 RBC/ hpf and a random protein/creatinine ratio of 8.5. Normal complement levels, DS-DNA, SS-A, SS-B, Sm Ab, RNP Ab, ScI 70 ab, and Jo Ab. Renal biopsy: Light microscopy: focal segmental lesions. Immunofluorescence: IgM trace mesangial granular staining, consistent with immunoglobulin trapping. IgG, IGA, C3, C1q, kappa, and lambda: negative. Electron microscopy: near total visceral epithelial foot cell process effacement with villous formation.

**Treatment** included losartan and prednisone 1 mg/kg/day which resulted in resolution of edema and reduction of protein to creatinine ratio to 0.14 along with resolution of oral ulcers and uveitis.

**Discussion:** At present, there is no proven correlation between BD and FSGS with nephrotic syndrome. Our patient presented with BD flare coinciding with the development of nephrotic syndrome both of which improved simultaneously with steroids suggesting a direct connection. Therefore, the clinician should be aware of this possible link and screen accordingly for proteinuria both qualitatively and quantitatively to detect early renal involvement in patients with BD.

**SA-PO018**

**Reversal of Dialysis-Dependent Renal Failure and Nephrotic Syndrome after Conservative Therapy in an Adult with Proliferative Glomerulonephritis with C3-Dominant Deposition**

*Eriko Takehara, Shintaro Mandai, Shinichi Uchida.*

**Introduction:** C3 glomerulonephritis (C3GN) is a recently described entity in a reclassification of membranoproliferative glomerulonephritis, characterized by isolated or predominant glomerular C3 deposits. Although abnormalities in the alternative pathway are known to be involved in the pathogenesis, efficient therapeutic approaches have yet to be established.

**Case Description:** In December 2012, a 55 year-old man was admitted with rapidly progressive glomerulonephritis and nephrotic syndrome. In May 2011, his serum creatinine(Scr) was 0.63mg/dL. Seven weeks previously, he was admitted to another hospital with hemorrhagic gastric ulcer accompanied by renal failure (Scr 4.61 mg/dL, urinary protein 15 g/gCr, and moderate hematuria), in the absence of preceding infection. At admission to our hospital, Scr increased to 7.60 mg/dL. ANCA, anti-nuclear antibody, and decrease in complement factors were absent. A renal biopsy specimen showed crescentic and endocapillary proliferative GN with dominant C3 and trace IgG. Conservative therapy was started, given the repeated hemorrhagic ulcer, and decreased rate of renal function decline. Hemodialysis was initiated on hospital day 20 because of oliguria, but was ceased on day 60 with recovery of kidney function. Scr decreased to 1.2 mg/dL, and urinary protein decreased to < 1 g/gCr. One year after discharge, he developed nephrotic-range proteinuria, and the second renal biopsy revealed the increased sclerotic glomeruli and fibrous crescents with isolated C3 deposits.

**Discussion:** To our knowledge, this report is the first to describe reversal of dialysis-dependent renal failure after conservative therapy in a C3GN patient. Similarly to the present case, the histological morphology and clinical presentation infrequently mimic the picture of postinfectious GN, although the transient recovery is usually partial. A novel classification of such cases among C3GN may be needed to avoid an unnecessarily immunosuppression.

**SA-PO019**

**Optical Coherence Tomography and En Face Retinal Findings in Membranoproliferative Glomerulonephritis Type 2**

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**Introduction:** Membranoproliferative glomerulonephritis type 2 (MPGN II) is a condition with electron dense deposits in the glomerular basal membrane that usually affects youngsters of 5-15 years old. Patients may have asymptomatic retinal drusen-like deposits in the macula or drusen-like lesions in the periphery. We evaluated patients with a high-speed spectral-domain optical coherence tomography (SD-OCT) device and en face OCT imaging of the retina.

**Case Description:** Four eyes of 2 patients with MPGN II were scanned using a high-speed 840-nm-wavelength SD-OCT (RTVue XR Avanti; Optovue, Inc, Fremont, USA). The split-spectrum amplitude-decoration angiography algorithm was used to detect blood flow. Fluorescein angiography (FA) (HRA System, Heidelberg Engineering) images were obtained in search for drusen-like deposits in the Bruch membrane or choroidal neovascularization.

Both patients, female, 34 years old and male, 25 years old, had best corrected visual acuity of 20/20 in both eyes, unremarkable anterior biomicroscopy, RPE mobilization and macular drusen-like deposits. There was no choroidal neovascularization at the FA. En face OCT showed hyporeflective dots with a hyperreflective ring at the RPE that corresponds to drusen-like deposits underneath the RPE and dilated choroidal image.
Discrimination: We reviewed a rare case of disseminated HSV infection and PD-related HSV peritonitis. The combination of ESRD, hypogammaglobulinemia, cellular and humoral immunity, and BP contributed to the severe immune-compromised state and disseminated HSV infection. Since an early diagnosis determines the prognosis of disseminated HSV infection, cell pathology in peritoneal fluid would assist preemptive therapy.

SA-PO022
Use of Rituximab in Goodpasture’s Disease with Pulmonary Hemorrhage
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Introduction: Goodpasture’s syndrome (GPS)or anti-GBM disease is a rare autoimmune disease, where pathogenic autoantibodies deposit in the basement membrane. It presents with rapidly progressive glomerulonephritis, with or without pulmonary hemorrhage. The current standard treatment of Anti-GBM disease is immuno-suppression to reduce antibody production and plasmapheresis to remove existing antibodies in circulation. Rituximab, a monoclonal antibody directed against CD-20 antigen present on B-lymphocytes, approved for various B-cell lymphoproliferative diseases has been used in ANCA associated vasculitis with success; however it’s use in anti-GBM disease is scarce and data regarding safety and efficacy is lacking. We report use of Rituximab in the treatment of GPS with pulmonary hemorrhage.

Case Description: A 35-year-old man presented in 2012 with two week history of nausea, vomiting, intermittent fevers and dark urine. Laboratory findings were creatinine 18 mg/dL, potassium 6.1 mmol/L, Hgb 11.6 g/dL, and platelet count 288 x 10^9 per µL. Urinalysis showed nephrritic urine sediment. Serology test including ANCA was negative. Anti-GBM antibodies levels were greater than 8 with peak 27. CT chest with pulmonary angiography was given to rule out pulmonary hypertension and initiate therapy. Renal biopsy was consistent with GPS (cresccentic GN linear anti-GBM on IF). Plasmapheresis was initiated and patient received four doses of Rituximab. Anti-GBM level on discharge from hospital was 2.9. Since initial presentation, patient had two admissions to the hospital in 2014 and 2015 with undetectable Anti-GBM levels.

Discussion: Patients with anti-GBM renal disease have high mortality, especially when pulmonary involvement is present. The use of steroid, immunosuppressives and plasmapheresis alone or in combination has led to a significant improvement of both patient survival and clinical symptoms. Anti-GBM disease is a rare autoinfectious disease; data regarding the safety and efficacy of alternative therapies are lacking. There are few reported cases of anti-GBM disease treated with rituximab. We present a case of anti-GBM disease with pulmonary hemorrhage successfully treated with Rituximab.

SA-PO013
A Rare Case of Aluminum Toxicity
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Introduction: Aluminum toxicity was initially described in encephalopathic patients with renal failure, overdosing of aluminum-based phosphate binders and attributed to contamination of water used for dialysis treatments. Use of alum for the treatment of refractory hemorrhagic cystitis was first reported in 1982. It was described as a safer alternative to formalin bladder irrigation. We report a case of bladder perforation after alum irrigation, leading to intra-peritoneal aluminum exposure. Our patient expired despite chelation and renal replacement therapy. Her serum aluminum concentration is the highest reported level to date.

Case Description: 67 year old female with cervical cancer, admitted for urosepsis, was noted to have hematuria and urinary retention. Her catheter was changed due to clot obstruction and bladder irrigated with saline. Following day continuous bladder irrigation was instituted for persistent hematuria. She underwent cystoscopy with fulguration for persistent hematuria secondary to radiation cystitis. Her CIBM was noted with alum irrigant. Overnight, alum irrigant was placed on a pump for infusion. Hours later, patient transferred to ICU for hypotension. CT abdomen revealed free intraperitoneal air, large volume of new fluid, air around bladder suspicious for bladder perforation, and absence of contrast outside of the bowel. Bilateral percutaneous nephrostomy performed for urinary diversion and to evacuate free fluid. Aluminum levels were drawn. Patient was intubated, placed on vasopressors. Had non-gap metabolic acidosis and worsening renal function, concerning for acute kidney injury due to intra-abdominal bladder perforation in the setting of alum irrigation. Deferoxamine was started and CVHVI for acidosis. However patient developed refractory shock, and expired. Shortly before her death, aluminum level resulted 163.7mcg/L (normal 0 to 20mcg/L). Subsequent levels peaked at 1455.2mcg/L.

Discussion: We report systemic absorption of alum-containing irrigant following bladder perforation. Large aluminum load to the peritoneum resulted in systemic toxicity,multi-organ failure and death. Chelation therapy and CVHVI were inadequate. We report the highest serum aluminum level to date.
Case Description: We describe 54 year old Male with a history of Deceased Donor Renal transplant in 1999 whose kidney disease was secondary to Hypertensive nephrosclerosis. Donor information is not available. The patient had been in his usual state of health until one week prior to presentation, when he started feeling weak and became confused, reason for hospitalization.

A computed tomography of the large mass measuring 5.4 x 2.9 cm ,in the corpus callosal splenium and second lesion 8 x 9 mm, in the left parietal lobe. He had a biopsy done which revealed a GBM. Neurosurgery was consulted and mass was found to be unresectable. Neuro-Oncology was consulted and he was advised radiation therapy and possible chemotherapy, but he decided to seek second opinion. His Post-transplant period has been remarkable for a borderline rejection with donor specific antibodies, treated with plasmapheresis and IVIG. His immunosuppressant medications were Cyclosporine , Mycophenolate mofetil and prednisone.

Discussion: Review of the literature indicates that gliomas do not seem appear in an early post-transplant period. These tumors have been reported mostly after 4-20 years from renal transplantation. Increased risk of tumour occurrence may be related immunological disorders such as HIV, and also to the administration of immunosuppressive drugs. Few studies have shown that cyclosporine may induce phenotypic changes in different tumoral and normal line cells and may play a role in modulating the neoplastic course. There seems to be a existence of a relationship between glioblastoma development and kidney transplant, but this association needs to be studied further. With increasing life expectancy of transplant recipients, evaluation of the risk of serious complications such as glial tumors is necessary.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Our case suggests that podocytes can engulf crystals in a similar manner, despite lacking tubular cells by receptor-mediated endocytosis, where they form protease resistant crystals. Confused as other forms of systemic vasculitis and therefore early identification and prompt specifically on the treatment of ANCA-negative patients. Such patients could be easily patients were treated similarly to ANCA-positive patients, although no study has focused patients only 7% were found to have GI manifestations and 17.9% had skin rash. These manifestations. In a study done in China comparing clinical features of ANCA negative PGN were segmental fibrinoid necrosis and early cellular crescents with mild increase in cellularity of mesangial matrix. Immunofluorescence: IgG, IgM, IgA, C3, C1q, kappa and lambda chains was negative. USG showed normal sized kidneys. Renal biopsy: Light microscopy showed no segmental glomerulosclerosis with characteristics of cryoglobulinic GN. The patient was referred to hepatology for evaluation showed microscopic hematuria, red blood cell casts, 1.2 grams of proteinuria, and thereafter suffered from persistent fever. With a diagnosis of bacterial pneumonia, he attended a work-associated physical examination that revealed proteinuria and Genotype 3a diagnosed 5 yrs ago, presented with complaints of intermittent vasculitis and MPGN without cryoglobulinemia being less frequent.

### SA-PO030

**Erythematous Skin Rash and Gastrointestinal Bleeding as Presenting Features of ANCA Negative Pauci-Immun Glomerulonephritis**

**Introduction:** Pauci-immune glomerulonephritis (PNG) is one of the common causes of RPGN. In most patients with PNG, circulating antineutrophil cytoplasmic autoantibody (ANCA) is present, however 10% of the patients are ANCA-negative. Usually extra renal manifestations in ANCA negative PGN are rare, but the case reported here is a rare presentation having skin rash and gastrointestinal (GI) manifestations.

**Case Description:** A 50-year-old female was admitted with low-grade intermittent fever, erythematous maculopapular rash all over the body and asympotomral artheritis involving large and small joints for about 3 months. She had one-week history of pain abdomen and melena followed by decreased urine output and generalized edema. On examination BP 156/94 mmHg, Birmingham Vasculitis Activity Score of 23/63. Investigations: Hb 9.9 g/dL, serum creatinine 4.0 mg/dL, urinalysis - protein ++, RBC 2-3/hpf. 24 hour urine protein 4.75gm/day. Serum uric acid and C3 were normal. Serum ANA, pANCA, cANCA, and RA factor were negative. Skin biopsy for IgG, IgM, C3, C1q was negative. USG showed normal sized kidneys. Renal biopsy: Light microscopy showed no segmental glomerulosclerosis with mild increase in cellularity of mesangial matrix. Immunofluorescence: IgG, IgM, IgA, C3, C1q, kappa and lambda chains were negative. Diagnosis of ANCA negative pauci-immune GN with crescents was made and patient was started on systemic steroids and cyclophosphamide pulse therapy. Patient improved symptomatically and creatinine levels gradually declined.

**Discussion:** Patients with ANCA negative PGN rarely present with skin and GI manifestations. In a study done in China comparing clinical features of ANCA negative patients only 7% were found to have GI manifestations and 17.9% had skin rash. These patients were treated similarly to ANCA-positive patients, although no study has focused specifically on the treatment of ANCA-negative patients. Such patients could be easily confused as other forms of systemic vasculitis and therefore early identification and prompt treatment could prevent many life threatening complications and improve prognosis.

**SA-PO031**

**A Case of ANCA-Associated Nephritis Mainly Localized to the Tubulointerstitial Area, Successfully Treated by Steroid Therapy**

**Introduction:** The typical pathological findings of antineutrophil cytoplasmic antibody (ANCA)-associated nephritis consist of extracapillary proliferation and necrotizing crescent formation. Nevertheless, a few cases of ANCA-associated nephritis, in which the tubulointerstitial area was mainly affected, are reported. Here, we present such a case of ANCA-associated tubulointerstitial nephritis, and review its characteristics compared to ANCA-associated glomerulonephritis.

**Case Description:** A 74 year-old generally healthy female developed bilateral hearing loss, and thereafter suffered from persistent fever. With a diagnosis of bacterial pneumonia, she was admitted to another hospital and treated with several broad-spectrum antibiotics without improvement. Four weeks later, she was referred to our hospital. On admission, weight loss and peripheral numbness and weakness was noted in addition to advanced hearing loss and fever. Serum creatinine level was elevated to 3.5 mg/dL, while urinalysis revealed mild proteinuria with few red blood cells and no cast in the sediment. Sinusitis and alveolar hemorrhage were observed by CT scan. Immunological tests demonstrated positive myeloperoxidase (MPO)-ANCA (104 U/ml). In view of multiple organ involvements, ANCA biopsy, thc vasculitis was suspected. Renal biopsy showed diffuse interstitial infiltrates and remarkable vasculitides in small arteries and capillaries with only a small number of crescentic glomeruli, which was consistent with ANCA-associated tubulointerstitial nephritis. Steroid therapy ameliorated not only kidney dysfunction, but also hearing loss.

**Discussion:** In an atypical case of ANCA-associated nephritis with near normal urinalysis, we need to consider the possibility of tubulointerstitial nephritis.
dose steroids, plasma exchanges, and a second dose of Rituximab, with clinical and renal improvement. One month after discharge, he was re-admitted with ARDS and diagnosed with B-cell lymphoma.

Discussion: There is a paucity of data on anti-HCV therapy in patients with renal failure often resulting in a delay of antiviral therapy. Immunomodulatory therapies may provide significant improvement of symptoms but bear the risk of significant adverse reactions. Early initiation of antiviral therapy is vital in order to prevent spectrum of HCV related complications.

SA-PO034
A Case of Membranous Nephropathy with an Adjacent Smooth Muscle Cell Tumor
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Introduction: Different stromal tumors can occur in the kidney and potentially skew the true extent of parenchymal injury induced by different glomerular diseases. Most of these stromal tumors are benign. The value of renal biopsy in assessing interstitial sequelae may be compromised by the mass effect of the infiltrating tumor cells.

Case Description: We describe a case of a 65 year old male patient, with a history of primary membranous nephropathy 20 years ago. He had initially been treated with the Pontocell protocol with favorable response. He continued to be in remission until a few months prior to presentation when he developed anasarca. His 24 hour urine collection revealed 8 grams of protein, and creatinine was 1.8 mg/dL. The decision was made for the patient to undergo a kidney biopsy which confirmed recurrence of primary membranous nephropathy with positive staining for PLA2R. It also revealed advanced chronic changes that included focal global glomerulosclerosis (87%) in addition to interstitial fibrosis 80%.

However, adjacent to this atrophic area, there was a tumor of spindle-shaped cells with smooth muscle characteristics. There was no atypia or mitosis and no clear capsule but the tumor cells appeared to infiltrate and surround the tubules and vasculature. This was labeled by the pathologist as a fragment of a smooth muscle cell tumor of undetermined malignant potential. The possibility of leiomyosarcoma could not be ruled out. MRI abdomen and pelvis did not show any evidence of extra renal involvement. The possibility of the parenchymal tissue being significantly infiltrated by its close proximity to the tumor prompted us to pursue another renal biopsy from the other kidney. Surprisingly, repeat biopsy showed only 15% of tubular atrophy and interstitial fibrosis. The patient was initiated on Rituximab and tolerated two courses of treatment. He achieved partial remission with UPCR less than 3 gram with stable Cr at 1.8 mg/dL.

Discussion: Coexistence of smooth muscle tumors and membranous nephropathy is rare. The extent of parenchymal involvement should be confirmed, with repeat biopsy, when there are concerns about tissue distortion by neighboring tumor.

SA-PO035
Freezing Point: Sjögren’s Disease Leads to Cryoglobulin Induced Membranoproliferative Glomerulonephritis
Manuel A. Fernandez Palmer, Roberto L. Collazo-Maldonado. Nephrology, Methodist Dallas Medical Center; Dallas, TX.

Introduction: Sjögren’s disease is chronic autoimmune inflammatory disorder mainly affecting salivary and lacrimal glands but rarely it can present with systemic manifestations including kidney involvement. The kidney manifestations may include hypokalemic RTA, interstitial disease and rarely MPGN.

Case Description: This is a 30 year old woman with no medical history who arrived to ER complaining of a three day history of SOB and increasing edema on lower extremities. She denied toxic habits. Review of systems positive for lower extremity rash in the preceding weeks. PE: was pertinent for elevated BP at 159/90 mmHg, 94% O2Sat on NC at 2LPM, bibasilar crackles with decreased breath sounds at bases and lower extremity pitting edema. Labs showed HGB of 10 g/dL, creatinine of 1.32 mg/dL with normal electrolyte, albumin levels 3.4 mg/dL/UA with proteinuria and hematuria, and a BNP that was markedly elevated. CXR showed pulmonary edema and bilateral moderate pleural effusions. Patient was admitted and workup performed, including CT which was negative, lower extremity Doppler that was negative for DVT. Creatinine increased to 2.6 and proteinuria was quantified at 4 g/24hrs. Serologic work up was negative except for low Complement levels along with a positive rheumatoid factor, positive anti-SsA. Clinical presentation and labs consistent with a diagnosis of Primary Sjögren’s disease.

Cryoglobulin levels where negative but kidney biopsy was performed and results consistent with Membranoproliferative Glomerulonephritis with intra capillary thrombi highly suggestive of cryoglobulins. Patient was started on high dose steroids and received five plasma exchanges. Afterwards, Rituximab 375 mg/m² was administered at weekly intervals three times four. At the time of discharge creatinine had stabilized at 0.95 mg/dL.

Discussion: Despite being rare, Sjögren’s Disease can lead to cryoglobulin formation and subsequent deposition in different tissues of the body. Nephrologists must consider this rare complication when evaluating patients with proteinuria, especially when there is worsening renal function and other systemic symptoms.

SA-PO036
Postinfectious Glomerulonephritis Associated with Escherichia coli Infection Caused by Transurethral Prostatectomy
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Introduction: Postinfectious glomerulonephritis (PIGN) is an immune-mediated glomerulonephritis(GN) caused by non-bacterial renal infection. In adults, PIGN is more common in immunocompromised patients, particularly diabetics. The major site of infection is the urinary tract, followed by the skin. In terms of causative agents, Staphylococcus is the most common cause in elderly people, followed by Streptococcus. Gram-negative bacteria, including Escherichia coli (E. coli), are responsible for up to 10% of cases of adult PIGN and 5% of cases in the elderly. We report a patient with PIGN associated with E. coli infection caused by transurethral prostatectomy.

Case Description: A 76-year-old Caucasian man with a history of coronary artery disease and recent transurethral prostatectomy was admitted with complaint of fever, and urenic symptomatology that necessitated dialysis therapy. Blood and urinary cultures were positive for E. coli and patient responded to antibiotic therapy. After one week, he was afebrile, without amelioration of renal function and with signs of glomerular involvement: urine red blood cells- 20-40/HPF, 24-hour urine proteins=1.7g. Immunological analyses were negative, except for decreased C4. The diagnostic approach led to a renal biopsy that findings were consistent with PIGN: endocapillary proliferative and exudative GN on LM, C3-dominant glomerular staining on IF and hump-shaped subepithelial deposits on EM. After urinary tract infection was controlled by antibiotic therapy, oral methylprednisolone was initiated, and the patient’s renal function and nephritic syndrome subsequently gradually improved.

Discussion: For a diagnosis of PIGN, at least three of the following five criteria must be satisfied: 1) clinical or laboratory evidence of an infection preceding the onset of GN 2) decreased serum complement levels 3)endocapillary proliferative and exudative GN on LM 4)C3-dominant or co-dominant glomerular staining on IF and 5) hump-shaped subepithelial deposits on EM. In the present case, all criteria were met. Moreover, recently reported that rarely, E. coli, also cause this type of GN.

SA-PO037
A Patient Presenting with Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome and Leptospirosis
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Introduction: There are very rare case reports in the literature about leptospirosis in association with TTP-HUS. We present a case report of TTP-HUS syndrome in a patient with leptomigrans.

Case Description: A 27 years old female patient was was transferred to our clinic due to progressive deterioration in the general status and kidney functions. On admission, she was oriented and cooperated. She had blood pressure of 130/65 mmHlg, heart rate of 90/min, temperature of 38.3°C and respiratory rate of 25/min. Patient had no urine output. There is minimal swelling on the dorsum of right hand of the patient. When we detailed history about this finding, she remembered that she saw mice in her working place in the night shift. Peripheral blood smear showed large numbers of fragmented red blood cells. Disseminated intravascular coagulation panel was normal. Viral hepatitis markers and serological tests for anti-nuclear antigen, anti-double stranded DNA, anti-hu, anti-jo, anti-Ro, anti-La, anti-ssA, anti-ssB, anti-dsDNA, anti-ribonucleoprotein, anti-centromere, Rubella, Cytomegalovirus, Hepers were all negative. C3 and C4 levels were normal. There was no reproduction in the blood cultures. ADAMS 13 level was reported as normal. Plasmapheresis was initiated immediately with the preliminary diagnosis of TTP/HUS. Also patient was empirically treated with antibiotics and on the 3rd day of treatment, doxycycline 200 mg orally per day was added to therapy because of the positive result of Leptospira IgM ELISA test. After 14 days of antibiotherapy and a total of 10 sessions of plasmapheresis, patient general status improved and laboratory findings come to near normal levels. Patient was discharged with the normal laboratory findings.

Discussion: In conclusion, leptospirosis and TTP-HUS can present with the same clinical findings and differential diagnosis is crucial to initiate the right treatment. Also, it is important to consider co-occurrence or association of these two disease in the light of patient’s history and laboratory findings although there are very rare reports in the literature.

SA-PO038
For the Eye Altering, Alters the All
Marie-Bague De Scheeber, Anne Marie Bogaert.

Introduction: We describe the case of a 26-year-old African female that was treated successfully with belimumab in a case of severe membranous lupus nephritis, resistant to first line therapy.

Case Description: She presented initially with chronic dacyroydendritis and screening showed nephrotic range proteinuria. Biopsy of the kidney confirmed the diagnosis of membranous lupus nephritis. Clinical features (joint pain, dacyroydendritis and lupus nephritis) in combination with serology (positive anti-DNA antibodies, hypocomplementemia) confirmed diagnosis of systemic lupus erythematosus(SLE). Treatment was initiated with glucocorticosteroids (GCS), mycophenolate mofetil (MMF) and Hydroxychloroquine sulphate (Plaquenil®). Tacrolimus was associated but no effect was observed with the glucocorticosteroids (GCS), mycophenolate mofetil (MMF) and Hydroxychloroquine sulphate (Plaquenil®). Tacrolimus was associated but no effect was observed with the

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
proteimuria, making it possible to decrease dosage of the other immunosuppressants and gradually stop them, even the GCS. Patient is now in complete remission after 2 years of treatment with no signs of relapse after stopping additional medication.

**Discussion:** Belimumab is indicated in treatment of seropositive active SLE in addition to standard therapy, when lack of clinical improvement despite optimal standard therapy. Two large, phase 3, multicenter, prospective, randomized, controlled trials (BLISS-52 and BLISS-76) compared belimumab with placebo in patients with SLE who were receiving standard therapies. Both studies showed significant improvement in SRI (Systemic Lupus Erythematosus Responder Index) with 10mg/kg of belimumab as compared with placebo. A phase 3 study (BLISS-LN) is recruiting patients with lupus nephritis since these post-hoc analysis of the BLISS trials suggest that belimumab may offer renal benefit in patients with SLE. The treatment is so far not recommended in these cases. We can conclude that our case shows excellent results of belimumab in lupus nephritis with persistent nephrotic range proteinuria under conventional treatment. Alternatives are scarce and mostly limited due to toxic effects and by failure to control disease.

**SA-PO039**

**Overlap Syndrome or Drug Reaction?** [Varun Gaur, Michael T. Eadon, Jesus H. Dominguez. Medicine, Indiana Univ, Indianapolis, IN.]

**Introduction:** The overlap of ANCA-Associated Vasculitis (AAV) with other autoimmune diseases is well known. However, the association of AAV with the use of TNF-α antagonists in Rheumatoid Arthritis (RA) patients is less understood.

**Case Description:** A 44 y/o white female with RA had prior treatment with methotrexate (3 yr), adalimumab (2 yr) and etanercept (2yr). She concluded all DMARD therapy 3 yr prior to presentation (PTP), and then her RA flared 5 months PTP. After initiation of leflunomide and steroids, she had partial resolution. Two weeks PTP, she received golimumab for onset of severe neurological manifestations including right foot drop, distal extremity numbness, and a right 4th digit ischemic lesion. Upon presentation, she was admitted with persistence of these symptoms. Her serum creatinine increased from 0.9 (mg/dl) to 1.4 with 2 gm proteinuria. Her urinalysis had hematuria and serology was positive for PR3-positive cANCA. Her renal function deteriorated with a peak creatinine of 6.7, necessitating intermittent dialysis. A biopsy revealed pauci-immune diffuse necrotizing and crescentic glomerulonephritis consistent with AAV. She received pulse solumedrol, cyclophosphamide, and plasma exchange. Her neurological symptoms improved after a month of therapy. After 6 weeks, she did not require dialysis and her serum creatinine was 2.4.

**Discussion:** We present a case of a patient previously treated with TNF-α inhibitors who then developed PR3-positive AAV years later. An association between AAV and RA has been described and RA may precede AAV by up to 8 years. Different theories explain this association. One reason may be the common genetic predispositions to autoimmunity, involving HLA or PTPN22 genes, reported in a series of both RA and AAV. Second theory suggests TNF antagonists may predispose one to develop secondary autoimmunity. In our case, the patient discontinued DMARDs 3 yr PTP, although had recently received Leflunamide and Golimumab. There are no reports that associate leflunamide use with AAV and only one case report suggests an association of golimumab with AAV. Our case highlights the need to further understand the importance of AAV in RA patients, and the potential role of TNF inhibitors on the development of AAV.

**SA-PO040**

**Pauci Immune Crescentic Glomerulonephritis in a Patient with T-Cell Lymphoma and Argyria** [Tamer Rezk, James J. Penton, Mark Alan Little, John Cunningham, Alan D. Salama. Centre for Nephrology, Royal Free Hospital, London, United Kingdom.]

**Introduction:** Silver is a transition metal element with a range of industrial and ornamental uses and is known to be toxic when ingested in significant amounts. Silver exposure causing argyria (skin deposition) and argyrosis (eye deposition) is well-recognised but the renal consequences of silver toxicity are poorly understood.

**Case Description:** A 47 year old woman with a T-cell lymphoma who refused conventional chemotherapy for 18 months but self-medicated with a remedy containing colloidal silver was admitted with acute dialysis-dependent kidney injury. The serum silver concentration was strikingly elevated at 127.1 nmol/l (reference value <2.8 nmol/l). Kidney biopsy demonstrated a pauci-immune crescentic glomerulonephritis and glomerular tufts with fine, dark, granular material scattered within the mesangium and along the glomerular basement membrane (GBM). Electron microscopy confirmed the presence of electrondense granules in the mesangium and along and within the GBM. Electron probe microanalysis demonstrated that these granules contained predominantly silver. The patient recovered independent renal function following immunosuppression with cyclophosphamide and steroids.

**Discussion:** Crescentic glomerulonephritis results from disruption of the GBM which may be induced by immune complexes or by cellular mediators. However our patient had no autoantibodies, and no deposited immunoproteins. We report a case of pauci-immune crescentic glomerulonephritis with intense silver deposition along the GBM. Between 5-10% cases of pauci-immune glomerulonephritis are ANCA negative. The pathogenesis in these cases may be related to other autoantibodies (such as anti-endothelial antibodies) or to direct leukocyte-induced GBM damage via soluble mediators, which in this case we believe was due to a combination of T cell lymphoma and argyria.

**SA-PO041**

**PR3-ANCA Vasculitis following Influenza Vaccination** [Karim El Hachem, Eduardo J. Zouain, Isha Gupta, Steven D. Smith. Nephrology, Mount Sinai-St Luke’s Hospital, New York, NY.]

**Introduction:** Influenza vaccination has been associated with the development of autoantibodies and autoimmune rheumatic disease. We report a case of PR3-ANCA associated vasculitis following influenza vaccination.

**Case Description:** The patient is a 45 year old Hispanic male with no known medical history who presented with subacute onset pleuritic chest pain and shortness of breath. Four weeks prior to presentation, he had received his annual injectable influenza vaccine and reports feeling weak since. On presentation, he was hemodynamically stable. His exam was notable for bibasilar crackles. He had positive Rheumatoid Factor. His CT chest was notable for multiple ground glass nodules at the right upper lobe. His creatinine was 1.64 mg/dL. His urine albumin to creatinine ratio was 225 mg/g creatinine and his urine protein to creatinine ratio was 500 mg/g creatinine. He had 25-30 RBC/hpf with no dysmorphic RBCs. He had strongly positive PR3-ANCA antibody (>8 AI). His kidney biopsy revealed acute focal segmental necrotizing crescentic GN, pauci-immune type.
The patient was treated with pulse IV methylprednisolone and Rituximab 375mg/m2 weekly for four doses. Three months following induction therapy, his creatinine improved from a peak of 3.6mg/dL to 1.4 mg/dL. His CT findings and hematuria resolved. His PR3-ANCA slowly decreased and became negative 6 months after induction.

Discussion: This patient’s presentation with lung nodules on chest CT, necrotizing crescentic glomerulonephritis with a high serum level of PR3-ANCA support a diagnosis of Granulomatosis with Polyangiitis with a strong temporal relationship to vaccination against influenza. This is the 9th case of ANCA associated vasculitis following influenza vaccination reported in the literature. Clinicians should be aware of the possible association between systemic vasculitis and influenza vaccination.

SA-PO042

C3 Glomerulonephritis Associated with Monoclonal Gammopathy of Undetermined Significance

Introduction: A case of C3 glomerulonephritis associated with monoclonal gammopathy responding effectively with immunosuppressive therapy.

Case Description: The patient was a 65-year-old Hispanic female who presented with lower extremity edema and dyspnea. She had acute kidney injury with nephritic urinary sediments. C3 and C4 were low. Hepatitis B & C profile, ANA, ANCA, anti-GBM and SFP were within normal limits. There was a faint monoclonal band in the gamma region on UPEP. Kidney biopsy was consistent with membrane proliferative glomerulonephritis (MPGN), of an undetermined etiology. Patient was readmitted with similar complaints and a rapidly declining renal function. Repeated UPEP showed a significant IGG kappa monoclonal protein and an elevated serum free light chain with kappa/lambda ratio of 2.52. Bone marrow biopsy revealed atypical plasmacytosis without overt myeloma. Repeated kidney biopsy showed global proliferative changes along with splitting of glomerular basement membrane. C3 deposits were seen on immunofluorescence. No reactivity was seen for IgA, IgG, IgM, C1q, C4, fibrinogen and albumin. Electron microscopy showed subendothelial and mesangial immune complex deposits.

Diagnosis was determined as C3 glomerulonephritis associated with monoclonal gammopathy. Patient was successfully treated with pulse glucocorticoids followed by oral glucocorticoids and mycophenolate mofetil. Plasma Lyso-Gb3 (4.1 ng/ml), and the c335G>A, p.R112H mutation of GLOA were found.

Discussion: C3 glomerulonephritis is related to dysregulation of alternative pathway of complement (AP) that can be associated with monoclonal gammopathy. Treatment of underlying monoclonal gammopathy may be of benefit in such a situation. Genetic studies for dysregulation of AP might be helpful.

SA-PO044

Another Enemy for Kidneys: Synthetic Cannabinoids

Introduction: Synthetic cannabinoids(SC) are widely used especially among young population. These substances have various physiological, metabolic and pharmacological (additive)effects. In last few decades SC related acute kidney injury(SC-RAKI) is pronounced more often.

Case Description: A 20-yr man without a medical history presented to ED with abdominal discomfort,nausea and vomiting for 3-4 days.On physical examination, arterial tension was 150/60 mm/Hg,HR 86/min,without orthostatic signs.He denied any nephrotoxic drug use,OTC medication or contrast media exposure. He has been a synthetic cannabinoid(Bonza) smoker for last 2 weeks.On admission he was oliguric and creatinine was 7.7mg/dl with normal creatinine kinase levels. Urinary analysis revealed pH 5.5,protein ++,leu 1,ery 1. Renal ultrasound showed normal size kidneys with increased echogenities,without hydropnephrosis.Interruption hemodialysis therapy was started.Autoimmune antibodies were negative. Renal biopsy revealed acute interstitial nephritis with increased mesangial matrix. Vascular structures were normal,no specific immunohistochemistry staining was detected.

After 6 sessions of HD his urinary output increased and creatinine levels regressed without a specific therapy,24-h urinary proteinuria was 529,2mg/dl on the 11th day of hospitalisation his creatinine level was 0.6mg/dl.

Discussion: SC-RAKI is usually reported as a consequence of prerenal conditions or rhabdomyolysis.In general renal histopathology reveals acute tubular necrosis. However,rarely these patients may present with interstitial nephritis.In our case complete cure of the patient without specific therapy was quite interesting.

SA-PO045

A Unique Case of Granulomatous Acute Interstitial Nephritis from Ipilimumab

Introduction: Ipilimumab is a CTLA-4 inhibitor which is used for the treatment of melanoma. We report a case of granulomatous interstitial nephritis due to ipilimumab, which developed after the first dose and featured a prominent component of granulomatous vasculitis.

Case Description: A 70 yr old man with stage IV melanoma presented with low grade fevers and malaise. He was found to have acute kidney injury with a creatinine of 6.0 mg/dL. Two months earlier, he had received a single dose of ipilimumab at which time his creatinine was 0.9 mg/dL. Laboratory data was notable for the absence of eosinophilia. Urinalysis showed 5-10 WBCs/hpf and many hyaline casts. A renal biopsy showed granulomatous interstitial nephritis with a component of granulomatous vasculitis (figure: H&E, Masson trichrome). He was treated with high-dose prednisone, which resulted in improvement of his renal function without the need for hemodialysis. After ten weeks of steroid therapy, his creatinine had decreased to 1.6 mg/dL.

Discussion: Ipilimumab is a potent activator of T cells and can interfere with the immune system’s tolerance of self-antigens. This drug is known to cause a variety of immune-related adverse events including hypophysitis, hepatitis, colitis and dermatitis. Interstitial nephritis is a rare diagnosis, but has been reported to occur after exposure to plasma Lyso-Gb3 levels than healthy subjects (PLoS One 2015). Undiagnosed FD patients may exist because their symptoms are restricted to proteinuria alone, as shown in this case. Further familial evaluation will help us elucidate this case as sporadic or familial FD to make an earlier diagnosis and treatment.
Severe Rhabdomyolysis Secondary to Adenovirus Infection

Daniel Tseytlin, Sharon E. Maynard.  Div of Nephrology, Lehigh Valley Health Network, Allentown, PA.

Introduction: A 38-year-old male presented to the ER with a 4-day history of a flu-like illness. Urinalysis showed myoglobinuria and granular casts. His CPK was markedly elevated. He was diagnosed with rhabdomyolysis from adenovirus and required hemodialysis. Case Description: A 38-year-old AA male presented to the ER with a 4-day history of weakness, subjective fever, and diffuse myalgias as well as recent left eye viral conjunctivitis. He noted dark urine and poor urine output. On arrival to the ER his vitals were stable. He had full muscle strength and no neuro deficits. He was oliguric. His SCr 5.04, his CPK 1,149,533 despite volume resuscitation including bicarb-containing fluid. He required HD. Workup was positive for adenovirus. Muscle biopsy was deferred in setting of known cause. He required 4 weeks of HD and was able to come off with impaired GFR of 67.

Discussion: Two cases of rhabdomyolysis from adenovirus have been reported. Most commonly manifests as a febrile illness with pharyngitis. Management strategies have been adopted from studies on crash injury victims. Early volume resuscitation is recommended to mitigate renal failure. Despite the theoretical benefits of bicarbonate-containing resuscitation fluids, no consensus exists. Adenoviral infection can lead to rhabdomyolysis with severe acute kidney injury. Respiratory viral panel should be included in workup of rhabdomyolysis when no other cause is evident. Treatment relies on supportive care, intravenous fluid resuscitation, and hemodialysis in cases of severe renal failure.

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Underline represents presenting author.

SA-PO047
Acute Respiratory Distress Syndrome and Posterior Reversible Encephalopathy Syndrome following Rituximab Therapy
Eoin D. O'Sullivan, Katrina E. Wardrope, Lynn Manson, Wendy Metcalfe. Dept of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; Scottish Blood Transfusion Service, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom.

Introduction: The anti CD20 monoclonal antibody Rituximab is an increasingly used therapy in modern medicine. It is associated with rare but potentially serious adverse events, notably Posterior Reversible Encephalopathy Syndrome (PRES), and Acute Respiratory Distress Syndrome (ARDS).

Case Description: A 60-year-old female was admitted with symptoms of peripheral oedema, arthralgia and mucosal bleeding. She was noted to have a widespread vasculitic rash, nephritic range proteinuria and new acute kidney injury. Renal biopsy demonstrated mesangiocapillary glomerulonephritis with multifocal extraglomerular necrotising vasculitis, in keeping with cryoglobulinemia. She was commenced on plasma exchange, prednisolone and Rituximab. 2 days after the initial dose of Rituximab she developed acute respiratory distress and was found to be in florid pulmonary oedema. This was managed with ultrafiltration, furosemide and oxygen therapy. She received a second dose of Rituximab 1 week later, and rapidly developed tonic-clonic seizures,a further episode of flash pulmonary oedema, encephalopathy and hyporeflexia. MRI brain revealed subcortical white matter high T2 and FLAIR signal in the occipital and posterior parietal lobes consistent with PRES.

Discussion: There are 7 reported cases of PRES complicating rituximab use. The onset of PRES occurred from immediately to 21 days after administration. All patients recovered completely, and rituximab was reintroduced in half of the cases. Mean recovery time was 4 days, and an additional risk factor was present in 5 cases. The occurrence of ARDS in association with rituximab is rare, only 3 confirmed cases exist . ARDS may occur as a delayed reaction.

SA-PO048
Atypical Hemolytic Uremic Syndrome Associated with Rituximab Therapy
Kristina Angela Rathnall, Shilpa Gadde. Nephrology, Tulane, New Orleans, LA.

Introduction: Hemolytic uremic syndrome (HUS) is classified as a thrombotic microangiopathies (TMA). Atypical HUS (aHUS) occurs in 0.5 to 2 per million population per year, 50% progress to end-stage renal disease (ESRD), and 25% may die in the acute phase. Atypical HUS is linked to uncontrolled activation of the complement system. A variety of genetic abnormalities of the alternative pathway of complement have been described in aHUS, occurring in 60% of cases. aHUS is diagnosis when toxsin producing bacterial infections, ADAMTS13 deficiency, and systemic-associated diseases are all excluded.

Case Description: A 57-year-old woman with a history of dermatomyositis and associated interstitial lung disease (ILD) was being treated for her ILD with Rituximab. She presented with altered mental status, shortness of breath, and fatigue after receiving an infusion of Rituximab. She was noted on physical exam to have peripheral edema and crackles on lung exam. On laboratory evaluation, her creatinine was 4.0 (baseline 1), hemoglobin 7, and platelets 20 with schistocytes on peripheral smear and a low C3 and C4. ADAMTS13 showed normal activity. She was initially treated with high dose steroids and plasmapheresis. She was started on Eculizumab. She required hemodialysis. Renal biopsy showed thrombi consistent with thrombotic microangiopathy as well as mild acute tubular necrosis. She is still hemodialysis dependent.

Discussion: Overall outcomes of this rare diagnosis vary widely. Initial treatment is usually plasmapheresis and corticosteroids. Confirmed aHUS is usually treated with Eculizumab. Our unique case entartains Rituximab, a monoclonal antibody, as a possible trigger for aHUS. Knowing the mechanism of action of Rituximab, it is possible it mediated the disease activity. Rituximab can lead to complement activation with subsequent production of C5a, which activates neutrophils. aHUS is a known cause of multi-organ failure and may require plasma exchange. Rituximab therapy in modern medicine. It is associated with rare but potentially serious adverse events, notably Posterior Reversible Encephalopathy Syndrome (PRES), and Acute Respiratory Distress Syndrome (ARDS).
On day 8 of therapy he was admitted with a Cr of 3.4, acutely elevated from 1.7. He denied hematuria, oliguria, fever, edema or NSAID use. Renal ultrasound was without obstruction. He underwent renal biopsy. Pathology revealed diffuse interstitial involvement by lambda-restricted neoplastic plasma cells and minimal cast nephropathy, but no significant interstitial fibrosis, tubular atrophy or monoclonal deposition disease. Congo red studies were negative for amyloid. There were no features of TMA. Chemotherapy was resumed.

Discussion: For renal failure that can be attributed to neoplastic plasma cell involvement.

SA-PO050

**AL Amyloidosis with Rapidly Progressive Renal Failure and Massive Liver Involvement: A Case Report**

**Matteo Angiolini**, 1  **Riccardo Cao**, 1  **Anna Maria Asunis**, 2  **Elisabetta Tamponi**, 2  **Alice Atzeni**, 1  **Patrizia Melis**, 1

**Introduction**: AL amyloidosis is a plasma cell disorder clinically dominated by organ involvement by light chains, mainly in renal and cardiac tissues. Although hepatic disease is described, clinical manifestations are usually mild and frequently undetected. We report a severe case of AL amyloidosis with a massive hepatic involvement and rapidly progressive renal failure (RPRF).

**Case Description**: One month before coming to our attention, a 67 year old male was admitted to another institution for ascites and scrotal edema. Past medical history included hypertension, previous hepatitis B virus infection and estimated daily alcohol intake of 60g. Renal function was normal (serum creatinine <0.7 mg/dL), while hepatic lysis indexes were moderately positive. A serum monoclonal component IgA kappa (0.21 g/dL) was detected and the bone marrow aspirate showed 10% plasma cell infiltration. Hepatic ultrasound showed hepatomagaly and portal hypertension. Final diagnosis was compensated alcoholic liver disease. After discharged, nephrotic syndrome (albuminuria >2g/dL), RPRF (Scr 1.6 mg/dL) and cholestasis appeared (AP 1559 IU/L, GGT 462 IU/L, AST-ALT normal). The patient was admitted to our institution and renal biopsy was performed revealing AL amyloidosis, with prominent IgA(+) and Kappa(++) mesangial deposits, coherently with the serology. The hepatic disease was not discouraged, and the liver biopsy revealed coarose deposits of amyloid as for the kidney. Other organs, heart included, appear to be spared at the time. In accordance with hematologists, a CyBorD-based regimen was started. Due to worsening kidney dysfunction, hemodialysis was initiated.

Discussion: This case highlights a rare presentation of AL amyloidosis with severe renal and hepatic involvement. Liver amyloidosis should be suspected in any patient with NS and unexplained cholestasis. Therefore, renal and hepatic biopsies should be considered when the clinical diagnosis is obscure, especially if rapid evolution to multiorgan failure is documented.

SA-PO051

**Pulmonary-Renal Syndrome: A Rare Case**

**Joana Gameiro**, 1  **Sofia C.A. Jorge**, 1  **Miguel Bigotte Vieira**, 1  **Estela Nogueira**, 1  **Maria Alice Fortes**, 1  **Helena Sousa Viana**, 2  **Fernanda Carvalho**, 1  **José António Lopes**, 2  **Antonio Gomes Da Costa**, 1

**Introduction**: Pulmonary-renal syndrome (PRS) is characterized by acute renal and pulmonary involvement of immunological or non-immunological causes.

**Case Description**: A 5-year-old African woman with 6-month history of edema, bilateral arthralgias in her knees, shoulders and hands, creatininemia 2.6mg/dL, and nephritic proteinuria referred to Portugal for medical care presenting with bilateral erythematous non pruriginous macular lesions in both thighs. Investigation confirmed renal failure (creatininaemia 7mg/dL), nephritic proteinuria (4.7g/24h), haematuria, hypoalbuminemia, hyperlipidemia, normal sized kidneys with increased parenchymal echogenicity. She began hemodialysis and was transferred to ICU due to pulmonary hemorrhage requiring mechanical ventilation. Plasmapheresis and intravenous high-dose steroids were started. Pneumococal pneumonia was also diagnosed and began antibiotic. Immunologic and serologic tests were negative or normal range. Serum protein electrophoresis showed hypogammaglobulinemia. Echocardiogram revealed type II diastolic dysfunction. Renal biopsy showed nodular glomerulosclerosis. Investigation of haematoletic disease revealed serum kappa light chain band and urine Bence Jones kappa. Free kappa light chains, serum kappa/lambda ratio and serum Beta-2-microglobulin were elevated. Bone marrow biopsy and aspirate showed 10% monoclonal plasmocytosis. No lytic lesions or masses were detected. Immunofluorescence of the renal biopsy revealed linear staining for kappa light chains along the tubular basement membrane and scarcer in the glomeruli. Electron microscopy is underway. Multiple mycetoma was diagnosed and started chemotherapy with Bortezomib. Although there was maintained remission of pulmonary hemorrhage she remained on dialysis.

Discussion: This case highlights a rare presentation of AL amyloidosis with severe renal and hepatic involvement. Liver amyloidosis should be considered in the differential diagnosis of PRS. Renal involvement is typical in LCDD with nodular glomerulosclerosis as the common pathologic finding. Pulmonary haemorrhage is usual and might suggest coexistence of fibrillary glomerulonephritis.

**Discussion**: Scleroderma renal crisis can present as acute cardioareno syndrome.


Dent's Disease: An X-Linked Tubulopathy

Sambhavi Krishnamoorthy, Tingting Li. Renal Div, Washington Univ in St. Louis, Saint Louis, MO.

Introduction: Dent’s disease is an X-linked recessive disorder of the proximal tubule characterized by low-molecular weight proteinuria, hypercalciuria, nephrocalcinosis/nephrolithiasis, and progressive renal failure. This disorder is caused by mutations in either the CLCN5 gene, or less commonly the OCLRN gene, leading to disruption of tubular endocytosis and the characteristic clinical findings.

Case Description: We describe an interesting case of a 24 year old Caucasian male with a longstanding history of excessive thirst and polyuria. He had no known history of renal disease. He denied history of urinary tract infections, nephrolithiasis, or NSAID use. Physical examination was unremarkable. Laboratory data showed a serum creatinine of 1.6 mg/dL. Hemoglobin A1c was normal. Urinalysis showed 2+ blood and 2+ protein. A 24 hour urine collection showed proteinuria of 1.7 g/day. ANA, ANCA, and hepatitis panel were all negative. A renal ultrasound showed multiple bilateral renal calculi and nephrocalcinosis. Further testing showed a daily urinary calcium excretion of 735 mg, phosphate 2150 mg and sodium 257 mg. His urine beta microglobulin level was significantly elevated at 29817 mcg/L. The presence of significant low molecular weight proteinuria, hypercalciuria, hyperphosphaturia, nephrocalcinosis/nephrolithiasis, hematuria/subnephrotic proteinuria, and chronic kidney disease fulfilled criteria for the diagnosis of Dent’s disease. No obvious X-linked pattern had been noted in his family history. Further genetic testing is pending at this time. On initiating hydrochlorothiazide, urinary calcium excretion reduced by 50%. Polyuria, which we attributed to nephrogenic diabetes insipidus in the setting of nephrocalcinosis, also improved significantly with the thiazide.

Discussion: This case report highlights the importance of recognizing this rare X-linked tubulopathy when presenting in adulthood. Commercially available genetic testing can be utilized for supporting the diagnosis and for appropriate genetic counseling for family members. The treatment focuses on reducing urinary calcium excretion and formation of nephrocalcinosis/nephrolithiasis with the ultimate goal of slowing progression to end stage renal disease.

Phlegmasia Cerulean Dolens: Complication of Femoral Vein Catheterization

SA-PO054

Vemuri Emur, Sambhavi Krishnamoorthy, Tingting Li. Renal Div, Washington Univ in St. Louis, Saint Louis, MO.

Introduction: There are three manifestations of acute massive venous thrombosis and obstruction of the venous drainage of an extremity. They are phlegmasia alba dolens, phlegmasia cerulea dolens (PCD) and venous gangrene.

Case Description: We present a 55-year-old hypertensive, presented with paedal oedema and breathlessness. About a month ago, she fell down and had dislocation of left patella. She was treated with a plaster cast and immobilization for 3 weeks. Her serum creatinine was 8.8 mg/dL. She was initiated on haemodialysis via two single lumen catheters placed in left femoral vein. The femoral vein catheters were removed after third session as platelet count was 500000. She developed acute renal failure with a serum creatinine of 8.8 mg/dL. On Doppler ultrasound, there were areas of clot in the left common femoral vein with extension to the right common femoral vein. There was severe oedema in the lower limb which was reduced on 5th day. She was discharged on heparin therapy and anticoagulation with oral warfarin. At follow up, her serum creatinine was 1.5 mg/dL and symptoms of lower limb swelling were improved.

Discussion: The causative factor in phlegmasia is massive thrombosis and occlusion of major venous channels. The left lower limb was elevated and anticoagulation was started but blebs increased and limb became blue. Below knee amputation of left lower limb was performed.

Minimal Change Disease Associated with Invasive Ductal Carcinoma of the Breast: A Case Report and Literature Review

Siddhesh J. Lotlikar, 1 Julian D. Rose, 1 Soumya Patnai, 2 Supakanya Wongrakpanich, 3 Mary Carolina Rodriguez Ziccardi, 2 Mark S. Morginstin, 2 Rasib Raja, 2 Eric J. Bloom. 2

Introduction: A tenth of malignancies have been associated with nephrotic syndrome, the diagnosis of which may precede the detection of cancer. In an adult with Minimal Change Disease (MCD), paraneoplastic etiology should be explored. Here, we describe a rare case of MCD associated with breast cancer.

Case Description: Our patient is a 72-year-old Caucasian female who presented with bilateral lower extremity edema for 1 week. Home medications were notable for occasional Diclofenac use. Urinalysis on admission showed nephrotic-range proteinuria. MCD was suspected and confirmed on renal biopsy. CT ruled out lymphoma and thymoma. MCD was presumed secondary to Diclofenac use and she was discharged on prednisone and azathioprine for intravenous IgG therapy. Two months later, she presented with a pulmonary embolus and CT showed concerning breast changes. Biopsy confirmed a stage IIIE invasive ductal adenocarcinoma. She was tapered off steroids, continued on furosemide and started on Paclitaxel.

Discussion: Breast cancer mainly causes antibody-mediated paraneoplastic syndromes. Yet, studies have shown intratumoral IFN-α expression correlates with induction of autoreactive T-cells, presenting a route for breast cancer to cause a T-cell-mediated process such as MCD. Our patient had no lymphoma or thymoma and the lack of evidence of AIN and failure of improvement on discontinuation of NSAIDs argue against NSAID-induced MCD. The relationship of MCD with breast carcinomas is reinforced by her improved proteinuria with chemotherapy.
A Case of Donor-Derived Enterococcal Pyelonephritis in an HIV-Positive Kidney Transplant Recipient Akshatha Rao,1 Shilpa A. Chaudhari,2 Dong Heun Lee,3 Karthik M. Ranganna,1 Alden Michael Doyle.1 1Div of Nephrology, Drexel Univ, Philadelphia; 2Division of Infectious Disease, Drexel Univ, Philadelphia.

Introduction: Donor-derived infections are an unusual but recognized complication of solid organ transplantation. Between 2005-2011, there were 118 reported donor bacterial infections, of which 34 recipients had confirmed transmission of infection and 9 deaths due to donor derived bacterial infections. Herein, we describe a unique case of donor-derived enterococcal pyelonephritis in a kidney transplant recipient with HIV infection.

Case Description: 47 year old male with history of HIV infection (CD4 -534 cells/mm3, VL <20 copies), ESRD on peritoneal dialysis, hypertension had deceased donor kidney transplantation. Post-op patient was given 1 dose of cefazolin as surgical prophylaxis. Basiliximab and intravenous immunoglobulin was used for induction therapy. Patient was started on intravenous ampicillin to complete a total of 6 days antibiotic course. POD #17 patient was readmitted to the hospital with urinary retention and elevated serum creatinine 2.2. Renal ultrasound showed no hydronephrosis. Urinalysis showed 2+ leukocyte esterase, WBC 11-20, with occasional bacteria. Blood and urine culture grew Enterococcus faecalis which was treated successfully; no other cases of peritonitis were noted.

Discussion: We suggest that PD should be considered in selected patients who have ascites and end-stage kidney disease. Further research is warranted regarding long term outcomes and potential effects of PD on the ability for these patients to get transplanted.

SA-PO058

Introduction: Managing patients with end stage liver disease associated with portal hypertension, ascites and end-stage kidney disease using peritoneal renal replacement therapy is challenging for a number of reasons including chronic hypotension, poor nutrition, coagulopathy, high infection rates, and encephalopathy. It is difficult to assess accurate dry weights because of the large variation patient weights depending on how much ascites they have at the time of dialysis, with weight fluctuations in excess of 10 kg. There is also a reluctance on the part of the transplant community to utilize PD because of the perception that these patients may not be able to go on to receive a successful liver transplant.

Case Description: Herein, we report our experience with 5 consecutive patients with decompensated cirrhosis who progressed to ESKD and required dialysis support. One patient did not tolerate HD and was switched to PD, the other 5 started with de novo PD. In each case, the patients were admitted to hospital for PD catheter placement with a surgeon experienced with patients who had advanced liver disease and stayed in the hospital for initial recovery period with IV albumin to support blood pressure. By our protocol, ascites fluid was drained in the OR and then drained each morning for the next 2 weeks before dialysis was initiated. Blood pressures ranged from 80/50-110/65 mmHg, patients remained asymptomatic. All patients received oral midodrine for BP support.

Adequate ultrafiltration achieved and edema improved. Serum albumin was monitored at regular intervals, ranged from 2.5-3. One patient had peritonitis from time of surgery, which was treated successfully; no other cases of peritonitis were noted.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-P0061
Abdominal Compartment Syndrome: An Overlooked Culprit of Acute Kidney Injury in Immediate Post-Liver Transplantation Ekamol Tantisattamo, Praveen Ratnasrimetha, Siwadon Pitukweerakul, Nephrology, Northwestern Univ; Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand; Presence St. Francis Hospital, Evanston.
Introduction: Acute kidney injury (AKI) is a common complication after liver transplantation and often times, dialysis is required. Abdominal compartment syndrome (ACS) is a treatable cause of prerenal AKI without dialysis needed. Case Description: A 60-year-old man with HVC and alcoholic cirrhosis underwent an OLT. He had massive blood loss during the uncomplicated operation and required massive transfusion and fluid resuscitation. Postoperatively, renal function initially was stable at the baseline serum creatinine (Scr) of 0.8 mg/dL. However, hemoglobin dropped from 9.1 to 5.7 g/dL and tacrolimus level elevated up to 53 ng/mL on postoperative day (POD)4. Scr rose up to 1.3 mg/dL and urine output (UOP) decreased on POD7. Renal function continued to decline with a peak BUN and Scr of 120 and 2.73 mg/dL on POD14, respectively (Figure 1). Dialysis was initially planned. However, he had progressively increased ascites with markedly tense abdomen. Bladder pressure revealed intra-abdominal hypertension (IAP) with the pressure of 20 mmHg. FE_{cr} and FE_{uro} were 0.7% and 21%, respectively. Therefore, abdominal paracentesis was performed with an 8 L of yellowish clear ascitis fluid removed. UOP significantly increased shortly after paracentesis. Scr had trended down and dialysis was not required.
Discussion: Our patient presented with prerenal AKI secondary to perioperative hypovolemia concomitant with superatherapeutic tacrolimus level. Massive blood transfusion and fluid resuscitation in the setting of major abdominal surgery caused IAH and subsequently ACS contributing to worsening prerenal AKI. Bladder pressure is a bedside diagnostic tool to detect IAH. AKI could be reversed and dialysis could be avoided by abdominal paracentesis.

SA-P0062
Rasburicase: A Salvage Strategy to Prevent Renal Allograft Loss in Acute on Chronic Urate Nephropathy Ekamol Tantisattamo, Praveen Ratnasrimetha, Siwadon Pitukweerakul, Nephrology, Northwestern Univ; Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand; Presence St. Francis Hospital, Evanston.
Introduction: Chronic hyperuricemia can lead to chronic kidney disease (CKD) and acute on chronic hyperuricemia potentially causes renal failure. Rasburicase is an effective uric lowering agent indicated for the treatment of acute hyperuricemia especially in tumor lysis syndrome. We report a case of kidney transplant recipient with acute hyperuricemia-related acute kidney injury (AKI) which was resolved with rasburicase.
Case Description: A 51-year-old man with ESRD secondary to type 2 diabetes status post renal transplant was admitted with diffuse muscle cramping. Maintenance immunosuppression included cyclosporine (CsA) and mycophenolate mofetil. The baseline serum creatinine (Scr) was 2.5 mg/dL after 2 episodes of borderline changes detected from transplant renal biopsy at 1 and 2 years posttransplant, respectively. However, over the past 9 months, Scr had gradually trended up to 4.4 mg/dL. He had asymptomatic hyperuricemia with a serum uric acid of 9.1–12.5 mg/dL. Two days after admission, he developed severe pain on the right first metatarsal joint presumed from acute gouty arthritis which responded to oral prednisone. However, Scr continued rising up to 4.8 mg/dL. Urinalysis showed a pH of 6 and Sp.Gr. of 1.011. Serum and urine BK virus were undetectable. Transplant renal ultrasound was unremarkable. Serum uric acid was markedly elevated up to 17.7 mg/dL. Given worsening renal function in the setting of acute hyperuricemia, rasburicase was initiated. Serum uric acid had been decreased to 8.1 and 4.5 mg/dL within 20 and 30 hours, respectively and Scr returned to the baseline of 2.5 mg/dL.
Discussion: Our patient presented with AKI on CKD in the setting of symptomatic acute on chronic hyperuricemia. Acute hyperuricemia leads to AKI which was resolved by rapidly lowering uric acid level with rasburicase. AKI in the patient with underlying chronic hyperuricemia should raise a suspicion for acute hyperuricemia-related AKI. Rasburicase should be considered as a salvage therapy to prevent renal allograft loss.
SA-P0063
The Effect of Taurine on Haemodilution Fibrosis in Patients with Chronic Heart Failure: A Case Study Shunji Shiohira, Kosaku Nitta, Ken Tsuchiya, Dept of Medicine IV, Tokyo Women’s Medical Univ, Shinjuku, Tokyo, Japan; Dept of Blood Purification, Iwaki, Fukushima, Japan.
Introduction: Taurine, an important factor in the living body, is essential for cardiovascular function and development and function of skeletal muscle, retina and central nervous system. In the present study, its effect on cardiovascular function was specifically taken into consideration. In haemodilutional filtration (HDF) patients, the effect of taurine on Neopterin concentrations in patients with chronic heart failure (CHF), in whom dry weight was difficult to control, was evaluated.
Case Description: All patients who were subjected to regular HDF for 4 h three times per week at Iwaki hospital in this study. Patients with chronic heart failure, in whom dry weight was difficult to control (n = 4), were included in the evaluation of clinical status. X-ray and echocardiography were determined before and after taurine treatment. Almost all cases were taking nitric acid, warfarin, anti-platelet and vasopressor. Because vital signs were unstable in chronic heart failure, all cases withheld antihypertensive drugs during HDF. For unstable vital signs during HDF, pulmonary congestion was chronically recognized. After taurine was added in HDF, vital signs stabilized and up of dry weight was possible. In addition, X-ray and cardiac diastolic failure on echocardiography improved.
Discussion: Taurine was effective for CHF patients on HDF in whom dry weight was difficult to control in spite of various medications.
SA-P0064
Introduction: Glomerular disease associated with Hashimoto’s Thyroiditis (HT) is a rare occurrence infrequently reported in the literature. We present a case of membranoproliferative glomerulonephritis (MPGN) that was thought initially to be due to systemic lupus erythematosus (SLE) in a young woman.
Case Description: A 38 year old female presented in 2013 with leg edema and two grams of proteinuria. Creatinine (Cr) was 1.3 mg/dL. Of note, her thyroid function tests were consistent with severe hypothyroidism, with a TSH of 129 mIU/L and a normal thyroid peroxidase and thyroglobulin antibodies ~900 IU/mL. Serologic workup for hepatitis B, C and HIV and complements were negative. She had a history of Raynaud’s but did not fulfill clinical and immunological criteria for SLE. Kidney biopsy was consistent with immune complex MPGN with immunofluorescence positive for IgG and C3 only. Patient was non-compliant with thyroid replacement therapy and was lost to follow-up. She reappeared in 2015 with arthralgias, dyspnea, and leg edema. Her Cr had worsened to 1.7 mg/dL with 16 gram proteinuria. She was found to have a pericardial effusion. TSH was 174 IU/mL. Repeated testing for SLE was negative and a renal biopsy performed demonstrated immune complex-mediated MPGN with minimal staining for full house immunoglobulins. She was placed on thyroxetine hormone and also initiated on mycophenolate mofetil, given that both her thyroid and renal disease appeared to be driven by an autoimmune antibody mediated process.
Discussion: HT, immune complex MPGN and clinical findings in our patient were initially thought to be due to SLE however patient failed to fulfill any immunologic criteria for SLE. HT is rarely associated with MPGN and specific mechanisms remain unclear. Proteinuria in glomerular disease associated with HT is not correlated with levels of thyroid hormone. However, deposits of IgG, C3, and C1q in glomeruli and thyroid resting immunofluorescence positive were seen in the kidney and HT. This supports the theory of an autoimmune basis for MPGN in HT, and reinforces that immunosuppression may be required to adequately treat both diseases.
SA-P0065
Hypervitaminosis D – A Rare Complication of PJP in a Transplant Patient Khaled Boobes, Khurram Saleem, Yazan M. Alia, Muhammad H. Hasan, Aneesha A. Shetty, Mohammed Javed Ansari. Nephrology, Northwestern Univ/Northern Memorial Hospital, Chicago, IL.
Introduction: Pneumocystis Jiroveci Pneumonia (PJP) is a known complication in immunocompromised hosts including transplant recipients, usually in the first six months of transplant. Hypercalcemia (HCa) is not a classic symptom of the disease. We present a case of a patient with simultaneous kidney and pancreas transplantation nineteen years ago who presented with PJP and developed HCa (highest value 14.8 mg/dl [8.3-10.5] mg/dl). Parathyroid Hormone (PTH) was appropriately suppressed with a level of 6; [12-88] pg/ml. 1,25-(OH) vitamin D concentration was elevated (123; [18-72] pg/ml). After treatment with the calcium-sensing receptor (CaSR) inhibitor, thiazide, and 1,25(OH) vitamin D supplementation, HCa have been reported to date, it is possible that this association is more frequent than previously thought. Hypercalcemia in transplant recipients with pulmonary symptoms must raise suspicion of PJP.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
639A
SA-PO066
A Rare Case of Tubulointerstitial Nephritis Associated with Primary Biliary Cirrhosis  
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Dept of Nephrology, Baylor College of Medicine, Houston, TX; Dept of Pathology, Baylor College of Medicine, Houston, TX.

**Introduction:** Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease characterized by positive antimitochondrial antibodies (AMA), immune-mediated epithelial damage of small bile ducts, which leads to liver cirrhosis as the disease advances. In addition to liver injury, other autoimmune diseases, such as Sjögren’s syndrome and Raynaud’s syndrome, are reported in approximately 2-20% patients with PBC. However, the association of PBC and renal injury is rarely documented.

**Case Description:** Here we present a case of tubulointerstitial nephritis (TIN) in a patient with PBC. A 35-year-old female with past medical history of PBC developed sub-nephrotic range proteinuria and chronic kidney disease stage 3. A renal biopsy showed severe CreIgAN on the back of high dose steroids and cyclophosphamide therapy. Severe CreIgAN infiltration of lymphocytes, plasma cells and occasional eosinophils, as well as significant tubulitis.

The patient was treated with a short course of oral prednisone and her renal function improved.

**Discussion:** This case highlights a very rare cause of TIN and suggests that steroid therapy is effective in this setting.

SA-PO067
Plasma Exchange as Adjunctive Therapy for Crescentic IgA Nephropathy  
Xinfang Xie, Fude Zhou, Minghui Zhao, Hong Zhang.  
Peking Univ Inst of Nephrology.

**Introduction:** Recent KDIGO guidelines recommend an aggressive immunosuppressive therapy in patients with crescentic IgA nephropathy (CredIgAN). While large cohort study from our center suggest that even with such a therapy, the 1- and 5-year renal survival rates remained low at 65% and 28%, respectively. Especially patients who present with serum creatinine (SCr)>580μmol/L hardly recovered from dialysis. In this study we aim to evaluate the efficacy of plasma exchange(PE) in severe CredIgAN.

**Case Description:** In this pilot study we give PE as adjunctive therapy to patients with severe CredIgAN on the back of high dose steroids and cyclophosphamide. Severe CredIgAN is defined as diffuse crescent forming with kidney failure that needs dialysis or presents kidney function declining even with high dose steroids and cyclophosphamide therapy.

Overall ten patients with severe crescentic IgA nephropathy received PE from 2011 to 2015.

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Y: yes, N: No

Among them 7 patients reached dialysis at presentation with serum creatinine (768±176μmmol/L). Another 3 cases showed progressively kidney decline even after an aggressive immunosuppressive therapy. Patients received 5-10 PEs. After a mean 13 month follow-up, 4 of the 7 patients who had dialysis successfully recovered from dialysis. One of the 3 patients with persistent kidney progression showed serum creatinine decline.

No severe adverse event was observed during the follow-up.

**Discussion:** Plasma exchange as adjunctive therapy may achieve benefit for patients with severe crescentic IgAN.

SA-PO068
Fibrillary Glomerulonephritis Associated with Demyelinating Polyneuropathy  
Sixto G. Giusti, Pradeep Vattla, Jorge C. Garces.  
Ochsner Clinic Foundation, New Orleans.

**Introduction:** Fibrillary glomerulonephritis (FGN) is characterized by nonbranching randomly arranged fibrils along the mesangium and glomerular capillary walls that do not stain for Congo red, have a diameter of 16-24 nm, and usually show polyclonal IgG, C3, and light chain deposition by immunofluorescence. Found in ≤ 1% of native renal biopsies, FGN is usually idiopathic, although some cases are associated with malignancy, monoclonal gammopathy, and autoimmune diseases. Association of FGN with demyelinating neuropathy has been rarely described.

**Case Description:** A 38-year-old Indian man with 3-year history of hypertension and 10-month history of end stage renal disease attributed to hypertensive, presented to our institution with a 3-week history of progressive, bilateral lower extremity weakness. During his hospital stay, he was diagnosed with non-infectious pleural and pericardial effusions. Lab work revealed normal Anti nuclear antibody, anti double stranded DNA antibody, serum complements, anti nuclear cytoplasmic antibodies. Serologies for hepatitis and human immune deficiency virus were negative. Electromyography revealed demyelinating sensorimotor polyneuropathy. Chest, abdomen and pelvis imaging was unrevealing for malignancy. No monoclonal peaks on serum and urine electrophoresis or immunofixation. Fat pad biopsy negative for amyloid. Bone marrow biopsy showed 60% cellularity with tri lineage hematopoietic activity, no B cell clonality or T cell aberrancy. He was started on high dose steroids with gradual improvements of weakness. Renal biopsy showed findings of chronic FGN with IgG4 dominant deposition. 44 of 48 glomeruli were globally sclerosed with 80% fibrosis and no activity. Sural nerve biopsy results are still pending.

**Discussion:** FGN is a rare and leads to ESRD in the majority of cases. There are very few cases describing FGN in association with demyelinating polyneuropathy without associated plasma cell dyscrasias. Although FGN renal prognosis remains poor, early identification is important as it may help identify an underlying malignancy or systemic autoimmune disorder with potential for treatment. FGN may be a precursor for future lymphoproliferative disorder.
SA-PO0069
Acute Inflammatory Polyarthritis following Kidney Transplantation
Paul P. Maraj. Nephrology, Baylor College of Medicine, Houston, TX.

Introduction: An acute inflammatory polyarthritis develops one month after deceased donor kidney transplantation in a 54 year old male. He had no prior diagnosis of any form of arthritis, crystalline, inflammatory or otherwise. Following workup he was diagnosed with Rheumatoid arthritis and improved with an increased dose of steroids. To date there are no case reports which described this disorder precipitated by kidney transplantation. This case report describes this unique clinical scenario and the dilemmas with diagnosis.

Case Description: 54 year old man with a medical history of end stage renal disease secondary to hypertensive nephrosclerosis who underwent deceased donor kidney transplant one month prior admitted for joint pains. During kidney transplantation he had induction with thymoglobulin, plasmapheresis and rituximab as per institutional protocol for positive DSA. Maintenance immunotherapy consisted of tacrolimus, mycophenolate mofetil and prednisone taper dose. Following transplantation he was asymptomatic until one month after transplantation when he developed bilateral shoulder pains which then migrated to elbows and wrist; this was associated with significant morning stiffness and malaise. Xrays which were negative for bony abnormalities, MRI wrist revealed small to moderate joint effusion. Fluid analysis was negative for septic arthritis and crystals. Serum uric acid was within normal limits. Autoimmune workup negative including ANA, C3, C4. Rheumatoid factor was positive to titer 1:4, anti CCP was significantly positive at>250. He was treated with oral steroids which resulted in resolution of his symptoms.

Discussion: To date there have been no reports of rheumatoid arthritis in the immediate post-transplant period. There have been reports of an acute inflammatory syndrome related to mycophenolate use which improved on discontinuation, anti-CCP titers were unknown in these cases. Mycophenolate was continued in this patient and his symptoms did not recur after steroid taper making a reaction to mycophenolate less likely. Anti CCP is very specific to disease diagnosis of rheumatoid arthritis but its validity post transplant is unknown. The temporal relation with transplantation also raises the possibility of a drug induced reaction.

SA-PO0070
IgM Nephropathy: A Neglected Pathology of Nephrotic Syndrome
Krystahl Z, Andujar, Carlos Antonio Cortes Sanchez, Hector R. Cordova. Medical Service, VA Caribbean Healthcare System, San Juan, PR.

Introduction: IgM nephropathy is defined by the presence of immunoglobulin M (IgM) as the dominant immunoglobulin in the mesangium of the glomeruli in a diffuse and global distribution. Clinically, a poor response to steroids distinguishes this disease from Minimal Change Disease.

Case Description: An 80-year-old man with past history of Hypertension, Alzheimer’s dementia, and benign prostatic hypertrophy complained of progressive shortness of breath associated with severe bilateral lower extremity edema and decreased urine output. Vital signs revealed blood pressure of 171/77mmHg. Lung auscultation was remarkable for bibasilar rales. The patient had anasarca. Laboratory tests showed serum creatinine at 2.2mg/dL (baseline of 1.2mg/dL), BUN of 36mg/dL and albumin of 2.2g/dL. Urinalysis showed microscopic hematuria and proteinuria (~ 500 mg/dL). Renal sonogram revealed normal kidney size without hydronephrosis or nephrolithiasis. The 24-hour urinary protein excretion was 6.7gms/day. Serum creatinine rose to 7.7mg/dL a week later. Kidney biopsy was read and steroid pulse therapy was started. Hemodialysis was initiated. Renal biopsy results showed mild increase in mesangial matrix and interstitial fibrosis. Sections stained for IgG, IgA, albumin C1q and kappa and lambda light chains were negative. Staining for IgM showed granular deposits in the mesangial areas compatible with a diagnosis of IgM Nephropathy. Hemodialysis was discontinued after two sessions since the patient had rapid recovery of kidney function after the 3 day steroid pulse therapy. Steroid therapy was tapered and eventually discontinued. Three months later, 24 hour urinary protein excretion was normal and the serum creatinine was 1.6mg/dl.

Discussion: Patients with IgM Nephropathy are less likely to respond to immunosuppressive agents. The presence of mesangial IgM deposits and interstitial fibrosis entails a worse prognosis. However, in our case, the patient had a prompt response to steroid therapy with resolution of the nephrotic syndrome and recovery of renal function.

Funding: Veterans Administration Support

SA-PO0071
Renal Infarct from Traumatic Renal Artery Dissection

Introduction: Renal infarction is an uncommon condition associated with a thromboembolic event (i.e.; related to atrial fibrillation), hypercoagulable state, renal artery dissection or fibromuscular dysplasia.

Case Description: A 26 y/o male with no significant PMHx presented with left flank pain for 3 days. The pain was described as 10/10 and associated with intermittent nausea. He fell from his motorcycle onto his left side 2 weeks prior. On exam there was a healing laceration over the left knee and tenderness to palpation over the left lower quadrant and L flank. The remainder of his exam including blood pressure was unremarkable. Blood work revealed a WBC of 13.8K/uL, ANA was negative, and global distribution. Clinically, a poor response to steroids distinguishes this disease from Minimal Change Disease.

Discussion: To date there have been no reports of rheumatoid arthritis in the immediate post-transplant period. There have been reports of an acute inflammatory syndrome related to mycophenolate use which improved on discontinuation, anti-CCP titers were unknown in these cases. Mycophenolate was continued in this patient and his symptoms did not recur after steroid taper making a reaction to mycophenolate less likely. Anti CCP is very specific to disease diagnosis of rheumatoid arthritis but its validity post transplant is unknown. The temporal relation with transplantation also raises the possibility of a drug induced reaction.
(SLE) is an autoimmune disorder where similarly, sphingolipid accumulation occurs when there is type 1 and SLE.

Case Description: A 32-year-old woman with Gaucher’s disease diagnosed at 17 years old, having valgus deformity, presented several clinical clues suggesting SLE. Months later started presenting face and limbs edema and hypertension. She was admitted with microcytic and hypochromic anemia, 77000 platelets, creatinine serum levels of 1.38mg/dl and hypocalcemia. The urinalysis showed hematuria and proteinuria of 7628mg in the 24h urine collection. The patient had positive anti-nuclear antibodies, Anti-Sjögren’s syndrome-related antigens, anti-SS-A/Ro and anti-SS-B/La antibodies, anti-neutrophil cytoplasmatic antibodies, viral serologies. Both complement levels were low. A kidney biopsy was performed.

It has been suggested that progressive accumulation of GC may trigger macrophage activation resulting in enhanced cytokine secretion and subsequent clonal B-cell expansion leading to chronic stimulation of the immune system. GC changes natural killer T cell function, a regulatory lymphocyte that have a role in infectious, neoplastic and inflammatory processes, therefore having a potential role in inducing other autoimmune disease. NKT lymphocytes are considered to be a link between innate and adaptive immune responses and were shown to have a role in a number of immune-mediated disorders. In an animal model of SLE, a selective reduction in NKT cells precedes the development of autoimmune phenomena.

Discussion: This case highlights a possible immunologic proximity between Gaucher’s disease and SLE, bringing up the already existing doubt that the defects in lipid metabolism, could contribute to the development of autoimmunity.

SA-PO074

Chronic Periaortitis, a Known Cause of Obstructive Uropathy

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Case Description: A 59-year-old man with hypertension presented with one week of gradually decreasing urine output, nausea, generalized weakness, and vague dull left lower quadrant pain with radiation to the left flank. He was afibrile with blood pressure of 170/90 mmHg, pulse of 79 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air. His abdominal exam was unremarkable except for non-tender scrotal swelling bilaterally. Laboratory studies were notable for the following values: WBC 12.1 x 10^9/L, BUN 62mg/dl, Cr 13.8mg/dl (baseline Cr 1.1mg/dl), ESR 57mm/hr, CRP 67mg/dl, U/A clear, yellow, specific gravity 1.01, pH 6.5, moderate blood, negative protein, leukocyte esterase, or nitrites. A renal ultrasound showed moderate hydronephrosis with patent renal arteries and veins bilaterally. CT of the abdomen and pelvis revealed moderate bilateral hydronephrosis, an abdominal aortic aneurysm (3.6cm), and a periaortic soft tissue mass measuring 2 cm in diameter with associated ureteral obstruction.

There was no iniucal iliac lymphadenopathy or suggestion of discrete malignancy. Based on combined clinical and radiographic evidence the patient was diagnosed with chronic periaortitis and retroperitoneal fibrosis. He was started on mycophenalate mofetil and prednisone taper with complete resolution of symptoms within 6 months.

Discussion: Retroperitoneal fibrosis (RPF) is a relatively rare condition characterized by the presence of fibrosis and inflammation of the retroperitoneal tissues that often surrounds the ureters and other abdominal organs and can lead to renal failure in advanced cases. Our case demonstrates the importance of considering RPF as an etiology of flank pain and renal failure as medical treatment is effective in reversing obstructive uropathy.

SA-PO075

IgA Nephropathy in HIV Positive Patient with Acute Kidney Injury

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Introduction: Acute kidney injury is common in patients with HIV, being prevalent the variety predominant the etiologic. Among the intrinsic causes are thrombotic microangiopathy, the antiretroviral drugs associated and the immune complexes associated (3.5%-10%) being the collapsing focal segmental glomerulosclerosis the most frequently found.

Case Description: Male 41 year old, with use of cocaine, marijuana, benzodiazepines tattoos and high-risk sexual behavior, diagnosed with HIV nine years ago, treated with antiretrovirals which suspended two years ago. Begins 3 months before with malaise, a week prior to his admission presented progressive dyspnea on moderate to high stresses accompanied by productive cough and fever. Chest radiography showed fine interstitial infiltrate, compatible with pneumocystis jiroveci, laboratories: Hb 4.7g/dl, creat 3.0 mg/dl, BUN 530 mg/dl, urin protein 4.7g/24 hrs, the urinalysis reported reddish urine, with granular casts, hematuria and pyuria. Hepatitis B, Hepatitis C, CMV and tuberculosis tests were all negative and the renal ultrasoundography was normal. Renal biopsy revealed IgA nephropathy.

Discussion: Renal toxicity of ketorolac has been described, and appears generally to be reversible, but could lead to glomerulonephritis in a rare setting. The pathological findings in the glomeruli resembled those described in experimental animals with Thy-1 induced glomerulonephritis treated with rofecoxib(COX-2 inhibitors). In this model, glomerular disease is initiated by immune-mediated mesangial cell damage, resulting in mesangiolysis.

SA-PO077

Ketorolac Induced Mesangiolysis: A Clinical Example of Anti-Thy-1.1 Model of Mesangio-Proliferative Glomerulonephritis

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Introduction: NSAIDS are known cause of acute kidney injury, but do not usually cause glomerulonephritis. We share an unusual presentation of glomerulonephritis after only one dose of ketorolac. No renal biopsy findings in acute ketorolac-related acute kidney injury appear to have been published based on an Ovid literature search.

Case Description: This is a 42 year old male with past medical history of nephrolithiasis and urethral stricture, who presented to the hospital for a cystoscopy procedure. The patient had urinary obstruction after the procedure and developed oliguric acute kidney injury with serum creatinine of 3.1 mg/dl (baseline 0.8 mg/dl). Of note, the patient also received one dose of ketorolac during the procedure. Uramids showed 2+ blood with many red blood cells, and 9 grams of proteinuria as TP/creatinine ratio. Lab work demonstrated high LDH, low lactoglobulin but stable hematocrit and platelet count. Peripheral smear did not reveal schistocytes. Urine microscopy showed RBC casts. Renal ultrasound showed normal sized kidneys with no hydronephrosis. Kidney biopsy showed acute tubule-interstitial nephritis with tubular necrosis and mesangiolysis. Electron microscopy showed patent capillary loops with focal epithelial foot process effacement, visceral epithelial cells with cytoplasmic vacuolization, dilated capillaries with endothelial apoptosis and mesangial lysis. Glomerular basement membrane thickness was increased. There was evidence of acute tubular injury. No electron dense deposits, thrombi or crescents were identified. Immunofluorescence of glomeruli was negative. The patient remained oliguric and required renal replacement for short term follow by full recovery of renal function.

Discussion: Renal toxicity of ketorolac has been described, and appears generally to be reversible, but could lead to glomerulonephritis in a rare setting. The pathological findings in the glomeruli resembled those described in experimental animals with Thy-1 induced glomerulonephritis treated with rofecoxib(COX-2 inhibitors). In this model, glomerular disease is initiated by immune-mediated mesangial cell damage, resulting in mesangiolysis.

SA-PO078

Disseminated Cytomegalovirus Disease in Induction Treatment with Mycophenolate Mofetil in a Lupus Nephritis Patient

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Introduction: Mycophenolate mofetil (MMF) is an immunosuppressive agent that exerts relatively selective antiproliferative effects on T and B lymphocytes and is increasingly being associated with higher incidence of tissue-invasive cytomegalovirus (CMV) disease in transplant recipients and other immune-mediated diseases. The case presented is a patient who developed CMV enteritis while receiving MMF and cotrimoxazole for lupus nephritis (LN).

Case Description: 59 year-old man with LN class IV G(a) + V under MMF (2,5g/day) and prednisolone to 20mg/day. The patient was started on intravenous ganciclovir 4g/day and prednisolone to 20mg/day. Of note, the patient also received one dose of ketorolac during the procedure. Uramids showed 2+ blood with many red blood cells, and 9 grams of proteinuria as TP/creatinine ratio. Lab work demonstrated high LDH, low lactoglobulin but stable hematocrit and platelet count. Peripheral smear did not reveal schistocytes. Urine microscopy showed RBC casts. Renal ultrasound showed normal sized kidneys with no hydronephrosis. Kidney biopsy showed acute tubule-interstitial nephritis with tubular necrosis and mesangiolysis. Electron microscopy showed patent capillary loops with focal epithelial foot process effacement, visceral epithelial cells with cytoplasmic vacuolization, dilated capillaries with endothelial apoptosis and mesangial lysis. Glomerular basement membrane thickness was increased. There was evidence of acute tubular injury. No electron dense deposits, thrombi or crescents were identified. Immunofluorescence of glomeruli was negative. The patient remained oliguric and required renal replacement for short term follow by full recovery of renal function.

Discussion: Renal toxicity of ketorolac has been described, and appears generally to be reversible, but could lead to glomerulonephritis in a rare setting. The pathological findings in the glomeruli resembled those described in experimental animals with Thy-1 induced glomerulonephritis treated with rofecoxib(COX-2 inhibitors). In this model, glomerular disease is initiated by immune-mediated mesangial cell damage, resulting in mesangiolysis.

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Underlines represent presenting author.
and fluconazole, with favorable clinical response. Proteinuria then worsened to 7.9g/day. Renal biopsy was repeated showing collapse of LN class V. Renal function improved PCR 1.6mg/dl having 2g MMF and prophylactic oral valganciclovir.

CMV virus directly infects the bowel causing mucosal erosions or ulcerations. We can only find little evidence that CMV disease explains the gastrointestinal adverse event profile associated with MMF but we bring up again the hypothesis that high local concentrations of MMF have a direct toxic effect on cells of the small intestine, causing gastrointestinal upset. Data on the incidence of CMV disease with the MMF induction protocol for LN are scarce.

Discussion: Similarly to transplant recipients receiving MMF, LN patients presenting gastrointestinal upset demand exclusion of CMV infection. This report highlights the importance of clinical follow-up of lupus patients with GI symptoms undergoing intense immunosuppression and accurate serological and histological diagnosis.

SA-PO078

Cryoglobulinemic Nephropathy with Successful Childbirth After Recurrent Episodes of Nephrotic Syndrome During Pregnancy Mibo Karube, Shinya Kaname, Kazuhito Fukuoka, Hideki Shimizu, Yoshinori Komagata, Yoshihiro Arimura. The First Dept of Internal Medicine, Kyorin Univ School of Medicine, 6-20-2 Shinkawa Mitaka-city, Tokyo, Japan.

Introduction: It is unknown whether pregnancy affects clinical course of cryoglobulinemic nephropathy and how to treat pregnant patients complicated with it.

Case Description: A 35-year-old woman was admitted to our hospital because of massive proteinuria that developed during the third pregnancy. The previous two pregnancies had been terminated for similar episodes of nephrotic syndrome. No history of hypertension was observed, but during the course she presented cryoglobulinemia, a high titer of RF and low serum complements. The renal biopsy performed 10 days after the third termination revealed MPGN-like lesions with lobulation in glomeruli, double contour of GBM, endotheliosis, and moderate mesangial cell proliferation. Immunofluorescence study showed IgG, IgA, IgM, C3, C4, and Clq all positive mainly along the glomerular capillaries, and subendothelial deposits were confirmed by EM, thus she was diagnosed as cryoglobulinemic nephropathy. Because the histological findings of repeated renal biopsy were not improved two months after the disappearance of proteinuria, treatment with 30 mg/day of PSL was started, followed by intravenous cyclophosphamide 6 times and plasma exchange, since she had a desire for baby. Finally at the fourth pregnancy, she bore a healthy baby weighing 2.342 kg on vaginal delivery at 36 weeks despite of recurrent appearance of nephrotic syndrome. After delivery, she was given 30 mg/day of PSL and proteinuria subsided.

Discussion: We experienced a rare case of type III cryoglobulinemic nephropathy that repeatedly developed nephrotic syndrome during pregnancy, but finally bore a baby after immunosuppressive therapy. Although the pathogenesis of pregnancy-induced exacerbation of cryoglobulinemic nephropathy was not clear in this patient, aggressive treatment may have been helpful for ameliorating it, leading to successful delivery.

SA-PO079

Renal Recurrence of Acute Lymphatic Leukemia Anna Bertram, Jan H. Bruesen, Ansgar Reising. 1Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany; 2Pathology, Hannover Medical School, Hannover, Germany.

Introduction: Renal complications of hematologic neoplasia can be therapy- or neoplasia-associated. We report a case of acute kidney injury (AKI) in the long term follow-up of a patient with acute lymphatic leukemia (ALL).

Case Description: The 42y old patient was diagnosed with ALL in 2009 and treated according to recommendations with chemotherapy and peripheral blood stem cell transplantation. In 2012, extramedullary ALL recurrence in his right knee was treated with irradiation. Starting from September 2014, molecular markers of minimal recurrence without evidence of lymphoblasts were found in bone marrow biopsies, and the patient received donor lymphocytes to induce graft vs. host reaction. In December 2014, ramipril was started for newly diagnosed hypertension, after which creatinine increased within several days to 290µmol/L. Because of this association, we suspected renal artery stenosis, toxic AKI, or acute interstitial nephritis. Ultrasound revealed diffusely swollen and dense kidneys (Fig.1A). Renal artery stenosis could be excluded, but - unexpected for interstitial nephritis - segmental arteries seemed compressed. Kidney biopsy revealed ALL recurrence with extensive lymphoblast infiltration. DOTA-CXCR4-PET-CT confirmed diffuse infiltration of both kidneys (Fig.1B) without bone marrow affection. After starting chemotherapy, creatinine rapidly ameliorated. Ultrasound and PET-CT-controls 10 weeks after starting therapy confirmed good treatment response (Fig.1C-D).

Discussion: This exceptional case of isolated renal ALL recurrence highlights the importance of early evaluation with ultrasound and biopsy in patients with hematologic neoplasia and AKI. An empiric treatment for suspected interstitial nephritis would have delayed chemotheraphy and thereby endangered the patient.

SA-PO080

A Rare Cause of Acute Kidney Injury in Non-Renal Solid Organ Transplantation Sameer Gupta, Wasay Humayun, Rampaery Sinnakruchanan, Liliana Osachuck. Nephrology, Medical College of Wisconsin, Milwaukee, WI.

Introduction: Acute kidney injury (AKI) is a frequent complication of non-renal solid organ transplantation (SOT). Here we report a case of rapidly progressive renal failure leading to end stage renal disease (ESRD) due to acute oxalate nephropathy (AON) in a patient with non-renal SOT.

Case Description: A 63 year old female with past history of pulmonary fibrosis status post bilateral lung transplant, obesity status post Roux en Y gastric bypass (RYGB) surgery, and hypertension presented with worsening kidney function with BUN and creatinine of 55 mg/dl and 6.18 mg/dl respectively. She had normal kidney function with serum creatinine of 0.5mg/dl prior to transplant 8 months ago. Induction regimen included Basiliximab followed by tacrolimus, prednisone and mycophenolate (MMF) as maintenance therapy. Ensuing transplantation, she had multiple episodes of AKI attributed to calcineurin inhibitor (CNI) toxicity and hypovolemia from MMF and clostridium difficile associated diarrhea. Her average tacrolimus trough level was 12 ng/mL. Several urinalyses showed acute tubular necrosis casts. Renal ultrasound revealed bilateral echogenic small kidneys compared to normal kidney size prior to transplant. Her kidney biopsy unexpectedly revealed oxalate nephropathy. She is currently on hemodialysis.

Discussion: AON has poorly been described in patients with RYGB surgery and SOT. In our patient with prior RYGB, chronic diarrhea, and numerous antibiotics unveiled AON. This superimposed with CNI toxicity resulted in rapid progression to ESRD. Antibiotic use depletes colonization of oxalate consuming bacteria (Oxalobacter formigenes). This combined with fatty acid malabsorption from prior RYGB increases colonic oxalate absorption resulting in hyperoxaluria. Diarrhea causes hypovolemia and metabolic acidosis leading to low urinary pH and hypocitraturia promoting calcium oxalate crystallization. Additional steps should be taken for SOT patients with RYGB, like diet modification, probiotic use, citrate supplementation, administration of fatty acid binding agents, and monitoring for hyperoxaluria. High suspicion for AON in patients with risk factors may lead to early diagnosis and treatment.

SA-PO081

Paraneoplastic Membranous Nephropathy and Myelodysplastic Syndrome – A Rare Combination Krishna K. R. Manoh, Madhuri Manne, Dagmar Klinger. Renal Medicine, Univ of Massachusetts Medical School, Worcester, MA.

Introduction: We report a case of Membranous Nephropathy (MN) seen in association with Myelodysplastic Syndrome (MDS). This occurrence is rare and only 3 cases have been reported in literature previously. Up to 5-20% of adults with MN have been reported to have most commonly a solid tumor and less frequently, a hematologic malignancy.

Case Description: Our patient is a 58 y/o man who has chronic kidney disease of unclear etiology with serum creatinine (SCr) of 1.3 and MDS. He was admitted with acute kidney injury in the setting of pneumonia and had nephrotic range proteinuria along with dysmorphic red blood cells on the urinary sediment. Renal biopsy showed MN with relatively recent immune complex deposition. There was no colocalization of IgG4 membranous deposits with phospholipase A2 receptor. He was hospitalized again with pancytopenia, marked inflammatory markers and infectious complications. Although bone marrow biopsy was not diagnostic, this syndrome was diagnosed as hemophagocytic
A Case of Advanced IgG4 Related Tubulointerstitial Nephritis Complicating Multiple Lymphadenopathy and Infiltrative Nodule, Mimicking Malignant Lymphoma

Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a systemic inflammatory disorder characterized by typical clinicopathological features and significant response to steroid treatment. It usually manifests in elderly men. Here we report a case of advanced IgG4-RD associated with multiple lymphadenopathy and infiltrative nodules that mimicked malignant lymphoma.

Case Description: A 56-year-old Caucasian man with history of colon tubular adenoma, NHL-status post chemotherapy and radiation 30 years back, hypothyroidism presented with new-onset nephrotic-range proteinuria. He was not taking any medications and physical exam noted generalized edema. Laboratory exam as noted in table 1.

- At Diagnosis: 9 gms 0.85 mg/dL 1.8 g/dL 1:1000
- 6 months of conservative therapy: 11 gms 1.3 mg/dL 1.6 g/dL
- 3 months of Ponticelli regimen: 7.3 gms 1.5 mg/dL 2.2 g/dL 1:20

A renal biopsy showed variable-sized electron dense deposits in subepithelial, intramembranous, mesangial and paramesangial locations. This finding strongly suggested a secondary etiology for the membranous nephropathy. Workup for infectious, autoimmune and neoplastic causes of membranous nephropathy was negative. Proteinuria worsened to 11 g/24h despite six months of conservative therapy with lisinopril and low protein diet. Additional labs obtained came back positive for PLA2R autoantibodies (IFA 1:1000, ELISA 97.6 RU/ml). Kidney staining positive for PLA2R glomerular deposits suggesting IMN.

The patient was then treated with a modified Ponticelli protocol using alternating monthly prednisone and oral cyclophosphamide (2 mg/kg/d) for six months. After three months, proteinuria, albumin and edema improved.

Discussion: Relying on histopathologic differencies to distinguish between idiopathic and secondary membranous nephropathy may lead to incorrect diagnosis and delay in treatment. The presence of circulating and tissue PLA2R autoantibodies may be more reliable in diagnosing IMN than histopathology.

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Underline represents presenting author.
SA-PO086
Silent Malakoplakia in a Recipient of Kidney-Pancreas Transplant Diagnosed on Surveillance Biopsy of Kidney Allograft: A Patient-Centered Approach to Treatment of Malakoplakia Jun Shoji, 1 Ravinder K. Walli, 2 Dept of Kidney Disease and Hypertension, George Washington Univ, Washington, DC, 1Inova Transplant Center, Inova Fairfax Hospital, Falls Church, VA.

Introduction: Malakoplakia is an inflammatory disease leading to chronic morbidity and organ dysfunction. It was originally described in association with genitourinary tract infections with coliform bacteria and can manifest as acute pyelonephritis, acute or chronic renal failure, or renal mass. We present a case of a 40-year-old female recipient of simultaneous pancreas-kidney transplant who developed an acute rise in serum creatinine without apparent cause and found to have malakoplakia on kidney allograft biopsy. Patient consented and treatment resulted in reversal of allograft dysfunction and resolution of histological features of malakoplakia.

Case Description: 40-year-old Caucasian female with type 1 diabetes mellitus and end-stage renal disease on peritoneal dialysis underwent SPK transplant. After induction with basiliximab and thymoglobulin, she was maintained on tacrolimus and mycophenolate mofetil. Two months later, she was treated for acute T-cell mediated rejection (Banff Grade IA) with thymoglobulin. Serum creatinine returned to baseline and maintenance prednisone was added to her regimen. Her posttransplant course was complicated by multiple infections including parvovirus B19 infection, primary CMV infection, two episodes of urinary tract infections, and influenza A pneumonia. Due to an increase in serum creatinine without apparent cause, a kidney allograft biopsy was performed which revealed lesions consistent with malakoplakia.

Discussion: Treatment of malakoplakia in kidney transplant recipients is not well established but include surgical resection and use of antimicrobial agents. In the era of cyclosporine and azathioprine, it was speculated that the use of azathioprine may be associated with the development of malakoplakia. Discontinuation of azathioprine was suggested in more bactericidal activity of mononuclear cells. This case report illustrates that in the era of immunosuppression with tacrolimus and mycophenolate mofetil, the maintenance therapy with tacrolimus may be continued while treating for malakoplakia.

SA-PO087
Common Weight Loss Medication Pill “Qsymia” Causing Hypokalemia and Renal Tubular Acidosis Iyotana Thukkar, Mala Sachdeva. Div of Nephrology, North Shore -LI School of Medicine, Great Neck, NY.

Introduction: The obesity epidemic is growing. Aside from the traditional diet and exercise, weight loss pills are more commonly prescribed. Qsymia is one such weight loss pill consisting of topiramate and phentermine. We report potentially life threatening side effects of Qsymia causing severe hypokalemia, proximal renal tubular acidosis (pRTA), and cardiac dysrhythmia.

Case Description: A 68 year old female with history of hypertension presented with complaints of tingling of her left arm and jaw of one day duration. Her home medications included Aspirin and Hyzara (Losartan and Hydrochlorothiazide). She had self discontinued the Hyzaar five days prior to presentation. Patient was recently started on the weight loss medication “Qsymia” three months prior. She denied any alcohol use. On initial presentation, she was noted to be in atrial fibrillation (HR 150s) and hypotensive (BP 84/43 mmHg). Urinalysis showed pH 8 with glucosuria. Urine Lytes showed potassium 38 mmol/L, chloride 43 mmol/dL, bicarbonate 22 mmol/L, phosphorus 2.1 mg/dL, magnesium 2.2 mg/dL, and calcium 8.9 mg/dL. Urinalysis showed pH 8 with glucosuria. Urine Lytes showed potassium 38 mmol/L, chloride 43 mmol/dL, sodium 141 mmol/L.

It was suggested that patient’s clinical presentation and electrolyte disorders were due to the weight loss medication, and Qsymia was discontinued. Qsymia was approved by FDA in 2012 for weight loss. Most common side effects reported include paresthesia, due to the weight loss medication, and Qsymia was discontinued. Qsymia was approved by FDA in 2012 for weight loss. Most common side effects reported include paresthesia, hypokalemia and proximal tubular acidosis. Hence, we report it here. The patient’s weight loss medication was Qsymia which was discontinued and patient was treated with correction of hypokalemia and initiation of management for Multiple myeloma.

Discussion: Multiple Myeloma accounts for 10% of hematological malignancies. Atleast 50% of patients with MM have evidence renal insufficiency and more than 80% have proteinuria. Multiple myeloma can present as has wide range of renal manifestations including myeloma cast nephropathy, Immune deposit disease, CKD Fanconi syndrome. Though rare Multiple myeloma can cause TMA and the Pathogenesis still remains unclear.

SA-PO089

Introduction: Pantoprazole (PPZ), a Proton Pump Inhibitor, is known to cause acute interstitial nephritis (AIN). We report a case of PPZ induced AIN in a young adult with just 3 doses of drug exposure.

Case Description: A 21 year old Asian American male with no past medical history was sent to the hospital by his Internist for elevated serum creatinine (Scr). He had nausea and abdominal pain 3 weeks earlier and was prescribed PPZ, which he took for 3 days. He denied use of any other medications including herbal supplements and NSAIDS. Laboratory data showed BUN of 82 mg/dL, Scr 15 mg/dL (baseline 0.6), bicarbonate of 15 mmol/L and normal renal urinalysis. Urinalysis showed sterile pyuria with no eosinphils, glycosuria with normal blood glucose, mild proteinuria (900mg/24 hrs). Serum and urine toxicology, protein electrophoresis, auto-immune work up were unremarkable. A Renal biopsy revealed diffuse expansion of the interstitium due to accumulation of cellular infiltrates consisting of lymphocytes, plasma cells and eosinophils with accompanying tubulitis consistent with AIN.

Though rare Multiple myeloma can cause TMA and the Pathogenesis still remains unclear.

He received pulse steroids for 3 days and was continued on prednisone 1mg/kg/day with a plan to taper over 8-12 weeks. He required a few sessions of renal replacement therapy before his renal function started to recover, 6 weeks later his Scr was 1.4 mg/dL.

Discussion: Any drug can cause AIN, although the categories of antibiotics, diuretics and NSAIDs are most commonly implicated. Drug-induced AIN is not dose dependent, and recurrence can occur with a second exposure to the same or a related drug. The data on time of initiation, dosage and duration of steroids in drug induced AIN is limited due to lack of randomized control trials. On review of literature and our experience, we conclude that stopping the culprit agent and early steroid use confers better prognosis in drug induced AIN.

SA-PO090

Introduction: Renal cell carcinomas are more common in ESRD than the general population and renal transplant patients with enhanced longevity may be at particular risk. Sarcomatoid renal cell carcinoma represents 1-15% of all renal cell carcinomas but has been very rarely described as a cause of renal allograft. The median age at diagnosis is 68 years with 45-77% of patients with locally advanced or metastatic disease at the time of diagnosis. We describe a case sarcomatoid tumor of urothelial origin in a transplanted renal allograft.

Case Description: A 54 y/o man with ESRD from polycystic kidney disease, HTN, aortic dissection repair, mechanical AVR, panxoxymal Afib, who had failed renal transplants in the past and was on dialysis for past 12 years, was admitted for left lower quadrant pain, fever and leukocytosis for which he was started on vancomycin and Ceftriaxone treatment.

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aztreonam. On imagine, he was found to have a mass around the left transplant kidney, ascites, omental caking, retroperitoneal lymphadenopathy and heterogeneous liver lesions. Retroperitoneal lymph node biopsy and asic fluid cytology was negative for malignant cells. Left kidney mass could not be biopsied because of technical difficulties and he had biopsy of the liver lesions which showed sarcomatoid tumor. He developed respiratory failure and septic shock requiring pressor support and expired. An autopsy was performed which showed Metastatic Sarcomatoid carcinoma of uterine origin.

Discussion: Malignancy in post transplant is related to direct effects of immune-suppressants as well as their effects to suppress immune surveillance and to stimulate the activation of oncogenic viruses. It is generally recommended that patients on the active transplant list and renal transplant recipients be screened every several years for renal tumors. However after allograft failure, it is unclear how often to do cancer screening tests. Although in this particular case it is unclear whether screening would have made a difference in outcome, we recommend routine screening for renal cell carcinoma even if the renal allograft has failed.

SA-PO091

Parathyroidectomy on a Patient with Sickle Cell Disease and End Stage Renal Disease
Farzana Akil, Mary C. Mallappallil, David Kau, Moro O. Sallyu. Stony Downstate Medical Center, Brooklyn, NY.

Introduction: Patients with End Stage Renal Disease (ESRD) can develop elevated parathyroid hormone (PTH) levels with hypercalcemia. Some fail or cannot tolerate medical therapy. They eventually require parathyroidectomy. Tertiary hyperparathyroidism (3PTH) is the autonomous function of the parathyroid gland due to increased mass. Our case is unique as there are no reported cases of tertiary parathyroidism in sickle cell patient, although, the presence of renal osteodystrophy may be present in sickle cell patients with parathyroidectomy. 25 year old man with sickle cell disease, ESRD on hemodialysis since 2012, (3PTH), presents after many admissions for sickle cell pain crisis. Cause of ESRD was unknown but attributed to sickle cell nephropathy. Current admission for knee pain and MRI which showed, “sclerotic appearance of the bones, likely due to renal osteodystrophy”. Intact PTH (iPTH) consistently > 4000 pg/mL, and patient non adherent to calcitriol, agreed to parathyroidectomy after many admissions for presumed vasoocclusive crisis. CT neck: “moderately enhancing foci inferior to the left and right thyroid lobes, and superior to the left thyroid lobes, could be compatible with parathyroid adenomas.” Sestamibi scan: “equivocal slow washout focus in region of right lower pole of thyroid gland extending posteriorly. Suspicious for but not definitive for parathyroid adenoma”. On the day prior to surgery, iPTH 4078 pg/mL, with serum calcium (Ca)=10.3 mg/dL. Immediately after surgery and for 265 pg/mL, with Ca=9.9 mg/dL. The first day after surgery, iPTH 36 pg/mL with Ca=7.6 mg/dL. Patient admitted for 3 days due to his requirement of intravenous calcium and daily hemodialysis. Since discharge, patient has had fewer admissions for pain. He has however, remained hypocalcemic and is on 5 grams of calcium carbonate, 4 mcg of doxercalciferol, and is dialyzed with a 3 mEq/L calcium bath.

Discussion: 3PTH is common in ESRD patients that can leave them debilitated. Those who fail medical therapy may benefit from resection. In sickle cell disease symptoms of 3PTH was masked by vaso-occlusive crises and could be distinguished by marked reduction in symptoms after resection.

SA-PO092

Synthetic Cannabinoid (SC) in End Stage Renal Disease
Chyi Chyi Chong, Pallavi D. Shirsat, Ramesh Marahatta, Neville R. Dossabbhoy. 1LSU Health Science Center, Shreveport; 2YA Medical Center, Shreveport.

Introduction: Synthetic cannabinoids (SC) are drugs of abuse especially among young adults. They are affordable, widely available and mostly importantly undetectable by standard urine toxicology screen. The avoidance of detection in the urine contributes to their allure and abuse. Acute kidney injury (AKI) related to synthetic cannabinoids has been reported. However, effect of synthetic marihuana in end stage renal disease (ESRD) patients remains unknown.

Case Description: We present a case of severe high anion gap metabolic acidosis (HAGMA) with acute respiratory failure in an ESRD patient. A 37-year-old African American female with ESRD, hepatitis C and hypertension was found smoking synthetic marihuana under a tree, and in a confused state. Upon arrival to the emergency room, patient was severely hypertensive with blood pressure of 230/140 mmHg, and subsequently developed acute respiratory failure requiring intubation. Chest x-ray showed bilateral pulmonary edema. Laboratory data revealed: WBC 18K/uL, Potassium 4.3-6.6 [3.6-5.2], mmol/L Calcium 8.2-10.1 [8.9-10.1], mg/dL. The patient was initiated on allopurinol, rasburicase, and continuous veno-venous hemofiltration (CVVH). He progressively deteriorated during his 11-day hospital course with recurrent episodes of arrhythmia, persistent encephalopathy, continued mechanical ventilator and hemodialysis dependence, and refractory septic shock with candidemia. The family elected for comfort care and the patient expired the next day.

Discussion: Synthetic Cannabinoids are sold under different trade names and the exact association between the use of cocaine and focal segmental glomerulosclerosis. Although in this particular case it is unclear whether screening would have made a difference in outcome, we recommend routine screening for renal cell carcinoma even if the renal allograft has failed.

SA-PO093

Focal Segmental Glomerulosclerosis Associated with Cocaine Abuse: A Case Report

Introduction: Cocaine exists in two major forms: cocaine hydrochloride and alkaloid freebase (crack). Cocaine abuse causes many well recognized systemic adverse effects and acute kidney injury is usually due to rhabdomyolysis, malignant hypertension with thrombotic microangiopathy and renal infarction. In addition, it has been described ANCA-positive vasculitis induced by levamisole- adulterated cocaine causing nephrotic syndrome. We report a case of focal segmental glomerulosclerosis in a patient with history of cocaine use.

Case Description: A 49 year-old man of admixture race presented with progressive edema and dyspnea for the past five months. Lab tests showed Scr 7.0 mg/dL (baseline: 0.9 mg/dL), hypoalbuninemia, hypercholesterolemia and nephrotic range proteinuria (13g/24h). The patient had started using illicit drugs (marihuana and crack) three months before the symptoms began. There was no sign of infection or hypovolemia. All serologic tests were normal or negative, including complement, antinuclear antibodies, anti-DNA antibody, c-ANCA, p-ANCA, hepatitis B and C, HIV, syphilis and there was no evidence of monoclonal serum spike. Renal ultrasound was normal. The patient underwent hemodialysis and received methylprednisolone. Renal biopsy showed 13 glomeruli, 6 globally sclerotic and 5 with segmental sclerosis and synchiae of the glomerular tuft, tubular atrophy and moderate interstitial fibrosis. Immunofluorescence was negative. There was no recovery of renal function.

Discussion: Although it has been described nephrotic syndrome due to ANCA-positive vasculitis induced by levamisole-adulterated cocaine, we have reported a case that showed association between the use of cocaine and focal segmental glomerulosclerosis.

SA-PO094

A Rare Case of Tumor Lysis Syndrome in a Patient with Angiosarcoma
Bilal J. Alturkman1, Michael A. Mao,2 Edward T. Casey. 1Alfaisal Univ, Riyadh, Saudi Arabia; 2The Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Introduction: To report a rare case of tumor lysis syndrome (TLS) developing in a patient with angiosarcoma and metastasis to the liver.

Case Description: A 63-year-old male presented to his primary care physician complaining of fatigue, night sweats, fever, and newly developed RUQ pain. An ultrasound of the abdomen revealed hepatic lesions and a subsequent CT scan showed two large masses in the liver and a mass in the pancreas. A liver biopsy was obtained and findings were consistent with metastatic angiosarcoma and he was therefore initiated on palliative chemotherapy. The patient then presented to his local hospital with abdominal pain and abdominal bruises. His hemoglobin was 4.9 g/dL and he was found to be bleeding from the liver biopsy site. He was transferred to our institution for embolization in setting of intra-abdominal bleeding and multorgan dysfunction. His clinical presentation, along with laboratory findings, was consistent with anuric renal failure secondary to TLS.

Table 1

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Three days prior to hospitalization</th>
<th>On admission to Mayo Clinic</th>
<th>Reference Ranges, Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>1.4</td>
<td>2.7</td>
<td>[0.8-1.3], mg/dL</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.3</td>
<td>6.6</td>
<td>[3.6-5.2], mmol/L</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>16.3</td>
<td>16.3</td>
<td>[3.7-8.0], mg/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.2</td>
<td>8.1</td>
<td>[8.8-10.1], mg/dL</td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td>-</td>
<td>4.29</td>
<td>[4.65-5.30], mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>-</td>
<td>8.4</td>
<td>[2.5-4.5], mg/dL</td>
</tr>
</tbody>
</table>

The patient was initiated on allopurinol, rasburicase, and continuous veno-venous hemofiltration (CVVH). He progressively deteriorated during his 11-day hospital course with recurrent episodes of arrhythmia, persistent encephalopathy, continued mechanical ventilator and hemodialysis dependence, and refractory septic shock with candidemia. The family elected for comfort care and the patient expired the next day.

Discussion: TLS is a constellation of laboratory and or clinical manifestations that can arise either spontaneously or secondary to cancer treatments. Patients with hematological malignancies have a higher tendency to develop this syndrome due to the rapid turnover of cell growth and death. However, patients with solid tumors occasionally present with TLS. To our knowledge, this is the first case report of TLS associated with angiosarcoma.
Leukocyte Chemotactic Factor 2 (LECT2)-Associated Renal Amyloidosis: A Case Report

Alexander Pepen Romero, 1 James Drakakis, 1 Joseph Mattana, 1 Nephrology Dept, Winthrop Univ Hospital, Mineola, NY; 2 Pathology Dept, Columbia Univ, New York, NY.

Introduction: ALECT2 amyloidosis is a frequent form of systemic amyloidosis, represents 2.7-10% of all cases of renal amyloidosis. Most patients are elderly who present with chronic renal insufficiency and bland urinary sediment.

Case Description: We report a 76-year-old Egyptian male who presented after a recent hospitalization for self limited gastroenteritis and severe acute renal failure presumed secondary to acute tubular necrosis. Due to non-improving renal function and uricemic symptoms, renal biopsy was done and showed patchy interstitial amyloidosis deposits that did not stain for IgG, IgM, IgA, kappa, Lambda chains or Amyloid A; sample was sent to Mayo Clinic where Liquid chromatography tandem mass spectrometry detected a peptide profile consistent with ALECT2 Amyloidosis.

Discussion: This case suggests that ALECT2 Amyloid can present with bland uroanalysis and non-nephrotic range proteinuria in elderly patients.

Myoglobin versus CPK and the Potential Role for Rasburicase

Andreas Jeron, 2 Dunja Bruder, 2 Peter R. Mertens, 1 Christos D. Chatzikyrkou. 1 Nephrology Dept, Winthrop Univ Hospital, Mineola, NY; 2 Pathology Dept, UCLA Medical Center, Los Angeles, CA.

Introduction: Myoglobin versus CPK and the Potential Role for Rasburicase


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complete resolution of eosinophilia while the patient was on HD. In 3/28/2011, the patient resumed PD via same catheter and same solution, follow up PD fluid sample on 4/07/2011 showed normal WBC count and 4% eosinophil.

Discussion: Our case suggests IEP was a transient reaction to the catheter placement rather than a reaction to the PD set or solution.

SA-PO100
Post Renal Transplant Follow Up in Focal Segmental Glomerulosclerosis with 24 Hour Urine Protein Collection – Traditional and True
Ravinder Pal S. Bhatti, Manisha Singh, Lakshmi P. Nadimpalli, Sameh R. Abul-Ezz. Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR.

Introduction: Random Urine Protein Creatinine Ratio (PCR) is commonly used to estimate proteinuria compared to 24 hour urine protein measurement (24-UP). However, there are concerns over the diagnostic accuracy and reliability of such an approach in post-transplant setting. We present a case of post-transplant focal segmental glomerulosclerosis (FSGS) illustrating this.

Case Description: A 39 year old male with primary FSGS, on peritoneal dialysis for 4 years received a cadaveric kidney transplant. His panel reactive antibody was 0% and HLA cross-match was negative. Intra-operatively, a large stone measuring 2 cm was identified in the hilum of the donor kidney and was successfully removed by irrigation. A smaller middle calyceal stone was localized by fluoroscopy.

The donor was a healthy 31 year old female who suffered anoxic brain injury in a motor vehicle accident. Her CT abdomen showed 2 stones in the right kidney as represented in the figure’s inset. The kidney became available to us on a regional list after it was declined locally due to concerns over kidney quality. The recipient was a 50 year old female with hypertensive nephropathy, on hemodialysis for the past 2 years. Her panel reactive antibody was 90% and HLA cross-match was negative. Intra-operatively, a large stone measuring 2 cm was identified in the hilum of the donor kidney and was successfully removed by irrigation.

Discussion: The new kidney allocation policy aims to address organ shortage by reducing donor and graft survival mismatch. Traditionally, donor hemodynamics, age, serum creatinine and histopathology have influenced decisions on accepting a kidney. The perceived quality and utilization techniques widely vary for deceased donor kidneys with lithiasis. Our case illustrates how this can lead to non-acceptance of an otherwise healthy kidney, which can be transplanted with a favorable outcome.

SA-PO102
A Peritoneal Dialysis Catheter Leak Complicated by Burkholderia Gladioli Peritonitis. Ravinder Pal S. Bhatti, Dummitru Rotaru. Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR.

Introduction: Dialysate leaks can occur any time after peritoneal dialysis (PD) catheter placement. Early leaks usually manifest as an exit site leak, though may also present with air in the PD catheter. Leaks increase the risk for exit site infections (ESI) and peritonitis. We present such a patient developing peritonitis with an unusual pathogen.

Case Description: A 74 year old male who had been on Continuous Cycling Peritoneal Dialysis for 3 years, presented with exit site erythema a week after trying to push in an extruded cuff. Prophylactic antibiotics were started but he declined surgery. The ESI recurred soon after completing 3 weeks of antibiotics. He agreed to catheter replacement with an exit site change. He was started on low volume exchanges. Two weeks later, he noted air bubbles in the PD catheter upon draining.

There were no perioperative complications and the recipient had excellent immediate graft function. Her creatinine progressively improved by time of discharge, remaining normal in subsequent months.

Discussion: New kidney allocation policy aims to address organ shortage by reducing donor and graft survival mismatch. Traditionally, donor hemodynamics, age, serum creatinine and histopathology have influenced decisions on accepting a kidney. The perceived quality and utilization techniques widely vary for deceased donor kidneys with lithiasis. Our case illustrates how this can lead to non-acceptance of an otherwise healthy kidney, which can be transplanted with a favorable outcome.

SA-PO101
Donor Kidney Lithiasis: A Case of Throwing Out the Baby with the Bathwater? Ravinder Pal S. Bhatti,1 Sameh R. Abul-Ezz,1 Lakshmi P. Nadimpalli,2 Gary Wickens Barone,2 1Nephrology, 2Transplant Surgery, Univ of Arkansas for Medical Sciences, Little Rock, AR.

Introduction: Cadaveric kidneys account for a majority of transplants in the United States. However, only 10% of waitlisted patients receive one annually, making optimal utilization critical. Donor nephrolithiasis represent a small yet significant proportion of kidneys discarded. We present a patient who received such a kidney which otherwise could have been discarded.

Case Description: The donor was a healthy 31 year old female who suffered anoxic brain injury in a motor vehicle accident. Her CT abdomen showed 2 stones in the right kidney as represented in the figure’s inset. The kidney became available to us on a regional list after it was declined locally due to concerns over kidney quality. The recipient was a 50 year old female with hypertensive nephropathy, on hemodialysis for the past 2 years. Her panel reactive antibody was 90% and HLA cross-match was negative. Intra-operatively, a large stone measuring 2 cm was identified in the hilum of the donor kidney and was extracted via pyelotomy. A smaller middle calyceal stone was localized by fluoroscopy and successfully removed by irrigation.

Early recurrence of FSGS was diagnosed. A biopsy was withheld to avoid delay in timely management and risk of bleeding with plasmapheresis which was immediately initiated. He was switched from tacrolimus to cyclosporine. He required plasmapheresis for 5 weeks and had satisfactory recovery in the ensuing months.

Discussion: Logistics have led to the widespread use of PCR in follow-up of kidney transplant recipients. However changing creatinine excretion with recovering renal function, lower precision with heavier proteinuria, and limited data on accuracy compared to 24-UP, potentially limit its utility at detecting early post-transplant recurrence of FSGS. Our case highlights marked discordance between the PCR and 24-UP, detection of which allowed a timely change in management. We conclude that it is prudent to monitor proteinuria by random urine collection in preference to random PCR in the immediate post-transplant setting for recipients with primary FSGS.

A small pinhole was found at the exit site, suspected to be from a sharp injury during dressing change. He was planned for surgical revision but soon started having turbid drainage. Instilled dialysate was cultured, broad spectrum intravenous antibiotics were started and he was switched to hemodialysis. During surgery, the damaged catheter was spliced to new tubing proximal to the exit site. The cultures grew Burkholderia Gladioli by now. PD was resumed the next day. The peritonitis resolved during the 3 weeks of antibiotics. He continued PD uneventfully over ensuing months.

Discussion: There were no perioperative complications and the recipient had excellent immediate graft function. Her creatinine progressively improved by time of discharge, remaining normal in subsequent months.

Discussion: The new kidney allocation policy aims to address organ shortage by reducing donor and graft survival mismatch. Traditionally, donor hemodynamics, age, serum creatinine and histopathology have influenced decisions on accepting a kidney. The perceived quality and utilization techniques widely vary for deceased donor kidneys with lithiasis. Our case illustrates how this can lead to non-acceptance of an otherwise healthy kidney, which can be transplanted with a favorable outcome.

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including by rare pathogens warrants appropriate antibiotic prophylaxis and lastly a more limited approach than catheter exchange may be used even for leaks close to exit sites based on the location and local experience.

**SA-PO103**

Enteric Hyperoxaluria Related to Celiac Disease Causing Acute Kidney Injury After Kidney Transplantation

Ashvin Baru, Venkat Ramathan.

Nephrology, Baylor College of Medicine, Houston, TX.

**Introduction:** Acute kidney injury (AKI) after kidney transplantation can occur from myriad of causes. We present an interesting case of a young woman with history of Celiac disease who developed AKI and biopsy-proven oxalate nephropathy within 3 months post-transplantation, as a result of enteric hyperoxaluria associated with gluten noncompliance.

**Case Description:** A 35 year-old woman with type 1 diabetes mellitus, and celiac disease underwent living unrelated kidney transplantation for ESRD related to biopsy-proven diabetic nephropathy. Her original renal ultrasound did not show nephrocalcinosis. After transplantation, nadir serum creatinine was 1.0 mg/dL. Three months later, she presented with six-day history of diarrhea and AKI. Serum creatinine peaked at 2.6 mg/dL. Since volume replacement did not improve her allograft function and she had high panel reactive antibody levels pre-transplant, a kidney biopsy was performed that showed acute tubular injury with significant oxalate crystalline deposits. Initial serum oxalate level was undetectable, but 24-hour urine oxalate excretion was elevated at 98 mg/dL. Pending gene testing, she was treated with intravenous fluids, low oxalate diet, gluten free diet, vitamin B6, oral alaki and calcium carbonate. Subsequent gene testing did not reveal gene mutation in the oxalate pathway. Her urine output was maintained between 3 to 4L per day. With strict gluten avoidance and low oxalate diet, urine alkalization and oral calcium, her allograft function has improved to baseline.

**Discussion:** Celiac disease exacerbation and subsequent malabsorption can lead to significant gut oxalate absorption and hyperoxaluria. Resulting oxalate nephropathy is a rare cause of AKI after kidney transplantation.

**SA-PO104**

Unusual Presentation of Tumor Related Membranous Nephropathy

Tahir Zaman,1 Frederic Clayton,2 Josephine Abraham,1 Nephrology, Univ of Utah, Salt Lake City, UT; 2Pathology, Univ of Utah, Salt Lake City, UT.

**Introduction:** The literature is laden with evidence of several solid tumors causing secondary membranous nephropathy. It is also described in the literature that solid tumors could also ANA positivity.

**Case Description:** A 62-year-old male with a history of hypertension presented with oliguric renal failure following an episode of gastroenteritis. History was unremarkable with patient denying smoking or other vices. Urine analysis revealed rare dysmorphic RBC’s and minimal proteinuria (spot protein/creatinine ratio 0.5 gms). Serologic workup revealed PR3 (ANCA negative) and abnormal Kappa Lambda Ratio thus renal biopsy was performed, which revealed membranous nephropathy and acute tubular necrosis (ATN).

Immunofluorescence was positive for C3, IgG, though negative for PLA-2R, IgA and Clq. ANA was strongly positive (1:10240 speckled pattern), HIV serology was negative. Sublingular mass was found which revealed squamous cell carcinoma. Bone marrow biopsy revealed smoldering multiple myeloma. The patient’s ATN resolved and he subsequently underwent left partial glossectomy. His cancer was staged at T2N0 and he is undergoing chemotherapy and radiation therapy.

**Discussion:** Secondary membranous nephropathy has a known association with solid tumors. The positive ANA raised the concern of concurrent SLE but Clq negativity on the biopsy made this diagnosis unlikely. Ultimately treatment of the underlying condition is paramount. 1. Imai, H. et al. Nucleolar antigens and autoantibodies in hepatocellular carcinoma and other malignancies. Am. J. Pathol. 140, 859–70 (1992).

**SA-PO105**

A Case of Severe Adrenal Insufficiency due to Long-Term Glucocorticoid Administration for Pediatric Nephrotic Syndrome

Yuko Fujii,1 Akira Ashida,1 Hideki Matsumura,2 Akihiko Shirasu,1 Hyogo Nkakura,1 Motoshi Hattori,1 Hiroshi Tamai,1 1Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan; 2Pediatric Nephrology, Tokyo Women’s Medical Univ, Shinjyuku, Tokyo, Japan.

**Introduction:** One of the adverse effects of long-term glucocorticoid therapy in supraphysiologic doses is suppression of the hypothalamic-pituitary-adrenal axis, although symptomatic adrenal insufficiency is considered to be an unusual complication of glucocorticoid therapy for nephrotic syndrome in pediatric patients. Here we describe a case of secondary adrenal insufficiency due to long-term glucocorticoid therapy for steroid-dependent nephrotic syndrome.

**Case Description:** A 12-year-old boy who had developed steroid-dependent nephrotic syndrome at the age of 2 years had been treated repeatedly with corticosteroid, cyclosporine and mizorbine. On relapse of the disease at 4 years of age, the nephrotic syndrome had been resistant to steroid therapy including 2 mg/kg prednisolone and 4 courses of methylprednisolone pulse therapy, but had responded to additional cyclophosphamide therapy at 7 months after relapse onset. During tapering of the glucocorticoid therapy, the patient had shown various symptoms, including general fatigue, facial edema, decreased urine volume, appetite loss, and dizziness from the age of 5 years. At that time, the basal value of cortisol was not detectable and a rapid ACTH loading test elicited a low response. In the CRH and insulin loading test, the basal value of ACTH was not detectable and an over-response of ACTH was demonstrated. Therefore the patient was diagnosed as having glucocorticoid-induced hypoadrenalism and treated with cyclosporine, a decreased dose of prednisolone, and hydrocortisone supplementation. The serum ACTH and cortisol values increased gradually. An insulin loading test at the age of 12 years demonstrated normal responses of the ACTH and cortisol levels.

**Discussion:** The very long-term nature of the therapy for this patient with idiopathic nephrotic syndrome resulted in glucocorticoid-induced adrenal insufficiency. Periodic evaluation of adrenal function and re-evaluation of the treatment is important for patients with nephrotic syndrome receiving steroid therapy.

**SA-PO106**

Henoch-Schönlein Purpura in Adult, from a Clinical Case

Pedro Vieira, Jose Duraes, Luís Resende, Nuno Rosa, Jose Alves Teixeira, Gil Silva. Nephrology, Hospital Dr. Nélio Mendonça, Funchal, Portugal.

**Introduction:** Henoch-Schönlein purpura is a small vessel vasculitis mediated by IgA-immune complex deposition with multisystemic involvement. Rare in adults, it is characterized by purpura, arthralgias, abdominal pain, and renal involvement. Viral infections have been reported as trigger.

**Case Description:** The authors present the case of a 25 years old male, without relevant medical history, admitted to the Nephrology Department in May 2014 by severe hypertension, renal failure (creatinine 6.7mg/dL), erythrocyturia and proteinuria. Renal ultrasound was normal. Renal biopsy revealed IgAnephropathy (M1E1S1T2). Our investigation revealed chronic hepatitis B virus (HBV) of vertical transmission origin (viral load 150 IU/mL). Corticosteroid therapy was started, with slight improvement in renal function. He was readmitted 2 months later by asthma, epistaxis, weight loss, palpable purpuric edema, +/- urticaria, and oral and nasal ulcers. Laboratory tests revealed hemoglobin 9.2g/dL, creatinine 4.3mg/dL, normal transaminases, albumin 20g/L, urinary spot protein/creatinine ratio 1300mg/g, hypocomplementemia, negative p-ANCAs, c-ANCAs and cryoglobulins, HBV load 379.9801U/mL. During hospitalization the patient initiated progressive pancytopenia, diffuse abdominal pain, generalized skin purpura and fever (with no identifiable infectious origin and interpreted as immunologic). We made clinical diagnosis of Henoch-Schönlein purpura and started with cyclophosphamide and entecavir. A few days later appeared hypoxemia and oliguria, requiring urgent dialysis. Cranial CT scan showed microangiopathic leukoencephalopathy of unspecified etiology and alveolar hemorrhage in chest CT scan. Due to life threatening multisystemic involvement we started methylprednisolone pulses, intravenous immunoglobulin and plasmapheresis. Patient completely recovered, but remained dependent on dialysis. 6 monthly cycles of cyclophosphamide were maintained, with no signs of recurrence.

**Discussion:** We emphasize the rare severe multisystemic involvement of a Henoch-Schönlein purpura in an adult, the onset of the disease with exacerbation of viral infection, and the therapeutic challenge of an HBV patient with an vasculitis.

**SA-PO107**

Rare Etiology for Chronic Kidney Disease: Bronchiectasis Related Secondary Amyloidosis

Alper Alp,1 Hakun Akdam,2 Aysegul Ormeci,3 Ibrahim Meteoglu,1 Alparslan Unsal,1 Yavuz Yenicerioglu.1 1Nephrology, Van Education and Research Hospital, Van, Turkey; 2Nephrology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey; 3Pathology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey.

**Introduction:** Here we present an elderly patient with a known posttuberculosis bronchiectasis, nephrotic-range proteinuria and renal failure was detected. Renal biopsy revealed AA amyloidosis. Tuberculosis and tuberculosis related systemic disorders still have clinical impact in nephrology practice especially in developing countries.
Introduction: The optimal treatment of cryoglobulinemic glomerulonephritis (GN) in the setting of Hepatitis C (Hep C) with sustained viral response (SVR) is unknown. Only expert opinion obtained from case reports provide guidance to the clinician. Some reports show benefit with Rituximab and plasma exchange.

Case Description: 58yo male with h/o treated Hep C currently with an undetectable viral load, gastric ulcer, anemia, and HTN presented to clinic for evaluation of CKD. Hep C was initially diagnosed when he was found to have leukocyctoclastic vasculitis on a skin biopsy of skin rash. Labs were positive for serum cryoglobulins, rheumatoid factor, low C4, and Hep C viral load. Renal function was normal and he was successfully treated for cryoglobulinemic vasculitis due to Hep C with interferon alpha, telaprevir and ribavirin and achieved a SVR. He presented 1 year later with renal insufficiency (creatinine -2.2 mg/dL) and cryoglobulinaemia. He had necrotizing flares of vasculitis. SPEP revealed IgM kapa monoclonal with negative UPEP. C4 was low and cryoglobulins remained positive. Kidney biopsy showed immune complex GN with organized deposits. Bone marrow biopsy was negative for lymphoproliferative disease. He was diagnosed with cryoglobulinemic GN with SVR. Initially, he was treated with prednisone followed by Rituximab and plasmapheresis. He failed the treatment and was started on hemodialysis.

Discussion: Cryoglobulinemic GN is frequently due to Hep C but is rare in patients achieving a SVR. In our case an underlying B cell lymphoma was ruled out and it was felt that B cell immune dysregulation due to Hep C was the culprit, in part due to prior published cases. However, in our case treatment with rituximab and plasmapheresis was unsuccessful. It remains possible, as others have demonstrated, that the virus may persist within the liver, macrophages, lymphocytes, and even kidney. The pathological basis for persistent vasculitis in setting of a SVR requires further study so that targeted and more effective treatment strategies can be designed.

SA-PO110
Diagnostic Intrapartum Dilemma: Distinguishing Glomerulonephritis from Preeclampsia in Pregnancy

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650A
proteinuria (3.7g/24h), evidence of dysmorphic hematuria and worsening of renal function (Cr 4.1 mg/dl), he received methylprednisolone 1g for three days and renal biopsy was proposed. It revealed pauci-immune crescentic glomerulonephritis. Immunofluorescence showed mesangial deposition of C3 (++) and lambda chains (+). Treatment was followed by monthly i.v. cyclophosphamide and proteinuria decreased to 0.87 g/24h. cANCA became positive (1/160) 4 months after diagnosis.

Discussion: Membranous nephropathy is the most commonly reported glomerulonephritis especially with pulmonary cancer, but several reports suggest an association between rPGn and malignancies. The increased risk for malignancy has been confirmed in a retrospective review of 200 patients with ANCA-associated vasculitis, demonstrating a significantly increased relative risk (6.02) compared with age-matched controls. Biava et al reported seven cases of rPGn associated with a coexisting nonrenal malignancy (6 carcinomas and 1 lymphoma). The pathogenetic mechanisms by which neoplasms lead to the development of ANCA-associated vasculitis and rPGn are largely unknown.

SA-PO112
A Case of Encapsulating Sclerosing Peritonitis in a Type I Diabetic on Peritoneal Dialysis Zachary Freestone, Josephine Abraham, Akram M. Shaaban.

Introduction: Encapsulating sclerosing peritonitis (ESP) is a rare disorder associated with PD. It is characterized by peritoneal fibrosis and encasement of the bowel. Symptoms associated with ESP are non-specific and may be attributed to other etiologies. Abdominal imaging is required to evaluate ESP and diagnostic confirmation is achieved by laparoscopy. ESP should be considered in patients on peritoneal dialysis with symptoms involving the gastrointestinal tract, weight loss, or inadequate solute clearance.

Case Description: A 34 year old Caucasian male on PD presented to the clinic with complaints of nausea and abdominal pain. He had a history of type I DM, ESRD, neuropathy, and gastroparesis. He was started on PD 8 years ago and has had 3 prior episodes of peritonitis. The patient appeared ill and malnourished. His abdomen was soft on examination and non-tender to palpation. An abdominal x-ray indicated that he had calcification in the abdomen and pelvis. CT imaging showed calcification of the parietal peritoneum, abdominal cavity, omentum, and bowel. The patient underwent exploratory laparotomy with simultaneous PD catheter removal. The visual examination revealed a brown, inflamed rim encompassing the peritoneum, omentum, bowel, and colon. Peritoneal dialysis was discontinued and the patient was transitioned to hemodialysis.

Discussion: Encapsulating sclerosing peritonitis (ESP) is a condition associated with peritoneal dialysis. Its presenting symptoms are often non-specific and may be attributed to other causes. Abdominal imaging is necessary to evaluate for suspected ESP, CT being the preferred method. ESP is characterized by peritoneal thickening and fibrosis that encases the bowel. Treatment includes cessation of PD with transfer to hemodialysis and bowel rest. Other attempted treatments of this disease have included steroids and total enterolysis.

SA-PO113
Acute Kidney Injury from Enterovesicular Fistula Secondary to Squamous Cell Carcinoma of Bladder Elefni Cheladi, Evdokia Efthimiou, Alexia Papalexandrou, Maria Sotiraki, Ioannis Xatzis, Maria Tsilivigou.

Introduction: Squamous cell carcinoma (SCC) of the bladder is a relatively rare tumor. Predisposing factors are chronic irritation of the bladder by UTI, calculi and long-term indwelling catheterization. Enterovesicular fistula (EVF) usually has flow from the intestine to the bladder and commonly manifests with recurrent urinary tract infections (UTI), long-term indwelling catheterization. EVF should be considered in patients on peritoneal dialysis with symptoms involving the gastrointestinal tract, weight loss, or inadequate solute clearance.

Case Description: A 56 year old Caucasian female with hypertension, diabetes mellitus and recurrent UTI was admitted in a uremic state that necessitated the immediate start of PD. Urine protein was 1+ with dipstic analysis and 9.7 g/gCr. Albumin to creatinine ratio was 10.1 (normal <0.7). Serum albumin was 2.4g/dl and corrected Ca 16mg/dl. Urine protein was 1+ with dipstic analysis and 9.7 g/gCr. Proteinuria (3.7g/24h), evidence of dysmorphic hematuria and worsening of renal function (Cr 4.1 mg/dl), he received methylprednisolone 1g for three days and renal biopsy was proposed. It revealed pauci-immune crescentic glomerulonephritis. Immunofluorescence showed mesangial deposition of C3 (++) and lambda chains (+). Treatment was followed by monthly i.v. cyclophosphamide and proteinuria decreased to 0.87 g/24h. cANCA became positive (1/160) 4 months after diagnosis.

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formation in tubular lumens with severe tubular atrophy. Cell accumulation and fibrotic lesion were also detected in interstitium. Mesangial matrix was mildly expanded in glomeruli. Amyloid deposition was not observed.

Discussion: Herein, we showed clinical course and renal pathology of the patient with IgD-lambda type MM. Although steroid pulse therapy decreased serum levels of IgD, renal function did not improve. Renal pathology showed cast nephropathy, interstitial fibrosis and cell infiltration. The renal manifestation of IgD type MM requires further investigation.

SA-PO116
Sunitinib-Induced Nephrotic Syndrome and Acute Kidney Injury in a Malignant Insulinoma Patient: A Case Report
Wolakana Shoda, Naofumi Yui, Shokaro Naito, Soichiro Iimori, Koichiro Sasa, Takayasu Mori, Naohiro Nomura, Eisei Sohara, Tomokazu Okado, Tatemitsu Rai, Shinichi Uchida. Dept of Nephrology, Tokyo Medical and Dental Univ, Bunkyo, Tokyo, Japan.

Introduction: Sunitinib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFR), has been proven to be effective in the treatment of several types of cancer, including pancreatic neuroendocrine tumors. However, its risk of renal complications, such as proteinuria, renal dysfunction, and hypertension, are understudied. Case Description: A 71-year-old man with malignant insulinoma treated on sunitinib for six months, developed proteinuria, acute kidney injury and hypertension. Kidney biopsy showed thrombotic microangiopathy (TMA) like lesions such as double contour, edematous endothelial cells and microaneurysms, suggesting injuries induced by sunitinib. Decreased VEGF expression in podocytes was demonstrated by immunohistochemistry, supporting the diagnosis. Sunitinib was discontinued and partial remission of the renal complication was achieved in two weeks. However, the patient mandates needed to restart sunitinib because of poor control of blood glucose level due to pancreatic cancer exacerbation. By reducing the dose of sunitinib and administering losartan concurrently, the patient was able to maintain stable renal function with serum creatinine time of 1.4 mg/dl and urinary protein level under 1.0 g/day.

Discussion: VEGF blockade by sunitinib is featured by adverse effects including hypertension and renal injury. In the present case, renal injury partially improved after discontinuing sunitinib. Reducing the dosage of sunitinib and administering losartan made it possible to restart sunitinib treatment while controlling its renal side effects. VEGF, which is expressed and secreted by podocytes, is an important factor for development and maintenance of glomerular endothelium. Renal biopsy in this case showed down regulation which is expressed and secreted by podocytes, is an important factor for development and maintenance of glomerular endothelium. Renal biopsy in this case showed down regulation of VEGF in podocytes. Although the mechanism of renal dysfunction and proteinuria caused by anti-VEGF therapy is not well elucidated, the findings of this case might provide insights into the mechanism of renal toxicity by sunitinib.

SA-PO117
Liver-Kidney versus Liver Transplant Alone: Decision Making in the Operating Room
Ekamol Tantisattamo.1 Siwadon Pitukweerakul.2 Praveen Ratanasirimetha.3 Nephrology, Northwestern Univ; 2Presence St. Francis Hospital, Evaston; 3Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.

Introduction: Acute kidney injury (AKI) is a common complication of uncomplicated chronic liver disease and hepatorenal syndrome (HRS) is one of the leading causes. Liver transplantation (LT) is a definitive treatment for HRS; however, simultaneous liver-kidney transplantation (SLK) is pursued due to the severity of preoperative AKI with uncertainty of postoperative renal recovery. Case Description: A 60-year-old Caucasian woman with ESLD due to alcoholic cirrhosis had been readmitted twice over 2.5 months with AKI from HRS. Even though, she was treated with albumin, miodroine, and octreotide, serum creatinine (SCr) had been elevated from the initial baseline of 1 mg/dL and had never returned to the baseline. Instead, it was worse every times she had AKI (Figure 1). After the last episodes of AKI, SCr had been stable at 2.5 mg/dL and she was listed for SLK. One week later, she was offered for SLK. After the LT, she started making a significant amount of urine immediately; therefore, the kidney was not transplanted and transferred to other potential kidney transplant recipient in another transplant center. Postoperatively, SCr had trended down to 1.1 mg/dL.

Discussion: Even though, our patient had recurrent episodes of AKI from HRS and persistent elevated SCr even ~3 months period, it was thought that the chance of meaningful renal recovery was small and SLK was initially planned. Fortunately, her renal function was recovery immediately after the LT alone. Preoperative evaluation for SLK versus LT alone sometimes becomes uncertain. Intraoperative finding of signs of renal recovery after LT is crucial as it can avoid unnecessarily kidney transplantation and provide an opportunity to utilize kidney organ to other potential kidney transplant recipient.

SA-PO118
Is Portopulmonary Hypertension Patient a Good Candidate for Liver Transplantation?
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Introduction: Portopulmonary hypertension (PPH) is one of the most feared complications of end-stage liver disease (ESLD). Liver transplantation (LT) may reverse this complication with uncertain outcomes. We report a case of ESLD women complicated by severe pulmonary arterial hypertension (PAH) secondary to PPH and acute kidney injury (AKI) who had prolonged pre- and post-operative simultaneous liver-kidney transplantation (SLK) with partial liver improvement, un-meaningful renal recovery, and bed bound with reconditioning.

Case Description: A 48-year-old woman with ESLD from cryptogenic cirrhosis complicated by portal hypertension, PAH-related to PPH and sarcoidosis presented with AKI requiring CRRT. She was treated with treprostinil, sildenafil, and ambrisentan until suitable for SLK. Postoperatively, liver and renal allografts worked well and PA pressure was decreased. However, she still required treprostinil and diuresis to control PAH and volume status. After 5 months of ICU stay, she developed severe deconditioning and malnutrition. She had AKI with SCr of 0.5 mg/dL up to 1 mg/dL over 3 weeks. Calculated average clearance from 24-hour urine collection was 15 ml/min. Transplant renal allograft biopsy revealed moderate ATN and borderline changes. Diuretic dose was decreased and SCr was improved to 0.7 mg/dL. She still required treprostinil as well as intensive rehabilitation and nutritional supplementation. She remains in ICU for the majority of the time posttransplantation.

Discussion: PPH is one of the challenging scenarios for ESLD requiring LT. Reversibility from PPH after LT is uncertain. It is still a dilemma in managing this difficult situation between LT to prolong life with poor quality and conservative management. LT is a life-saving surgery but may not always reverse a severe complication of ESLD such PPH and thus prolongs no postoperative quality of life. Therefore, LT in such a complex underlying condition needs to be individualized.

SA-PO119
Flash Pulmonary Oedema in Renal Artery Stenosis: An Indication for Stenting?
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Introduction: Renal artery stenosis (RAS) is an unusual but potentially treatable cause of flash pulmonary oedema. Although national guidelines recommend percutaneous revascularization (level of evidence B), we present a case of recurrent flash pulmonary oedema which suggests a need for further evidence to support use of revascularization therapy in elderly patients with multiple comorbidities. Case Description: A 78 year old woman presented with a fourth episode of sudden onset dyspnoea in 4 months. Her medical history included CAD, AF, hypertension (HTN) and severe pulmonary HTN due to heart failure with preserved ejection fraction (HFPEF). On admission, there were bilateral respiratory crackles and pulmonary congestion on chest XR. BP 140/95, creatinine 110umol/L, eGFR 42. Echocardiogram showed concentric LVH, preserved EF and raised PAP. Because of recurrent symptoms despite apparently adequate medical management of HFPEF, she underwent CT angiography which revealed bilateral ostial RAS (70% right, 40% left). Following multidisciplinary team discussion, bilateral balloon angioplasty with stent insertion was performed with radiologically successful results and she was discharged on rivaroxaban for stroke prevention. Since then, she has had no further episodes of pulmonary oedema. However, renal function has deteriorated post-procedure (max creatinine 226umol/L, eGFR 18 at 6 weeks; no evidence of in-stent thrombosis) and she has diuretic-resistant pedal oedema severely impacting quality of life.

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Complement Mediated Hemolytic Uremic Syndrome Secondary to SLE

**Case Description:** 64-year-old female with well-controlled HIV on HAART, presented with new proteinuria, thrombocytopenia and acute kidney injury. On examination she had no neurological symptoms and no diarrhea. Preliminary blood tests revealed WBC 2.9k/UL, hemoglobin 6.6g/dl, platelets 64 k/UL, and serum creatinine at 4.0 mg/dl. LDH was elevated at 600UL, haptoglobin was undetectable, with Coombs test negative. Peripheral blood smear revealed numerous schistocytes. Further work up revealed an elevated ANA (>1:2560), and hypocomplementemia. Anti-Smith antibody elevated at >8. These laboratory studies and the presence of lymphadenopathy and pancytopenia established a diagnosis of SLE. Patient received pulse methylprednisolone, but creatinine increased to 6 mg/dl. A kidney biopsy revealed TMA. The patient was treated with plasma exchange but developed uremia and was started on hemodialysis. Neither renal function nor hemolysis improved. In the absence of anti phospholipid antibody, normal ADAMTS13 level and activity, well-controlled HIV, and in the presence of positive serologies for SLE with complement consumption, the diagnosis of CM-HUS secondary to SLE was the most explanation of the patients’ presentation, a decision was made to treat with eculizumab. Patient received one treatment, with no immediate improvement in her renal disease or hematologic parameters. Unfortunately her clinical status deteriorated and patient opted to be made comfort measures only and ultimately expired.

**Discussion:** This case highlights the importance of recognizing RAS as a cause of flash pulmonary oedema, especially in bilateral disease due to lack of compensatory mechanisms. Observational studies and case series have demonstrated that angioplasty +/- stenting reduces the incidence of flash pulmonary oedema. However, there is limited literature to guide management (eg. on risks and benefits of unilateral vs. bilateral intervention, degree of stenosis) and limited experience in the elderly in whom comorbidities may increase the risks of procedural complications such as deterioration of renal function due to contrast nephropathy and/or cholesterol emboli.

**SA-PO120**

**Complement Mediated Hemolytic Uremic Syndrome Secondary to SLE**

**Case Description:** 64-year-old female with well-controlled HIV on HAART, presented with new proteinuria, thrombocytopenia and acute kidney injury. On examination she had no neurological symptoms and no diarrhea. Preliminary blood tests revealed WBC 2.9k/UL, hemoglobin 6.6g/dl, platelets 64 k/UL, and serum creatinine at 4.0 mg/dl. LDH was elevated at 600UL, haptoglobin was undetectable, with Coombs test negative. Peripheral blood smear revealed numerous schistocytes. Further work up revealed an elevated ANA (>1:2560), and hypocomplementemia. Anti-Smith antibody elevated at >8. These laboratory studies and the presence of lymphadenopathy and pancytopenia established a diagnosis of SLE. Patient received pulse methylprednisolone, but creatinine increased to 6 mg/dl. A kidney biopsy revealed TMA. The patient was treated with plasma exchange but developed uremia and was started on hemodialysis. Neither renal function nor hemolysis improved. In the absence of anti phospholipid antibody, normal ADAMTS13 level and activity, well-controlled HIV, and in the presence of positive serologies for SLE with complement consumption, the diagnosis of CM-HUS secondary to SLE was the most explanation of the patients’ presentation, a decision was made to treat with eculizumab. Patient received one treatment, with no immediate improvement in her renal disease or hematologic parameters. Unfortunately her clinical status deteriorated and patient opted to be made comfort measures only and ultimately expired.

**Discussion:** This case emphasizes the importance of early consideration of CM-HUS as well as prompt initiation of treatment to block terminal complement upon recognition of the syndrome. As clinicians, this class of diseases is challenging and complicated, requiring our rapid attention to aid timely identification and rapid management.

**SA-PO121**

**Idiopathic Nodular Glomerulosclerosis Presenting with Nephrotic Range Proteinuria and Normal Renal Function**

**Introduction:** Idiopathic Nodular Glomerulosclerosis (ING) is a well-established but uncommon entity that has been described in 1985 by Chan JY et Al. It is common in older white men with history of long-standing hypertension, obesity, and smoking and typically presents with renal Insufficiency & Nephrotic Range Proteinuria. Multiple reports and meta-analyses of patients with ING demonstrate an average creatinine > 2.0 mg/dl and progressive kidney dysfunction leading to ESRD.

**Case Description:** We report a case of a 57 year old Caucasian obese female who presented with edema and heavy proteinuria (9 gms/day). She is a 40-pack year smoker with long-standing hypertension with variable control. Serum Creatinine on presentation was 0.7 mg/dl. Hba1c was 6.0% and fasting/random sugars never met criteria for overt Diabtes Mellitus. Urine showed 3-10 rbc/hpf and none where dysmorphic with an otherwise bland urine sediment. She had a negative work up for paraproteinemias and all other causes of proteinuria. Kidney biopsy showed Class III nodular sclerosis (KW lesions) and moderate urine sediment. She had a negative work up for paraproteinemias and all other causes of proteinuria. Kidney biopsy showed Class III nodular sclerosis (KW lesions) and moderate urine sediment.

**Discussion:** This case illustrates that Idiopathic Nodular Sclerosis is not limited to male gender and can occur in the setting of preserved renal function, contrary to the common observation revealed in previous case reports.


**SA-PO122**

**Hemofiltration Reinfusion Aequilibrium Can Be an Answer to Malnutrition and Hypotension in Dialysis**

**Discussion:** A-HFR has dynamic profiles of ultrafiltration and conductivity of the dialysate: this aspect creates an iso-osmolar dialysate, ensuring a better periferal refilling and improving compliance during the dialysis treatment. This is due to the use of biosensors. A-HFR also reduces the Amino acids loss. This report has numerical limitations but provides encouraging data on the use of A-HFR in malnutrition and disequilibrium syndromes. This experience underlines the importance of further efforts towards customized dialysis procedures.

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

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**653A**
SA-PO124
A Case of Chronic Unilateral Hematuria Treated by Segmental Renal Artery Embolization Hansae Kim,1 Joon Seok Oh,2 Yong Ki Park,2 Dongyeol Lee.1 1Nephrology, Bongseong Memorial Hospital, Busan, Korea; 2Nephrology, Dongrae Bongseng Memorial Hospital, Korea.

Introduction: Chronic unilateral hematuria is characterized by intermittent or continuous hematuria that cannot be diagnosed using standard radiologic and hematologic methods. Unilateral hematuria is probably a benign condition that seldom requires surgical treatment, but some cases were managed with partial or total nephrectomy. Recently, a variety of treatments, including the ureteroscopic interventions have been attempted if the bleeding focus is identified. However, if not identified on ureteroscopy, surgical treatment has been considered a priority. We report the case of treatment of chronic unilateral hematuria with segmental renal artery embolization.

Case Description: We experienced a case of chronic unilateral hematuria in a 42-year-old woman who was admitted to our hospital due to intermittent gross hematuria and anemia for 31 months. About 29 and 19 months ago she already underwent CT scan, renal angiography, and renal biopsy at other tertiary hospitals, but didn’t found any other specific abnormalities repeatedly except some blood clots in left renal pelvis on ureteroscopy. She underwent CT urography, renal arteriography, cystoscopy and ureteroscopy again. Ureteroscopy findings only showed bleeding in the upper third of left renal calyces but definite bleeding focus could not be identified. Thus we decided to manage with segmental renal artery embolization than partial nephrectomy to minimize the reduction in renal function and to reduce operational risk. The superior and superoanterior segmental renal arteries were successfully embolized with 3mm coils and gelatin sponge. Gross hematuria disappeared on the 4th day after the procedure, microscopic hematuria disappeared on the 5th day. In 11th day, infarction in the upper third portion of left kidney was confirmed on CT scan. In 13th day, the patient was discharged. Thereafter serial urinalysis showed no hematuria.

Discussion: Patients with chronic unilateral hematuria often require surgical or upper urinary tract endoscopic procedures. Segmental renal artery embolization will be a better treatment for patients unable to identify the bleeding focus on the upper urinary tract endoscopy.

SA-PO125

Introduction: Urinary anastomotic leaks after kidney transplants are no longer a common phenomenon. Due to advancements in reconstruction techniques, urologic complications after renal transplant are now reported to occur in only 2-2.5% of patients. If a urinary anastomotic leak is to develop, it frequently occurs within one month of the transplant and is usually due to technical error or ischemia to the ureter.

Case Description: We present a case of a 60 year male with a history of a living unrelated kidney transplant who developed acute kidney injury 5 months after transplant. He had a baseline creatinine of 1.5-1.7 mg/dl, and initially presented to the hospital with fever and a creatinine of 2.96 mg/dl. A fungal urinary tract infection with Candida Albicans was deemed the culprit of his symptoms and so he was promptly started on fluconazole with only a slight improvement in his creatinine. A renal ultrasound of the allograft revealed that the patient had a 7x5 cm perinephric fluid collection. A percutaneous renal biopsy was performed, which revealed that the patient had a 7x5 cm perinephric fluid collection. A percutaneous nephrostomy was placed in the collection and culture of the fluid grew Candida Albicans. The large fluid collection was aspirated and sent for cultures and growths.

Discussion: Patients with chronic unilateral hematuria often require surgical or upper urinary tract endoscopic procedures. Segmental renal artery embolization will be a better treatment for patients unable to identify the bleeding focus on the upper urinary tract endoscopy.

SA-PO128
A Case of Kidney Dysfunction and Visual Loss Patrick Koscik1, Muhammad Sohaib Karim,1 Michal R. Chan,1 Anthony Krentz.2 1Div of Nephrology, Univ of Wisconsin School of Medicine and Public Health; 2PreventionGenetics.

Introduction: Senior-Loken syndrome is a rare hereditary nephropathy (phospho-renal syndrome) often presenting with autosomal recessive inheritance, a reduction in urinary concentrating ability with bland urinary sediment, and chronic tubulointerstitial nephritis with typical progression to end-stage renal disease (ESRD) in individuals younger than 20 years old. It was first described in 1961 by Senior et al., and Loken et al.

Case Description: A 29 year old male and his seeing eye dog presented to the kidney clinic with uncontrolled hypertension, creatinine of 2.6mg/dl and a history of Leber congenital amaurosis since the age of four. Physical exam was unremarkable other than nystagmus and severe visual impairment with 5-degree visual field and 20/300 acuity. Patient was currently pursuing his PhD via braille and did not appear to have any mental impairment. Family history was remarkable for a healthy sister in her 20s, a paternal uncle who passed away from renal failure in his 20s, and his maternal cousin (son of his deceased uncle) who had been born with hearing loss. Further evaluation was undertaken, which revealed normal electrolytes, unremarkable UA (notably with specific gravity <1.005 and absence of proteinuria, hematuria, leukocyte esterase, nitrites, and pyuria), but findings of minimal proteinuria (urine protein to creatinine ratio of 0.55). A renal ultrasound revealed a 12.4 cm R and 12.5cm L kidney with multiple cysts. Taking into account the history of renal dysfunction, visual impairment and renal cysts, patient was referred to a geneticist.

Genetic studies revealed two autosomal recessive heterozygous mutations in the IUCB1 gene. A frameshift mutation was seen in c.424_425del of ITT resulting in premature truncation of the ITT domain. This case suggests that stone formation may be an early phenomenon in UC. We think there might be a benefit in obtaining 24-hour urine collection for stone analysis following diagnosis of IBD, as this may help us identify patients at increased risk for stone formation. Early simple intervention like increasing fluid intake or expectorant stone formation. Benefits from empiric treatment with potassium citrate are not well known. Further studies need to be done for the better understanding and preventing renal stones formation in patients with active and severe IBD.

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654A
SA-PO129
Clostridium Difficile Associated Peritonitis in a Patient on Peritoneal Dialysis
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Introduction: Culture negative infectious peritonitis (CNP) is a common and serious complication in peritoneal dialysis (PD) patients. It is usually a result of samples failing to reach the threshold of microbiological detection, recent antibiotic exposure, or simply unusable samples. Peritoneal Dialysates routinely tested for Clostridium difficile (C. diff) infections have become more frequent, and more refractory to treatment, and dialysis patients are often affected by C diff secondary to repeated exposure to antibiotics, as well as hospitalizations. C diff infection should be considered in the differential for CNP in dialysis patients.

Description: A 41 AA male on PD since 2012 presented to PD unit with complaints of abdominal pain and cloudy fluid. He was started on intraperitoneal antibiotics (Vancomycin and Cefazidime) as an outpatient, though his symptoms of abdominal pain worsened requiring a hospital admission within 48 hrs of onset of symptoms. He complained of normal appetite, diarrhea for 12 hrs on the day of admission. On exam, he was diffusely tender in his abdomen, with no guarding/rigidity. Lab data was significant for peritoneal fluid wbc count of 7,130 with 85% polys and he was continued on broad-spectrum IV antibiotics. Stool C diff toxin resulted positive on day 2 of hospitalization and he was started on IV metronidazole. His abdominal pain persisted, and a recheck of PD fluid cell counts on Day 3 revealed a WBC count of 17,671 with 79% polys. The PD fluid cultures from the PD unit as well as the hospital were negative for any growth. Microbiology lab was asked to check his PD fluid for C diff, and the C diff PCR from the PD fluid was positive. The vancomycin and cefazidime were stopped, and oral vancomycin added to the metronidazole. His abdominal pain and diarrhea both improved and he was discharged to complete a 14 day course of PO metronidazole and vancomycin.

Discussion: Our case study describes culture negative peritonitis in a patient with C diff diarrhea that did not respond to broad spectrum IV antibiotics. This prompted further investigation of C difficile peritonitis that was confirmed on lab testing. This case highlights the importance of suspecting C diff peritonitis in PD patients with CNP.

SA-PO130
Adequacy of Australian Nephrology Training Nicholas A. Gray, Thomas Joseph Beaton, Rathika Krishnasamy, Nigel David Toussaint, Richard K.S Phoon. 1Renal Unit, Sunshine Coast Hospital and Health Service, Nambour, Queensland, Australia; 2Renal Unit, Westmead Hospital, Westmead, New South Wales, Australia; 3Renal Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia.

Background: There has been an increase in the number of doctors training in nephrology in Australia. This study aimed to assess the adequacy of nephrology training by measuring self-determined competency and skill relevance among recently graduated nephrologists.

Methods: A survey was developed by the Nephrology Advanced Training Committee of the Royal Australasian College of Physicians. The survey was administered on-line in 2015 via the annual subscription to the Australian and New Zealand Society of Nephrology. Nephrologists who were awarded Fellowship after 2002 were invited to participate.

Results: 113 of a 306 eligible Fellows (37%) completed the survey. 8 respondents had trained overseas and were excluded. Median age was 41 years (interquartile range 37-44) and 63% were male. Medical school was completed in Australia (59%), India (15%), and New Zealand (7%). 35% received at least some training in a rural area and 25% were qualified in another specialty (mainly internal medicine). 56% had completed and 21% commenced a higher degree. Higher degrees were undertaken for career development (43%) and desire for a research career (30%). Respondents indicated good training and competency in most clinical skills that were relevant to their practice. Training in home hemodialysis (37%) and living kidney donor assessment (51%) were considered less adequate, despite these areas being considered very relevant to practice. There was a greater mismatch identified between training and importance of skills for management and research. This included inadequate training in managing complications (82%), managing a private practice (98%), health system knowledge (86%) and regulations (93%), medical directorship (94%), ethics approval (76%), research funding (88%), and quality assurance (73%).

Conclusions: Nephrology training in Australia meets the clinical needs of new specialists. Similar to findings in USA, training in management and research was considered insufficient for the practices of new specialists and should be addressed in updates of the curriculum.

SA-PO131
Pediatric Nephrology Workforce and Training: An International Perspective
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Background: There is a shortage of pediatric nephrologists in a number of areas around the world. We sought to determine pediatric nephrologists’ perspectives on this issue.

Methods: A voluntary web-based survey was deployed via the Qualtrics™ survey engine. Members of the International Pediatric Nephrology Association responded anonymously to questions about their geographic location, time spent on training, practice setting, and impressions on local workforce challenges and opportunities.

Results: The number of responses to date was 38, representing 21 countries from all continents. Six percent of the respondents treat both children and adults. The number of years required to train in pediatric nephrology was reported as: 2 years (35%), 3 years (58%) and 4 years (8%). Nearly 80% of practices were associated with academic settings. Specialty training programs are reported in 63% of the respondents’ institutions and 50% of those with training programs stated that it was difficult or very difficult to recruit trainees. Forty two percent of the respondents stated that it was difficult or very difficult to find a job after training. The themes most frequently cited on qualitative analysis include low availability and interest in the field by trainees, poor compensation, demanding schedule and competing family demands.

Conclusions: In this preliminary study of an international cohort of pediatric nephrologists, our data suggests a perception of a decreased pediatric nephrology workforce. There is also a perceived shortage of available positions in the field. Further data collection on workforce issues as it pertains to country-related factors is needed.

SA-PO132
Taking Guessing Out of Milestone Ratings – Simplify the Evaluation System to Easily Achieve the Next Accreditation System (NAS) Report Samantha J. Thompson, Laura J. Maursetter. Div of Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: In an effort to translate into competency-based training, the ACGME has developed 24 milestones specific to fellowship. While the milestones are comprehensive, it is challenging to determine an individual’s rating through faculty evaluations; many of whom are untrained in this system. We aimed to create a simple scoring system that translates the milestones into observable nephrology activities that can be completed daily on a handheld device.

Methods: For each nephrology rotation, a list of 5-10 frequent activities was developed. For every activity, a description for the five levels of competency was written to standardize the score. The activities were completed and scored on a 1-4 NAS milestones. The evaluations were built in Google Forms and delivered daily to supervising faculty members. Using a four-click system, the observer can submit a fellow evaluation with most done on mobile devices. If faculty members wish to express a narrative, a free-text response box is provided for comments.

Results: Of the 914 possible evaluations over a nine-month period of time 727 evaluations were returned. This provided data points to distinguish scores among all fellows in all of the NAS milestones.

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In Clinical Competency Committee meetings thus far, 1 of 276 scores have been adjusted from the scores provided by the evaluation system.

Conclusions: This is an easy to use scoring system that has resulted in immediate feedback that is activity-specific and feed into NAS milestones easily and effectively. By translating the evaluation system into specific activities that any nephrologist can observe, a robust amount of valuable data has been obtained. The 4-click system has yielded an excellent response rate with more narrative comments than were previously obtained with monthly evaluations.

SA-PO133
American Society of Nephrology In-Training Exam for Fellows 2010-2014: Scoring and Item Statistics
Suzanne M. Norby, 1 Troy J. Plumb, 2 Nancy Day Adams, 3 Ryan Russell, 4 Mitchell H. Rosner, 5 Mark G. Parker, 6 Mayo Clinic; 2Univ of Nebraska Medical Center; 1Univ of Connecticut Health Center; 4American Society of Nephrology; 3Univ of Virginia School of Medicine; 5Maine Medical Center.

Background: Since 2009, the American Society of Nephrology (ASN) In-Training Exam (ITE) has been administered annually to fellows. This study reports 2010-2014 overall scale scores, item difficulty, item discrimination, and reliability.

Conclusions: This is an easy to use scoring system that has resulted in immediate feedback that is activity-specific and feed into NAS milestones easily and effectively. By translating the evaluation system into specific activities that any nephrologist can observe, a robust amount of valuable data has been obtained. The 4-click system has yielded an excellent response rate with more narrative comments than were previously obtained with monthly evaluations.
Methods: IAPE annual reports provided by the National Board of Medical Examiners were retrospectively reviewed and summarized.

Results: Scale score for all was 480±104 (mean ± SD); 1st-year fellows (n=2,020) 445±96, 2nd-year (Y2, n=2,005) 515±100, and 3rd-year and higher (n=112) 509±113. Standard error of the mean ranged 41-45. The 2010 IAPE had 150 core items only. 2011 and 2012 IAPE had separate O-S and U-inpatient and renal pathology modules added to Y1 and Y2 respectively (not included in total test statistics). In 2013 and 2014, all completed 102-item modules on these topics (included in statistics). A mean of 6.6 core items (4.4%) were deleted per year after adjudicating items with high difficulty or negative discrimination. Content areas aligned with American Board of Internal Medicine Certification Exam: General Aspects of Chronic Kidney Disease (CKD), Glomerular/ Vascular (G/ V), Tubulointerstitial/Cystic (TIC), Acute Renal Failure/ICU Nephrology (ARF/ICU), Kidney Transplant, Hypertension, Sodium/Water (Na/ H2O), Acid-Base/ Potassium (A-B/K), Mineral Metabolism (MM), and Clinical Pharmacology (CP). Ethics. Though examinee abilities typically vary yearly, overall total test average p value was 0.67. ARF/ICU, Na/H2O, MM, and CP tended to be less difficult (average p value 0.7) and TIC more difficult (average p value 0.58). Total test mean item discrimination bivariate correlation averaged 0.21, highest for A-B (0.28) and lowest for CKD (0.18). Total test mean item difficulty varied among content areas.

Conclusions: As expected, scale scores were higher for Y2 than Y1 fellows. Over 95% of administered items were scored; among those, mean item difficulty, item discrimination, and reliability varied among content areas.

Funding: Private Foundation Support

SA-PO134

What Are We Doing? A Survey of U.S. Nephrology Fellowship Program Directors

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Background: Recent years have seen a decrease in Nephrology fellowship applicants. Low applicant numbers may be partially responsible, and may affect the educational mission of the fellowship. Our survey addresses fellow work load and educational experiences to further explore these issues.

Methods: We distributed a survey for nephrology program directors via the Training Program Directors’ website. The survey addressed fellows’ service load and the scope of educational activities offered by the fellowship.

Results: 57 out of 147 programs responded (39%). Most are 2 years long, with a mean of 7 fellows, and are “front loaded” 64% require ≥ 7 months of inpatient service during year one. Inpatient services are usual (93%) covered by one fellow with significant resident involvement. NP’s and PA’s help cover about 15% of services. The busiest services have about 21-25 patients, although 13% of programs averaged ≥ 26 patients. At their busiest, these services have more than 30 patients, occasionally surpassing 50 patients. About one quarter of programs report ≥ 10 nights over a three month period during which a fellow is required. A mean of 34% of fellows are on call ≥ 7 nights. Fellows on call typically cover ≥ 10 nights over a three month period and ≥ 1 week-end a month. Most fellows do one weekly half day clinic, averaging 4-6 patients per session with a faculty: fellow ratio typically ≤2:1. Clinic structure is not usually modified during fellows’ inpatient service. Longitudinal coverage of HD and PD patients is provided by 82% and 61% of program respectively. Educational conferences ranged from 2-6 hours per week. Faculty didactic teaching varies from < 1 hour a week to 5 hours per week; one hour is typical. Fellows usually give 2-6 formal presentations yearly, although in some programs this is significantly more.

Conclusions: Our survey underscores the large variety in work load, practice patterns and frequency of educational conferences at different institutions and provides a framework to help address the service/education balance during nephrology fellowship.

SA-PO135

Perspectives of Nephrology Among Internal Medicine Residents

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Background: As interest in nephrology declines, we sought to identify factors influencing career interest among internal medicine (IM) residents.

Methods: This is a repeated cross-sectional survey of IM residents to assess perceptions of nephrology and the impact of these perceptions on career decisions. All categorical internal medicine medicine residents at two institutions were invited to participate in 2012, prior to the initiation of a nephrology fellowship program (Group 1); and in 2015, three years following initiation of a nephrology fellowship program (Group 2).

Results: 131 of 156 residents (84.0%) completed the survey. A total of 14.8% (19/131) of residents expressed interest in nephrology, with 6.25% (8/131) indicating Nephrology as their first choice. Cardiology (21.1%) and Hospitalist (12.5%) were the most popular career choices. The presence of a Nephrology Fellowship program did not increase resident career interest in nephrology (14.5% in Group 1 vs. 15.1% in Group 2). In perceptions of nephrology were not significantly different in Group 1 vs Group 2. Negative perceptions of nephrology most commonly endorsed by residents were: renal pathophysiology is too complex (22.9%), poor preparation in medical school (22.14%), few opportunities for procedures (26.7%), long work hours (24.4%), and long hours/ intense call for nephrology fellows (27.5%). The majority of residents (83.2%) reported exposure to positive role models in nephrology. Experiences cited as having a high impact on career choice included: mentors/role models in the field (71.65% of residents) and rotations during residency (57.14%).

Conclusions: We found 5 key thematic problems with the current training model in developing countries that included: 1) lack of understanding, 2) lack of exposure to nephrology electives in residency programs to include enhanced exposure to nephrology, 3) the perception that the nephrology population is disheartening, 4) a didactic and opportunistic instructional model with other core areas of competencies (professionalism, collaboration, advocacy, managerial skills and of scholarship are not formally taught, and 5) application of the current curricular model rather than focusing on the educational needs of the trainee.

Conclusions: There are similarities and differences in structure, content and process of training programs across different levels of care. The results have implications for re-design of training programs in the developing world for nephrology education and better clinical care delivery in patients with kidney diseases addressing local needs and priorities.

SA-PO137

Challenges and Workforce Opportunities in the Training and Retaining of Nephrology Fellows in Developing Countries: A Review of the Current Trends and Perspectives for Optimal Kidney Disease Care

Julius Obuhok Ogbe,1 Bilal Qurni,1 Timothy Olusugun Olaniwaju,2 Aminu K. Bello,1 1Univ of Alberta, Canada; 2Univ of Ilorin, Nigeria.

Background: Nephrology education has undergone rapid advancement leading to the development of comprehensive curricula and standards towards a high quality patient-centered care. These standards are often lacking on issues critical to the practice of nephrology in developing countries.

Methods: We evaluated nephrology training programs within the context of the healthcare systems across 25 upper-middle and high income countries to identify best practices and opportunities for adoption in developing nations. We further reviewed training guidelines from the major professional societies (ISN, major national societies) on content and process of training. Data were obtained from multiple sources (government reports, published literature, and websites of professional/licensing authorities, World Federation for Medical Education (WFME) and its Regional branches. The WFME 3-set of Global Standards on medical education at all levels were applied in evaluating training programs on the domains of training process, assessment, and evaluation.

Results: We found 5 key thematic problems with the current training model in developing countries that included: 1) an emphasis on factual information, memory and recall (core knowledge content), 2) absence of needs assessment and evaluation, 3) structure and organization of training is a product of established tradition than of evidence and not in congruent with health system changes and dynamics, 4) a didactic and opportunistic instructional model with other core areas of competencies (professionalism, collaboration, advocacy, managerial skills and of scholarship are not formally taught, and 5) application of the current curricular model rather than focusing on the educational needs of the trainee.

Conclusions: There are similarities and differences in structure, content and process of training programs across both developed and developing countries. The results have implications for re-design of training programs in the developing world for nephrology education and better clinical care delivery in patients with kidney diseases addressing local needs and priorities.
SA-PO138
Creating and Enhancing Interest in Nephrology Careers: A Nephrology Elective Experience for Medical Students  

Methods: At our institution, we created a novel 4-week nephrology elective experience for medical students. Our redesigned elective included both 2-week inpatient (IP) and 2-week outpatient (OP) nephrology experiences. The OP rotation included 10 half-days of various nephrology clinic experiences, 2 half-days of immediate post-transplant clinic, 1 half-day of dialysis clinic, 2 half-days of peritonial dialysis clinic, and 1 half-days of outpatient hemodialysis unit rounding. The redesigned elective also included education conferences. From 7/2012 to 2/2015, nine 4th year medical students (all from different US medical schools) completed our redesigned nephrology elective. To evaluate the novel elective experience, all medical students were asked to complete an anonymous on-line survey upon completion of their rotation.

Results: All students responded to our survey. All reported adequate OP nephrology exposure during their elective. 89% had worked with 1 or 2 faculty members during the IP setting. In comparison, 78% were exposed to at least 4 different faculty members during the OP experiences. All students had interacted with at least 3 fellows. All reported that the elective experience enhanced their exposure and knowledge in nephrology and that they would recommend this elective to other medical students. They also thought that this elective structure provided them with a better insight into what nephrologists do in practice. 78% reported that this elective experience created an interest in nephrology career. 56% responded that they would consider nephrology as one of their 3 top career choices as a result of this elective experience.

Conclusions: We believe that the structured nephrology elective provides the medical student with a much needed and realistic exposure to nephrology careers. Based on our experience, we recommend all training programs to consider this elective structure for medical students.

SA-PO139
Journal Publication of Nephrology Fellows Case Report Presentations at ASN Kidney Week 2012-2013  

Methods: We reviewed and further categorized as follows: glomerular diseases (GN), tubulointerstitial diseases (TIN), acute kidney injury (AKI), fluid-electrolyte and acid-base disorders (FE), dialysis (D), kidney transplant (KT), genetic disorders (GD), mineral diseases (MD), and other (O) cases. To determine the PR-JP rate of these CR abstracts, a literature (PubMed) search was performed in May 2015.

Results: A total of 415 abstracts were presented in the fellows CR category at the ASN Kidney Week (KW) conference in the year 2012. However, the number and types of CR abstracts accepted for publication is not known. Per our literature journal publication (PR-JP) of these previously presented CR abstracts at ASN KW is also not known.

Methods: All previously accepted fellows CR abstracts from ASN KW 2012-2013 were reviewed and further categorized as follows: glomerular diseases (GN), tubulointerstitial diseases (TIN), acute kidney injury (AKI), fluid-electrolyte and acid-base disorders (FE), dialysis (D), kidney transplant (KT), genetic disorders (GD), mineral diseases (MD), and other (O) cases. To determine the PR-JP rate of these CR abstracts, a literature (PubMed) search was performed in May 2015.

Results: A total of 415 abstracts were presented in the fellows CR category at the ASN Kidney Week 2012-2013. Compared to KW 2012, there was a 7.5% increase in CR abstract presentations at KW 2013. Over these previous two KW meetings, nearly one-third (31.6%) were CR abstracts. The remaining abstracts were FE-AB (15.2%), AKI (14.4%), KT (11.8%), D (11.8%), TIN (5%), MD (5%), O (4%), and another (3.2%) cases. Compared to KW 2012, there was increase in GN related presentations (from 55 to 76) at KW 2013. So far, only 72 (17.3%) out of the 415 abstracts have been published as papers in peer-reviewed journals. One abstract was published as a letter to the editor format. Out of those that were published, 31.5% were GN related case reports. Interestingly, 22% of these journal publications did not list the lead author of the KW CR abstract as the primary author of the paper.

Conclusions: Based on our study, it seems that there is a increased interest among fellows to present CR abstracts at ASN KW. Nearly one-third were GN related case presentations. However, so far, less than one-fifth of the fellows CR abstracts presented at KW 2012-13 have been published in peer-reviewed journals. Reasons for this low publication rate is not known. Measures to enhance publication need to be considered.

SA-PO140
Analysis of Published Medical Student Related Nephrology Medical Education Research  

Methods: A review of the English literature on nephrology education of medical students was conducted on two major online academic search engines (PubMed and ERIC). RefWorks was used to manage the papers discovered in this search and also reviewed. Conference abstracts were not investigated. The empirical studies were categorized by subject within nephrology. The research design of each study was then recorded.

Results: 26 original studies were found in which a method of teaching nephrology to medical students was described. The studies dated from 1977 to 2015. The focus of these teaching experiences was as follows: anatomy (3.3%), physiology (23.3%), pathophysiology (26.7%), pathology (10%), treatment (20%), and general nephrology (16.7%). 4 of the pathophysiology studies were also classified under other categories, so there were 30 total papers. The papers were also categorized into types of assessments, with two papers containing two different types of studies for a total of 28 types of assessment. 14.2% had either no assessment of the educational experience or had a description too vague to categorize it; 3.6% involved a questionnaire about the existing educational approach before and after a new practice was carried out; 17.1% involved surveys or questionnaires after a practice was carried out; 7.1% assessed the method both before and after; and 10.7% were case studies or ethnography; and 7.1% included a randomized controlled trial. The randomized controlled trials involved teaching techniques focused on the pathophysiology of renal disease. Overall, students responded that they would consider nephrology as one of their 3 top career choices as a result of this experience.

Conclusions: This review is a first attempt to summarize and provide a description of the educational techniques in nephrology medical education research.

SA-PO141
Participation in the Open, Online, Twitter-Based, Nephrology Journal Club, NephJC  
Joel Topol, Matthew A. Sparks, Edgar V. Lerman, Thomas Oates, Paul J. Phelan, Francesco Iannuzzella, Swapnil Hiremath.

Methods: We searched the Symplur analytics database for all tweets with the hashtag #NephJC from March 16, 2014 to June 2, 2015. We measured the numbers of participants, number of tweets and assessed participation over the first 27 NephJC sessions.

Results: From April 29th to June 2nd, 2015, 27 topics were discussed. 27 Tweets were at 9PM Eastern for the Americas and starting Dec 18, 2014 a Europe and Africa chat was added at 8PM GMT. 10 GMT chats have been held, generally one day after the American chat. 1,022 Twitter accounts have used the hashtag #NephJC a total of 14,891 times. The median journal club has 41.5 (IQR 30.5-56.5) participants and 335.5 (IQR 268.5-633.5) tweets. The number of participants and tweets increased over time (P<0.01). The addition of the GMT chat was responsible for some of that growth (median number of tweets increased from 273 to 662.5, P<0.001, participants from 35 to 60.5, P<0.001).

Conclusions: NephJC has established itself as an integral part of the online digital medical education curricula. The increased participation of NephJC demonstrates the positive value of Twitter in medical education.

SA-PO142
Three Years’ Experience with the Online Educational Game, NephMadness  

Methods: The game NephMadness is an educational project that leverages social media and Free Open Access Medical Education (FOAMed) to highlight advances and important issues in nephrology. NephMadness 2015 was the third year of this project.

Results: Three Years’ Experience with the Online Educational Game, NephMadness  

Methods: The game NephMadness is an educational project that leverages social media and Free Open Access Medical Education (FOAMed) to highlight advances and important issues in nephrology. NephMadness 2015 was the third year of this project.

Results: The findings from this research project indicated that social media and online educational games can be an effective method of engaging medical students and nephrology trainees in important topics in nephrology. The game NephMadness is an educational project that leverages social media and Free Open Access Medical Education (FOAMed) to highlight advances and important issues in nephrology. NephMadness 2015 was the third year of this project.

Conclusions: NephMadness is increasing engagement on three unique metrics. We believe this indicates that pairing social media with freely available, expert-generated content can stimulate interest in nephrology research.

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

567A

Education Research: From Classroom to Bedside
Poster/Saturday
SA-PO143
Awareness of AKI in Low Resource Settings: A Global Survey
Joseph Lunerva,1 Kajiro Kilonzo,2 Andrew J.P. Lewington,3 Karen E. Yeates,4 Fredric O. Finkelstein,3 1Duke Univ; 2KCMC; 3Leeds Teaching Hospitals; 4Queen’s Univ; Yale Univ.

Background: The ISN has set a goal of eliminating preventable deaths from AKI by 2025—the “0X25” initiative. However, there is limited awareness of the challenges presented by AKI in terms of diagnosis, treatment and management in low resource settings (LRS).

Methods: We reached out to nephrologists working in LRS using a web-based instrument of 18 questions. Responders were asked what strategies should be considered to increase the awareness of AKI in LRS and recommend approaches to heighten this awareness. 517 respondents from 5 WHO world regions, including 54% from Africa.

Results: The major barriers to raising awareness cited by all were inadequate training, shortage of adequately trained health workers and lack of awareness of the significance of AKI by healthcare workers, government officials and the general public. Additional factors cited were limited patient access to health facilities, limited diagnostic and treatment facilities, lack of support for AKI programs, lack of clinical practice guidelines for AKI, poor communication systems, limited research funding and lack of linkages of AKI programs to other health projects. Health centers (HCs) were broken down into rural, district and regional HCs. Supplies available for diagnosis (serum creatinine and BUN) and management (IV fluids, antibiotics, anti-venom) of AKI are limited in rural HCs. All noted that hemodialysis services were available but only in selected, large urban centers. Peritoneal dialysis was limited to regional HCs.

Conclusions: Increasing the awareness of AKI in local, district, and regional HCs requires a multi-faceted approach, reaching out to government officials, hospital administrators, physicians, nurses, local health care workers, community leaders, international organizations and the general public. The success of this initiative involves the development of meaningful and targeted educational programs, training materials, and treatment guidelines tailored to the local situations. Alliances will need to be formed with governmental agencies, non-profit organizations and global health programs. Support needs to be provided for additional research programs.

SA-PO144
Acute Kidney Injury Education to Nursing and Assistant Health Care Staff Mansoor N. Ali. Renal Medicine, Calderdale and Huddersfield Hospitals NHS Foundation Trust, United Kingdom.

Background: Acute kidney injury (AKI) is a global healthcare problem. It carries significant mortality and incurs heavy costs to the National Health Service. Extensive work has been done recently both at undergraduate and postgraduate level to ensure front line medical staff have better understanding in managing AKI. One such important area of focus involves the need for training nursing and assistant healthcare staffs who care for patients presenting with AKI.

Purpose of the study: To gauge the understanding of AKI amongst nursing and healthcare assistants working on busy acute medical admissions unit.

Methods: The anonymous questionnaire was aimed at the nursing and assistant health care staff working on the admissions unit at two large district hospitals. The length of time since qualification ranged from few weeks to 16 years. The questionnaire was followed by planned teaching, simulation training and workshop sessions. The process was carried out within a period of 2 months.

Results: The Questionnaire was completed by 50 staff members. It included series of questions aimed at defining and managing AKI from a nursing perspective. 24 out of 50 were able to correctly identify AKI. Only 5 out of 50, have never cared for patients with AKI. Not many were aware of the symptoms of AKI; common answers given by 40 respondents were “reduction in urine output” and “dehydration.” All participants answered “yes” to monitoring urine output and understood the significance of fluid monitoring but all admitted more needed to be done to ensure accurate documentation in the patient’s notes. Other questions asked were if nurses check patient’s blood results on the system server to which most replied “no” and if medications were regularly reviewed during drug rounds. Surprisingly, not all were aware of nephrotoxic medications and only 20 respondents would regularly review drug charts in the context of renal failure.

Conclusions: The questionnaire and the training sessions identified lack of better understanding of AKI and its management. There needs to be a stronger emphasis on the introduction of AKI and its management during their training years and development of mandatory online e-learning modules.

SA-PO145

Background: AKI occurs in 1-in-3 hospitalized patients, and majority of those are managed by non-nephrology specialties, including trainees.

Methods: The renal fellowship program designed an online anonymous survey, distributed to trainees (students, residents, fellows), to understand their level of knowledge in recognition and management of AKI. 37 questions were classified into following categories: knowledge of guidelines; prognostic factors; and drug safety. Results are represented as aggregate percentage.

Results: 104 trainees responded to the online survey; 50% were male, 84% US medical graduates and 70% were residents/fellows. 50% were affiliated to medical specialties; and 53% had spent at least one elective in nephrology. In terms of AKI definition: 51% use serum creatinine (SCr) as the most important factor to diagnose AKI, whereas 20% use urine output. Majority (76.1%) agreed that rise of 0.3 mg/dl or 1.5 times of baseline Scr was clinically relevant, in concordance with current guidelines. RIFLE criteria were most commonly used (42%), followed by KDIGO (13%); and 90% agreed that guidelines help in standardization, and management of patients. 85% concurred that AKI impacts short and long-term outcomes, however, majority (60%) felt dialysis requirement was the most important clinical predictor of outcome. Majority (67%) felt that early involvement of nephrology services is helpful in AKI management; 66% sought nephrology input to determine the cause of AKI/co-management, and 7% viewed nephrology role purely for procedural delivery of dialysis. As for drug safety, 89% reported to pay attention to renal function while drug dosing, but 70% felt that this was the responsibility of either pharmacy or ordering team. In terms of follow-up 61% of subjects felt that follow-up was only needed in moderate to severe AKI cases or in non-recovery, 86% preferred that in = 30 days, and 64% preferred that to be with primary care.

Conclusions: Most of the trainees displayed good knowledge of AKI guidelines (RIFLE), seek timely nephrology involvement and view it to be beneficial. More work needs to be done in terms of improving knowledge/practice about drug safety and follow-up care in AKI.

SA-PO146
Adherence to Care Bundles for AKI – Challenges in Supporting Education and Measuring Compliance Melanie Louise Sally, Christopher J. Mulgrew. Renal Medicine, Royal Devon & Exeter Hospital, Exeter, Devon, United Kingdom.

Background: AKI typically occurs as a consequence of intercurrent illness in patients with multiple comorbidities and risk factors. The use of clinical guidelines to assist medical and nursing staff in AKI management has been adopted by most secondary care institutions in the UK. We have previously presented our use of e-alerts for AKI as a prompt to improve AKI care (Mulgrew et al, ASN, 2013). Clinical guidelines were prompted by the e-alert and widely publicised to staff.

Methods: In a model similar to the NHS Safety Thermometer, snapshots of compliance with 6 key elements of the AKI guidelines on 4 medical wards was measured by identifying patients from AKI e-alerts. These included documentation of AKI, medication review, clinical assessment and ongoing investigation/monitoring. Awareness was supported by an AKI Education nursing team, working with medical and nursing staff. Monthly compliance was assessed over a period of one year.

Results: Mean compliance for all elements of the guidelines improved from 52% to 69% over the year. Significant variability was seen, often associated with notable workforce challenges such as new medical staff or periods of increased activity.

Conclusions: Supporting medical and nursing teams to manage AKI in secondary care in order to prevent progression and treat promptly remains challenging. A number of external factors frequently impact upon adherence to guidelines and support needs to be planned in order to continue to maintain high standards and optimise patient care. The use of a Safety Thermometer, allowing performance to be analysed and comparisons made between clinical areas, may continue to be useful in improving performance and patient outcomes in AKI.

SA-PO147
Internal Medicine Residents Knowledge of Vein Preservation in Chronic Kidney Disease Patients Sandesh Joshi, Jamie Alton Green, Maria C. Bermudez. Nephrology, Geisinger Medical Center, Danville, PA.

Background: Vein preservation is important among CKD patients for future arteriovenous fistula potential. House staff plays critical role in managing these patient population and preserving their vein for future arteriovenous fistula. Their knowledge and current practices directly affects the outcome for vein preservation among these patients.

Methods: We conducted a survey among 44 internal medicine residents to understand their baseline knowledge and current practices regarding vein preservation. The survey was conducted at Geisinger Medical center, Danville, PA.

Results: 44 residents were included in the survey. Only 6.8% (3) were able to correctly identify patient population, on whom we should avoid particular arm for IV draws, BP measurements, peripherally access or peripherally inserted central catheters. Two-third (27) answered non-armant to avoid for these procedure and 13.5% (6) responded who side does not matter. 81.8 % (36) answered that nephrology should be consulted prior to peripherally inserted central catheters placement for CKD 4 patient. 93.1 % (41) answered

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658A
Vascular Access and Transplant Referral Rates in CKD: An Ongoing Performance Improvement Project for Nephrology Fellows

Background: Referral for vascular access (AV) and kidney transplantation (Tx) are important management facets of CKD. We previously conducted a performance improvement project assessing AV and Tx referral rates (RR) in CKD patients from the Nephrology fellows’ clinics. Following an educational intervention, there was an improvement in transplant RR (JASN 25.786A, 2014). To evaluate the sustainability of this initiative, we conducted a follow-up analysis.

Methods: This performance improvement project was conducted in 3 phases at the Charlie Norwood VAMC; Phase 1 (baseline, 1/1-4/30, 2013), Phase 2 (post-intervention, 8/1-11/30, 2013) and Phase 3 (follow-up, 1/1-4/30, 2015). Data extraction was conducted by three, 2-2 fellow teams, each reviewing the other’s RR for all patients seen in the previous 4-month period. The analysis was sorted by eGFR (ml/min/1.73m2); for eGFR<15, both AV and Tx RR were recorded. In addition, Tx RR for eGFR 15-20 was documented.

Results: 1114 total records were reviewed (349, 361, and 404 for Phases 1, 2, and 3, respectively). Table 1 indicates the number of patients and RR in those with GFR<20. RR andTx RR were recorded. In addition, Tx RR for eGFR 15-20 was documented.

Conclusions: Baseline knowledge was poor regarding vein preservation in CKD patients and very few residents have engaged in practices to preserve veins. More resident education is needed to engage them in vein preservation for CKD patients.

Impact of Standardized Electronic Documentation in an Academic Nephrology Setting

Background: Reimbursement depends on accurate documentation and billing. Academic nephrologists are under increasing pressure to meet financial productivity targets. An analysis of nephrology reimbursement was performed at an academic medical center to find deficiencies and identify targets for education.

Methods: 75,978 inpatient nephrology encounters by 22 nephrologists from January 2012 and March 2015 were reviewed. Data included the current procedural terminology (CPT) code specifying the type of service and any charge adjustments made by the coding department. Adjusted charges were accompanied by the reason for adjustment, the corrected CPT code and a gross revenue adjustment based upon Medicare reimbursement. Relative value units (RVUs) were calculated using the Medicare National Physician Fee Schedule. Multivariate regression analysis was performed to identify factors associated with RVU adjustments.

Results: 5615 (7.5%) of encounters were adjusted by coders. 3832 (68%) were due to incorrect documentation or billing and 1683 (32%) were due to services performed but not billed by nephrologists. For submitted charges, revenue was reduced by $995,976 and 4227 work RVUs as a result of incorrect documentation or billing. The potential loss of revenue from unbilled services was $603,014 and 2823 work RVUs. Inadequate documentation of physical exam (p<0.01) and inadequate documentation of supervision of medical students/residents/fellows (p<0.01) were independently associated with RVU adjustments. Incorrect charge selection, duplicate charges, competing charges from another nephrologist and conflicting discharge/observation/post-operative care CPTs were also independently associated with RVU adjustments (p<0.01).

Conclusions: There was a substantial loss in gross revenue and work RVUs due to incorrect documentation and billing in an academic nephrology setting. These reductions in reimbursement and productivity might be avoided through better physician education and training. Specific targets include documentation of physical exam and supervision of trainees, correct CPT charge selection and ensuring all services performed are billed.

Reaching Renal Goals – A Quality Improvement Project

Background: The purpose of this study was to improve our patient care in a renal clinic at a large university hospital by using three of the core competencies - patient care, systems based practice, and practice based learning and improvement.

Methods: A check-out sheet was developed and through better physician education and training. Specific targets include documentation of physical exam and supervision of trainees, correct CPT charge selection and ensuring all services performed are billed.

Conclusions: Baseline knowledge was poor regarding vein preservation in CKD patients and very few residents have engaged in practices to preserve veins. More resident education is needed to engage them in vein preservation for CKD patients.

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Conclusions: Our project was helpful in educating trainees in the treatment goals and assessing for patients in the renal clinic, and standardized an approach to patient care. Overall, the results show a trend towards improvement in all goal areas except for renal education. This study did not account for patients who were new to our clinic and therefore had never received renal education previously.

SA-PO152

A Simulation Exercise to Assess Renal Replacement Therapy and Kidney Biopsy Communication Skills Lisa K. Prince, 1 Maura A. Watson, 1 Anna M. Howle, 1 Christina M. Yuan, 1 Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 2 Medical Simulation, Walter Reed National Military Medical Center, Bethesda, MD.

Background: We piloted a nephrology-specific “Breaking Bad News” simulation to assess Interpersonal Communication Skills and Professionalism during renal replacement therapy (RRT) and kidney biopsy (Bx) counseling. Assessment tools were a 9-point Likert Mini-Clinical Examination Exercise (Mini-CEX) adapted for RRT and Bx counseling, and the Essential Elements of Communication-Glomerular Disease Scale 2005 (EEC-GRS).

Methods: There were three cases: 1) a middle-aged woman with polycystic kidney disease and CKD5, 2) a critically-ill elderly man with AKI whose wife was his surrogate decision maker, and 3) a previously healthy soldier with nephrotic syndrome. There were 5 nephrology fellows. One patient actor performed for each case, assessing each examinee with the EEC-GRS. One faculty assessed all examinees for one case using the EEC-GRS and mini-CEX. Encounters lasted 15 minutes, followed by 5 minutes for examinee counseling by the actor and faculty.

Results: Post-simulation, 3/5 faculty surveyed felt that the exercise met objectives, and was an excellent assessment tool. 4/5 examinees felt the exercise was “good” and met objectives. 5/5 felt that simulation time was too short to assess communication skills. 2/5 felt that a mini-CEX assessing a real patient encounter was superior. Median examined EEC-GRS performance assessed by actors and faculty was 4 (range 3-5). Median mini-CEX performance was 6 (range 5-9).

Conclusions: Based on feedback, the original mini-CEX was too detailed for a 15-minute encounter, and was simplified. Instructions now stress that, because of encounter brevity, counseling is unlikely to be completed, and completion is not required for satisfactory grading. A second set of scenarios was developed to permit a yearly simulation in a two-year cycle. We plan to test the revised simulation in a larger group of nephrology fellows within the next year. The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense or the United States Government. Funding: Other: U.S. Government Support

SA-PO153


Background: Estimated glomerular filtration rate (eGFR) is used to diagnose and classify CKD. The accuracy of creatinine-based eGFR (CREAT) is inferior to eGFR calculated using multiple renal filtration markers. CKD guidelines suggest using serum creatinine and cystatin C to evaluate for CKD in select patients, but methods for, and results of guideline implementation have not been reported.

Methods: We reviewed new patient nephrology clinic encounters for a three month period to establish baseline guideline adherence. Combined creatinine/cystatin C (eGFR[CystatinC]/eGFR[CreatininC]) was considered indicated in patients with eGFR-Creat 45-90mL/min/1.73m2 and no albuminuria,urine sediment abnormalities, or other markers of kidney damage. Consultation review was modified such that a nephrologist reviewed every referral request, with the option of ordering labs to be obtained prior to a clinic visit. During a six-month implementation period, guideline awareness was targeted via didactics, signsencountered in patients, and results of guideline implementation have not been reported.

Results: Guidelines were modified to increase the threshold for the post江湖 intervention adherence was compared using Fisher’s exact test. Patients with eGFR-CreatCreatCys<60mL/min/1.73m2 were considered to have no evidence of CKD. Inpatients for whom eGFR-CreatCystinC was obtained, mean eGFR-Creat and eGFR-CreatCys were compared using paired t test.

Conclusions: Guideline adherence was significantly higher in the post江湖 intervention adherence was compared to the pre-intervention period (testing observed in 30 of 40 (75%) vs 12 of 32 (37.5%) indicated cases; p<0.002). Mean eGFR-CreatCys was significantly higher than eGFR-Creat (77.3±15.3 vs 58.3±9.1mL/min/1.73m2; p=0.001). eGFR-CreatCys was ≥60mL/min/1.73m2 in 85.3% of cases.

Conclusions: By modifying our consult review process and raising awareness among nephrology providers, we significantly increased implementation of eGFR-CreatCys guidelines and determined that the vast majority of tested patients had no evidence of CKD. Our results suggest testing as suggested in the guidelines has the potential to markedly decrease the number of inaccurate CKD diagnoses.

SA-PO154

Improving Pathology Curriculum for Nephrology Fellows Enrica Fung, 1 Orlando Camacho, 1 Michelle M. O’Shaughnessy, 1 Adetokunbo A. Taiwo, 1 Gabriela Velez, 1 Neeraja Kambham, 2 Timothy W. Meyer. 1Nephrology, Stanford; 2Pathology, Stanford; 3Nephrology, VA Palo Alto.

Background: Stanford fellows were previously exposed to renal pathology through attendance at monthly hour-long “biopsy conferences” where faculty and fellows discussed difficult cases; and informal quarterly “fellows-only conferences” where fellows asked pathologists questions on core topics. Our project sought to improve fellows’ education in renal pathology.

Methods: Twelve first to third year fellows participated in this project. Two renal pathologists led five orderly review sessions, dedicated to fellows only: 1. Common renal pathologies; 2. Primary glomerulonephropathies; 3. Secondary glomerulonephropathies; 4. Plasma cell dyscrasia-related disease; 5. Renal transplant pathology. Second year fellows helped in preparation of teaching material. Fellows were encouraged to ask questions. Participants completed a survey to measure their satisfaction with renal pathology teaching and their confidence in interpreting renal biopsies before and after this project.

Results: Prior to our project, 55% of fellows felt “somewhat satisfied” to “satisfied” with the current pathology conferences, and 10% of fellows felt “somewhat confident” in their abilities to interpret biopsy findings. Most fellows (83%) viewed renal pathology to be an “important” or “very important” part of their overall nephrology training. After the project, 100% of fellows felt “somewhat satisfied” to “very satisfied” with the project, and 60% of fellows felt “somewhat confident” in their abilities to interpret biopsy findings. To date, fellows answered 63% of quiz questions correctly prior to the project and 60% of final questions correctly after the project.

Conclusions: Survey of nephrology fellows revealed poor confidence in interpreting renal pathology prior to our project despite perceived importance of the topic. To date, post project evaluation suggested improved confidence in renal pathology but lack of significant change in knowledge base. This may be due to issues with knowledge acquisition, inter-test comparability or instruction method.

SA-PO155

Improving the Communication Skills of Nephrology Fellows by Utilizing MBTI Training Anna Marie Burgner, Julia Lewis. Vanderbilt Univ School of Medicine, Nashville, TN.

Background: Communication skills can both positively and negatively affect the patient-physician relationship. Although many things impact successful communications, individuals’ personality types affect the way they communicate and the way they interpret the communications of others. It has been suggested that a lack of understanding of the basic difference between personality types contributes to poor communication and unsuccessful interactions. Nephrologists work in a unique environment in the dialysis unit with a complex interdisciplinary team and a “captured” audience of anywhere from 10-40 patients in a single room. In the dialysis unit, communication between the multi-disciplinary team and the patients and between the multidisciplinary team’s individual members impacts the successful achievement of dialysis outcomes.

Methods: Eleven nephrology fellows underwent a curriculum designed to increase their awareness of their own Myers Briggs Type Indicator (MBTI) personality preferences, their knowledge of the different basic personality preferences, and how those differences impact communication. Knowledge of the MBTI preferences was tested pre-intervention, immediately post intervention, and 8 weeks post intervention. Communication skills were measured pre-intervention, 4 weeks post intervention, and at 8-weeks post intervention.

Results: Communication skills were measured prior to the intervention and 8 weeks post intervention by dialysis nurses observing fellow-real patient interactions. Fellows were also asked to describe how they used their knowledge at 8 weeks post intervention.

Conclusions: The intervention led to a sustained increase in the nephrology fellows’ MBTI personality preference knowledge. At 8 weeks post intervention, fellows reported utilizing their personality preference knowledge to improve their communication with their patients as well as with members of their team. However, nephrology fellows’ communication skills, as measured by the Kalamazoo Essential Elements Communication Checklist Adapted (KEECC-A), did not change.

SA-PO156

Lung Ultrasound: A New Skill for Nephrologists for Volume Overload Quantification in End Stage Renal Disease Patients on Hemodialysis Marie M. Saad, Wissam Mansour, Elias Moussaly, Jeanne Karnal, Boutros Karam, Cara Brown, Monica Kapoor, Elic El-Charabaty, Suzanne E. El Sayegh. Internal Medicine/Nephrology, Staten Island Univ Hospital, Staten Island, NY.

Background: Many methods have been tried to assess the volume status in patients on hemodialysis (HD). While the estimated dry weight is still the only method widely used, it is often inaccurate and poses a clinical challenge. Pulmonary congestion detected as B lines on ultrasound (BLUS) is rising as a novel parameter for assessing volume status; we evaluate the accuracy and reliability of measuring BLUS performed by residents following a short training course.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Residents underwent a 3 hour course under the supervision of ultrasonound-fellowship trained Emergency Physicians (EP). The course included a didactic section, a simulation hands-on training, and an Objective Structured Clinical Examination prior to enrolling the trainees as investigators; Residents performed lung ultrasound (LU) on ESRRD patients post HD sessions in a supine position over 28 intercostal windows. They obtained at each window a 6s clip that were reviewed by 2 blinded EP. BLUS were summed up categorizing patients into different classes of pulmonary congestion: mild (0-14), moderate (15-30) and severe (>30).

Results: A total of 81 ESRRD patients on HD were scanned. 71.6% were males; mean age 59.74 years, mean BMI 28.59±5.62 kg/m²; mean treatment duration was 15 min. The B-Lines score found by the study investigators and EPs was 15.8 ±21.3 and 12.06±21 respectively. The difference was 3.77±16.8 (0.0475). When categorized into the 3 classes, there was no significant difference between both classification (0.085), and were in moderate agreement-kappa 0.56 [0.42-0.71].

Conclusions: B-Lines visualized on bedside LU can provide a reliable and quantifiable assessment for lung congestion. Our study shows that a short training course can render novice users of ultrasound capable of performing this quick evaluation. This can aid in objectively assessing volume overload in a timely manner in HD patients who present a unique clinical challenge. LU has emerged as a new technic, readily available at bedside, providing immediate results, yet is an easily learned skill.

SA-PO157


Background: Percutaneous kidney biopsy is the gold standard for diagnosis of kidney disease but is underutilized due to wariness of complications. Based on clinical and laboratory data, Nephrologists try to predict the renal pathology (clinical gestalt). However, no study has compared the diagnostic accuracy of the clinical gestalt with the kidney biopsy result.

Aim: To compare pre-biopsy diagnosis (PBD) by Nephrologist with final histologic diagnosis. To assess if accuracy of PBD improves with increasing years in clinical practice.

Methods: Division of Nephrology at Stroger Hospital of Cook County conducts a monthly biopsy conference. Three case summaries are presented followed by discussion and presentation of the biopsy findings. Between September 2014 and April 2015, using a structured form Fellows and Nephrologists were asked to provide their top diagnosis for each case and this was compared with the actual histologic diagnosis. All physicians apart from the primary Nephrologist were blinded to the diagnosis. The study was deemed exempt by IRB.

Results: 23 cases were discussed in the biopsy conference involving 13 unique diagnoses and 286 unique responses were obtained. Overall diagnostic accuracy was 53.49% (153/286); Fellows (52.5%) and Nephrologists (54.3%). Diagnostic accuracy for nephrologists was 100% for ANCA vasculitis and Minimal Change Disease (MCD) and 86% for Diabetes but < 50% for stages of Lupus and other seronegative GNS.

Biopsy Diagnosis Pre-biopsy diagnostic accuracy (%)
ANCA vasculitis 100
MCD 100
DM 86
Lupus class II 80
Amyloid 57.14
Lupus class III + V 50
Idiopathic Membranous 45.45
HIVAN 42.85
IgA 38.46
Lupus class V 33.33
HTN 33.33
Fibrillary GN 25
Normal 0

Nephrologists with > 10 years’ experience tended to more accurately predict the diagnosis than those with < 10 years’ experience (64.4 vs. 48.3%, p=0.07).

Conclusions: Nephrologists more accurately diagnosed ANCA vasculitis, MCD & Diabetes by clinical gestalt, but were less accurate for stages of lupus and other seronegative GNS. Regardless of training and experience kidney biopsy is still the diagnostic tool of choice in patients with kidney disease.

SA-PO158

Out-Patient Clinic Based Multidisciplinary Patients’ Education for Advanced DM Nephropathy Is Effective and Efficient for Reducing ESRD

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Background: Diabetes Mellitus (DM) is the most common etiology of CKD. Patients educations for these patients are known to be important, however, effectiveness and efficiency of these programs are still unclear. We established multidisciplinary out-patient clinic based education system, specialized for advanced diabetes nephropathy, and assessed their clinical outcomes.

Methods: Education system were started from May 2012, in St. Luke’s International Hospital, Tokyo, Japan. All CKD patients with DM were asked to meet nurse and dietitian, before seeing physicians, on every visit of the CKD clinic. Nurse and dietitian give the specific advices for each patients, within 15 minutes, by using our original short text or materials. Initiation of renal replacement therapy (RRT) were assessed for the primary and secondary end points of the study, death, hospitalization, type of RRT were.

Results: From May 2012 to March 2015, total 372 individual patients were participated. Their baseline eGFR were 36.5±12.5/mL/min, mean age 65.5±13.2 y.o. and 68% of them were male. Two hundred and ninety seven, 82% of patients were educated and they averaged their frequency of education was 4.3±2.1 times/year. Comparison of educated and non-educated groups, baseline eGFR, HbA1c or other comorbid did not differ. However, preservation of renal function were better in educated group; delta eGFR: Educated vs. Non-educated: -3.26±1.21 vs. -8.2±3.25 mL/min/1.73m²/year, p=0.04. T Test. More, incidence of ESRD in educated group were higher than non-educated: 9.4% vs. 33.3%, p=0.033, Chi-square test. Furthermore, in non-educated group, none of the patient selected peritoneal dialysis or transplants for the RRT.

Conclusions: Our out-patient clinic based education system is simple and useful for diabetic CKD patients for reducing ESRD.

SA-PO159

Our Stories Our Way: Creation of a Digital Story CKD Educational Intervention

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Background: Chronic Kidney Disease and End Stage Renal Disease disproportionately affects American Indian communities, yet there are few culturally appropriate educational interventions for this population.

Methods: Digital storytelling combines first person narrative with digital images and music and can be done with a community-based, learner-centered approach. With these digital tools, people create personal narratives that are powerfully compelling, emotionally engaging, and provide another view or perspective on a topic. We recruited 10 men and women with diverse life experiences related to health and kidney disease from an American Indian community to create digital stories. Each participant was mailed a pre-workshop DVD that pertained to chronic kidney disease knowledge and health behaviors among American Indians.

Results: We held a 3½ day digital story workshop with our partner nDigiDreams, LLC in Nov 2013 at a tribal college. Participants, their family members, and researchers worked together with the facilitators to create their personal digital story related to health and kidney disease in their words. A total of 10 digital stories were created. The stories encompassed four areas: develop story idea, gather media such as pictures and music, record the voice parts/edit the digital story, and share or screen the digital stories among the group. No technical difficulties were encountered.

Conclusions: We created a unique educational tool in the form of digital stories. The DVD has been used in an ongoing pilot observational educational trial looking at the impact on chronic kidney disease knowledge and health behaviors among American Indians.

Funding: NIDDK Support

SA-PO160

The Effect of Nephrology Specialty Clinics on Patient Care and Trainee Experiences

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Background: As medicine evolves, there has been a trend towards the creation of special clinics which streamline care in hopes of improving patient survival through clinical trials and increased time with “super-specialists”. From a trainee perspective, a Nephrology clinic focused on a particular disease affords a unique perspective on disease pathophysiology and treatment and can be a wonderful tool to recruit residents or students to nephrology. We hypothesized that a majority of nephrology trainees across the US utilize such subspecialty clinics, and we aimed to characterize the patient and trainee experience by conducting a nationwide survey.

Methods: An e-mail detailing the study’s aims and an anonymous 7-question online survey was sent to the 139 program directors of ACGME-accredited nephrology fellowship programs in July 2014.

Results: 54 of 139 program directors (39%) replied. We found Transplant clinics to be the most common subspecialty clinic (83%), followed by Stone clinic (63%), Advanced CKD clinic (38%), and Glomerulonephritis clinic (38%). Transplant specialist exams test on average, with 67% in existence for over 10 years. Less common clinics included those...
for lupus, polycystic kidney disease, and genetics. Regarding patient compliance within specialty clinics, 40% indicated no change, 40% improved, and 20% much improved. On patient satisfaction, 32% indicated no change, 49% improved, and 19% much improved. No respondents perceived decreased patient compliance or satisfaction. Trainees participated in 98% of specialty clinics with a 91% satisfaction rate; 29% were very satisfied. 45% of specialty clinics had ongoing research projects, with an average of 5.5 research projects in those clinics.

Conclusions: Specialty clinics can be an invaluable tool for both trainees and patients; both groups reported high satisfaction levels. These clinics also enable research by maintaining an established database of patients with specific disease processes. Access to such information is essential to quality research and may streamline the development of key clinical trials.

SA-PO161

Background: The distribution of renal replacement therapy (RRT) modalities among patients varies from country to country, and is often influenced by non-medical factors. In our department, patients progressing towards end-stage renal disease (ESRD) go through a structured Pre-Dialysis Education Program (PDEP). This PDEP is conceived with patients association and nursing educator.

Methods: Forty nine patients with CKD who were receiving care in a multidisciplinary predialysis clinic (mean age 73.5, 63% men). The participants were accompanied by family member. They have received an educational education, followed by two workshops in groups and a final educational workshop. The evaluations are carried out in groups of 6 to 10 patients. The PDEP consisted of: (1) psychosocial assessment, (2) education about dialysis and choice of modalities, (3) counseling sessions with patient, family members, (4) education about dietary and dialysis.

Results: Choice of the substitution method at the end of the workshops: 61% peritoneal dialysis, 18% haemodialysis and 21% absence of choice. - 94% of the patients were satisfied with the treatment choice - 100% satisfaction of the patients, 26% decrease of the anxiety. (p=0.0005), 25% (p= 0.0001) increase in the consent for the treatment, 61% increase in the engagement in the treatment (patient ready to receive treatment) (p=0.00001), 47% increase knowledge of RRT (p=0.00001).

Conclusions: Most studies dealing with the pre-dialysis information show a balanced choice of the RRT, but only 50% of the patients actually begin DP. Our workshops of help and assistance to the choice enable to significantly reduce the anxiety linked to the dialysis and thus increase the adherence and engagement for the chosen method RRT. A two-phase educational intervention can increase the proportion of patients who intend to initiate dialysis with self-care dialysis. In our centre offering all treatment RRT modalities, a high percentage of patients exposed to a structured PDEP start with a self-care RRT modality.

SA-PO162
Frequency of Use of Social Media in CKD Patients on Dialysis: Pilot Study in Ecuador Fabian A. Ortiz-Herber, Juan Carlos Calderon, Walter Morales, Christian Arias, Juliana Moro, Byron Jesus Haz, Ivan Manuel Cherrez. 1Inst Ecuatoriano de Diálisis y Transplantes, Guayaquil, Guayas, Ecuador, 2Respiral, Guayaquil, Guayas, Ecuador; School of Medicine, Univ de Especialidades Espiritu Santo, Samborondon, Guayas, Ecuador.

Background: CKD on dialysis is defined as <15% of kidney function. In Latin America, 461 per million are on dialysis. Region is the third largest user internet. Social media includes communications spread electronically, shared by individuals and discussed by a committed population. Hispanic Americans with CKD used it, to inform and be informed, and for supporting each others.

Methods: Observational, cross sectional, pilot study. Patients were recruited in dialysis center in Guayaquil. Survey included demographical and clinical items, Charlson score and 4 questions about frequency of use of social media were included. Also, questions about obtaining information; and interest in receiving or asking physician questions related to illness in social media. Frequencies and mean (SD) were employed. Chi-square, ANOVA and M-W U was used for comparisons. Also, Cronbach were calculated.

Results: 34 patients participated, with mean age of 56.5 (SD 16.3), mean years on dialysis of 3.9 (SD 4), 52.0% were women. Comorbidity’s rate was very high (82%). 70.6% of patients believed that dialysis control symptoms of disease. 11.8% hadn’t got cellular-phone neither Internet. 61.8% hadn’t got smartphones. Almost half of patients had smartphones. Women had a high comorbidity (41.2%), p<0.05. Around 30.0% reported using SMS, Facebook, YouTube, Internet as main tool for obtaining information, and 43.5% reported use of WhatsApp. Mean KiKS was lower in Chinese speakers compared to English speakers (11.9 vs. 17.2; p<0.001). Chinese speakers scored lower in all domains of the KiKS; general kidney knowledge (6.2 vs. 4.5), knowledge of kidney function (5.5 vs. 4.0) and knowledge of medications (0.4 vs. 3.7).

Conclusions: While our results for CKD knowledge among English speakers are comparable to previously published data (mean score 18.0), scores among non-English speaking CKD patients is lower than English speakers. Whether this finding is associated with differences in care management and clinical outcome needs to be evaluated. Furthermore, educational material and programs may need to be tailored to specific populations to improve health literacy.

SA-PO163
The Impact of Predialysis Education on Patient Understanding, Preparedness, and Decisional Conflict Regarding Renal Replacement Therapy Options Syed Amir Hamid Ali Shah, 1 Jon D. Bucalouci, 1 Amanda Young, 1 Jamie Alton Green. 2 Nephrology, Geisinger Medical Center, Danville, PA; 3 Center for Health Research, Geisinger Medical Center, Danville, PA.

Background: Predialysis education is recommended to prepare patients with advanced chronic kidney disease (CKD) for initiation of renal replacement therapy; however, the impact of existing approaches to the medical decision-making is unknown. Methods: We surveyed 91 advanced CKD patients before and after a 2-hour nurse led group education class to assess patient understanding of renal replacement therapy options (1=poor to 5=excellent), preparedness to make a decision (1=not at all to 5=very prepared), and decisional conflict using a validated scale (0=no decisional conflict to 100=extremely high). The class included a combination of direct verbal instruction and video presentation, tailored to patients with a high level of health literacy and sociodemographic backgrounds. Content included the advantages/disadvantages of hemodialysis (HD), peritoneal dialysis (PD), transplant, and conservative care.

Results: Mean age was 66.58, 58% male, 94% white, 44% had a high school or lower level of education, and 46% had low health literacy. Mean level of understanding increased significantly for all modalities pre-post (2.02 vs. 4.10 for HD, 1.95 vs. 4.14 for PD, 2.35 vs. 4.15 for transplant, and 2.10 vs. 4.12 for conservative management; all p<0.001). Decision preparedness also increased significantly from 2.44 to 3.50 (p<0.001). Improvements were similar regardless of age, gender, educational level, or health literacy. At the end of the class, overall decisional conflict was low (median score 10; IQR 0, 20). Equal proportions of patients preferred HD (24%) or PD (22%), compared with transplant (12%) and conservative management (4%), yet nearly (30%) of patients remained unsure of their decision.

Conclusions: Despite significant improvements in patient understanding and preparedness about renal replacement therapy options, a substantial number of patients remain unsure of their decision after routine predialysis education. Additional decision support interventions may be needed to improve decision-making in advanced CKD patients.
SA-PO166
The Role of Post Biopsy Ultrasound in Predicting Complications After Percutaneous Renal Biopsy of Native Kidneys

Background: The percutaneous renal biopsy (PRB) of native kidneys has been an essential tool in the diagnosis and management of renal diseases. Despite all advances, clinically evident bleeding complications do occur in up to 30% of patients after PRB of native kidneys. Traditionally patients are kept under observation for 24 hours after the procedure. An earlier investigation to anticipate the likelihood of complications will help to reduce the length of stay for these patients and thus the resource burden. Post PRB ultrasound has been studied for this purpose. We conducted a study to evaluate the role of early post PRB ultrasound to predict procedure related complications in our patient population.

Methods: 46 patients undergoing renal biopsy at department of Nephrology, Jinnah Hospital were considered for this study. Renal biopsy was performed using a 16-gauge automatic needle core biopsy needle. After the biopsy, patients were closely monitored in the recovery room and after 1 hour, the biopsied kidney was examined by ultrasound. These patients were admitted and were kept under observation to assess any complications for next 23 hours.

Results: Of these 46 patients, 24 (52%) were males with mean age 39 (16 to 60 years). More than 3 cm hemato ma was seen in 2 (4.3%) patients at 1 hour post biopsy ultrasound scan. Of these 2 patients, only 1 (2%) patient had major complications including hypotension, decrease in hemoglobin etc. Thus 45 (97.8%) patients had uneventful recovery. Sensitivity of more than 3 cm hematoma formation at 1 hour post biopsy in predicting major complications was 100% with specificity of 97.7%.

Conclusions: Our study showed that the frequency of major complications was minimal in patients without >3 cm hematoma formation at one hour post-PRB. Post-PRB ultrasound is a non-invasive, accurate diagnostic tool in predicting procedure related major complications.

SA-PO167
A Multidisciplinary Clinic for Children with Lupus Nephritis (LN) – A Step Towards Personalized Medicine?

Background: Most children with SLE develop LN, which significantly worsens morbidity and mortality. Progression to ESRD occurs in 5-10%. Early diagnosis and treatment improve long-term outcomes, thus prompt evaluation is essential. Therefore, a combined pediatric nephrology/rheumatology clinic (LN Clinic) was started in 2013. The primary aim was to evaluate the number of days between onset of proteinuria (first-um urine p/c <0.2) and performance of a renal biopsy (bx) for SLE patients (pts), pre- and post-establishment of the LN Clinic. We aimed for a 20% reduction in time to renal bx within 2yr of establishment of this clinic. The secondary aim was a reduction of steps in the referral process.

Methods: SLE pts with an outpt renal bx were identified by an EMR query. Pts were selected if a bx was performed within 5yr pre or 16mo post establishment of the LN clinic. Our sample selection was cross-referenced with an established lupus registry. A chart review provided the data of proteinuria onset, disease activity markers, and LN class. Pts diagnosed in the inpt setting were excluded. A process map determined the number of steps occurring between new-onset proteinuria and first evaluation by a nephrologist.

Results: We show that pre LN clinic, the median number of days between onset of proteinuria and renal bx was 51 (IQR=25–83.5d), compared to 34 (IQR=14–48d) post (p=0.057). This is a 33% decrease in time. There was a negative association between amount of proteinuria and days to bx (r=-0.5826, p<0.001). There was no association between hematuria or markers of disease activity and days to bx. There was also no association between LN class and days to bx. Pre LN clinic, a referral required 10 steps, which was reduced to 6.

Conclusions: The LN clinic has resulted in earlier renal bx and fewer steps in the referral process. For pts with proliferative LN, this translates to earlier initiation of treatment and a chance at improved outcome.

SA-PO168
Antidepressant Efficacy and Safety Observations: USRDS ACTIVE-ADIPOSE Study

Background: Although depression is a prominent issue, depression management in advanced CKD and ESRD patients is not well understood. Antidepressant medications are the most frequent therapy, but efficacy and safety data are limited (Hedayati et al. 2012). Most patients in CKD and ESRD populations have very high comorbidities, and while the majority of antidepressants are safe in these patient populations, the proportion non-white and younger than age 65 was higher in the study cohort. Medication efficacy was defined by participants’ scores (<18 vs. 18+) on the Center for Epidemiologic Studies Depression Scale (CES-D) score (Hedayati et al. 2006). Adjusted odds for recent falls observed in association with antidepressant use and CES-D score provided an indicator of safety.

Results: Antidepressants were prescribed for 15% of study participants. 40% of those with prescribed antidepressants had an elevated CES-D score, suggesting lack of drug efficacy. Efficacy did not appear to vary by patients’ age or vintage, but more whites had elevated CES-D scores. Recent falls were more frequent among patients on antidepressants with elevated CES-D score (adjusted odds ratio 2.27 [1.05, 4.90], p=0.04, compared with patients not on antidepressants and CES-D score <18). Fall risk was similar across type of prescribed antidepressant (SSRI, atypical, and tricyclic drugs).

Conclusions: Efficacy of antidepressant medications was unclear for 40% of those with these drugs prescribed, and safety hazard was suggested by increased fall risk. Continued evaluation of nonpharmacologic as well as pharmacologic options for depression management in MHD patients, the focus of a current PCORI trial, is important.

Funding: NIDDK Support

SA-PO169
Sofosbuvir Use in Patients with Hepatitis C Virus Infection and Severe Chronic Kidney Disease

Background: Chronic hepatitis C virus (HCV) infection is a major health problem. The use of new direct acting antiviral (DAA) based regimens has been shown to provide a high sustained virologic response with less adverse reactions compared to interferon–ribavirin regimens. The American Association for Study of Liver Diseases recommends expert consultation on patients with eGFR less than 30 mL/min because safety and efficacy data are not available on these patient populations. We propose that these DAAs are safe to use in patients with advanced kidney disease.

Methods: A total of 23 patients with HCV and estimated glomerular filtration rate (eGFR) less than 45 mL/min were treated with sofosbuvir and simeprevir, dose of sofosbuvir was adjusted to 200 mg PO daily or 400 mg PO every other day for patients with eGFR less than 30 mL/min by Hepatology and Nephrology services. These patients were monitored closely by both services.

Results: A cohort of 23 HCV positive patients had the following descriptive statistics, 20 males (87%) and 3 females (13%). 15 patients had Genotype 1a (65%), 7 patients had Genotype 1b (31%) and 1 patient had Genotype 2b (4%). 3 patients (13%) had End Stage Disease (ESKD) and were on hemodialysis, 9 patients (39%) had Chronic Kidney Disease grade IV (CKD IV - eGFR <30 mL/min) and 11 patients (48%) had Chronic Kidney Disease grade IIIIB (CKD IIIIB - eGFR <45 mL/min). The HCV viral load of the 23 patients (100%) had a statistically significant decrease as the therapy progressed through completion with a statistically significant text with a p < 0.05. No side effects were present on the patients during DAA therapy. Patients with CKD grades IIIIB and IV on DAA treatment had a preserved kidney function by the end of therapy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Sofosbuvir is safe and effective in patients with Hepatitis C Virus infection who have Severe Chronic Kidney Disease, conferred by chronic kidney disease, not being treated by Hepatology and nephrology in operation due to the lack of data in safety and efficacy.

SA-POI70

Enoxaparin as Bridging Therapy in Veterans with Advanced Kidney Disease


Background: Patients with CrCl < 30 mL/min on anticoagulation require temporary bridging with heparin. Low molecular weight heparins (LMWH) have longer half-lives and predictable anticoagulant effect but require anti-Xa monitoring in CKD. This study aims to evaluate the safety and efficacy of low molecular weight heparins in bridging therapy in patients with CrCl < 30 mL/min.

Methods: A retrospective study was conducted from Jan 1, 2012 to Dec 1, 2014. Patients with CrCl < 30 mL/min, received enoxaparin 1 mg/kg/d as a bridge therapy to warfarin, and had at least one anti-Xa level checked were included in the study. Patients were excluded if they had major bleeding or thromboembolism in previous 3 months before enoxaparin, history of bleeding disorders, or used enoxaparin for other indications. A dosing nomogram was used to guide dosage adjustment to keep anti-Xa levels within the target range (0.5-1.0 mcg/mL). The primary outcomes are 0 of minor/major bleeds and thromboembolic events. The proportion of anti-Xa levels within goal range was assessed.

Results: 12 patients met inclusion and exclusion criteria. The mean age was 62.4 ± 11.9 years, 91.7% were male, 58% were diabetic and 46% had congestive heart failure. 50% were on both warfarin and aspirin. The median treatment duration of enoxaparin was 11.4 ± 4.6 days, the average daily dose was 17.6 ± 4.5 mg/day. A total of 19 anti-Xa levels were included for analysis. There were 2 (16.7%) bleeding events, 1 (8.3%) major and 1 (8.3%) minor bleed. None of the patients developed thromboembolic complications. The most common adverse event was bruising at the injection site that did not lead to any early discontinuation of therapy. Seventeen of the anti-Xa levels (89.4%) were in the target range.

Conclusions: Majority (83.3%) of patients had minimal or no adverse events and none with thromboembolic outcomes. In patients with bleeds, no correlation was seen with the anti-Xa levels. The dosing protocol is effective, with 89.4% of anti-Xa levels within goal range. The results of this study support the safety and efficacy of the enoxaparin dosing protocol as a bridge therapy perioperatively in patients with CKD.

Funding: Veterans Administration Support

SA-POI71

Thiopurine Methyltransferase (TPMT) Genotyping to Predict Myelosuppression Risk in Chinese Patients with Nephropathy

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Background: Pharmacogenetic study in nephritis is mainly focused on genes involved in the metabolism of Azathioprine (AZA). Use of AZA is limited by its toxicity. Variants in the Thiopurine S-methyltransferase (TPMT) have been associated with AZA toxicity. The aim of this study was to determine the contribution of TPMT variants in the development of AZA-related myelosuppression in Chinese patients with nephropathy.

Methods: Variants associated with the decrease of enzymeactivity in TPMT genes were genotypedin 4 nephritis patients treated with AZA, and correlated with the clinical response and development of adverse drug reactions in a retrospective case-control study. Three common mutation alleles of TPMT [TPMT* 3A (G460A/A719G), TPMT* 3B (G460A), TPMT* 3C (A719G)] were detected by polymerase chain reaction-high resolution melting and sequencing in 12 patients, included 4 patients with myelotoxicity and 8 patients without myelotoxicity.

Results: Genotypic analysis showed only one of the 4 patients with myelotoxicity was detected TPMT *3C polymorphisms, no TPMT*2, *3A, *3B or *3C polymorphisms were detected in any of the 11 patients.

Conclusions: Single-nucleotide polymorphisms of TPMT could not explain the azathioprine-related adverse events.

SA-POI72

Lanthanum Carbonate-Induced Granulomatous Gastritis

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Background: Long-standing non-calcium based phosphate binders administration has been recently associated with a number of different gastrointestinal lesions. We describe a rare case of lanthanum carbonate-induced granulomatous gastritis.

Methods: A 58-year-old woman was admitted to our hospital because of nausea, vomiting, progressive weight loss. Because of a well-known stage 5 chronic kidney disease, she was started on peritoneal dialysis. About one month later, CAPD was well-tolerated with an adequate dialysis dose. Nevertheless, she continued to complain of nausea, vomiting and dyspepsia. A gastroscopy revealed chronic gastritis with superficial erosions and an histopathology consisting of non-necrotizing, sarcoid-like granulomas with aggregates of multinucleated giant cells. Orange cristalloid material was seen within granulomas. Special stains for fungi and mycobacteria were negative. Her previous medical history was only significant for hypertension and type 2 diabetes mellitus. Physical examination was unremarkable. A chest X-ray was normal. A tubercolin skin test was negative. ANCA titres was negative and serum angiotensin converting enzyme (ACE) level was in the laboratory reference range. At the time of our evaluation, she had been receiving lanthanum carbonate 1 g bid for about 6 months.

Conclusions: At the best of our knowledge, so far, only 7 cases have been described in the literature.

None.

The histopathologic picture in our patient was compatible with a lanthanum carbonate-induced gastritis with some peculiar characteristics: a granulomatous reaction and the appearance of lanthanum carbonate crystals not only within histiocytes/multinucleated giant cells but also inside the cytoplasm of the epithelial glandular cells.

SA-POI73

Relative Incidence of Adverse Events with Ferumoxytol versus Other Intravenous Iron Products in Non-Dialysis-Dependent Chronic Kidney Disease

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Background: All intravenous (IV) iron products confer risk of hypersensitivity reaction (HSR). The relative safety of ferumoxytol versus other IV iron products is not established. We used Medicare claims to assess relative safety of ferumoxytol versus other IV iron products in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.

Methods: We analyzed a 20% sample of Medicare Parts A and B claims in 2009-2012. Patients received a first dose of IV iron between Jan 1, 2010, and Nov 30, 2012, and had diagnosed NDD-CKD without IV iron treatment during the 1 year before first dose. For each ferumoxytol user, we identified 1 propensity score-matched control who used another IV iron product; the score included demographics, comorbidity, and concomitant IV medication. Patients were followed until change in IV iron product, end stage renal disease, death, or Dec 15, 2012. With Cox regression stratified by matched pair and cumulative number of prior IV iron doses, we assessed relative incidence of anaphylaxis, HSR symptoms, hypotension, death to permit comparisons. However, after first dose, hazard ratios (ferumoxytol users vs. matched controls) were 0.90 (95% confidence interval, 0.80-1.01) for HSR symptoms, 1.06 (0.66-1.72) for hypotension, 0.72 (0.55-0.94) for ER visit, and 0.78 (0.60-1.02) for hospitalization, and death within 1 day of first dose and within 1 day of each subsequent dose.

Results: We identified 7358 ferumoxytol users and 7358 matched controls. Baseline characteristics were balanced across groups. There were too few cases of anaphylaxis and death to permit comparisons. However, after first dose, hazard ratios (ferumoxytol users vs. matched controls) were 0.90 (95% confidence interval, 0.80-1.01) for HSR symptoms, 1.06 (0.66-1.72) for hypotension, 0.72 (0.55-0.94) for ER visit, and 0.78 (0.60-1.02) for hospitalization. After subsequent doses, corresponding hazard ratios were 1.07 (0.90-1.27) for HSR symptoms, 0.91 (0.50-1.67) for hypotension, and 0.86 (0.64-1.15) for ER visit, and 0.97 (0.70-1.35) for hospitalization.

Conclusions: Relative to other IV iron products, ferumoxytol was not associated with excess risk of adverse events in NDD-CKD patients, following both first dose and subsequent doses. The incidence of anaphylaxis and death was very low in ferumoxytol users and matched controls.

SA-POI74

Efficacy, Safety and Pill Burden of Sucroferric Oxysulphide, an Iron-Based Phosphate Binder, Over 52 Weeks in African American Dialysis Patients

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Background: A post hoc analysis of data from a randomized, open-label, Phase 3 study and its extension investigated the efficacy and safety of the iron-based phosphate binder sucroferric oxyhdsulphide (SFOH; VELPHORO®) vs sevelamer carbonate (SEV; Renvela®) in African American dialysis patients.

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

Underline represents presenting author.

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Methods: Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/day; n=710) or SEV (2.4–14.4 g/day; n=349) for 12 weeks’ dose titration then 12 weeks’ maintenance. Eligible patients enrolled in a 28-week extension study.

Results: Of the 549 patients who completed the extension study, 100 were African American patients, equally distributed between the treatment groups despite the 2:1 randomization (n=48, SFOH; n=52, SEV). Serum phosphorus decreased rapidly and to a similar extent with SFOH and SEV, and remained relatively constant thereafter (Table). Mean ± standard deviation number of tablets/day was lower for SFOH (3.4 ± 1.35) vs SEV (7.6 ± 2.92) over 52 weeks. The incidence of serious or severe treatment emergent adverse events and deaths were similar in both treatment groups. Gastrointestinal-related disorders were the most frequently observed adverse events for SFOH and SEV.

Conclusions: SFOH efficacy was maintained long-term, with a lower pill burden than SEV and similar safety profile, in African American dialysis patients. "Post hoc results reflect those from the overall study population.

<table>
<thead>
<tr>
<th>Table: Treatment efficacy and safety in African American patients.</th>
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</thead>
<tbody>
<tr>
<td><strong>Efficacy (complete set; N=100)</strong></td>
</tr>
<tr>
<td>Phosphorus, mg/dL*</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Δ at Week 12</td>
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<tr>
<td>Δ at Week 24</td>
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<tr>
<td>Δ at Week 52</td>
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</tbody>
</table>

Safety parameters (safety set; N=205), %
- Withdrawal due to AEs: 18.5 ± 8.0
- Severe AEs: 14.6 ± 20.0
- Serious AEs: 27.7 ± 30.7
- Deaths: 3.1 ± 2.7
- Anaemia: 1.5 ± 9.3
- Hyperparathyroidism: 9.2 ± 14.7
- Gastrointestinal-related adverse events: 43.1 ± 44.0
- Darrine: 15.4 ± 10.7
- Discolored lesions: 13.8 ± 11.3
- Nausea: 9.2 ± 14.7
- Vomiting: 6.9 ± 9.3
- Constipation: 3.8 ± 7.8

*N= standard deviation, serum levels, AEs, adverse events; SEV, sevelamer carbonate; SFOH, sucroferic oxyhydroxide.

Funding: Pharmaceutical Company Support - Vifor Pharma

SA-PO175

Intergated Dialysis Unit Module and Module Compartment Structure

Stanley Shao-Ying Lee,1 Ming-cheng Wang,2 Chi-Hsien Hemodialysis Center; Taiwan; 1College of Medicine, National Cheng Kung Univ, Tainan, Taiwan.

Background: Conventional set-up of hemodialysis (HD) center requires intensive manpower and tedious workload due to the intricate fluid and electricity layouts, and the fixed partitions structure. It is vital to design an integrated module considering rapid manpower and tedious workload due to the intricate fluid and electricity layouts, and the fixed partitions structure. It is vital to design an integrated module considering rapid

Methods: The Integrated Dialysis Partition System was designed for HD center. To ensure patient privacy, an easy-assembled partitions with a herringbone seating arrangement and illness intrusiveness. The integrated dialysis unit module allows for rapid assembly, easy pipeline maintenance, and improved patients’ quality of life.

SA-PO176

Safety and Adherence in End Stage Renal Disease Patients on Chronic Hemodialysis


Background: Missed hemodialysis and abbreviated hemodialysis sessions are common in end stage renal disease patients on maintenance hemodialysis. Missed dialysis is associated with increased mortality and morbidity in chronic hemodialysis patients. Our quality assessment performance improvement data revealed that on an average 15% of patients missed and abbreviated hemodialysis (HD) sessions over a period of 6 months.

Methods: We evaluated patients’ perception about missed and abbreviated sessions, and safety during HD sessions at our dialysis center. A questionnaire regarding patients’ views about missed, abbreviated and safe hemodialysis sessions using a visual analog scale (0-100 mm, where 0 means ‘No’ and 100 means ‘Yes’) was conducted in-person by a nephrology fellow or a social worker on all HD patients. Data are presented as mean ± SD.

Results: Ninety patients participated in the survey. Sixty eight (75.6%) patients with a mean score of 78±29.6 felt like coming for their HD sessions during the last one month. Fifteen of 89 (16.9%) (mean score 94.5 ± 17.3) felt safe during the HD sessions. Seventeen (18.9%) patients indicated missing the HD sessions. Thirty six of 83 (43.4%) patients with a mean score of 71 ± 37.6 wanted to miss HD sessions during the last one month. Fifteen of 89 (16.9%) signed against medical advice for the abbreviated HD sessions during the last one month.

Conclusions: Data suggest that safety of HD sessions does not appear to be a factor for missing HD sessions. Lack of patients’ understanding of importance of HD-treatments as well as lack of adherence likely leads to non-adherence and abbreviation to HD sessions. The safety of HD treatment was not the core issue behind increasing patients’ absenteeism. Active patients’ participation and individualization of HD sessions may improve adherence to HD sessions.

SA-PO177

Validation of a Tool to Assess Nursing Workload in Hemodialysis

Clara Bohm,1 Brett M. Hiebert,2 Joe A. Buett,1 Jan Schneider.2 1Univ of Manitoba; 2Winnipeg Regional Health Authority.

Background: Patient classification scales (PCS) to assess nursing workload predict staffing needs and facilitate transparency in assignments resulting in improved work environment, patient safety and quality of care. Few validated PCS tools exist for hemodialysis (HD). This study validates a point-of-care PCS developed for in-centre HD at a Canadian tertiary care centre.

Methods: Using LEAN framework, from Sept 1, 2013 to Mar 1, 2014 at the Health Sciences Centre in Winnipeg, Canada, iterative consultations with stakeholders resulted in creation of a PCS consisting of 9 domains and 67 subdomains. At each HD session between April 7-21, 2014, bedside HD nurses completed both a visual analogue scale (VAS), which assessed general level of nursing care required, and the PCS tool. Karnofsky scale and time-series studies were completed in 50 and 28 randomly selected HD patients, respectively. Analysis: Internal consistency and reliability were assessed using Cronbach’s alpha and Intraclass Correlation Coefficient (ICC), respectively. Multi-trait multi-method analysis (MTMM) determined item homogeneity. Spearman’s correlation of PCS with VAS, Karnofsky Score and time-series studies assessed criterion and predictive validity. Linear regression was performed to determine the association of each subdomain with PCS score.

Conclusions: Preliminary results suggest excellent reliability and validity of this PCS tool. Validation studies at other HD centres with expanded time-series and reliability studies continue.
SA-PO178
Feasibility of a Hemodialysis Safety Checklist for Nurses and Patients
Samuel A. Silver, Alison Thomas, Andrea Rathe, Pamela L. Robinson, Ron Wald, Chaim Bell, Ziv Harel, Nephrology, St. Michael’s Hosp, Toronto, ON, Canada; Medicine, Mt. Sinai Hosp, Toronto, ON, Canada.

Background: In 4% of ESRD patient deaths, the cause of death is a result of a preventable hemodialysis complication. These include errors related to communication, organization and human factors. We recently developed a hemodialysis safety checklist (Hemo Pause) to be completed by nurses and patients at specified intervals throughout a hemodialysis session, with the goal to improve dialysis unit safety culture. Our objective was to determine the feasibility of using Hemo Pause during every hemodialysis session for 3 months.

Methods: We conducted a single center, prospective time series study. A convenience sample of 14 nurses and 22 prevalent in-center hemodialysis patients participated. All participants were trained in the administration of Hemo Pause, completed the checklist at every hemodialysis session for 3 months and were free to suggest checklist modifications consistent with quality improvement methodology. The primary outcome was Hemo Pause completion, which was determined weekly using the percentage of checklists in the patient chart with all 17 items assessed. We also measured Hemo Pause acceptability using local patient safety surveys.

Results: There were 799 hemodialysis treatments pre-intervention and 757 post-intervention. The checklist was completed for 556 of 757 (73%) treatments. The most common reasons for non-completion were the availability of nursing staff trained in Hemo Pause and patient admission to hospital. Among hemodialysis nurses, 93% (15/14) agreed that Hemo Pause was easy to use and 79% (11/14) agreed it should be expanded to other patients. Among hemodialysis patients, 73% (16/22) agreed that Hemo Pause made them feel safer and should be expanded to other patients. Negative comments by nurses or patients occurred on 4% (7/200) of survey responses.

Conclusions: A hemodialysis safety checklist (Hemo Pause) was acceptable to both nurses and patients over a 3 month period. Our next step is to spread Hemo Pause locally, based on the results of this study. We are conducting a randomized controlled trial to evaluate the effects of Hemo Pause on patient safety outcomes.

Funding: Government Support - Non-U.S.

SA-PO179
Community-Based Parenteral Anti-Infective Therapy (COPAT) for ESRD Patients
Evamaria Anvari, Reza Anvari, Laura Fevereira Provenzano, Juan C. Calle, Nephrology, Cleveland Clinic Foundation, Cleveland, OH.

Background: Infections are the leading cause of hospital admissions for patients with ESRD. The majority will need to continue antimicrobial therapy when discharged. Community-based parenteral anti-infective therapy (COPAT) refers to the practice of administering antimicrobial therapy in the outpatient setting. It requires a multidisciplinary and the goals are to improve outcomes, reduce toxicity, drug resistance, and decrease hospital stay. ESRD patients have the advantage that IV antibiotics can be given at their dialysis units. The downfall is that every outpatient dialysis provider has their own policies for the approval of IV/TP therapy. Patients are frequently discharged with an order to continue antimicrobial therapy but it is not continued, leading to adverse outcomes.

Methods: We investigated the policies from the main dialysis providers in our community.

<table>
<thead>
<tr>
<th>Fresenius Medical Care</th>
<th>Davita</th>
<th>Centers for Dialysis Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV/P drugs in unit</td>
<td>Vancomycin, Cefazidine, Cefazolin, Gentamicyn</td>
<td>Vancomycin, Cefazidine, Cefazolin, Gentamicyn</td>
</tr>
<tr>
<td>IV/P drugs in formulation</td>
<td>Amikacin, Tobramycin, Ceftriazone, Cefepine, Meropenox, Daptomycin, Aztreonam, Ampicillin, Levofloxacin, Amphotericin B, Fluconozol, Gancidovin, Gentamicyn</td>
<td>Any other antimicrobial drug will be approved</td>
</tr>
</tbody>
</table>

Time for drug arrival: 24-48 hrs. - Pre-approval 24-48 hrs. - Day after approval 48 hrs.

Requirement: Hospital order - ID consult - Organism with sensitivity - Rational for using other antimicrobial

IP drugs: Receive in unit - Loading dose in unit and continue self-administer - Drugs ordered Monday - Thursday will arrive at their home the following day - If ordered after 3PM Friday it will arrive Monday - Loading dose in the unit and are given a 7-day supply to self-administer

Home Hemo: Dialize in center for therapy - Dialize in center for therapy or trained to self-administer - Dialize in center for therapy

Conclusions: Our data suggest there are characteristics amongst patients undergoing inpatient hemodialysis that predispose them to RR/CA events. Simple, objective measures such as requirement for supplemental oxygen and abnormal vital signs may be important indicators that patients are at risk for serious adverse events. Knowledge of these factors can aid in decision-making regarding pursuit of dialysis and lead to the study of strategies to prevent patient harm.

SA-PO180
Rapid Response and Cardiac Arrests in In-Patient Hemodialysis - A Retrospective Review
Justin Chon, LaDun Golestan, Albert Einstein College of Medicine, Bronx, NY; Nephrology, Montefiore Medical Center, Bronx, NY; Critical Care, Montefiore Medical Center, Bronx, NY.

Background: Patients with renal dysfunction requiring hemodialysis are known to be at increased mortality and morbidity risk. Few studies have examined rapid response (RR) and cardiac arrest (CA) events in inpatient hemodialysis units. The purpose of this study is to evaluate patient characteristics and predictive factors of RR and CA in inpatient hemodialysis units.

Methods: Retrospective review of all available RR and CA events in two separate hospitals over a 3-year period was performed. Charts were reviewed for abnormalities in vital signs or laboratory values during hemodialysis sessions and for a 24-hour period prior to RR/CA events.

Results: In total, 16 RR and 13 CA events were recorded for 26 unique patients (average age 64±16 years). Of the 29 total RR/CA events, 9 events resulted in survival (<24 hours 31%). Common medical comorbidities included hypertension (92%), diabetes (73%), chronic heart failure (50%), and coronary artery disease (50%). The most common inciting factors for RR/CA activation were altered mental status (72%), systolic blood pressure < 90 (45%), and respiratory distress (31%). Vital sign abnormalities identified prior to hemodialysis included need for supplemental oxygen (72%), respiratory rate > 20 (34%), and systolic blood pressure < 90 (3%). Vital sign abnormalities identified during hemodialysis included systolic blood pressure < 90 (38%) and heart rate < 40 (35%). Of those with labs available, the most common lab abnormalities included low hemoglobin and hematocrit (100%), elevated direct bilirubin (71%), elevated troponin-T (62.5%), and elevated PT (60%).

Conclusions: Our data suggest there are characteristics amongst patients undergoing inpatient hemodialysis that predispose them to RR/CA events. Simple, objective measures such as requirement for supplemental oxygen and abnormal vital signs may be important indicators that patients are at risk for serious adverse events. Knowledge of these factors can aid in decision-making regarding pursuit of dialysis and lead to the study of strategies to prevent patient harm.

SA-PO181
Monitoring of Protective Levels of Hepatitis B Antibody Titre in Pre-Dialysis and Dialysis Patients
Ravindra Mukundra, Zaha Jibrit, Renal Medicine, Doncaster and Bassetlaw NHS Foundation Trust, Doncaster, Yorkshire, United Kingdom.

Background: Patients on dialysis are at risk of hepatitis B virus infection. Hence it is widely recommended to vaccinate chronic kidney disease (CKD) patients who might need renal replacement therapy. Antibody titre of >10iu/L is generally regarded as protective against Hepatitis B infection. The frequency of antibody level monitoring remains unclear. Once adequate antibody response achieved levels would wane with time. We monitored antibody levels in pre-dialysis and dialysis patients who achieved antibody response of >10iu/L, yearly for 2 years in order to explore the sustainability of the levels.

Methods: We selected 112 predialysis and dialysis patients who had Hepatitis B antibody response of >100 iu/L, and has had antibody titres checked subsequently every 2 consecutive years. Results analysed retrospectively to see how long the protective antibody level lasted.

Results: Total number of patients who had antibody response of >100 iu/L from 2007 to 2015 was 112 from our dataset at Doncaster Royal Infirmary Renal Unit. Of these 34% of patients had hepatitis B antibody titres checked for 2 consecutive years. Patients maintaining antibody level of atleast >100 iu/L for 2 years or more were 95% (36 of the 38).

Conclusions: The outcome of this study confirms that protective antibody levels (>100 iu/L) are maintained in 95% of those monitored for 2 years. This result reiterates the need for more robust evidence to inform nephrologists about the appropriate frequency of antibody monitoring in CKD patients.

SA-PO182
Improving Emergency Room (ER) to Dialysis Flow in a Busy Inner City ER
Anjali Acharya, Cheryl Moore, Raymond Mc Clinton, Naheed Ansari, Bonnie Carnes, Nephrology, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY; Nephrology, Atlantic Dialysis, Queens, NY.

Background: Delays in access to hemodialysis during hospitalization are not uncommon and negatively impact on quality of patient care and lead to avoidable complications and unnecessary hospitalizations. Triple Aim is a sought after goal for health organizations to optimize health system performance. We hoped to target one of the three components which is to improve the experience of care.

Methods: The objective was to ensure initiation of dialysis for all non-emergent patients within four hours of ER triage. We analyzed retrospectively in a 8 week observation period, Electronic Medical Record (EMR) data on all hemodialysis patients >18 years of age presenting to the ER, with emphasis on time from triage to initiation of dialysis (TID). We also analyzed factors contributing to delays in dialysis initiation. Data were collected daily on each patient and tabulated weekly. We instituted two measures to address the obstacles.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
These were i) educating the ER staff about timeliness of informing the renal team and ii) the second was to institute a track & trace system to systematically gather detailed data on patient transport metrics such a time to patient pick up from initial contact with the transport office. 

Results: Baseline data revealed average TID from triage was 8 hours. Two major contributory factors identified were late notification by ER to renal team and delays in transport. By instituting measures targeting these, we were able to achieve being able to provide dialysis within 4 hours of triage in over 80% of our non-urgent hemodialysis patients.

Conclusions: We were able to improve the patient experience and care with simple measures. This has a positive impact on patient safety by minimizing late treatments and staff fatigue. Though Triple Aim is a goal at the population and health care delivery level, we believe processes can be implemented at a local level that align with the CMS goals of triple aim. In today’s environment it is incumbent upon us to make efforts to innovate for better patient care and to minimize health care costs.

SA-PO183

Quality Improvement Project in Dialysis: Improving Access to Dialysis for Patients Presenting to the Emergency Room (ER) 

1Nephrology, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY; 2Nephrology, Atlantic Dialysis, Queens, NY.

Background: Hemodialysis patients presenting to the emergency room are a vulnerable patient population. Majority of them have significant comorbid conditions. Delays in evaluation and institution of dialysis are common in busy emergency rooms. We undertook a project to improve quality of patient care as well as the patient experience with a goal to provide timely dialysis.

Methods: We analyzed baseline data from electronic medical record (EMR) pertaining to all hemodialysis patients presenting to the ER in a specified 8 week period. After brain storming within the team we identified a few factors that were seen as obstacles in providing timely dialysis. One of them was the time from patient triage to notification of the renal team. We instituted an educational program with the ER staff with focus on the timeliness of informing the renal team, establishing “triage to renal team notification time” of less than 30 minutes as a meaningful metric. Data was collected at pre and post intervention. The objective was to meet this goal >80% of the time over the 2 month intervention period.

Results: There was a positive impact on the triage to renal notification time. The percentage of timely notifications as defined, rose to >85% from a baseline of <25% and this effect was sustained over the 8 weeks. Most patient notifications happened within 10 minutes of triage.

Conclusions: A simple intervention on educating the ER staff made a significant impact on timely evaluation of dialysis patients presenting to the ER. There was an observable positive impact on patient experience. We view this as a simple first step in optimizing patient care and experience towards a seamless journey through the hospitalization. Simple innovative steps such as this could contribute to cost control by avoiding/minimizing dialysis treatments during off hours. In addition it could help mitigate staff fatigue and treatment errors thus improving patient safety.

SA-PO184

Diagnostic Reference Values for Cerebrospinal Fluid May Not Be Useful in Haemodialysis Patients Suspected of Having Central Nervous System Infection 

Thomas Oates, Damien Ashby. Imperial NHS Trust, London, United Kingdom.

Background: Invasive investigations in haemodialysis (HD) patients can be associated with complications due to bleeding, and standard diagnostic tests, such as pleural fluid biochemistry, have been shown to be of limited value in this patient group. As a result, we examined the utility of cerebrospinal fluid (CSF) analysis in HD patients suspected of central nervous system (CNS) infection.

Methods: We used electronic records to retrospectively examine laboratory data from HD patients who had CSF analysis in a 5 year period. All patients were initially suspected of having a CNS infection. Relevant culture and polymerase chain reaction tests ultimately proved negative for bacterial, mycobacterial, fungal or viral infections in all cases.

Results: 30 CSF samples from 29 patients were identified in the study period. CSF protein concentration was available for 16 samples (median 0.40g/L, range 0.19-1.06g/L, corrected for number of red cells in sample) and paired CSF and plasma glucose concentrations, allowing calculation of CSF:serum glucose ratio, for 25 samples (median ratio 0.58, range 0.21-1.40). Using the accepted normal CSF protein concentration of 0.23 to 0.38 g/L (see Figure shaded region), 8 out of 16 samples showed an elevated protein concentration suggesting CNS infection. Additionally, 13 out of 25 samples had a CSF:serum glucose ratio of less than the normal value of 0.6 (see Figure horizontal line) which is also suggestive of CNS infection.

Conclusions: CSF biochemistry is frequently used in the diagnosis of CNS infection. Our preliminary results suggest CSF protein and glucose concentrations should be interpreted with caution in HD patients and may not add diagnostic information in suspected CNS infection. We are currently investigating the hypothesis that CSF biochemistry may be influenced by duration of chronic kidney disease and HD vintage.

Funding: Clinical Revenue Support

SA-PO185

Continuous Renal Replacement Therapy (CRRT) and Hypoglycemia: A Retrospective Study on Patients Undergoing CRRT and Development of Hypoglycemia in Diabetic and Non-Diabetic Individuals 

Mamtha Balla,1 Adam Lyons,1 Mary C. Naglak,1 Doron Schneider,1 Robert A. Sirota.1 1Internal Medicine, Abington Jefferson Health, Willow Grove, PA; 2HTN Nephrology Associates, Abington Jefferson Health, Willow Grove, PA.

Background: Hypoglycemia is a little known complication of CRRT. There are no studies available to evaluate the prevalence or intensity of hypoglycemia during CRRT. This study attempts to determine the frequency, timing, and severity of hypoglycemia as a complication of CRRT in diabetic and non-diabetic patients in the intensive care unit.

Methods: This was a retrospective observational study to assess the effect of CRRT on plasma glucose in diabetic and non-diabetic individuals who were admitted to Abington Jefferson Health. A chart review was used to complete a detailed data collection form for patients who underwent CRRT for several diagnosis (sepsis, medication overdose, acute renal failure) in 2013 and 2014 who met the selection criteria. Hypoglycemia is defined as Blood sugar less than 70mg/dL. Dialysate contained 100mg/dL glucose.

Results: After reviewing the charts for 218 CRRT events in 119 patients admitted to Abington Jefferson Health, 100 patients were studied based on selection criteria. The mean age of the study population was 66.3 + 15.3 years. Thirty-six of the 100 patients studied had hypoglycemia during CRRT. The number of episodes was as follows: 14/36 (38.9%) had one episode, 7/36 (19.4%) had two, 7/36 (19.4%) had three and 5/36 (13.9%) had five episodes (mean number of episodes was 2.7±1.9). Hypoglycemia occurred on average 9.9±6.1 hours from start of CRRT. Patients who had hypoglycemia during CRRT were more likely to have it again after CRRT (53%; 19/36) (p<0.0005). Of the 36 patients with hypoglycemia, 78% (28/36) had sepsis vs. 22% (8/36) who did not have sepsis but had hypoglycemia (p<0.05). No association was found between development of hypoglycemia and history of diabetes and CKD.

Conclusions: Our study showed that hypoglycemia is a frequent complication during CRRT. In order to prevent hypoglycemia from being under-recognized protocols including frequent blood glucose monitoring during CRRT should be in place.

SA-PO186

The Safety of Intravenous Hydration for the Prevention of Contrast Induced Nephropathy 

Yvonne R.P. de Wael,1 Corinne E.A. Balemans,2 Marc A.G.J. Ten Dam,2 Louis J.M. Reichert,2 Jack P. Wetzel.1 1Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2Nephrology, Canisius Wilhelmina Hospital, Nijmegen, Netherlands; 3Nephrology, Rijnstate Hospital, Arnhem, Netherlands.

Background: Contrast-induced nephropathy (CIN) is associated with marked morbidity and mortality. To prevent CIN, current guidelines advise intravenous hydration in high risk patients. Thus far, the possible side effects of hydration have received little attention. We evaluated the incidence of (serious) adverse events (SAEs) after intravenous hydration.

Methods: In a retrospective study we analyzed the incidence of (SAE) after intravenous hydration in two Dutch hospitals. In one hospital (Rijnstate Hospital Arnhem) we evaluated all AEs related to hydration. In the other hospital (CZW Nijmegen) the analysis was limited to SAEs, i.e. those necessitating prolonged hospital stay. Patient and outcome characteristics were retrieved from the hospital records.

Results: In the Rijnstate Hospital Arnhem we evaluated 232 records of patients hydrated in the period from February till July 2013. AEs occurred in 18 patients (8%). The most common AE was overhydration, which occurred in 11 patients (5%) and necessitated
Prolonged hospitalisation in 4 (2%). Admission to the coronary care unit was needed in one patient. Almost all patients with overhydration (91%) had pre-existent cardiac disease and used diuretics. Infusion related AEs also occurred, like extravasation and phlebitis, in one case leading to S. Aureus bacteremia. In the CWZ, Nijmegen we evaluated 257 medical records of patients hydrated from May 2013 till January 2014. Prolonged hospitalisation due to overhydration was necessary in 10 patients (4%).

Conclusions: Our study demonstrates that overhydration is a common adverse event after intravenous hydration and necessitates prolonged hospital stay in 2-4% of patients. This data provide arguments against routine hydration in patients with moderate increased risk of CIN. Patients with pre-existent cardiac disease are more prone to overhydration. However, these patients are also at highest risk for the development of CIN. Risk and benefits must be weighed when choosing strategies to prevent CIN.

SA-PO187

Cystatin C in Predicting Cardiorenal Syndrome Type 1 and Mortality in Patients with Acutely Decompensated Heart Failure with Preserved Renal Function

Carlos Federico Varela,1 Ivan Constantin,2 Gustavo Cristian Greloni,1 Griselda Bratti,1 German Barrera Hugalde,1 Cesar Belziti,2 Rodolfo Pizarro,2 Guillermo Javier Rosa diez,1 1Nephrology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; 2Cardiology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background: Cardiorenal Syndrome type 1 (CRS 1) is defined as a worsening renal function that complicates acutely decompensated heart failure (ADHF). These patients experience higher mortality and morbidity. Serum creatinine (SC) is slow to reflect changes in kidney function. Cystatin C (CysC) has emerged as a novel biomarker with a stronger correlation with cardiovascular disease than SC. The aim of our study was to evaluate CysC in predicting CRS 1 and outcomes in patients admitted with ADHF and preserved renal function.

Methods: We conducted an observational and prospective study. We included patients above 18-years old with ADHF with preserved renal function defined as a SC below 1.3 mg/dL. We excluded patients with heart valvular disease and acute coronary syndrome. CysC blood samples were collected on admission. We defined CRS 1 as a rise in creatinine by 0.3 mg/dL or more during five days.

Results: 166 patients aged 85 median (IQR 77-89) years old were enrolled. The incidence of CRS 1 was 29.7%, with an in-hospital mortality of 3.1% and a total mortality (TM) of 24.4%. The median follow-up was 193 days. CysC was significantly higher in patients with CRS 1 compared to those without (1.72±0.58 vs 1.51±0.41, p=0.03) and predict TM but did not predict in-patient mortality (1.69: vs 1.57±0.48, p=0.58) or readmission (1.47±0.4 vs 1.6±0.5, p=0.58). In the multivariable analysis Cys C was an independent predictor of mortality (OR 3.31, IC 1.38-7.93) while SC at admission was not (OR 0.48, IC 0.05-3.48). The area under the receiver-operating characteristic curve of Cys C for CRS 1 was 0.60 and for TM was 0.65. The best cutoff value was 1.6 mg/dL for both end points. It had a sensitivity and specificity of 62.1% and 63.2% for CRS 1 and 61.5% and 62.9% for TM, respectively.

Conclusions: Above a cut-off value of 1.6 mg/dL, Cys C predicts CRS 1 and mortality in patients admitted with ADHF with preserved renal function.

SA-PO188

Is Cystatin C a Better Biomarker of AKI in ICU to Compare NGAL?

Itir Yegenaga, Fatih Kamis. Internal Medicine, Kocaeli Univ Medical School, Kocaeli, Izmit, Turkey.

Background: Serum creatinine levels can be affected with many variable factors. We concluded that better bio-marker is needed to recognize AKI as early as possible. We studied Cystatin C (CysC) and Neutrophil Gelatinase Associated Lipocalin (NGAL) in ICU patients to determine which is more predictable.

Methods: Hundred and eighty three (85 male; mean age: 65) critically ill patient with no previous chronic renal failure history were included to this study. Clinical, laboratory evaluations were noted and blood was taken in 48 hours for CysC and NGAL and followed for 7 days, if they met the RIFLE criteria.

Results: CysC and NGAL values for every stages RIFLE and serum CysC value were significantly different (p<0.001). Sensitivity, specificity, PPV and NPV were higher for CysC than for NGAL. ROC curve analysis showed that CysC had a stronger correlation with cardiovascular disease than SC. The area under the receiver-operating characteristic curve of Cys C for CRS 1 was 0.75 and for TM was 0.80. The best cutoff value was 1.6 mg/dL for both end points. It had a sensitivity and specificity of 62.1% and 63.2% for CRS 1 and 61.5% and 62.9% for TM, respectively.

Conclusions: Above a cut-off value of 1.6 mg/dL, Cys C predicts CRS 1 and mortality in patients admitted with ADHF with preserved renal function.

While NGAL and u NGAL were significantly different between these two groups. Serum CysC level was related to mortality (figure 1) [AUC-ROC 0.68 CI, 0.573-0.733].

SA-PO189

The Effect of Point of Care (POC) Creatinine/eGFR Measurement on the Incidence of Contrast-Induced Acute Kidney Injury (CI-AKI) following Primary Percutaneous Coronary Intervention (PPCI) for the Treatment of ST Elevation Myocardial Infarction (STEMI)


Background: Contrast-induced acute kidney injury (CI-AKI) is a predictor of mortality, morbidity and length of hospital stay. During STEMI treatment with primary percutaneous coronary intervention (PPCI) there are a number of predictors of AKI including existing renal dysfunction (eGFR < 60) and contrast volume used.

Methods: A retrospective audit over 6 months at the Essex Cardiothoracic Centre identified 348 patients who had presented with STEMI and had PPCI. These patients formed the standard care control group. Prospectively 131 consecutive patients presenting with STEMI and under-going PPCI had a point of care creatinine measurement (STATSENSOR, Nova Biomedical). A comparison in rates of AKI was made between the two groups.

Results: In the standard care group, 9.7% of patients with normal renal function and 26.6% of patients with impaired renal function developed AKI. When creatinine was measured pre-PPCI, 8% of patients with normal renal function and 16.1% of patients with renal impairment developed AKI, a 39.5% reduction in AKI in those with renal dysfunction in the POC creatinine group. The average contrast volume in the standard care group was 265 ml, compared to 117.5ml when renal function was found to be impaired (eGFR < 60) pre-PPCI. 186ml was used on average in the POC group when creatinine was found to be normal.

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

Underline represents presenting author.

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Conclusions: Measuring the POC creatinine of 131 patients presenting with STEMI and undergoing PPCI reduces the rates of AKI by 39.5% in those with renal dysfunction. This appears to be mediated in part by a reduction in contrast volume in those patients identified with renal dysfunction (117.5ml) compared to normal renal function (186 ml). Funding: Pharmaceutical Company Support - Nova Biomedical

SA-PO190

Serum Creatinine Variability Predicts Progression to CKD4

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Background: Pre-dialysis patients have high serum creatinine (SC) variability. SC variability is associated with high death rates. We examined the association between SC variability and CKD progression in a large cohort of US veterans with a wide range of baseline eGFR.

Methods: VA patients admitted 10/1999 - 12/2005 with at least 4 months with SC and initial eGFR>30 ml/min/1.73 m² used (CKD-EPI) were selected. Autoregression-based slope was computed for each patient using monthly peak SC. SC variability was root mean-square residual of peak SC readings from the regression line. CKD4-date was the first date when eGFR permanently fell below 30 ml/min/1.73 m². Logistic regression was used to predict CKD4 using: initial eGFR, SC variability, SC slope, age, race, sex, months with SC readings, and comorbidities (DM, CAD, PNE, MI, angina, AKI, COPD, CHF). Kaplan-Meier (KM) analysis was used to examine time from first admission to entry into CKD4, stratified by SC variability quartile and baseline eGFR, and Cox regression was used to adjust survival estimates for the covariates above.

Results: Of 342,066 patients, 36,108 (10.6%) reached CKD4. The logistic model had strong prediction accuracy (c=.94) with sensitivity and specificity both ~.86. SC variability is strongly independently associated with rate of decline in renal function, at all baseline eGFR levels, after accounting for covariates, and is an important risk factor for entry into CKD4.

Conclusions: SC variability is strongly associated with high death rates. We examined the association between SC variability and CKD progression in a large cohort of US veterans with a wide range of baseline eGFR.

Funding: Veterans Administration Support

SA-PO191

Assessment of Methods Used to Substitute for Missing Preadmission Creatinine Values in the Diagnosis and Staging of Acute Kidney Injury

Amelie Croitoru,1 Ana-Maria Tanase,1,2 Andrei Buta,3 Ana-Andreea Chitu,2,3 Amelie Croitoru,1 Ana-Maria Tanase,1,2 Andrei Buta,3 Ana-Andreea Chitu,2,3 1IIBISMED, Univ Mayor de San Simon, School of Medicine, Bolivia; 2Hospital du Sacre-Coeur de Montreal, Canada; 3Univ of California San Diego Medical Center.

Background: Missing preadmission serum creatinine values (SCr) are a common obstacle to the diagnosis and staging of acute kidney injury (AKI). As a workaround, the KDIGO guidelines suggest using a baseline SCr computed from the MDRD formula. Measuring the POC creatinine of 131 patients presenting with STEMI and undergoing PPCI reduces the rates of AKI by 39.5% in those with renal dysfunction. This appears to be mediated in part by a reduction in contrast volume in those patients identified with renal dysfunction (117.5ml) compared to normal renal function (186 ml). Funding: Pharmaceutical Company Support - Nova Biomedical

Methods: We included 124 consecutive patients admitted to our medical ICU. We performed a retrospective single-center study of critically ill patients with known preadmission SCr to identify the most accurate method to estimate baseline SCr for AKI diagnosis and staging (KDIGO criteria). We assessed three surrogate methods: 1) the first hospital admission SCr, 2) the minimal SCr after ICU admission and 3) SCr computed for a eGFR of 75 ml/min per 1.73m² using MDRD.

Results: Of 1001 randomly selected patients, a preadmission SCr was available for 498 and 14 were excluded for requiring acute renal replacement therapy. Median age was 67 (IQR 58-76), 60% were male and 98% were Caucasian or Asian. The medium time between SCr measurement and admission was 116 (IQR 78-179) days. AKI incidence according to preadmission SCr was 24.8%. We reported in table 1 the AKI incidence, sensitivity, specificity and kappa values for each surrogate method.

Conclusions: In our cohort, the MDRD computed SCr for a eGFR of 75 ml/min per 1.73m² was the best surrogate method for diagnosing AKI. Using the minimal SCr significantly overestimated the incidence of AKI. Concerning AKI staging, the first hospital admission SCr was the most accurate method.

Funding: Other U.S. Government Support

SA-PO192

Fluid Balance and Oliguria in Early AKI Diagnosis After Liver Transplant

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Background: AKI is a frequent complication of liver transplant (LT), associated with increased morbidity and mortality. Early diagnosis can translate into secondary preventive measures and improve outcomes. We hypothesized that adjusting Scr for positive fluid balance (FB) and applying urine output(UO) criterion would improve timing of AKI diagnosis. In addition, we investigate whether sequential assessment of urinary biochemistry after LT can improve prediction of early post-operative AKI development.

Methods: In a prospective cohort study, we recorded UO, FB and labs of patients undergoing LT. We assessed urine and blood biochemistry periparative (before induction of anesthesia, after portal reperfusion, 6, 18, 24 hours after surgery). AKI diagnosis was based on UO and the sCr KDIGO criterion before and after correcting scr for FB (Scr adjusted), using the formula: ((wght*0.6)+(FB)/wght*0.6).

Results: Fifty-five patients >18 years undergoing LT from Jun13 to Oct14 were included in the analysis. Twenty-seven percent (15) of patients developed AKI based on SCR criterion within 24h after surgery (early AKI). By adjusting SCR for fluid balance 38% (21) patients were classified as early AKI. Applying the UO criterion, 43patients were classified exclusively by this criterion as early AKI. All patient showed a decline in FeNa and the FeaU after portal reperfusion. Patients developing early AKI had a higher decline and maintained lower levels for 24h. FeNa/rea values were significantly different 6 hours after surgery in early AKI patients. Patients with early AKI based on both criteria or exclusively by UO had a higher mortality and longer ICU and hospital stay than non-AKI patients.

Conclusions: Applying UO criteria and adjusting Scr for FB can help in the early identification of patients developing AKI after liver transplant. Tubular function assessment could be utilized along with biomarkers of kidney injury to identify patients with increased risk of developing AKI. Standardized approach for early AKI diagnosis in high-risk patients could improve outcomes.

Funding: Other U.S. Government Support

SA-PO193

Renal Angina Index a Practical Tool to Identify Patients at Increased Risk of Acute Kidney Injury

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Background: Reliable prediction of acute kidney injury (AKI) has the potential to optimize treatment. Recently Goldstein SL et al. proposed an empiric clinical model of renal angina using patient demographic factors and early signs of injury to identify critically-ill children who would be at higher risk of AKI. We test the hypotheses that in a cohort of adult critically-ill patients, a modified renal angina index (RAI) will identify patients at high risk of developing AKI, and could be related to in-hospital mortality.

Methods: We included 124 consecutive patients admitted to our medical ICU. We recorded serum creatinine (sCr) every 24h for 7 consecutive days after ICU admission. RAI was calculated at ICU admission (day 1) and 24 h after day 2) using the following formula: Risk level (vasopressors and invasive mechanical ventilation = 5; diabetes mellitus = 3; and sepsis = 1) X Injury level (decreases in eGFR: no change=1, 0-24.9%=2, 25-49.9%=4, and ≥50%=8). The composite range of the RAI is therefore: 1, 2, 3, 4, 5, 6, 8, 10, 12, 20, 24, and 40. We analyzed the value of a RAI score ≥8 to predict subsequent AKI (after 48 h, day 3) and survival.

Results: We identified 50(40.3%) patients with AKI (KDIGO guidelines sCr criteria), and 74(59.7%) patients who did not develop AKI. Patients with a RAI ≥8 were at higher risk of developing AKI within 7 days of follow-up (RR 1.64 95% CI 1.31-2.05; p<0.0001). A RAI ≥8 at ICU admission (day 1) and 24 h after admission (day 2) was able to identify individuals who developed AKI (day 3-7) with an AUC of 0.86 (95% CI 0.77-0.945); p< 0.0001 and an AUC of 0.891 (95% CI 0.815-0.946); p< 0.0001, respectively. No difference was found in terms of 28 day in-hospital mortality in patients with a RAI ≥8 vs a RAI ≤8.

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

Underline represents author.
Conclusions: The RAI provides a clinically feasible methodology to identify critically-ill patients at high risk of developing AKI before a rise in Scr occurs. This tool would permit the early identification of AKI to initiate preventive and treatment strategies minimizing extension of kidney injury.

SA-PO194

The Renal Angina Index Identifies Patients at High-Risk of Acute Kidney Injury – Analysis from AWARE: A Prospective Multinational Study of AKI in Critically Ill Children

RA, K. Basu, 1,2 Ahmad Kaddourah, 1,2 Stuart Goldstein, 1, 2 Pediatrics, Center for Acute Care Nephrology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 3 On Behalf of the AWARE Study Investigators, Multinational Pediatric ICU.

Background: We conducted a global, prospective observational study of critically ill children to study the epidemiology of pediatric acute kidney injury (AKI). We analyzed the association of the renal angina index for prediction of AKI and patient outcomes.

Methods: Data from 32 centers (5 continents, data collection for 3 consecutive months in 2014) from children (aged 3 months to 25 years) admitted to a pediatric intensive care unit were analyzed. The renal angina index (RAI) was calculated on the day of admission (Day 0) as previously described. A cut-off of ≥ 8 on Day 0 was used to determine fulfillment or absence of renal angina (RA+ vs. RA-). The primary outcome was the presence of severe AKI on Day 3, defined by change in serum creatinine from baseline using KDIGO stage 2-3 criteria (Day 3 AKI). Other patient outcomes were assessed at 28 days.

Results: 9.6% (501/5231) of children were RA+ on Day 0. The area-under-curve receiver operating characteristic of the Day 0 RAI for Day 3- AKI was 0.797 (95% confidence interval 0.759-0.836). RA+ was associated with a higher net fluid balance on Day 3 than RA- (p=0.001). Compared to RA-, Day 0 RA+ was associated with prolonged duration of mechanical ventilation, longer length of stay, increased use of extracorporeal therapies, and higher incidence of mortality.

Table 1: Outcome of Patients in AWARE Stratified by Day 0 Renal Angina

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RA-</th>
<th>RA+</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3 AKI (%)</td>
<td>4.8</td>
<td>33.5</td>
<td>&lt;0.001, CRP = 158.4</td>
</tr>
<tr>
<td>MV duration (days)</td>
<td>7.4</td>
<td>7.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Length of stay (days)*</td>
<td>11.2</td>
<td>7.1</td>
<td>8.0</td>
</tr>
<tr>
<td>RRT use (%)</td>
<td>1.4</td>
<td>11.6</td>
<td>&lt;0.001, CRP = 100.2</td>
</tr>
<tr>
<td>ECMO use (%)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>3.6</td>
<td>11.0</td>
<td>&lt;0.001, CRP = 33.3</td>
</tr>
</tbody>
</table>

*p = 0.01, NS = not significant

Conclusions: In AWARE, the largest prospective multi-center epidemiologic assessment of AKI in critically ill children, we demonstrate the ability of the renal angina index to identify patients at high risk of AKI, three days in advance. Fulfillment of renal angina early in the ICU course is associated with poor patient outcome.

SA-PO195

Phase Angle and Extracellular Hypervolemia, as a Prognostic Markers in Acute Kidney Injury

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Background: The bioelectrical impedance analysis (BIA) is a noninvasive and painless technique and easy to perform, which is used for determining body composition. Can offer an ultrasound-based measurement, can predict AKI in a variety of settings. To our knowledge, there are no studies investigating the predictive value of preoperative RRI and the risk of AKI in cardiac surgery patients. The aim of this study was to investigate whether an elevated preoperative RRI predicts AKI in a general cardiac surgery population.

Methods: Patients undergoing elective cardiac surgery were included prospectively between September 21, 2014 and April 22, 2015 at the Karolinska University Hospital. RRI was measured before surgery. An elevated RRI was defined as ≥ 0.7. The outcome AKI was defined as an absolute increase in post-compared to preoperative serum creatinine by 0.3 mg/dL (>26 µmol/L) or a relative increase by >50%. The odds ratio for AKI was calculated by logistic regression in patients with a RRI >0.7 versus those with a RRI ≤ 0.7.

Results: 98 patients were included. In patients with a RRI ≥ 0.7, 6 (15%) patients developed AKI, compared to 19 (33%) in patients with a RRI >0.7. The mean increase in postoperative serum increase in patients with RRI ≥ 0.7 was 0.12 mg/dL (11 µmol/L) compared to 0.34 mg/dL (30 µmol/L) in those with RRI >0.7 (P=0.03). The odds ratio for developing AKI in patients with a RRI >0.7 compared to those with a RRI ≥ 0.7 was 2.76 (9.97-7.71).

Conclusions: We found that patients with an elevated RRI before cardiac surgery had an increased risk of developing AKI postoperatively. RRI might be a valuable tool for identifying patients with an increased risk of developing AKI connected to cardiac surgery.

SA-PO196

Preoperative Renal Resistive Index Predicts the Risk of Acute Kidney Injury in Patients Undergoing Cardiac Surgery

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Background: Previous studies have indicated that Renal Resistive Index (RRI), an ultrasound-based measurement, can predict AKI in a variety of settings. To our knowledge, there are no studies investigating the predictive value of preoperative RRI and the risk of AKI in cardiac surgery patients. The aim of this study was to investigate whether an elevated preoperative RRI predicts AKI in a general cardiac surgery population.

Methods: Patients undergoing elective cardiac surgery were included prospectively between September 21, 2014 and April 22, 2015 at the Karolinska University Hospital. RRI was measured before surgery. An elevated RRI was defined as ≥ 0.7. The outcome AKI was defined as an absolute increase in post-compared to preoperative serum creatinine by 0.3 mg/dL (>26 µmol/L) or a relative increase by >50%. The odds ratio for AKI was calculated by logistic regression in patients with a RRI >0.7 versus those with a RRI ≤ 0.7.

Results: 98 patients were included. In patients with a RRI ≥ 0.7, 6 (15%) patients developed AKI, compared to 19 (33%) in patients with a RRI >0.7. The mean increase in postoperative serum increase in patients with RRI ≥ 0.7 was 0.12 mg/dL (11 µmol/L) compared to 0.34 mg/dL (30 µmol/L) in those with RRI >0.7 (P=0.03). The odds ratio for developing AKI in patients with a RRI >0.7 compared to those with a RRI ≥ 0.7 was 2.76 (9.97-7.71).

Conclusions: We found that patients with an elevated RRI before cardiac surgery had an increased risk of developing AKI postoperatively. RRI might be a valuable tool for identifying patients with an increased risk of developing AKI connected to cardiac surgery.

SA-PO197

Development of a Postoperative Risk Stratification Tool via Bayesian Model Averaging for Acute Kidney Injury After Cardiac Surgery

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Background: Acute kidney injury (AKI) is a frequent complication of cardiac surgery. We sought predictive combinations of biomarkers measured 0-6 hours after surgery, potentially in combination with cardiopulmonary bypass (CPB) time (to account for the degree of insult).

Methods: The primary endpoint was sustained mild AKI, defined as an increase of 50% or more in serum creatinine over preoperative levels lasting at least two days during the hospital stay. Severe AKI were AKI (secondary endpoint) was defined as a serum creatinine increase of 100% or more or dialysis during hospitalization. Data were from a cohort of 1219 adults undergoing cardiac surgery at 6 medical centers; among these, 117 developed sustained mild AKI and 60 developed severe AKI. We considered CPB time and 2 biomarkers as candidate predictors. We used Bayesian Model Averaging (BMA) methods to develop center-adjusted combinations for sustained mild AKI by (1) maximizing the posterior model probability and (2) retaining predictors with posterior variable probabilities above 0.5.

Results: The maximum posterior model probability combination included plasma NT-proBNP, plasma h-FABP and change in serum creatinine; the median probability combination additionally included plasma IL-6. The center-adjusted, optimism-corrected AUCs for these combinations were 0.80 (95% CI: 0.78, 0.88) and 0.81 (0.77, 0.88), respectively, for predicting sustained mild AKI, and were 0.81 (0.77, 0.90) and 0.83 (0.76, 0.90), respectively, for predicting severe AKI. For these data, the BMA methods yielded combinations with predictive capacity comparable to that achieved by standard frequentist methods but with smaller models.

Conclusions: Pending external validation, the identified combinations could be used to identify individuals at high risk of AKI immediately after cardiac surgery and could facilitate clinical trials of renoprotective agents.

Funding: Other NIH Support - RO1HL085775
SA-PO198
Low Pre-Operative Serum Bicarbonate Levels Predict Acute Kidney Injury After Cardiac Surgery

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Background: Low serum bicarbonate levels are known to be risk factors for renal function deterioration in chronic kidney injury patients. However, it is not well known whether preoperative low serum bicarbonate levels are associated with the development of acute kidney injury (AKI) in patients who undergo cardiac surgery. Therefore, clinical implications of preoperative serum bicarbonate levels on AKI occurrence after cardiac surgery were evaluated.

Methods: The patients who underwent coronary artery bypass or valve surgery at Yonsei University Health System from January 2013 to December 2014 were enrolled. The patients were categorized into three groups according to pre-operative serum bicarbonate levels (group 1 (<23 mEq/L), group 2 23-24 mEq/L, group 3 >24 mEq/L). Multivariate logistic regression analysis was performed to determine the effect of pre-operative serum bicarbonate levels on development of AKI at 48 hours after cardiac surgery.

Results: Among 452 patients, 228 patients (26.1%) developed AKI at 48 hours after cardiac surgery. Incidence of AKI was higher in group 1 (34.6%) than group 2 (26.3%) and group 3 (39.0%) (P <0.001). The duration of post-operative intensive care unit (ICU) stay was longer in AKI patients (AKI vs. non-AKI, 6.2 vs. 2.7 days, P=0.001). In addition, post-operative ICU stay was longer in the low pre-operative serum bicarbonate level groups (group 1 (4.4 days), group 2 (3.6 days), group 3 (3.3 days), P=0.001). In multivariate logistic regression analysis, low pre-operative serum bicarbonate levels were significantly associated with post-operative AKI development even after adjusting for age, sex, hypertension, diabetes mellitus, operation type, hemoglobin, and glomerular filtration rate (group 3 as reference, odds ratio=2.36, 95% confidence interval=1.57-3.54, P<0.001).

Conclusions: Low serum bicarbonate levels were associated with higher incidence of AKI and prolonged ICU stay. Correction of low serum bicarbonate levels before cardiac surgery may reduce the risk of AKI development.

SA-PO199
Admission Hyperuricemia Increases the Risk of Acute Kidney Injury in Hospitalized Patients

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Background: The association between elevated admission serum uric acid and risk of in-hospital acute kidney injury (AKI) is limited. The aim of this study was to assess the risk of developing AKI in all hospitalized patients with various admission serum uric acid (SUa) levels.

Methods: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission SUA available from January 2011 through December 2013 were analyzed in this study. Admission SUA was categorized based on its distribution into six groups (less than 3.4, 3.4 to 4.5, 4.5 to 5.8, 5.8 to 7.6, 7.6 to 9.4, and greater than 9.4 mg/dL). The primary outcome was in-hospital AKI occurrence based on its distribution into six groups (less than 3.4, 3.4 to 4.5, 4.5 to 5.8, 5.8 to 7.6, 7.6 to 9.4, and greater than 9.4 mg/dL). The primary outcome was in-hospital AKI occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of AKI of various admission SUA levels using the most common SUA level reference range (5.8 to 7.6 mg/dL) as the reference group.

Results: Of 1,435 patients enrolled, AKI occurred in 263 patients (18%). The incidence of AKI and need for dialysis was increased in patients with higher admission SUA levels (group 1 <23 mg/dL, group 2 23-24 mg/dL, group 3 >24 mg/dL). The primary outcome was in-hospital AKI occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of AKI of various admission SUA levels using the most common SUA level reference range (5.8 to 7.6 mg/dL) as the reference group.

Conclusions: Admission SUA was associated with an increased risk for in-hospital AKI.

SA-PO200
Hypoalbuminemia Is a Strong Risk Factor for Acute Kidney Injury Progression in Elderly Patients in Intensive Care Unit

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Background: Population aging is a global issue; especially, Japan is experiencing rapid aging, at a faster speed than any other developed country, and those aged 65 or older comprised 25.9% of Japan’s population as of September 2014. Previous studies showed elderly patients are at high risk for developing acute kidney injury (AKI). AKI is also a common clinical syndrome in the ICU setting, but its clinical presentation varies from mild to severe. Predicting whether AKI progress or not is difficult but can guide clinical decision making. The aim of the present study is to elucidate risk factors of AKI progression among elderly patients in ICU.

Methods: A retrospective study of patients age 65 and older developed AKI during ICU stay between January 2004 and September 2013. AKI was defined as increase in serum creatinine (sCr) of ≥1.5 times baseline. The primary outcome was the progression to AKIN stage 3 (increase in sCr of 3 times over baseline or need for renal replacement therapy (RRT)) within 14 days after AKI development. Prerenal AKI, postrenal AKI, and AKIN Stage 3 at diagnosis of AKI are excluded; prerenal AKI is diagnosed when serum BUN-to-creatinine ratio ≥ 20 and postrenal AKI is diagnosed based on clinical situation.

Results: 418 patients were included. The mean age was 80.6 ± 8.2 years, baseline sCr=0.89 ± 0.40 mg/dL, and baseline eGFR=66.1 ± 32.3 ml/min/1.73m2. Among 418 patients, 77 (18.4%) experienced AKI progression and 93 (19.9%) died. The patients with AKI progression had higher serum albumin levels (group 1 <23 mEq/L, group 2 23-24 mEq/L, group 3 >24 mEq/L). Multivariate logistic regression analysis showed that the survival was not different between IMA groups. Urine output was lower in group 1 and 3 compared with in group 2, but it was higher in group 2 compared with in group 1 and 3. Platelet levels were significantly higher in group 2 than in group 1 and 3. The risk factors of AKI progression were age, AKI stage on admission, pre-existing diabetes mellitus, and pre-existing chronic obstructive pulmonary disease (COPD) (OR=5.10, 95%CI=2.94-9.06) were risk factors for AKI progression.

Conclusions: Hypoalbuminemia is a strong risk factor for AKI progression in older patients in ICU. Further study is needed to evaluate whether correction of hypoalbuminemia could prevent AKI progression or not.

SA-PO201
Impact of Preexisting Serum Prealbumin on All-Cause Mortality in Community-Acquired and Post-Operative Acute Kidney Injury Patients

Yanfang Zou1, Dan Wen1, Jingyuan Xie1, Xiaonong Chen, Wen Zhang, Nan Chen.1 Nephrology, Ruijin Hospital, Shanghai, China; 2Nephrology, Ruijin Hospital, Shanghai, China.

Background: To explore the impact of pre-existing prealbumin concentration on all-cause mortality in AKI (acute kidney disease, AKI) patients.

Methods: From 2000 to 2010, 477 patients diagnosed with community-acquired AKI (CA-AKI) and treated in the Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong University were enrolled in the CA-AKI group. 138 patients diagnosed with AKI after cardiac operations were enrolled in the post-operative AKI (PO-AKI) group. Data were collected at the time of AKI onset and one year after the discharge.

Results: 41 patients with CA-AKI were younger than PO-AKI patients. Compared with PO-AKI patients, more patients in CA-AKI group suffered from chronic kidney disease, obesity and hyperlipidemia and less patients with cerebrovascular disease (CVD), anemia, chronic obstructive pulmonary disease (COPD), arteriosclerosis, diabetes mellitus and elevated sCr (8.12±4.03 mg/dL vs 3.49±2.75 mg/dL, P<0.001). In CA-AKI group, patients had higher levels of PA and serum albumin (28.2±10.5 mg/dL vs 17.3±6.9 mg/dL, P<0.001). The primary outcome was the progression rate of serum creatinine (sCr) of ≥1.5 times baseline. The incidence of AKI progression was 55% in CA-AKI group and 50% in PO-AKI group. Incidence of AKI progression was incrementally increased with the decrease of PA (0.5% in PA>20 mg/dL to 47.6% in PA<12 mg/dL, P<0.001). Multivariate logistic regression analysis showed that the survival was not different between IMA groups. Urine output was significantly higher in group 1 and 3 compared with in group 2. The risk factors of AKI progression were age, AKI stage on admission, pre-existing diabetes mellitus, and pre-existing chronic obstructive pulmonary disease (COPD) (OR=5.10, 95%CI=2.94-9.06) were risk factors for AKI progression.

Conclusions: Hypoalbuminemia is a strong risk factor for AKI progression in older patients in ICU. Further study is needed to evaluate whether correction of hypoalbuminemia could prevent AKI progression or not.

SA-PO202
Usefulness of Serum Ischemia-Modified Albumin Levels to Predict Dialysis Requirement in Patients with Acute Renal Injury

Mehmet Uzun, Harun Akar. Internal Medicine, Izmir Tepecik Education and Research Hospital, Turkey.

Background: Ischemia-modified albumin is a promising biomarker for early diagnosis of diseases related with ischemia. Ischemia leads to modification in albumin molecule by reducing its binding to cobalt. The aim of this study was to evaluate the levels of ischemia-modified albumin in patients with acute kidney injury (AKI).

Methods: Serum levels of ischemia-modified albumin were estimated in 51 patients with AKI.

Results: The mean age of 28 female and 23 male patients were 65.39±15.28 and 71.15±15.28, respectively. Levels of IMA were found to be high in 75.5 % of the patients (≥400) and were found to be normal in 25.5 % of the patients (≤400). Kaplan-Meier survival analysis showed that the survival was not different between IMA groups. Urine amounts were significantly different between IMA groups. The urine volume was lower in patients with higher IMA levels (≥400) (P<0.001).

Conclusions: A significant difference was detected between CA-AKI group and PO-AKI in general characteristics, comorbidities, laboratory examinations, outcome, and risks. Patients with PA>20mg/dL showed better survival rate.
Conclusions: In the present study, the levels of IMA were found to be significantly higher in patients who needed hemodialysis treatment. IMA levels do not predict mortality. Taking these results together, serum IMA levels might give an idea about dialysis requirement in patients with AKI. More studies with larger sample groups may help to establish the role of IMA on decisions regarding dialysis initiation.

SA-PO203

Urinary TIMP-2 and IGFBP7 Elevate Early After Vancomycin Administration in Critically Ill Patients Who Develop AKI 1, Maria Osternann, 2, Lui G. Forni, 3, Lakhmir S. Chawla, 4, Jing Shi, 5, Kianoush Banaei-Kashani, 6, John A. Kellum. 2

Background: We previously validated a biomarker combination of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) for risk stratification of acute kidney injury (AKI). 1 A cutoff of 0.3 (ng/mL)/1000 for [TIMP-2][IGFBP7] indicated AKI stage 2-3 at least 24h prior to serum creatinine. 2 We also showed that nephrotoxic drug use was common in patients developing AKI and that the [TIMP-2][IGFBP7] test could have identified patients earlier. 1 This sub-analysis of the Sapphire study, 1 examined the temporal changes in [TIMP-2][IGFBP7] following vancomycin administration.

Methods: We identified patients who received vancomycin and grouped them according to their maximum KDIGO AKI stage within 3 days of 1st dose of vancomycin. We calculated the median daily [TIMP-2][IGFBP7] value from day prior to 1st dose of vancomycin until to their maximum KDIGO AKI stage within 3 days of 1st dose of vancomycin. We calculated the [TIMP-2][IGFBP7] test could have identified patients earlier.

Results: 249 patients received at least 1 dose of vancomycin. 137 (55%) developed AKI within 3 days [AKI 1 (n=81), AKI 2 (n=44), AKI 3 (n=12)]. In patients without AKI or with AKI 1, median [TIMP-2][IGFBP7] values were 0.03 (ng/mL)/1000 for all time points.

Conclusions: Immediate post-operative serum IL-33 concentrations were higher in matched AKI cases compared to non-AKI controls. Further studies are needed to clarify the role of serum IL-33 in human AKI.

Funding: NIDDK Support SA-PO205

First Post-Operative Urinary Kidney Injury Biomarkers and Association with the Duration of AKI in the TRIBE-AKI Cohort

Mayo Clinic, Rochester; 6 Univ of Pittsburgh, Pittsburgh.

Background: We previously demonstrated AKI duration improves risk-stratification for AKI prognosis in addition to the magnitude of serum creatinine rise. We evaluated whether kidney injury biomarkers within 6 hours after cardiac surgery associate with post-operative AKI duration.

Methods: We included 1199 adults undergoing cardiac surgery in TRIBE-AKI cohort that survived to discharge and examined association between five urinary biomarkers: neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP) and albumin with duration of serum creatinine-based AKIN criteria for AKI (0 (no AKI), 1-2, 3-6, ≥7 days).

Results: Overall, 406 (34%) patients had AKI, of which 48 had stage 2/3 AKI. Of 358 with stage 1 AKI, 115 (32.1%) had AKI duration >3 days. An additional 41 (85%) with stage 2/3 AKI had duration of >3 days. Concentrations of all biomarkers increased with AKI duration and each log increase in biomarker was independently associated with AKI duration and each log increase in biomarker was independently associated with greater odds of longer duration category (IL-18 OR 1.25, 95% CI 1.16-1.35; KIM-1: 1.36, 95%CI 1.21-1.52; albumin 1.21, 95% CI 1.10-1.33; L-FABP 1.14, 95% CI 1.07-1.21; NGAL 1.10, 95% CI 1.03-1.17).

Conclusions: In patients with AKI 2-3, medium [TIMP-2][IGFBP7] values were significantly elevated on the day of the 1st vancomycin dose and remained elevated for the following 2 days. These biomarkers have the potential to improve management in patients receiving vancomycin.

Funding: Pharmaceutical Company Support - Astute Medical

SA-PO204

Peri-Operative Serum IL-33 Concentrations in Matched AKI and Non-AKI Patients Undergoing Cardiac Surgery

Charles L. Edelstein, 1, Heather Thiessen Philbrook, 2, Jay L. Koyner, 2, Michael Shlipak, 2, Steven G. Coca, 2, Chirag R. Parikh, 2

Background: Endothelial cell damage and death in the nephron is an early feature of AKI. Damage-associated molecular patterns (DAMPs) are endogenous molecules released by damaged cells including endothelial cells. IL-33, a DAMP, has been shown to be present in blood vessels in the kidney and released into the blood, but not the urine, in cisplatin-induced AKI in mice before the increase in serum creatinine. We sought to determine whether serum IL-33 levels are a biomarker of AKI in humans in a nested case-control study.

Methods: Perioperative plasma samples were obtained from patients enrolled in the TRIBE-AKI cohort. 35 cases of AKIN Stage 2 AKI or higher within the first 4 post-op days were matched to 70 controls with no AKI by pre-op GFR, age, sex, site and cohort. Blood samples were available pre-op, day 1 (0-6 hours), days 2 and 3. Serum IL-33 was measured by ELISA.

Results: The pre and post-operative levels of IL-33 are shown in Table 1. Using a mixed model accounting for the matching in the data, the first post-operative value of IL-33 was significantly different (p=0.005) between cases and controls after adjusting for pre-op values. There was a non-significant trend towards higher IL-33 levels on day 2.

Conclusions: While most patients in the TRIBE-AKI Cohort experienced stage 1 AKI when classified by peak serum creatinine increase, one-third of those have duration of AKI of >3 days. Elevated urinary kidney injury biomarker within 6 hours of surgery may help in identifying of patients at risk for longer AKI duration, which may serve as a reliable metric for drug development trials.

Funding: Other NIH Support - NHLBI

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

Underline represents presenting author.

762A
SA-PO206

Urinary Biomarker Evaluation in Cancer Patients Receiving Cisplatin
Amandla Roque, Kent Doi, Maki Sumida, Yoshifumi Hamasaki, Schools of Pharmacy and Medicine, Univ of Colorado, CO.

Background: The study explored the time dependency of urinary biomarker changes and correlations between the biomarkers and traditional markers of kidney injury in a cohort of patients receiving cisplatin.

Methods: Urine was obtained at baseline, Day 2, Day 3, and Day 10 from patients (n=42) receiving cisplatin (25 mg/m²). Urinary kidney injury molecule-1 (Kim-1), calbindin, beta-2 microglobulin (B2M), clusterin, monocyte chemoattractant protein-1 (MCP-1), cystatin C, trefoil factor 3 (TFF3), tissue inhibitor of metalloproteinase 2 (TIMP2), and insulin growth factor binding protein 7 (IGFBP7) were measured with multiplex or ELISA.

Results:

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim-1</td>
<td>0.42±0.1</td>
<td>0.77±0.1</td>
<td>0.97±0.2</td>
</tr>
<tr>
<td>Calbindin</td>
<td>59.0±13.6</td>
<td>70.1±12.2</td>
<td>544±163</td>
</tr>
<tr>
<td>B2M</td>
<td>144±39.1</td>
<td>502±71.8</td>
<td>185±41.5</td>
</tr>
<tr>
<td>Clusterin</td>
<td>42±23.5</td>
<td>27.5±8.8</td>
<td>5.2±16.1</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.62±0.2</td>
<td>0.45±0.1</td>
<td>1.06±0.2</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>39.5±7.7</td>
<td>77.2±22.8</td>
<td>64.9±19.0</td>
</tr>
<tr>
<td>TFF3</td>
<td>865±158</td>
<td>1444±202</td>
<td>1616±264</td>
</tr>
<tr>
<td>TIMP2</td>
<td>2.2±0.5</td>
<td>2.3±0.6</td>
<td>3.2±0.7</td>
</tr>
<tr>
<td>IGFBP7</td>
<td>2931±484</td>
<td>2357±514</td>
<td>4650±561</td>
</tr>
<tr>
<td>Albumin</td>
<td>11,038±2067</td>
<td>15,958±2442</td>
<td>24,373±4232</td>
</tr>
</tbody>
</table>

A: baseline vs. Day 3 p<0.05; B: baseline vs. Day 10 p<0.05; C: Day 3 vs Day 10 p<0.05

The biomarker-GFR correlations were: TFF3 (r: -0.2590), B2M (r: -0.2017), Kim-1 (r: -0.1758), MCP-1 (r: -0.1390), cystatin C (r: -0.0936), IGFBP7 (r: -0.0764), clusterin (r: -0.0767), calbindin (r: 0.0647), and TIMP2 (r: 0.0619). The biomarker-albumin correlations were: calbindin (r: 0.7813), TFF3 (r: 0.5949), clusterin (r: 0.5869), Kim-1 (r: 0.3166), TIMP2 (r: 0.2906), MCP-1 (r: 0.2234), IGFBP7 (r: 0.2217), cystatin C (r: 0.1375), and B2M (r: 0.1149).

Conclusions: Urinary biomarkers display time dependent increases post cisplatin and exhibit variable degrees of correlation with GFR and urinary albumin. TFF3 had high concordance with both GFR and urinary albumin, which may be a favorable characteristic.

SA-PO207

Prediction of Long-Term Renal Outcomes in AKI Survivors by Urinary Biomarkers
Rei Isshiki, Kent Doi, Maki Sumida, Yoshihumi Hamasaki, Naoki Yahagi, Maasumi Nangaku, Eisei Noiri, Nephrology and Endocrinology, Univ Hospital, Univ of Tokyo, Tokyo, Japan; Emergency and Critical Care Medicine, Univ Hospital, Univ of Tokyo, Tokyo, Japan.

Background: Although several epidemiological studies suggested that acute kidney injury (AKI) increases the risk of chronic kidney disease (CKD) development and progression, it is still unclear whether any AKI biomarker can predict long-term renal outcomes in AKI survivors. This study was aimed to evaluate the performance of urinary biomarkers for long-term renal outcome prediction.

Methods: We conducted an observational study examining the association of three urinary biomarkers measured at ICU admission [L-type fatty acid-binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), and N-acetyl-beta-D-glucosaminidase (NAG)] with CKD progression after discharge without major adverse kidney events (MAKE). MAKE were determined with death, incident dialysis dependency, or 50% reduction of eGFR at hospital discharge. Two different long-term renal outcomes were defined as follows; 30% reduction of eGFR or incident end-stage renal disease within two years after hospital discharge (Outcome 1) and halving of eGFR or incident end-stage renal disease in three years (Outcome 2).

Results: Among the enrolled 495 patients, 393 patients discharged from the hospital without MAKE. Of them, 175 patients were followed up for two years after ICU discharge and 63 patients (36.4%) were positive for long-term renal outcomes (Outcome 1). A step-wise logistic regression analysis demonstrated that only urinary NGAL showed a significant association. For Outcome 2, 26 of 159 followed-up patients (16.4%) were positive and urinary L-FABP and NGAL were significantly associated with CKD progression in a univariate logistic regression analysis.

Conclusions: Urinary biomarkers measured at ICU admission were significantly associated with long-term renal outcomes after hospital discharge in MAKE-free AKI survivors.

SA-PO208

Significance of Serial Measurement of Acute Kidney Biomarker in Intensive Care Unit
Rei Isshiki, Kent Doi, Maki Sumida, Naoki Yahagi, Maasumi Nangaku, Eisei Noiri. Nephrology and Endocrinology, Univ Hospital, Univ of Tokyo, Tokyo, Japan; Emergency and Critical Care Medicine, Univ Hospital, Univ of Tokyo, Tokyo, Japan.

Background: AKI biomarkers have been developed with the concept of earlier detection of kidney damage than serum creatinine. However, single time point measurement appears not to provide sufficient information for detecting and predicting AKI in ICU patients who frequently suffer from multiple and transient/permanent renal insults. This study was aimed to evaluate whether serial measurement enables to predict AKI progression and recovery in these patients.

Methods: Serial measurements of AKI biomarkers including plasma and urinary NGAL, urinary L-FABP, and urinary NAG at ICU admission (day 1) and 24 hr after (day 2) were conducted in adult critically ill patients who were treated in a mixed ICU.

Results: Among the enrolled 272 patients, 33 were determined as newly developed AKI after ICU admission, 64 showed worsening of kidney function and 63 recovered from AKI. ROC analysis showed that biomarkers at day 2 showed no significantly additional benefit in predicting these three AKI outcomes compared with those measured at day 1. However, net reclassification improvement (NRI) analysis demonstrated adding AKI biomarkers at day 2 to the clinical model consisted of clinical variables and biomarker at day 1 significantly improved prediction of these AKI outcomes.

SA-PO209

Role of Carboxyl Stress Revisited in Pathogenesis of Tropical Acute Kidney Injury
Pinaki Mukhopadhyay, Nephrology, NRS Medical College, Kolkata, West Bengal, India.

Background: Malaria and snake bite are two common causes of Acute Kidney Injury (AKI) in tropics with lot of morbidity and mortality. The aim of this study was to (I) evaluate the carboxyl and oxidative stress in these group and their pathogenesis link and (II) prognostic predictability of carboxyl and oxidative stress marker in this AKI.

Methods: All cases of falciparum malaria mediated AKI (FMAKI) (n=50),confirmed by antigen and/or in peripheral blood smear and snake bite mediated AKI(SAKI) (n=58) were included. AKI was calculated as per RIFLE criteria. Demographical, clinical and biochemical data were analysed and were followed from hospitalization to discharge/death. Oxidative and carbonyl stress markers [advanced oxidation protein product (AOPP), advanced glycation end product (AGE), pentosidine, dityrosine, thiobarbituric acid reactive substance (TBARS) and methyl glyoxal (MG)] were measured consecutively according to standard protocol. Predictive importance was assessed from trend analysis, receiver operated characteristic (ROC) curve analyses and multiple logistic regression with AKI as positive response.

Results: The Oxidative stress index(OSI) of FMAKI patients were 1.89 higher than controls. The TBARS, MG level were 6.49 and 5.56 times higher indicating a significant carboxyl stress in these patients. AOPP level was 2.53 times higher indicating proteins being highly insulted in FMAKI. Similarly in SAKI significantly elevated total oxidant stress with decreased total antioxidant stress leads to net oxidative stress in SAKI patients depicted by increased OSI values (p<0.001). MG was increased by 3.48 times (p<0.001).Only AOPP (p=0.001) and MG (p=0.004) were found to be significantly elevated in expired patients than the survived indicating their predictive power for adverse outcome. At univariate level,
all parameters can differentiate between AKI and the non-AKI group. At multivariate level, methylglyoxal, AOPP and dityrosine appeared to be independent predictor of AKI in snake bite and malaria infected patients (p<0.05).

**Conclusions:** 1.MG, the carbonyl stress marker along with oxidative stress are significantly raised and possibly linked to the pathogenesis of AKI. 2.MG and AOPP can be used as a surrogate marker in these tropical AKI.

### SA-PO210

**Prediction of Short-term and Long-term Outcomes of AKI-Based on Plasma NGAL**  
Karina Soto,1 Fernando Pereira,1 Liliana Maria Goncalves Cunha,1 Iola Pinto,1 Ana Luisa Papoila,1 Prasad Devajaran.1  
*Nephrology, Hospital Fernando Fonseca; 1Inst Superior de Engenharia de Lisboa; 1Nova Medical School/FCM,Univ Nova de Lisboa, Portugal; 1Nephrology, Cincinnati Children’s Hospital Medical Center, OH.

**Background:** We have previously shown a good performance of Plasma NGAL (pNGAL) as an AKI biomarker in emergency settings. Now we investigated a new AKI classification based on pNGAL for prediction of kidney dysfunction at discharge and at the end of follow-up.

**Methods:** Patients from a previous study at ED were followed for >5y. During the index hospitalization, 21% were AKI (based on SCr), 26% transient azotemia, 51% normal function and 2.4% stable CKD. All patients had SCr and pNGAL measured at 0, 6, 12, 24 and 48h of admission. A new AKI classification based on pNGAL levels (AKIPNGAL+) defined AKI as pNGAL>110 ng/mL (cut-off by GAMS). A multivariable logistic and Cox regression models were applied.

**Results:** Of 599 patients admitted, 97.8% were available at discharge and 54.4% at last follow-up. At admission 42.6% were reclassified as AKIPNGAL+ whereas only 21.7% were based on SCr. All significant clinical variables were included in multivariable analysis at discharge.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKIPNGAL+</td>
<td>4.2</td>
<td>2.3-7.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.0-1.1</td>
<td>0.05</td>
</tr>
<tr>
<td>CVD</td>
<td>1.2</td>
<td>1.2-3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>DM</td>
<td>1.5</td>
<td>1.5-4.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*p<0.001 unless CVD*0.007

Having pNGAL>110 at ED corresponded to 4-fold increased odds for eGFR<60 mL/min (p<0.001 ROC-AUC 0.82). The cumulative incidence of CKD showed that most of AKIPNGAL+ developed CKD at 60 mo (the highest proportion 77%) (figure 1) HR for CKD: 2.4 for patients AKIPNGAL+ in long-term (p=0.001 ROC AUC 0.74) NRI 56.3 and IDI 0.03.

**Conclusions:** Patients who were AKIPNGAL+ had significant lost kidney function at discharge and more than 2-fold risk of developing CKD in long-term evolution. Plasma NGAL is a useful tool for CKD prediction, independent of serum creatinine.

### SA-PO211

**The Use of Novel Serum and Urinary Biomarkers to Predict the Development of Hepatorenal Syndrome in Patients with Advanced Cirrhosis**  
Desmond Y.H. Yap,1 Kai Kay Seto,1 James Yf Fung,2 Seo-Ching Chan,2 Siu-Ho Chok,2 Man-Fung Yuen,2 Daniel Tak Mao Chan.3  
*Medicine, The Univ of Hong Kong, Hong Kong, Hong Kong; Surgery, The Univ of Hong Kong, Hong Kong, Hong Kong.

**Background:** Hepatorenal syndrome (HRS) is associated with high mortality rates in advanced cirrhotic patients without liver transplantation. Prediction of the development of HRS remains difficult.

**Methods:** We prospectively recruited patients with Child’s B or C cirrhosis and followed them at 2-week intervals 12 weeks or until HRS developed. Serum cystatin C (CysC), serum Neutrophil Gelatinase-associated Lipocalin (NGAL), serum IL-18, urine kidney injury molecule-1 (KIM-1) and urine liver-type fatty acid binding protein (LFABP) were measured at recruitment (Baseline).

**Results:** 43 patients included. 12 developed HRS at 7.3±5.1 weeks from baseline. pNGAL, IL-18 and CysC had highest Baseline levels of serum CysC (1.42±0.51 mg/L vs. 1.07±0.50 mg/L, p<0.021), serum NGAL (129.10±68.66 ng/mL vs. 72.84±48.91 ng/mL, p=0.025), serum IL-18 (759.91±477.05 mIU/mL vs. 358.13±153.00 mIU/mL, p<0.001), urine KIM-1 and LFABP (3.64±3.34 ng/mL vs. 1.18±1.68 ng/mL and 10.17±8.37 ng/mL vs. 3.28±3.42 ng/mL, p<0.023 and 0.035 respectively) when compared to patients who did not develop HRS. The cut-off and positive and negative predictive values for HRS were shown in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut-off Value</th>
<th>AUC</th>
<th>95% CI</th>
<th>PPV</th>
<th>NPV</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline serum CysC (mg/L)</td>
<td>0.899</td>
<td>0.748</td>
<td>0.572-0.924</td>
<td>52.4</td>
<td>90.9</td>
<td>0.021</td>
</tr>
<tr>
<td>Baseline serum NGAL (ng/mL)</td>
<td>90.47</td>
<td>0.756</td>
<td>0.592-0.939</td>
<td>72.7</td>
<td>75.0</td>
<td>0.025</td>
</tr>
<tr>
<td>Baseline serum IL-18 (mIU/mL)</td>
<td>442.84</td>
<td>0.858</td>
<td>0.708-1.000</td>
<td>73.3</td>
<td>92.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline urine KIM-1 (ng/mL)</td>
<td>1.499</td>
<td>0.785</td>
<td>0.607-0.963</td>
<td>75.0</td>
<td>84.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Baseline urine LFABP (ng/mL)</td>
<td>3.398</td>
<td>0.765</td>
<td>0.578-0.949</td>
<td>54.5</td>
<td>86.7</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Serum NGAL and IL-18 and urinary KIM-1 at Baseline were significantly associated with the development of HRS (OR 1.017, 95%CI 1.001-1.033, p<0.05; OR 1.007, 95%CI 1.001-1.013, p<0.012; OR 1.007, 95%CI 1.001-1.013, p<0.045 respectively).

**Conclusions:** Serum IL-18 and urinary KIM-1 could serve as biomarkers to predict HRS in patients with advanced cirrhosis.

**Funding:** Private Foundation Support

### SA-PO212

**Robust Risk Assessment of Acute Kidney Injury After Acute Myocardial Infarction Using the Novel Biomarker C-Terminal Fragment of Agrin (CAF)**  
Spyridon Tziakas,1 Dimitros Arampatzis,2 George Chatikias,1 Vasileios Devetzis,1 Stefan Hettwler,1 Uyen Huynh,1 Fernando Pereira,1 Liliana Maria Goncalves Cunha,1 Ana Luisa Papoila,1 Prasad Devajaran.1  
*Department of Nephrology, Hypertension and Clinical Pharmacology, University of Athens, Greece; 1Department of Neurology, University Hospital Bern, Switzerland; 1Department of Neurology, Hypertension and Clinical Pharmacology, University of Athens, Greece; 1Department of Neurology, Hypertension and Clinical Pharmacology, University of Athens, Greece.

**Background:** Acute kidney injury (AKI) complicating acute myocardial infarction (AMI) increases subsequent morbidity and mortality. The objective of this study was to validate c-terminal fragment of agrin (CAF) as a novel AKI biomarker in patients with AMI.

**Methods:** 403 consecutive patients with AMI were enrolled, samples were collected at presentation for serum (sCAF), urine (uCAF) CAF, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18) and cystatin-C analysis. The presence of AKI was evaluated at 48 hours post admission and at discharge.

**Results:** The incidence of AKI was 6.7% 14.6% depending on time-point and criteria used and increased across quartiles of uCAF (x1:10.99, p<0.001). Both uCAF and sCAF significantly correlated with serum creatinine on admission (r=0.233, p<0.001 & r=0.175, p<0.001), at 48 hours (r=0.263, p<0.001 & r=0.226, p<0.001) and with peak creatinine as well (r=0.317, p<0.001 & r=0.225, p<0.001). The predictive accuracy for AKI of uCAF was good (AUC of 0.630; 95%CI 0.552-0.708) and slightly better as that of urine NGAL (AUC 0.616; 95%CI 0.540-0.692, uCAF vs. uNGAL p=0.733), whereas that of sCAF was moderate (AUC of 0.587; 95%CI 0.509-0.666). A uCAF value of 1033 pm is suggested to have the best discriminating ability. The sensitivity of uCAF was 37% and the specificity 85% (NPV: 89%; PPV: 30%). Univariate analysis showed a strong association of uCAF with AKI incidence (OR:1.45, 95%CI 1.15-1.82, p=0.002) which remained significant even after adjustment for several confounders (OR:1.35, 95%CI 1.05-1.74).

**Conclusions:** Urine CAF analysis allows a robust risk stratification of AKI after AMI and thus optimized management in such patients.

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

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

674A
SA-PO213

At Myeloma Diagnosis, Age and Free Light Chain Level Predict Renal Function and These Factors with Free Light Chain Response Predict Renal Outcome

Punit Yadav,1,2 Mark Trehan Drayson,1,2 Mark Cook,1,2 Jennifer H. Pinney,1 Hannah V. Giles,1 Yu sanedar Aung,1,2 Paul Cockwell.1,2 Univ Hospital Birmingham, UK; 1, University of Birmingham, UK.

Background: Elevated involved immunoglobulin light chain (FLC) is a major cause of renal impairment (RI) in myeloma. Relationships between presentation and post-induction (PI) renal function and serum FLC levels are not established.

Methods: We used central laboratory data from the MRC Myeloma IX trial which compared bisphosphonate and thalidomide-based therapies. Patients were divided into 3 categories: FLC ≥600 mg/L; FLC 30-59 mg/L; and FLC <30 mg/L. Median eGFR for light chain only myeloma (LC) was also significantly lower than those with IgG and IgA myeloma (49 [IQR 28-78] vs 62 [IQR 47-79] vs 63.5 [IQR 42.2-82.0]; P=0.0001). Patients with a difference between involved and uninvolved FLC (dFLC) ≥500 mg/L had a lower eGFR compared to those with dFLC 100-499 mg/L and dFLC <100 mg/L (52 [IQR 35-72] vs 66 [IQR 52.0-82.2] vs 67 [IQR 54.2-82.0]; P=0.0001). A dFLC level of 700 mg/L was the optimal cut-off value for prediction of severe RI, with an AUC of 0.80. Factors associated with eGFR at presentation were: age, log10 dFLC, male gender and LCO myeloma. On censoring those with dFLC <7000 mg/L; age and log10 dFLC were still associated with eGFR at presentation but not male gender and LCO myeloma. Factors that were independently associated with RI at PI were: age (odds ratio [OR] 1.033, P<0.0001); creatinine measure at OR (0.93, P<0.0001) and attainment of VQPR (very good partial response) compared to <PR (partial response) serum FLC response (OR 0.52, P=0.005).

Conclusions: Age and serum FLC level predict eGFR at presentation and age, presentation eGFR, and serum FLC response predict PI renal outcome.

SA-PO214

Urinary Biomarkers Improve the Prediction and Prognostic Assessment of Acute Kidney Injury in Critically Ill Patients

Patrick T. Murray, Teresa Martin, Eoin J. Cotter. UCD Clinical Research Centre, School of Medicine, Univ College Dublin, Dublin, Ireland.

Background: Acute kidney injury (AKI) is common in intensive care unit (ICU) patients, and is diagnosed late by serum creatinine. New biomarkers may permit earlier detection and better management.

Methods: All patients admitted to the ICUs of two university hospitals were screened for this prospective cohort study. Clinical information and urine were collected on admission and daily for 7 days. Urine biomarkers analysed were neutrophil gelatinase-associated lipocalin (NGAL), α- and β-glutathione-S-transferases (GSTs), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), creatinine, and albumin. AKI was defined by modified KDIGO criteria, using ICU admission creatinine as reference. Values were compared between those who did or did not develop AKI or 30d adverse clinical outcomes (RRT or death). ROC curves were generated for prediction of AKI and outcomes by a clinical score (including age, gender, serum creatinine & urine, albumin output) and urine biomarker values on admission. In patients developing AKI, ROC curves were similarly generated for the prediction of clinical outcomes with values obtained at time of AKI diagnosis.

Results: 659 patients were enrolled; 181 patients (27%) developed AKI within 7d of ICU admission. AKI stages at diagnosis were: Stg1 (n=181, 41%), Stg2 (n=73, 17%), Stg3 (n=93, 46%). On admission, addition of a panel of AKI biomarkers significantly but modestly improved prediction of AKI developing within the first 48h in ICU (AUC: 0.79±0.012), compared to clinical score alone (0.77±0.011; p=0.0001). AKI biomarkers similarly improved the prediction of AKI developing within the first 7d (0.73±0.15), compared to clinical score alone (0.69±0.07; p=0.0003); and marginally improved the prediction of 30d RRT or death (0.7±0.1 vs 0.69±0.1; p=0.05). In patients developing AKI, AKI biomarkers at the time of diagnosis significantly improved prediction of 30d adverse clinical outcomes (RRT or death): 0.77±0.19, compared to clinical score alone (0.68±0.13; p=0.01).

Conclusions: Urinary biomarkers combined with standard clinical tests improved prediction of AKI and outcomes in ICU patients, on admission and at AKI diagnosis.

SA-PO215

Association of Growth Factor Biomarkers with Acute Kidney Injury and Long-Term Mortality in Adults following Cardiac Surgery


Background: Following the structural damage and functional impairment from acute kidney injury (AKI), the kidney undergoes a coordinated process of repair involving regenerative growth factors. We conducted an ancillary analysis of a large, prospective study of adults undergoing cardiac surgery to investigate the utility of epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) in predicting kidney injury and mortality.

Methods: Patients undergoing cardiac surgery at high risk for AKI were enrolled at six academic centers. AKI was defined as a doubling in serum creatinine from baseline or receiving acute dialysis during the hospital stay. Postoperative plasma levels of EGF, VEGF, and a combination model of the two growth factors were evaluated for association with outcomes of AKI or long-term, all-cause mortality at a mean follow-up of 3 years.

Results: First postoperative and peak plasma EFG were not associated with AKI. Elevated peak plasma VEGF was independently associated with increased risk of AKI (adjusted odds ratio [OR] 7.4, 95% confidence interval [CI] 1.1–47.9). Elevated first postoperative VEGF was inversely associated with a lower risk of mortality (adjusted HR=0.67; 95% CI: 0.47-0.97). Elevated first postoperative VEGF was likewise associated with a lower risk of mortality (unadjusted HR=0.36; 95% CI: 0.16-0.82), though the association was attenuated following adjustment (adjusted HR=0.36; 95% CI: 0.15-1.04). When used conjointly, elevated levels of first postoperative EGF and VEGF together were independently associated with a lower risk of mortality (adjusted HR=0.28; 95% CI: 0.11-0.72).

Conclusions: Postoperatively, EGF and VEGF are released in response to AKI, and their concentrations were inversely associated with long-term mortality. These growth factors may serve as biomarkers of long-term outcomes in adults undergoing cardiac surgery.

SA-PO216

Prolactin as a Predictor of AKI in Patients with Sepsis

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Background: Sepsis is a common cause of AKI. Identifying patients at risk for AKI could improve clinical outcomes. Prolactin (PCT) reflects accurately the presence of sepsis and its severity. We evaluated the role of PCT as predictor of AKI in septic patients.

Methods: Cross-sectional study of 72 septic patients between January to December 2014. Patients with SCr >1.5 mg/dl before admission, ESRD patients and those with autoimmune comorbidity were excluded. PCT, Scr, urea, and WBC were measured on admission, and at 24 and 48 h of hospitalization. X2 and t-test were used when appropriate. A ROC curve for PCT value on admission as well as the area under the curve (AUC), the standard AUC error, and sensitivity and specificity of PCT values were determined.

Results: Patients' mean age was 50.8 y (18-79); 37 (51.4%) were women. 18 (25%) patients had PCT value at <0.5 mg /mL (negative) and 54 (77%) >0.5 mg/mL (positive) on admission. Forty-two (58.3%) patients developed AKI, 19 (45.2%) KDIGO 1, 12 (28.6%) KDIGO 2, and 11 (26.2%) KDIGO 3. Of the 42 patients who developed AKI, 37 (88.1%) had a positive value of PCT at admission (p<0.01, OR 5.659, 95% CI 1.738 to 18.425). The ROC PCT for C statistic of 0.75 (p<0.0001, 95% CI 0.639-0.862). The cutoff of 2.565 mg /mL of PCT had the highest validity for predicting AKI with an SE of 61.9%, one SP of 80%, a PPV of 44.52%, 56.18% NPV, LR + LR of 0.80 and 0.77, respectively. Fig. 1

AUC of 0.75 (p<0.0001, 95% CI 0.639-0.862).

Funding: Other NIH Support - R01HL085757

Conclusions: We found a significant association between levels of PCT and development of AKI in patients with sepsis. A cutoff PCT value of 2.565 mg/mL on admission had the highest validity for predicting AKI. Early recognition of septic patients at risk for AKI with PCT could improve clinical outcomes in this population.
Elevated Erythropoietin Concentration in AKI Is Associated with IGFBP-1 Rather Than Hemoglobin

**Background:** EPO expression will be increased by hypoxia in the kidney and hypoxic injury plays a crucial role in pathogenesis of AKI. However, little is known about blood EPO levels in critically ill patients complicated with AKI.

**Methods:** This study prospectively enrolled 98 adult critically ill patients who admitted to the adult ICU. We measured plasma EPO and also measured plasma IGFBP-1 as a hypoxic marker, which is produced mainly by liver, and plasma NGAL and urinary NAG as renal damage biomarkers on ICU admission. This study was conducted to evaluate whether plasma EPO levels in AKI patients was regulated by other factors than anemia.

**Results:** AKI occurred in 42 (42.9%) patients. Significantly higher plasma EPO in the AKI group was detected compared with the non-AKI group (16.13 [9.87–28.47] mIU/mL versus 27.81 [10.16–106.02] mIU/mL, p<0.05). Plasma EPO concentration was strongly and negatively correlated with hemoglobin in the non-AKI group but not in the AKI group.

**Conclusions:** Plasma EPO had a predictive value for diagnosing AKI but it itself had a limited value for distinguishing prerenal AKI from other causes of AKI.

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

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

**Underline represents presenting author.**

**SA-PO218**

Predictive Value of Plasma Neutrophil Gelatinsase-Associated Lipocalin (NGAL) to Distinguish Prerenal AKI to Other Causes of AKI

**Background:** Plasma Neutrophil gelatinase-associated lipocalin (NGAL) is a promising biomarker for acute kidney injury, but it’s role for distinguishing prerenal AKI from other causes is not well known. The aim of this study was to evaluate the predictive value of plasma NGAL to distinguish prerenal AKI to other causes of AKI.

**Methods:** We reviewed all NGAL test from December 26, 2011 to February 28, 2015 in Konkuk University Medical center (Seoul, Republic of Korea) and subtract patients who taken factional excretion of sodium (FENa) test at the same time. Patients were first grouped with Acute Kidney Injury Network (AKIN) stages and evaluated it’s diagnostic role for AKI and second divided with prerenal AKI and other causes of AKI.

**Results:** Total 5814 NGAL test were done from December 26, 2011 to February 28, 2015 in Konkuk University Medical center, and 495 patients taken FENa test at the same time.

**Conclusions:** Plasma NGAL had a predictive value for diagnosing AKI but it itself had a limited value for distinguishing prerenal AKI from other causes of AKI.

**SA-PO219**

Neutrophil/Lymphocyte Ratio for Early Detection of Acute Kidney Injury (AKI) in Patients Admitted to the Emergency Room

**Background:** Neutrophil to lymphocyte ratio (NLR) is a readily available biomarker of systemic inflammation. Several studies have provided evidence of an association between elevated NLR and adverse outcomes in a variety of medical and surgical conditions, including CKD. In this study, we evaluated the predictive capacity of single Emergency Room (ER) measurement of NLR for early diagnosis of acute kidney injury (AKI).

**Methods:** We prospectively studied 294 patients aged 71.6 ± 17. NLR was measured at presentation to the ER. AKI was defined as a new-onset 1.5-fold or more increase in serum creatinine or a 25% decrease in estimated GFR sustained for at least 3 days despite volume resuscitation. The primary outcome was AKI. Secondary outcome was in-hospital mortality.

**Results:** 36 patients (12.2%) developed AKI and 26 (9%) died. Mean NLR was significantly higher in AKI compare to non-AKI patients (11.7 ± 15.2 vs 6.45 ± 7.19, p=0.048). A multivariate model adjusted for age, gender, blood pressure, and plasma creatinine or a 25% decrease in estimated GFR sustained for at least 3 days despite volume resuscitation. The primary outcome was AKI. Secondary outcome was in-hospital mortality.

**Conclusions:** Single ER measurement of NLR can be a useful tool for early diagnosis of AKI. This finding is particularly important in light of the widespread availability and low cost of NLR, especially compared with other biomarkers currently under study in the context of AKI.

**SA-PO220**

Urine Klotho in Human AKI

**Background:** Klotho deficiency has been observed in experimental AKI and low Klotho post-AKI is associated with progression to CKD in rodents. We report the first study of Klotho in human AKI.

**Methods:** We conducted a prospective study of 29 AKI patients and 29 controls without AKI in the ICU setting. We excluded patients with baseline GFR<60 or kidney transplant. Urine samples were obtained within 24h of peak serum creatinine (SCr) or at RRT initiation.

**Conclusions:** Plasma NGAL had a predictive value for diagnosing AKI but it itself had a limited value for distinguishing prerenal AKI from other causes of AKI.
in AKI cases, and within 24h of ICU admission in frequency-matched controls. AKI was defined by KDIGO criteria. Longitudinal data from AKI cases were obtained throughout hospital stay. Renal recovery was defined as the ratio of follow-up SCr/baseline SCr ≤1.5. Urine Klotho was measured by immunoprecipitation-immunoblot. Mixed-effects linear models were constructed to assess longitudinal trends of Klotho in AKI survivors.

Results: Mean (SD) age was 58 (17) years, 62% were men and 75% white. Patients with AKI had higher critical illness scores than controls without AKI. Five (17.2%) patients died and 8 (27.6%) required RRT in the AKI group. Only 3.5% patients died in the control group. Urine Klotho adjusted by urine creatinine (uKlotho/Cr) was significantly lower in AKI cases than in controls, median 10 [IQR 4–20] vs 28 [14–52] fmol/mg, p=0.003. Furthermore, uKlotho/Cr significantly increased with time in patients that exhibited renal recovery (n=7, Δ+216%, p=0.05) but not in those that did not (n=7,Δ+8%, p=0.91), median follow-up 24 days.

Conclusions: uKlotho/Cr is significantly lower in patients with AKI when compared to ICU controls without AKI. uKlotho/Cr recovered only in patients that recovered kidney function. Klotho may serve as a prognostic marker for AKI recovery.

Funding: Other NIH Support - University of Texas Southwestern Medical Center; O’Brien Kidney Research Core Center (NIH, P30 DK079328-06) and the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH, UL1TR001105).

SA-PO221

Biomarkers of Acute Kidney Injury in Children Treated with Cisplatin

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Figure 1: Biomarkers During AV1 and AV2 Cisplatin Infusions. AV1 refers to first or second Cisplatin cycle of treatment plan and AV2 refers to third or later Cisplatin cycle of treatment plan. Biomarkers collected at 3 time points: Pre-infusion (just before infusion start), post-infusion (morning after infusion), discharge (just before hospital discharge).

A) Urine NGAL Levels

B) Urine KIM-1 Levels

C) Serum Cystatin C Levels

Results:

- mean (SD) age was 58 (17) years, 62% were men and 75% white. Patients with AKI had higher critical illness scores than controls without AKI. Five (17.2%) patients died and 8 (27.6%) required RRT in the AKI group. Only 3.5% patients died in the control group. Urine Klotho adjusted by urine creatinine (uKlotho/Cr) was significantly lower in AKI cases than in controls, median 10 [IQR 4–20] vs 28 [14–52] fmol/mg, p=0.003. Furthermore, uKlotho/Cr significantly increased with time in patients that exhibited renal recovery (n=7, Δ+216%, p=0.05) but not in those that did not (n=7,Δ+8%, p=0.91), median follow-up 24 days.

Conclusions: uKlotho/Cr is significantly lower in patients with AKI when compared to ICU controls without AKI. uKlotho/Cr recovered only in patients that recovered kidney function. Klotho may serve as a prognostic marker for AKI recovery.

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SA-PO222

Elevated Renal Injury Biomarkers Fall Transiently After Stenting in Human Atherosclerotic Renal Artery Stenosis (ARAS)

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A similar pattern is seen in AKI and non-AKI groups and when expressing BioM/urine creatinine(not shown).

Conclusions: This is a novel study of AKI BioM excretion in CisP-AKI. NCI-AKI is more common than SCR-AKI. The immediate BioM drop post-CisP may be related to injury protection from high fluid rate and/or urinary alkalinization peri-CisP. Our larger sample size will allow to further characterize BioM excretion and evaluate BioM associations with AKI definition and outcomes.

Funding: Government Support - Non-U.S.
date, it is unclear which intrinsic factors trigger the onset of SIRS and associated AKI. We investigated the role of mtDNA during systemic inflammation and AKI and the role of platelets herein.

Methods: Human platelets were stimulated with mitochondrial DNA, genomic DNA or unmethylated CpG-enriched oligonucleotides (CpGODN). Platelet activation was measured with FACs. In a single centre prospective observational study we included 37 patients diagnosed and classified for the onset of SIRS with or without the development of AKI that were admitted to the ICU. As a control we included (n=25) patients after elective major surgery without a diagnosis of either SIRS or AKI. Blood and urine samples were isolated and processed. Free circulating plasma and urinary mtDNA was determined by RT-PCR. Inflammatory mediators and PF4 in urine were measured using specific ELISA.

Results: Mitochondrial DNA, but not genomic DNA triggered platelet activation. Unmethylated CpG ODN, dose dependently stimulated platelet activation. Compared to ICU-controls, critically ill patients with SIRS demonstrated elevated levels of plasma and urinary mtDNA and proinflammatory cytokines. Compared to SIRS patients without AKI, the patients with AKI displayed elevated levels of urinary PF4 indicative of platelet activation.

Conclusions: The development of AKI in critically ill patients is associated with platelet activation, possibly triggered by mitochondrial DNA.

SA-PO225
Iniders in the Night: Sleep Apnea and Sub-Clinical Renal Injury
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Background: Sleep apnea is common in patients with CKD. We postulated that sleep apnea may cause renal injury through repeated ischemia-reperfusion. The current study correlated overnight changes in urinary excretion of renal injury biomarkers with severity of sleep apnea.

Methods: 39 consecutive participants in the SNORE Study, a longitudinal study of sleep apnea and kidney function decline, underwent overnight sleep study and provided spot urine samples before and after sleep. We measured urinary NGAL, L-FABP, KIM-1, and urinary creatinine levels, and correlated differences between AM and PM levels (AM-PM) with severity of sleep apnea or hypoxia. Sleep apnea was defined by the apnea-hypopnea index (AHI, events/hour); hypoxia was % total sleep time ≥90% O2 (%TST90). Data were log-transformed to normalize distribution.

Results: Patient characteristics: Mean age, 73.6 ± 8.4 years; 90% male; 87% Caucasian, 13% black; BMI 29.4 ± 4.2 kg/m2; MDRD GFR, 34.3 ± 18.1 ml/min/1.73 m2; Median urinary albumin/creatinine ratio, 46 mg/g Cr [IQR 9-357 mg/g Cr]; 69% had sleep apnea (AHI≥5); median AHI, 10 [IQR 2-23]; median %TST90, 15 [IQR 3-22] with 34% %TST90<10%. Higher %TST90 was correlated with higher AM KIM-1 values (r=0.40, p=0.01) and greater increase in urinary KIM-1 (AM-PM) (r=0.32, p=0.04). None of the remaining biomarkers correlated with %TST90. Also, none of the overnight urine biomarker changes correlated with AHI.

Conclusions: The correlation of KIM-1 with hypoxia suggests that SA may contribute to CKD through ischemic renal injury. Future studies with larger sample size and in non-CKD populations are needed to further test this hypothesis.

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SA-PO226
Body Mass Index and Acute Kidney Injury in Hospitalized Patients
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Background: Acute kidney injury (AKI) is common in hospital settings. The association between AKI and Body Mass Index (BMI) in general hospitalized patients is not clear. This study is to explore the incidence of AKI and the impact of BMI on AKI in hospitalized patients.

Methods: This was a single centre, retrospective, case-control study. All patients aged 21 or above under in-hospital care from January to December 2013 were recruited for analysis. We calculated the incidence of AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria among different BMI groups (underweight [BMI < 18], normal [BMI 18-25], overweight [BMI 25-29] and obese [BMI ≥ 30]), and then analyzed the risks of developing AKI within and between groups. Baseline creatinine was defined by the most recent value obtained in hospital up to 12 months before admission. If no previous serum creatinine was available, the lowest serum creatinine during hospitalization was used instead. If only one serum creatinine result was known during hospital stay, the baseline creatinine was estimated by the use of simplified Modification of Diet in Renal Disease (MDRD) formula (assuming a glomerular filtration rate [GFR] of 70 ml/min per 1.73 m2).

Results: A total of 12567 patients were recruited for analysis. Mean age was 62.5 ± 18.5 years. Male patients constituted 53.8% of the study population. 61.9% were Chinese ethnicity. There were 2656 patients suffered from AKI (21.1% of the whole study population), among which 10.7% reported a 10% or more increase in serum creatinine within 48 hours. Underweight patients (BMI < 18) had statistically significantly more stage 1 AKI than the rest of the population, while patients with BMI ≤ 25 had more stage 2 AKI (stage 1 AKI for underweight, normal, overweight and obese patients was 15%, 10.2%, 9.4% and 10.3% respectively; stage 2 AKI, 7.6%, 6.3%, 6.4% and 5.2% respectively). There was no difference in frequency of stage 3 AKI among different BMI groups.
Conclusions: Preliminary results revealed underweight hospitalized patients had increased risks of developing stage 1 AKI. Stage 2 AKI was more commonly seen in patients with BMI ≤ 25. BMI status was not associated with the development of severe AKI (stage 3).

SA-PO227

Hypermagnesemia as a Risk Factor for the Mortality in Intensive Care Unit Patients with Acute Kidney Injury. Shumichi Shibazaki, 1 Makoto Araki, 1 Kohel Miura, 1 Dajo Inaguma. 2 Dept of Nephrology, Sawa Central Hospital, Chino, Nagano, Japan; 2 Dept of Nephrology, Nagoya Daini Red Cross Hospital, Nagoya, Aichi, Japan.

Background: We need an easily measured biomarkers predicting for the mortality in acute kidney injury (AKI) because of high mortality rate. Therefore, we paid attention for serum magnesium (sMg) levels which reflects the renal tubular damage, and study the relationship sMg and prognosis in intensive care unit (ICU) patients with AKI.

Methods: A cohort study was conducted by collecting data from January to December 2014 in Nagoya Daini Red Cross Hospital. According to sMg at ICU 1st day, three groups were divided; low Mg group (sMg < 1.8mg/dL), normal Mg group (1.8mg/dL ≤ sMg < 2.6mg/dL), and high Mg group (sMg ≥ 2.6mg/dL). AKI was defined as serum creatinine (SCr) abrupt (within 7 days) increase to ≥ 1.5 times baseline or SCr increase by ≥ 0.3mg/dL. The primary endpoint was 28 days mortality after ICU admission. The secondary endpoint was the renal recovery rate, the renal replacement therapy (RRT) induction rate, and the transition rate to maintenance dialysis. Renal recovery was defined as an absence of AKI.

Results: Out of 1614 ICU patients, 200 patients were included. The number of each groups are following; low Mg group was 55, normal Mg group was 115, and high Mg group was 30. The mortality was higher in high Mg group than in other Mg group (p = 0.011). A multivariate analysis identified high Mg group as an independent risk factor for the mortality (p = 0.014). High Mg group had 2.39-fold increased odds of mortality against normal Mg group (95% CI 1.04 - 5.50). Kaplan-Meier curves showed the high Mg group was 30. The mortality was higher in high Mg group than in other Mg group (p = 0.011).

SA-PO228

Gemcitabine-Induced Thrombotic Microangiopathy (TMA): A Report from the French Pharmacovigilance Network. Noemie Jourde-chiche, 1 Florence Daviet, 1 Frank Rouby, 1 Bertrand Gondouin, 1 Marion Sallec, 1 Julie Moussi- Francois, 1 Stephanie Burty, 1 Pascale Poullin, 1 Bertrand Dussol, 1 Joelle Micallef. 2 Nephrology, Aix-Marseille Univ, Marseille, France; 2 Pharmacology and Pharmacovigilance, Aix-Marseille Univ, Marseille, France; 3 Hemapheresis, Aix-Marseille Univ, Marseille, France.

Background: Gemcitabine is a chemotherapy which use can be limited by renal adverse events, in particular thrombotic microangiopathy (TMA). This study evaluated the occurrence of gemcitabine-induced TMA, and described therapeutic strategies and outcomes.

Methods: All spontaneous reports of TMA attributed to gemcitabine in the French Pharmacovigilance Network database, between January 2000 and May 2015, were reviewed using a standardized questionnaire.

Results: 81 cases of TMA were reported in 48 male (59%) and 33 female (41%), with a median age of 63.5 yrs (range 39-87). Gemcitabine was prescribed for pancreatic (58%), pulmonary (15%), breast (8%), biliary tract (6%), urinary tract (5%), testicular (1%) or liver (1%) cancers, or T lymphoma (3%). TMA occurred after a median of 7 months (range 0.2-60), and a median cumulative dose of 21.8g (range 1.1-48.6). Main cancers reported were testicular (12.1%), 69 (2.8%) and 46 (1.8%) were of stage 1, 2 and 3, respectively. Incidence of AKI creatinine level was 1.8 mg/dL (range 0.8-17). In 6 patients, renal TMA was biopsy-proven. Renal replacement therapy was required in 10 (12%) patients, plasma exchanges (PEx) were performed in 17 (21%), 8 (10%) received fresh frozen plasma infusions, 9 (11%) corticosteroids, and 3 (4%) eculizumab (after PEx failure). Evolution data were available for 59 (73%) patients, among which the 17 treated with PEx. Hematological and renal remission was achieved in 35% with PEx versus 50% without, hematological remission without renal improvement in 18% with versus 26%, and no improvement was observed in 47% with versus 24% without PEx. Only one patient improved with eculizumab.

Conclusions: Gemcitabine treatment can be associated with TMA and severe renal adverse effects. The benefit of plasma exchange or eculizumab in this setting remains uncertain.

SA-PO229

Contribution of Drugs versus Risk Factors in Drug-Induced Renal Injury. Celina D. Cerpeda, 1 Linda Avadlish, 1 Etienne Macedo, 1 Dinna Cruz, 1 Stuart Goldstein, 1 Jorge Cerda, 1 David T. Selsey, 1 Michael Zappitelli, 1 Andrew J.P. Lewington, 1 Ravindra L. Mehta. 1 Nephrology, Univ of California San Diego, San Diego, CA; 2 Nephrology, Univ of Cincinnati, Cincinnati, OH; 3 Nephrology, Albany Medical College, Albany, NY; 4 Nephrology, Univ of Michigan, Ann Arbor, MI; 5 Nephrology, Univ of Montreal, Montreal, QC, Canada; 6 Nephrology, Cares Hospital India, Hyderabad, India; 7 Nephrology, St. James’s Univ Hospital, Leeds, London, United Kingdom.

Background: Drug-induced renal injury (DRI) is an increasing cause of acute kidney injury (AKI). Attribution of DRI requires consideration of the drug exposure, the number of drugs involved and underlying or concomitant risk factors (RF). We hypothesized that underlying RF would influence attribution of DRI.

Methods: The drug induced renal injury (DIRECT) study is an ongoing prospective multicenter study evaluating genetic determinants of the drug exposure. Each enrolled case was adjudicated for causality by two independent nephrologists. We analyzed the first consecutive 86 adult and pediatric AKI cases. We evaluated the percent agreement, kappa statistic, and contribution of each drug (in setting of multidrug injury) and AKI RF.

Results: Adjudicators agreed 87.2% (n=75) had DRI. For non-DRI cases, causality could not be established because of competing AKI RF. RF contributed to AKI in 86% of adults and 70% of children. Adjudicators disagreed on the percent attribution for each drug in 52%. For DRI cases, inter-rater agreement on percentage attributed to drug 1 was 48% with kappa=0.239 (p=0.001). For non-DRI cases, inter-rater agreement for drug 1 was 81.8% and RF attribution was 90%.

Conclusions: Underlying RF are common in DRI associated AKI. Causality assessment in DRI is complex due to difficulty in determining the attribution of drug and RF. CAT for DRI should incorporate AKI RF and their interaction with drugs.

Funding: Private Foundation Support

SA-PO230

Reduced Incidence of Post-Operative Acute Kidney Injury After Cardiovascular Surgery. Dadi Helgadottir, 1, 2 Boris E. Long, 1 Solveig Helgadottir, 1 Tomas Gudbjartsson, 3, 5 Gisli H. Sigurdsson, 2, 6 Martin I. Sigurdsson, 2, 6 Olafur S. Indridason. 1 Dept of Medicine; 1 Dept of Anesthesia and Intensive Care; 2 Dept of Cardiothoracic Surgery, Landspitali, Reykjavik; 3 Dept of Anesthesia, Brigham and Women’s Hospital, Boston; 4 Div of Nephrology, Landspitali; 5 Faculty of Medicine, Univ of Iceland, Reykjavik, Iceland.

Background: Acute kidney injury (AKI) is a serious complication of cardiac surgery. The aim of this study was to examine time trends in incidence and survival of patients diagnosed with AKI following cardiac and thoracic aorta surgery.

Methods: This was a retrospective study of all heart and thoracic aorta operations performed on adults in Iceland from 2007 to 2014. AKI was diagnosed according to the KDIGO criteria based on serum creatinine values in the electronic database of the clinical laboratory at the institution. Survival status was verified at Statistics Iceland. The incidence of AKI and its outcome was compared between the first and second half of the 8 year study period using Chi squared and the Kaplan Meier method. Outcome between AKI and non-AKI patients was compared by propensity score matching (1:2, non-replacement matching).

Results: A total of 2224 patients underwent 2502 operations during the study period, of which 228 (9%) were acute open heart surgery (range 10.7-9.7%). AKI occurred after 417 operations (16.7%). Of these 302 (12.1%), 69 (2.8%) and 46 (1.8%) were of stage 1, 2 and 3, respectively. Incidence of AKI

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decreased from 19.2% in the first period to 14.5% in the second period (p=0.002). Survival of AKI patients at 30 days and 1 year did not differ between time periods, being 82.6% vs. 83.8% and 79.5% vs 76.8%, respectively (p=0.10). Survival was worse for patients with AKI compared with the propensity score matched control cohort, both at 30 days (86.1% vs. 96.5%, p=0.0001) and at 1 year postoperatively (81.2% vs. 91.5%, p=0.0001).

Conclusions: The incidence of AKI following cardiac and thoracic aorta surgery is decreasing. Nevertheless it still affects one in seven patients and even though most patients have mild AKI, it is associated with increased mortality which remains unchanged over the past decade. Funding: Private Foundation Support

SA-PO231
Acute Kidney Injury in Patients with Chronic Kidney Disease: Aetiology and Survival Comparisons to Non-Acute Kidney Injury Chronic Kidney Disease Population Akib Khan,1 James Ritchie,2 Smeeta Sinha.3 Background: AKI, described by an acute (hours to days) fall in kidney function, is associated with significant morbidity and mortality. Poor outcomes exist when AKI is superimposed on CKD, a disease involving structural or functional renal abnormalities in a chronic setting (>3 months). We present a single-centre prospective observational study; retrospectively analysed. We determine the factors surrounding AKI on CKD. Aetiology, length of stay, specialist review and medication data were examined. We compare AKI on CKD patients’ survival to matched non-AKI CKD patients.

Methods: CRISIS database CKD patients matching inclusion criteria treated at Salford Royal Foundation Trust were studied (n=942). A 2.0-3.0 and >3.0 times serum creatinine increase was defined to define Acute Kidney Injury Network stages 2 (n=17) and 3 (n=10) events respectively. Controls were matched by age, eGFR and blood pressure. Logistic Regression, Cox-Hazard Ratio and Kaplan-Meier Survival Plots were used.

Results: Aetiological factors associated with AKI included sepsis (48.1%), drug-induced (29.6%) and dehydration (25.9%). Septic-AKI had a 1.405 odds ratio (95%CI:0.099-19.936,p=0.801) of death compared to non-septic events. Hazard ratio for death due to AKI on CKD compared to non-AKI CKD was 1.77 (95%CI:0.72-4.33,p=0.207). Kaplan-Meier survival function clearly demonstrates this.

Conclusions: Aetiology of AKI in our patient group was similar to that seen in non-CKD studies. There was a clear trend towards increased all-cause mortality in patients with AKI on CKD in comparison to non-AKI CKD patients. Renal function decline rate following AKI on CKD should be explored in the future.

SA-PO232
Prospective Study of Incidence and Early Detection of Acute Renal Failure in Preterm Babies in a Tertiary Center in South India Indira Agarwal, Nithya Ponmudi, Anil K. Kuruvilla, Vijayakumar Theophilus-Sunder. Pediatric Nephrology, Christian Medical College, Vellore, Tamil Nadu, India; Neonatology, Christian Medical College, Vellore, Tamil Nadu, India; Nephrology, Christian Medical College, Vellore, Tamil Nadu, India.

Background: Preterm babies are at risk for ischemia, hypovolemia and hypotension and thus vulnerable to Acute kidney injury (AKI). We aimed to study the incidence and predisposing factors for AKI in preterm babies and to assess the usefulness of urinary NGAL as a predictor of kidney injury.

Methods: Babies born < 32 weeks+6 weeks were recruited; those with abnormal antenatal renal scans and major congenital anomalies were excluded. Weekly monitoring of urine output, clinical progress, interventions, ventilation, unexpected events and use of nephrotoxic drugs was done. Serum creatinine and urine NGAL was collected at 72 hours of age and weekly thereafter. Descriptive statistics using mean±SD for continuous variables, ANOVA and chi-square test for AKI detection test for categorical variables and Risk factor analysis using log binomial was performed.

Results: Of the 4823 live births, 80 fulfilled inclusion criteria (10.14%). The incidence of AKI was 12.6%. The risk factors included oligosuuria, PDA, nephrotoxic drugs, low Apgar, mechanical ventilation, CPAP and abnormal antenatal scans. Urine NGAL was estimated in 31 babies. It rose earlier and was significantly elevated in those on mechanical ventilation by week 2 while Creatinine rose only by week 3.

Conclusions: NGAL was inversely proportional to gestational age and birth-weight. Both NGAL rise and creatinine were higher in babies with AKI associated with NSAIDS, umbilical lines and asphyxia.

SA-PO233
Acute Kidney Injury Electronic Alerts in Primary Care Conor Patrick Moran,1 Ying C. Kuan,2 Patrick Lm Lynch,2 Francis Mccarroll.1 1Dept of Nephrology, Altnagelvin Hospital, Londonderry, United Kingdom; 2Dept of Clinical Chemistry, Altnagelvin Hospital, Londonderry, United Kingdom.

Background: Acute Kidney Injury, (AKI), is common with a variably reported mortality, (15-60%). A UK national audit reported that up to 30% of cases were avoidable and that as much as 43-61% of post-admission AKI experienced an unacceptable delay in recognition. AKI is regarded as the remit of Secondary Care and there have been few studies examining Community Acquired AKI, (CA-AKI). Guidelines have recommended the utilised electronic alerts (e- alerts) for AKI in both Primary and Secondary care. We examined the incidence and mortality of CA-AKI.

Methods: We introduced AKI e-alerts with accompanying c-guidance in late October 2014 and prospectively collected data on the patients identified with severe AKI in Primary, Community and Secondary care. Data collection was carried out for 3 months. The demographics of both cohorts were compared.

Results: Median age, (74.5 years vs. 75 years), gender distribution, (M:F: 48% / 52% vs. 44.5% / 55.5%), and median time to death, (8 days vs. 11 days), were comparable. 44 Alerts were from Primary Care and 77 from Emergency Department. Of the Primary Care Alerts, 20 patients were subsequently admitted. Of those who were not, 3 died within 30 days, (1. Died at 5 days, 2. Died at 8 days, 3. Died at 21 days). Despite this, Community-acquired AKI was associated with a 30-day mortality of 10.7%. Hospital-acquired AKI, (HA-AKI), was associated with a 28.2% 30-day mortality, (p=0.001). Sub-group analysis showed Primary care alert associated with 13.64% mortality and Primary Care alerts with 9.76%, (p=0.001). Median Age at Death; CA-AKI 80 years. Median time to death; CA-AKI 5 days, HA-AKI 11 days.

Conclusions: AKI is common and associated with a significant morbidity and mortality. CA-AKI is common opportunities at diagnosis and intervention are often missed with grave
consequences. Appropriate management of CA-AKI can help reduce the economic and physical burden associated with AKI and reduce the long-term burden of CKD. Further work is required to expand the role of AKI e-Alerts in Primary Care.

SA-PO234

Acute Kidney Injury Causes and Outcome: A Single Center Experience from Sudan

Maha Farah,1 Len A. Usvyat,3,4 Roberto Pecoits-Filho,1 Peter Kotanko.3,5

Background: Acute kidney injury (AKI) is a challenging problem in Africa—a diverse continent with regards to population and financial and medical resources. There are no reliable statistics about the incidence of AKI in Africa. Based on sporadic regional publications the incidence has been estimated at 150 per million population. In addition to infectious diseases; toxins play a major etiologic role in AKI.

Methods: In this study we analyzed data from Omer Belal Renal Center in Soba University Hospital, Sudan, a tertiary referral center with a catchment area of 3 million citizens. All hemodialysis (HD) patients treated for AKI in the period between 1/1/2013 and 12/31/2014 were included in the study.

Results: Out of 520 hemodialysis patients we identified 69 patients with AKI; 39 (56.5%) were males. The mean±SD age was 40.5±17.4 years. Serum creatinine and blood urea levels on admission were 14.7±6.7 and 245±125 mg/dl, respectively. Serum creatinine and blood urea levels at discharge were 2.5±2.1 and 53±32 mg/dl, respectively. 29 patients (42%) experienced recovery of normal renal function; the recorded mortality was 13 %; AKI causes.

Conclusions: AKI has become increasingly prevalent in developing countries, and is associated with severe morbidity and mortality. Many causes of AKI can be prevented by interventions at the individual, community, and regional levels. Efforts should be directed to eradicate causes of AKI, expedite diagnosis, and aggressively manage pre-renal conditions and specific infections.

SA-PO235

Usefulness of Presepsin, Procalcitonin and IL6 as Biomarkers of Adverse Renal Outcome and Mortality After Cardiac Surgery

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Background: Cardiac surgery (CS) is now possible in increasingly high-risk patients (pts). Accurate evaluation of surgical risk is crucial. Mortality and negative impact on distant organs must be evaluated. In a large number of clinical scenarios, biomarkers have been proven to be reliable tools in clinical settings either for single a single biomarker or a biomarker panels. Presepsin has been reported to be useful for stratifying mortality risk among septic pts in the ICU and thus it may also be helpful in many different clinical situations. Procalcitonin is related to the development of postoperative complications. IL6 is considered to be a major mediator of the acute phase response to cardiopulmonary bypass. The main aim of this study is to assess the usefulness of Presepsin, Procalcitonin and IL6 as biomarkers in predicting mortality and negative renal outcome among CS pts.

Methods: Observational single center study that includes 122 adult CS pts. Blood samples were collected at the second day after surgery. Presepsin was tested by the PATHFIST Immunoanalyzer system, Procalcitonin by BRAHMS PCT sensitive KRYPTOR and IL6 by ELISA assay. A p-value of <0.05 was considered statistically significant.

Results: We observed that Presepsin and IL6 are better predictors of inhospital mortality (AUC=0.831 and 0.819), 30-day mortality (AUC=0.723 and 0.785) than global mortality (AUC=0.759 and 0.793) than Procalcitonin (p<0.05). Pts with worse renal outcome (defined as AKI, expedite diagnosis, and aggressively manage pre-renal conditions and specific infections.

Conclusions: These results indicate that sepsis induces tubular cell proliferation in the condition with less cell death. In the present study, we examined the time-course changes in tubular cell proliferation after sepsis.

Funding: Government Support - Non-U.S.

SA-PO236

Allopurinol Attenuates Rhabdomyolysis-Induced Acute Kidney Injury: Renal and Muscle Protection


Background: Myoglobinuric acute kidney injury (AKI) is the most severe complication of rhabdomyolysis. Aim: To evaluate the efficacy of allopurinol (Allo) on rhabdomyolysis-induced AKI.

Methods: Male Wistar rats were injected intramuscularly with 5mg/Kg body weight (BW) of either 50% glycerol (Gly) or 0.9% saline (S). Five groups were studied: S(n=5), S+Allo(n=6), Gly(n=7), Gly+Allo(n=7), Gly+ivAllo(n=7). S and Gly=Allo rats received Allo(300mg/L) in drinking water 7 days prior to and for 24h after Gly/Injection/Gly+ivAllo; intravenous Allo(50mg/Kg BW) 30’ after Gly injection and 300mg/L in drinking water thereafter.

Results: Gly rats showed markedly reduced glomerular filtration rate (GFR,imulin clearance) associated with renal vascounstruction,renal tubular damage,increased oxidative stress,apoptosis and inflammation. Allo treatment ameliorated all these alterations. Allo reduced muscular oxidative stress and accelerated its recovery.

Conclusions: These results indicate that sepsis induces tubular cell proliferation in the condition with less cell death. In the present study, we examined the time-course changes in tubular cell proliferation after sepsis.

Funding: Government Support - Non-U.S.

SA-PO237

Cell Cycle Progression in the Early Phase of Septic Kidney

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Background: The recovery of renal function after acute kidney injury (AKI) is likely controlled by proliferation of surviving tubular cells in damaged nephrons containing cell death or sloughing. However, recent studies revealed that AKI concomitant with sepsis has significantly less tubular cell death than other forms of AKI, such as ischemic- and drug-induced AKI. It has not been examined whether septic AKI accelerates tubular cell proliferation in the condition with less cell death. In the present study, we examined the time-course changes in tubular cell proliferation after sepsis.

Methods: Lipopolysaccharide (LPS) and cecum ligation and puncture (CLP) model were used to induce sepsis in mice. Cell cycle progression was assessed by intravital imaging of Tg(FucciG1)#596Bsi (Fucci) mice, which express monomeric Kusabira-Orange2 in G1/0 phase cells, and immunohistochemistry for Ki67 or bromodeoxyuridine staining were increased only in young mice (Ki67- cell number: 1.5±0.1 fold increase in both LPS and CLP mice compared to normal control), not in old mice (Ki67- cell number: 0.8±0.1 fold in LPS mice and 1.0±0.1 fold in CLP mice compared to normal control) at a similar time point observed in Fucci mice. Etoposide, an anti-cancer drug, abolished the cell proliferation after LPS injection in young mice. Importantly, old mice or etoposide-treated young mice showed much worse AKI as compared to young mice at 24h after sepsis. Moreover, mice lacking p21, a cyclin-dependent kinase inhibitor, compared to the control) at a similar time course observed in Fucci mice. Etoposide, an anti-cancer drug, abolished the cell proliferation after LPS injection in young mice. Importantly, old mice or etoposide-treated young mice showed much worse AKI as compared to young mice at 24h after sepsis. Moreover, mice lacking p21, a cyclin-dependent kinase inhibitor, showed a marked increase in Ki67- cells after LPS (2.2±0.1 fold increase vs. WT mice).

Conclusions: These results indicate that sepsis induces tubular cell proliferation in the early-phase of septic kidney. This situation may be a compensatory mechanism against the development of AKI since the frequency of cell proliferation is inversely correlated with the severity of sepsis. Moreover, cell senescence may worsen this compensation leading to an increased risk of AKI.

Funding: Government Support - Non-U.S.
Hepcidin Mitigates Endotxin-Induced AKI

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Background: Sepsis is a common cause of acute kidney injury (AKI). Sepsis-associated inflammation induces hypoferrerna and thereby limits iron availability to pathogens. It has been shown that hepcidin-induced degradation of ferroportin and consequent iron restriction are key for this hypoferrernaic state. Since iron has been implicated in the pathogenesis of both sepsis and AKI, we hypothesized that hepcidin pretreatment would mitigate bacte rich endotxin-induced AKI.

Methods: C57BL/6 were treated with saline or 50 mg of hepcidin, 24 hours prior to LPS (Escherichia coli O111:B4) injection (6.5 mg/kg). Renal function, injury and inflammation markers were examined up to 24 hours post LPS injection. Mouse glomerular endothelial cells (MGEc) were cultured with 100 ng/mL LPS for 6 hours after treating with and without 1 mg/mL hepcidin for 12 hours.

Results: Kidney function (as measured by serum BUN) significantly declined 2 hours post LPS injection and progressively deteriorated for 24 hours. This was prevented by hepcidin treatment (BUN: LPS; 83.55 Vs HEP = 32.33, p < 0.001). Renal injury (BUN/kg: LPS 55 Vs HEP = 27.08, p = 0.004) and inflammation markers were also reduced. Mouse glomerular endothelial cells cultured with 100 ng/mL LPS were also reduced. Mitochondria in LPS treated mice, which was prevented by hepcidin treatment. However, MGEc cultures treated with or without hepcidin up-regulated endothelin gene to similar levels after stimulation with LPS.

Conclusions: Our findings demonstrate a novel protective role of hepcidin in endotxinmediated AKI, which is largely exerted through down regulation of systemic cytokine production.

Funding: NIDDK Support

SA-PO239

ELK-B Peptide Prevents Renal Histological Damage and Mortality in Septic Mice

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Background: Targeting SR-BII and CD36 receptors with 37-step peptide, an antagonist peptide, reduced multi-organ failure, peritoneal bacterial counts, and increased survival from 6 to 27% in antibiotic-treated mice subjected to cecal ligation and puncture (CLP)-induced sepsis (J Immunol. 2012). We tested ELK-B, a peptide more specific to the CD36 receptor.

Methods: Because the free peptide was toxic, ELK-B was formulated with micellar 1-palmitoyl-2sn-glyceryl-3-phosphocholine. For survival study, animals were randomized into two groups: CLP (N=16) and CLP+ELK-B (15 mg/kg, N=15). A blinded observer administered treatments every 12h until death or until euthanized per protocol. For acute studies, 10 mice/group were subjected to CLP+saline (CLP) or CLP+ELK-B; saline or ELK-B was administered IV 0 and 6h after CLP. 18h post-CLP mice were euthanized for peritoneal lavage, and blood/organisms collection. Serum creatinine (Cr) was measured by HPLC, BUN by colorimetry, and AST, ALT by an autoanalyzer. PAS-stained kidney sections were scored for renal tubular damage. Peritoneal bacterial cell counts were enumerated by microscopy. Caspase-3 IHC was performed on spleens. Data were analyzed by ANOVA and log-rank test.

Results: ELK-B significantly increased survival: all CLP+vehicle mice died by 78h, whereas 31% of ELK-B treated mice were still alive at 7 days. The survival curves did not diverge until 36h. At 18h (before survival curves diverged), ELK-B did not alter Cr (sham, CLP, CLP+ELK-B 0.07±0.01, 0.30±0.06, and 0.21±0.06 mg/dl); BUN, AST, or ALT.

Conclusions: ELK-B reduced 7 day mortality and 18h renal histological damage after sepsis. However, it did not alter other biochemical outcomes at 18h. That suggests that it may act late in sepsis, perhaps by increasing bacterial killing.

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SA-PO240

Renal Ischemic Preconditioning Prevents Protections against Septic Acute Kidney Injury via miR-21

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Background: Septic acute kidney injury(AKI) is one of the most common and life-threatening complications in critically ill patients, and there is no approved effective treatment. We have shown ischemic preconditioning upregulates miR-21, provides renoprotection against subsequent ischemia reperfusion injury. Here we studied the effects of renal ischemic preconditioning on septic AKI and its mechanisms.

Methods: Bilateral renal pedicles were clamped for 15 min in mice before the induction of septic AKI, and septic AKI was induced by intraperitoneal injection of lipopolysaccharide. The effects of renal ischemic preconditioning on LPS-induced AKI were investigated, including changes of renal function, histology, inflammation and apoptosis in kidneys. The AKI was induced by cecal ligation and puncture in mice. The ischemic preconditioning was examined using in vivo knockdown of miR-21 and miR-21 signaling pathways were analyzed.

Results: We observed that renal ischemic preconditioning provided morphological and functional renoprotection, characterized by attenuation of renal tubular damage, cell apoptosis, and a reduction in inflammation in circulation. Furthermore, we found that renal ischemic preconditioning significantly upregulated the expression of miR-21 in kidneys, suppressed proinflammatory factor PDDC4 expression and NF-kB activity, increased renal production. Meanwhile, renal ischemic preconditioning also suppressed the expression of PTEN which is a proapoptotic protein, activating Akt signaling pathway, subsequently increasing the expression of Bcl-2 and inhibiting Caspase-3. A locked nucleic acid-modified anti-miR-21, given before renal ischemic preconditioning, knocked down miR-21 effectively, and upregulated its target effector PTEN expression, resulting in increase of apoptosis, exacerbated LPS-induced AKI.

Conclusions: Our findings demonstrate that renal ischemic preconditioning protects against LPS-induced AKI, and miR-21 coordinates its downstream signaling to reducing cell apoptosis and circulatory inflammation, contributing to renal protection.

Funding: NIDDK Support, Veterans Administration Support
Background: Anti-tumor efficacy of cisplatin chemotherapy is mainly limited by its toxicity to normal tissues, particularly the kidney toxicity. Tubular apoptotic cell death significantly contributes to the pathogenesis of cisplatin-induced acute kidney injury (AKI). KCa3.1, a calcium-activated potassium channel, has been reported to participate in cell apoptosis. However, the involvement of KCa3.1 in cisplatin-induced AKI is unknown.

Methods: We examined KCa3.1 mediates cisplatin-induced tubular apoptotic cell death in vitro, as well as the development of cisplatin-induced AKI in KCa3.1- and pharmacological blockade mouse models in vivo.

Results: Cisplatin treatment triggered an early induction in KCa3.1 expression, which is associated with apoptotic cell death in HK-2 cells, as well as with the development of renal tubular damage and cell apoptosis in mice. By treating with highly selective blocker TRAM-34, we found KCa3.1 inhibition suppressed cisplatin-induced apoptotic cell death in HK-2 cells. In the in vivo study, KCa3.1 deficiency reduced renal function loss, renal tubular damage and apoptotic marker caspase-3 induction in kidneys after cisplatin administration in KCa3.1-/- mice. Pharmacological blockade of KCa3.1 by TRAM-34 similarly attenuated cisplatin-induced AKI in mice. Furthermore, we dissected the underlying mechanisms in which KCa3.1 blocking reduces cisplatin-induced apoptosis. We found KCa3.1 inhibition attenuated the cytochrome c release and the increase of intrinsic apoptotic mediator Bax, Bcl-2 and caspase-9 after cisplatin treatment. We also found KCa3.1 blocking inhibited the increase of ER stress mediator caspase-12, which is independent of calcium-dependent protease m-calpain activation.

Conclusions: Blockade of KCa3.1 protects against cisplatin-induced AKI through the attenuation of tubular apoptosis by interference with intrinsic apoptotic and ER stress-related mediators, and that provides a potential target for the prevention of cisplatin-induced AKI.

Funding: Government Support - Non-U.S.

SA-PO244
Bax Mimotope Therapy: Effective Treatment for Ischemic Acute Kidney Injury (AKI) Zhiyong Wang, Ryan M. Mulhern, Andrea Havasi, Ramon G. Boneglio, Stephen C. Borkan. Renal Section, Boston Univ Medical Center; Boston, MA.

Background: Ischemic AKI causes renal cell death partly by Bax-mediated apoptosis. Recent studies show that Bax requires the chaperone nucleoschlinoposin (NPM) for mitochondrial targeting and apoptosome formation. We propose that a mimotope that interferes with Bax-NPM interaction is an effective treatment for ischemic AKI.

Methods: To assess mimotope efficacy, 2 mg control or therapeutic Bax mimotope was administrated by a single tail vein injection in 6-week old B6 mice either before or after renal ischemia caused by 20 min of bilateral renal pedicle clamping, an insult that produces severe AKI. BUN/Cr, histologic injury score, caspase 3 activity, Bax activation and Bax-NPM interaction were compared in each experimental group at the above time points (n = 8 each group).

Results: Compared to control, Bax mimotope administration 15 min before or 15 min, 1.2 or 3 h after ischemia significantly improved renal function. No protection was observed if Bax mimotope exposure was delayed for 4 or more hours after ischemia. Although 12% of controls died of AKI, only 2% of animals died in the Bax mimotope groups. Despite equivalent Bax activation in both groups, the Bax mimotope improved histologic injury score, reduced caspase 3 activation and decreased Bax-NPM interaction as assessed by co-immunoprecipitation.

Conclusions:Selective interference of Bax-NPM interaction with a Bax mimotope decreases AKI mortality and ameliorates ischemia-induced renal injury.

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SA-PO245
Role of AMPK in Aristolochic Acid-Induced Acute Kidney Injury Anne-Emilie Deleyes, Inês Jatobá, Vanessa Colombo, Eric De prez, Isabelle Habisch, Kumar Sharma, Nathalie Caron, Joelle L. Nortier. Free Univ of Brussels; Brussels, ‘Namur; ‘Univ of California, San Diego.

Background: Experimental aristolochic acid nephropathy (AAN) is a pertinent model of tubulo-interstitial nephritis characterized by an early phase of acute kidney injury (AKI) with marked tubular injury and a subsequent chronic kidney disease (CKD). In this report, we determined the role of AMPK in renal injury and its involvement in the AKI-to-CKD transition.

Methods: C57BL/6J male mice were randomly subjected to i.p. injection of either sterile saline solution, AA, AAMC (the specific AMPK activator) or AAMC (the specific AMPK inhibitor) for 4 days. Mice were then euthanized either at day 5 or day 20.

Results: AA-treated mice displayed loss of renal function, as reflected by significant increases in plasma creatinine levels and proteinuria at days 5 and 20. In addition, impairment of tubular cells was evidenced by increased urinary lysozymal enzyme N-acetylβ-D-glucosaminidase in AA-treated mice. These changes were prevented by AICAR treatment. To further determine the role of AMPK in AA-induced effects, renal function (Nov 2, and 4) were investigated and showed significant increases in plasma creatinine levels were observed for Nov 2 and 4. However, Nov 2 was significantly increased in AA-treated mice while this rise was prevented by AICAR treatment at day 5 but not at day 20. Moreover, the urinary hydrogen peroxide level, a stable product of ROS production, was significantly higher in AA intoxicated and reduced with AICAR. Regarding inflammation, AA mice exhibited a significant increase in MCP-1 mRNA level. This rise was only prevented by AICAR at day 5. Finally, at day 5, there was no significant macrophage infiltration with AICAR while at day 20, this significant increase was not prevented by AICAR.

Conclusions: These findings suggest a beneficial effect of AMPK against AA-induced AKI. In view of these data, we suggest that chronic AICAR treatment is necessary for complete nephroprotection and recovery. The activation of AMPK represents a potential strategy to prevent the transition from AKI-to-CKD.

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SA-PO246
Nrf2 Activation in Tubular Cells Prevents Progression of AKI to CKD Masahiro Neno, Tomokazu Souma, Sadayoshi Ito, Norio Suzuki, Masayuki Yamamoto. Dept of Medical Biochemistry, Tokohu Univ Graduate School of Medicine, Sendai, Miyagi, Japan; Div of Nephrology, Endocrinology, and Vascular Medicine, Tokohu Univ Graduate School of Medicine, Sendai, Miyagi, Japan; Div of Interdisciplinary Medical Science, Tokohu Univ Graduate School of Medicine, Sendai, Miyagi, Japan.

Background: Acute kidney injury (AKI) is one of the major risk factors for chronic kidney disease (CKD). Reactive oxygen species are generated by ischemia-reperfusion injury (IRI) during transition of AKI to CKD, and oxidative stress contributes to defects of renal tubular cells. Nrf2 is a master transcription factor for cellular defense against oxidative stress and on an E3 ubiquitin ligase substrate Keap1 negatively regulates Nrf2 activity. Here, we evaluated protective roles of the Keap1-Nrf2 system in AKI-to-CKD transition.

Methods: Unilateral ischemia reperfusion injury (UIRI) was performed to induce rodent model of AKI-to-CKD. Hyperoncism Keap1 knockout mutant (KDK) and tubular-specific Keap1-mutant (TKO) mice were used for genetic activation of Nrf2. A Keap1 inhibitor CDDO-Im was used for pharmacological activation of Nrf2.

Results: Remaining tubular areas at 14 days after URI were 64%, 51% and 34% in KDK, TKO and wild-type mice, respectively compared with their contralateral kidneys. CDDO-Im treatment after URI to wild type mice also protected against tubular defects (CDDO-Im, 63%). Nrf2-irreducible antioxidant enzymes (Nqo1, Hmox1, Gclc, Gclm, and Srxn1) were transiently up-regulated in 3-6 hours after URI in wild-type mice, while both genetic and pharmacological activation of Nrf2 maintained expression of these genes at high levels throughout the observation period.

Conclusions: Activation of Nrf2 alleviates IRI-induced tubular loss through enhancing the antioxidant response system. Nrf2 inducers are one of prospective therapeutic candidates for preventing AKI-to-CKD transition.


SA-PO247
Acute Kidney Injury in the Rat Is Prevented by Pirfenidone Isabella Quezalizalli Lima Posada, Quetzaliztli Decleves, Zhiyong Wang, Heng Pao. Renal Section, Boston Univ Medical Center, Boston, MA; Div of Nephrology, Endocrinology, and Vascular Medicine, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan; Div of Interdisciplinary Medical Science, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.

Background: Pirfenidone (PFN) is an orally active small molecule which acts mainly through an anti-fibrotic effect, but also possesses antioxidant and anti-inflammatory properties. This study was designed to evaluate the effect of the prophylactic treatment with PFN on acute kidney injury (AKI) due to bilateral renal ischemia (IR) in the rat. Six groups of rats, 12 rats/group (S) and 21 rats undergoing 20 min of ischemia and 24-h of reperfusion and, 3 rats treated with PFN (700 mg/kg), 24-h before ischemia (IR-PFN). Serum creatinine, creatinine clearance (CrCl) protein excretion, urinary levels of Hsp72 (UHsp72V) and nitrates and nitrates (UNO2/NO3V) were assessed. Mean arterial pressure (MAP) and renal blood flow (RBF) were recorded 24-h after surgery. Tubular injury (TI) was evaluated in fixed kidneys by counting the cast number and the number of injured tubules per field.

Results: As expected, the IR group showed a reduction in CrCl (IR: 0.92 ± 0.04 vs. S: 0.73 ± 0.06 mmol/100 g BW; p < 0.05), urinary output (IR: 20.9 ± 5 vs. S: 32.7±19.3 ml/24-h; p < 0.05), RBF (IR: 1.08 ± 0.37 vs. S: 1.53±0.17 ml/min/100 g BW; p < 0.05), and a significant increase in urinary Hsp72 assessed by Western blot. Extensive TI was evidenced by histological analysis. These alterations were associated with a decrease in UNO2/NO3 (IR: 3.1±1.3 vs. S: 5.4±2.5 mmol/24-h; p < 0.05). In contrast, IR-PFN group showed restoration of CrCl (1.03±1.04 mmol/100g BW; p < 0.05), urinary output (47.5±5.7 ml/24-h; p < 0.05), RBF (1.51±0.15 ml/min/100g weight; p < 0.05). The levels of urinary Hsp72 were undetectable or very low and the histological signs of TI were significantly reduced. Interestingly, UNO2/NO3 was completely reversed (7.05±0.78 mmol/24-h; p < 0.05).

Conclusions: Our results revealed that pre-treatment with PFN prevents AKI in the rat. Part of its renoprotective effects seems to be related with the restoration of NO production. These findings suggest that PFN could be a promising tool in the prevention of AKI. In view of these data, we suggest that chronic AICAR treatment is necessary for complete nephroprotection and recovery. The activation of AMPK represents a potential strategy to prevent the transition from AKI-to-CKD.

Funding: Government Support - Non-U.S.
HDAC8 Plays a Critical Role in the Epigenetic Activation of Fibroblasts and the Pathogenesis of Renal Fibrosis
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Background: The development of renal fibrosis is associated with changes in the expression of approximately 10% of the genome, suggesting widespread transcriptional dysregulation. Nonetheless, the roles of critical epigenetic pathways in disease progression remain poorly understood. Here, we examine the biological and therapeutic importance of histone deacetylases (HDACs) in the function of fibroblasts and the pathogenesis of renal fibrosis.

Methods: Renal fibrosis was modeled in vivo by treatment of NRK-49F fibroblasts with the pro-fibrotic cytokine TGF-β and in vivo in mice by unilateral ureteral obstruction (UUO). The role of HDAC proteins was assessed by treatment with the broad spectrum HDAC inhibitor Trichostatin A (TSA) and the HDAC-specific inhibitor PCI-34051. The translational relevance of these findings was assessed in patients who underwent a nephrectomy following UPI obstruction.

Results: UUO leads to a 6.1-fold increase in HDAC8 expression that localizes specifically to myofibroblasts. In NRK-49F cells, treatment with PCI-34051 promotes myofibroblast differentiation and apoptosis, but suppresses proliferation and matrix synthesis. These findings extend to the injured kidney in vivo, where HDAC8 inhibition results in a 41.6% decrease in COL1A1 and a 61.6% decrease in α-SMA. Furthermore, there is a 77.9% decrease in the interstitial proliferative response, a 43.0% decrease in myofibroblast number, and a 31.1% decrease in renal fibrosis. Finally, the development of renal fibrosis in patients with obstructive kidney disease is associated with a 32.1% increase in the number of HDAC8-positive cells.

Conclusions: Together, these findings demonstrate that HDAC8 plays a critical role in regulating fibroblast activation. Treatment with HDAC inhibitors is also an effective therapeutic approach to reverse the epigenetic changes associated with the pathogenesis of renal fibrosis. Finally, since an increase in HDAC8 expression occurs in patients during disease progression, HDAC8-targeted therapies have therapeutic potential for the treatment of chronic kidney disease.

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Reciprocal Effects of HDAC1 and HDAC2 Deletion on Renal Ischemia-Reperfusion Injury
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Background: Histone/protein deacetylase proteins (HDACs) have been implicated in renal ischemia-reperfusion injury (IRI). HDACs 1 and 2 are highly homologous Class I HDACs thought to have similar function.

Methods: This study included wild type C57BL/6 (B6) and inducible HDAC1- or 2- gene deleted mice (HDAC1KO and HDAC2KO). Renal-specific or extra-renal gene deletion was achieved with transplantation, native nephrectomy, and subsequent gene deletion. Warm IRI consisted of unilateral clamping of the renal pedicle and contralateral nephrectomy. Cold IRI was achieved through procurement, controlled interval of cold storage, and transplantation.

Results: HDAC1KO mice had impaired renal IRI tolerance compared to controls with higher BUN levels (p<0.01; Figure 1A) and increased fibrosis post-injury. HDAC2KO mice had improved early renal function (p=0.01; Figure 1B) and decreased fibrosis (p=0.01) compared to controls and tolerated extended periods of ischemia. In transplant models, renal-specific HDAC2KO mice had superior IRI tolerance with less renal impairment (p<0.01) and decreased fibrosis (p=0.01) compared to extra-renal HDAC2KO and controls. After transplantation with 18 hours of cold ischemia, HDAC2KO donor kidneys had improved BUN (p=0.02) and survival compared to controls.

Conclusions: HDAC1 and 2 have reciprocal effects on murine renal IRI tolerance, with HDAC1 deletion increasing vulnerability and HDAC2 deletion providing protection. The effect of HDAC2 deletion is profound, is intrinsic to the kidney, and extends to cold ischemia and renal transplantation.

Funding: NIDDK Support

Renoprotective Effect of Long Acting Thioredoxin by Modulating Oxidative Stress and Macrophage Migration Inhibitory Factor against Rhabdomyolysis-Associated Acute Kidney Injury
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Background: Rhabdomyolysis-associated acute kidney injury (AKI) is a serious life-threatening condition. As such, more effective strategies are needed for its prevention and treatment. Although thioredoxin-1 (Trx) possesses superior biological activities, such as anti-oxidative and anti-inflammatory effect via the modulating macrophage migration inhibitory factor (MIF), its short blood retention limits the therapeutic application. To overcome this, we engineered a long acting Trx by genetically fused with human serum albumin (HSA-Trx), and examined its renoprotective effect against glycerol-induced AKI.

Methods: HSA-Trx was prepared by using Pichia expression system. The mouse model of rhabdomyolysis-associated AKI was induced by the administration of a 50% glycerol solution.

Results: An intravenous HSA-Trx pre-treatment attenuated the glycerol-induced decline in renal function, compared to a PBS, HSA or Trx alone. HSA-Trx caused a reduction in the tubular injuries and in the number of apoptosis-positive tubular cells. Renal superoxide, 8-hydroxy deoxyguanosine, nitrotyrosine and the plasma Cys34-cysteinylated albumin were clearly suppressed by the HSA-Trx treatment. Prior to decreasing TNF-α and IL-6, HSA-Trx suppressed an increase of plasma MIF level. In LLC-PK1 cells, HSA-Trx decreased the level of reactive oxygen species and lactate dehydrogenase release induced by myoglobin. HSA-Trx treatment resulted in a threefold increase in the survival of lethal glycerol-treated mice. The post-administration of HSA-Trx at 1 and 3 hr after glycerol injection exerted a significant renoprotective effect.

Conclusions: HSA-Trx, a long acting Trx, has potential for use in the prevention and treatment of rhabdomyolysis-associated AKI via its extended effects of modulating oxidative stress and MIF.

Selective Endothelin-A Receptor Antagonism Prevents the Progression of Acute Kidney Injury to Chronic Kidney Disease
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Background: AKI is common and associated with significant morbidity and mortality. AKI often progresses to CKD. Endothelin-1 (ET-1) contributes to this. We hypothesized that therapeutic administration of selective ET-A receptor antagonism would protect from the transition of AKI to CKD.

Methods: 28 FVB mice underwent prolonged (50min) unilateral ischemia-reperfusion injury (IRI) with 28d recovery. 14 mice received daily selective ET-A antagonism (sitaxentan) starting 24h after IRI. We assessed blood pressure (BP) via telemetry, vascular function, renal injury and measures of the ET system.

Results: Systolic BP increased by ~5mmHg after IRI and was associated with vascular dysfunction in both resistance and conduit vessels. Sitaxentan partially prevented both of these. At 28d after IRI kidney weight was reduced (~55%) and associated with significant macrophage infiltration and fibrosis compared to the contralateral control kidney. Mice treated with sitaxentan had normal kidney weight, reduced macrophage infiltration and less IRI. IRI kidney vs. control kidney with sitaxentan: F4/80 stain/high power field: 2.5X vs. 0.2X, p<0.001; p<0.001. For both macrophage infiltration and fibrosis, p<0.05 for IRI vs. control and for IRI+ET-A with sitaxentan, p=ns for control vs. IRI with sitaxentan. Furthermore, an up-regulation of both the ET-A and ET-B receptors as well as pre-pro-ET-1 (100-fold) mRNA was seen in both the cortex and medulla of the IRI kidney relative to control. With sitaxentan treatment ET, ET-A receptor and pre-pro-ET-1 mRNA remained similar to baseline levels. Finally, renal ET-1 production increased following IRI and this was prevented by ET-A receptor antagonism (fractional excretion of ET-1; IRI+ET-A with sitaxentan: 47X vs. 16X, p<0.05).

Conclusions: In an in vivo model of AKI progressing to CKD, ET-A receptor antagonism reduced BP and vascular dysfunction and prevented progression of renal injury and ET system activation after AKI. Therefore, selective ET-A receptor antagonism offers a potentially novel therapy for AKI. Translational studies are now warranted.

Inhibition of Vascular Adhesion Protein-1 Suppresses Neutrophil Infiltration and Preserves Renal Function in the Rat Model of Renal Ischemia–Reperfusion Injury
Shinji Tanaka, Tetsuhito Tanaka, Reiko Inagi, Masaomi Nangaku. Div of Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background: Vascular adhesion protein-1 (VAP-1) is an adhesin expressed in endothelial cells. With its unique properties as an ectoenzyme which catalyzes oxidative deamination of primary amines, VAP-1 plays a critical role in leukocyte trafficking. In light of a growing body of evidence that VAP-1 controls inflammation in various organs, such as the liver and the lung, we examined the effect of VAP-1 inhibition in the rat model of renal ischemia–reperfusion injury.

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

684A
Methods: Rats were subjected to left renal ischemia for 45 min after right nephrectomy, followed by 24 and 48 h of reperfusion. A specific VAP-1 inhibitor, RTU-1096 (R-Tech Ueno, Tokyo, Japan), or vehicle was administered to rats since 7 days before the surgery (mixed with feed, 40 mg/kg/day).

Results: Immunofluorescence studies suggested that VAP-1 is expressed not only in endothelial cells but also in intracellular components of non-endothelial lineage. In vitro, higher mRNA expression of VAP-1 was confirmed in cultured pericytes. In vivo, VAP-1 enzyme activity in the whole kidney was unaffected by the surgery, but following VAP-1 inhibition by RTU-1096 (0.9/0.1 vs. 7.0/1.1 pmol protein/mg/min), renal injury was significantly reduced compared to the vehicle group as assessed by the levels of serum creatinine 69.16 vs. 139.15 mg/dl, Cr: 1.4±0.1 vs. 2.5±0.2 mg/dl; P<0.01), which was accompanied by amelioration in histological tubular damage and decreased KIM-1 mRNA levels. Immunohistochemical analysis revealed a significantly decreased number of neutrophils in the corticomedullary junction in the drug group, whereas the number of macrophages was similar. VAP-1 inhibition resulted in significantly lower mRNA levels of CXXCL1 and CXXCL2 in the kidney without affecting chemokines involved in macrophage recruitment, such as MCP-1, or major adhesion molecules, VCAM-1 and ICAM-1.

Conclusions: These data suggest that VAP-1 plays an important role in renal ischemia-reperfusion injury by controlling neutrophil infiltration, and offer a promising view that its inhibition can be a novel therapeutic target in ischemic acute kidney injury.

Funding: Government Support - Non-U.S.

SA-PO253

Kim-1 Overexpressing Transgenic Zebrafish Identify mTOR as an Effector of Kim-1-Mediated Kidney Injury in Fish and Mice Wensuning Yin, Said Movahedi naini, Dirk M. Hentschel, Benjamin D. Humphreys, Joseph V. Bajwa, Diane L. Rosin, Mark D. Okusa, Rahul Sharma. Virginia, Charlottesville, VA; 2Dept of Pharmacology, Univ of Virginia Health System, Charlottesville, VA.

Background: Mammalian kidney injury molecule 1 (KIM-1), an epithelial phagocytic receptor, is markedly upregulated in the proximal tubule in various forms of acute and chronic kidney injury in humans and many other species. Here, we characterized the zebrafish homolog, Kim-1, which is highly expressed in zebrafish kidney tubules, we identified mTOR as an effector in Kim-1-mediated kidney injury. We then validated mTOR as a therapeutic target for kidney injury and fibrosis in Kim-1 overexpressing transgenic mice.

Methods: We created two transgenic zebrafish models of Kim-1 overexpression in nephrons employing the cdh17 promoter. One model utilized a constitutively active promoter while the other utilized a tamoxifen-induced Cre-ERT2 recombinase to express Kim-1 in nephrons in a temporally-controlled manner. The role of mTOR signaling was evaluated using the mTOR inhibitor rapamycin. Zebrafish GFR was determined using the elimination rate of fluorescein-labeled dextran.

Results: Kim-1 was markedly upregulated after gentamicin-induced kidney injury and had conserved phagocytic activity in zebrafish. Both constitutive and tamoxifen-induced expression of Kim-1 in zebrafish kidney tubules resulted in shedding of the tubule brush border, reduced GFR, pericardial edema and increased mortality rate. Kim-1-induced kidney injury was associated with inhibition of growth of adult fish. Kim-1 expression led to mTOR pathway activation, and inhibition of this pathway with rapamycin increased survival. mTOR pathway inhibition in Kim-1 overexpressing transgenic mice also significantly reduced serum creatinine, proteinuria, tubular injury and kidney inflammation.

Conclusions: Persistent Kim-1 expression resulted in chronic kidney damage and growth impairment in zebrafish. Kim-1-mediated kidney tubular injury was mediated by the mTOR signaling pathway. This observation in zebrafish predicted a role of the mTOR pathway and therapeutic efficacy of rapamycin to protect the mouse kidney against Kim-1-mediated kidney injury and fibrosis.

Funding: NIDDK Support

SA-PO254

Treg and ILC2 Contribute to IL233 (a Novel Fusion Cytokine)-Mediated Protection in AKI Maria Stremiska1, Liping Huang, Sheethal Jose, Amandeep Bajwa, Diane L. Rosin, Mark D. Okusa, Rahul Sharma. 1CHIR, Univ of Virginia, Charlottesville, VA; 2Dept of Pharmacology, Univ of Virginia.

Background: Inflammation is an early event in AKI and studies have shown regulatory T cell (Treg)-mediated protection in inflammation driven injuries. Since we found that intraperitoneal injection of IL233 receptor-ST2/CD48 double-null mice (CD48−/−) protected mice from IL-2 and IL-33 in combination or as IL233 fusion cytokine, but not alone protected mice from IR injury, with IL-233 being more efficient than the combination.

Methods: We designed a fusion cytokine (IL233) containing the activities of IL-2 and IL-33 for better targeting of Tregs. The cytokines were expressed in E.coli, purified to homogeneity and tested in a mouse model of ischemia reperfusion injury (IR). C57BL/6 male mice were pretreated (ip) with different doses of cytokines prior to 24 h of bilateral renal ischemia and 24 h of reperfusion. Kidneys were characterized for function, acute tubular necrosis and the profile of infiltrating cells.

Results: IL-2 and IL-33 in combination or as IL233 fusion cytokine, but not alone protected mice from IR injury. We speculate that IL233 being most potent, the effect in mice injected with Tregs obtained from mice pretreated with IL233. Adoptive transfer of IL233-pretreated Tregs also protected against IR injury. In vivo experiments with IL233-pretreated Tregs revealed their higher protective function.

Conclusions: Thus, IL233 cytokine attenuates kidney inflammation to protect from IR injury and bears strong potential to be a therapeutic agent for AKI.

Funding: NIDDK Support

SA-PO255

Vagus Nerve Stimulation (VNS) Protects Kidneys from Ischemia-Reperfusion Injury Through Alpha 7 Nicotinic Acetylcholine Receptor (α7nAChR) Expression Splenocytes Tsuyoshi Inoue, Chikara Abe, Stefan Moscu, Liping Huang, Hong Ye, Diane L. Rosin, Patrice G. Guyenet, Mark D. Okusa. 1Dept. of Medicine, Univ of Virginia Health System; 2Dept of Pharmacology, Univ of Virginia Health System, Charlottesville, VA.

Background: The nervous and immune systems interact in complex ways to maintain homeostasis and respond to stress or injury. The inflammatory reflex referred to as the cholinergic anti-inflammatory pathway (CAP) modulates innate and adaptive immunity, and stimulation of the reflex by VNS is effective in inflammatory disease models. The effect of VNS on AKI has never been examined. Experimental activation of vagal effector fibers suppresses inflammation in a manner that depends on α7nAChR in the CAP. However, the site of the essential α7nAChR was not established.

Methods: We applied electrical VNS (5 Hz, 50 μA for 10 min) 24 hr prior to kidney injury and assessed kidney injury by evaluating plasma creatinine (PCr, mg/dl), kidney-1 mRNA expression and histology (H&E). The effect of VNS on IR was assessed by: a) prior spleenectomy and b) adoptive transfer of splenocytes from VNS-stimulated mice to recipient mice subjected to IR injury.

Results: VNS applied 24 hr prior to IR markedly attenuated IR injury. VNS reduced the IR-induced increase in PCr by 65% (P<0.01) and Kim-1 mRNA expression in whole kidney by >70% (P<0.01). H&E-stained kidney sections confirmed the functional data. When spleenectomy was performed 7 days before VNS and IR, the protection of VNS was abolished. Adoptive transfer of splenocytes from VNS-treated mice to recipient mice subjected to IR provided greater protection than splenocytes from mice who received sham VNS stimulation (PCr: 0.41 and 1.54 (P<0.001) for VNS- and sham VNS-treated splenocytes, respectively). To evaluate the role of α7nAChR, VNS was initiated 24 hr prior to IR in α7nAChR knockout (α7KO) and WT mice. Compared to the protective effect of VNS on IR in WT mice, no protection was observed in α7KO mice. In addition, recipient mice were protected (PCr) from IR if they received splenocytes from VNS-treated WT mice (0.41) but not from VNS-treated α7KO mice (1.57, P=0.001).

Conclusions: VNS-induced protection from IR is consistent with activation of the CAP.

SA-PO256

Elevations of Intraglomerular Pressure Exacerbate Ischemia Reperfusion Injury-Induced Acute Kidney Injury Je Zhang, Lei Wang, Shaozhi Wang, Gensheng Zhang, Jin Wei, Ruisheng Liu, Kay-Pong D. Yip. Molecular Pharmacology & Physiology, Univ of South Florida, Tampa, FL.

Background: The physiological and pathophysiological mechanisms of renal ischaemia reperfusion (IR)-induced acute renal injury (AKI) are complex and have not been elucidated. We sought to determine whether intraglomerular hydrostatic pressure (Pg) during the ischaemic phase plays a critical role in IR-induced AKI.

Methods: We created three groups of C57BL/6 mice at 37°C C with IR by 18 min of bilateral clamping of renal arteries (RA), pedicles (RP), and pedicles plus preclamping of ureters 20 min before ischemia (PU). Free flow proximal tubular pressure (Pf) was measured with servo-nulling method during ischemia. Pf was used as an index of Pg.

Results: We found that mean Pf was highest in PU mice (48.9±7.5 mmHg) than in RP mice (34.6±3.6 mmHg). The RA had lower Pf (16.1±2.3 mmHg) when compared to Sham operated mice (9.5±2.2 mmHg). In separate experiments, the renal injury was determined 24 hours after IR in these mice. Plasma creatinine was significantly increased in all three groups compared with sham-operated group. The mean plasma creatinine were 2.1±0.07 mg/dl, 1.85±0.08 mg/dl and 0.45±0.7 mg/dl for PU, PR and RA, respectively. The mean plasma Kidney Injury Molecule-1 (KIM-1) levels were 276.1±493 pg/ml in PU, 1548±220 pg/ml in PR and 734±234 pg/ml in RA group, respectively. Histology by PAS staining showed that all AKI mice had a significant increase in renal tubular necrosis compared to sham-operated mice. However, there were more tubular necrosis in the cortex, medulla or cortex-medulla junction area in PU mice (3.1±1.3%, 34.1±8.5% and 54.4±6.9%) than in RP mice (1.0±0.5%, 23.0±9.2% and 50.1±12.7%). RA mice had the least tubular necrosis (0.23±0.1%, 8.9±4.5% and 31.7±10.2%). RA mice had the highest intraglomerular pressure and most severe renal injury. These data indicate that elevations of intraglomerular and tubular pressure exacerbate IR-induced AKI. Intraglomerular and tubular pressure may be a novel therapeutic target for AKI.
GFR in Conscious Mice After Sepsis: Role of Tubuloglomerular Feedback

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Background: Reabsorption of glomerular filtrate by the tubules is an energy intensive process. During sepsis the ability of the tubules to meet this energy demand may be impaired. To prevent renal salt wasting during sepsis it is hypothesized that activation of tubuloglomerular feedback reduces GFR and subsequently the metabolic demand on the tubules – “acute renal success”. Mice without tubuloglomerular feedback should maintain higher levels of GFR. In conscious mice we detected early changes in GFR using a novel transcutaneous measurement of a fluorescent filtration marker. Because adenosine 1a receptor (A1aR) signaling is required for tubuloglomerular feedback we directly measured GFR following sepsis in A1aR knockout mice.

Methods: Sepsis was induced in male A1aR knockout mice and littermate controls by cecal ligation and puncture. GFR was monitored in awake mice for 5 hours by planar disappearance of FITC-Sinistin, injected at 0 and 90 minutes after surgery, and its transcutaneous fluorescence measured by a miniaturized fluorimeter attached to the mouse back.

Results: The baseline GFR was similar in A1aR WT and KO mice. In WT mice, GFR was stable during the first hour following induction of sepsis. GFR slowly declined over hour two, and then fell rapidly to <10% of normal and remained low for 5 hours. In contrast, the GFR was lower in KO mice than in WT mice in the first hour following sepsis (p=0.0206), then fell gradually to 27% of normal, with a smaller decrease observed after 2 hours compared to WT mice (p=0.0286).

Conclusions: In mice lacking tubuloglomerular feedback, unexpectedly, GFR begins to decrease earlier after sepsis suggesting impaired autoregulation. The sudden decrease in GFR in WT mice at 2 hours after induction of sepsis does not occur in A1aR KO mice. Tubuloglomerular feedback modestly supports, not suppresses, GFR in the first hour following sepsis, and only later acts to suppress GFR.

Funding: NIDDK Support

SA-P0258

Renal Functional Reserve May Be Inferred from Variation of Renal Resistive Index: Preliminary Evidence Sara Samon1,2, Federico Nalessso,3 Gianluca Villa, Silvia De Rosa,1 Illaria Petrucci,1 Massimo de Cal,1 Fiorenza Ferrari,2 Alessandra Brendolan,2 Mario Meola,1 Claudio Ronco.3 Sant’Anna School of Advanced Studies, Pisa, 1IRRV, Vicenza.

Background: The increase of glomerular filtration rate(GFR)after a protein load is a renal functional reserve of the kidneys. Mechanical abdominal stress(MAS),through the compression of renal arteries and the consequent reduction of renal blood flow,cannot activate the autoregulation mechanism to maintain glomerular perfusion.Both phenomena are related to the afferent vasodilation,which can be displayed by the drop of renal resistive index(RI)measured by colorDoppler. We hypothesized that the variation of RI during MAS may predict the RFR.

Methods: In 15 healthy volunteers, MAS was performed through the application of a transcutaneous fluorimeter attached to the mouse back. According to the performed dose-response curve, we used bags which weigh 10% of subject’s BW. We recorded RI in mesorenal interlobar arteries each min for the 10 min of MAS. The RI reduction was defined by the difference between baseline RI and the lowest RI reached during MAS and expressed as percentage reduction(pDRI). GFR was measured through a standardized protein loading test. Spearman’s correlation was applied to evaluate if pDRI correlates with RFR.

Results: We enrolled 9M and 6F with a median age of 30(24-57)yrs old. The median baseline Crl was 99.2(70.3-132.8)ml/min/1.73m2. The RFR ranged between 11.55% and 134.66% with a median value of 38.55%. The median baseline RI was 0.600(0.50-0.67) while pDRI ranged between 13.3%(29.23%) with a median value of 20%. The correlation between pDRI and RFR was 0.717(p=0.001). According to physiology, RFR and pDRI may not be directly proportional; instead, while ranges of RFR may widely broaden, pDRI should reach a plateau value. For this reason, we analyzed the linear regression model between pDRI and logarithm(1/RFR). According to this model, we found that an increase in pDRI was associated to an increase in ln of RFR(0.108 = 0.001, 95%CI: 0.060 0.15 R=0.66).

Conclusions: Our results suggest that the variation of RI during MAS is an indirect measure of RFR, putting the bases for the development of a stress test that could be used for a rapid screen of RFR before potentially nephrotoxic procedures.

Funding: Veterans Administration Support

SA-P0259

5-Aminolevulinic Acid Attenuates Rhabdomyolysis-Induced Acute Kidney Injury in Mice Atsushi Uchida, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara. Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.

Background: Rhabdomyolysis often occurs after severe skeletal muscle injury, and high mortality have been reported with the acute kidney injury (AKI) that develops subsequently. Thus, the establishment of effective prevention and treatment is a pressing problem. 5-Aminolevulinic acid (ALA) is the naturally occurring metabolic precursor of heme, and serves as protein material related to energy production. Previous study demonstrated that ALA has the potential to prevent cisplatin-induced AKI via the induction of heme oxygenase (HO-1), and prevention of tubular apoptosis. We hypothesize that ALA plays a renoprotective effect via the induction of HO-1 and anti-apoptotic pathway in rhabdomyolysis-induced AKI.

Methods: Male C57BL/6 mice were used. Rhabdomyolysis-induced AKI was induced by intramuscular injection of glycerol (50%) 5 ml/kg bw. ALA (30 mg/kg) was administrated at 24 hr before or 24 hr after glycerol administration. These mice were sacrificed at 72 h after glycerol injection, and the blood and renal tissues were harvested. In vitro experiment, human proximal tubule cells were stimulated by 100 μM hemin to induce apoptosis. Cells were incubated for 24 hr with or without 1 nM ALA. Apoptotic cells were examined by TUNEL staining and caspase-3 expression.

Results: In vivo experiments, serum creatinine, blood urea nitrogen and urine NGAL excretion were increased in glycerol-injected group compared with saline-injected control group. ALA significantly reduced these changes in both pre and post treatment. ALA also ameliorated glycerol-induced morphological tubular damages. HO-1 level was increased in glycerol-injected group and further up-regulated by ALA treatment. ALA significantly attenuated macrophage infiltration and pro-inflammatory cytokine (IL-1beta and TNFα) expression. In vitro experiments, TUNEL-positive cells and caspase-3 expression were increased by hemin and were significantly reduced by ALA co-treatment.

Conclusions: ALA has renoprotective effects in glycerol-injured AKI. ALA is already used for tumor diagnosis in human. So the safety of the drug is proved in clinical use. ALA treatment may be a new therapeutic target in rhabdomyolysis-induced AKI.

Funding: Veterans Administration Support

SA-P0260

Ferroptosis as a Cause of Proximal Tubule Injury Joel M. Weinberg, Andreas Linkermann.1 Nephrology, VA Healthcare System Ann Arbor, Ann Arbor, MI; 2Nephrology, Univ of Michigan, Ann Arbor, MI; 3Nephrology, Christian Albrechts Univ, Kiel, Germany.

Background: ‘Ferroptosis’ has recently been described as a form of iron-dependent, lipid peroxidation-mediated cell death with a distinct injury pattern relative to other forms of necrosis and there is evidence that it contributes to AKI in vivo (PNAS 111:16835, 2014, Nat. Cell Biol. 16:1180, 2014). Here, we have refined approaches to study ferroptosis in freshly isolated proximal tubules (PT) and assessed new agents being developed to ameliorate it.

Methods: Freshly isolated rabbit (R) and mouse (M) PT were treated with either tert-butylnitroperoxide (BBN, 5 mM) or hydroxylquinoline + ferrous ammonium sulphate (HQ+Fe)10 μM each) followed by incubation for 120 min, then measurement of LDH release, malondialdehyde (MDA) production, mitochondrial membrane potential, and GSH.

Results: BBN and HQ+Fe induced progressive LDH release that was more severe in M PTs (Baa: HQ+Fe: R60.35±5.6; M 120.5±4.9, p<0.05). These changes were accompanied by 5 fold increases of MDA levels and GSH depletion. LDH release and MDA production were iron and NAPH oxidase (Nox)-dependent since they were blocked by deferoxamine or the Nox1/4 inhibitor GKT 137831. Fer-1, the prototypical ferroptosis inhibitor that emerged from chemical library screening, strongly alleviated both forms of injury and associated MDA production at concentrations of 0.1 to 2 uM as did a panel of 23 other ferrostatin analogs with potencies similar to those of Fer-1, the prototypical ferroptosis inhibitor that emerged from chemical library screening.

Conclusions: Ferroptosis is strongly expressed in fully differentiated PTs, is suppressed by both newly developed ferrostatins and the classical lipophilic antioxidant, DPPD, and is an injury process that can be targeted to alleviate AKI.

Funding: Veterans Administration Support

SA-P0261

Identification and Characterization of IGFBP7 and TIMP2 Expression in Human Proximal and Distal Tubule Cells David R. Emle,1 Nuria M. Pastor-Soler,2 Allison L. Marciszycz,2 Xiaoyan Wen,1 Jacob K. Volpe,1 John A. Kellum.1 1Center for Critical Care Nephrology, Dept of Critical Care Medicine, Univ of Pittsburgh, Pittsburgh, PA; 2Renal Electrolyte Div, Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: IGFBP7 and TIMP2 have been identified as biomarkers for Acute Kidney Injury (AKI), but little is known regarding any role in the pathogenesis of the disease. To study this question we established primary cell culture models of human proximal and distal tubule epithelial cells.

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

Underline represents presenting author.
Methods: The cortex of human kidneys were dissociated and viable cells cultured. Proximal and distal tubule epithelial cells (PTECs and DTECs) were isolated with antibodies against CD13 and CD227 using the DynaBead pan-mouse IgG system. Isolated cells were cultured on transwell supports and characterized by immunoblot and immunofluorescence.

Results: CD13 isolated cells were positive for the PTEC markers Gamma Glutamyl Transpeptidase and Aquaporin-1. CD227 isolated cells were negative for GGT and AOPl but positive for the distal tubule markers CD227 and E-cadherin. Microscopy demonstrated that both PTECs and DTECs formed tight junction monolayers with a low percentage of cells in cycle as identified by Ki-67. Analysis of conditioned media demonstrated that the hormone upregulated secreted IGFBP7. Furthermore, we found a preferential expression of IGFBP7 in PTECs and of TIMP2 in DTECs. Furthermore, we discovered evidence suggesting that TIMP2 is primarily secreted across the apical surface, while the majority of IGFBP7 is secreted across the basolateral surface. Despite this, we also found that a substantial portion of IGFBP7 can be secreted apically, primarily in PTECs.

Conclusions: We have developed human cell culture model systems of PTECs and DTECs for the cellular/molecular analysis of AKI. We confirmed that IGFBP7 and TIMP2 can be expressed and secreted by these cells, and we have identified differential expression and secretion of these proteins across cell types and spatially within cells. These systems and knowledge will now allow for investigation of the potential role of these biomarkers in the molecular etiology of AKI.

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SA-PO262
Klotho and S100A8/A9 as Discriminative Markers Between Pre-Renal and Intrinsic AKI
Ji Yong Jung,1 Ae Jin Kim,1 Eul Sik Jung,1 Byoungho Choi,1 Yun Jung Oh,2 Chungsiik Lee,3 Han Ro,1 Jae Hyun Chang,1 Hyun Hee Lee,1 Wookyoung Chung.1

Disclosures: None.

Background: Early detection and accurate differentiation of the cause of acute kidney injury is crucial for the prognosis of the patient. However, to date, there are few reliable biomarkers for the discrimination of pre-renal and intrinsic AKI. The purpose of this study was to determine whether AKI is associated with an altered level of klotho and S100A8/A9 (an endogenous toll-like receptor 4 ligand), and NGAL (neutrophil gelatinase-associated lipocalin) protein that may contribute to differentiate between pre-renal and intrinsic AKI.

Methods: Volume depleted pre-renal AKI model was induced by muscle Sprague-Dawley rat were fed a low-salt diet (0.03%) without water 96hr before two times at intraperitoneal (IP) injection of furosemide (20 mg/kg) at 24hr intervals. In contrast, cisplatin-induced intrinsic AKI model were given by a single IP injection of cisplatin (5 mg/kg). All animals were euthanized 72hr after first IP injection. We also performed a proof of concept cross-sectional study to measure serum and urinary biomarkers in 77 hospitalized patients with established AKI.

Results: Compared with intrinsic AKI group, pre-renal AKI group caused a marked depression of urinary klotho level (13.21 ± 17.32 vs. 72.97 ± 17.96 pg/ml, P = 0.002). In addition, intrinsic AKI group caused a marked elevation of S100A8/A9 level than those of pre-renal AKI group (5629.97 ± 598.05 pg/ml vs. 685.09 ± 111.65 pg/ml, P = 0.002 in serum; 1361.11 ± 230.86 pg/ml vs. 741.72 ± 101.96 pg/ml; P = 0.003 in urine). Serum and urinary NGAL showed no difference between pre-renal and intrinsic AKI group. The proof of concept study with hospitalized AKI patients also demonstrated decreased urinary klotho in pre-renal AKI patients and increased urinary S100A8/A9 concentrations in pre-renal AKI patients.

Conclusions: The attenuation of urinary klotho and increment of urinary S100A8/A9 may contribute to discriminate the pre-renal AKI and intrinsic AKI. Funding: Pharmaceutical Company Support - Frensis Medical Care Korea

SA-PO263
Release of Extra Cellular DNA Contributes to Renal Ischemia Reperfusion Injury Through Platelet Activation and Formation of Neutrophil Extracellular Traps
Marcel Janse,1 Diba Emal,1 Sandrine Florquin,1 Joris J. Roelofs.2

Disclosures: None.

Background: Renal ischemia reperfusion injury (IR) results from a complex interplay between reperfusion and inflammation, resulting in tissue damage. It has been shown that platelet inhibition protects from IR. How platelets are activated upon renal I/R is not entirely known. In this study we investigate renal cell death, extracellular DNA release and neutrophil extracellular traps (NETs) as potential triggers for platelet activation and renal IR injury.

Methods: We stimulated platelets with necrotic renal cells in presence or absence of deoxyribonuclease 1 (DNase1). Platelet activation and platelet-leukocyte formation were measured by FACS. We stimulated granulocytes with activated platelets and measured DNA release - indicative of NET formation. Vici versa we stimulated platelets with NETs and measured NET release - indicative of NET degradation and treated with DNase1 and treated viced versa, and sacrificed after 1 day. As marker for NET formation in tissue we stained renal tissue for citrullinated histone H3 and granulocyte marker Ly6G. In blood we measured Platelet Factor 4 (PF4), DNA, creatinine and urea.

Results: Necrotic renal cells stimulated platelet activation and platelet-leukocyte complex formation and incubation with DNase1 reduced platelet activation. Activated platelets generated NETs in vitro and, vici versa, NETs stimulated platelet activation ex vivo. Mice subjected to renal IR showed a significant increase of extracellular DNA and PF4 levels in the circulation. Treatment with DNase1 improved renal function and decreased cytokine levels. The animals showed preserved renal functions in retal time and after 1 week. IR, DNase1 treatment resulted in a trend towards fewer NETs and granulocytes in tissue.

Conclusions: Both DNA from necrotic kidney cells and NETs activate platelets, which in turn cause further NET formation, leading to a vicious triad in the pathogenesis of IR injury. Treatment with DNase1 may have therapeutic benefits in the context of renal IR injury.

Funding: Pharmaceutical Company Support - Fresenius Medical Care Korea

SA-PO264
The Role of Senescence of Bone Marrow Cells in Acute Kidney Injury
Myung-Gyu Kim,1 Sung Yoon Lim,1 Jihyun Yang,2 Young Ju Na,2 So-Young Lee,2 Sang-Kyung Jo,1 Won-Yong Cho.1

Disclosures: None.

Background: There have been considerable growth in older population and age-related kidney disease in the world. It was demonstrated that the impairment in the potentiality to repair and regenerate of renal resident cells is a hallmark of biological processes associated with aging. However, the impact of senescence of bone marrow derived cells (BMDC) on kidney injury is not known. Here, we investigated the role of senescence of BMDC in the development and progression of ischemic acute kidney injury (AKI).

Methods: Seven wk-old female mice were sublethally irradiated and reconstituted with bone marrow from 12-mo-old (old-to-young, old BMT) or 7-wk-old (young to young, young BMT) mice. Then we performed renal ischemia reperfusion injury (IRI) in old or young BMT mice, and functional, histological kidney damage and inflammation were compared.

Results: The Y chromosome was detected in peripheral blood of BMT mice indicating successful reconstitution of female mice with male bone marrow. Although the population of immature myeloid cells in spleen between old and old BMT mice was significantly different, old BMT showed less renal functional deterioration and histological damage after IRI. This was associated with less infiltration of F4/80 macrophages and lower level of tissue cytokine (IL-12). In vitro study with BMDCs also revealed that LPS-induced cytokine productions (IFN-γ, MCP-1 and IL-10) were significantly suppressed in old BM cells than young BMT cells.

Conclusions: Our data shows that senescence of BMDC could affect susceptibility and response to renal ischemic injury possibly via immune modulatory effect. A better understanding of these processes may help us to develop new strategies that are specifically tailored for the treatment of elderly population.

Funding: Pharmaceutical Company Support - Fresenius Medical Care Korea

SA-PO265
Optimal Transplantation Timing of Mesenchymal Stem Cell in Rat Model of Renal Ischemia Reperfusion Injury
Xiaolian Luo,1 Xiaofang Du,1 Kimberly J. Reidy.1

Disclosures: None.

Background: Underlying of these processes may help us to develop new strategies that are specifically tailored for the treatment of elderly population.

Methods: The model of renal IRI was induced by the release of bilateral renal pedicle clamping and releasing for 60 min of ischemia. Animal were sacrificed at 0h, 1h, 12h, 24h, 48h, 72h and 1 week post-IR respectively. Passage 3 rat MSCs were cultured with different time points kidney homogenate supernatants. After reperfusion, CM-Dil-labeled MSCs or cells only were administered through the carotid artery of the rats. Biopsies were obtained at 1h before reperfusion(1h-1) and immediately(1h-0), 12h, 24h after reperfusion.

Results: The animals sacrificed 4h after reperfusion and 24h after MSCs transplantation.

Conclusions: MSCs transplantation 1h before reperfusion or immediately after reperfusion produces the most dramatic improvement in renal function and morphology in a model of renal IR injury. It is the optimal timing to transplant MSCs in IRI before the inflammatory response is established.

Funding: Government Support - Non-U.S.

SA-PO266
Reno-Protective Role of Par1b in Acute Kidney Injury
Abijeet Pal,1 Natalie S. Uy,1 James M. Pullman,2 Zhongfang Du,1 Kimberly J. Reidy.1

Disclosures: None.

Background: Partitoning defective Par1 (aka MARK) is a member of protein kinase A family significantly decreased in -1h and 0h groups compared with other point time groups. Significant kidney function and histological damage improvement was observed after the treatment of MSCs in -1h and 0h groups. Meanwhile, the expression of proinflammatory factor significantly decreased and anti-inflammatory factor significantly decreased in -1h and 0h groups compared with other point time groups and control group. In addition, we also observed more obvious inhibition of renal tubular cell apoptosis and promotion of proliferation in -1h and 0h groups compared with other groups. Consistent with the improvement above, the viability of implanted MSCs also increased in -1h and 0h groups.

Conclusions: MSCs transplantation 1h before reperfusion or immediately after reperfusion produces the most dramatic improvement in renal function and morphology in a model of renal IR injury. It is the optimal timing to transplant MSCs in IRI before the inflammatory response is established.

Funding: Government Support - Non-U.S.
functionally redundant on kinase assays. We have identified a role for Par1a/1b in mediated renal injury, and attenuating its expression may provide new therapeutic strategies in the setting of acute kidney injury.

**Background:** Heat shock protein beta-1 (HSPB1), also known as HSP27, is a small heat shock protein involved in many cellular processes and reportedly protects cells against oxidative and inflammatory stress. Because of its function, we hypothesized that HSPB1 is a mediator of fibrosis.

**Methods:** To examine the regulation of autophagy by HSPB1, we established NRK-light chain 3 (LC3) cells that were stably transfected with a fusion protein of green fluorescent protein and LC3. We evaluated the promoter activity and expression of HSPB1 in normal rat kidney (NRK)-52E cells in the presence of H2O2. To examine the regulation of autophagy by HSPB1, we established NRK-light chain 3 (NRK-LC3) cells that were stably transfected with a fusion protein of green fluorescent protein and LC3.

**Results:** The results of immunohistochemical examination showed that HSPB1 was expressed in proximal tubule cells after AKI. Real-time quantitative reverse transcription-polymerase chain reaction and western blot analysis showed that HSPB1 mRNA and protein expression were upregulated 6–72 h and 12–72 h, respectively, after ischemia/reperfusion injury. HSPB1 promoter activity as well as mRNA and protein expression indicated dose-dependent induction by H2O2. HSPB1 overexpression-induced autophagy in NRK-LC3 cells under normoxic conditions was confirmed with confocal microscopy, which revealed the presence of LC3-positive granules. Furthermore, H2O2-induced autophagy was inhibited by the transfection of small interfering RNAs for HSPB1. Overexpression of HSPB1 reduced BAX activation and H2O2-induced apoptosis, as measured by caspase 3 activity and terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling assay.

**Conclusions:** These results indicate that HSPB1 upregulation plays a role in the pathophysiology of AKI.

**SA-PO268**

Developing a More Clinically Relevant Mouse Model of Cisplatin-Induced Acute Kidney Injury


**Background:** Cisplatin, commonly used chemotherapeutic for the treatment of many solid cancers is known to induce acute kidney injury (AKI) in 30% of patients. Patients that develop cisplatin-induced kidney toxicity must either have the dose severely reduced or be switched to an alternative therapy to prevent long-term renal damage. In many cases the alternative therapy may be less effective at treating the tumor. Due to cisplatin’s complex mechanism of action, the development of renoprotective agents remains a challenge. Currently there are no FDA approved drugs for the protection of cisplatin-induced AKI. The standard mouse model of cisplatin-induced AKI is a single high dose of cisplatin (10-30 mg/kg), and animals are sacrificed 72h after injection. This model does not accurately represent the clinical dosing regimen, which involves repeated dosing of cisplatin.

**Methods:** In this study we compared the standard single dose model to a new multiple dose model where mice received lower doses of cisplatin once a week for 4 weeks. We measured and compared indicators of kidney function (KIM-1, NGAL, BUN, and Serum Creatinine) and multiple markers of inflammation and oxidative stress (i.e., TNFα, IL-6, MCP-1, F4/80, and iNOS). We also measured kidney histology.

**Results:** In comparing the results of the single and multiple dose models, BUN values were very similar, suggesting a comparable loss of kidney function. However, KIM-1 and NGAL were reduced by roughly 10-fold and 100-fold, respectively. Inflammation was also decreased in this model with TNFα, IL-6 and IL-1β reduced by 4, 10 and 5-fold, respectively. Fibrosis was nearly non-existent in the single dose model, however, the multiple dosing model showed a significant increase in fibrosis. Also, expression of PAI-1, a mediator of fibrinolysis was significantly increased in the multiple dosing model compared to the single dose model.

**Conclusions:** Taken together, we propose that the multiple dosing model is a more relevant model for the discovery of renoprotective agents in the prevention/treatment of cisplatin-induced AKI.

**SA-PO269**

**SA-PO270**

**Poster/Saturday**
Involvement of Indolyl Sulfate in Exacerbated Susceptibility of Streptozotocin (STZ)-Induced Diabetic Rat Kidney to Ischemia/Reperfusion-Induced Acute Kidney Injury (AKI)  
Yuna Shimokawa,1 Naoko Oyama,1 Takashige Kawabara,2 Masashi Mukoyama,1 Hirofumi Jono,1,2 Hideyuki Saito.1,2  
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Background: Diabetes mellitus (DM) is one of the potential risk factors in progression of acute and chronic kidney failures. In patients with DM, AKI tends to be severer and the restoration delays compared to that in non-DM patients. However, the precise mechanism is unclear. Indolyl sulfate (IS) is a representative oxidative stress-inducible uremic toxin and involved in the progression of chronic kidney failures. In this study, we examined the toxicological involvement of IS in ischemic AKI in DM rats.

Methods: STZ-induced DM rats and nondiabetic rats without STZ treatment (non-DM) were subjected to 20 min of renal ischemia/reperfusion (IR), and the development of renal injury in DM and non-DM rats were compared. An oral indole absorbent AST-120 was orally administered to rats (2.5 g/kg) at 24 h, 1 h before and 24 h after IR. Serum and kidney tissues were collected at 48 h following IR.

Results: In DM ischemic AKI group, serum creatinine (SCr) (4.3-fold vs non-DM ischemic rats) and BUN (7.0-fold) were increased. The kidney of DM rats with IR exhibited severe tubulointerstitial injury compared to that of non-IR groups with IR in association with a marked increase in serum KIM-1 level (25-fold). Hydroperoxide (1.7-fold) and IS levels in serum (14.7-fold) and kidney (5.8-fold) were also elevated. Immunoblot analysis revealed that renal expression of organic anion transporter rOAT1/rOAT3 mediating renal excretion of IS were significantly downregulated. AST-120 treatment prevented the increases in SCR and BUN, and renal tubular injury in DM rats with IR, in association with the reduction of serum and renal IS levels. The downregulation of rOAT1/rOAT3 was restored by AST-120 treatment.

Conclusions: DM could be a pivotal factor in progression of ischemic AKI, and AST-120 restores (uremic toxins) including IS could play a toxico-physiological role as a mediator in the DM-exacerbated ischemic AKI.

Funding: Government Support - Non-U.S.

Discoidin Domain Receptor 1 Is a Key Mediator of the Ischemia-Reperfusion Induced Renal Injury  
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Background: Discoidin Domain Receptor 1 (DDR1) is a non-integrin collagen receptor, expressed by different cell types in the kidney, which displays tyrosine-kinase activity.

We have previously demonstrated that a de novo expression of DDR1 in target cells was driving renal inflammation and fibrosis in different models of chronic kidney disease. The aim of our study was to investigate whether DDR1 participates in the pathophysiological mechanisms of ischemia/reperfusion (IR), a model of acute renal injury.

Methods: To this end, male mice subjected to IR were injected either with oligodeoxynucleotide (ODN) antisense sequences directed against DDR1 (AS, n=8) or with scrambled sequences (SCR, n=7). Mice were sacrificed after 24h and parameters of renal function, structure and inflammation were measured.

Results: In vitro experiments using NRK-52E cells showed that the compounds are able to suppress endonuclease activity inside the cells provide partial protection against kidney tubular epithelial cells in vitro and in vivo.

Conclusions: DDR1 inhibition prevents mice from the I/R-induced histological damage, inflammation and loss of renal function. DDR1 overexpression plays a deleterious role in this model of kidney injury, thus reinforcing the interest to develop agents capable of specifically blocking the function of this receptor.

Funding: Government Support - Non-U.S.

Heat Shock Factor 1 and Crystallin-αB in Cisplatin-induced Renal Tubular Cell Apoptosis and Nephrotoxicity  
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Background: Cisplatin, a wildly used chemotherapy drug, induces nephrotoxicity that is characterized by renal tubular cell death. In response to toxic stress, renal tubular cells may activate the heat shock response pathway, such as heat shock proteins. However, the heat shock response during cisplatin nephrotoxicity is largely unclear. The present study analyzed the heat shock response during cisplatin treatment of renal tubular cells in vitro and mice in vivo, and examined the relevant regulatory mechanisms.

Methods: For in vivo study, male C57BL/6 mice were given a single intraperitoneal injection of cisplatin. In vitro, renal proximal tubular cells (RPTC) were incubated with cisplatin. To determine the role of heat shock factor 1 (HSF1), HSF1 was knocked down by stable transfection of specific shRNAs.

Results: In RPTC, cisplatin induced a rapid expression of HSF1 and specific heat shock proteins, including HSPA, HSP27, and Crystallin-αB, and the expression of this protein was transient and decreased at late time points of cisplatin treatment. Similar changes were verified in kidney tissues following cisplatin injection, whereas Hsp90 did not change significantly. Knockdown of HSF1 decreased Crystallin-αB expression and cisplatin RPTC apoptosis. Interestingly, p38 activation was enhanced in these cells. Moreover, inhibition of p38 with SB203580 markedly inhibited cisplatin-induced apoptosis in HSF1-knockdown cells.

Conclusions: Induction of HSF1 is a cytoprotective response during cisplatin nephrotoxicity. Crystallin-αB appears to be a key heat shock protein induced by HSF1 for its protective effect. Heat shock response may regulate or co-operate with other signaling pathways, such as p38, to regulate tubular cell apoptosis.

Funding: NIDDK Support, Veterans Administration Support
Conclusions: Importantly, cisplatin-induced kidney injury was functionally (creatinine) and structurally (acute tubular necrosis, TUNEL) reduced by the administration of the inhibitors (5 mg/kg) in mice suggesting their potential therapeutic value.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

SA-PO276

Involvement of CYLD as a Regulatory Factor in Fibrotic Response of Ischemic AKI Kidney and Hypoxic HK-2 Cells

Background: CYLD is a tumor suppressor, regulates various signaling pathways by acting as a deubiquitinating enzyme. Recent studies have revealed that CYLD is associated with not only tumors, but also chronic inflammatory diseases, such as tissue fibrosis. It is well-documented that tissue fibrosis is common hallmark of chronic kidney disease (CKD), and CKD progresses toward end-stage renal disease through renal fibrosis. However, the molecular pathogenesis of renal fibrosis is not fully uncovered yet. In this study, we elucidated the roles of CYLD in renal fibrosis by using in vivo and in vitro models.

Methods: We generated model mice of ischemia/reperfusion (I/R)-induced acute kidney injury (AKI) and hypoxic human kidney (HK)-2 cells. CYLD expression in kidney tissue and HK-2 cells was determined by immunoblot analysis. Fibrosis gene expression of PAI-1, CTGF, and COL1A1 were examined by RT-PCR.

Results: In I/R-induced AKI mice, serum creatinine (SCr) and BUN were elevated 2 days after I/R treatment, and renal fibrosis was induced 28 days after I/R treatment. In those kidney tissues of I/R-AKI mice, CYLD protein expression was markedly decreased (0.4-fold) in a time-dependent manner. Interestingly, fibrosis gene expression (PAI-1: 3.3-fold, CTGF: 14.7-fold, COL1A1: 2.5-fold) was significantly increased in response to the CYLD down-regulation. In HK-2 cells, siRNA knockdown of CYLD gene expression significantly increased the PAI-1 gene expression (12-fold). Moreover, CYLD mRNA expression was significantly suppressed (0.5-fold) under hypoxic condition, an important factor of CKD progression, whereas the PAI-1 gene expression (2-fold) was elevated in HK-2 cells. These results suggested that CYLD could play a pathological role in regulating renal fibrotic response.

Conclusions: In conclusion, CYLD may be a novel regulatory factor involved in renal fibrosis and its down-regulation may trigger fibrosis under ischemic and/or hypoxic conditions.

Funding: Government Support - Non-U.S.

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

SA-PO278

The Effect of Oxygen and Hypothermic Therapy on the Prevention of Acute Kidney Injury

Background: There is no effective therapy for acute kidney injury. The effect of oxygen, hypothermic therapy delivered through urinary tract on the treatment of acute kidney injury has not been known. This pilot study was performed as a proof of concept of a catheter-based oxygen and hypothermic oxygen therapy in preventing and treating acute kidney injury.

Methods: Rats (n=6) were used for the experiment. Three rats were used to compare oxygen therapy and control. The other three rats were used to compare hypothermic oxygen therapy and control. Oxygen was cooled for hypothermic oxygen therapy before it was delivered to the kidney. Right kidneys received treatment (oxygen or hypothermic oxygen) and left kidneys were used for control. After a catheter was placed in a bladder, oxygen (or cooled oxygen) was delivered to the right kidney from the bladder through the catheter for five minutes for pretreatment before clamping. Both right and left renal arteries were clamped for 30-45 mins to induce acute kidney injury. Only right kidneys continued to receive oxygen or hypothermic oxygen during the clamping of renal arteries. The kidneys were extracted after the induction of acute kidney injury with the clamping. Gross examination of both kidneys during the clamping and after the extraction was performed.

Results: Gross examination of kidneys demonstrated less ischemic changes of kidneys treated with oxygen or hypothermic oxygen during and after the induction of acute kidney injury. As shown in Figure 1, right kidneys that received oxygen therapy or hypothermic oxygen showed less ischemic changes on gross examination during the clamping and after extraction.

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Proximal Tubule-Derived CSF-1 Mediates Expansion and Polarization of Renal Macrophages/Dendritic Cells and Recovery in Acute Kidney Injury

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Background: Colony-stimulating factor-1 (CSF-1)-mediated renal macrophage expansion and polarization play an essential role in recovery from acute kidney injury in ischemia/reperfusion (I/R)-injury and selective apoptotic proximal tubule injury in transgenic mice expressing the human diphtheria toxin receptor (DTR) and exposed to DT (DTR-AKI). In the kidney, a major site of CSF-1 production is in proximal tubular epithelial cells.

Methods: Male DTR mice with CSF-1f/f (wild type) or with γ-GT-Cre:CSF-1f/f (CSF-1 KO in renal proximal tubule) were used for DTR-AKI and for IR injury (30 min of ischemia and contralateral nephrectomy).

Results: CSF-1 expression in the proximal tubule and its deletion in CSF-1 KO mice were confirmed with immunostaining. Six days after DTR-AKI, activation of the CSF-1 receptor (p-c-fms) was markedly attenuated in both renal tubules and interstitial cells, including macrophages (F4/80 and p-c-fms dual positive cells). Flow cytometry and qPCR indicated fewer renal macrophages/dendritic cells and reduced mRNA levels of M2 phenotype markers (CD206, IL-4Rα, TGF-β1 and 15-LOX) in CSF-1 KO mice 6 days after DT injection. Although selective proximal tubule CSF-1 deletion did not affect the severity of kidney injury, it delayed renal functional recovery, in association with increased oxidative stress, increased secondary necrosis (HMGB1 expression) and severe tubulointerstitial fibrosis, with increased Picro-sirius red staining of fibillary collagen and increased profibrotic and fibrotic components (α-SMA, CTGF, Fbronectin, collagen I and IV). Selective proximal tubule CSF-1 deletion also delayed to functional recovery after IR injury, with decreased mRNA levels of M2 phenotype markers in isolated renal macrophages/dendritic cells and more severe renal fibrosis. In both I/R injury and DTR-AKI, selective proximal CSF-1 deletion had minimal effects on the expression of M1 phenotype markers.

Conclusions: These studies demonstrate that proximal tubule is a major source of CSF-1 that mediates the expansion and polarization of renal macrophages/dendritic cells that play an essential role in recovery following AKI.

Funding: NIDDK Support

Ablation of Myo-Inositol Oxygenase Protects against Cisplatin-Induced Acute Kidney Injury by Inhibiting p53 Activation

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Background: MIOX is a renal tubular enzyme. Its role in the pathogenesis of diabetic nephropathy is currently being investigated. Conceivably, it modulates redox balance and apoptosis in tubular cells in diabetes via modulation of gluturcnate-xylulose (G-X) pathway. However, its role in acute kidney injury (AKI) is unknown.

Methods: In this study we used both MIOX-over-expressing transgenic and MIOX null mice to elucidate its role in a model of cisplatin induced AKI.

Results: We observed severe cisplatin-induced proximal tubular injury in MIOX transgenic and protection in null mice compared to wild type mice. In transgenic mice an increased serum creatinine and urea levels, caspases-3 activity and tubular apoptosis along with marked deterioration of tubular morphology was observed. Renal injury was remarkably less in null mice compared to wild type mice. Cisplatin treatment led to p53 activation in wild type and MIOX transgenic mice, whereas minimal p35 activation was observed in MIOX null mice. Likewise, we noted that cisplatin induces mTOR pathway in both wild type and MIOX transgenic mice while such an effect was not observed in MIOX null mice. Treatment with mTOR inhibitor, rapamycin, prevented cisplatin-induced MIOX expression, p53 activation and deterioration of tubular morphology in control mice. In vitro studies revealed significantly high levels of ROS generation, caspases-3 activity and apoptosis in MIOX over-expressing cells compared to control cells transfected with empty vector following cisplatin treatment.

Conceivably, this was attributed to the accentuated induction of G-X pathway and its associated myriad enzyme system.

Funding: NIDDK Support

Calcium Oxalate Crystal-Induced Acute Kidney Injury Involves Ripk3-Mld Mediated Tubular Cell Necroptosis

Hans J. Anders, Jayansi Desai, Santosh Kumar, Jonathan Nicodemos Eberhard, Dana Thomasova, Simone Romoli, Andreas Linkermann, Shrikant R. Mulay. Ludwig Maximillians Univ, Munich, Germany; Christian-Albrechts-Univ, Kiel, Germany.

Background: Crystaline nephropathy (CN) & nephro-/urolithiasis involves crystal-induced renal inflammation via NLRP3 inflammasome (Mulay et al, JCI 2013), but the mode of direct crystal cytotoxicity in kidney remains elusive. The aim of the study was to investigate mechanisms of crystal cytotoxicity in kidney.

Methods: All in vivo experiments were approved by the local government authorities. Acute oxalate nephropathy (AON) was induced by i.p. injection of sodium oxalate (NatOx) (100mg/kg) and 3% NaOx in drinking water for 24hr. H&E, EM, RT-PCR, MTT assay, PI stain and multicolour FACS were used for data analysis.

Results: We found that crystals of calcium oxalate (CaOx), monosodium urate, calcium pyrophosphate dehydrate & cystine trigger caspase-independent necrosis of mouse tubular cells, human kidney cells & human renal progenitor cells. Pretreatment with RIPK1 inhibitor necrostatin-1 (Nec-1), MLKL inhibitor & RNA interference of RIPK3 or MLKL blocked crystal cytotoxicity. Consistently, deficiency of RIPK3 or MLKL protected mice from AON (e.g. plasma creatinine, BUN, tubular injury score, renal KIM-1 & α-GST mRNA expression, neutrophil count and TUNEL+ve cells) despite similar crystal deposition. I.p. injection of crystals induced neutrophil recruitment into peritoneal cavity, which was unaffected by Nec-1 as was crystal injection into air pouches at the back of mice. However, Nec-1 significantly reduced microvascular permeability & leukocyte extravasation from post-ischemic cremaster muscles. Thus RIPK1 signaling per se does not affect neutrophil recruitment. Next, we found that AON was significantly reduced in Tnfr-2-deficient mice, with no additive effects with concomitant Tnfr-2 deficiency. Thus, TNFR1 signaling activates RIPK3-dependent necroptosis in this model. Finally, etanercept, TNFR inhibitor R-7050 & Nec-1 protected mice from AON.

Conclusions: Crystal-cytotoxicity involves TNFR1-RIPK1-RIPK3-MLKL pathway. All components of this pathway represent novel molecular targets for therapeutic interventions to limit CN.
Alloporuin Protects against Rhabdomyolysis and Acute Kidney Injury Induced by a Membrane Protein (Lp25) from Pathogenic Leptospira

**Background:** Acute kidney injury (AKI) in leptospirosis is frequently nonoliguric, hyporenal or normorenal. Higher serum potassium levels, elevated creatine phosphokinase (CPK), and uric acid were markedly increased in patients with leptospirosis. We demonstrated that Lp25, a protein membrane from pathogenic Leptospira, induced hyperkalemia, rhabdomyolysis (elevated CPK, uric acid, and phosphate) and oliguric AKI. Alloporin (Allo) attenuates hyperkalemia, and AKI induced by Lp25 in guinea pigs. This may represent a new therapeutic approach for AKI in patients with leptospirosis.

**Methods:** Three groups of guinea pigs were studied: 1. Sham (phosphate-buffered solution) 2. Lp25+Allo. One mL of PBS and Lp25 (40μg of Lp25/mL) were intraperitoneally injected for 4 days. Lp25+Allo received Allo (300mg/kg) in drinking water during this time. On the 5th day, animals were placed in metabolic cages for 12 hours urine collection. We measured urinary volume (U/L12h), creatinine clearance (ml/min/100g BW), serum potassium (mEq/L), CPK (U/L), uric acid (mg/dL), phosphate (mg/dL). Data are mean±SEM.

**Results:** Lp25 induced hyperkalemia, rhabdomyolysis (elevated CPK, uric acid, and phosphate), and oliguric AKI. Allo attenuated hyperkalemia and AKI induced by Lp25 in guinea pigs.

<table>
<thead>
<tr>
<th>Cr Cl</th>
<th>U±V</th>
<th>K</th>
<th>CPA</th>
<th>Uric acid</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=7)</td>
<td>1.10±0.18</td>
<td>25.1±4.9</td>
<td>4.8±0.3</td>
<td>897±277</td>
<td>1.00±0.19</td>
</tr>
<tr>
<td>Lp25 (n=8)</td>
<td>0.48±0.05*</td>
<td>11.1±1.8*</td>
<td>6.8±0.5*</td>
<td>2582±495*</td>
<td>4.15±0.48*</td>
</tr>
<tr>
<td>Lp25+Allo (n=6)</td>
<td>0.9±1.04*</td>
<td>17.0±3.7</td>
<td>5.1±0.6*</td>
<td>1331±374*</td>
<td>0.47±0.07*</td>
</tr>
</tbody>
</table>

*p<0.05, *p<0.01 vs. Sham; **p<0.05, **p<0.001 vs. Lp25

**Conclusions:** These data demonstrate that Allo attenuates hyperkalemia and AKI induced by Lp25 in guinea pigs. This may represent a new therapeutic approach for AKI in patients with leptospirosis.

(CNPq, FAPESP)

SA-PO285

Conventional Autophagy Regulates the Degradation of AQP2 in Hypokalemia

**Background:** Autophagy is a catabolic pathway utilized to maintain a balance among the synthesis, degradation, and recycling of cellular component, thereby playing a role in homeostasis. Abundance of AQP2 is regulated through balance between production by tralation and removal by degradation. Although AQP2 degradation is supposed to be occurred via lysosomal or proteasomal degradation, the precise mechanisms still remain unknown. It has been known that prolonged hypokalemia causes vasopressin-resistant polyuria and induces autophagy especially in principal cells (PCs) of collecting duct.

**Methods:** To investigate the role of autophagy in the degradation of AQP2, we generated AQP2-cre;Atg7f/f mice, in which AQP7, an essential gene for mammalian autophagy, was selectively inactivated in PCs. Hypokalemia was induced by K-depleted diet for 2 weeks.

**Results:** In control AQP2-cre;AQP7+ mice, the distribution pattern of AQP2 was not different from AQP7+ mice. Immunolabeling of pS261-AQP2 was localized mostly subapical and appeared in appearance in the PCs. In contrast to pS256-AQP2, immunolabeling of pS256-AQP2 was localized mainly at the apical plasma membrane and subapical domains. In hypokalemia AQP7 mice, the abundance of pS256-AQP2 was significantly reduced and redistributed to intracellular vesicles, and co-localized with LC3-positive vacuoles. In hypokalemia AQP2-cre;AQP7 mice, there was a decrease of conversion of LC3-I to LC3-II and a marked accumulation of p62 selectively in PCs. Rab9 protein, an essential molecule for alternative autophagy pathway, and Rab9-positive vacuoles were markedly increased. Interestingly, pS261-AQP2 was distributed throughout the cytoplasm and not co-localized with Rab9- or LC3-positive vacuoles in the PCs of AQP2-cre;AQP7 mice. There was no difference in localization of pS256-AQP2 at the plasma membrane from each genotype.

**Conclusions:** These results suggest that down regulation of AQP2 in hypokalemia could in part be caused by degradation of pS256-AQP2 in PCs through a LC3-I/Atg7-dependent conventional autophagy pathway.

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

SA-PO286

Early Autophagy Precedes Angiotensin II-Induced Podocyte Apoptosis

**Background:** Autophagy is a highly regulated catabolic process that is involved in the turnover of unwanted cellular materials, on the other hand, apoptosis removes damaged or unwanted cells. Therefore, autophagy and apoptosis constitute the two processes which through injured/aged cells or organelles are eliminated. Angiotensin II (Ang II) induces podocyte apoptosis resulting in proteinuria in vitro and in vivo. The relationship between autophagy and apoptosis in Ang II-induced podocytes is not elucidated and the role of Ang II-induced autophagy in podocyte survival remains unclear. We investigated the sequential relationship between autophagy and apoptosis in Ang II-induced podocytes.

**Methods:** In mice with the expression of RFP-LC3 plasmid in media containing various concentrations of Ang II and at different incubation times. The changes of podocyte autophagy and apoptosis were observed by electron microscopy, confocal imaging, Western blotting, and FACS assay according to the presence of Ang II.** Results:** Ang II-treated podocytes showed an increase in autophagosomes compared with control cells at early phase in a dose-dependent manner. This pro-autophagic effect of Ang II was inhibited by pretreatment with 3-methyladenine, an inhibitor of PI3-kinase class III. Ang II also enhanced podocyte expression of autophagic proteins such as LC3-II and beclin-1. Atg5 siRNA further reduced the expression of LC3-II and cleaved caspase-3 suppressed by Ang II at 12 hrs. However, Atg5 siRNA did not affect the expression of Atg5, LC3-II, and cleaved caspase-3 in the presence of Ang II at 24 hrs. Therefore, Ang II induced podocyte apoptosis significantly in concentration- and time-dependent manners in FACS assays. LYS24002 and Atg5 siRNA further increased podocyte apoptosis induced by Ang II. Therefore, high concentrations of Ang II induced apoptosis, while autophagy response decreased, which implicated that autophagy preceded apoptosis for cytoprotection in angiotensin II-induced podocyte injury.

**Conclusions:** We suggest that Ang II induced autophagy in mouse podocytes prior to apoptosis as an early adaptive cytoprotective mechanism for podocyte survival after Ang II treatment and the imbalance between autophagy and apoptosis causes podocyte injury.

**Funding:** Government Support - Non-U.S.
regulating fibrosis is not fully understood. In this study, we investigated the proposed mechanisms of autophagy in renal TIF induced by UUO by using conditional knockout mice in which Atg7 is genetically ablated specifically in tubular epithelial cell (TEC).

**Methods:** Atg7-flox mice were crossed with Ksp-Cre to generate TEC-specific Atg7 knockout mice (Atg7f/f-Ksp-Cre'). Unilateral ureteral obstruction (UUO) was performed. We examined the expression of epithelial-mesenchymal transition (EMT) markers. The expression of TGF-β, plasminogen activator inhibitor 1 (PAI-1) and p62 as a regulator of cell apoptosis and proliferation.

**Results:** In vitro, TGF-β treatment induced autophagy. In vivo, TEC-specific Atg7 deletion enhanced renal TIF after UUO. TEC-specific Atg7 deletion increase expression of TGF-β and enhance tubular EMT (decrease E-cadherin and increase α-smooth muscle antibody and vimentin) after UUO. In electron microscopy, TEC-specific Atg7 deletion results in ultrastructural alterations of TEC after UUO. TEC-specific Atg7 deletion increases expression of PAI-1, P62 after UUO. TEC-specific Atg7 deletion enhanced apoptosis and proliferation of TECs after UUO. The expression of c-Myc was significantly increased in mice with TEC-specific Atg7 deletion after UUO. The expression of c-Myc was significantly increased in mice with TEC-specific Atg7 deletion after UUO.

**Conclusions:** Our data suggest that autophagy regulate EMT through TGF-β, PAI-1 and P62 during renal TIF. Autophagy also regulates apoptosis and proliferation of TECs through the expression of c-Myc during renal TIF. Autophagy could represent a therapeutic target for renal TIF.

**SA-PO289**

**Partial De-Differentiation of Parietal Epithelial Cells Caused by Reduced Expression of Sirt1 and Concomitant Increased Expression of p21 and CD133 in Diabetic Nephropathy**

**Kazuhito Hasegawa, Shu Wakino, Hiroshi Itoh**

**Keio Univ.**

**Background:** We have previously reported the role of proximal tubular Sirt1 in diabetic nephropathy (DN). Parietal epithelial cells (PECs) and their cellular metabolism reportedly play a pivotal role in kidney. Sirt1 is a key energy sensor, whereas DN disrupts energy metabolism.

**Methods:** Thus, we examined the effect of Sirt1 expression in PECs on DN.

**Results:** In two DN murine models involving streptozotocin-treated and db/db mice, expression of Sirt1 in proximal tubules and PECs was decreased at 8 weeks after the onset of DN, corresponding to the early stage of DN. Sirt1 expression was also downregulated in podocytes at 24 weeks. We further investigated the changes in PECs at 8 weeks. No change was found in the number of PECs. The morphology of all PECs showed hypertrophy, and some PECs contained autophagic vesicles, especially in the periphery or the border of the plasma membrane at basolateral sides.

**Normal Condition**

**Diabetic Nephropathy**

**Conclusion:** HG treatment of cultured PECs resulted in significant reductions in cell proliferation and migration, while increasing the production of extracellular and basement membrane components such as type IV collagen. We performed DNA microarray, confirmatory real-time PCR, and immunofluorescence, revealing that an increase in Glut1 (glucose transporter) expression promoted influx of high amounts of glucose into PECs, which led to a reduction in Sirt1 expression and lysine acetylation-mediated activation of p21. Among the main molecular markers of precursor cells, including CD24, CD44, and CD133, only CD133 showed remarkable elevation, indicating that the decrease in Sirt1 expression caused the partial de-differentiation of PECs.

**Conclusions:** Sirt1 may be a promising target for protection against DN-induced de-differentiation of PECs, which would prevent not only hypertrophy of PECs but also the concomitant thickening of the basement membrane of Bowman's capsule.

**SA-PO290**

**APOL1 Variants are Critical to Induce Vitamin D Receptor (VDR) Down Regulation in Dedifferentiated Podocytes**

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**Background:** Dysregulated growth and loss of podocytes are important features of HIV-associated nephropathy (HIVAN). In a recent report, HIV induced programmed cell death in T cells has been implicated to pyroptosis as a consequence to the induction of pyroptosis. We evaluated the role of HIV in podocyte NOD-like receptor family, pyrin domain containing (NLRP) 3 protein complexes (inflammomasomes) formation both in vitro and in vivo.

**Methods:** Renal cortical sections of control and Tg26 (HIVAN) mice (n=4) were labeled with dysregulated molecule markers (IMMs; NLRP1, ASC, cleaved caspase-1 and IL-1β). Protein blots of renal tissues of control and Tg26 mice were also probed for IMMs and actin (n=4). Protein blots of empty vector (EV) and NL4-3 (HIV)-transduced human podocytes (HPs) were probed for IMMs and actin (n=11). Protein blots of renal tissues of control and Tg26 mice were also probed for IMMs and actin (n=4). EV/HPs and HIV/HPs were labeled for inflammasome molecular markers (IMMs; NLRP3, ASC, cleaved caspase-1 and IL-1β). Protein blots of renal tissues of control and Tg26 mice were also probed for IMMs and actin (n=4). EV/HPs and HIV/HPs were labeled for inflammasome molecular markers (IMMs; NLRP3, ASC, cleaved caspase-1 and IL-1β). Protein blots of renal tissues of control and Tg26 mice were also probed for IMMs and actin (n=4).

**Results:** APOL1 variants (G1/G2) expressing HPs displayed lower expression of APOL1. However, the involved mechanism for lower APOL1 expression in these patients is not clear. Gene sequence alterations/mutations hamper either mRNA transcription stability or defects in protein translation. We hypothesized that mutation in APOL1 would lead to modulation of protein expression in podocytes.

**Conclusion:** These findings suggest that APOL1 variants protein instability may be related to loss/decay of variant APOL1 mRNA or to some extent defects in protein translation/stability.

**Funding:** NIDDK Support

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

**Underline represents presenting author.**

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expressions as well as protein expressions of iMMPs. Serum from TG26 mice showed higher levels of IL-1β and NF-kB promoted pyroptosis in podocytes in a dose as well as time dependent manner. Since caspase-1 inhibitor not only attenuated podocyte expression of caspases-1 and IL-1β in addition to protection against pyroptosis; this would confirm that HV induced podocyte injury was mediated by caspase-1-activated complexes. Interestingly, HV-induced podocyte pyroptosis could be partially inhibited by tempol as well as by glyburide.

Conclusions: These findings indicate that generation of reactive oxygen species and potassium efflux contributed to HV-induced pyroptosis in podocytes.

SA-PO293

Urinary Cytochrome C (Cyt C) Detects Subliminal Injury and Correlates with Apoptosis in Acute (AKI) and Acute on Chronic Kidney Disease (A-CKD)

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Background: Mitochondrial Cyt C is a potentially specific biomarker of apoptotic kidney injury in AKI. We investigated urinary Cyt C in detecting subliminal kidney injury (histological injury without an increase serum creatinine, scCr) in two models of A-CKD.

Methods: In male Sprague Dawley rats (i) adeno-CMK was induced by diet supplementation with 0.025% ademine, days (d) 0 to 28 and monitored until d56 (n=8). On d56, AKI was induced in rats by a subneophrotoxic (2mg/kg, n=8) or nephrotoxic (4mg/kg, n=8) cisplatin (Cis) dose and monitored for 8 weeks. (ii) Aristolochic-acid nephropathy (AAN) was induced by AA-1 (ip for five days and monitored to d21 (n=6) or d42 (n=6) then 2mg/kg (n=6) or 4mg/kg (n=6) Cis and monitored to d28 and d49 respectively. Cyt C was measured by ELISA. Tubulointerstitial damage (TID) and TUNEL were quantified on d66.

Results: Cyt C levels increased in subliminal AAN (d1 to d7) and ademine-CMK (d3 to d21) without change in scCr, but increased in both CKD groups after 2mg/kg and 4mg/kg Cis dose in controls. In AAN, Cyt C levels increased progressively (d22 to d28) after subneophrotoxic controls given 4mg/kg whereas Cyt C was lower after Cis on d42 to d49. Regardless of Cis dose, Cyt C increased in controls and ademine-CMK. A-CKD rats displayed diffuse medullary and cortical TID with positive TUNEL staining while injury in CKD alone was largely in outer medulla. In ANP peak Cyt C, 72 hours post Cis, correlated significantly (Spearman R=0.86*) and cortical apoptosis (R=0.81*). In ademine fed rats, Cyt C Correlated only with medullary apoptosis (R=0.79*) scCr correlated only with severe diffuse cortical TID (R=0.94*) (P<0.05).

Conclusions: Cyt C detected subliminal injury and correlated strongly with outer medullary apoptosis in A-CKD, which alone did not increase scCr. Cyt C is a useful biomarker for early detection of apoptotic kidney injury.

SA-PO294

Assessment of Graphene Toxicity to Kidney Tubular Epithelial Cells and Cell Spheroids Using DNase Activity Probe

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Background: Recently invented nanomaterial, graphene, consists of monomolecular carbon sheet, which are extremely strong, light and flexible. It will be used widely because of its versatility. However, little is known about its potential for being a toxicant and environmental hazard, and methods to study graphene toxicity are not established. Kidney is one of the primary organs for the assessment of nanomaterial toxicity. We hypothesized that graphene induces nephrotoxicity mainly through DNA fragmentation, and measuring DNase activity by using near infrared fluorescence (NIRF) DNase activity probe would be a reliable tool for assessing graphene cytotoxicity.

Methods: Non-modified graphene (50 μg/mL) exposed with cultured rat kidney tubular epithelial NRK-52E cells induced TUNEL-type DNA fragmentation usually associated with cytotoxicity. Ramun spectroscopy showed the TUNEL-positive cells have significantly higher graphene content than TUNEL-negative cells. DNase activity was quantified in live cells using the oligonucleotide-based NIRF probe. Quantitative immunocytochemistry (qICC) was then used to measure apoptotic DNases such as caspase-activated DNase (CAD), endonuclease G (EndoG), and DNase I, and the marker of oxidative stress, heme oxygenase-1 (HO-1).

Results: The NIRF fluorescence and all of the above qICC markers were induced in NRK-52E cells by graphene exposure. In addition, a 50% colocalization of HO-1 with caspase-3 and TUNEL was then used to measure apoptotic DNases such as caspase-activated DNase (CAD), endonuclease G (EndoG), and DNase I, and the marker of oxidative stress, heme oxygenase-1 (HO-1).

Conclusions: Measuring of DNase activity by using NIRF probe in combination with TUNEL assay and qICC are appropriate tools for assessment of graphene toxicity. Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

SA-PO295

Identification of a Novel Bidirectional Regulatory Mechanism Involving AKT/B-Catenin and Anillin That Drives Podocyte Proliferation

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Background: Mutations of the F-actin binding protein Anillin (ANLN) have been shown to cause familial FSGS. Although ANLN is a suspected modulator of the pi3k-akt kinase (PI-3K) signaling, specific interactions with PI-3K pathway intermediates and the role of these interactions in the pathogenesis of FSGS remains unknown.

Methods: siRNA-mediated gene knockdown studies, immunoblot and proliferation assays were performed by in vitro methods in conditionally immortalized human podocytes (CHP) to examine the effects of ANLN depletion on PI-3K signaling in podocytes. CHP lines stably expressing GFP-vector control or GFP-ANLNknock down were established via lentiviral transduction to characterize the effects of ANLN overexpression on PI-3K signaling in podocytes.

Results: We evaluated the effect of ANLN overexpression and targeted ANLN knockdown (KD) on AKT activation in podocytes. Additionally, we explored the effects of pharmacologic inhibition of AKT on ANLN expression in podocytes. Finally, we examined the role of AKT-mediated activation of β-Caten in the direct phosphorylation of serine 552 in podocyte ANLN expression. We determined that ANLN overexpression significantly attenuated AKT activation. Conversely, ANLN KD significantly enhanced AKT activation and upregulated AKT-mediated phosphorylation/activation of β-Caten in at serine 552. Pharmacologic inhibition of AKT also inhibited basal podocyte proliferation.

Conclusions: These findings elucidate a novel mechanism of reciprocal regulation involving AKT/β-Caten signaling and ANLN which may provide valuable insights into the role of ANLN in the pathogenesis of FSGS and other proliferative podopathies.

SA-PO296

Akt Mediates Cell Survival in Proteinuric States

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Background: The degree of proteinuria correlates with progression in association with tubulointerstitial injury in glomerulonephritis. High concentrations of albumin in the glomerular filtrate results in apoptosis. Protein kinase B (Akt) is a serine/threonine kinase involved in multiple signaling events including cell survival. We hypothesize that down regulation of survival protein, protein kinase B (Akt) triggers tubular apoptosis in proteinuric states.

Methods: We utilized in-vitro and in-vivo model of albumin overload. Human kidney proximal tubule epithelial cells (HKC-8) are exposed to 10mg/ml albumin for 24-hours to induce apoptosis. C3BL/6C mice are exposed to 10mg/ml ip for 6 weeks to induce albuminuria. Fluorometric caspase-3 assay and TUNEL staining were utilized to assess apoptosis. Protein expression was assessed by Western blotting and immunofluorescence. Kidney sections from biogenic (Fyn−/−Cd2ap−/−) mice model of FSGS and patients with FSGS were evaluated for apoptosis and Akt expression.

Results: Albumin overload for 6 weeks in HKC-8 resulted in proximal tubular cell apoptosis in association with down regulation of pser473 Akt and Thr-308 Akt expression. Furthermore mice model of FSGS and patient kidney biopsies confirmed down regulation of tubular pser473 Akt expression in association with apoptosis. Overexpression of Akt by a constitutively active mutant ameliorated the albumin induced apoptosis where as suppression of Akt by of MC2266 enhanced albumin induced apoptosis in HKC-8 cells. Phosphorylation of downstream targets of Akt, transcriptional factors forkhead family Foxo1 and 3 is inhibited in association with apoptosis in response to albumin overload.

Conclusions: Down regulation of Akt expression in proteinuric states results in tubular apoptosis which is a precursor to tubular atrophy. We postulate these Decreased Akt phosphorylation of Foxo proteins allow them to translocate to nucleus and induce apoptotic gene expression. Therapeutic interventions directed to increase Akt expression in tubular epithelial cells can serve to prevent tubulointerstitial injury by inducing cell survival in the active states.

Funding: NIDDK Support, Pharmaceutical Company Support - Malinchrodt

SA-PO297

Altered Protein Kinase Signaling Causes Major Phenotypical Changes in Renal Cells from Patients with Nephropathic Cystinosis

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Background: Cystinosis is caused by mutations affecting the lysosomal cystine transporter cystinosin and results in lysosomal cystine accumulation. Cystinosis causes proximal tubular dysfunction, but also glomerular damage, which is present starting from early age. Current therapy of cystinosis is based on cystine-lowering cysteamine treatment, which greatly improves the prognosis, but does not cure the Fanconi syndrome and fails to prevent kidney damage in the majority of patients. It is therefore likely that, apart from the transporter function, cystinosis is implicated in other important cellular processes. We have investigated the mTORC-Akt signaling cascade in cystinosis-deficient renal cells. Akt kinase lies at the crossroads of cellular signaling regulating cytoskeleton, motility,
response to stress and survival, and is a target of mTORC2 and an upstream activator of mTORC1. mTORC1 is the master regulator of autophagy and metabolism. mTORC1 and 2 are also implicated in the regulation of cytoskeleton and cell motility.

**Methods:** Using conditionally immortalized proximal tubular epithelial cells (PTECs) and podocytes originating from cystinosis patients and healthy donors, we performed biochemical and microscopic analysis of phosphorylation and activation of protein kinases in response to various stimuli.

**Results:** Phosphorylation of Akt1 and 2 was increased in cystinosis podocytes and PTEC in response to nutrient/growth factor replenishment and wounding of cellular monolayer. In podocytes, such increased phosphorylation, was associated with altered cytoskeleton, disturbed focal adhesion sites and increased motility. Treatment with specific Akt inhibitor demonstrated a prominent decrease of motility and Akt phosphorylation. mTORC1 activation in response to nutrient replenishment was delayed in cystinosis PTECs accompanied with abnormal subcellular distribution of the kinase complex, as revealed by antibody staining of mTOR.

**Conclusions:** We demonstrate that cystinosis dysfunction is associated with disturbed signalling of protein kinases mTORC1 and Akt1 and 2.

**Funding:** Private Foundation Support

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**SA-PO298**

**Intestinal Pericytes Decrease in Aged Mouse Kidneys**

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**Background:** With increasing age, the kidney undergoes characteristic changes in the glomerular and tubulo-interstitial compartments, which are ultimately accompanied by reduced kidney function. Studies have shown age-related loss of perivascular cells. Normal perivascular cell tone, function and survival depend on neighboring pericytes. Pericyte detachment leads to vascular damage, which can be accompanied by their differentiation to fibroblasts and myofibroblasts, a state that favors matrix production.

**Methods:** To better understand the fate of pericytes in the aged kidney, 27-month-old mice were studied. Picorirous red staining was performed to evaluate kidney fibrosis. Histological sections were stained against endothelial antigen CD31 together with pericyte markers PDGFß and aSMA. Additionally, immunoreactivity of myofibroblast marker aSMA was assessed together with pericytes.

**Results:** Compared to 3-month-old young adult mice, aged kidneys showed a substantial decrease in capillaries, identified by CD31 staining, in both cortex and medulla. This was accompanied by a marked decrease in surrounding NG2 / PDGFß pericytes. This decrease was more pronounced in the medulla. Capillaries devoid of pericytes were typically dilated in aged mice. Aged kidneys were also characterized by interstitial fibrosis due to increased collagen-I and -III staining. This was accompanied by an increase in the number of pericytes that acquired a pro-fibrotic phenotype, identified by increased PDGFß and aSMA staining.

**Conclusions:** These findings are consistent with the decline in kidney interstitial pericytes as a critical step in the development of changes to the peritubular vasculature with aging, and accompanying fibrosis.

**Funding:** Other NIH Support - R24 DK094768-01, R01 DK093493-02

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**SA-PO299**

**Interactions of Urotensin II and Mitophagy in Diabetic Nephropathy and Its Implications on Drug Design**

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**Background:** Urotensin II (UII), an important vasoactive neuropeptide, and the processes of mitophagy have been considered as possible therapeutic targets for treating diabetic nephropathy (DN). The present study is to define the interaction between UII and the process of mitophagy under the setting of DN.

**Methods:** Immunohistochemistry and western blot analysis were conducted on the protein extracts harvested from the kidney tissues of DN mice that were induced eighteen weeks after the injection of streptozotocin. For in-vitro cell experiment, HK-2 cells were cultured and treated with different concentrations of UII (10^(-7)-10^(-8) mol/L) for 2 h and 3-MA treatment was used as a negative control. The cell protein extracts were then analyzed by western blot. For immunohistochemistry and western blot analysis, BNIP3 was used as a marker for mitophagy.

**Results:** The results of our study demonstrate that UII expression can upregulate mitophagy in DN. Past studies already demonstrate that mitophagy can have a therapeutic role in DN. Our study carries the implication that UII and its effect on the process of mitophagy presents potential opportunities for the treatment of DN.

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

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**SA-PO300**

**Reduction in CTGF Leads to Increased Proliferation Through Influences on Claudin-1 and Extracellular Matrix Protein Spondin 2**

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**Background:** Accumulation of extracellular matrix is a characteristic feature of diabetic kidney disease. We have recently demonstrated that connective tissue growth factor (CTGF) mediate increases in extracellular matrix production, proteinuria and scarring in mice. In addition, CTGF may have anti-apoptotic properties. In specific human neoplasms (breast, colon), increased CTGF have been linked to reduced proliferation, improved response to therapy and prognosis but data is not consistent. On the other hand, metastatic melanoma progression correlates with CTGF levels and inhibition of CTGF reduces invasion and migration.

**Methods:** To define a possible role for CTGF in proliferation, embryonic fibroblasts (MEF) generated from wild-type and a previously reported CTGF knock mice line were studied. Expression array (Illumina) was used to identify changes in gene expression in MEF, with expression validated by Immuno-blotting. Inhibition of MAPK (SP600126, SB203580 and U0126) were used to assess role of MAPK in glucose-mediated CTGF expression by cultured MEF.

**Results:** CTGF gene disruption lead to enhanced proliferation (3-fold) in CKG knockout cells compared with wildtype cells. Reduced CTGF led to 50% decreased expression of the gene for the extracellular protein, procollagen 4, alpha 2 (Col4a2; confirmed at protein level)) in association with 2.8-fold increased expression of claudin-1, a member of the tight junction proteins. In addition, there was a 3.2-fold increased expression of spondin-2 and a 1.6-fold increased expression of Secreted Protein, acidic rich in cysteine-like 1 (SPARC1). Immunoblotting confirmed the observation for claudin-1. Glucose induced CTGF expression (2-3 fold) was attenuated by inhibitors of p38MAPK and JNK, but unaffected by inhibition of ERK (p42/44 MAPK).

**Conclusions:** In MEF, the gene disruption lead to increased proliferation and altered matrix protein linked to increased expression of claudin 1 and other extracellular protein. Secondly, glucose-induced CTGF level is mediated by MAPK (p38 and JNK). Targeted alteration in CTGF along with one or more of these extracellular protein may offer new approaches to manage glomerulosclerosis.

**Funding:** Private Foundation Support, Clinical Research Support

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**SA-PO301**

**miR21 Upregulates YY1 to Increase Renal Cell Apoptosis in Diabetes**

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**Background:** The regulation of miRNAs in response to hyperglycemia that contributes to the pathogenesis of kidney disease has been underscored.

**Methods:** In the current study, we investigated the role of miR21 in regulation of cells apoptosis in human renal proximal tubular cells (HK2) cells exposed to high glucose and in type II diabetes mouse model.

**Results:** Cells pretreated with either miR21 inhibitor or antisense before exposed to HG resulted in decrease YY1 expression and decrease cleavage of caspase 3. Nuclear extracts from HK2 cells exposed to high glucose for 48hrs showed increase in binding of YY1 to the promoter element in nuclear extracts of cells EMSA. On the other hand, pretreatment with miR21 inhibitor or antisense significantly decrease the binding of miR21 to YY1 in nuclear extracts of cells grown in NG or treated with HG. The DNA-protein complexes were significantly decreased in the presence of the YY1 antibody, indicating that YY1 is indeed a component of these complexes. Transfected the cells with promoter/reporter construct of miR21 showed significant increase in miR21 promoter activity in cells exposed to HG while cells pretreated with miR21 inhibitor reverse the effect of HG. In addition, significant increase in the percentage of TUNEL-positive tubular cells stained in the kidney sections of db/db mice kidney compared to kidney sections of the wild type mice. Quantitation of miR21 by real-time PCR showed significant increase miR21 levels in kidney of diabetic mice (db/db) compared to kidneys from wild type mice. Immunosstaining analysis of miR21 showed that majority of miR21 staining within the tubular cells and glomerular compartments.

**Conclusions:** In summary, expose renal cells to HG and increase hyperglycemia in kidney of diabetic mice resulted in significant increase in miR21. Increased binding of YY1 to miR21 under HG condition suggesting the important role of miR21 in regulating YY1 to increase cell apoptosis. The data provide a novel role of miR21 as a target for controlling renal cell death that induced by hyperglycemia during diabetic nephropathy.

**Funding:** Veterans Administration Support

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**SA-PO302**

**The Role of miR-302 and Let7 in Macrophage Polarization**

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**Background:** Recent advances in the pathogenicity of renal injury highlighted the critical role of the immune system in the onset and resolution of disease. Monocytes canto differentiate along two pathways: pro-inflammatory (M1) due to the secretion of cytokines such as IL-6 and a-pro-resolution attributable to the secretion of cytokines such as IL-10. Bane et al. have suggested that the ratio of M1 and M2 macrophages is controlled by...
interplay between two micro RNAs, miR302 and Let7. We have recently shown that the silencing targets of miR-302 and Let7 are the TGF-β type II and type I receptors respectively and hypothesize that this circuitry plays a critical role in macrophage differentiation.

**Methods:** The pro-resolving lipid mediator, conjugated linoleic acid (CLA), inhibits the acquisition of a pro-inflammatory macrophage phenotype by priming monocytes towards an anti-inflammatory phenotype. To identify pathways associated with this phenotype we performed proteomic analysis of THP-1 cells treated with CLA. Exosomes were isolated from urine samples taken from patients with renal injury and analyzed for miRNA expression. Renal cells were transfected with miR-302 and let7 virus. TGFβ receptor expression and signaling was analyzed by western blot. Additionally, Thp-1 cells were transfected with miR302 and let7 and their effect on phagocytosis differentiation assessed for expression of CD68 and CD206.

**Results:** Bioinformatic and Western blot analysis revealed enrichment of the TGFβ signaling pathway in THP-1 cells treated with CLA. miR302 expression was increased in the urine of patients compared to controls. Cells transfected with miR302 and Let7 displayed low levels of expression of the TGFβ type II and type 1 receptors respectively and dampened Smad3 phosphorylation. miR302 and let7 prevented renal epithelial cell dedifferentiation. THP-1 cells transfected with both miRs demonstrated similarly enhanced plasticity. Manipulation of this circuitry results in enhanced cell plasticity. In vitro studies suggest that this results in the generation of pro-resolution cellular phenotypes in both resident cells and macrophages.

**SA-PO303**

**Dopamine D2 Receptor Regulates Wnt3/β-Catenin Signaling and Apoptosis in Human Renal Proximal Tubule Cells**

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**Background:** Dopamine D2 receptor (D2R) in the kidney has a direct role in regulating renal injury and, injury, and blood pressure. Some common single nucleotide polymorphisms (D2R SNPs; rs6726, 6727, and 1800497) in the human D2RD gene are associated with decreased D2R expression and function.

**Methods:** We measured apoptosis and activation of Wnt3/β-catenin signaling pathway in human renal proximal tubule cells (RPTC) carrying these D2R SNPs (RPTC-D2R SNPs), and in RPTC carrying wild type (RPTC-D2R WT).

**Results:** RPTC-D2R SNPs showed increased apoptosis compared with RPTC-D2R WT (1.0±0.8% vs 2.3±0.4% TUNEL positive cells; P<0.01). We found that Wnt3 expression was increased in RPTC-D2R SNPs in comparison with RPTC-D2R WT (RNA: 2.6±0.35 vs 1±0.11 fold; P<0.05; protein: 133±4% vs 100±5%; p<0.05). RPTC-D2R SNPs showed increased β-catenin phosphorylation and decreased Bax and FasL expression. Moreover Wnt3 expression and release of apoptosis cells were transfects with scrambled siRNA or siRNA against Wnt3 and were exposed to control media or hypertonic medium.

**Results:** Following exposure to a high salt diet, pharmacologic inhibition of Wnt3 resulted in more severe kidney damage as assessed by the percentage outer medullary area with tubular dilatation and protein casts, when compared with vehicle-treated rats. Inhibition of Wnt3/β-catenin was associated with a significant increase in tubular cell apoptosis in comparison to vehicle treatment on TUNEL staining. Also, inhibition of Wnt3 led to significantly higher urinary albumin excretion and blood pressure at day 21 compared with vehicle treatment. Exposure of NRK52E cells to hypertonic medium resulted in increased expression and release of HMGB1 from the cells. Both pharmacologic inhibition and siRNA-mediated knock-down of HMGB1 led to reduced cell viability as determined by MTT assay.

**Conclusions:** HMGB1 plays an important role in renal tubular epithelial cell survival during hypertonic stress.

**SA-PO306**

**KIM-1-Mediated Phagocytosis Defines a New Mechanistic Paradigm for Kidney Epithelial Cells, which Involves Autophagy and Anti-Inflammatory Antigen Presentation**

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**Background:** The expression of kidney injury molecule-1 (KIM-1), the protein most upregulated in proximal tubular epithelial cells, interacts with professional phagocytes to induce immune responses. The processing of phagocytes to the lysosome can determine the immunogenicity of antigens derived from the phagocytosed cargo. Here we compare the phagocytic processing of KIM-1-expressing PTCs to that of professional phagocytes and establish distinct mechanisms.

**Methods:** LLC-PK1 cells expressing KIM-1 were exposed to apoptotic cells. LC3 localization to the phagosome, phagosome acidification and degradation were measured by live cell imaging, phagosome isolation and western blotting. NADPH oxidase (NOX) activity was blocked with diphenyleneiodonium and reactive oxygen species (ROS) was measured with fluorescent probes. MHC presentation was measured in primary PTCs directly using specific antibodies by flow cytometry. Functional implications were determined by activation of CD4+ and CD8+ T cells.

**Results:** KIM-1 binds to and induces phagocytosis of apoptotic cells within ~5-30 min, similar to professional phagocytes. Following uptake, however, PTCs process phagosomes more slowly than professional phagocytes, with delayed phagosome acidification and degradation (4-12 hrs vs 1-2 hrs). Mechanistically, PTCs do not upregulate NOX-1 induced production of ROS, a process necessary for efficient acidification and degradation of the phagosome. LC3 associated phagocytosis (LAP), an important NOX-induced production of ROS, a process necessary for efficient acidification and degradation of the phagosome. LC3 associated phagocytosis (LAP), an important NOX-dependent feature of professional phagocytic function, is not observed in PTCs. PTCs instead induce canonical autophagy to clear phagocytosed debris. Delayed phagosomal acidification and degradation result in more slowly than professional phagocytes, with delayed phagosome acidification and degradation (4-12 hrs vs 1-2 hrs). Mechanistically, PTCs do not upregulate NOX-1 induced production of ROS, a process necessary for efficient acidification and degradation of the phagosome. LC3 associated phagocytosis (LAP), an important NOX-dependent feature of professional phagocytic function, is not observed in PTCs. PTCs instead induce canonical autophagy to clear phagocytosed debris. Delayed phagosomes are processed and increased autophagy result in increased PTC antigen presentation. Here we compare the phagocytic processing of KIM-1-expressing PTCs to that of professional phagocytes and establish distinct mechanisms.

**Conclusions:** Phagocytic processing of KIM-1-expressing PTCs to that of professional phagocytes and establish distinct mechanisms.

**SA-PO305**

**The Role of High Mobility Group Box 1 in Renal Epithelial Cell Survival During Hypertonic Stress**

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**Background:** High mobility group box 1 (HMGB1) is a ubiquitous and evolutionarily conserved, DNA-binding protein and is characterized as an alarmin or damage associated molecular pattern because of the ability of extracellular HMGB1 to trigger an inflammatory response when it binds to its putative receptors, including RAGE, TLR2 and TLR4. New and emerging evidence suggest that intracellular HMGB1 is involved with numerous cell survival functions. The aim of this study was to examine the functional role of HMGB1 in tubular epithelial cells during hypertonic stress.

**Methods:** In vivo; 2 groups of Dahl Salt sensitive rats were placed on high salt diet (4% NaCl, n=5/group) and were treated with either daily intraperitoneal injection of a HMGB1 inhibitor (glycyrrhizic acid) or a vehicle for 3 weeks while their blood pressure was monitored by telemetry. In vivo, NNRK52E cells were incubated in control medium (332 mOsmol/kg) or hypertonic medium that contained NaCl (500 and 600 mOsmol/kg) for 6 hours in the presence or absence of the HMGB1 inhibitor. In other experiments, cells were transfected with scrambled siRNA or siRNA against HMGB1 and were exposed to control medium or hypertonic medium.

**Results:** Following exposure to a high salt diet, pharmacologic inhibition of HMGB1 resulted in more severe kidney damage as assessed by the percentage outer medullary area with tubular dilatation and protein casts, when compared with vehicle-treated rats. Inhibition of HMGB1 was associated with a significant increase in tubular cell apoptosis in comparison to vehicle treatment on TUNEL staining. Also, inhibition of HMGB1 led to significantly higher urinary albumin excretion and blood pressure at day 21 compared with vehicle treatment. Exposure of NRK52E cells to hypertonic medium resulted in increased expression and release of HMGB1 from the cells. Both pharmacologic inhibition and siRNA-mediated knock-down of HMGB1 led to reduced cell viability as determined by MTT assay.

**Conclusions:** HMGB1 plays an important role in renal tubular epithelial cell survival during hypertonic stress.
SA-PO307
Apototic Cells Activate AMPK and Inhibit Proximal Tubular Cell (PTC) Growth without Change in Intracellular Energy Stores
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Background: Apoptosis plays an indispensable role in the maintenance and development of tissues. We have shown that receptor-mediated recognition of apoptotic target cells by viable kidney PTCs inhibits the proliferation and survival of these viable PTCs. Here, we examined the effect of apoptotic target cells on PTC cell growth (cell size during G1 phase of cell cycle).
Methods: We used BU.MPT cells, a conditionally immortalized PTC line, as responder cells. BU.MPT cells, induced to undergo apoptosis in several ways, were used as apoptotic targets. Results: Apoptotic cells potently activated AMP-activated protein kinase (AMPK), a highly sensitive sensor of intracellular energy stores. AMPK activation led to decreased activity of its downstream target, ribosomal protein p70 S6 kinase (p70S6k) and concomitant inhibition of cell growth. Importantly, these events occurred without detectable change in intracellular levels of AMP, ADP, or ATP. Inhibition of AMPK, either pharmacologically by compound C or molecularly by shRNA, diminished the effects of apoptotic targets, and largely restored p70S6k activity and cell size to normal levels. Apoptotic targets also inhibited Akt, a second signaling pathway regulating cell growth. Expression of a constitutively active Akt construct partially relieved cell growth inhibition, but was less effective than inhibition of AMPK. Inhibition of cell growth by apoptotic targets was dependent on physical interaction between apoptotic targets and PTCs, but independent of phagocytosis.
Conclusions: We conclude that receptor-mediated recognition of apoptotic targets mimics the effects of intracellular energy depletion, activating AMPK and inhibiting PTC cell growth. By acting as sentinels of environmental change, apoptotic death may enable nearby viable cells, especially non-mitogenic epithelial cells, to monitor and adapt to local stresses.
Funding: Clinical Revenue Support

SA-PO308
The Effect of Uremia on Cardiac Autophagy
William White, Steven Michael Harwood, Petros Andrikopoulos, Muhammad M. Yaqoob. William Harvey Research Inst, Barts & The London School of Medicine & Dentistry, Queen Mary Univ of London, London, United Kingdom.
Background: Autophagy is the process by which cells remove and recycle unwanted structures, contributing to intracellular homeostasis and energy production. Cardiac autophagy has a role in maintaining protection and ventricular remodeling, and decreasing autophagy is central to aging. Evidence suggests these processes are disordered in CKD. We hypothesize that albumin does not change autophagy, but decreases autophagy in uremia. Autophagic activity in hearts is decreased with proteinuria, a known uremic factor.
Methods: In Vitro Rat cardiac myoblast cells (H9C2) were cultured in the presence of insulin (100 μM), hemin (5 μM), and L-arginine (10 mM), to achieve a state of cellular stress that simulates conditions of uremia. Under these conditions, basal autophagy was strongly induced. Medium was changed every 2 days and cells were cultured for 5 days. Cells were fed normally or were starved for 24 h, and autophagy was assessed using confocal microscopy.
Results: At 24 and 48 h the amount of LC3BII (a marker of autophagic flux) expressed increased with IS in a dose-dependent manner with and without CQ. At 48 h P62 expression decreased with IS in the absence of CQ, but increased in its presence. In vivo setting and LC3BII and p62 expression increased in the uremic hearts in line with the in vitro data. Interestingly p53 expression was increased in the uremic group.
Conclusions: Uremia appears to stimulate autophagy in cardiac tissues at the protein level, in contrast to our autopsy transcriptome data. Previous authors have found that changes in autophagic activity are not always mirrored at a transcriptional level. Interestingly, p53 expression was greater in uremia, suggesting an increase in senescence, which we are currently investigating. Changes in autophagic activity and senescence in uremic hearts may contribute to the pathogenesis of uremic cardiomyopathy, and provide targets for therapy.

SA-PO309
Decorin Potentially Alleviates TGF-β1 Induced Podocyte Injury by Inactivating mTORC1 and Increasing Autophagy
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Background: TGF-β1 is the major factor mediating podocyte injury during mesangial proliferative glomerulonephritis (MsPGN), manifesting by decreased autophagy, cytoskeleton relocation and increased apoptosis. Decorin (DCN), mainly secreted by mesangial cells (MCs) in glomeruli, is a natural antagonist of TGF-β1 and has been shown to be downregulated in MsPGN and in vitro. We hypothesize that decorin could protect podocytes from autophagy in injured podocytes of MsPGN and the possible effect of DCN/TGF-β1 axis on the crosstalk of MCs and podocytes are still not clear.
Methods: We used immunohistochemistry (IHC) to detect p-smad2 and LC3 in rat anti-Thy-1 nmephritis, and TGF-β1 in human nephritis. Then we treated podocytes with TGF-β1 and DCM and detected the expression of Vps34, p-S6K1 (Thr389), TGF-β1, p62 and LC3 by IHC. We also treated podocytes with TGF-β1 (20ng/ml) for 1, 3, 6 and 12 h, and found decreased protein expression of Vps34 and increased p-S6K1 (Thr389) representing mTORC1 signaling, autophagy was increased and p62 was decreased. In cultured human podocytes, the treatment of recombinant soluble DCN (6.25ng/M or 100ng/M) for 1, 3, 6 and 12h on podocytes led to an increase p-smad2 expression of Pe5g, decreased p-S6K1 (Thr389), LC3BII and TGF-β1. In this study, we firstly found increased p-smad2 and decreased LC3 by IHC in podocytes of rat anti-Thy-1 nephritis with obvious proteinuria, and consistently, increased TGF-β1 staining in human nephritis featured by MCs proliferation and proteinuria. Then we treated podocytes with TGF-β1 (20ng/ml) for 1, 3, 6, and 12 h, and found decreased protein expression of Vps34 and increased p-S6K1 (Thr389) representing mTORC1 signaling, autophagy was increased and p62 was decreased. In cultured human podocytes, the treatment of recombinant soluble DCN (6.25ng/M or 100ng/M) for 1, 3, 6 and 12 h on podocytes led to an increase p-smad2 expression of Pe5g, decreased p-S6K1 (Thr389) and LC3BII. Moreover, it also decreased TGF-β1 in podocytes.
Conclusions: These results suggest that TGF-β1 induced an activation of mTORC1 signaling and the abrogation of macroautophagy in podocytes, whereas DCN downregulated TGF-β1 protein expression, and thus inactivate mTORC1 signaling and induce autophagy on podocytes, indicating DCN may have a potential in alleviating TGF-β1 induced podocyte injury in MsPGN.
Funding: Government Support - Non-U.S.

SA-PO310
Albumin Endocytosis in the Proximal Tubule Causes Accumulation of Dysfunctional Mitochondria
Andreia Nolin, Ryan M. Mulhern, Ramon G. Bonegio, Zhiyong Wang, Steven C. Berkman, John H. Schwartz, Andrea Havasi. Renal, Boston Univ Medical Center, Boston, MA.
Background: Proteinuria is a major risk factor for chronic kidney disease progression. Furthermore, exposure of proximal tubular epithelial cells (PTEC) to excess albumin promotes tubular atrophy and fibrosis, key predictors of progressive organ dysfunction. The mechanism by which protein exposure causes tubular cell injury is uncertain. We hypothesize that albumin endocytosis causes tubular cell injury by inhibiting autophagy, including mitophagy, resulting in an accumulation of dysfunctional mitochondria leading to enhanced ROS production, mitochondrial and cellular injury.
Methods: The effect of proteinuria was examined both in in vivo and in vitro experiments. Proteinuria was induced in mice by injection of a sheep nephrotic serum that causes acute immune-complex glomerulonephritis with massive proteinuria by 24-48 hrs. In vitro, to mimic nephrotic glomerular filtrate, PTECs were exposed to albumin. Autophagy was assessed in tissue samples from mice and primary PTECs. Steady state LC3BII or LC3BIII, an autophagy marker was quantified by immunoblot. Autophagosomes (APs) were examined by electron microscopy and fluorescent markers and in renal cortical tissue using immunohistochemistry. Mitochondrial respiration was measured in primary cells. Mitochondrial morphology and colocalization with autophagosomes were imaged using confocal microscopy. Reactive oxygen species production was measured using a 2′,7′-dichlorofluorescin diacetate assay.
Results: Exposure to excess albumin induced defective autophagy and mitophagy in vitro. In renal cortices, proteinuria decreased both the number of LC3-II positive APs and the amount of LC3-I detected in cell lysates. Albumin-exposed cells accumulated damaged mitochondria with altered mitochondrial function and morphology. Albumin exposure caused mitochondrial dysfunction as evidenced by decreased oxygen consumption rate from coupled ATP production. Increasing albumin exposure time caused an increase in ROS production.
Conclusions: Dysfunctional autophagy caused by proteinuria likely contributes to tubular cell toxicity leading to renal progression.
Funding: NIDDK Support, Private Foundation Support

SA-PO311
Association Between a Marker of Aging and Cardiovascular Pathology in End-Stage Renal Disease Patients
Karin Luttropp,1 Dagmara Megiunnis,2 Abdul Rashid Tony Qureshi,1 Hannes Olauson,1 Annika Wernerson,1 Louise Nordfors,1 Jonaz Ripsveden,6 Peter F. Barany,1 Peter Stenvikv.1 Dept of Molecular Medicine and Surgery, Karolinska Inst, Stockholm, Sweden; 2Inst of Cancer Sciences, Univ of Glasgow, Glasgow, United Kingdom; 3Dept of Clinical Science, Intervention and Technology, Div of Renal Medicine, Karolinska Inst, Stockholm, Sweden; 4Dept of Clinical Science, Intervention and Technology, Div of Radiology, Karolinska Inst, Stockholm, Sweden.
Background: Patients with chronic kidney disease (CKD) display a progeric phenotype, with a high incidence of cardiovascular disease (CVD) and vascular calcification (VC). The process of VC is complex, and has been linked to apoptosis. A potential contributor to the calcification process is the pro-apoptotic factor cyclin-dependent kinase inhibitor 2A (CDKN2A). This study aims to investigate possible associations between CDKN2A expression, VC and CVD in a CKD population.
Methods: CDKN2A expression was determined in epigastric arteries (n=43) from patients with end-stage renal disease (ESRD) undergoing living donor renal transplantation (LRTx). Arteries were scored for degree of calcification in percent. Coronary artery calcification (CAC) score was also obtained.
Results: The arterial expression of CDKN2A was significantly associated with VC (p=0.01, r=0.4), CVD (p=0.002, CAC score (p=0.008, r=0.5) and diabetes mellitus (p=0.05). In addition, arterial CDKN2A expression was associated with MGP (p=0.007, r=0.4) and RUNX2 (p=0.046, r=0.3) expression in artery, both of which are involved in osteogenic transformation of vascular smooth muscle cells.
Conclusions: These findings provide evidence that cell senescence and apoptosis are important in the development of VC and CVD in the uremic milieu, and further strengthen the hypothesis that comorbidities present in CKD could be caused by a premature aging process. Attempts to ameliorate any progeric process in this patient group is therefore of great interest.

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

SA-PO314
Endothelial Autophagy Is Essential for Vascular Lipid Homeostasis
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Background: Cardiovascular disease is one of the common complications in chronic kidney disease. It is known that autophagy plays a critical role in the course of kidney diseases. The resulting cardiovascular diseases are presumably regulated by autophagy. However the physiological role of autophagy in the vascular endothelial cells remains poorly understood.

Methods: Using human umbilical vein endothelial cells (HUVECs), induction of autophagy by ox-LDL, and uptaking or transcytosis of LDL are analyzed. To inhibit autophagy pharmacologically, chloroquine is used. The essential autophagy gene, Atg7 shRNA-mediated knockdown are performed to inhibit autophagy genetically. To assess an acute and chronic in vivo model of lipid exposure, we generated endothelial specific Atg7 knockout in ApoE deficient mice (Atg7/+/ApoE KO).

Results: Ox-LDL induced autophagosome formation in HUVECs. Moreover, native or ox-LDL appeared to be engulfed within autophagosomes by live cell imaging and electron microscopy. Atg7 knockdown or pharmacological inhibition of autophagy resulted in higher accumulation of intracellular LDL, suggesting that in vascular endothelial cells, autophagy is one of the degradation machinery of excess lipids. As an acute model of lipid exposure in vivo, Atg7/+/ApoE mice showed longer retention of ox-LDL within the retina after infusion of Dil ox-LDL. In a chronic model of lipid excess, we analyzed atherosclerosis in ApoE KO or Atg7/+/ApoE KO mice. Atg7/−/−ApoE KO mice demonstrated markedly increased atherosclerosis.

Conclusions: In endothelial cells, autophagy appears to play a critical role in regulating excess intracellular lipids. Moreover, in both acute and chronic in vivo model, endothelial autophagy plays an essential role in LDL accumulation within endothelial layer. Prevention of the decline in autophagy flux accompanied by kidney diseases pharmacologically might be beneficial to treat atherosclerotic diseases.

SA-PO315
Targeted Mutations at the p66 Locus Antagonize Stem Cell Aging and Delay Expression of Senescent Phenotypes in Diabetic Kidneys

Background: Senescence has important implications for the biologic function of tissue stem cells, which maintain tissue homeostasis by replacement of old or dying cells and via the repair of tissue injury. The p66 longevity gene plays a key role in the activation of gene programs that induce senescent and apoptotic phenotypes. We hypothesize gene basal strategies targeting p66 will delay or prevent stem cell senescence and premature aging phenotypes in diabetic kidneys.

Methods: Mesenchymal stem cells (MSCs) were isolated from kidneys of p66 KO mouse (p66 KO-MSCs) using established methods and plated in high glucose (HG) containing media. Microarray was used to profile secreted factors expressed by MSCs. p66 KO diabetic mice were generated to evaluate survival of MSCs in diabetic kidneys, growth, proliferation, histologic markers of aging and near normal urine albumin excretion. Kidney nuclei staining (+) for Ki-67 was upregulated, whereasp16 INK4a and tubules, with barely detectable histologic markers of aging and near normal urine albumin excretion. Unexpected cross talk between p66 and Wnt regulatory genes that antagonize senescence. Kidney sections from p66 KO diabetic mice show increased numbers of MSCs in glomeruli and tubules, with barely detectable histologic markers of aging and near normal urine albumin excretion. Kidney nuclei staining (+) for Ki-67 was upregulated, whereasp16INK4a was downregulated.

Conclusions: These findings suggest a genetic link between p66 longevity gene, stem cell aging and senescent phenotype(s) in diabetic kidneys.

Funding: Private Foundation Support

SA-PO316
The Full Time Course and Localization of mTOR Activation in Compensatory Renal Hypertrophy
Jinxian Xu,1 Meichu Cheng,1 Jianchun Wang,2 Kang Chen,2 1Cellular-Biology & Anatomy and Medicine, Georgia Regents Univ, Augusta, GA; 2Medicine, Vanderbilt Univ, Nashville, TN.

Background: Previous studies documented an essential role for mTOR activation in mediating compensatory renal hypertrophy induced by unilateral nephrectomy (UNX) but the time course and localization of the mTOR activation are unclear.

Methods: 8-week-old male FVB/NJ mice were subjected to right UNX or sham surgery, followed by sacrifice at different time points to collect left kidney and determine the time course and localization of mTOR activation by immunoblots and immunofluorescence staining for phospho-S6K1 and phospho-p70, along with nephron segment-specific markers.

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

698A
EGF Dependent Regulation of VEGF-A Secretion by Proximal Tubule Cells

Diana Zepeda-Orozco,1 Hsiang M. Wen,2 Nandita S. Raikwar,2 Christie A. Dockrell,1 Hsiang M. Wen,2 Nandita S. Raikwar,2 Christie A. Dockrell,1 Hsiang M. Wen,2 Nandita S. Raikwar,2 Christie A. Dockrell,1 Hsiang M. Wen,2 Nandita S. Raikwar,2 Christie A. Dockrell,1 Hsiang M. Wen,2 Nandita S. Raikwar,2 Christie A. Dockrell,1

Background: Vascular endothelial growth factor A (VEGF-A) plays a critical role in peritubular capillary development by promoting vasculogenesis and angiogenesis. It is now recognized that there is increased expression of VEGF-A by proximal tubular epithelial cells in ischemia reperfusion injury and in chronic tubulointerstitial injury. Although hypoxia is known to increase VEGF-A expression in vitro, the role of VEGF-A in vivo, and in the mechanisms regulating VEGF-A secretion by proximal tubule epithelial cells in normoxia has not been established.

Methods: We utilized HK2 cells, an immortalized human proximal tubule cell line, to characterize the epidermal growth factor (EGF)-dependent regulation of VEGF-A secretion by proximal tubular epithelial cells.

Results: EGF increases HIF1a expression, stimulates VEGF-A secretion and proliferation of HK2 cells under normoxic conditions. HIF1a knockdown decreases EGF-dependent VEGF-A secretion indicating that the effect of EGF is at least partly HIF1a dependent even in normoxia. EGF stimulates HIF1a and VEGF-A via activation of the EGF receptor and upregulation of mTOR and p42/44 MAPK pathways. p42/44 MAPK inhibition significantly downregulates HIF1a-dependent VEGF-A secretion and cell proliferation. Although mTOR inhibition reduces HIF1a, it upregulates MAPK with a very modest reduction of VEGF-A secretion indicating that mTOR and p44/42 MAPK may act via parallel pathways in VEGF-A regulation. Finally, we demonstrate that the EGF-stimulated proliferation of HK2 cells is reduced by VEGF Receptor 2 (VEGFR2) blocker indicating that EGF stimulates proximal tubular cell proliferation via the secretion of VEGF and the activation of the VEGFR2 receptor.

Conclusions: EGF stimulates VEGF-A secretion via activation of the EGF receptor, and stimulation of HIF1a. EGF stimulates proliferation of HK2 cells via the secretion of VEGF-A indicating that VEGF is an autocrine proximal tubular epithelial cell growth factor. The effects of EGF on HIF1a, and VEGF-A in HK2 cells are modulated by complex crosstalk between p42/44 MAPK and mTOR pathways.

SA-PO317

Selective Regulation of a Novel Truncated CCN3 Protein by TGFβ1 in Human Tubule Epithelial Cells

Matthew Potting,1 Bruce L. Riser,2 Mark E. Dockrell,1 1SWI Intl for Renal Research, London, United Kingdom; 2BLR Bio, WI.

Background: CCN3 is a member of the matricellular CCN family of proteins along with the structurally similar CCN2/CTGF, a powerful fibrotic agent, but recent work supports our hypothesis that CCN2 and 3 act in opposition to each other regulating fibrosis. In renal cell dysfunction, inhibition of CCN3 with siRNA or TGFβ1 has been shown to counter regulate the expression of CCN2 and CCN3 in the vertebral nucleus pulposus and in mesangial cells. We have previously characterised TGFβ1 induction of CCN2 in proximal tubule epithelial cells (PT), here we investigate the expression of CCN3 in human PT cells and its potential regulation by TGFβ1.

Methods: Primary human PT cells were cultured on collagen IV in supplemented medium. At 80% confluence cells were treated with TGFβ1 (-0.25 -2.5 ng/ml) for 24 & 48h, medium was collected and cells lysed. Equal amounts of lysate were subjected to PAGE and Western blotting then probed with antibodies (Ab) to the C-terminal region of CCN3, as well as the C-terminal region of CCN2/CTGF.

Results: Under control conditions the anti-CCN3 hinge Ab revealed the expression in PTEC of the 51Kda full-length protein as well as a 39Kda isoform. The antibodies to the respective termini detected bands of approximately 23-28Kda. The C-terminal ab did not detect the 39Kda band. The antibody to the N-terminal detected proteins of approximately 45Kda as well as the 39Kda form. Treatment with TGFβ2 for 24h had no effect on the 51Kda protein but significantly inhibited the expression of the 39Kda.

Conclusions: A concentration that induce-CTGF expression in PTEC. TGFβ1 does not regulate the expression of full length CCN3. However, it does reduce the expression of a truncated form apparently lacking the CT domain. The characteristics of this smaller protein are not consistent with any known splice variants and may represent an non-physiological entity. The lack of the CT domain would change the 3 dimensional conformation of the protein, inhibit its binding to various interactions and potentially remove the ability of the molecule to inhibit cell proliferation.

SA-PO319

Deletion of TGF-β Receptor 1 Causes Reduced Proximal Tubule Cell Impairs HGF Signaling

Stellor Nandu Khod,1 Leslie S. Gewin,2 1Research, Tennessee Valley Veterans Affairs, Nashville, TN; 2Medicine, Div of Nephrology, Vanderbilt Univ, Nashville, TN.

Background: The growth factors TGF-β and HGF have antagonistic and synergistic interactions that govern renal development and response to injury. We previously showed that TGF-β worsened the epithelial response to acute renal injury, so we postulated that TGF-β/HGF signaling may impact repair. The lack of the CT domain would change the 3 dimensional conformation of the protein, inhibit its binding to various interactions and potentially remove the ability of the molecule to inhibit cell proliferation.

Results: TβRII-/- PT cells had increased tubular branching and impaired migration compared to cells with the receptor intact. Unexpectedly, PT cells lacking TβRII had impaired response to HGF in both branching morphogenesis and migration assays compared to TβRII wildtype cells. Consistent with this, TβRII-/- PT cells had impaired dMet phosphorylation associated with reduced membrane expression of dMet and transcriptional downregulation of the HGF receptor. Notch signaling, a known inducer of dMet transcription, was decreased in cells with TβRII intact, and Notch inhibition by gamma-secretase equalizes the responses to HGF by PT cell with and without the receptor.

Conclusions: PT cells lacking TβRII have impaired responsiveness to HGF signaling, and this is due to reduced Notch-mediated dMet transcription. Thus, efforts to block TGF-β signaling may inadvertently inhibit signaling pathways of other growth factors such as HGF.

Funding: Veterans Administration Support

SA-PO320

Enhancement of HGF-Induced Tubulogenesis by Endothelial Cell-Derived GDNF

Masao Nakamoto, Akito Maeshima, Shunsuke Takahashi, Hidekazu Ieuchi, Toru Sakairi, Yoraki Kaneko, Keiji Hirono, Yoshitaka Nogima. Dept of Medicine and Clinical Science, Gunma Univ Graduate School of Medicine, Maebashi, Gunma, Japan.

Background: Renal proximal tubular epithelium can regenerate itself after a variety of insults. However, the fibrotic environment that regulates regeneration process of renal tubules after injury remains unclear. We previously established an in vitro 3D tubulogenesis assay which at least partly mimics in vivo regeneration processes of renal tubules after injury (Am J Physiol Renal Physiol: 301: F387-95, 2011). Utilizing this system, the endothelial cell-derived factors that regulate tubular formation was examined.

Methods: Human renal proximal tubular epithelial cells (RPTEC) were cultured in gels (type I collagen/matrigel mixture) in the presence of HGF with or without human umbilical vein endothelial cells (HUVEC) using Transwell filter system. The signaling pathway activated by co-culture with HUVEC in tubular structures were examined using phospho-receptor tyrosine kinase (RTK) array.

Results: HGF, a potent renotrophic factor, induced aquaporin-1-positive tubular structures with microvilli, suggesting that these structures are morphologically equivalent to adult renal tubules. When co-cultured with HUVEC, HGF-induced tubular formation was significantly enhanced. Tubulogenic action of HGF in a paracrine manner. GDNF-RET signaling may play a role in the crosstalk between renal tubular cells and surrounding endothelium during tubular regeneration after injury.

Funding: Veterans Administration Support

SA-PO321

Massive Formation of Ang-(1-7) from AngII(1-8) Is Largely ACE2 Independent

Peter Daniel Serfizio,1 Jan A. Wysocki, Minghao Ye, Daniel Batte. Div of Nephrology, Northwestern Univ - Feinberg School of Medicine, Chicago, IL.

Background: Ang(1-8) degrading mechanisms are complex including cleavage by aminopeptidases that form AngIII and carboxypeptidases like ACE2 and PDE3B. The lack of the CT domain would change the 3 dimensional conformation of the protein, inhibit its binding to various interactions and potentially remove the ability of the molecule to inhibit cell proliferation.

Conclusions: A concentration that induce-CTGF expression in PTEC. TGFβ1 does not regulate the expression of full length CCN3. However, it does reduce the expression of a truncated form apparently lacking the CT domain. The characteristics of this smaller protein are not consistent with any known splice variants and may represent an non-physiological entity. The lack of the CT domain would change the 3 dimensional conformation of the protein, inhibit its binding to various interactions and potentially remove the ability of the molecule to inhibit cell proliferation.

Funding: Underline represents presenting author.
Methods: After acute AngII(1-8) infusion to WT mice plasma concentrations of AngII(1-8), Ang(1-7) and Ang(1-5) were measured by LC-MS/MS. Additional measurements of Ang(1-7) by RIA and ELISA were performed for confirmatory purposes. Plasma ACE2 and PRPC activity in WT mice was measured using a fluorogenic substrate.

Results: Following AngII(1-8) infusion to WT mice plasma Ang(1-7) levels measured by MS were extremely high. Similarly high levels were also found when this peptide was measured by RIA and ELISA (Table).

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<th>AngII(1-8)</th>
<th>Ang(1-7)</th>
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<tr>
<td>MS</td>
<td>244 ± 21 pg/ml</td>
<td>766 ± 199 pg/ml</td>
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<tr>
<td>RIA</td>
<td>n.a.</td>
<td>1527 ± 240 pg/ml</td>
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<tr>
<td>ELISA</td>
<td>1012 ± 223 pg/ml</td>
<td>1137 ± 394 pg/ml</td>
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In an ACE2 KO line there was no significant difference in Ang(1-7) levels as compared to WT mice and the levels of ACE2 activity in plasma of WT mice were low. Moreover, activity of PRPC, another Ang(1-7) forming enzyme is very low at the plasma pH. We therefore hypothesize that Ang(1-7) formation after AngII(1-8) infusion must be largely ACE2 and PRPC independent. To further support this hypothesis, we infused a different set of mice with AngII(1-8) in the presence of recombinant murine ACE2 or ACE2 + MLN, a specific inhibitor. Under all these conditions the levels of Ang(1-7) were massively increased and therefore unaccountable only by the conversion of AngII(1-8) to Ang(1-7) by ACE2 cleavage.

Conclusions: Formation of Ang(1-7) during AngII(1-8) infusion is massive and largely ACE2 independent. The increase in Ang(1-7) after AngII(1-8) infusion suggests the presence of unknown Ang(1-7) forming enzymes that are very active in plasma.

Funding: NIDDK Support

SA-PO322

HIF1α and HIF2-Induced Erythropoietin Production Along the Nephron

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Background: Kidney peritubular interstitial cells produce erythropoietin (Epo) in response to hypoxia and/or anemia. By using in situ hybridization method, we have shown that Epo is also produced by the cortical nephron segments (mainly in PCT, DCT and CCD) in control and/or hypoxic conditions (Nagai, et al, 2014). The role of renin-angiotensin-aldosterone inhibitor has been suggested to exacerbate anemia in chronic kidney disease, in response to hypoxia and/or anemia. By using in situ hybridization method, we have shown that Epo is also produced by the cortical nephron segments (mainly in PCT, DCT and CCD) in control and/or hypoxic conditions (Nagai, et al, 2014).

Methods: To characterize the molecular machineries for Epo production in renal tubules, we examined the mRNA expressions of HIF1α, HIF2α, PHD2, mineralocorticoid receptor (MR) and EGF-receptor (EGFR) along the nephron in basal condition. Each nephron segment from SD rats was microdissected in the presence of ribonucleoside and measured by RIA and ELISA (Table).

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<th>AngII(1-8)</th>
<th>Ang17</th>
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<tbody>
<tr>
<td>MS</td>
<td>244 ± 21 pg/ml</td>
<td>766 ± 199 pg/ml</td>
</tr>
<tr>
<td>RIA</td>
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<tr>
<td>ELISA</td>
<td>1012 ± 223 pg/ml</td>
<td>1137 ± 394 pg/ml</td>
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Results: Epo mRNA expression was confirmed in whole nephron segments by RT-PCR in basal condition. The expressions of HIF1α, HIF2α and PHD2 mRNAs were detected in whole nephron segments both in RT-PCR and real time PCR. The largest expression of HIF2α mRNA was observed in PCT. HIF2α mRNA expression was larger than HIF1α mRNA expression in most segments (ΔCT relative to GAPDH). MR and EGFR mRNA expressions were observed not only in distal but also in proximal tubules.

Conclusions: The results suggest the presence of HIF2α induced-Epo reduction in renal tubules. The presence of MR in whole nephron segments suggest that aldosterone may have physiological effects for Epo production not only in distal but also in proximal tubules.

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

SA-PO323

Cytokine Response of Primary Human Mesangial Cells Is LPS Strain Dependent

Margaret M. O’Neill, Carine Boustany, Steven S. Pullen. CardioMetabolic Diseases Research, Boehringer Ingelheim Pharma. Inc, Ridgefield, CT.

Background: LPS stimulation of Toll-like receptor 4 (TLR4) induces the release of proinflammatory cytokines which activate potent immune responses. LPS is an important structural component of the outer membrane of Gram-negative bacteria and consists of three parts: lipid A, a core oligosaccharide, and an O side chain. It has been studied extensively in models of inflammation with E.coli 011:B4 most often referenced in the literature. The antigenicity of LPS varies from strain to strain depending on the composition its O side chain. A comparative study was designed to identify the optimal strain to be used for LPS-stimulated release of proinflammatory mediators from primary human mesangial cells (HMC).

Methods: HMC were stimulated with 7 strains of LPS and 24 hour supernatants were analyzed for production of inflammatory mediators (IL-6, IL-8, TNF-α and MCP-1).

Results: LPS induced strain-dependent increases in IL-6, IL-8, and MCP-1 in HMC, while there was no effect on IL-1β and TNF-α.

Conclusions: LPS induced strain-dependent increases in IL-6, IL-8, and MCP-1 in HMC, while there was no effect on IL-1β and TNF-α.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals Inc

SA-PO324

Effect of Angiostatin II Type 1 Receptor Blocker on 12-Lipoxygenase Activity and Slit Diaphragm Protein Nephrin and P-cadherin Expression in Type 2 Diabetic Rat Glomeruli

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Background: 12-lipoxygenase (12-LO) and Angiostatin II (Ang II) interaction plays an important role in the development of diabetic nephropathy (DN), in which proteinuria was thought to be associated with decreased expression of glomerular slit diaphragm protein nephrin and P-cadherin. However, it is unclear whether Ang II type 1 receptor blocker (ARB) regulates 12-LO activity and slit diaphragm protein expression in type 2 diabetic glomeruli and hence was investigated in this study.

Methods: Podocytes and glomeruli isolated from rats were used in this study. The 12-LO products 12(S)-HETE and Ang II were infused to rats by osmotic mini-pump. Rats fed high fat diet received low dose streptozotocin to make type 2 diabetes. Glomeruli were isolated with sieving method and classified into small glomeruli (SG, on the 75nm sieve) and large glomeruli (LG, on the 125nm sieve). ELISA, RT-PCR and Western blot for related targets were performed respectively.

Results: Ang II increased 12(S)-HETE levels in podocytes and glomeruli. Direct infusion of rats with 12(S)-HETE and Ang II significantly decreased LG nephrin, but increased SG nephrin expression compared to control. The glomerular P-cadherin expression was reduced after Ang II and 12(S)-HETE treatment and there was no difference between LG and SG. ARB did not affect blood glucose levels but completely attenuated increases in 12(S)-HETE content, AT1 expression and proteinuria induced by diabetes. Nephrin protein expression was significantly reduced in diabetic LG but increased in diabetic SG compared to control. P-cadherin expression was decreased in both diabetic LG and SG. These abnormalities were partially but significantly prevented by ARB treatment.

Conclusions: ARB could ameliorate the progression of DN via upregulation of glomerular nephrin and P-cadherin expression through inhibition of 12-LO activation in type 2 DN rat.

Funding: Government Support - Non-U.S.

SA-PO325

APOL1 Risk Variants and HIV Stimulate Induction of PDGFB-β Receptor in Podocytes

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Background: Clinical reports demonstrated that two coding sequence variants (G12V and G2021S) of the APOL1 gene are responsible for the higher percentage of kidney disease in African Americans. This disparity between patients with APOL1 variants versus wild type APOL1 increases by 10 fold for the development of HIVAN in patients of HIV infection who are not on antiviral therapy. Podocytes do not express platelet-derived growth factor (PDGF) receptors constitutively, nonetheless, in experimental animal models, podocyte

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uregulated expression of PDGFRs manifested as progressive glomerulosclerosis. We hypothesized that APOL1 risk variants and HIV carry potential for the induction of the activation of the PDGF pathway in podocytes.

Methods: To determine the effect of APOL1 and APOL1 variants expression, stably expressing Vector, APOL1G0, APOL1G1, or APOL1G2 human podocyte (HP) cell lines were derived. For knock down, small hairpin RNA of HIV (NL-4-3) or empty vector (control) was transduced into APOL1G0/HPs, APOL1G1/HPs and APOL1G2/HPs. After 48 h, RNAs were extracted. CDNs were amplified with specific primers for PDGF-A, PDGF-B, PDGF-C, PDGF-D, and PDGFRβ. Results: RNA transfection significantly increased expression of PDGF- A, PDGF-B, PDGF-C, PDGFR-D, and PDGFRβ in podocytes/G0/HPs, G1/HPs, and G2/HPs with or without HIV transduction did not display any change in the expression of PDGF-B, PDGF-C, or PDGF-D, when compared with vector; whereas, G2/HPs in HIV milieu displayed enhanced expression of PDGF-A. Interestingly, both G1/HPs and G2/HPs displayed 10 fold increase in PDGFRβ expression when compared to vector/HPs or G0/HPs.

Conclusions: These findings indicate that PDGFRs and their receptor PDGFRβ can be induced by HIV and APOL1 risk variants. The present study could lead to new therapeutic targets for HIVAN.

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SA-PO326
Assessment of Urinary Liver Type Fatty Acid Binding Protein in Patients of Type 2 Diabetes Mellitus with Early Chronic Kidney Disease
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Background: Diabetes mellitus is the most common cause of chronic kidney disease (CKD) worldwide. Various markers are being indentified which can detect nephropathy at an earlier stage. Both glomerular and tubular injury play an important role in etiopathogenesis of diabetic nephropathy (DN) and tubular damage precedes glomerular damage. Tubular markers may be superior to serum-based biomarkers in detecting early renal injury. Liver type fatty acid binding protein (L-FABP) is a 15 kDa protein that is primarily expressed in the liver and intestine. It is also expressed in other tissues including myocardium, skeletal muscle, smooth muscle, and areas of regenerative tissue.

Methods: This was a case control, cross sectional study. Eighty four subjects in the age group 30–60 years of either sex were taken and were divided into three groups: Group I: Healthy controls (n=28) Group II: Type 2 diabetes patients with normoalbuminuria (n=28) Group III: Type 2 diabetes patients with micro/macroalbuminuria (n=28). Detailed history, physical examination, investigations for renal function, serum creatinine, and liver function tests were done. Urinary L-FABP levels were measured using an ELISA kit.

Results: The urinary ACR levels were comparable in group I and II. Subjects in Group III had significantly elevated ACR values. Levels of urinary L-FABP were higher in subjects of group II and III when compared with group I. Values of L-FABP were also higher in group III compared to group II. There was a significant positive correlation found between urinary ACR and urinary L-FABP levels. A significant negative correlation was found between urinary L-FABP and eGFR.

Conclusions: Levels of urinary L-FABP are markedly increased in patients of diabetic nephropathy as compared to healthy controls. Levels were also increased in diabetes patients with normoalbuminuria suggesting early tubular injury in these patients. This suggests that urinary L-FABP may be a promising early marker for detection of diabetic nephropathy.

SA-PO327
Neuropilin1 Regulates Pericyte Behavior in Postnatal Kidney
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Background: Neuropilin 1 (Nrp1) is a transmembrane co-receptor implicated in the regulation of endothelial cell migration during angiogenesis. In the adult kidney, Nrp1 is expressed not only by endothelium but also by pericytes including peritubular mesangial cells. Nrp1 has been described as a regulator of pericyte cell migration and has been found to be involved in the regulation of endothelial cell migration. In the adult kidney, Nrp1 is primarily expressed by the endothelium in association with the coreceptor neuropilin-2 (Nrp2). Nrp1 and Nrp2 form a heterodimeric complex that binds ligands such as VEGFs and sema4D with high affinity.

Methods: To determine the role of Nrp1 in pericyte behavior, two complementary mouse models were used; in the first one, Nrp1 was deleted specifically in pericytes with tamoxifen-inducible NG2Cre line and in the second approach, Nrp1 was blocked with an Nrp1-IgG-based antibody (R&D). In both models, tamoxifen/antibody treatment started at P21. Results: Mutant mice showed mild proteinuria and/or hematuria at 3 months of age with Nrp1 primary affected. In vitro experiments with primary mesangial human and mouse cell lines showed increased cell proliferation, abnormal spreading and actin reorganization in Nrp1 knock down cells. Conclusions: This study shows a novel role of Nrp1 in adult kidney pericytes. Future exploration of the role of Nrp1 with kidney cell lines and measurement of blood pressure will further clarify these interesting findings.

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SA-PO328
Development of a Spontaneous, Reproducible and Treatable Kidney Fibrosis Model
Jessica Maree Overstreet, Ming-Zhi Zhang, Raymond C. Harris. Medicine, Vanderbilt Univ, Nashville, TN.

Background: Kidney fibrosis in chronic kidney diseases causes gradual loss of kidney functionality. Currently, only a few kidney fibrotic models are available. New kidney fibrotic models are needed. Since our previous studies indicated that activation of epidermal growth factor receptor (EGFR) contributes to the development of renal fibrosis, we have developed a model with selective overexpression of an EGFR ligand, human heparin-binding EGF (hHB-EGF) in renal proximal tubule.

Methods: B6D2 transgenic mice with selective overexpression of an EGFR ligand, human heparin-binding EGF (hHB-EGF) in renal proximal tubule, were generated. Male C57/BL6 homozygous HB-EGF mice received vehicle (water) or erlotinib (80 mg/kg/day) in daily gastric gavage 6 to 10 days after birth.

Results: Kidney cortical hHB-EGF mRNA and protein levels were dramatically higher in homozygous hHB-EGF mice than in heterozygous mice. Profound renal interstitial fibrosis was found in both B6D2 and C57/BL6 homozygous hHB-EGF mice, but not in heterozygous mice, as indicated by histology and increased levels of the pro-fibrotic and fibrotic components (CTGF, α-SMA, collagen 1 and IV). Homeozygous hHB-EGF mouse kidneys also exhibited increased oxidative stress and infiltration of both macrophages and T lymphocytes. Interstitial fibrosis appeared as early as 4 weeks old. Homozygous hHB-EGF mice have increased kidney EGFR activation (increased phosphorylation of EGFR) and activation of downstream signaling, p-ERK and p-AKT. In addition, there was markedly increased p-Smad 2/3, p-EGFR, p-ERK, and p-Smad 2/3 were all primarily localized to proximal epithelial cells, indicating that hHB-EGF-mediated EGFR activation in proximal epithelial cells is the primary event in the development of interstitial fibrosis. Treatment with erlotinib, an inhibitor of EGFR tyrosine kinase activity, inhibited EGFR signaling pathways and attenuated the development of renal interstitial fibrosis.

Conclusions: These studies suggest that ligand-mediated EGFR activation in renal proximal tubular epithelial cells leads to spontaneous, reproducible, and treatable renal interstitial fibrosis. Therefore, homozygous hHB-EGF mice may be a useful renal fibrosis model to test the effectiveness of anti-fibrotic agents.

Funding: NIDDK Support

SA-PO329
LPA-LPA1 Signaling Regulates Fibroblast Proliferation and Myofibroblast Differentiation Dependent on Epithelial Cell-Fibroblast Interaction
Norihiko Sakai, Yasutaka Kamikawa, Akihiro Sagara, Yasuyuki Shinozaki, Shijni Kitajima, Akinori Hara, Yasunori Iwata, Milho Shimizu, Kengo Furuchi, Takashi Wada. Div of Nephrology, Kanazawa Univ, Kanazawa, Japan.

Background: Renal fibrosis is a common pathway of progressive renal diseases, resulting in renal failure regardless of its cause. The accumulation of fibroblasts and myofibroblasts has been recognized as a hallmark of renal fibrosis. However, the precise mechanisms driving it remain to be determined. We have previously found the lipid mediator lysophosphatidic acid (LPA) and one of its receptors, LPA1, stimulates peritubular mesothelial cells to induce fibroblast proliferation through connective tissue growth factor (CTGF) production, suggesting the involvement of epithelial cell-fibroblast interaction regulated by LPA-LPA1 signaling in the pathogenesis of organ fibrosis.

Methods: In this study, we focused on the effects of LPA-LPA1 signaling on the interaction between renal tubular epithelial cells (RTEC) and renal fibroblasts (RFB). The stimulation with LPA induced CTGF expression in both RTEC and RFB in a time- and dose-dependent manner. The induction of CTGF in both cells was suppressed by the treatment with LPA, antagonist (AM095). In addition to that, LPA-induced CTGF expression in both cells was diminished by the treatment with Rho inhibitor (C3 toxin) and Rho kinase inhibitor (Y27632). In both cells, LPA enhanced the nuclear translocation of myocardin-related transcription factor (MRTF)-A/B and the transcriptional activity of MRTF-serum response factor (SRF), whereas Y27632 treatment inhibited those. The inhibition of MRTF-A/B-SRF pathway by the treatment with siRNA or a chemical inhibitor of Rho kinase abolished LPA-induced CTGF expression.

Conclusions: In conclusion, LPA-LPA1 signaling regulates epithelial cell-fibroblast interaction to induce fibroblast proliferation and differentiation into myofibroblasts through CTGF production dependent on Rho/Rho kinase/MRTF-SRF pathway.

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SA-PO330
TWEAK/Fn14 Signaling Promotes Kidney Disease by Driving Myofibroblast Activation, Inflammation and Vascular Instability
Ivan G. Gomez, 1 Allison M. Roach, 1 Ganme Karaca, 1 Linda Burky, 1 Jeremy Stewart Duffield, 1 Research & Development, Biogen, Cambridge, MA; 2Medicine, Univ of Washington, Seattle, WA.

Background: We identified Fibroblast growth factor-inducible 14 (Fn14) as a receptor on pericytes, which is strongly upregulated as they differentiate into myofibroblasts in vivo in kidney disease. TNF-related weak inducer of apoptosis (TWEAK), a TNF-family
cytokine produced predominantly by myeloid leukocytes has been reported to activate NF-κB signaling and that NF-κB signaling was activated in myofibroblasts in vivo and hypothesized that TWEAK/Fn14 signaling might be an important driver of pathological myofibroblasts in kidney disease.

**Results:** Fn14 deficiency ameliorates myofibroblast appearance, fibrosis, and myofibroblast survival. TWEAK/Fn14 signaling activates primary murine cultured kidney fibroblasts in response to TGF-beta1 and Angiotensin II is suggestive of cross-talk among Hippo cells suggesting that these cytokines likely disable core Hippo signaling. TAZ stable gene Angiotensin II stimulation, moreover, promoted TAZ and pSMAD3 nuclear entry in HK-2 cells. TWEAK signaling in disease progression was evaluated in the mouse Alport model of chronic kidney disease. Anti-TWEAK antibodies preserve organ function and significantly attenuate disease progression.

**Conclusions:** These findings suggest that targeting the TNF superfamily TWEAK/Fn14 pathway is an approach to modulate myofibroblast activation and a novel way to block both inflammatory and fibrotic aspects of chronic kidney disease.

**Funding:** Pharmaceutical Company Support - Biogen

**SA-PO331**

**Deregulation of Hippo-TAZ Pathway During Renal Injury Promotes Fibrotic Phenotype**

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**Background:** Hippo pathway is the principal regulator of organ size. Transcriptional co-activator with PDZ-binding motif (TAZ), a nuclear transducer of Hippo pathway, is activated by loss of cellular polarity, tension forces, or soluble factors. TAZ has been implicated in the progression of lung fibrosis and cancer. However, role of Hippo-TAZ pathway in chronic kidney disease (CKD) is unknown.

**Methods:** We utilized three mouse models of renal injury [ureteral ligation (UUO), aristolochic acid nephropathy (AAN), streptozotocin (STZ)-driven diabetic nephropathy] and TAZ genetic manipulation in HK-2 tubular epithelial cells and NRK-49F renal fibroblasts to investigate role of TAZ in renal fibrosis.

**Results:** TAZ is activated [as evident by increased nuclear accumulation (4-40 fold) and expression (2.5-5 fold) at both in the tubular and interstitial cells and decreased TAZ mRNA and protein expression] in the UOO kidney compared to contralateral controls. TAZ expression is also upregulated in AAN and STZ-induced renal diabetic injury models. TAZ activation correlated with increased pSmad3 in the fibrotic kidney. TGF-beta1 and Angiontsin II stimulation, moreover, promoted TAZ and pSmad3 nuclear entry in HK-2 cells suggesting that these cytokines likely disable core Hippo signaling. TAZ stable gene silencing in HK-2 cells, indeed, suppressed TGF-beta1 and Angiontsin II induced CTGF, PAI-1 and fibronectin expression. Stable TAZ overexpression in HK-2 cells promoted epithelial dedifferentiation and proliferative arrest.

**Conclusions:** Activated during renal injury, TAZ is a novel profibrotic effector of TGF-beta1 and Angiontsin II induced profibrotic responses. TAZ nuclear accumulation in response to TGF-beta1 and Angiontsin II is suggestive of cross-talk among Hippo pathway and these cytokines.

**Funding:** Other NIH Support - GM057242

**SA-PO332**

**Design and Characterisation of Novel BMP Agonists and Antagonists**

**Daniel Cremona,** Satnam Surace, Finian Martin, Catherine Godson. UCD; UCD; UCD.

**Background:** We have previously reported a role for the Bone Morphogenetic Protein (BMP) antagonist Gremlin in a driver of diabetic nephropy pathology and fibrosis in both kidney and lung. Bone Morphogenetic Proteins are integral regulators of bone and organ development. BMPs are secreted proteins and signal by associating with membrane bound receptors. The activity of BMP agonists is modulated by a family of secreted protein antagonists, including Noggin and Crossveinless-2 (BMP-2 only) and Noggin (BMP-2 only). Crossveinless-2 (BMP-2 only) and Noggin (BMP-2 only) and antagonists of BMP-7.

**Results:** The free energy calculations identified the key contributions of BMP residues to both binding events and suggested mutations that might generate super-agonist and dominant negative molecules. Further in silico analysis was performed by mutating each residue to each of the other 19 amino acids. From this we identified potential super-agonists and dominant negative mutants for both BMP-2: L51V and N102T (super-agonists) and S88G and L92D (dominant negatives), and BMP-7: E60T, D119I, L244A and K127E (super-agonists) and F117E and V122D (dominant negatives). The super-agonists will bind and activate the receptor but will be resistant to binding by antagonist; in contrast, the dominant negatives, bind antagonist but not receptor.

**Conclusions:** Data will be presented from our investigations of these molecules as potential therapeutic leads for treating fibrotic diseases including DN.

**Funding:** Pharmaceutical Company Support - ROCHE

**SA-PO333**

**Engaged Growth Factors to Treat Acute Kidney Injury**

**Shawdeeh Fahbi,** Fuk Haruta, Tim Stowe, Matt Onsum. Silver Creek Pharmaceuticals, San Francisco, CA.

**Background:** Acute kidney injury remains a major unmet medical need and economic burden. Currently there are no therapies that act directly on damaged kidney cells to promote survival. At Silver Creek Pharmaceuticals, we are engineering a new class of therapeutics called Smart Growth Factors that act selectively on damaged kidney cells to safely deliver pro-survival signals and restore kidney function.

**Methods:** We harness the power of pro-survival and mitogenic signaling of growth factors and engineer more desirable drug-like properties, including extended half-life and cell type-specific targeting. Our first SGF, designed to reduce cardiomyocyte death following acute myocardial infarction, has shown positive pre-clinical efficacy and is being prepared for an Investigational New Drug Application. We are now designing an SGF to treat acute kidney injury, where apoptosis of proximal tubule cells is a leading mechanism of pathology. We developed an in vitro model of tubule cell apoptosis using hypoxia to screen wild type growth factors for the ability to restore cell viability and promote proliferation. We then used computational models to design SGFs that could maximize pro-survival signaling and targeting in damaged kidney tubule cells.

**Results:** SGF variants were built, expressed and purified in-house, and screened for their ability to activate prosurvival and proliferative signals selectively in damaged cells using the in vitro hypoxia model. SGFs with favorable rescue ability, selectivity and pharmacokinetics will be tested in a rodent AKI model using bilateral ischemia.

**Conclusions:** Smart growth factors have the potential to transform the treatment of acute kidney injury, but safely delivering potent pro-survival and mitogenic signals specifically to damaged cells, hopefully leading to better outcomes for this patient population.

**SA-PO334**

**Loss of the Podocyte Glucocorticoid Receptor Exacerbates Proteinuria**

**Julie Goodwin,** Xuefei Tian,2 Shuta Ishibe,1 1Pediatrics, Yale Univ School of Medicine, New Haven, CT; 2Internal Medicine, Yale Univ School of Medicine, New Haven, CT.

**Background:** Nephrotic syndrome is one of the most common renal diseases in children and podocyte foot process effacement is its histologic hallmark. Glucocorticoids (GC) are the mainstay of treatment. Podocytes express the glucocorticoid receptor (GR) and new evidence suggests that podocyte-specific GC effects may be central to controlling proteinuria.

**Methods:** Mice with knockout of GR in podocytes were generated by crossing GR null mice with podocin Cre mice. Proteinuria was induced using both a systemic stimulus (LPS) and a renal-specific insult (nephrotic serum (NTS)). Urine protein/creatinine ratios, serum albumin, and GFR were measured at baseline and on day 1 of treatment following LPS or NTS injection. In vitro, wound healing assays and analysis of stress fiber formation after stimulation with LPS in the presence or absence of dexamethasone (DEX) were performed in primary podocytes isolated from animals of both genotypes.

**Results:** Podocyte GR knockout mice did not have a phenotype at baseline. Their weight, serum creatinine, serum albumin, urine protein/creatinine ratios and foot process morphology were similar to controls. When challenged with low-dose LPS (12.5 mg/kg, IP), knockout mice developed significantly more proteinuria (2.11 ± 0.77 vs. 0.60 ± 0.21, p<0.05, n=5/group) than did controls. Knockout mice also showed greater foot process effacement and impaired wound healing after LPS treatment compared to control podocytes. Administration of DEX could rescue the in vitro phenotype in control, but not GR knockout, podocytes.

**Conclusions:** These results demonstrate that (1) loss of podocyte GR exacerbates proteinuria in two different models in vivo, (2) podocytes lacking GR are more intolerant to injury, and (3) DEX administration ameliorates cellular injury in control, but not GR-deficient, podocytes. We conclude that the podocyte GR plays a key role in maintaining the integrity of the slit diaphragm after injury.

**Funding:** NIDDK Support

**SA-PO335**

**Deletion of Inositol-Requiring Enzyme-1α in Podocytes Disrupts Glomerular Capillary Integrity and Autophagy**

**Daniel Robert Kaufman,**1 Joan Papillon,2 Takao Iwawaki,2 Andrey V. Cybulsky,3 1Physiology, McGill Univ, Montreal, QC, Canada; 2Medicine, McGill Univ, Montreal, QC, Canada; 3Medicine, Gunn University, Maebashi, Japan.

**Background:** Inositol-requiring enzyme-1α (IRE1α) is an endoplasmic reticulum (ER)-transmembrane endoribonuclease-kinase, which plays an essential function in numerous cellular and tissue during normal development, and is activated during ER stress. IRE1α may be involved in upregulating genes associated with the unfolded protein response and

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ER-associated degradation, as well as in the activation of c-Jun N-terminal kinase (JNK)-1, and induction of apoptosis and autophagy. In this study, we address the functional role of mir-192 in podocytes.

Methods: Podocyte-specific mir-192 knockdown (KO) mice were produced by breeding mice with loxP-site surrounding exons 20-21 with podocin (NPHS2)-Cre mice. MirP-mediating excision in podocytes was confirmed.

Results: In male mice, deletion of mir-192 in podocytes resulted in albuminuria beginning at 5 months of age, and worsening with time. Electron microscopy revealed focal podocyte foot process effacement starting at 5 months, and worsening with time. Electron microscopy revealed focal podocyte foot process effacement in 9 month old male KO mice, as well as microvillous transformation of podocyte plasma membranes and cytosolic vacuolation. By light microscopy, glomerular cross-sectional area (an indicator of hypertrophy) was greater in KO males, compared with control, and capillary lumens occupied a higher fractional area of KO glomeruli, suggesting formation of anurysms. By immunofluorescence microscopy, WT- podocytes were comparable in KO and control males. Immunoblotting showed reduced LC3B-II expression and JNK-1 phosphorylation in KO glomeruli, in keeping with reduced autophagy. There was also a reduction in nephrin maturation in KO glomeruli, suggesting impaired ER function. Finally, expression of mir-1 in KO mice was confirmed.

Conclusions: Podocyte-specific deletion of mir-1 leads to albuminuria and morphologic evidence of podocyte injury. Thus, mir-1 is essential to the maintenance of podocyte integrity as well as age. The mechanism may, at least in part, relate to disruption of autophagy.

Funding: Government Support - Non-U.S.

SA-PO336 Consistent Downregulation of Autophagy Gene Atg12 Through MicroRNA-192 in Diabetic Nephropathy Supriya Deshpande, Mitsuo Kato, Mei Wang, Rama Natarajan. City of Hope; City of Hope; City of Hope.

Background: Autophagy (Atg) plays a key role in the pathogenesis of kidney diseases, however its role in Diabetic Nephropathy (DN), and particularly in mesangial cells (MC) is not clear. TGF-b1, a key player in the pathogenesis of DN, regulates expression of various microRNAs (miRs) including miR-192. Also, several miRs regulate expression of various Atg genes. We hypothesized that miR-192 plays an important role in Atg regulation in DN.

Methods: Atg gene expression was analyzed in type-2 diabetic (db/db) and in STZ-injected type-1 diabetic mice. To analyze the role of miR-192 in Atg regulation, STZ-injected mice were treated with control locked-nucleic-acid (LNA) oligonucleotides (oligos) or LNA oligos targeting miR-192 (anti-mir-192-LNA), and Atg gene expression was analyzed in kidneys. Activation of caspase-12 was also analyzed in kidneys of WT and STZ-injected miR-192 knock-out (KO) mice. The effect of TGF-b1 on Atg gene expression and GFP-RFP-LC3 puncta formation was analyzed using mouse MC (MMC).

Results: Expression of several Atg genes was decreased in kidneys of type-1 and type-2 diabetic mice compared to controls. Treatment with LNA-anti-mir-192 reversed the effect of diabetes on some of the Atg genes. Further, Atg gene expression was not affected in kidneys of diabetic mirR-192 KO mice compared to controls. In vitro studies using MMC treated with TGF-b1 also showed a decrease in Atg gene expression compared to control. Transfection of MMC with mir-192 mimic oligos decreased expression of certain Atg genes. In addition, transfection of MMC with a GFP-RFP-LC3 plasmid decreased the average number of GFP-RFP-LC3 puncta/cell following TGF-b treatment, and this effect was reversed in MMC from mirR-192 KO mice. All Atg genes analyzed, except Atg12 expression was consistently decreased in these mouse models, and its decrease was reversed by anti-mir-192 LNA oligos as well as in mirR-192 KO mice.

Conclusions: These results demonstrate that consistent downregulation of Atg12 through mir-192 contributes to an overall decrease in autophagy and subsequent increase in cellular hypertrophy in response to TGF-b1 in MC and in glomeruli of diabetic mice leading to DN.

SA-PO337 mTOR Dependent Regulation of the Podocyte Metabolic Profile Tillmann Bork, Wei Liang, Tobias B. Huber. Renal Div Univ Hospital Freiburg, Freiburg, Baden-Wuerttemberg, Germany.

Background: Podocytes play a critical role in the formation and maintenance of the kidney filtration barrier. Previous studies have highlighted the role of mTOR signaling as regulator of podocyte adaption, differentiation and size-control. However, the eventual link between podocyte size control and the regulation of podocyte metabolism by mTOR remains elusive.

Methods: Mice models of mTOR hyperactivation (Tsc1 -PckO) and mTOR loss of function (Raptor -PckO) were crossed to a Tomato/GFP reporter line to efficiently isolate podocytes for primary cell culture studies. Mitochondrial respiration and ATP synthesis were assessed using Seahorse bioanalyzer with specific inhibitors of glycolysis and oxidative phosphorylation.

Results: Lipids are the main source for ATP synthesis due to oxidative phosphorylation in podocytes. Anerobic glycolysis is the dominating pathway to use glucose. Active mTOR signaling pathway massively enhances basal metabolic activity and the capacity for oxidative phosphorylation compared with anaerobic glycolysis.

Conclusions: Podocyte metabolism relies on 0-oxidation of lipids and anerobic glycolysis. mTOR signaling regulates metabolic activity without affecting the preferences for the used metabolic pathways. Targeting the predominant metabolic pathways of podocytes might help to ameliorate diabetic nephropathy or podocyte ageing.

Funding: Government Support - Non-U.S.

SA-PO338 Derlin-2 Knockout Mice Unravel an Essential Role for Protein Dislocation in Podocytes Guohui Ren, Kwi Hye Koh, Jing Li, Changli Wei, Mehmet M. Altintas, Jochen Reiser. Dept of Medicine, Rush Univ Medical Center, Chicago, IL.

Background: Protein quality control plays a critical role in the information in podocytes and is associated with cellular injury. mTOR-2, a component that regulates cellular dislocation machinery, has been identified as an important element in skeletal and matrix producing cells.

Methods: Western blot and immunofluorescence staining were used for detection of protein expression. Derlin-2 knockout or overexpression in podocytes was achieved with transfection of lentiviruses containing shRNA or CNDA. Podocyte-specific Derlin-2 knockout mice were generated by crossing Derlin-2-flox mice with podocin-Cre mice. Autophagy was detected with the conversion of LC3-1 to LC3-II. Activation of caspase-12 was measured by cleavage of procaspase-12.

Results: Derlin-2 was expressed in both mouse and human podocytes. Derlin-2 deficiency in podocytes could be compensated for by insitol-requiring enzyme 1 (IRE1) induced autophagy at basal conditions. However, in situations where induced ER stress was involved in diabetes, cell damage or in other conditions, the compensatory response of autophagy was overwhelmed. Meanwhile, caspase-12 mediated apoptosis pathway was activated, and severe cellular injury ensued, leading to heavy proteinuria in podocyte-specific Derlin-2 knockout mice, as compared with wild type C57BL/6J control mice. In contrast, Derlin-2 overexpression in vitro attenuated podocyte injury. Derlin-2 expression was induced in cultured podocytes during segmental glomerulosclerosis (FGS) and diabetic nephropathy (DN) as well as in ADR nephropathy in BALB/cJ mice, streptozocin (STZ)-induced diabetic mice and B6.B1B1.D2/D2J mice.

Conclusions: Podocytes like osteoclasts and chondrocytes emerge from mesenchyme and belong to a group of cells that employ Derlin-2 to guarantee protein quality and minimize ER stress for cellular homeostasis. Overexpression of Derlin-2 may be a mechanism to rescue damaged podocytes. Induction of Derlin-2 expression in vivo may have applications for prevention and therapy of glomerular diseases.

SA-PO339 Protein O-GlcNAcylation Is Essential for Normal Podocyte Structure and Function Shinya Ono, Mako Yasuda, Shinnji Kume, Osamu Sekine, Jun Nakazawa, Hisazumi Araki, Masami Kanasaki, Shin-ichi Araki, Daisuke Koya, Masakazu Haneda, Takashi Uzu, Hiroshi Maegawa. Dept of Medicine, University of Chicago, Chicago, IL; Division of Diabetes, Endocrinology, Kanazawa Medical Univ, Kanazawa, Japan; Division of Metabolism and Biohythosystems Science, Asahikawa Medical Univ, Asahikawa, Hokkaido, Japan.

Background: Podocytes play a critical role in the formation and maintenance of the kidney filtration barrier. Previous studies have highlighted the role of O-glycosylation of podocytes for proper protein folding, and belong to a group of cells that employ Derlin-2 to guarantee protein quality and minimize ER stress for cellular homeostasis. Overexpression of Derlin-2 may be a mechanism to rescue damaged podocytes. Induction of Derlin-2 expression in vivo may have applications for prevention and therapy of glomerular diseases.

Methods: O-GlcNAc is a critical enzyme for O-GlcNAcylation in mammals, and resides on the X chromosome. To examine the physiological role of O-GlcNAcylation in podocytes, we analyzed the renal phenotype of male podocyte-specific Ogt-knockout (Podo-OgtKO) mice, which were generated by crossing breeding Ogt-flox mice with podocyte-specific Cre-line transgenic mice.

Results: O-GlcNAc was immunochemically observed in the nuclei of podocytes in wild-type mice, and was completely absent in Podo-OGTKO mice. Podo-OGTKO mice showed normal birth rate and growth up to 32 weeks of age. Proteinuria was first apparent at 8 weeks of age and increased with age up to 32 weeks. Scanning transmission electron microscopy showed disruption of podocyte foot processes in Podo-OGTKO mice after 8 weeks of age. Immunofluorescence showed podocytes to have a punctate distribution in Podo-OGTKO podocytes and to be at a reduced level compared with wild-type mice. Furthermore, the numbers of podocytes in 16-week-old Podo-OGTKO mice were significantly decreased compared with wild-type mice. Finally, severe glomerular sclerosis with tubulointerstitial damage was observed in Podo-OGTKO mice at 32 weeks of age.

Conclusions: O-GlcNAc/Ylation of intracellular proteins by OGT is necessary to maintain podocyte numbers and normal foot process structure. Our results provide new insight into podocyte biology.

SA-PO340 Identification of Novel Gene Products That Regulate Podocyte Function Davide Pietro Cina, 1, 2 Chengjin Li, 1 Jason Moffatt, 1, 2 Susan E. Quaggin. 1, 2 Div of Nephrology, Northwestern University, Chicago, IL; 2 Feinberg Cardiovascular Research Inst, Northwestern University, Chicago, IL; 7Tannenbaum-Lunenfeld Research Inst, Mount Sinai Hospital, Toronto, ON, Canada; 2Donnelly Centre and Banting and Best Dept of Medical Research, Univ of Toronto, Toronto, ON, Canada.

Background: Podocyte function is linked to the organization of its cytoskeleton and adhesion to the glomerular basement membrane. To identify genes that regulate podocyte function, we designed an in vivo genome-wide screen for factors involved in podocyte adhesion to fibronectin, an integrin mediated pathway, or fliT1/Fc, a heparin sensitive pathway, using a pooled 9000 shRNA library.

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Methods: A pool of knockdown podocytes was generated using this library and plated on both coverslips followed by separation of the adherent and floating fractions and deconvolution by illumina sequencing. We developed a stringent method for statistical analysis and ‘hit’ determination and performed a small-scale validation of this method by interrogating top candidate genes individually. We also performed a larger scale validation using a secondary, focused pooled Cas9 mediated knockdown screen.

Results: We identified 121 genes that increased adhesion to fibronectin and 145 genes that increased adhesion to sFLT1/Fc. We also identified 66 genes that decreased adhesion to fibronectin and 106 genes that decreased adhesion to sFLT1/Fc, DP1, DP112, DP115 and DP117. The top five hits in the top ten hits for increased adhesion to both fibronectin and sFLT1/Fc were in the top five dynamin-related GTPases, including Oma1, mitofusin, and Drp1. Drp1 is an evolutionary conserved protein whose loss results in elongated mitochondria. We have previously reported that Rock1-mediated Drp1 activation leads to increased mitochondrial fragmentation and podocyte apoptosis. We hypothesized that attenuation of Drp1 expression and activity in podocytes may ameliorate features of DN.

Methods: To investigate the role of Drp1 in podocytes, we deployed a genetic and pharmacological approach using a model of Type 2 diabetes (LepRdb). First, we crossed conditional Drp1 (Dbm/Dp1f/v) mice with a Podocyte-specific tamoxifen, inducible Cre recombinase (Dbm/Dp1f/v, Dbm/Dp1f/v, Pod-Drap1f/v). Second, we employed the Drp1 GTase activity inhibitor, Mdivi-1, to pharmacologically assess the therapeutic potential of targeting Drp1 in diabetic mice.

Results: Both Drp1-specific, Drp1−/− and pharmacological inhibition of Drp1 by Mdivi-1 in diabetic mice exhibited significantly attenuated albuminuria, mesangial matrix expansion, increased podocyte numbers, reduced podocyte foot process effacement and attenuated glomerular basement membrane thickening. Ultrastructure analysis revealed significantly elongated mitochondria in Drp1−/− diabetic mice compared to non-induced diabetic mice. Drp1−/− diabetic mice displayed increased cell proliferation, as evidenced by BrdU pulse studies. Analysis of the phosphorylation of proteins was carried out by western blot analysis and deconvolution by illumina sequencing. We developed a stringent method for statistical analysis and ‘hit’ determination and performed a small-scale validation of this method by interrogating top candidate genes individually. We also performed a larger scale validation using a secondary, focused pooled Cas9 mediated knockdown screen.

Conclusions: Our Data Suggest that Drp1 as a key regulator of mitochondrial dynamics in podocytes, and point to Drp1 as a potential therapeutic target in DN.

Funding: NIDDK Support

SA-PO343

Cytosolic Phospholipase A2 Alpha Regulates G1 Progression Through Modulating Forhead Box Protein 01 Activity. Sayd Movahedi nasi1, Gabriel Choukroun,2 Dirk M. Hentschel, Joseph V. Bonventre.1,2 Brigham and Women Hospital, Renal Division, Boston, MA;1 Amiens Southern Hospital, Renal Division, Amiens, Picardie, France.

Background: Mesangial cell (MC) proliferation is characteristic of a number of chronic progressive glomerular diseases. cPLA2α is expressed in MCs and plays a role in cellular proliferation, however the mechanisms involved remain unclear. Here, we show for the first time a novel regulatory role for cPLA2α in the regulation of G1 phase of the cell cycle that is conserved in zebrafish and mammals.

Methods: Mouse embryonic fibroblasts (MEFs) and MCs were derived from cplaα−/− mice. cPLA2α was knocked down in zebrafish using morpholinos (MOs). Cell cycle progression was assessed by flow cytometry in zebrafish larvae and in G0, synchronized cells after stimulation with PDGF. S phase population was assessed in zebrafish and MEFs by BrdU pulse studies. Analysis of the phosphorylation of proteins was carried out by western blot assays using phosphospecific antibodies.

Results: We identified two zebrafish cplaα genes, termed zcplaαa and zcplaαb, with conserved phospholipase activity. In zebrafish and MEFs cPLA2α promotes G1 progression via its phospholipase activity and through PGE, production. PGE, through the PI3′-K/AKT pathway, regulates FOXO1 phosphorylation and FOXO1 nuclear export. This, in turn, inactivates FOXO1 resulting in upregulation of cyclin D1 and downregulation of p27Kip1, thus promoting G1 progression. These data indicate an evolutionary conserved mechanism between lower vertebrates and mammals. Further, using pharmacological inhibitors, we show that cPLA2α, RAFT/M203 in development (using the podocin cre driver) pharmacologically cooperatively regulate G1 progression in response to mitogenic stimulation.

Conclusions: cPLA2α is a critical effector of the G1 phase of the cell cycle through its phospholipase activity. Pharmacological targeting of this enzyme may have important therapeutic benefits in disease mechanisms that involve excessive cell proliferation including progressive acute and chronic glomerulonephritis.

Funding: NIDDK Support

SA-PO344

Podocyte Specific Glycogen Synthase Kinase 3 Is Critical for Neonatal Survival and for Renal Function in Maturity. Jenny Hurcombe1, Abigail Charlotte Lay2, Gavin Iain Welsh3, Peter D Matheson, Satish Patel, Susan E Quaggin, James R. Woodgett, Richard Coward,1 Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom;2 Samuel Lunenfeld Research Inst, Univ of Toronto, Toronto, ON, Canada;3 Feinberg School of Medicine, North Western Univ, Chicago, IL.

Background: GSK3 is a multi-functional serine/threonine kinase existing as two distinct isoforms, GSK3α and GSK3β. Knockout mouse models suggest that the GSK3 isoforms have different and cell type specific functions. This study aims to examine the importance of GSK3 in the podocyte.

Methods: We have used Cre/LoxP technology to generate mice with podocyte-specific ablation of GSK3α and/or GSK3β. Knockout mouse models suggest that the GSK3 isoforms have different and cell type specific functions. This study aims to examine the importance of GSK3 in the podocyte.

Conclusions: Mice developmentally lacking either GSK3α or GSK3β specifically in the podocyte are viable with normal life span (up to 2 years) and normal renal histology. In contrast, mice null for both GSK3α isoforms, born at normal Mendelian frequency, die at 10-16 days with massive albuminuria and acidosis. These mice have vacuolated glomeruli and glomerulosclerosis. Knockout of GSK3α and β after full glomerular development, at 4 weeks of age, also results in significant renal disease which develops within 2 weeks of knockdown. It consists of significant albuminuria with renal failure in some mice. Furthermore, there is evidence of a crescentic proliferative glomerulopathy, together with massive fibrosis and glomerulosclerosis. Mechanistically the wnt signalling pathway is up-regulated and β-catenin activated throughout the kidney. Contemporaneous knockdown of β-catenin in the developmental model dramatically improves albuminuria and renal histology but not acidosis or survival indicating the involvement of other pathways. These are currently being investigated through a glomerular transcriptomic approach.

Conclusions: Podocyte specific GSK3 is critical for glomerular and renal function in development and full maturity. Loss of single isoforms can be compensated throughout life but loss of both is catastrophic.

Funding: Government Support - Non-U.S.
Podocyte Oxidative Stress Coupled with Ubiquitin C-Terminal Hydrolase Deletion Exacerbates Renal Damage

**Background:** Ubiquitin C-terminal hydrolase L1 (UCHL1) may promote antioxidation by degrading oxidized proteins and by the enzymatic activity of UCHL1. Podocytes show increased oxidative stress and downregulated UCHL1 expression in FSGS. Expression of podocyte UCHL1 may be a disease modifier in FSGS, and the role of UCHL1 in FSGS remains to be determined.

**Methods:** UCHL1 was detected by immunoblot analysis of FSGS biopsies. Renal UCHL1 levels were assessed in podocyte cultures stimulated with siRNAs to UCHL1 or by treatment with NOX5 interference. Podocytes from UCHL1 knockout mice were compared with wild-type podocytes. Podocyte injury was evaluated using cell retraction, cell density, and cell hypertrophy.

**Results:** UCHL1 levels were significantly lower in FSGS biopsies compared to normal kidneys. Podocyte UCHL1 expression was reduced by NOX5 interference. Podocytes from UCHL1 knockout mice showed increased retraction, cell density, and cell hypertrophy compared to wild-type podocytes.

**Conclusions:** These findings suggest that UCHL1 protects podocytes from oxidative stress and that UCHL1 expression is a potential therapeutic target for FSGS.

Insulin Receptor Isoform A Is Implicated in Podocyte Injury in Diabetic Kidney Disease

**Background:** Podocytes are the key players in maintaining glomerular integrity and function. Perturbations in podocyte injury and proliferation have been linked to diabetic kidney disease (DKD). The insulin receptor (IR) is a key player in insulin signaling, and its isoforms are expressed in podocytes. The role of IR isoforms in podocyte injury in DKD remains unclear.

**Methods:** Podocyte injury was assessed in a mouse model of DKD using a surgical protocol that results in diabetes, insulin resistance, and podocyte injury. Podocytes from wild-type and insulin receptor isoform A (IRA) knockout mice were cultured and subjected to hyperglycemic conditions. Podocyte injury was assessed using cell retraction, cell density, and cell hypertrophy.

**Results:** Podocytes from IRA knockout mice showed increased cell retraction, cell density, and cell hypertrophy compared to wild-type podocytes. Podocytes from IRA overexpression mice showed decreased cell retraction, cell density, and cell hypertrophy compared to wild-type podocytes.

**Conclusions:** These findings suggest that IRA expression plays a crucial role in podocyte injury in DKD, and targeting IRA may represent a potential therapeutic strategy for the prevention of podocyte injury in DKD.

SMPDL3b overexpression augments IRA/Cav1 interaction and suppresses IRB/Cav1 interaction.

**Background:** SMPDL3b is a sphingomyelinase that regulates lipid rafts and contributes to podocyte injury. IRA and IRB are two isoforms of the insulin receptor that play different roles in podocyte function. The interaction between IRA and IRB with Cav1, a key component of lipid rafts, has been shown to be crucial for podocyte function.

**Methods:** Podocytes were treated with SMPDL3b overexpression or control vectors, and the interaction between IRA/Cav1 and IRB/Cav1 was assessed using co-immunoprecipitation (co-IP). The effects of SMPDL3b overexpression on podocyte function were assessed using cell retraction, cell density, and cell hypertrophy.

**Results:** SMPDL3b overexpression augmented IRA/Cav1 interaction and suppressed IRB/Cav1 interaction. Podocytes with SMPDL3b overexpression showed decreased cell retraction, cell density, and cell hypertrophy compared to control cells.

**Conclusions:** These findings suggest that SMPDL3b overexpression augments IRA/Cav1 interaction and suppresses IRB/Cav1 interaction, potentially contributing to podocyte injury in diabetes.

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

Underline represents presenting author.
ORO staining and prevented the development of mesangial expansion in KO+CD group compared to KO+Vehicle. A significant reduction in ACR was observed after 3 weeks of CD treatment in KO+CD compared to KO+Vehicle mice (p < 0.001), as shown by a trend in reduced serum creatinine. CD treatment did not affect ACR, renal function or mesangial expansion in WT mice.

Conclusions: Based on these results, we conclude that CD improves renal function in a mouse model for AS and could be a new therapeutic strategy for the treatment of AS patients.

Funding: NIDDK Support, Pharmaceutical Company Support - Hoffman La Roche

SA-PO350

The Glomerular Matrisome in Alport Syndrome Is Altered prior to the Onset of Albuminuria

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Background: Alport Syndrome is caused by genetic defects in COL4A3, COL4A4 or COL4A5, but despite this knowledge there are currently no targeted therapies. We aimed to build our basic understanding about the glomerular extracellular matrix (ECM) in Alport syndrome and performed global analysis of composition and ultrastructural imaging in the Col4a3/-/- mouse.

Methods: Cellular and extracellular matrix (ECM) fractions from wild type and Col4a3/-/- mice of at least 6 and 16 weeks of age were analysed by mass spectrometry (MS) and imaged using serial block face-scanning electron microscopy (SBF-SEM).

Results: MS analysis revealed moderate changes in the composition of glomerular ECM at 6 weeks, even prior to the onset of barrier dysfunction. These included complete absence of type IV collagen α1-3, α4-6, and upregulation of type VI collagen α1, α2, and type V1 collagen. At 16 weeks more dramatic changes were detected including elevated type IV collagen α1, α2, fibronectin, type I collagen, laminin α2 and fibronectin. Global and pathway analysis of cellular fractions indicated changes in actin regulating proteins at 6 weeks and mitochondrial dysfunction at 16 weeks. SBFSEM demonstrated thickened and irregular glomerular basement membranes with evidence of podocyte protrusions into this ECM.

Conclusions: Our data demonstrate that Alport syndrome progresses with distinct early changes in ECM followed by more profound ECM accumulation, disruption and thickened and irregular glomerular basement membranes with evidence of podocyte dysfunction prior to the onset of albuminuria.

Funding: Private Foundation Support

SA-PO351

Creation and Analysis of Mouse Models of Human Nephrotic Syndrome Caused by the Laminin b2 (LAMB2) S80R Mutation

Steven Daniel Funk, Jeffrey H. Miner. Renal Div, Washington Univ School of Medicine, St. Louis, MO.

Background: Most cases of congenital nephrotic syndrome in the first year of life are due to mutations in 4 genes expressed in podocytes: NPHS1, NPHS2, WT1, and Lamb2. LAMB2 encodes laminin b2, a glomerular basement membrane component critical for glomerular filtration. We previously created transgenic mice using the urinary promoter to study missense mutations discovered in patients with congenital nephrotic syndrome, including R246Q and C321R, which inhibit laminin β2 secretion and/or induce podocyte ER stress. Here we aimed to characterize a new mutation (S80R) in Lamb2 mice (BMC Nephrology 2014, 15:54). Here, we explored whether CLIC4 regulates ERM protein activation, similar to CLIC5A.

Methods: Confocal immunofluorescence (cIF) microscopy was used to visualize CLIC4 expression in mouse kidney sections. Western blot analysis (WB) was used to study total and cytoskeletal fractions from isolated mouse glomeruli and cultured human glomerular endothelial cells (EC).

Results: By cIF CLIC4 colocalized exclusively with moesin in mouse glomerular endothelial cells (EC). WB showed that CLIC4 is absent from LAMB2-/- mice, and that the ratio of pERM : tubulin is lower in CLIC4+/- compared to LAMB2-/- (1.28 ± 0.11 vs. 2.26 ± 0.30, respectively, p < 0.01, mean ± SD, n=3). Total ERM protein was also reduced, and much less ERM protein was observed in the cytoskeletal fraction of CLIC4+, compared to LAMB2-/-. In cultured human glomerular EC, CLIC4 siRNA reduced LAMB2-/- protein by >90% and resulted in ERM dephosphorylation and dissociation from the cytoskeleton, all rescued by over-expression of CLIC4. CLIC4-induced ERM phosphorylation was abolished by PLC activation with m-3M3FBS, indicating that PI4,5P2 dependence.

Conclusions: Hence, CLIC4 co-localizes with moesin in glomerular EC in vivo. Like CLIC5A, CLIC4 promotes ERM phosphorylation in a PI4,5P2-dependent fashion. We speculate that defective ERM phosphorylation may be responsible, in part, for the morphological and physiological abnormalities in LAMB2-/- mice.

Funding: NIDDK Support

SA-PO352

Differential Roles of Cell Surface Proteoglycans in Podocyte-Glomerular Basement Membrane Adhesion

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Background: Cell surface proteoglycans (PG), via their heparan sulfate (HS) chains, work in a cooperative fashion alongside integrins to mediate podocyte (PG)-glomerular basement membrane (GBM) interactions. Results of our previous studies have shown that complete loss of HS at the POD cell surface leads to reduced cell attachment to the GBM. However, the mechanism by which HS contributes to these interactions is unknown. The purpose of this study was to determine the effects of selective depletion of the cell surface PG, syndecan-1 (Sdc1) or syndecan-4 (Sdc4) on POD in vivo.

Methods: Frozen tissue sections of POD-knockout (KO) mice were immunostained with antibodies against the core proteins of Sdc1 and Sdc4, HS (antibody HS4C3), syndapinin (SYN), nephrin, and α-actinin-4. To determine the potential for loss of anionic charge associated with HS, 500 nm sections of unfixed kidneys from POD-KO mice were treated with polyethyleneimine (PEI) followed by fixation and processing for transmission electron microscopy.

Results: TEM studies showed that the GBMs of both Sdc1 and 4 KO mice had GBP irregularities. The POD in Sdc4 KO mice showed moderate foot process effacement. Immunostaining for HS did not show differences in staining intensity for HS between Sdc1 and Sdc4 KO mice. However, PEI labeling showed that the GBMs in Sdc4 KO mice had larger aggregates of PEI than those found in the GBM of Sdc1 KO mice. Immunostaining showed that a compensatory increase in Sdc4 expression in Sdc4 KO glomeruli or Sdc1 expression in Sdc4 KO glomeruli did not occur. The glomeruli of Sdc1 KO mice showed disruption of nephrin organization compared to Sdc4 and WT mice. Immunostaining for α-actinin-4 in both Sdc1 KO and Sdc4 KO glomeruli was also disrupted compared to control.

Conclusions: The data show that disruption of either Sdc1 or Sdc4 interactions with the GBM significantly affect the manner by which POD interact with the GBM. Although loss of Sdc4 was associated with the development of foot process effacement, the loss of either Sdc1 or Sdc4 has effects on POD cytoskeletal organization.

Funding: NIDDK Support

SA-PO353

ERG Protein Activation by CLIC4 in Glomerular Endothelial Cells

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Background: We reported (J. Cell Sci. 2014, 127:1564) that the podocyte-predominant CLIC5A stimulates PI4,5P2 production and consequent ER (rins, radixin, moesin) protein phosphorylation (pERM). CLIC4, a homolog of CLIC5A, is expressed at high levels in glomerular and peritubular capillary endothelial cells (EC), and in proximal tubule brush border and basolateral membranes. CLIC4 deficient mice (CLIC4−/-) have fewer glomeruli and a lower peritubular capillary density than wild-type mice (BMC Nephrology 2014, 15:54). Here, we explored whether CLIC4 regulates ERM protein activation, similar to CLIC5A.

Methods: Confocal immunofluorescence (cIF) microscopy was used to visualize CLIC4 expression in mouse kidney sections. Western blot analysis (WB) was used to study total and cytoskeletal fractions from isolated mouse glomeruli and cultured human glomerular endothelial cells (EC). In cultured human glomerular EC, CLIC4 was silenced with CLIC4-specific siRNA ± CLIC4 cDNA rescue.

Results: By cIF CLIC4 co-localized exclusively with moesin in mouse glomerular endothelial cells (EC). WB showed that CLIC4 is absent from LAMB2−/- mice, and that the ratio of pERM : tubulin is lower in CLIC4−/- compared to LAMB2−/- (1.28 ± 0.11 vs. 2.26 ± 0.30, respectively, p < 0.01, mean ± SD, n=3). Total ERM protein was also reduced, and much less ERM protein was observed in the cytoskeletal fraction of CLIC4−/- compared to LAMB2−/-. In cultured human glomerular EC, CLIC4 siRNA reduced LAMB2−/− protein by >90% and resulted in ERM dephosphorylation and dissociation from the cytoskeleton, all rescued by over-expression of CLIC4. CLIC4-induced ERM phosphorylation was abolished by PLC activation with m-3M3FBS, indicating that PI4,5P2 dependence.

Conclusions: Hence, CLIC4 co-localizes with moesin in glomerular EC in vivo. Like CLIC5A, CLIC4 promotes ERM phosphorylation in a PI4,5P2-dependent fashion. We speculate that defective ERM phosphorylation may be responsible, in part, for the morphological and physiological abnormalities in CLIC4−/− mice.

SA-PO354

Vascular Glycoalyx Syndeac (SDC) 4 Loss Coincides with Albuminuria in Diabetic Nephropathy

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Background: The endothelial glycoalyx is a critical determinant of vascular health and a key regulator of vascular permeability. Increasing evidence points to disruption of the endothelial glycoalyx as a contributor to development of albuminuria (albumin in the urine) and eventually DN. TNFα which is important in the development of microvascular disease in diabetes caused a disruption of the glomerular endothelial cells (GEC)}
glycosylated through shedding of SDC4 and heparan sulphate (HS). We seek to investigate the role of vascular endothelial glycosylation in DN and determine the mechanisms involved in its disruption in DN.

**Methods:** DN was induced in DBA2 mice by giving daily intraperitoneal injection of streptozotocin (STZ) at 50mg/kg for 5 days. The mice became hyperglycemic at 2 weeks and significantly albuminuria in glomeruli in DN, suggesting that MMP2 could mediate SDC4 shedding. My in vitro data in human EHS showed that gelatinase MMP9 was upregulated and resulted in the shedding of SDC4 and HS. This resulted in an increase in BSA permeability across the monolayer.

**Conclusions:** MMP2,9-mediated shedding of SDC4 is likely to contribute to vascular endothelial glycosylation disruption and albuminuria observed in DN. Potential therapies targeted at glycosylation protection will be of benefit not only in DN but also in ameliorating systemic vascular disease in diabetes.

**Funding:** Private Foundation Support

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**SA-PO355**

**Blood Cell Velocities in Glomerular Capillaries Measured by 2-Photon In Vivo Microscopy Reveal Heterogeneous Blood-Flow**

Deimarin Pedoto,1,2 Eugenio Gutierrez,1 Luca Bordoni,1 Sara Damiano,1 Francesco Trepiccio,1 Giovanni Rota Capurro,1,2 Sebastian Frische.1,3

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**Background:** Theoretical models have shown that the blood-flow within a glomerulus may be heterogeneous and that flow heterogeneity may affect the ultrafiltration coefficient and thus GFR. The aim of this study is to provide experimental data to test these model predictions by measuring glomerular capillary flow velocities by in vivo 2-photon microscopy.

**Methods:** Male Munich-Wistar rats were intubated, anesthetized with isoflurane, and mechanically ventilated. Blood pressure and heart-rate were monitored. The left kidney was externalized and the rat placed in the 2-photon microscope. Blood plasma was labeled by incubation with 6-carboxyfluorescein succinimidyl ester (CFSE) for 1 hour. The blood flow in superficial glomeruli was scanned at a frequency of >700 Hz. The axial movement of single blood cells was measured. 308 different capillaries were analyzed in 17 glomeruli from 5 different rats.

**Results:** Blood cell velocity was 2.99 μm/ms ±0.54. A Gaussian distribution and a Gamma-distribution were fitted to data from 13 glomeruli in which >12 capillaries were studied. C-tests (α=0.05) showed 5 of 13 datasets not to follow a Gaussian distribution and 1 of 13 not to follow a Gamma-distribution. The data from all 308 capillaries normalized to the mean of the respective glomerulus did not follow a Gaussian distribution (P<0.05). The Gamma-distribution allows an asymmetrical distribution around the mean and provided the best description.

**Conclusions:** This study provides experimental evidence of heterogeneity and an asymmetrical distribution of blood cell velocity in glomerular capillaries. This new experimental evidence calls for refinement of current models of glomerular blood flow heterogeneity and invokes the possibility to investigate the potential regulatory control of the ultrafiltration coefficient by regulation of capillary flow heterogeneity, e.g. by the action of mesangial cells.

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

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**SA-PO356**

**Assessment of Exosomes Derived from Mesangial Cells Stimulated with High Glucose**

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**Background:** Exosomes and microvesicles (MV) are extracellular vesicles (EV) that communicate through the exosomes may have pathophysiological implications in the diabetic kidney.

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

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**SA-PO357**

**Axl Receptor Tyrosine Kinase Is Involved in Proliferation of Human Mesangial Cells Activated by PDGF**

Qi Bian,1,2 Joshua Charles Anderson,1 Xiaoan Chen,2,3 Xiubing Fan,1,2 Shanrong Zhao,1 Xiaowen Zhang,1 Zhi Qiang Huang,1 Kerstin Ebeforo,4 Jenny C. Nyström,5 Stacy D. Hall,1 Bruce A. Julian,1 Christopher D. Willey,1 Jan Novak.1

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**Background:** Proliferation of mesangial cells (MC) is an important feature in many glomerular diseases, including IgA nephropathy (IgAN). Platelet-derived growth factor (PDGF) is a potent stimulator of MC, activating multiple signaling pathways associated with proliferation of MC. Our global kinomic profiling revealed that activity of multiple kinases in MC increased after PDGF stimulation, including tyrosine kinase Axl. As there is limited information on the association of PDGF signaling and activation of Axl in human MC, we studied details of Axl involvement in human MC stimulated by PDGF.

**Methods:** MC were obtained from a commercial source or isolated from biopsy specimens of patients with IgAN or other glomerular diseases. Quiescent primary human MC were stimulated by PDGF AB in the presence or absence of different inhibitors. MC lysates were analyzed by global tyrosine-kinome profiling using PamsStation®12 platform and Western blotting. MC proliferation was measured by BrdU incorporation. The expression and distribution of Axl in MC were assessed by immunofluorescence.

**Results:** Tyrosine-kinome profiling indicated that PDGF AB increased Tyr30, Abl, and Lck kinase activities. Further data analyses predicted Axl as one of the key upstream kinases activated in PDGF-AB-stimulated MC. We found that Axl was expressed in all tested primary human MC. PDGF AB stimulated proliferation of MC; this effect was inhibited by Axl-specific inhibitor R428. Signaling studies revealed that PDGF AB increased phosphorylation of multiple signaling proteins, including Axl, PDGFR-β, AKT1, and ERK1/2. R428 significantly inhibited phosphorylation of Axl and Axl1, and, to a lesser extent, also of ERK1/2 and PDGFR-β. MEK1/2 inhibitor U0126 and PI3K inhibitor LY294002 did not affect phosphorylation of Axl.

**Conclusions:** Axl is involved in PDGF-induced proliferation of cultured MC through multiple signaling pathways. Targeting Axl may provide a new therapeutic strategy for IgAN.

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

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**SA-PO358**

**Different Effects and Mechanisms of Prostaglandin E2 Receptor Subtypes EP2/EP4 in TGF-β1 Induced Mesangial Cell Injury**

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**Background:** To study effects of prostaglandin E2 receptor subtypes 2 and 4 (EP2 and EP4) in mesangial cell injury by transforming growth factor-β1 (TGF-β1) and relevant signal pathways.

**Methods:** 1. The primary cultures of EP2 gene knockout (EP2-/-), EP4 gene knockout (EP4flox/flox) and wild type (WT) mice mesangial cells were established; 2. grouping: A: Q WT; WT + TGF-β1; B: EP2-/-; EP2-/- + TGF-β1; C: EP4flox/flox + AD-CRE (EP4KO); D: EP4flox/flox + AD-CRE (EP4KO) + TGF-β1; Group F: EP2-/-; EP2-/-+ TGF-β1; EP4flox/flox + AD-CRE (EP4KO) + TGF-β1 as control; 3. the level of PGE2 ,cAMP ,the PKA activity of mesangial cell was tested ; PKA (H89) and ERK (PD98059) inhibitors were used to interdict PKA activity and ERK pathway in WT mesangial cell; EP2 or EP4 receptor agonist was used to pretest WT MCs.

**Results:** 1. After TGF-β1 stimulation, expression of FN and CTGF increased; the expression of FN and CTGF in Group EP2KO increased; the expression of FN and CTGF in EP4KO decreased; 3. after TGF-β1 stimulation, the Smad3 phosphorylation level in EP2KO increased; while the Smad3 phosphorylation level markedly decreased in EP4KO; 4. the PGE2 level of WT mesangial cell increased at 12h after TGF-β1 treatment; 5. the AMP content in EP2KO was less than that of the control; PAKa activity obviously declined; the cAMP content has no obvious changes in EP4KO; after stimulation with TGF-β1, the PAKa activity increased; 6. ERK inhibitor blocks the function caused by agonist EP4; while PAKa inhibitor block the inhibition function of agonist EP4.**

**Conclusions:** EP2 and EP4 have different regulating effects on injury and renal fibrosis of mesangial cells: EP2 receptor mediated PGE2 induced up-regulation of the level of cAMP and PAKa activity, as to inhibit interaction effects of TGF-β1/Smad3 pathway and reduced the occurrence of injury and fibrosis of mesangial cell; while EP4 may mediate the promotional effect of mesangial cell injury induced by TGF-β1 by activating phosphorylation ERK pathway, resulting in regulating effects different from that of EP2.

**Funding:** Government Support - Non-U.S.
Mesenchymal Stem Cells in the Repair of the Damaged Mesangium: A Step by Step Ultrastructural Account of the Events Taking Place

**Background:** Not much is known about repairing the damaged mesangium. The use of mesenchymal stem cells (MSCs) to repair the injured mesangium is a rather novel concept. The present study aimed at analyzing the entire process using transmission electron microscopy in an effort to better understand the various steps involved.

**Methods:** Mesangial cells (MCs) cultured single layer in dish (2D) and on Matrigel (3D), MCs were first cultured to confluent and quiescent for 48 hours. Then they were incubated with glomerulopathic light chains (GLCs) (10 ug/ml) purified from the urine of patients with FSGS. After incubation with renal biopsy-proven light chain-related amyloidosis (AL-Am) (n=3) and light chain deposition disease (LCDD) (n=3) for 4 days and subsequently labeled MSCs were added. Samples were collected 10 days after the introduction of the MSCs (day 14) and processed for light and transmission electron microscopy.

Results: MSCs revealed evidence of direct damage by the GLCs including apoptosis with apoptotic bodies released. MSCs identified and migrate to areas where cellular damage was present. When MSCs became activated they acquired a "macrophage" phenotype. They then became active in phagocytosing cell debris, apoptotic bodies damaged extracellular matrix and non-extracellular matrix material. Their process of cleaning the damaged mesangium resulted in MSCs full of cellular debris and eventually disposing of the internalized material. After performing this function, they proceeded to differentiate into mature MCs.

**Conclusions:** MSCs actively clean the injured mesangium by phagocytosing apoptotic cells and other material. They do so by transforming into a macrophage phenotype. Once the cleaning process is completed, they differentiate into MCs acquiring their characteristic smooth muscle morphology and functional properties. The entire sequence of events was documented by transmission electron microscopy providing an added dimension to the understanding of MSCs in repair of the damaged mesangium.

**Funding:** Private Foundation Support

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**SA-PO360**

Characterization of Circulating APOL1 Complexes and Their Kidney Distribution in African Americans

**Background:** The apolipoprotein L1 gene (APOL1) G1 and G2 renal-risk variants associate with non-diabetic nephropathy and cardiovascular disease in African Americans (AAs). Although substantial APOL1 protein is present in the circulation, with enrichment in podocytes compared to other renal cells, little is known about circulating APOL1 protein.

**Methods:** Total serum APOL1 levels were examined by Western blot in a cohort of healthy AAs who had a 1st degree relative with kidney disease. APOL1 protein complexes were isolated from fast protein liquid chromatography (FPLC) peak fractions and characterized by proteomic analyses. Results were subsequently verified by co-immunoprecipitation and Western blot.

**Results:** No significant differences were detected in serum APOL1 protein concentration based on APOL1 genotypes. However, serum APOL1 protein binds to other protein complexes. Non-denaturing gel electrophoresis and FPLC demonstrated that serum APOL1 protein existed in two non-overlapping peaks (12.2nm and 20.0nm in diameter, respectively). The smaller complex was labeled complex A and the larger complex B. Density gradient ultracentrifugation and agarose gel electrophoresis confirmed that neither APOL1 protein complex was associated with HDL or LDL cholesterol. The exposure of APOL1 complex A surface epitopes appeared to be altered by G1/G2 renal-risk variants based on avidity to a specific monoclonal antibody from a non-G1/G2 associated immunogen (p=0.01). APOL1, haplotype-related protein (HPR), and complement C3 were present in APOL1 complex A. APOL1, HPR, IgM, and fibronectin were present in APOL1 complex B. In APOL1 complex A, HPR-α was more abundant in those with G1 and G2 renal-risk variants, relative to G0 (GENMOD p=0.04, total N=12). Serum HPR-α was only present in APOL1 complexes. Small amounts of HPR protein were detected in renal tubule cells but not glomeruli, whereas HPR mRNA was absent in the kidney.

**Conclusions:** Results provide unique insights on the composition of circulating APOL1 complexes. The role of circulating APOL1 in kidney and cardiovascular disease in AAs requires further investigation.

**Funding:** NIDDK Support

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**SA-PO361**

Deep Mapping of the Native Mouse Podocyte Proteome

**Background:** The identity of proteins expressed within a podocyte is still not known.

**Methods:** We performed mass spectrometry based absolute and relative quantification of the proteome of FACS-sorted native mouse podocytes.

**Results:** We resolved the podocyte proteome at a near-comprehensive resolution (more than 8000 identified proteins). Absolute copy numbers of proteins correlated with copy numbers obtained from deep-sequencing transcriptomic analysis. The dataset indicates agreement between transcriptome and proteome regarding expression of proteins which are mutated in hereditary forms of proteinuria and FSGS in humans. 541 proteins were enriched within podocytes at very high ratios and significance. This study suggests that the podocyte is not only target to inflammatory stimuli such as TNFalpha and IFNgamma, but also unanticipated other stimuli. In addition, this study delineates podocyte enriched tyrosine kinases, a few of these are drugable. Protein domains significantly enriched in podocyte proteins comprise not only PDZ and Fn3 domains, but also i-set domain, an adhesion domain. The majority of podocyte specific proteins also contain positive findings for homology in human samples, with a weak correlation between staining intensity and absolute protein abundance measured by MS/MS.

**Conclusions:** This initial, near comprehensive draft of the podocyte proteome reveals untapped molecules and mechanisms. This dataset will be of benefit to understand podocyte physiology, pathobiology and develop potential therapeutic strategies.

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**SA-PO362**

Maternal Obesity Is a Significant Risk Factor for the Development of Diabetic Nephropathy

**Background:** We have studied whether a second-hit such as diabetes may further exacerbate diabetic nephropathy in offspring exposed to maternal obesity.

**Methods:** Female C57Bl6 mice were fed either normal or high-fat diet (HFD) for 6 weeks prior to pregnancy, during pregnancy and weaning and their offspring were weaned to chow diet or HFD. At Week 8, the male offspring were randomized to streptozotocin (STZ) 55mg/kg/day for five consecutive days, 100 mg/kg once only or placebo. Weight and glucose levels were tested fortnightly. 24 h urine collection was performed at Week 20 and 30. The kidneys were harvested at Week 32. The renal structure was observed.

**Results:** Development levels of podocyte, inflammatory and oxidative stress markers were measured by real time PCR and confirmed with protein quantification with Western blot and/or immunohistochemistry.

**Conclusions:** Offspring exposure to maternal obesity accelerates the severity of damage to the kidney caused by diabetes. Fetal programming of renal inflammation and oxidative stress may be a key component to the accelerated risk. Offspring diet has a powerful effect on renal outcome.

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

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**SA-PO363**

Leucine-Rich Glycoprotein 1: A Candidate Biomarker for Early Renal Function Decline in Type 2 Diabetes

**Background:** Identification of patients with type 2 diabetes and early renal function decline may improve our ability to intervene and slow progression to end-stage renal disease. In a Phase I preclinical exploratory study, we tested whether leucine rich glycoprotein-1 (LRG1), a candidate biomarker discovered in db/db mice, would identify patients with early decline in renal function.

**Methods:** Patients with type 2 diabetes were recruited into training (n=56) and independent, non-overlapping test (n=37) groups (median baseline eGFR = 80.3 ± 29.5 ml/min/1.73m²). LRG1 was measured in spot urine collections by ELISA, and performance was assessed as area under the receiver operating characteristic curve (AUC) with adjustment for clinical covariates of DKD.

**Results:** Urine LRG1 was associated inversely with eGFR (r = -0.546, P<0.001) and positively with ACR (r = 0.283, P = 0.034). The AUC of LRG1 for identifying participants with baseline eGFR < 60 was 0.815 ± 0.103; in contrast, the AUC of the albumin/creatinine ratio was 0.465 ± 0.093 (P < 0.01 versus LRG1). Adjustment for age, sex, race, duration of diabetes, and HbA1c, did not alter the AUC for LRG1, and these results were replicated in the test group. In participants with eGFR >= 60 ml/min/1.73m² at baseline, LRG1 predicted a 5-year outcome of eGFR < 60 or ESRD better than ACR (0.702 ± 0.085, P = 0.01 versus ACR, 0.520 ± 0.119).

**Conclusions:** Taken together, these results suggest LRG1 may identify patients with early renal function decline more accurately than ACR. Evaluation of LRG1 in prospective cohort studies of type 2 diabetes may lead to a better biomarker for identifying and monitoring DKD.

**Funding:** Other NHI Support - NIH RO1 DK 096549
A Longitudinal Study on Kidney Function, Pathology, and Multiple Urinary Biomarkers in ZSF1 Rat Model of Type II Diabetic Nephropathy  
Renal Discovery, Abbiev, North Chicago, IL.

**Background:** Obese ZSF1 rats display many clinical features of human type II diabetic nephropathy (DN). To further understand this model and to identify relevant biomarkers of disease progression, we followed the development of DN by measuring glomerular filtration rate (mGFR), histopathology, and a variety of urine and tissue biomarkers over 24 weeks after uninephrectomy (Unx). Correlations between mGFR and individual urinary biomarkers were assessed.

**Methods:** Male rats (9-week old) underwent either a sham or Unx (right kidney) surgery and were fed a high carbohydrate diet. GFR was measured by transradial clearance of FITC-sinistrin. Urine samples were collected once every 2-4 weeks for biomarker analysis, and renal tissue was examined for collagen deposition as well as for the levels of key inflammatory and fibrotic genes.

**Results:** Kidney hypertrophy was observed (2.0-3.0 fold increase in mGFR) in obese rats 2-week after surgery lasting until week 4. The mGFR subsequently declined over time in these rats and was 2-fold lower than control rats by end of study. Compared to lean rats, obese rats also demonstrated time-dependent increases in urinary excretion of protein, KIM-1, L-FABP, NGAL, Cystatin C, Cluseterin, Betaz-2-microglobulin, alpha-1-acid glycoprotein, VEGF, MCP-1, TIMP-1, Collagen IV, TGF-b, and TGF-b2. A significant correlation was found between mGFR and a number of urinary biomarkers (L-FABP, KIM-1, TIMP-1, Cystatin C, and TGF-b2). Kidney fibrosis was significantly elevated by week 12 post surgery and continued to expand in the following weeks. Unx increased the weight and glomerulosclerosis of the remaining kidney and accelerated the decline of mGFR in obese rats during late weeks of observation.

**Conclusions:** ZSF1 rats showed a progressive increase of fibrosis and loss of mGFR over the 24-week study. A number of urinary biomarkers demonstrated a strong inverse correlation with the time-dependent changes in mGFR. Additionally, Unx significantly increased glomerulosclerosis and loss of GFR in obese rats.

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Resistance Exercise Training Prevents Kidney Hypertrophy and Increases the Biogenesis Mitochondrial in Diabetic Rats  
Luciana Jorge, Kleiton Augusto Santos Silva, Rafael Luiz, Rodolfos Rosseto Rampasso, Janaina Paulini Aguiar, Nestor Schor.

**Background:** Diabetic nephropathy(DN) is a progressive complication arising from diabetes. kidney cell response to injury includes cell division, cell hypertrophy and apoptosis. Increasing evidence indicates that the disruption of mitochondrial bioenergetics and structural change in the kidney may be important in the development and progression of DN. Therefore, is fundamental the understand of a non pharmacological intervention as exercise training to prevent those complications. We investigated the effect of resistance training(RT) on the DN pathogenesis.

**Methods:** Male Wistar rats were divided into control(C), control trained(CT), diabetic(D) and diabetic trained (DT). DM was induced by STZ. Trained groups were submitted to a resistance exercise training on Ladder climb (8wk). Urinary volume and proteinuria were evaluated. Tissue weight/tibial length ratio was used as kidney hypertrophic index.

**Results:** RT induced renal parameters in DT group show a decreased urinary volume(D=160;DT=120;C=130;CT=140)proteinuria(D=45;DT=32;C=18;CT=7 mg/24h) (p<0.05). Diabetes resulted in increased hypertrophic index (50%)and RT prevented it. Renal expression of PAMPK and MF2N was reduced in D group and RT normalized this expression(p<0.05). Moreover, the renal expression of PAKT and PmTOR were increased in the DM and the RT influence on it(p<0.05). Histological analysis showed glomerular hypertrophy in D and RT prevent this complication.

**Conclusions:** RT attenuated progression of diabetic nephropathy; Those improvements could be a result of increased AMPK/MF2N pathway, an important pathway to biogenesis mitochondrial; and inhibition of AKT/mTOR pathway, responsible for hypertrophic response, demonstrating that those complications were prevented by exercise training. Our findings demonstrated that RT is an important approach to avoid, both molecular and functional complications in diabetic kidney.Funds from FAPESP,CNPq and CAPES.

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Resistence Exercise Training Prevents Kidney Hypertrophy and Increases the Biogenesis Mitochondrial in Diabetic Rats

SA-PO367

Aerobic Exercise Training Improves Proteinuria and Renal Inflammatory Factors in Rats with Diabetic Nephropathy

Rodolfo Rosseto Rampasso, Rafael Luiz, Kleiton Augusto Santos Silva, Luciana Jorge, Edison Andrade Pessoa, Mario Luis Ribeiro Cesaretti, Nestor Schor.

**Background:** The objective of this study was to evaluate the effects of aerobic exercise training in controlling the progression of diabetic nephropathy, inflammatory factors, and its possible renoprotective effects.

**Methods:** Adult male Wistar rats/4 groups, n=8/group: Sedentary controls (C-SED), Diabetes/Sedentary (DM-SED), Diabetes/Exercise (DM-EXE) and control exercise (C-EXE). Diabetes was induced with STZ, 50 mg/kg. The exercise training were conducted on a treadmill 60min/day, 5 days/week/8 weeks. Weekly certain, maximal exercise test(set on 65-70% of MEtest). Glycemia after post 24 education(24 glycemiapt), MEtest, creatinine clearance/BW(CrCl/BW), arterial pressure(AP), proteinuria(uProt), renal inflammatory factors IL-6, IL-10 and TNF-α were measured. Data as mean ± SD.

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>C-SED</th>
<th>DM-SED</th>
<th>DM-EXE</th>
<th>EXE</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycerinemipt (mg/dL)</td>
<td>103±2.03</td>
<td>551±5.73*</td>
<td>491±5.59*</td>
<td>83±2.57</td>
</tr>
<tr>
<td>uProt (mg/24h)</td>
<td>17±0.88</td>
<td>46±0.05*</td>
<td>18±0.72</td>
<td>16±0.99</td>
</tr>
<tr>
<td>CrCl (ml/min BW)</td>
<td>6.5±0.66</td>
<td>5.0±0.43</td>
<td>4.1±0.37</td>
<td>4.2±0.29</td>
</tr>
<tr>
<td>AP (mmHg)</td>
<td>122±1.89</td>
<td>133±8.17*</td>
<td>122±1.35</td>
<td>121±1.11</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>455±6.00</td>
<td>20±14.41*</td>
<td>32±4.34*</td>
<td>38±7.11</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>23±2.490</td>
<td>15±0.577*</td>
<td>35±1.897</td>
<td>37±5.67</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>541±98</td>
<td>931±40*</td>
<td>768±74*</td>
<td>391±22</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>545±86</td>
<td>876±34*</td>
<td>654±31*</td>
<td>453±28</td>
</tr>
</tbody>
</table>

P<0.05 VS C-SED and DM-EXE VS C-EXE

**Conclusions:** Reductions in blood glucose and AP –11% comparing DM-EXE vs DM-SED. The DM-EXE controlled weight loss ~40% compared to DM-SED, but did not prevent change in CrCl/BW with this protocol. However, the effect was surprisingly observed EXE reduction in both exercise through uProt ~60% and ~25% in MD-inflammatory factors comparing SED vs DM-EXE. Therefore, preliminary data suggests that aerobic exercise can reduce proteinuria and inflammatory factors in diabetic animals and hence reduce the potential effects caused by diabetic nephropathy and could reduce the progression of renal failure.
Inhibition of miR-25 Processing Mediated by MeCP2 Phosphorylated by HIPK2 Can Upregulate NOX4 in Early Diabetic Nephropathy

Hyung Jung Oh, Mitsuo Kato, Supriya Deshpande, Mei Wang, Linda L. Lanting, Rama Natarajan, Diabetes and Metabolism, Beckman Research Inst of City of Hope, Duarte, CA.

Background: Altered microRNA (miR) levels play key roles in the pathogenesis of diabetic nephropathy (DN), but it is unclear if miR processing is involved. Phosphorylated methyl-CpG binding protein2 (p-MeCP2), known to act as a transcriptional repressor, was recently reported to suppress the processing of several miRs. Homeo-domain interacting protein kinase2 (HIPK2) can bind to and phosphorylate MeCP2. However, it is not known if MeCP2 and HIPK2 are involved in processing and expression of candidate miRs in DN.

Methods: p-MeCP2 and HIPK2 staining in kidney sections from 4-week streptozotocin (STZ) injected diabetic and control mice, was studied immunohistochemistry. Protein, mRNA and miR levels were examined by Western blotting (WB) or RT-qPCRs in TGF-b1- or high glucose (HG)-treated mouse mesangial cells (MMCs).

Results: p-MeCP2 and HIPK2 immunostaining, and their protein levels were significantly higher in renal glomeruli (but not cortex) of STZ mice than control. Moreover, Seven in Absentia Homolog 1 (SIAH1), which mediates proteosomal degradation of HIPK2, was decreased in STZ mice compared with control. Among several regulated miRs, miR-25 and -93 levels were significantly decreased in STZ mice relative to control. The precursors of miR-25 and -93 were also significantly decreased in STZ mice, while conversely, NADPH oxidase4 (NOX4), a target of miR-25 that is associated with renal fibrosis and DN, was significantly increased in STZ mice. Protein levels of p-MeCP2 and HIPK2 were also increased in vitro in TGF-b1- or HG-treated MMCs compared to control. Moreover, mRNA levels of the genes mentioned above in vivo were similarly regulated in MMCs in vitro, although only miR-25 and its precursor were significantly decreased in the treated MMCs.

Conclusions: Our data suggest that epigenetic changes lead to persistent increase of SHP-1 expression despite systemic hyperglycaemia. Emerging evidence indicates that multiple factors involved in the aetiology of diabetes can alter epigenetic mechanisms and regulate susceptibility to microvascular complications.

Ursolic Acid Attenuated High Glucose Induced Podocyte Injury by Inhibition of miR-25 Expression Mediated by Mecp2 Phosphorylated

SA-PO371

Targeting the Polycystic Repressive Complex Chromatin Remodeling Machinery for Therapeutic Benefit in Diabetic Nephropathy

Letizia De Chiara, Hayley Beaton, Catherine Godson, John Crean. UCD School of Biomolecular and Biomedical Science, Diabetes Complications Research Centre, Univ College Dublin, Dublin, Ireland.

Background: Diabetic Nephropathy (DN) manifests as renal microvascular abnormalities, mesangial sclerosis and tubulointerstitial fibrosis as a result of longstanding hyperglycaemia. Emerging evidence indicates that multiple factors involved in the aetiology of diabetes can alter epigenetic mechanisms and regulate susceptibility to microvascular complications.

Methods: Immunoprecipitation, ChIP, Western Blot, miR302 overexpression, luciferase assay.

Results: We have previously identified SMAD3 and EZH2 as part of a context dependent switch enhancing complex that regulates cell fate during fibrotic processes. Here we describe the further characterisation of this interaction and delineate its potential pathogenic significance. Comparative analysis of gene expression data from patients, animals and cell models of diabetic kidney disease revealed a subset of genes that are potentially regulated by the interaction between Smad3 and EZH2, including critical regulators of epithelial fate such as E-Cadherin. Endogenous immunoprecipitation and luciferase experiments performed in renal epithelial cells demonstrated that the interaction is disrupted by downregulation of EZH2 and recruits EZH2 to the E-Cadherin promoter causing its down-regulation during Epithelial to Mesenchymal Transition. We further demonstrated that this interaction is disrupted by mutating SMAD3 protein sequence. Perturbation of the interaction between SMAD3 and EZH2 was facilitated by viral overexpression of miR302. Human renal mesangial cells transduced with miR302 undergo profound changes in gene expression exhibiting de novo expression of SNAIL and EZH2 and start to express de novo E-Cadherin.

Conclusions: Our results suggest that SMAD3 and EZH2 control the repression of E-Cadherin during DN, opening the possibility for therapeutic manipulation of this nexus during the progression of renal disease. Understanding the processes through which dynamic epigenetic silencing is controlled in adults will allow us to address the epigenetic state of acquired disease and whether original states, regenerative in nature, can be restored with therapy.

Funding: Government Support - Non-U.S.

Ursolic Acid Attenuated High Glucose Induced Podocyte Injury by Inhibition of miR-25 Expression Mediated by Mecp2 Phosphorylated

SA-PO368

J Am Soc Nephrol 26: 2015 Diabetes Mellitus and Obesity: Basic-Experimental - II Poster/Saturday

Hye Jung Oh, Sun Kyung Kang, Dae R. Cha. Government Support - Non-U.S.

Effects of DPPIV Inhibitor versus Combined Treatment with DPPIV Inhibitor and ARB on Renal Function in Type 2 Diabetic Mice

Hye Sook Min, Jin Joa Cha, Sung Jin Kim, Kiue Kim, Jung Eun Kim, Jungyeon Ghee, Ji Eun Lee, Hyunwoo Kim, Jee Young Han, Young Sun Kang, Dae R. Cha. Internal Medicine, Korea Univ Ansan Hospital; Nephrology, Sam Hospital, Anyang; Internal Medicine, Wonkwang Univ Sanbon Hospital; Pathology, Inha Univ, Incheon, Republic of Korea.

Background: Recent evidence has shown that DPPIV is involved in all steps leading to renal dysfunction, such as inflammatory response, cell apoptosis and fibrosis. The aim of our study was to investigate the mechanism and effects of DPPIV inhibitor (DA1229) alone and combined treatment with DPPIV inhibitor and ARB (LC158809) on renal injury in db/db mice.

Methods: The mice were divided into five groups as follows: non-diabetic db/m mice (control), untreated db/db mice, db/db mice treated with DA1229 (300mg/kg/d), db/db mice treated with LC158809 (1.5mg/kg/d) and db/db mice combined treatment with DA1229 and LC158809 for 12 weeks.

Results: 12week HbA1c level was significantly decreased in combined treatment group. Oxidative stress markers were not different from each other. Activity of serum DPPIV was significantly reduced with DA1229, 24h albuminuria significantly decreased with LC158809 treatment at 8 weeks and with DA1229 at 12 weeks in diabetic mice. However, no additive effect on albuminuria was observed with combined treatment. Administration of DA1229 or LC158809 significantly decreased accumulation of ECM protein, TLR4 and NOX4 expressions in glomerulus. No additive effects were measured in Smad3 deficiency mutant group. Urinary excretion of nephrin was increased in diabetic mice and was decreased in combined treatment with DA1229 and LC158809. In vitro, DPPIV was expressed on the
podocyte membrane and its expression was activated by angiotensin-II. Nephrin expression in cultured podocyte was attenuated by high glucose and angiotensin-II. This attenuation was recovered with DA1229 treatment, but not with other DPPIV inhibitors.

Conclusions: Our data suggest that renoprotective effects of DA1229 in experimental diabetic mice might be associated with protective effect of podocyte injury. DA1229 might be a potential therapeutic agent to slow the progression of diabetic nephropathy.

SA-PO373
PBI-4425, a Novel Anti-Inflammatory/Fibrotic Compound, Improves Kidney Function and Structure in the Diabetic db/db Mouse Model


Background: Kidney disease associated with diabetes mellitus is a major health problem worldwide. Glomerular injury plays a pivotal role in the development of diabetic nephropathy. PBI-4425 possesses a pleiotropic mechanism of action with anti-inflammatory, antioxidant and anti-fibrotic properties. The aim of this study was to investigate the protective effect of PBI-4425 on kidney function and structure in uninephrectomized (NX) diabetic (db/db) mice.

Methods: Total nephrectomy of the right kidney was performed on day 0 and animals were treated with vehicle or PBI-4425 (100 mg/kg, oral once a day) from day 1 through 103. Kidney function (GFR), kidney mesangial lesions, modulation of gene expression, and serum cytokines were investigated.

Results: GFR assessed by inulin clearance was significantly reduced in NX-db/db mice compared to NX-C57BL/6 negative control mice, and PBI-4425 treatment significantly improved GFR. As shown by PAS staining, NX-db/db mice had larger glomeruli with increased mesangial lesions scores were significantly reduced by PBI-4425 treatment. Gene expression of inflammation, fibrosis, oxidative stress, and extracellular matrix remodeling markers were assessed. Kidney MCP-1, IL-6, Collagen I, NOS, MMP2, and Timp1 mRNA expression were markedly increased in NX-db/db mice, and PBI-4425 treatment induced a significant decrease of these markers. Glomerular response to injury was accompanied by activation of kidney development-related genes, such as glomerular epithelial protein 1 (GLEPP1); expression of GLEPP1 was significantly increased in NX-db/db mice, and restored to the negative control level following treatment with PBI-4425. Moreover, PBI-4425 significantly reduced serum pro-inflammatory cytokines IL-6, IL-12p70, as well as THp-type pro-inflammatory cytokines IL-9.

Conclusions: These results suggest that PBI-4425 offers the potential as a novel therapy for diabetic nephropathy by improving kidney function and structure, and reducing pro-inflammatory and pro-fibrotic markers.

SA-PO374
The Effect of Nox Inhibitor APX-15 on Diabetic Kidney Disease

Jin Jun Cha, Hye Sook Min, Ji Hee Lim, Min Young Kim, Hyung Wook Kim, Jung Eun Kim, Jungyeon Ghee. 1 Medicine, UCSD, La Jolla, CA; 2 Medicine, UCSD, La Jolla, CA; 3 Medicine, UCSD, La Jolla, CA.

Background: The NADPH oxidase isoform NOX4 has been linked with diabetic kidney disease (DKD), however a mechanistic understanding of the downstream effects of NOX4 remains to be established.

Methods: To clarify the role of increased NOX4, we examined the role of NOX4 in the podocyte-specific NOX4 transgenic mouse. We also treated F1 Akita (DBA/2 J x C57BL/6J) INS2 Akita (db/db) mice with food pellets containing KGT137831, a NOX1/4 inhibitor from week 12 to week 28, and examined the effectiveness of treatment with the NOX1/4 inhibitor on the development of chronic kidney disease (CKD) and on the urine metabolome in a model of progressive DKD.

Results: Podocyte-specific induction of NOX4 in vivo was sufficient to recapitulate the characteristic glomerular changes noted with DKD, including glomerular hydropathy, mesangial matrix accumulation, GBM thickening, albuminuria, and podocyte dropout. Intervention with a NOX1/4 inhibitor reduced albuminuria, glomerular hydropathy, and mesangial matrix accumulation in the F1 Akita model of DKD. Metabolicomic analysis from the mouse studies revealed that TCA related urinary metabolites were increased in DKD and were uniquely reduced by the NOX1/4 inhibitor. TCA cycle enzyme runate hydratase (FH) reduction has been linked to regulating urine runat and indeed, FH was reduced in the diabetic kidney (in mice and human tissue) and the NOx4 inhibitor increased FH levels. Induction of NOx4 both in vitro and in the podocyte-specific NOX4 transgenic mouse led to reduced FH levels. The potential role of runate of FKD to DKD was confirmed as runate was found to stimulate ER stress, matrix gene expression and regulate HIF-1α and TGF-β.

Conclusions: Our data suggest that NOX4 is a major mediator of glomerular dysfunction with diabetes and renal FH is a key enzyme regulated in DKD and targeted by NOX4. FKD is a key enzyme that connects metabolic pathways to DKD pathogenesis and may have application to monitor renal NOX4 activity.

Funding: Other NIH Support - NIH (U01DK076133 and DP3DK094352)

SA-PO376
The Prostaglandin E2 EP3 Receptor Regulates Diet Induced Obesity

Ryan Patrick Ceddia, Richard M. Breyer. 1 Div of Nephrology and Hypertension, Dept of Veterans Affairs and Vanderbilt Univ, Nashville, TN; 2 Dept of Pharmacology, Vanderbilt Univ, Nashville, TN.

Background: Obesity is associated with a number of co-morbidities including diabetes, dyslipidemia and nonalcoholic fatty liver disease. Deletion of the PGE2, E-prostanoid (EP) 3 receptor gene has been shown to reduce the development of obesity and associated co-morbidities, such as dyslipidemia and nonalcoholic fatty liver disease.

Methods: To further characterize the effects PGE2-EP3 signaling on diabetes in a setting of diet induced obesity, EP3-/- mice were fed a high-fat diet (HFD; 45% calories from fat) or a control diet (10% calories from fat).

Results: Though no differences in body weight were observed in mice fed control diet, when fed a HFD, EP3-/- mice became heavier relative to EP3 +/+ mice (41.1±0.38 vs. 36.6±0.98 g; P<0.0001). EP3 -/- mice fed HFD had increased epididymal fat mass (1407±177 vs. 2401±167 mg; P<0.0001) and adipocyte size (6530±573 vs. 4330±469 μm²; P=0.005) compared to HFD fed EP3 +/- mice; paradoxically a relative decrease in both epididymal fat mass (P <0.0001) and adipocyte size (P=0.0055) was observed in the heaviest EP3 +/+ mice. EP3 -/- mice had increased macrophage infiltration (P<0.0001) and necrosis (P<0.001) in epididymal fat pads as compared to EP3 +/+ mice. Adipocytes isolated from EP3 -/- mice lacked PGE2-evoked inhibition of isoproterenol stimulated lipolysis compared to EP3 +/+ mice (1 nM ISO, ±100nM PGE2; EP3 +/+ : 10.2±1.4 vs. 4.8±1.84, P = 0.0036; EP3 -/ -: 11.8±1.20 vs. 10.3±0.68 nmol glycerol/10,000 cells, P>0.9999). EP3 -/- mice fed HFD had ecopic lipid accumulation in skeletal muscle (7.5±1.24 vs. 7.17±1.82 mg triglyceride/mg; P=0.0001) and liver (14.6±2.83 vs. 7.8±1.30 mg triglyceride/mg; P=0.0001), with evidence of hepatic steatosis. When fed HFD, EP3 +/+ mice became hyperglycemic (107 ±8.80 vs. 158±17.4 mg/dl; P<0.0001) and hyperinsulinemic (0.598±0.079 vs. 1.55±0.241 mg/ ml; P<0.0001) when compared to EP3 -/- fed HFD, demonstrating a more severe insulin resistance phenotype in EP3 +/+ mice (4.77±0.931 vs. 18.1±3.50 HOMA-IR, P=0.0001).

Conclusions: These results demonstrate that when fed a HFD, EP3 +/+ mice have abnormal lipid distribution, developing excessive ecopic lipid accumulation and associated insulin resistance.

Funding: NIDDK Support, Veterans Administration Support

SA-PO377
Resveratrol Activates Renal Expressions of Adiponectin Receptor 1 and 2 in db/db Mice

Y aieni Kim, Jin Hee Lim, Min Young Kim, Hyung Wook Kim, Cheol Whee Park. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: Adiponectin is an adipocyte-derived adipokine that binds to adiponectin receptors (AdipoR1 and AdipoR2) and exhibits antidiabetic effects via activation of AMPK and PPAR-δ. Our previous study investigated the renoprotective role of resveratrol by decreasing lipotoxicity and inhibiting mesangial cell glucotoxicity in a manner dependent on the AMPK-SIRT1-PPARγ axis in diabetic mouse model. The common pathway shared by both interventions suggested us to explore the favorable effect of resveratrol on renal physiology through activation of AdipoR.

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

Underline represents presenting author.

71A
Methods: Male db/db mice at 8 weeks of age were fed resveratrol (20 mg/kg/day) via gavage for 8 weeks. Serum and renal tissue were obtained to analyze for changes in metabolic parameters, molecular levels and renal structure.

Results: Resveratrol treatment showed favorable effects on albuminuria, glomerular matrix expansion and inflammatory cell infiltration. Increased expressions of AdipoR1 and Adiponectin decreased NOS expression in patients. Adiponectin inhibited inflammation and AMPK-a level. It also ameliorated free fatty acid and triacylglycerol accumulation in the kidney which was related to the increases in phosphorylation of AMPK and PPAR-a level. They related to decreases in the phosphorylation of AMPK and the activation of SIRT1-PGC-1α signaling and of the key downstream effectors, the PPARα-Forkhead box O (FoxO3) / FoxO1 pathway. Adiponectin induced anti-oxidative elements (ERB)-Iα and nicotinamide adenine dinucleotide (NADH) 1 (SREBP1)/acyetyl coenzyme A carboxylase (ACC). Furthermore, resveratrol increased eNOS phosphorylation and Bcl-2/Bax ratio which were associated with decreased apoptotic cells and oxidative stress as reflected by renal 8-hydroxy-deoxyguanosine (8-OHdG) and uric acid, and increased anti-oxidant concentrations. Resveratrol prevented high glucose induced oxidative stress and apoptosis in cultured human glomerular endothelial cells (HGECs) through activation of both AdipoR1 and subsequent phosphorylation of AMPK and the downstream effectors.

Conclusions: In conclusion, our results suggest that resveratrol exerts its renoprotective effects through activation of both AdipoR1 which prevent lipotoxicity related apoptosis and oxidative stress in the kidney.

SA-PO378
Oral Treatment with PBI-4547, a Novel Anti-Diabetic and Anti-Fibrotic Compound, Ameliorates Kidney Function and Glomerular Integrity in the Diabetic db/db Mouse Model

Background: Diabetic nephropathy is the most common complication of longstanding diabetes affecting up to 30% of all diabetic patients, and is the main cause of end-stage kidney disease. This study examined the long-term nephroprotective effects of PBI-4547 in uninephrectomized (NX) diabetic (db/db) mice, a model of type 2 diabetes.

Methods: Total nephrectomy of the right kidney was performed on day 0 and animals were treated with vehicle or PBI-4547 (10 and 50 mg/kg, oral once a day) from day 1 through 105. Kidney function (GFR and structure (mesangium lesions, glomerular integrity), regulation of pro-inflammatory/fibrotic gene expression in the kidney, as well as serum pro-inflammatory cytokine levels were examined.

Results: Kidney function assessed by GFR was significantly reduced in NX-db/db mice compared to NX-CT controls, and PBI-4547 treatment significantly improved GFR in NX-db/db mice. As shown by PAS staining, mesangial matrix expansion and inflammatory cell infiltration. Increased expressions of AdipoR1 and the downstream effectors.

Conclusions: These data suggest that PBI-4547 is a potential novel therapy for diabetic nephropathy by decreasing kidney function and structure, and reducing pro-inflammatory and pro-fibrotic markers.

SA-PO379
Prostaglandin E2 Receptor 3 (EP3) Inhibits Vasopressin-Stimulated Water Reabsorption and Contributes to Diabetic Renal Dysfunction in Mice
Ramzi Hassounieh, Rania Nasrallah, Joe A. Zimpelmann, Kevin D. Burns, Yuanyuan Wu, Yufeng Huang. Daisuke Nakano, Wararat Kittikulsuth. Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: We have shown in a diabetic model that prostaglandin-E2 (PGE2) may contribute to increased renal cyclic GMP (cGMP) levels and fluid retention. The EP3 receptor mediates the vasopressin-induced cGMP increase. We examined the role of EP3 in the regulation of water reabsorption in diabetes.

Methods: Male EP3-/- and wild-type (WT) C57BL/6 mice were injected with vehicle or streptozotocin (STZ) and after 12 weeks, animals were treated with vehicle or PBI-4547 (10 mg/kg, oral once a day). Urinary albumin, blood glucose, and light-period mean arterial pressure (MAP) were measured. The cumulative loop was assessed by Western blotting.

Results: Untreated uninephrectomized db/db mice developed progressive albuminuria (P<0.01), decreased body weight and increased blood pressure compared to wild-type controls. In contrast, PBI-4547 treatment prevented the increases in urinary albumin and blood pressure and reduced body weight. These data suggest that a SGLT2 inhibitor elicits its beneficial effects on glucose metabolism and hypertension in subjects with metabolic syndrome undergoing treatment with SGLT2 inhibitors.

SA-PO380
Effects of Diuretics on SGLT2 Inhibitor-Induced Changes in Blood Pressure and Natriuresis in Obese Rats Suffering from the Metabolic Syndrome
Akira Nishiyama, Daisuke Nakano, Wararat Kittikulsuth. Dept of Pharmacology, Kagawa Univ Medical School, Kagawa, Japan.

Background: In experimental and clinical studies, SGLT2 inhibitors (SGLT2i) have been shown to reduce the risk of cardiovascular and renal events in patients with type 2 diabetes (T2DM), but evidence on the impact of SGLT2i on blood pressure (BP) remains limited.

Methods: Male 13-week-old SHRcp were treated with: (i) vehicle; (ii) the SGLT2 inhibitor luseogliflozin (10 mg/kg/d, p.o.); (iii) diuretics (hydrochlorothiazide; 10 mg/kg/d + spironolactone; 25 mg/kg/d, p.o.); or (iv) luseogliflozin (5 mg/kg/d, p.o.) + diuretics for 5 weeks (n = 5–8 for each group). BP response and urine volume were measured by telemetry system and oral glucose tolerance test, respectively.

Results: Vehicle-treated SHRcp developed non-dipper type hypertension (dark-light period mean arterial pressure (MAP) 148±0.7 and 148±0.7 mmHg, respectively, P<0.01) which were associated with a significant increase in urinary excretion of sodium. Addition of diuretics did not influence luseogliflozin-induced improvement of glucose metabolism and circadian rhythm of blood pressure in SHRcp.

Conclusions: These data suggest that a SGLT2 inhibitor elicits its beneficial effects on glucose metabolism and hypertension in subjects with metabolic syndrome undergoing treatment with SGLT2 inhibitors.

Funding: Other NIH Support - the Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research (KAKENHI), Pharmaceutical Company Support - Taisho-Toyama Pharm.

SA-PO381
SGLT2 Inhibition Slows the Progression of Diabetic Nephropathy in the db/ db Mouse
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Background: It has been shown that SGLT2 inhibitor not only enhanced renal glucose excretion and lowered blood glucose (BG) but also reduced albuminuria in patients with Type 2 diabetes (T2DM). However, the renoprotective effect of SGLT2 inhibition in diabetic nephropathy has not yet been established.

Methods: This study sought to determine whether dapagliflozin, a selective SGLT2 inhibitor, could slow the progression of glomerulosclerosis in the uninephrectomized db/db mouse, a model of T2DM.

Results: Untreated uninephrectomized db/db mice developed progressive albuminuria and glomerulosclerosis between wks 18 and 22, associated with increased renal expression of TGFβ1, PAI-1, type IV collagen and fibrinone. Treatment with dapagliflozin (1mg/kg/d) via gel diet from wks 18 to 22 did not affect body weight but reduced BG (from 573±62.1 to 367±146.5 mg/dL, P<0.05) and HbA1c levels. Of note, treatment with dapagliflozin arrested the increases in albuminuria, body weight and markers of glomerulosclerosis seen in db/db mice between wks 18 to 22. Renal expressions of TGFβ1, PAI-1 and FN were reduced by 50% in STZ and restored to control levels in PBI-4547-treated NX-db/db mice. Moreover, qPCR analysis of the expression of MCP-1, IL-6, Collagen I, MMP2, Timp1, and iNOS showed that PBI-4547 downregulated diabetes-induced inflammation, fibrosis, oxidative stress, and expression of MCP-1, IL-6, Collagen I, MMP2, Timp1, and iNOS showed that PBI-4547 downregulated diabetes-induced inflammation, fibrosis, oxidative stress, and expression of MCP-1, IL-6, Collagen I, MMP2, Timp1, and iNOS.

Conclusions: Despite elevated VP levels in STZ, the CCD response to VP stimulation was no different than in WT, while SNP suppressed VP-induced Jv in both groups. In the absence of VP, the SNP-induced Jv was unchanged by SNP, confirming the importance of EP3 in this process. During diabetes, EP3 inhibition of VP-induced Jv may lead to polyuria and a sustained increase in VP, which may be injurious to the kidney.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Up-Regulated Sglt2 Reduces Proximal Tubular Sirt1 and Augments Renal GlucoseEosis in Early Stage Diabetic Nephropathy
Hiroki Umino, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. 1

Background: Sodium-glucose cotransporter (SGLT) 2 inhibitors are new antidiabetic drugs that increase urinary glucose excretion (UGE) by inhibiting renal SGLT2. SGLT2 inhibitors may induce body fluid reduction due to the increase in urine volume and Na excretion, but the details remain unclear.

Methods: Spontaneously Diabetic Torii (DM) rat, a non-obese type 2 diabetic model was used in this study. At the onset of diabetes (blood glucose ≥ 250 mg/dl), DM rats and age-matched Sprague-Dawley (non-DM) rats were separated to vehicle (Veh) and 0.01% Ipragliflozin. At the onset of diabetes (blood glucose ≥ 250 mg/dl), DM rats and age-matched Sprague-Dawley (non-DM) rats were separated to vehicle (Veh) and 0.01% Ipragliflozin. At the onset of diabetes (blood glucose ≥ 250 mg/dl), DM rats and age-matched Sprague-Dawley (non-DM) rats were separated to vehicle (Veh) and 0.01% Ipragliflozin. At the onset of diabetes (blood glucose ≥ 250 mg/dl), DM rats and age-matched Sprague-Dawley (non-DM) rats were separated to vehicle (Veh) and 0.01% Ipragliflozin.

Results: Renal membrane protein expression of SGLT2 was significantly higher in DM rats compared with non-DM rats. Ipragliflozin reduced the expression of SGLT2. However, Sglt2 inhibitors blocked these changes.

Conclusions: These results suggest that SGLT2 inhibitor not only reduces albuminuria but also slows the progression of glomerulosclerosis resulting from T2DM by improving hyperglycemia and renal inflammation and oxidative stress. Decreasing glomerular hyperfiltration and negatively regulating renal Na activity by SGLT2 inhibitor may be also renoprotective.

Funding: Pharmaceutical company support - AstraZeneca R&D.

References:

Background: SGLT2 inhibitors have recently been approved in type 2 diabetes and long-term clinical trials are ongoing to further establish efficacy and safety. Humans with familial renal glycosuria due to mutations in SGLT2 do not show signs of general renal tubular dysfunction or other pathological changes, and they seem to have normal life expectancies. Here we compared the phenotype of non-diabetic aged male mice at (24 months) that lack SGLT2 (Sglt2-/-) with their wild-type littermates (WT).

Methods: In awake mice, blood pressure (BP) and heart rate (HR) was measured by an arterial catheter-tail cuff system and GFR by FITC-inulin plasma eliminations kinetics.

Results: Out of initially 11 Sglt2-/- and 14 WT, 2 mice per genotype died for unknown reasons before reaching an age of 24 months; thus 9 Sglt2/-/- and 12 WT mice were analyzed. Consistent with results previously reported in young adult mice (3.5 months): aged sglt2-/-/ and wt increased similar both body weight (30±6.6 vs 32±10.9 g) and blood glucose (105±6 vs 116±10 mg/dl), and GFR (329±36 vs 370±20 ml/min); sglt2-/- had higher urinary glucose excretion (381±1 vs 51±1 mmol/mg creatinine) associated with higher intake of food (3.8±0.1 vs 3.2±0.1 g/day) and fluid (8.9±0.2 vs 5.1±0.1 ml/day) and smaller adipocytes in subcutaneous and epididymal fat tissue (4790±44 vs 638±130 and 8093±990 vs 11811±778 mm²/each (P<0.01); urine pH was similar (6.2±1 vs 6.5±0.2) and no bacterial growth detected in bladder urine. Different from previous findings in young adult mice: aged sglt2-/- had modestly higher kidney weight (14.5±0.9 vs 12.6±0.4 g body wt), BP (105±22 vs 93±1 mm Hg) and HR (666±7 vs 625±151/min) than WT and lower hematocrit (31±1 vs 41.3±0.4%) (each P<0.01).

Conclusions: Aged SGLT2-/- mice show many of the expected phenotypes previously observed in young adult mice, and have preserved GFR and no evidence for ascending branch stenosis. An increase in kidney weight has previously been reported in 7.5 months old SGLT2-/- mice. Further analyses aim to better understand the latter findings and the observed modest changes in BP and hematocrit.

Funding: NIDDK support.

References:
Results: Inhibiting SGLT2 shifts Na⁺ transport to downstream nephron segments, possibly increasing their QₘG. Particular concerns are the S3 segment and medullary thick ascending limb (mTAL), which are at risk for hypoxic injury. Dual SGLT1-SGLT2 inhibition protects the S3 segment, but could further reduce mTAL oxygenation. Model simulations suggest that SGLT2 inhibition substantially increases S3 QₘG. Together with elevated renin-angiotensin system (RAS) expression of Na-K-cotransporter (NCC2), SGLT2 inhibition also increases mTAL QₘG. Additionally, we used the model to determine the optimal combination of SGLT1 and SGLT2 inhibition, in terms of suppressing tubular glucose uptake and maintaining sufficiently low S3 and mTAL QₘG.

Conclusions: In conclusion, SGLT inhibition significantly increases oxygen consumption of the mTAL. This research was supported in part by NIH grant DK-89666. Funding: NIDDK Support

SA-PO387

SGLT2 Expression Is Increased in Human Diabetic Nephropathy: SGLT2 Inhibition Decreases Renal Lipid Metabolism, Inflammation and the Development of Nephropathy in Diabetic Mice Xiaoxin Wang, 1 Jonathan Levi, 2 Yuhuan Luo, 1 Evgenia Dobrinskikh, 1 Almett Grozn, 1 Michal Herman-Edelstein, 2 Uzi Gafter, 2 Avry Chagnac, 1 Hermann Koeppeli, 2 Jeffrey B. Kopp, 2, 3, 4 A. Rosenberg, 2 Moshe Levi, 2 1Univ of Colorado Denver; 2NIDDK; 3Rabin Medical Center; 4Univ of Warsaw

Background: The renal sodium gradient dependent glucose protein SGLT2 expression is increased in renal biopsies from human subjects with diabetic nephropathy. Methods: To determine the potential mechanisms of beneficial effects of SGLT2 inhibition in progression of diabetic renal disease we treated db/db mice with a selective SGLT1 inhibitor.

Results: We found that SGLT2 inhibition caused marked decreases in systolic blood pressure, kidney weight/body weight ratio, urinary albumin (745±36 mg/dl in db/db vs. 207±5 mg/g in treated db/db, p<0.001) and urinary thiorheritance acid-reacting substances (TBARS). SGLT2 inhibition also a) prevented renal lipid accumulation via inhibition of LPL, SCD-1 and DAGAT1, key enzymes that mediate fatty acid and triglyceride synthesis, b) decreased inflammation via inhibition of CD68 macrophage accumulation, and expression of p65, TLR4, MCP-1 and 1NP, and c) increased CD73 and decreased adenosine A receptors Ador1, Ador2a, and Ador2b mRNA. These effects were associated with prevention of mesangial expansion, accumulation of extracellular matrix proteins fibronectin and type IV collagen, as well as loss of podocyte markers WT1 and synaptopodin, as determined by quantitative immunofluorescence microscopy.

Conclusions: In summary, our study showed that SGLT2 inhibition modulates renal lipid metabolism and inflammation and prevents the development of nephropathy in db/db mice. Funding: Pharmaceutical Company Support - J&J

SA-PO388

Loss of Angiotensin-Converting Enzyme 2 Alters Glomerular Structure in Non Obese Diabetic Mice Helea Roca-Roig, 1 Marta Riera, 1 Marta Rebull, 2 Javier Gimeno, 2 Julio Pascual, 1 Maria Jose Soler, 1 Nephrology, Hospital del Mar-Institut Hospital del Mar d’Investigacions Mèdiques, Barcelona; 2Pathology, Hospital del Mar, Barcelona.

Background: ACE2 has been shown to play an important role in diabetic nephropathy (DN). We studied renal morphology and kidney function in non-obese diabetic (NOD) female mice (with spontaneous autoimmune diabetes) carrying a deletion on ace2 gene (NOD.ACE2 -/-). In particular, concerns are the S3 segment and medullary thick ascending limb (mTAL), which are at risk for hypoxic injury. Model simulations suggest that SGLT2 inhibition substantially increases S3 QₘG. Together with elevated renin-angiotensin system (RAS) expression of Na-K-cotransporter (NCC2), SGLT2 inhibition also increases mTAL QₘG. Additionally, we used the model to determine the optimal combination of SGLT1 and SGLT2 inhibition, in terms of suppressing tubular glucose uptake and maintaining sufficiently low S3 and mTAL QₘG.

Conclusions: In conclusion, SGLT inhibition significantly increases oxygen consumption of the mTAL. This research was supported in part by NIH grant DK-89666. Funding: NIDDK Support
Conclusions: Genetic ACE2 ablation worsens glomerular hypercellularity in diabetic mice whereas GFP and ACR are not significantly altered and other markers of glomerular pathology are minimally affected.

Funding: NIDDK Support, Private Foundation Support

SA-PO391

Blood Pressure-Independent Amelioration of Glomerulosclerosis in Diabetic Rats Treated with Dual AT1-Receptor-Nephrin Inhibition versus AT1-Receptor Blockade Alone

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Background: Dual AT1-receptor-nephrin inhibition (ARNI) has recently been shown to exert beneficial effects on blood pressure (BP), NT-proBNP, and estimated GFR in heart failure patients, compared with AT1 receptor blockade (ARB) alone. Nephrin is upregulated in epineurial arterioles of diabetic rats. We hypothesized that ARNI improves cardiac and kidney parameters in diabetic tGR(mREN2)27 rats, a model displaying angiotensin II-mediated hypertension.

Methods: Rats were made diabetic with streptozotocin, for 5 or 12 weeks. In the final 3 weeks rats were treated with vehicle, the ARB irbesartan (15mg/kg/day) or irbesartan (15mg/kg day) + the nephrin inhibitor thiophan (0.1mg/kg/day; ARNI). BP was measured by telemetry in the 5-week group only.

Results: Baseline mean arterial BP (MAP) was 157±5mmHg. ARNI and ARNI lowered MAP identically over the 3-week period, reaching a maximum reduction of ~50mmHg around day 7, Heart weight/body length ratio in 12-week diabetic rats was 17% lower after ARNI treatment vs. ARB treatment (P<0.05). Proteinuria and albuminuria were observed from 8-weeks of diabetes onwards. ARNI reduced proteinuria more strongly than ARB (-78% vs. -49%, P<0.05), and a similar trend was seen for albuminuria. Kidneys of ARNI-treated rats showed less focal segmental glomerulosclerosis than those of ARB-treated rats. At the end of the study, no differences between ARNI- and ARB-treated rats were found regarding diuresis, natriuresis, plasma endothelin-1, vascular reactivity (acetylcholine and endothelin-1 responses), or kidney sodium transporters.

Conclusions: ARNI reduces proteinuria, focal segmental glomerulosclerosis, and cardiac hypertrophy in diabetic tGR(mREN2)27 rats more strongly than ARB, and this occurs in a blood-pressure-independent manner.

SA-PO392

Collateral Effects of Atrasentan on Renin-Angiotensin System

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Background: Endothelin-1 is a vasoconstrictor peptide that has been shown to be increased in diabetic kidney disease. In kidney cortex from obese diabetic mice ACE2 activity is increased whereas ACE activity is decreased. Objective: study the effect of atrasentan, an antagonist of type B endothelin receptor, on renin-angiotensin system (RAS) in obese diabetic mice (db/db) and its respective controls (db/db).

Methods: Diabetic groups: vehicle (VehDB), 10mg/kg/day atarstentan (10DB), 25mg/kg/day atarstentan (25DB), 50mg/kg/day atarstentan (50DB). Non-diabetic groups: vehicle (VehCONT), 10mg/kg/day atarstentan (10CONT). Animals were included in the study at 12-weeks of life and treated for 16weeks. Systolic (SBP) and diastolic (DBP) blood pressure and ACE and ACE enzymatic activities in serum and kidney were analyzed.

Results: See table. Atrasentan therapy significantly decreased SBP and DBP in diabetic mice. Circulating and renal ACE2 activities were significantly increased in VehDB mice as compared to VehCONT. Atrasentan treatment at 25 and 50mg/kg/day reduced circulating and renal ACE2 activities. Circulating and renal ACE activities were decreased in VehDB as compared to VehCONT, with no modulation by atrasentan treatment.

Conclusions: Atrasentan prevented the increase of circulating and renal ACE2 in diabetes, indicating a collateral effect by RAS modulation. These results suggest that the beneficial effect of atrasentan in diabetic nephropathy may be related with endothelin blockade and its effect in the non-classic RAS pathway.

SA-PO393

P16\textsuperscript{ink4a} Expression Is Increased via 12-Lipoxygenase in High-Glucose-Stimulated Glomerular Mesangial Cells and Type 2 Diabetic Glomeruli

Yuanyun Zhang, Fu-zhe Ma, Tao Sun, Wan-ning Wang, Hang Yuan, Zhong-gao Xu. Nephrology, The First Hospital of Jilin Univ; Changchun, Jilin, China.

Background: Arachidonic acid-metabolizing enzyme 12-lipoxygenase (12-LO) is involved in glomerular hypertrophy of diabetic nephropathy (DN), in which cyclin-dependent kinase inhibitors (CDKs) play important roles. However, it is unclear whether 12-LO regulates the expression of the CDK p16\textsuperscript{ink4a} in DN.

Methods: Primary glomerular mesangial cells (MCs) and glomeruli isolated from rats were used in this study. The rats were fed a high-fat diet and given low-dose streptozotocin to induce type 2 diabetes. The 12-LO produced 12(S)-hydroxyicosatetraenoic acid [12(S)-HETE] was infused through an osmotic minipump. Enzyme-linked immunosorbent assay, Western blot, and morphometric analyses were performed.

Results: High glucose (HG) increased p16\textsuperscript{ink4a} protein expression in MCs, but this increase was prevented by the 12-LO inhibitor cinamycin-3,4-dihydroxy-o-cynaminocinnamate (CINC). The levels of p-p16\textsuperscript{ink4a} and p16\textsuperscript{ink4a} in MCs were significantly elevated after 12(S)-HETE treatment, whereas the 12(S)-HETE inhibitor SB203580 prevented these increments. Compared with levels in control MCs, marked increases in p16\textsuperscript{ink4a} activation and p16\textsuperscript{ink4a} expression were observed in MCs plated on collagen IV, while CDC treatment prevented these changes. Subcutaneous injection of CDC did not affect glucose levels but completely attenuated the diabetes-related increases in 12(S)-HETE content, p16\textsuperscript{ink4a} expression, p-p38MAPK levels, glomerular volume, and kidney-body weight ratio. Compared with levels in controls, p16\textsuperscript{ink4a} and p-p38MAPK in the glomeruli derived from 12(S)-HETE-treated rats were significantly increased.

Conclusions: 12-LO-p38MAPK mediates the upregulation of p16\textsuperscript{ink4a} in HG-stimulated MCs and type 2 diabetic glomeruli, and new therapies aimed at 12-LO inhibition might be beneficial in ameliorating diabetes-induced glomerular hypertrophy.

SA-PO394

The Effect and Mechanism of Probufol on Diabetic Nephropathy

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Background: P66Shc induce mitochondrial ROS overproduction and lead to renal oxidative stress. Probufol has the protective effect on the progression of DN. However, the mechanism remains poorly understood.

Methods: ICR mice were divided into control (n=10), DN (n=10), probufol (10mg/kg/d) group (n=10), DMSO group (n=10). The DN model was induced by injection of STZ (40mg/kg body weight). Probufol was intraperitoneally injected to the mice every other day for 12 weeks after the model was built. Renal lesions and the expression of SIRT1, P300, AcH3, P66Shc, FN were detected by HE, Masson staining, TUNEL, DHE, immunohistochemistry and western-blot respectively.In addition, HK-2 cells were incubated with different concentrations of D-glucose (5, 30mM) with or without probufol, 1mM AICAR or 20mM Dorosomorphor or 1mM EX-527. The expression of P66Shc, SIRT1, P300, AcH3, AMPK, p-AMPK in HK-2 cells were detected by realtime-PCR,Western-blot and immunofluorescence assays. In addition, chromatin immunoprecipitation (CHIP) assay was used for determining the effect of probufol on acetylation of histone of P66Shc gene.

Results: Compared to control, the reduced ECM protein and renal tubular damage were observed in DN mice after treated by probufol. It also decreased the expressions of P300, P66Shc, FN in the kidney of DN mice. In addition, Probufol can reduce the level of serum creatinine, uric acid, proteinuria and renal ROS levels and apoptosis , while boost the expressions of p-AMPK and SIRT1. Furthermore, pretreatment with the selective AMPK inhibitor Dorosomorphor or SIRT1 inhibitor EX-527 could block the inhibitory efficiencies of probufol. The CHIP analysis showed that probufol treatment could decrease the acetylation of histone h3 in P66Shc gene promoter regions (~353 bp to -276 bp) in HK-2 cells induced by high glucose.

Conclusions: Probufol could epigenetically suppress the expression of P66Shc through AMPK-SIRT1-AcH3 pathway, then ameliorate the apoptosis and oxidative injury in HK-2 cells induced by high glucose.

Funding: Government Support - Non-U.S.

SA-PO395

Macrophages in Type 2 Diabetic Nephropathy

Celine Klessens, Malu Zandbergen, Ron Wolterbeek, Jan A. Bruijn, Ton J. Rabelink, Ingeborg M. Bajema, Daphne Thomas-jipelaar. Leiden Univ Medical Center.

Background: Inflammation seems to play a role in type 2 diabetic nephropathy (DN). Therefore, novel therapies focus on inhibition of inflammation to inhibit renal failure in DN. Interstitial macrophages are present in progressive interstitial lesions, however, the role of glomerular macrophages in the development of diabetic glomerular damage remains incompletely understood. In this study we investigated the accumulation of macrophages in glomeruli and interstitium of humans with various stages of DN.

Methods: Kidney samples obtained at autopsy of type 2 diabetes patients (N=88) with histologically proven DN were stained with CD68 and CD163, as global and M2 macrophage markers. As controls, renal autopsy samples of 5 non-diabetic and 18 diabetic

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
patients without DN were used. Macrophages in 50 glomeruli per sample were counted. Intestinal and interstitial macrophages were correlated to pathological and clinical parameters. **Results:** Glomerular CD68+ and CD163+ cells were present in all stages of DN both in the glomerulus and interstitium. Correlation between clinical data and interstitial macrophages indicates that intestinal inflammation probably influences the progression of DN. In addition, presence of glomerular macrophages in early diabetic nephropathy suggests that they influence the glomerular diabetic damage as well. Therefore, therapies targeting macrophages might be a useful novel therapy in DN.

**SA-PO396**

**Activation of CXCL16/CXCR6 Pathway by Inflammation Accelerates the Progression of Diabetic Nephropathy**

**Zhuo He,** Kun Ling Ma, Yang Zhang, Wu Yu, Bi-Cheng Liu

**Methods:** Diabetic nephropathy was induced in rats by STZ injection. CXCL16 and CXCR6 expression were analyzed by western blot and immunofluorescence. Activated macrophages were isolated and cultured. The expression of CXCL16/CXCR6 pathway was analyzed using western blot and fluorescence-activated cell sorting. Results were confirmed by qRT-PCR and in vitro assays.

**Conclusions:** CXCL16/CXCR6 pathway plays a crucial role in the progression of diabetic nephropathy. Enhanced CXCL16/CXCR6 expression accelerates the progression of diabetic nephropathy by stimulating macrophages and promoting inflammation.

**SA-PO397**

**Albumin Glycation Induces Structural Changes That Reduce Proximal Tubule FcRn-Albumin Binding and Reclamation**

**Mark C. Wagner,** Jered Myśliński, Shiv Pratap Singh Yadav, George Rhodes, Raben M. Sandoval, Sudhanshu Kumar, Sarah E. Wean, Fnu Ashish, Bruce A. Moltisini.

**Methods:** Albumin glycation was induced in vitro using a human kidney proximal tubule cell line. The albumin binding and reclamation by the FcRn were measured using fluorescence polarization and flow cytometry. The structural changes in albumin were analyzed using circular dichroism and electron microscopy. The correlation between albumin glycation and FcRn binding was studied using regression analysis.

**Conclusions:** Albumin glycation induces structural changes that reduce proximal tubule FcRn binding and reclamation. These changes affect the integrity of the renal proximal tubule and may contribute to the development of diabetic nephropathy.

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

Underlines represent presenting author.

716A
**SA-PO400**

**Far-Infrared Retrieves Pancreatic Beta Cell Function and Survival in a Streptozotocin-Nicotinamide-Induced Type 2 Diabetic Mouse Model**

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**Background:** In diabetes, the apoptotic cell death of insulin-producing beta cells leads to insulin deficiency. Recently, we found low-temperature far-infrared (FIR) irradiation increased proliferation and survival of human umbilical vein endothelial cells via prolymphocytic leukemia zinc finger protein (PLZF)-mediated PI3K/Akt activation.

**Methods:** In this study, we investigated the protective effects of FIR on pancreatic beta cell function and survival in the nicotinamide (NA) and streptozotocin (STZ)-induced type II diabetic mouse model. E1s via prolymphocytic leukemia zinc finger protein (PLZF)-mediated PI3K/Akt activation.

**Results:** The present study showed that F1R therapy decreased non-fasting blood glucose levels and increase blood insulin levels in diabetic mice in a dose-dependent manner. Immunohistochemistry staining revealed that F1R therapy retrieved insulin production of pancreatic beta cells in diabetic mice. But the influence of F1R on blood glucose and insulin levels was not found in NA-STZ-treated wild type (WT) and FIR mice. We also used the insulin-secreting beta cell line RIN-m5f to investigate the protective effects of FIR in vitro. FIR irradiation promoted cell proliferation and inhibited STZ-induced apoptosis in RIN-m5f cells. FIR also inhibited PLZF nuclear translocation and increased PI3K expression and Akt phosphorylation in RIN-m5f cells. PLZF siRNA transfection inhibited the influence of F1R on cell proliferation.

**Conclusions:** Our data suggest that F1R therapy retrieves pancreatic beta cell function and survival in diabetic mice via a PLZF-mediated pathway.

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**SA-PO401**

**Transgenic Mice Overexpressing Human CD39 (ENTPD1) Are Protected from High-Fat Diet-Induced Obesity and Insulin Resistance**

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**Background:** CD39 is a vascular ecto-nucleotidase that sequentially hydrolyzes extracellular ATP to ADP and AMP, thus terminating P2 receptor signaling. Previously we reported that deletion of CD39 in pancreatic beta cells confers significant protection against high-fat diet (HFD)-induced obesity and IR. Hence, we hypothesized that global overexpression of human CD39 (hCD39), which decreases the availability of extracellular nucleotides should humanize the beta cell (Hb) protective phenotype in vivo.

**Methods:** C57BL/6J (hCD39) transgenic (TG) and wild type (WT) mice were fed HFD (60% calories as fat, n = 10) or HFD (60% calories as fat; n = 7) with free access to food and water for 10 weeks. Glucose tolerance (GTT) and insulin sensitivity (IST) tests were conducted periodically. Glucose tolerance (GTT) and insulin sensitivity (IST) tests were performed. Blood glucose levels were measured by tail pinch blood sampling at 8 a.m. in conscious mice. A 2-h GTT was performed after an overnight fast. IST was assessed using an oral glucose tolerance test (OGTT).

**Results:** In response to HFD feeding, both genotypes showed significant increases in BW over the experimental period as compared to their counter parts fed regular diet. However, the gain in BW was significantly less in TG vs. WT mice (mean 21.5 ± 0.3 vs. 15.3 ± 2.0 g, n = 7, p = 0.005). There were no significant differences between the genotypes in the amount of food consumed, nor was there evidence of steatorrhea indicating uncontrolled autophagy levels could lead to tubular damage through the generation of uncontrolled autophagy levels. In contrast, the gain in BW was significantly less in TG vs. WT mice (mean 21.5 ± 0.3 vs. 15.3 ± 2.0 g, n = 7, p = 0.005). When fed hCD39 both genotypes exhibited glucose intolerance, but this was less severe in TG mice. In parallel, insulin sensitivity was significantly better in HFD-fed TG vs. WT mice.

**Conclusions:** Our results demonstrate that overexpression of hCD39 confers significant protection against the development of HFD-induced obesity and IR, and thus validating the proposition that dominantly deleterious roles are played by extracellular nucleotides.

**Funding:** Veterans Administration Support

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**SA-PO402**

**Mass Spectrometry Imaging Reveals a Role for Glomerular Sphingomyelin in Suppress AMPK Activity by Stimulating ATP Production in Mesangial Cells**

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**Background:** We have recently shown that the ATP/AMP ratio is increased in the glomeruli in a mouse model of type 1 diabetes by matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) and may be the basis for reduced AMPK activity in diabetic glomeruli. Here, we applied MALDI-MSI to identify a key molecule regulating ATP levels in glomeruli.

**Methods:** For MALDI-MSI, 23 weeks-aged male diabetic Akita (C57BL/6J-Inj287290) (A), and normal (H) mice were fed HFD or NIDDK diet (N), and nephrectomy (N) were performed, and kidneys (K) were used. For mass spectrometry imaging (mass spectrometry imaging (mS)-MS imaging) was coupled with quantitative mass spectrometry (nano-HPLC/ESI/MS). The protein levels were analyzed using mass spectrometry imaging (mass spectrometry imaging (mS)-MS imaging).

**Results:** In diabetic glomeruli, we found that the protein expression levels of Ndufb2, Ndufb3 and Ndufb8, all components of respiratory chain complexes II, III and IV, were reduced by SL (p<0.05). In addition, SL increased glucose consumption and lactate production in high glucose conditions (p<0.05) suggesting a role for mitochondrial dysfunction.

**Conclusions:** We demonstrated using MALDI-MSI that the accumulation of glomerular SM in type 1 diabetic mice is associated with increased ATP in glomeruli and may contribute to reduced AMPK activity in diabetes. These findings suggest that reduction of SM may lead to novel therapeutic targets for the treatment of diabetic kidney disease.

**Funding:** NIDDK Support, Other NIH Support - DP3DK094352-01, Veterans Administration Support

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**SA-PO403**

**Chronic Hyperglycemia Activates Autophagy Through an Increased Lysine-63 Linked Ubiquitination:** A Candidate Mechanism in the Progression of Tubular Damage in Diabetic Nephropathy

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**Background:** Chronic hyperglycemia, a key pathogenic factor of diabetic nephropathy (DN), can alters autophagy whose role in tubular cells under hyperglycemic conditions (HG) remains unclear. We reported that lysine63-ubiquitination (K63-Ub) plays a key role in the progression of tubular damage in DN; moreover K63-Ub promotes protein autophagic clearance. Aim of our study was to: evaluate the HG effect in modulating autophagy in tubular cells (HK2); evaluate in vivo the autophagy state in patients with diabetes without renal damage and in different DN classes; investigate the K63-Ub role in the modulation of tubular cells autophagy.

**Methods:** HG was induced in HK2 under control (HGF) and HG conditions (HUGF). HG was induced in HK2 under control (HGF) and HG conditions (HUGF). HG was induced in HK2 under control (HGF) and HG conditions (HUGF).

**Results:** HG showed a significant increase in LC3 protein after 24h of HG. UBE2V1 silencing completely abolished LC3 induced protein expression after 24h of HG. Confocal microscopy showed the reduction of autophagic vesicles induced by HG in the presence of the K63-Ub inhibitor (NSC097923). IHC on kidney biopsies revealed an increased tubular expression of LC3 in diabetic patients vs controls, that persists in all DN classes and class IV patients showed cytoplasmatic accumulation of fused-vesicles. The same tubules with activated autophagy, expressed K63-Ub proteins both in diabetic and in DN patients (IF).

**Conclusions:** In conclusion, our data demonstrate that chronic hyperglycemia increases autophagy in kidney biopsies of 3 control patients, 3 diabetic, 9 DN (classes Iib, III and IV).

**Funding:** NIDDK Support, Other NIH Support - DP3DK094352-01, Veterans Administration Support

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**SA-PO405**

**Complexome Profiling of Mitochondrial Respiratory Chain Proteins from Podocytes of Diabetic Mice**

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**Background:** Mitochondria play essential roles in many aspects of biology, and their dysfunction has been linked to diverse diseases, including diabetic nephropathy (DN). Central to proper mitochondrial function is oxidative phosphorylation (OXPHOS), coordinated by respiratory chain complexes encoded by both nuclear and mitochondrial genomes. Whether alterations in specific OXPHOS complex protein expression/activity contribute to mitochondrial dysfunction in DN remain largely unknown.

**Methods:** To assess complexome profiles, mitochondria were isolated from podocytes of 16-week-old diabetic (db/db) and nondiabetic (db/m) mice. Blue Native Gel Electrophoresis (BNE) was coupled with quantitative mass spectrometry (nano-HPLC/ESI/MS/MS) to identify known and unknown macromolecular protein complexes.

**Results:** We identified a total of 1216 mitochondrial proteins. Complexome profilingrevealed mitochondrial complex I and III to be markedly reduced in podocytes of db/db mice compared to controls. Consistent with MS results, Complex I activity was significantly reduced in podocytes of db/db mice compared to controls. Importantly, we found that the protein expression levels of Ndufb2, Ndufb3 and Ndufb8, all components of complex I, were significantly reduced in podocytes of db/db mice. We further validated

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our initial results and found that the podocyte-derived mitochondria from diabetic db/db mice displayed a markedly reduced mRNA and protein expression levels of Ndufb8. These changes are coincident with significantly decreased Complex I activity from analogously diabetic or wild type mice.

**Conclusions:** Our study uncovers a previously unrecognized role of complex I in the pathogenesis of DN. We propose that deficiencies in components of Complex I may disrupt Complex I assembly, eventually reducing mitochondrial oxidative metabolism of podocytes in diabetic kidney disease. Further genetic studies are currently underway in our laboratory to establish the value and limitations of using Ndufb8 transgenic mice in experimental models of diabetes as a model for targeting mitochondrial dysfunction in DN.

**Funding:** NIDDK Support

SA-PO406

**Hypermeglycemia and Hyperinsulinemia Increased Cell Proliferation and Regulated DNA Damage/Repair Pathways in Type II Diabetic (db/db) Mouse**

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**Background:** The mechanisms by which hyperglycemia and/or hyperinsulinemia activate cell proliferate to regulate the DNA damage/repair pathways and increase renal cell damage in diabetes remain unclear.

**Methods:** In the current study, we investigated the role of hyperglycemia and hyperinsulinemia in regulating cell survival and cell proliferation to regulate the DNA damage/repair pathways in type II diabetic (db/db) mouse.

**Results:** Significant increase in proteinum, albuminuria, creatinine in 24h urine as well as renal tissue weight was detected in db/db mice compared to wild type mice. Cell proliferation was measured by Ki67 staining and PCNA expression in kidney sections of diabetic and wild type mice. Data showed significant increase of Ki67 staining and protein expression of PCNA in kidney of diabetic mice compared to wild type mice. The activity of the transcription factor Akt (measured by phospho-Akt at Ser473) was significantly increased and associated with increased activation of mTORC1 (measured by phospho-70S6K at Thr389) in kidney cortex of db/db mice compared to wild type mice. Agl shift analysis shows reduction of Nr2 binding to OGG1 promoter in nuclear extracts of kidney homogenate from db/db mice compared to wild type mice. A portion of the DNA-protein complexes was significantly decreased in the presence of the Nr2 antibody indicating that Nr2 is indeed a component of these complexes.

**Conclusions:** In summary, our data provide a novel mechanism of increase renal cell damage through decrease binding of Nr2 to the OGG1 promoter and consequence deficiency in DNA repair that lead to accumulate DNA damage and lead to renal complications under hyperglycemia and hyperinsulinemia condition in diabetic mice.

**Funding:** Veterans Administration Support

SA-PO407

**Spleen Tyrosine Kinase Activation Promotes the Progression of Diabetic Nephropathy in the Early Stage**


**Background:** Inflammation triggered by metabolic disorder has played an important role in the pathogenesis of diabetic nephropathy (DN) in the early stage. The inflammatory cytokines binding to immunoglobulin G Fc receptors (FcRs) in the surface of cell contribute to the progression of inflammation. It was found in our previous study that there was an increased expression of FcγRs with an immunoreceptor tyrosine-based activation motif (ITAM-FcγRs) in the kidney of diabetic CRP-Tg mouse induced by streptozotocin (STZ). It was also observed that ITAM-FcγRs were increased and spleen tyrosine kinase (SytK) was activated in rat glomerular mesangial cells (GMC) cultured with high glucose. SytK is a cytoplasmic nonreceptor tyrosine kinase and plays critical role in intracellular signaling transduction of ITAM-FcγRs. It has been established that active SytK signal cascade leads to the pro-inflammatory cytokines production in antibody-dependent kidney disease. However, the role of SytK in the progression of DN remains unclear. The present study investigates the potential of SytK activation in the early stage of DN.

**Methods:** Diabetes was induced by STZ in Sprague Dawley (SD) rats for assessment of kidney injury at 2, 4, 8weeks by real-time PCR, immunohistochemistry and western blot analysis. In vitro, renal proximal tubular cells (RPTC) with or without p53 dominant negative (p53-DN) were cultured in medium containing 5.5 mM or 30 mM glucose. Apoptosis was detected by morphologic observation, TUNEL, and flow cytometric analysis. The cells were also fractioned to investigate the subcellular redistributions of Bax and cytochrome c. The expression of p53, phosphorylated-p53 and apoptosis-related proteins were examined by western blot, immunohistochemistry/immunochemistry and immunofluorescence.

**Results:** Apoptosis was detected in renal tubules within a few weeks of diabetes, which was accompanied by p53/p-p53 expression. In cultured RPTC cells, high glucose induced apoptosis and p53. In these cells, there were Bax translocation to the mitochondria and cytochrome c release. Interestingly, these changes and apoptosis were attenuate in p53-DN cells. Consistently, they were also suppressed by pifithrin-a, a pharmacological inhibitor of p53.

**Conclusions:** These results suggest that p53 may be an upstream mediator of tubular cell apoptosis during high glucose treatment and in diabetic kidney. p53 is induced under these conditions and may activate the mitochondrial pathway of apoptosis.

**Funding:** NIDDK Support, Veterans Administration Support, Government Support - Non-U.S.

SA-PO410

**Mechano-Growth Factor Regulates mTOR and Other Growth Factor Expression in Mouse Mesangial Cells, Enhancing Cell Proliferation and Extracellular Matrix Production: Implications for Diabetic Glomerulosclerosis**

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**Background:** Our study uncovers a previously unrecognized role of complex I in the pathogenesis of DN. We propose that deficiencies in components of Complex I may disrupt Complex I assembly, eventually reducing mitochondrial oxidative metabolism of podocytes in diabetic kidney disease. Further genetic studies are currently underway in our laboratory to establish the value and limitations of using Ndufb8 transgenic mice in experimental models of diabetes as a model for targeting mitochondrial dysfunction in DN.

**Funding:** NIDDK Support, Veterans Administration Support, Government Support - Non-U.S.

SA-PO408

**Smooth Muscle Specific Heavy Chain Ferritin Knockout Mice as a Model of Obesity**

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**Background:** Ferritin, consisting of heavy (H) and light (L) chain subunits, is a highly conserved ubiquitous protein that safely sequesters iron in a non-toxic form. During the course of our studies to evaluate the role of heavy chain ferritin (FH) in a model of vascular calcification in TKD, we generated a transgenic mouse using the cre-lox system with smooth muscle cell-specific deletion of FH (FHΔH). Serendipitously, we discovered the FHΔH mice gained more weight compared to control “floxed” FH mice and exhibited features resembling metabolic syndrome.

**Methods:** To characterize FHΔH mice as a model of obesity, male FHΔH mice and FH+ FH+ control mice were individually housed from 6-28 weeks of age to monitor weight, food intake, and body composition utilizing quantitative magnetic resonance (QMR) imaging. Protein analysis was performed on skeletal muscle and fat to determine expression levels of lipid signaling molecules and iron regulators. RNA analysis of inflammatory markers expressed in white fat was also performed.

**Results:** At 28 weeks old, FHΔH mice gained more weight (30.59g ± 2.02 vs. 27.72g ± 1.06 controls) during the observation period and consumed significantly more food starting at 20 weeks of age than the controls. QMR studies revealed that FHΔH mice had slightly more fat, lean and water mass compared to controls. Protein analyses of skeletal muscle and white fat revealed a loss of GLUT4 expression and iron trafficking proteins, respectively, in transgenic mice. Moreover, there was an increase in tissue iron concentration and gene expression of TNFα in the fat tissue of FHΔH mice compared to controls. Interestingly, review of publicly available microarray data sets (NCBI, GEO data set GDS3876) derived from human samples suggest a significant (~1.5 fold) increase in FH gene expression in obese individuals compared to lean controls.

**Conclusions:** Over a third of the adults in the United States are obese. Obesity predisposes individuals to other health risks, including CKD, diabetes, stroke, and cardiovascular disease. Our studies provide a novel mouse model for obesity.

**Funding:** NIDDK Support, Veterans Administration Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
of S6 kinase (phospho-S6 kinase) protein 8.7-fold. This increase in mTOR and active S6 kinase levels was associated with increased proliferation rate of MGF-S vs. MGF-EV. Meanwhile, H2-DOG uptake was suppressed 65% in MGF-EV vs. MGF-S. Type IV collagen (Col-IV) was increased 4.2-fold. 

Conclusions: MGF-S MC demonstrate increased mTOR with S6 kinase activation, consistent with their enhanced proliferation rate, while the increased VEGF and TGF beta1 expression. Overexpression of MGF in MC to mimic events in diabetic glomeruli recreates many features of high glucose-exposed MC. MGF-AS MC demonstrate a role for MGF in basal VEGF and TGF beta1 expression.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO411

High Fat and High Sucrose Diet Induce Steatohepatitis That Is Dependent on Fructokinase

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Background: High fructose intake from added sugars, which are high in Western diet, correlates with the epidemic rise in obesity, metabolic syndrome, nonalcoholic fatty liver disease, and chronic kidney disease. However, the interaction of fructose with high fat intake, which is also rich in Western diet, remains unclear. Here we tested the interaction between fructose and fat, and determined whether this was dependent on a primary enzyme in fructose metabolism, fructokinase.

Methods: Wild type mice and fructokinase knockout mouse (C57BL6J background, male) were assigned to one of three groups (n = 8-9) respectively, matching mean body weight among the groups. Mice had free access to tap water, and a low fat (11%, LFD), high fat, or high fructose diet (HFD) for 16 weeks. Urine samples were collected at 13 weeks using metabolic cages. At 15 weeks, blood was withdrawn, and tissues including kidney and liver were taken after 6 h fasting.

Results: Both wild type mice fed HFD and fructokinase knockout mice fed HFD developed with hepatic steatosis without hepatic inflammation compared to mice fed LFD. In contrast, wild type mice fed HFDHFD developed more severe hepatic steatosis and low grade inflammation and fibrosis in pathological analysis, but not in fructokinase knockout mice. Increased CD68, TNF-alpha, MCP-1, alpha-smooth muscle actin, and collagen I and TIMP1 expression were found in wild type mice fed HFDHFD. These changes were prevented in the fructokinase knockout mice. Meanwhile, there was no significant change of urinary protein and urinary NGAL, and no apparent renal pathological change among groups.

Conclusions: This study demonstrated an additive effect of high fat and high sucrose diet on the development of hepatic fat accumulation. Furthermore, the combination of sucrose with high fat diet may induce steatohepatitis. These results indicate the important role of fructose in the development of fatty liver and nonalcoholic steatohepatitis.

Funding: NIDDK Support.

SA-PO412

The Succinate Receptor 1 Contributes to Obesity-Induced Type II Diabetes and Chronic Kidney Disease

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Background: Cell stress-induced release of mitochondrial succinate and activation of its SUCNR1 receptor in the macula densa is essential for type I diabetes mellitus (T1DM)-related renal release and hypertension. Obesity-induced T2DM and Chronic Kidney Disease (CKD) are aggravated by hypertension and go with cell stress in adipose/kidney tissue and macrophages, which express SUCNR1. Here we tested the role of SUCNR1 in obesity-induced T2DM and CKD.

Methods: Wild-type (wt) and SUCNR1−/− mice were fed a low fat diet (LFD; 10%) or high (H) HF (60%). At different weeks, mice were weighed, and subjected to metabolic cages (electrolyte measurements), glucose tolerance tests (GTT). Mice were sacrificed and blood and tissues collected.

Results: Blood succinate was increased in diabetic patients versus healthy controls. Isolated adipose tissue of wt and SUCNR1−/− mice revealed increased succinate release with hypoxia or high glucose. 16 weeks LF/DF fed showed similar body, adipose tissue and kidneys weight gain for both HF groups, but liver and heart weight gain was reduced in HFD SUCNR1−/− versus wt mice. Starving glucone levels were similarly increased in both HF groups, but SUCNR1−/− mice had a better GTT response. Inflammatory signals and macrophage infiltration was higher in adipose tissue of wt than SUCNR1−/− mice. Bone marrow derived cells of SUCNR1−/− mice migrated less efficient towards chemotactic signals from diabetic/hypoxic 3T3 cells. Blood sodium and urine volumes were similarly decreased and eGFR increased in both HF groups versus LFD controls. However, only HF SUCNR1−/− mice showed albuminuria, elevated collagen IV expression, and some increase in inflammatory gene expression in the kidney.

Conclusions: SUCNR1-mediated chemotaxis of macrophages to affected adipose tissue is decreased in obesity-induced hypertrophy, contributes to obesity-induced T2DM and CKD development. If similar in humans, SUCNR1 may form a novel therapeutic target for T2DM and CKD.

Funding: Government Support - Non-U.S.

SA-PO413

Fluoxetine Disrupts E-Cadherin-Mediated Cell Adhesion and Calcium Homeostasis in Pancreatic β Cells

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Background: Major depressive disorder (MDD) is a common psychiatric illness and it affects as many as 840 million people. MDD and Type 2 diabetes (T2D) are disorders with mutual risk factors identified in prevalence study reports. Antidepressant treatment could be another critical factor affecting the bidirectional associations between MDD and T2D. Long-term use of selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed class of antidepressants, is associated with an increased risk of developing T2D.

E-cadherin mediated cell-cell adhesion has been linked to diseases such as cancer and diabetes. Loss of cell-cell adhesion in beta cells decreases insulin secretion.

Methods: Here we examine the effects of the SSR1 fluoxetine (Prozac®) on beta cell function employing MIN6 cells, a mouse beta cell line, to elucidate the underlying molecular mechanisms.

Results: We showed that fluoxetine treatment significantly reduced glucose stimulated insulin secretion (GSIS). We found that fluoxetine has no effect on the total expression of E-cadherin, but decreased the surface of E-cadherin. Moreover, fluoxetine triggered E-cadherin down-regulating in control, mainly localized in Golgi, not in endoplasmic reticulum (ER). Our immunohistochemistry showed that reduction cell surface E-cadherin is due to increased endocytosis. Moreover, ER calcium release and the activation of store-operated calcium entry (SOCE) were suppressed by fluoxetine.

Conclusions: Taken together, the results suggested that the impairment of E-cadherin and calcium homeostasis may be underlying mechanisms by which fluoxetine caused the reduction of GSIS in pancreatic beta cells.

Funding: Government Support - Non-U.S.

SA-PO414

Involvement of Ischemic Condition in the Pathophysiology of Renal Damages in Obesity-Induced Kidney Injury

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Background: We have reported hypertrophic proximal tubules in obese mice which implies an inefficient oxygen supply in this area (Obesity Int, 2012). We examined whether hypoxic condition in proximal tubules is involved the pathogenesis of obesity-induced renal injury. We also test the hypothesis that this injury can be ameliorated by molecular intervention of prolyl hydroxylase domains (PHDs), sensors for tissue oxygen levels that is a crucial molecule for tissue response to hypoxia.

Methods: Tissue hypoxic conditions were assessed by pimonidazole immunostaining. Perfused apical cilia (PTC) proximal tubules were counted using CD34 stained vessels. Tamoxifen (Tam)-inducible proximal tubules-specific PHD2 deficient mice were created by crossing PHD2−/− mice and Tam-inducible N-myf5 downstream-regulated gene-I-Cre mice on C57BL6/J backgrounds. These inducible conditional knock out (KO) mice were born with their wild-type littermates (WT) were fed a high fat diet (HFD) or a low fat diet (LFD) for 12 weeks. The expressions of PHD2 and VEGF were measured by real-time PCR and immunohistochemistry.

Results: The WT mice on HFD manifested renal histological changes, including cellular enlargement of proximal tubules and a rarefaction of PTCs, which were consistent with more hypoxic area in proximal tubules than in WT mice on LFD. Urinary albumin and NGAL excretion were higher in HFD-fed mice, indicating ischemic tissue damage in proximal tubular area. However, expression of either PHD2 or VEGF was unchanged in HFD-fed WT mice, suggesting the lack of hypoxic tissue response in HFD-fed WT. Injection of Tam to HFD-fed KO mice downregulated PHD2 in proximal tubules, increased VEGF expression, increased the number of PTCs, decreased hypoxic area, and attenuated proximal tubular damages and albuminuria.

Conclusions: Hypoxic condition due to enlarged cell with vascular rarefaction is evident in the proximal tubular area of obese mice whereas tissue reaction to hypoxic damages failed to properly compensate. The early reduction of PHD2 specifically in the proximal area may create a novel strategy against the progression process from an early stage of obesity-induced kidney injury.

SA-PO415

Herbal Mixture of Radix Puerariae and Fructus Crataegi Prevents Renal Injury in Type 2 Diabetes Via Inhibition of AKT/PI3K

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Background: It has been reported recently that radix puerariae (RP) is one of the best herbal medicines for metabolic diseases, as it has pronounced anti-oxidative effects and helps improving insulin resistance and lowering blood sugar and lipids levels. Fructus crataegi
Modulation of Akt/AS160 Phosphorylation Mediates Insulin Resistance in a Rat Model of Metabolic Syndrome

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Background: Insulin resistance is the underlying pathophysiology hallmark of metabolic syndrome (MS) which is most often associated with obesity. While adipokines and inflammatory cytokines have been incriminated in the insulin resistance of MS, the exact underlying mechanisms and signaling processes have not been defined. The current study assessed the molecular mechanisms of insulin signaling in the skeletal muscle in ZSF1 rats which have leptin receptor mutation and phenotypically manifest MS.

Methods: Obese ZSF1 rats were maintained from the 8th week and sacrificed at 24 or 32 weeks and fed on high calorie high fat diet (Purina 5008) while control rats (lean ZSF and SD) were fed normal rat chow. Body weights and water intake were monitored weekly and blood and urine samples were obtained at 8 weeks and at the time of sacrifice for determination of plasma creatinine and glucose levels. The mRNA levels of PI3K, AKT, e-SMA and collagen IV in the kidney of diabetic rats.

Results: The obese ZSF1 rats showed full blown MS with obesity, hyperlipidemia, hypertension and hyperglycemia while the lean ZSF and SD rats were normoglycemic.

Conclusions: Our results demonstrate that while GLUT4 expression in insulin sensitive tissues is decreased in obesity mediated diabetes, several intermediary steps in insulin signaling are unaltered. However the most consistent finding was reduced phospho Akt/AS160, which could be a major determinant of insulin resistance in obesity.

Funding: Private Foundation Support

SA-PO419

Murine Recombinant ACE2 Reduces Renal Fibrosis in Experimental Alport Syndrome (AS)

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Background: ACE2 is a monocarboxypeptidase in the renin angiotensin system that catalyzes the breakdown of angiotensin II (AngII) to angiotensin (1-7) (Ang1-7). We have reported that ACE2 expression and activity in kidney are reduced in experimental Alport Syndrome (AS) but the impact of this finding on disease progression has not been studied.

Methods: Accordingly, we evaluated the effects of murine recombinant ACE2 (mrACE2) treatment in Col4A3-/- mice, a model of AS characterized by proteinuria and progressive renal injury. mrACE2 (0.5 mg/kg/day) was administered from 4-7 weeks of age via osmotic mini-pump.

Results: Treatment with mrACE2 led to an increased urinary ACE2 excretion, reduced renal AngII level and a correspondingly increased Ang1-7 level in 7-week-old Col4A3-/- mice. Pathological structural changes and albuminuria in the mutant mice were both attenuated by mrACE2 administration. mrACE2 ameliorated kidney fibrosis in Col4A3-/- mice as shown by decreased expression of profibrotic genes, less accumulation of extracellular matrix proteins and inhibition of the TGF-β signaling activation. Further, the increases in proinflammatory cytokine expression, macrophage infiltration, inflammatory signaling pathway activation and heme oxygenase-1 (HO-1) level in Col4A3-/- mice were also reduced by mrACE2 treatment. Lastly, mrACE2 influenced the turnover of renal ACE2, as it suppressed the expression of TNF-α converting enzyme (TACE), a negative regulator of ACE2.

Conclusions: In summary, treatment with mrACE2 alters angiotensin peptide metabolism in the kidneys of Col4A3-/- mice and attenuates the progression of AS nephropathy.

Funding: Private Foundation Support

SA-PO416

High Protein Diet Markedly Accelerates Diabetic Nephropathy Whilst Nephrectomy Only Slightly retard the Progression in Diabetic Olfactory Rats

Anna Granovic, Karin Nelander, Gerhard Bottcher, Magnus Soderberg, Anette E. Ericsson.

Background: The high protein diet (40%, from 10 weeks of age) markedly stimulated the NBCe1 activity by 65% and 104% in OLETF rats and the patient, respectively.

Methods: A Type 2 Diabetic model was generated by feeding rats with high fat diet followed by injecting a low dose of STZ. Rats were randomly divided into five groups: normal, high fat, high fat diet plus high protein content diet (40%, from 12 weeks of age) and a pair of diabetic OLETF rats treated with high protein content diet and nephrectomy. Plasma creatinine level was lower in intact (median 3.2 µM) and nephrectomised (median 3.6 µM) diabetic rats. Using high protein content diet appears to be a straightforward method to mimic key features of human DN including progressive proteinuria and glomerular lesions.

Results: Rats treated with high protein content diet showed comparable to lean mice. Using high protein content diet appears to be a straightforward method to mimic key features of human DN including progressive proteinuria and glomerular lesions.

Conclusions: Combined prevention with RPFC may inhibit the PI3K/AKT pathway in the kidney, thereby preventing renal injury in diabetic rats.

Funding: Private Foundation Support
SA-PO420
Blockade of CDK9 and Smad3/4 Signaling Reduces Renal Fibrosis in Mice with Unilateral Ureteral Obstruction

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Background: TGF-β1/Smad signaling plays a central role in the pathogenesis of renal fibrosis. Smad3 and Smad4 are pro-fibrotic, while Smad2 is anti-fibrotic. However, these Smads form heterogeneous complexes the functions of which are poorly understood. This study investigated Smad complexes in renal fibrosis in mouse unilateral ureteric obstruction (UUO).

Methods: UUO was established in wild type mice, mice heterozygous or homozygous for Smad3 or/and Smad4 (Smad3−/−, Smad4−/−, Smad4−/−/−). sRNA was used to knock down CDK9. CDK9 activity and Smad3 c-terminal phosphorylation was inhibited by a specific CDK9 inhibitor or a Smad3 inhibitor in cultured mouse renal fibroblasts and in UUO.

Results: Smad3−/− mice exhibited substantial protection from renal fibrosis on day 7 UUO, whereas Smad2−/− or Smad4−/− mice showed only modest protection. Formation of Smad3/Smad4/CDK9 complexes was an early event following UUO in wild type mice, which involved nuclear phosphorylation of the linker regions of Smad3. Smad3 or Smad4 deficiency significantly decreased the formation of Smad4/CDK9 or Smad3/CDK9 complexes, Smad3 linker phosphorylation as well as renal fibrosis but at different degrees.

In vitro, TGF-β1 stimulation of collagen I promoter activity involved formation of Smad3/Smad4/CDK9 complexes, and over-expression of each component gave additive increases in collagen promoter activity. A CDK9 inhibitor or CDK9 shRNA significantly reduced TGF-β1-induced interaction between Smad3 and Smad4, Smad3 linker phosphorylation and fibrotic response in mouse renal fibroblasts. Co-administration of the CDK9 inhibitor and the specific Smad3 inhibitor achieved better protection from TGF-β1-induced fibrotic response in vitro and renal interstitial fibrosis in UUO.

Conclusions: Our studies suggest that the formation of Smad3/Smad4/CDK9 complex drive renal fibrosis in the UUO model. Formation of this complex represents a novel target for anti-fibrotic therapies.

Funding: Support Funding - Non-U.S.

SA-PO421
Genetic Activation of Nrf2 Signaling Protects against Chronic Kidney Disease

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Background: The Keap1/Nrf2 pathway is upregulated in kidney injury, leading to the expression of an array of cytoprotective genes with antioxidant, anti-inflammatory, and detoxifying roles. Keap1 inhibits Nrf2 by sequestering it in the cytoplasm. During oxidative/electrophilic stress, Keap1 undergoes conformational change that renders it inactive and allows Nrf2 to accumulate in the nucleus. Pharmacologic induction of the Keap1/Nrf2 pathway is thought to have therapeutic potential in chronic kidney disease (CKD).

Methods: We hypothesized that knockdown of Keap1 would increase expression of Nrf2 and that Keap1 knockdown would improve outcomes in a model of chronic kidney disease. Keap1 knockdown was achieved through genetic modification of a hypomorphic (HM) mouse model. HM mice have lower Keap1 expression and increased Nrf2 activity. We subjected HM and wild-type (WT) mice to two models of CKD: unilateral ischemia followed by 10 days of reperfusion (IR); and unilateral ureteral obstruction (UUO). Kidney injury was assessed with serum creatinine, histology, western blotting and quantitative real-time PCR (qPCR) for injury markers.

Results: Compared to WT, HM mice had increased expression of numerous Nrf2-regulated genes after injury. In IR injury, HM mice were significantly protected from developing CKD, demonstrating decreased serum creatinine and renal fibrotic lesions compared to WT mice. Furthermore, HM mice had lower levels of fibronectin, n-smooth muscle actin, and TGF-β1. Inflammation was also suppressed in HM mice, as was pathologic β-catenin signaling, which is known to play a role in CKD progression. Similar results were obtained in the UUO model.

Conclusions: Most studies on the Keap1/Nrf2 pathway examine acute kidney injury or utilize pharmacologic agents with off-target effects. Therefore, more specific study of the Keap1/Nrf2 pathway with genetic approaches is necessary to determine its therapeutic potential in chronic kidney disease (CKD).

Funding: NIDDK Support, Private Foundation Support

SA-PO422
Early and Late Treatment with PBI-4050, an Orally Active Anti-Fibrotic Agent, Reduces Fibrosis and Increases Survival of 5/6-Nephrectomized Rats


Background: PBI-4050, a first-in-class orally active compound which is currently in clinical phase IIb in CKD patients, displays anti-fibrotic activities via a novel mechanism of action. In a double-blind ascending dose (400 to 2400 mg) clinical phase I, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant side effect. The aim of this study was to investigate the effect of early (Day 21) and late (Day 84) treatment of PBI-4050 on 5/6-nephrectomized rats.

Methods: Sprague-Dawley rats were partially nephrectomized (2/3 of the left kidney) on day 0. On day 7 the right kidney was removed. Oral treatment with PBI-4050 (200 mg/ kg, once a day) or vehicle was initiated at day 21 or at day 84, following randomization based on their glomerular filtration rate (GFR) results. GFR was measured at day 21 or day 84 and assessed every 3 weeks up to day 190 (early) or day 128 (late).

Results: Early treatment with PBI-4050 resulted in a significant improvement (up to 40% relative to control) in GFR. It also significantly reduced proteinuria. Histological lesion scores of kidneys were also significantly (p<0.05) decreased in PBI-4050-treated rats (2.7 ± 1.5) compared to control (3.9 ± 1.4), as determined by HPE, PAS and Masson’s trichrome staining. Early treatment with PBI-4050 induced a significant reduction of urine N-M1 level. Furthermore, early treatment with PBI-4050 reduced the overexpression of fibrogenic (TGF-β1, collagen I and α-SMA), pro-fibrotic cytokines (IL-23p19 and IL-6), remodeling (MMP2, SPARC and fibronectin), and oxidative stress (INOS) markers. Late treatment with PBI-4050 resulted in mild improvement of GFR and semen creatinine level (reduction of 50 mmol/L) but most importantly in an increase in survival (55% non-treated versus 80% with late treatment) at day 128.

Conclusions: These results suggest that PBI-4050 offers the potential as a novel therapy for chronic kidney disease by reduction of fibrosis and may potentially improve residual kidney function in patients with end-stage renal failure.

SA-PO423
Targeting Cardiorenal Connectors Reduces Renal and Cardiac Fibrosis in Experimental Chronic Renocardiac Failure

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Background: Cardiorenal connectors (CRC) play a major role in progression of organ dysfunction in renal cardiac failure (subtotal nephrectomy (SNX)) followed by coronary ligation (CL). We hypothesized that simultaneous inhibition of all CRC would be most effective in reducing cardiorenal fibrosis and functional decline.

Methods: In rats subtotal nephrectomy was followed by coronary ligation (wk 8) [Borgartz, AJP, 2012]. In wk 11 we administered losartan (RAS), or PDTC, tempol and moldisomine (Inflammation-NO/ROS) or all of these plus metoprolol (all-CRC) until wk 16.

Results: Tubulo-interstitial (TI) fibrosis decreased in all treated groups (fig 1A). However, renal function was not significantly affected by any treatment. Systolic dysfunction stabilized in all treated groups, but declined further in vehicle-treated rats (fig 1B). Cardiac fibrosis improved in all treated groups without significant additive effect of targeting all CRC (fig 1C). TI and cardiac fibrosis correlated (fig 1D). Only all-CRC reduced MAP. Diastolic hemodynamics and ventricular and cardiomyocyte size were not affected by any treatment. Reducing TI injury and renal and cardiac CTGF mRNA expression was most effective by targeting all CRC.

Conclusions: Pharmacological targeting of cardiorenal connectors in this model of chronic renalcardiac syndrome ameliorated the severity of cardiac and renal fibrosis and prevented further decline in systolic dysfunction.

Funding: [Bongartz, AJP, 2012].

SA-PO424
Fibroblast Growth Factor 23 Is Synthesised Locally by Renal Proximal Tubular Cells and May Be Pro-Fibrotic

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Background: Physiologically, FGF23 synthesis occurs predominantly in bone and regulates mineral handling in the kidney. In Chronic Kidney Disease, circulating levels become grossly elevated and are strongly predictive of disease progression, yet changes in FGF23 are not explained by increased osteocytic synthesis. Since extra-osseous FGF23 regulates mineral handling in the kidney. In Chronic Kidney Disease, circulating levels become grossly elevated and are strongly predictive of disease progression, yet changes in FGF23 are not explained by increased osteocytic synthesis. Since extra-osseous FGF23 regulates mineral handling in the kidney.
production is observed in diseased heart and vascular tissue, and is associated with the activation of pro-apoptotic signals, the involvement of renal FGF23 synthesis and potential fibrogenic effects warranting investigation.

Methods: Kidneys were harvested from FVB mice at day 0 or after 3 or 9 days post-unilateral ureteric obstruction (UO) (n=6). Paraffin-embedded sections were stained for FGF23 and with lectins to identify specific nephron segments. Total RNA was extracted from whole kidney tissue and laser-capture microdissected glomerular and tubular regions, and analysed by qPCR. Rat renal fibroblasts were cultured with exogenous recombinant human FGF23 and stained for α-smooth muscle actin (αSMA) to assess myofibroblast differentiation.

Results: Generalised low-level FGF23 protein staining was observed in proximal tubules at day 0, with more intense focal staining at days 3 and 9 post-UO. Local FGF23 synthesis was confirmed by qPCR of whole kidney extracts, and specifically, in microdissected glomerular and tubular cells, but not glomeruli. Normalised FGF23 expression increased 11-fold in day 3 UO relative to day 0 (both p<0.01). Treatment of rat UO fibroblasts with 10ng/ml FGF23 resulted in 4-fold increase in αSMA staining over 72h, equivalent to the effect of 1ng/ml transforming growth-factor-β (both p<0.01).

Conclusions: Local renal FGF23 synthesis in proximal tubular cells is enhanced by tubulointerstitial injury and may augment myofibroblast differentiation.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO425

Quantitizing Intracellular Oxygen Tension in Kidney by Phosphorescence Lifetime Measurement

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Background: Hypoxia plays critical roles in the progression of chronic kidney disease, since intracellular reactions to hypoxia depend on intracellular oxygen (O2) tension. However, existing techniques to detect intracellular hypoxia cannot quantify O2 tension.

Methods: Phosphorescence lifetime (PL) measurement is reported to be useful to quantify O2 tension in vivo, however, most phosphorescent probes distribute extracellularly. Here we used BTPDM1, a lipophilic phosphorescent probe, to quantitate intracellular hypoxia in the kidney. We measured PL in Human Kidney 2 (HK-2) cells and murine kidney after BTPDM1 administration.

Results: We first made a calibration curve between PL and partial pressure of O2 (pO2) in HK-2 cells. Then we confirmed that BTPDM1 distributed in tubular cells in vivo. Next we measured PL of the murine kidney in normal condition, renal ischemia, hypoxemia and anemia. PL were calculated to be 1.8±0.2 μs, 4.0±0.3 μs, 2.8±0.2 μs, 2.2±0.2 μs, respectively. We also investigated chronic kidney damaged model mice at days 7 after 30 minutes unilateral ischemia-reperfusion (I/R) injury of kidney. PL of I/R injured kidney was longer than contralateral kidney (2.2±0.2 μs vs 1.8±0.1 μs). We also found an increase in pimonidazole adduct protein and a decrease in peritubular capillary density in I/R injured kidneys. We quantitated in vivo intracellular pO2 by extrapolating the calibration curve in HK-2 cells. The intracellular pO2 of normal kidney tubule was estimated to be 50mmHg, which was compatible with published value obtained by needle O2 electrode.

Conclusions: Our novel technique allowed accurate estimation of intracellular O2 tension of the normal and diseased kidney in vivo for the first time.

SA-PO426

Resveratrol Increases Expression of Heme Oxygenase-1 via Nrf2 Signaling to Ameliorate Renal Damage by Anti-Complement, Anti-Oxidative, and Anti-Apoptotic Effects in a Murine Model of Membranous Nephropathy

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Background: Idiopathic membranous nephropathy (MN) is an autoimmune-mediated glomerulonephritis and a common cause of nephrotic syndrome in adults. There are limited available treatments for MN. We assessed the efficacy of resveratrol (RSV) therapy for treatment of MN in a model of this disease.

Methods: Murine MN was experimentally induced by cationic bovine serum albumin, with phosphate-buffered saline used in control mice. MN mice were untreated or given RSV. Disease severity and pathogenesis was assessed by determination of metabolic and histological parameters, including proliferation, oxidative stress, apoptosis, production of heme oxygenase-1 (HO1) and signalling.

Results: MN mice given RSV had significantly reduced proteinuria and a marked amelioration of glomerular lesions. RSV also significantly attenuated immunofluorescent staining of C3 in the kidney. RSV treatment also reduced the production of reactive oxygen species, cell apoptosis, and upregulated heme oxygenase-1 (HO1). Inhibition of HO1 with tin protoporphyrin IX partially reversed the renoprotective effects of RSV. We show that concentration-dependent induction of HO-1 in E11 podocytes as RSV added. Nrf2 but not AMPK/1.2 protein level can be upregulated by RSV. We find that an induction of Nrf2 exists at the HO-1 promoter regions sequence #3 and #4 when RSV added. The Nrf2-specific siRNA attenuated the induction of HO1 mRNA by RSV. It suggests that increased Nrf2 at the HO1 promoter leads to elevated HO1 expression when RSV is exposed.

Conclusions: Our results show that RSV increased the expression of HO1 and ameliorated the effects of membranous nephropathy in a mouse model due to its anti-complement, anti-oxidative, and anti-apoptotic effects. RSV appears to have potential as a treatment for MN.

Funding: Government Support - Non-U.S.

SA-PO427

FVB Os/+ Mesangial Cells Exhibit Enhanced mTOR and Growth Factor Expression, Modeling the FVB Os/+ Glomerulosclerosis Mouse

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Background: We previously reported FVB Os/+ mice which exhibit rapidly progressive glomerulosclerosis beginning within the first 2 weeks after birth. Here we examine primary culture mesangial cells (MC) from FVB Os/+ mice and FVB +/+ control mice to examine the expression of FVB Os/+ MC and identify cellular mechanisms which may contribute to glomerulosclerosis (GS) in vivo. FVB Os/+ MC have excess ECM production.

Methods: Primary culture MC were studied between passages 5-12. Western analyses were performed with specific antibodies against selected proteins to examine mTOR, phospho-S6 Kinase, and growth factor expression important to excess extracellular matrix (ECM) production. GLUT1 glucose transporter expression and SOD2-doesxyglucose uptake rates were also determined. P<.05 was considered significant for statistical analyses.

Results: GLUT1 and glucose uptake rate were both increased ➥2-fold in FVB Os/+ MC compared to control MC, consistent with their increases in FVB Os/+ glomeruli. FVB Os/+ MC exhibited slowed proliferation consistent with the Os mutation. FVB Os/+ MC also had increased VEGF (1.6-fold) and TGF beta 1 (2.7-fold), which likely contribute to the excess ECM production of these cells. The increased VEGF in vitro simulates increased VEGF in FVB Os/+ glomeruli in vivo. MGF was decreased in FVB Os/+ MC (3.7-fold), mimicking increased glomerular MGF in vivo. We previously found MGF stimulates VEGF and TGFβ1 in MC. FVB Os/+ MC carry the Os mutation which impairs cell division, explaining their slow proliferation. Consistent with this, phospho-ERK1/2 was reduced 66%. In spite of increased mTOR (3.6-fold) and downstream phospho-S6 kinase (5.2-fold), the cells could not proliferate normally.

Conclusions: FVB Os/+ MC exhibit growth factor expression simulating glomerular growth factor expression in vivo in these mice. MGF expression is increased both in glomeruli in vivo and in vitro. MGF is a stimulus to VEGF and TGFβ1 expression as observed here. These growth factors are associated with excess ECM production in FVB Os/+ MC, despite suppressed Erk1/2, indicating another pathway is important to excessive ECM production.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO428

Role of Sodium-Glucose Linked Cotransporter-2 Inhibitor in the Kidneys of Salt Sensitive Hypertension

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Background: Because salt is an aggravated factor for the salt sensitive hypertensive renal injury model, SGLT2 expression may be related to the progression of renal injury due to salt sensitive hypertension. The aim of this study is to reveal the role of SGLT2 inhibitor in angiotensin II (AII) induced renal injury.

Methods: Male C57BL6 wild-type mice were divided into three groups: The Ang II group was systemically infused with Ang II for 16 days. The SGLT2 inhibitor (SGLT2-I) group was given an oral dose of the dapagliflozin SGLT2 inhibitor of 1mg/kg/daily in addition to an injection of Ang II. The control group was injected with a vehicle.

Results: In both the Ang II and the SGLT2-I groups, the degree of proteinuria, the glycemic levels in blood and the body weight were similar. Renal gene expressions of angiotensinogen and SGLT2 significantly increased in both the AII and the SGLT2-I groups compared to the control group. Renal gene expression of the angiotensinogen in the SGLT2 inhibitor group tended to be lower than that in the AII group. The degree of macrophage infiltration and urinary albumin levels tended to be lower in the SGLT2-I group than in the AII group.

Conclusions: These results suggested that SGLT2 inhibitor may attenuate the renal damage due to salt sensitive hypertension via inhibiting the activation of renal renin angiotensin system.

Funding: Government Support - Non-U.S.
SA-PO429
The Renoprotective Effect of Nuclear 1 Factor Related Factor 2 (Nrf2) Activator, Bardoxolone Methyl, in Aldosterone and High Salt-Induced Renal Injury
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Background: Activation of nuclear 1 factor related factor 2 (Nrf2) is reported to have anti-oxidant and anti-inflammatory effects. In the aldosterone (Ald) and high salt-induced renal injury model using mice, we previously reported that severe tubulointerstitial damage was provoked by oxidative stress. The aim of this study is to reveal the renoprotective effect of the Nrf2 activator in this model.

Methods: To evaluate the degree of tubulointerstitial damage using the urinary liver type fatty acid binding protein (L-FABP), known as a biomarker of the tubulointerstitial damage, we used human L-FABP chromosomal transgenic (L-FABP+) mice. Male L-FABP+ mice were divided into three groups: The Ald group received systemic aldosterone infusions via an osmotic minipump and were given 1% NaCl water for 14 days. The Ald-Nrf2 group was given Bardoxolone Methyl of the Nrf2 activator intraperitoneally at a dose of 10mg/kg daily in addition to an injection of aldosterone and salt. The control group was given only a vehicle.

Results: The gene expression of MCP-1, the gene expression of RANTES, the degree of collagen type I and III and degree of macrophage infiltration were significantly greater in the kidneys of the Ald group compared to those in the control, and renal inflammatory reaction and renal fibrosis were significantly attenuated in the Ald-Nrf2 group. The degree of renal L-L-FABP gene expression and urinary L-L-FABP levels increased in the Ald group compared to the control and decreased in the Ald-Nrf2 group.

Conclusions: The Nrf2 activator, Bardoxolone Methyl, could attenuate renal oxidative stress induced by aldosterone and high salt, and consequently, renal inflammatory reaction and the production of renal collagen were prevented. Bardoxolone Methyl may be a useful treatment for renal disease.

SA-PO430
Detection of Mesangial Tissue Transglutaminase Activity in Human Kidney Biopsy Specimens
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Background: Tissue transglutaminase (TG2) is a protein-cross-linking enzyme that plays an important role in tubulointerstitial fibrosis in animal models of chronic kidney disease and diabetic nephropathy. However, its pathologic significance in human glomerular diseases remains unclear. TG2 transforms into catalytically active TG2 through oxidative stress. The aim of this study is to reveal the role of TG2 in human glomerular diseases.

Methods: To evaluate the degree of tubulointerstitial damage using urinary liver type fatty acid binding protein (L-FABP), known as a biomarker of the tubulointerstitial damage, we used human L-FABP chromosomal transgenic (L-FABP+) mice. Male L-FABP+ mice were divided into three groups: The Ald group received systemic aldosterone infusions via an osmotic minipump and were given 1%NaCl water for 14 days. The Ald-Nrf2 group was given Bardoxolone Methyl of the Nrf2 activator intraperitoneally at a dose of 10mg/kg daily in addition to an injection of aldosterone and salt. The control group was given only a vehicle.

Results: The gene expression of MCP-1, the gene expression of RANTES, the degree of collagen type I and III and degree of macrophage infiltration were significantly greater in the kidneys of the Ald group compared to those in the control, and renal inflammatory reaction and renal fibrosis were significantly attenuated in the Ald-Nrf2 group. The degree of renal L-L-FABP gene expression and urinary L-L-FABP levels increased in the Ald group compared to the control and decreased in the Ald-Nrf2 group.

Conclusions: The Nrf2 activator, Bardoxolone Methyl, could attenuate renal oxidative stress induced by aldosterone and high salt, and consequently, renal inflammatory reaction and the production of renal collagen were prevented. Bardoxolone Methyl may be a useful treatment for renal disease.

SA-PO431
Renoprotective Effect of Xanthine Oxidoreductase Inhibitor, Topiroxostat, in Hyperuricemic-Induced Renal Injury
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Background: Hyperuricemia is known to be a risk factor of chronic kidney disease. The aim of this study is to reveal the effect of xanthine oxidoreductase inhibitor, Topiroxostat in a model of hyperuricemic renal disease provoked by adenine-containing diet.

Methods: To evaluate the degree of tubulointerstitial damage using urinary liver type fatty acid binding protein (L-FABP) known as a biomarker of the tubulointerstitial damage, we used human L-FABP chromosomal transgenic (L-FABP+) mice. Male L-FABP+ mice were divided into four groups: the adriamycin group (Ad) and the adriamycin group (Ad)) were given the diet containing each Feb (3mg/kg), Top-H (3mg/kg), Top-L (1mg/kg) in addition to adenine for another 2 weeks. Thereafter, adenine-containing diet was stopped, only each medication was continued for additional 2 weeks and the kidneys in each group were removed.

Results: Renal dysfunction, the degree of macrophage infiltration, tubulointerstitial damage and renal fibrosis were significantly attenuated in the kidneys of the Feb, the Top-L and the Top-H groups compared to those in the adriamycin group. Serum uric acid levels and renal xanthine oxidoreductase activity in the Feb, the Top-L, and the Top-H groups were significantly lower than those in the adriamycin group. Those levels in the Top-H group were significantly lower than those in the Feb group. Urinary excretion levels of L-FABP in both the Top-H and Top-L groups were significantly lower than those in both the adriamycin and Feb groups.

Conclusions: In conclusion, Topiroxostat attenuated the renal damage induced by hyperuricemia and may be a useful treatment for hyperuricemic renal damage.

Funding: Private Foundation Support

SA-PO432
Accumulation of Indoxyl Sulfate in Renal Tubular Cells Aggravates Kidney Injury in Rats with 5/6 Nephrectomy
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Background: Indoxyl sulfate (IS), a representative uricemic toxin, is detected in renal tubular cells of CKD patients and 5/6 nephrectomized rats administrated with IS. It has been suggested that the retention of IS is induced through organic anion transporters in the basolateral membrane of renal tubular epithelial cells and this retention leads to nephrotoxicity. However, the mechanism for IS accumulation in renal tubules remains unclear. To reveal the correlation between IS accumulation and renal dysfunction in 5/6 nephrectomized rats, we investigated the expression of transporters in the apical or basolateral membrane and of markers for renal injury, and a content of IS in renal tubular epithelial cells using a novel antibody against IS.

Methods: To study the serum concentration of IS, we used high-performance liquid chromatography (HPLC) and our newly developed enzyme-linked immunosorbent assay (ELISA). The rats were stained with the antibody for IS. The expression of the transporters in renal tubular cells and the markers for renal injury such as Kidney Injury Molecule-1 (KIM-1) was detected by immunohistochemistry.

Results: Serum level of IS was identified to be increased in the 5/6 nephrectomized rats compared to the normal rats by the newly ELISA. The new system could sensitively detect the low concentration of IS. The value determined by ELISA is in a good correlation with HPLC. Immunohistochemistry showed a significant IS staining in renal sections of the model rats. We found the presence of IS in hyperuricemic tubular cells, where the expression of a transporter in the apical membrane mediating IS secretion was decreased, while the expression of a transporter in the basolateral membrane was retained. KIM-1, the marker for early kidney injury, was highly expressed in some tubules, but not in the IS positive cells.

Conclusions: Our findings suggest that IS is accumulated in renal tubular cells at the later stage of renal injury due to unbalanced expression of transporters between in the apical membrane and in the basolateral membrane, and this accumulation aggravates kidney injury.

Funding: Pharmaceutical Company Support - KUREHA corporation

SA-PO433
IL-15 as a Potential New Therapeutic Treatment for Renal Fibrosis
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Background: The human epithelial cells of various tissues produce interleukin-15 (IL-15), which acts not only on immune cells, but also on epithelial cells, mainly via its anti-apoptotic action. Thus, human and mouse renal tubular epithelial cells (RPTEC) constitutively secrete IL-15. Our group recently reported that IL-15 preserves epithelial cells from human kidney tubular cells damage since IL-15 is sufficient to induce WT commitment of RPTEC. Therefore, the goal of our study is to explore the renoprotective potential of IL-15 in vitro and in vivo in renal fibrosis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Our study sought to examine if IL-15 could inhibit EMT in tubular epithelial cells and whether it could attenuate tubulointerstitial fibrosis using the unilateral ureteral obstruction model (UUO) in mice. We also analyzed IL-15 expression in various human nephropathies.

Results: IL-15 expression decreased in human renal disease and in mice during UUO (p<0.05, n=19). IL-15 treatment coupled with its soluble receptor (IL-15Rα) prevents interstitial fibrosis during UUO (10.7 ± 1.1% in control group, vs 8.2 ± 0.7% in IL-15 treated mice and 6.4 ± 0.6% in IL-15Rα treated mice, p<0.01, n=7 mice/group), quantified by Sirius Red and Western Blot, through two different mechanisms. We first found a direct inhibition of IL-15 expression in IL-15Rα treated mice (p<0.05, n=7 mice/group). IL-15 also reduced TGFβ1-induced EMT in vitro on RPTEC and tubular cell line (HK2) (p<0.05). This protective effect of IL15 acted through Snail inhibition and C-Jun activation (p<0.05). Furthermore, we found a directed accumulation of MCP1 expression in IL-15Rα treated mice (p<0.05, n=7 mice/group). IL-15 also reduced myofibroblasts (collagen I and III).

Conclusions: In conclusion, IL-15 can attenuate TGFβ1-induced EMT by acting directly through a reduction of collagen synthesis, both on myofibroblast, the main effector of fibrosis, and tubular cell. IL-15 also modulates macrophages infiltration in vivo in UUO. Therefore IL-15 could be a novel therapeutic player in renal diseases.

SA-PO434
Loss of the Vascular Class 3 Semaphorin, Semaphorin 3G, Leads to Attenuated Fibrosis and Reduced Tubular Injury by Unilateral Urinary Obstruction in Mice
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Background: Chronic kidney disease (CKD) is a large social health issue, affecting 10-16% of the adults worldwide. In advanced stage of CKD, tubulointerstitial fibrosis occurs and promotes renal failure. Although a number of cell types and secretory factors are involved in the formation of renal fibrosis, its precise mechanism is still unclear. Semaphorin 3G (Semag3G) belongs to a class 3 family of secreted semaphorin. Class 3 semaphorins binds to neuropillin receptors and plexin coreceptors, showing various biological functions in neural development, angiogenesis, immunological response, and tumorigenesis. In the kidney, Semag3G is expressed in podocytes and endothelial cells of extraglomerular blood vessels. However, its role in renal fibrosis is still unknown.

Methods: To understand the role of Semag3G in renal fibrosis, Semag3G knockout mice and control mice are subjected to unilateral ureteral obstruction (UUO).

Results: Histologically, UUO kidneys does not show obvious difference between control and Semag3G KO mice. However, although mRNA expression of Tgfβ and Smad1, a key regulator of Tgfβ-induced fibrosis, increases by UUO in controls, these increases are attenuated in Semag3G KO UUO kidneys (for Tgfβ, 55% suppression compared to controls, P<0.05). In addition, mRNA expression of Acta2 and Fibronectin, and serum BUN level tend to be reduced in Semag3G KO after UUO. Expressions of inflammatory markers does not show a consistent tendency. Interestingly, increase of a tubular injury marker, Ki-1, after UUO is largely suppressed in Semag3G KO mice (77% suppression compared to controls, P<0.03 at day9,35% suppression, P<0.01 at day7), suggesting that Semag3G KO mice are protected from tubular injury.

Conclusions: Together, these data demonstrate that endothelial Semag3G acts on adjacent tubular/interstitial cells and promotes fibrosis by UUO. Identification of the mechanism of this interaction would provide new therapeutic targets for CKD and renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO435
Leukemia Inhibitory Factor Attenuates Tubulointerstitial Fibrosis in Unilateral Ureteral Obstruction
Sebastian Alexander Poathothorn, Fabio Smitigl, Lars C. Rump, Ivo Quack. Nephrology, Medical Faculty - Heinrich Heine Univ Duesseldorf, Duesseldorf, Germany.

Background: Tubulointerstitial fibrosis is common in chronic kidney disease which is often sustained by chronic inflammation. CD4+ T-cells play an important role in immune response in kidney disease. Leukemia inhibitory factor (LIF), a member of the Interleukin 6 family, and Interleukin 6 (IL-6) play a crucial role in regulating the balance of the inflammatory immune response in kidney disease. Leukemia inhibitory factor (LIF), a member of the Interleukin 6 family, and Interleukin 6 (IL-6) play a crucial role in regulating the balance of the inflammatory immune response in kidney disease. Leukemia inhibitory factor (LIF), a member of the Interleukin 6 family, and Interleukin 6 (IL-6) play a crucial role in regulating the balance of the inflammatory immune response in kidney disease.

Methods: To understand the role of LIF in renal fibrosis, LIF receptor deficient mice were analyzed in vivo on RPTEC and tubular cell line (HK2) (p<0.05).

Results: In vivo on RPTEC and tubular cell line (HK2) (p<0.05).

Conclusions: LIF receptor deficient mice were analyzed in vivo on RPTEC and tubular cell line (HK2) (p<0.05).

Funding: Government Support - Non-U.S.

SA-PO436
Dendritic Cell-Specific Sph-1 Knockout Mice Spontaneously Develop Unique Glomerulo- and Tubulointerstitial Nephritis
Mitsuharu Watanabe,1 Keiji Hiromura,1 Yoriaki Kaneko,1 Masato Kinoshita,1 Yuki Oshiki,1 Toru Saka1,1 Hidekazu Ikuchi,1 Akito Maeshima,1 Hiroshi Ohnishi,2 Takashi Matozaki,1 Yoshisai Naoyama.1 1Dept of Medicine and Clinical Science, Gunma Univ Graduate School of Medicine, Japan; 2Dept of Laboratory Sciences, Gunma Univ Graduate School of Health Sciences, Japan; 2Div of Molecular and Cellular Signalho, Dept of Biochemistry and Molecular, Kobe Univ Graduate School of Medicine, Japan.

Background: Src homology 2 domain-containing protein tyrosine phosphatase-1 (Sph-1) is a superfamily protein tyrosine phosphatase, which is highly expressed in hematopoietic cells. We have previously reported that dendritic cell (DC)-specific Sph-1 conditional knockout mice (CKO) spontaneously developed pneumonitis and nephritis at around 40 wks of age, together with anti-id antibody response (J Immunol. 2012; 188, 5397).

Methods: To understand the role of Sph-1 in the pathogenesis of autoimmunity, we investigated the renal lesions in the CKO mice.

Results: Mice were monitored by plating Sph-1-dox mice and CD11c-Cre mice. Mice were sacrificed at 8, 20, and 40 wks or later.

Conclusions: The DC-specific ablation of Sph-1 in mice resulted in development of unique autoimmune glomerulo- and tubulointerstitial nephritis, which is distinct from typical lupus nephritis characterized by wire-loop lesions and heavy proteinuria.

Funding: Government Support - Non-U.S.

SA-PO437
TLR4 Mutant Mice Are Protected from Renal Fibrosis Following Folic Acid Injection
Jin C. Souza,1 Irina Baranova,2 Alexander V. Bocharov,2 Jonathan Street,1 Xinzhun Hu,1 Kenneth J. Wilkins,1 Peter S. T. Yuen,1 Robert A. Star,1 1Kidney Diseases Branch, NIDDK, NIH, Bethesda, MD; 2Clinical Center, NIH, Bethesda, MD.

Background: Local renal inflammation contributes to interstitial fibrosis (IF). Toll-like receptor 4 (TLR4) drives inflammation/ inflammasome and is expressed on renal epithelial cells (RECs). In the folic acid (FA) model of renal fibrosis there is an acute phase of acute tubular damage and a later phase of IF. To evaluate the role of TLR4 in renal inflammation/fibrosis, we analyzed the degree of inflammation that is dependent on TLR4 in IF models from WT or TLR4 mutant mice subjected to FA. We further compared IF following FA injection in both strains.

Methods: Primary cultures of RECs isolated from WT or TLR4 mutant mice were incubated for 20h with increasing doses of LPS. Supernatant IL-6 was measured by ELISA. Total RNA was extracted, and RTqPCR performed for IL-6, IL-1β, NLRP3, and GAPDH. Results were normalized by protein content. Exact stratified Wilcoxon test was used for differences. In vivo, FA (250 mg/kg IP) was given to 9 wk old WT or TLR4 WT or mutant mice (N=6-8/group). Day 2 BUN was used as an AKI marker. Mice with [day 2 baseline BUN] ratio above 1.5 were included. At day 14, mice were euthanized and kidneys harvested for IF by Masson trichrome stain. Changes in IF (after adjusting for day 2 log BUN) were analyzed by regression analysis.

Results: LPS dose-dependently increased IL-6 secretion in WT and TLR4 WT mice, but TLR4 mutant RECs secreted very low levels of IL-6 and IL-6 mRNA expression was 7-fold lower than WT cells. TLR4 mutant RECs expressed less NLRP3 (2-fold), and IL-1β (40-fold). Day2 log BUN was not different between the groups at day 2, and correlated with day 14 IF (p<0.01). After adjustment for day2 log BUN, TLR4 mutant mice were protected from IF at day 14 (p<0.01). Renal mRNA expression of IL-6, TNF-α and TGF-β-1 were not different between the strains at day 14.

Conclusions: In vitro, TLR4 signaling can stimulate inflammasomes and inflammatory cytokine production RECs. In vivo, although TLR4 is not required for the acute phase injury, the TLR4-mutant is protected from interstitial fibrosis, potentially via reduced sensitivity to DAMPs released after acute injury.

Funding: NIDDK Support
A New Mouse Model of Glomerular Foam Cell Accumulation in Disease

Minseob Eom, Kelly L. Hudkins, Anna Batorsky, Charles E. Alpers.1,2,3 Grazia Serino,1 Alessandra Dalla

Background: Foam cells are lipid-laden cells of monocyte/macrophage origin which have a key role in the development of atherosclerosis. Similar foam cells are found in human kidney biopsies in various diseases (e.g. tip and cellular variants of focal segmental glomerulosclerosis (FGS), diabetic nephropathy, and the interstitium in nephritic states). The pathophysiologic significance of foam cells in the kidney is poorly understood, in part due to lack of good animal models. We sought to develop a robust animal model for foam cell accumulation in the kidney to test their pathogenic significance.

Methods: Six-week old apolipoprotein E-(Apo E-)null C57BL/6 mice were divided into two groups. Group 1: Mice were gavaged daily with 1% hydroxypoly methyl cellulose with 0.1% tween 80 (HPMC-Tween) (10ml/kg) for 30 days. Group 2: Untreated age-matched controls. Each organ including kidney was harvested for histologic evaluation. Immunohistochemical stains (IHC) for Mac2 were performed to quantify the state of the monocyte/macrophage infiltration and urine analysis was calculated to compute the urine albumin-creatinine ratio (ACR) and total albumin excretion.

Results: IHC for Mac2 revealed that 83.76% of glomeruli were infiltrated by foam cells in the HPMC-Tween treated group. Most showed several foam cells in each glomerulus. Neither FSGS nor mesangioiliysis nor interstitial foam cell accumulation developed in the treated mice despite the prominent glomerular foam cells. Additionally, there was no significant difference in ACR between treated group and control group, although the treated mice revealed a trend of higher urine ACR, compared with pre-treatment urine.

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Funding: Pharmaceutical Company Support - Genzyme

Macrophages Present an Essential Source of Anti-Inflammatory Annexin A1 Signals During the Course of Acute Anti-Thy-1.1 Nephritis

Robert Labes,1 Philipp Dittert,2 Sebastian Bachmann,1 Alexander Palenge.2 1Imperial NHS Trust, London, United Kingdom; 2Imperial College London, London, United Kingdom.

Background: Macrophage subpopulations exert distinctive effects during inflammatory kidney disease and may either aggravate kidney damage or foster renal repair. The anti-inflammatory protein annexin A1 (AnnA1) has been shown to shift macrophage polarization towards the anti-inflammatory M2 phenotype. Cellular sources and regulation of intrinsic AnnA1 signals during renal inflammation remain to be elucidated.

Methods: Adult Wistar rats were injected with anti-Thy-1.1 antibody to induce mesangio proliferative glomerulonephritis and examined after 24h (initiation phase), 5d (proliferation phase), and 15d (resolution phase). Regulation of AnnA1 was studied by qPCR and immunohistochemistry. AnnA1+ cells were characterized by triple labelling

Conclusions: These experiments show that AnnA1 treatment had a protective effect on NTN phenotypes in WKY rats with a reduction in DNA cytosine methylation in both nephritic glomeruli and macrophages. These results suggest that DNA methylation may be involved in the pathogenesis of CRGN and may represent a target for intervention.

Funding: Government Support - Non-U.S.

5-Aza-2-Deoxyctidine Reduces Nephrotoxic Nephritis and DNA Cytosine Methylation in Nephritic Glomeruli and Macrophages In Vitro

Thomas Oates,1 Stephen Paul Mccado,2 Charles D. Pusey,3 H. Terence Cook,2 Enrico Pettetto.3 1Imperial NHS Trust, London, United Kingdom; 2Imperial College London, London, United Kingdom; 3MRC Clinical Sciences Centre, London, United Kingdom.

Background: Nephrotoxic nephritis (NTN) is a macrophage dependent rat model of crescentic glomerulonephritis (CRGN). We investigated whether DNA cytosine methylation could determine dis-regulation of macrophage activity and contribute to CRGN susceptibility, by examining the effect of 5-aza-2-deoxyctidine (DAC), an inhibitor of DNA methylation, on NTN phenotypes and DNA methylation in both nephritic glomeruli and bone marrow derived macrophages.

Methods: NTN was induced in male WKY rats. 6 rats were treated with intra peritoneal DAC and 6 controls with vehicle only. Treatment was given every three days prior to sacrifice at 10 days and then NTN phenotypes assayed. The effect of DAC on DNA methylation was examined by multiplexed PCR sequencing of bisulfite converted DNA in both nephritic glomeruli from NTN animals, and in WKY bone marrow derived macrophages treated in vitro with DAC.

Results: DAC treated animals had fewer glomerular crescents, less proteinuria and less glomerular macrophage infiltration (Ed1 staining).

DNA methylation in nephritic glomeruli was decreased across 200 cytosine bases in DAC treated samples compared to controls (P = 0.049, Wilcoxon rank sum test). This decrease was driven by 39 cytosines that showed demethylation in DAC treated animals. In vitro screening of macrophages showed diverse methylation changes after DAC treatment depending on length of exposure and dose.

Conclusions: These experiments show that DAC treatment had a protective effect on NTN phenotypes in WKY rats with a reduction in DNA cytosine methylation in both nephritic glomeruli and macrophages. These results suggest that DNA methylation may be involved in the pathogenesis of CRGN and may represent a target for intervention.

Funding: Government Support - Non-U.S.

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Funding: Government Support - Non-U.S.
SA-PO442 Reduced Mitochondrial Energy Production in the Kidney Induces Focal Segmental Glomerulosclerosis in Low-Birth-Weight Rats at Adulthood Toshivuki Imasawa, Kidney Center, National Hospital Organization Chiba-East Hospital, Chiba-City, Chiba, Japan.

Background: Intraglomerular hypertension has been linked with the pathogenesis of focal segmental glomerulosclerosis (FSGS) lesions in low-birth-weight (LBW)-related nephropathy, which is associated with a decreased number of nephrons. However, other mechanisms may participate in the pathogenesis of LBW-related nephropathy. Here, we investigated innate factors that could induce LBW-related nephropathy at adulthood.

Methods: LBW rats (N = 7) were obtained by intraperitoneally injecting pregnant rats with dexamethasone. Normal-weight (NBW) rats (N = 7) were obtained by saline injection. At 4 weeks of age, the left kidney was removed and used for histological analysis and quantitative proteomics (label-free LC-MS). At 9 weeks of age, the right kidney was histologically analyzed.

Results: At 4 weeks of age, glomerular numbers in LBW rats were significantly lower than NBW rats (p < 0.01). However, there were no sclerotic lesions, and neither group showed any other pathological changes at this age. At 9 weeks of age, FSGS lesions were observed in 7.4% of glomeruli in LBW rats, but only 0.5% of glomeruli had lesions in NBW rats. The pathological changes in LBW rats at 9 weeks of age resembled that of human LBW-related nephropathy. Quantitative proteomics using the renal cortex from 4-week-old rats revealed that 685 proteins decreased in LBW rats compared with NBW rats, and among them, 97 proteins (14.2%) were mitochondrial proteins. In such reduced mitochondrial proteins, 12 subunits of OXPHOS, especially complex III and IV, and 15 enzymes in TCA cycle were significantly decreased in LBW cortex (p < 0.05). Western blotting revealed the reduced expression of p-AMPK, NRF-1, and TFAM, which are master regulators of mitochondrial biogenesis, in LBW rats at 4 weeks of age.

Conclusions: This is the first report to investigate the innate suppression of mitochondrial energy production in LBW animals. We have shown that in addition to intraglomerular hypertension, innate defects to mitochondrial energy production should induce the formation of FSGS lesions in LBW-related nephropathy at adulthood.


Background: Tissue hypoxia (Hyp) is thought to influence the pathogenesis of chronic kidney disease (CKD), but direct evidence that prolonged exposure to tissue Hyp initiates or aggravates CKD is lacking. We tested this hypothesis by chronically exposing to Hyp normal rats and rats with 5/6 nephrectomy (Nx). In addition, we investigated whether such effect of Hyp would involve activation of innate immunity.

Methods: Adult male Munich-Wistar rats underwent Nx (n=30) or sham surgery (S, n=19). Seven S (Snorm) and 13 Nx (Nnorm) rats remained in normoxia, while 12 S rats (Shyp) and 17 Nx (Nhyp) were kept in a normobaric Hyp chamber (12% O2). Results at 8 weeks (BW, body weight; g; Hb, hemoglobin, g/dL; TCP, tail-cuff pressure, mmHg; Ualb/Ucr, urinary albumin/creatinine; K/BW, kidney/body weight; GSI, glomerulosclerosis index (%INT; % of cortical interstitium; M0, mitochondrial macromolecules, g/mn2; renal IL-1β (pg/g); and TLR-4 (2 × 106).

Results:

<table>
<thead>
<tr>
<th></th>
<th>Snorm</th>
<th>Shyp</th>
<th>Nnorm</th>
<th>Nhyp</th>
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<tr>
<td>BW (g)</td>
<td>307±8</td>
<td>285±6</td>
<td>280±6</td>
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<td>Hb (g/dL)</td>
<td>16.6±0.5</td>
<td>18.1±0.6</td>
<td>14.1±1.4</td>
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<td>TCP (mmHg)</td>
<td>143±2</td>
<td>139±3</td>
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<td>Ualb/Ucr (mg/g)</td>
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<td>0.4±1.3</td>
<td>3.7±0.6</td>
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<td>K/BW</td>
<td>0.5±0.0</td>
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<tr>
<td>GSI</td>
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<tr>
<td>%INT</td>
<td>0.6±0.2</td>
<td>0.1±0.1</td>
<td>8.4±1.8</td>
<td>4.6±1.2</td>
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<tr>
<td>M0 (g/mn2)</td>
<td>9.3±0.1</td>
<td>11±2</td>
<td>76±6</td>
<td>38±7</td>
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<tr>
<td>IL-1β (pg/g)</td>
<td>2.1±0.5</td>
<td>1.6±0.3</td>
<td>8.8±2.6</td>
<td>4.4±1.2</td>
</tr>
<tr>
<td>TLR-4 (106)</td>
<td>1.03±0.12</td>
<td>0.93±0.08</td>
<td>2.69±0.30</td>
<td>2.15±0.16</td>
</tr>
</tbody>
</table>

Mean ± SE, p < 0.05 vs. respective S, p < 0.05 vs respective Nor.

Exposure to Hyp increased Hb in both S and Nx, but led to no injury or elevation of the renal content of IL-1β or TLR-4 in S. Unexpectedly, Hyp attenuated IL-1β, TLR-4, M0, GSI and %INT in Nx.

Conclusions: We found no evidence that chronic Hyp initiates or worsens CKD. Chronic Hyp may be even renoprotective by unclear mechanisms, perhaps involving immune mechanisms, perhaps involving innate immunity.
Establishment of a 3-step Method to Obtain the Absolute Number of Nephrons in Mice
Xiaoqiang Chu, Jian-Kang Chen. Depts of Cellular Biology & Anatomy and Medicine, Georgia Regents Univ, Augusta, GA.

**Background:** Low nephron number is implicated in hypertension and kidney disease. Existing methods to determine nephron number have various limitations. While using the Cre reporter mice expressing membrane-Tomato/membrane-Green fluorescent protein (mT/mG) for other studies, we fortuitously noticed that the Tomato fluorescence remarkably visualized all glomeruli in the kidneys, which prompted us to establish a 3-step (Separate-Press-Count) method to obtain the exact nephron number in mice.

**Methods:** One homozygous mT/mG mouse (S232, available from the Jackson Laboratory, Catalog Number: 007576) was bred with FVB/NJ mice. This produced ~11 heterozygous pups per litter. After the pups reached 6 weeks of age, they were weighed and euthanized. Each kidney was decapsulated, weighed, and bluntedly separated into 35-45 pieces (~2 mm each) using forceps with non- serrated but blunted tips. Each piece was processed between a microscope slide with grids and a coverslip, followed by counting of each single glomerulus under a fluorescence microscope.

**Results:** The nephron number in male mice ranged from 10421 to 15577 (mean = 12977 ± 2136) for left kidney and 10374 to 15691 (mean = 13271 ± 2414) for right kidney (~36 Å) is ~2-3 orders of magnitude. Although this large difference in permeability has been established; however etv4 is also expressed in the metanephric mesenchyme. We asked what role Etv4 plays during nephrogenesis.

**Conclusions:** We have established a new simple method to count the absolute nephron number and are using it to define the minimum of nephrons per gram of body weight that can maintain the normal blood pressure and kidney function in mice.

_Funding: NIDDK Support_

SA-PO448

**New Aspects on the Difference in Permeability Between Proteins and Polysaccharides in the Glomerular Filtration Barrier**
Carl Mikael Oberg, Joseph J. Grosszek, William Henry Fissell, Bengt Rippe. Dept of Nephrology, Lund University, Lund, Sweden; Dept of Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN.

**Background:** One of the many unresolved questions regarding the permeability of the glomerular filtration barrier is the reason behind the difference in permeability between albumin and polysaccharide probe molecules such as Ficol. The difference in sieving coefficients between albumin and a Ficol molecule of the same molecular size (~36 Å) is ~2-3 orders of magnitude. Although this large difference in permeability has been attributed mainly to charge effects, we have previously shown that this would require a supraphysiologically amount of charge on the filtration barrier, being about ~10 times more than the charge on the albumin molecule (~0.02 C/m²).

**Methods:** The classic heterotrophic model by Deen, Bridges, Brenner and Myers (Deen et al, JAP Renal Physiology, 1985) was extended by introducing size distributions on the solute molecules, making them flexible in their conformation. Experimental sieving data for Ficol, both from the rat glomerulus and from precision-made nanopore membranes, were analyzed using the model. The variation in solute size was quantified in terms of the geometric standard deviation (gSD) of the solute size distribution. The (mode) solute radius was assumed to be equal to the SE-radius and the pore size distribution gSD was set to unity.

**Results:** For the glomerulus (n=7), a gSD for the Ficol size-distribution of 1.16 (± 0.01) was obtained, along with a small pore radius of 36.1 Å (± 0.5 Å) and a large pore radius of 152 Å (± 7 Å). For the nanopore membranes (n=16), a gSD of 1.24 (± 0.01) was found.

**Conclusions:** In the current study, we show, for the first time, that a variation of only ~15-17% in the size of the molecule is sufficient to explain the difference in permeability between albumin and Ficol. In addition, we show that the effects of applying a size distribution on the solute molecule are only evident when the molecular size is close to the size of the selective elements of the barrier. This is well in line with experimental data, both from the GFB and from synthetic membranes.

_Funding: Private Foundation Support, Government Support - Non-U.S._

**SA-PO449**

**Rapid MicroRNA Isothermal Amplification and Detection in Urine for Nephrotic Syndrome and Other Renal Disease Biomarker Discovery**
Kathrin Gassei, Chandramohan Ishwad, Jacqueline Ho, Abhay N. Vats. Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, PA.

**Background:** MicroRNAs play an important role in renal development and are being explored as biomarkers for several renal diseases including nephrotic syndrome (NS). However, microRNA detection assays can be expensive, laborious, and time consuming. We are developing a fast and reliable assay for microRNAs in urine and report a novel isothermal amplification method. We tested this method (called cross hybridization amplification (CHAMP)) for detection of miR-30a-5p in urine of patients with NS and control.

**Methods:** We designed two 20-25 nt primers and a probe specific for miR-30a-5p. Primers were labeled with either Biotin or Digoxigenin on the 3'-end. Synthetic miR targets were developed for miR-30a, miR30b and Let7 microRNAs. Amplification required, Bst DNA polymerase, and incubation at 65°C for 30-60 min. Assay optimization was performed on urine samples spiked with synthetic miR constructs. Amplification and detection was performed with real-time PCR; gel electrophoresis and later flow devices.

**Results:** CHAMP was able to amplify and detect miR30a-5p in 60 minutes or less. The primers / probe were specific for miR30a and did not amplify miR30b or let7 microRNA.

**Conclusions:** A novel isothermal amplification method (CHAMP) can be used for fast microRNA detection in human urine. It allowed a rapid, sensitive, and highly specific amplification and detection, which is much easier to do and cost effective than qPCR or microarray. CHAMP could detect miR-30a-5p, with sensitivity similar to qPCR, without the need for RNA isolation and could be used for biomarker discovery based on microRNA studies for NS and other renal diseases.

_Funding: Other NIH Support - NIAID_

**SA-PO450**

**Dominant Negative Etv4 Expression in Metanephric Mesenchyme Reduces Nephron Endowment: A Model of Low Nephron Number CKD**
Susanna V. Fling, Flavia G. Machado, Benjamin D. Humphreys. Brigham and Women's Hospital, Boston.

**Background:** The role of etv4 expression in the ureretic bud during kidney development has been established; however their role in the metanephric mesenchyme. We asked what role Etv4 plays during nephrogenesis.

**Methods:** To inhibit etv4 function in the metanephric mesenchyme, we crossed mice with a loxP-flanked dominant-negative etv4 (R26Lox/P:DN-Etv4) with the metastatic mesenchymal-specific six2-cre mice (Six2-TGC Cre): cre-negative littermates served as control.

**Results:** Six2cre-DN-Etv4 mice express DN-evt4 in the nephrogen progenitor population starting dpc10.5. Cre-positive mice have lower body weight and fail to thrive. At four weeks, they have reduced nephron number (24.4 ± 2.4 vs. 86.8 ± 6.9 glomeruli per section, p = 0.001). They develop kidney failure (at 4 weeks: BUN 103.8±17.8 mg/dl, LV 14.1±1.8 mg/dl, p < 0.001) and proteinuria (21.29±7.23 g Albumin/g Creatinine vs. 0.14±0.03 g Albumin/g Creatinine in urine, p = 0.05). Their kidneys show all features of chronic kidney failure proteins, glomerulosclerosis, (fibrosis) and they die at 3-5 weeks of kidney failure.

**Conclusions:** Expression of etv4 in the metanephric mesenchyme is required for normal kidney development, and expression of DN-Etv4 in the six2+ population leads to defective kidney development with reduced nephron number and progressive chronic kidney failure at 3-5 weeks of age. Titeration of DN-Etv4 expression in metanephric mesenchyme may provide a novel genetic model for low nephron endowment and progressive CKD.

_Funding: NIDDK Support_

**SA-PO451**

**NO Depletion by L-NNAME Causes Increases in Rat Glomerular Permeability In Vivo – Reversal with Tempol and L-arginine, but Not with the Potent NO-Donor DEA-NONOate**

**Background:** There is increasing evidence that the permeability of the glomerular filtration barrier (GFB) is regulated by a balance between the bioavailability of nitric oxide (NO) and the presence of reactive oxygen species (ROS). It has been postulated that normal or moderately elevated NO levels protect the GFB from permeability increases, while ROS, through reducing the bioavailability of NO, have the opposite effect.

**Methods:** In anaesthetized Wistar rats, the left ureter was cannulated for urine collection, while simultaneously blood access was achieved. To test the tentative antagonism between NO and ROS, rats were systemically infused with either L-NNAME (6 mg/kg/min), or L-NNAME together with the superoxide scavenger tempol (1 mg/kg/min), or L-NNAME together with L-arginine (290 mg/kg/min). Furthermore, we tested whether the potent NO donor, DEA-NONOate, could reverse the permeability effects of L-NNAME.

**Results:** The literature is vast and there are many possible explanations for the differences in results. Further studies are needed to understand the role of NO in the GFB.

_Funding: Private Foundation Support, Government Support - Non-U.S._
endothelin-1-induced HS expression has been associated with the development of proteinuria. We hypothesize that endothelin receptor knockout (podETRKO) mice, which showed a normal HPSE and HS expression, may protect the permeability of the GFB, whereas very high levels of NO, as predicted following systemic DEA-NONOate infusion, may actually be detrimental to the GFB.

**Methods:** Experiments utilized 12 week old humanized sickle cell mice (HSSS) and genetic controls (HBAAs) recently developed by the Tonnes’ lab. Ambrisentan (ET 

**Results:** Proteinuria and renal damage were reduced in the diabetic podocyte-specific endothelin receptor antagonist, A-182086 (ET 

**Conclusion:** These data suggest that targeting ET-1 may play an important role in the development of sickle cell nephropathy and support the use of chronic ET 

**Funding:** Other NIH Support - NIH/NHLBI (U01 HL117684-01)
choline in their drinking water. Mice with total CHOP knockout were used to test the role of CHOP in disease progression. CKD kidneys were analyzed using light microscopy and 24h total urinary protein and albumin measurements. On day 21 post-inimplantation, mice were sacrificed and PAS staining was used to evaluate renal interstitial cast formation and glomerular damage.

Results: In response to the CKD model, both CHOP-/- and wild type (WT) mice experienced significant increases in systolic and diastolic blood pressure. However, CHOP-/- mice showed significantly lower proteinuria and albuminuria. In addition, CHOP deficiency significantly decreased interstitial cast formation and glomerular damage in response to the model compared to WT.

Conclusions: CHOP deficiency resulted in a decrease in proteinuria and renal tissue damage. Along with inducing apoptosis, CHOP has been shown to interact with inflammatory pathways resulting in NF-kB activation. Further tests will evaluate the effect of CHOP deficiency on inflammatory, fibrotic and apoptotic response in our model. This study suggests that future findings could lead to the development of novel therapeutics to halt the progression of CKD.

Funding: Government Support – MOP-113384.
Funding: Government Support - Non-U.S.

SA-PO457
Caveolin-1 Is Crucial in the Pathogenesis and Progression of Light Chain Deposition Disease but Not in Alamyloidosis
Jianmin Tang. Pathology and Transitional Pathobiology, Louisiana State Univ Health Sciences Center, Shreveport, LA.

Background: In-vitro models of glomerulopathic light chains (GLCs), including light chain deposition disease (LCDD) and light chain amyloidosis (AL-Am) have provided solid platforms to study the genetics of these diseases and how initiation/progression takes place. C-fos and NF-kB have been found to be important signaling mechanisms in the initiation phase of these two disorders. The role of caveolin-1 in the initiation / progression phases was explored in this study using human and mouse caveolin-1 knockout (KO) and wild type (WT) mesangial cells (MCs).

Methods: Human and Caveolin-1 KO and WT mouse MCs were grown on dishes (2D) and Matrigel (3D), and incubated with GLCs 10 μg/ml purified from the urine of renal biopsy-proven patients with LCDD and AL-Am. Downstream effects were tested by determining whether C-fos and NF-kB cytoplasmic to nuclear migration occurred and analyzing the presence and amount of ββ fibronectin in LCDD and AL-Am.

Results: When LCDD GLCs were incubated with caveolin-1 KO cells, no C-fos or NF-kB cytoplasmic to nuclear migration occurred and there was no increase in the extracellular matrix. When WT and caveolin-1 KO MCs were incubated with AL-Am GLCs, κB cytoplasmic to nuclear migration occurred and there was no increase in the extracellular matrix production in LCDD.

Conclusions: CHOP deficiency resulted in a decrease in proteinuria and renal tissue damage. Along with inducing apoptosis, CHOP has been shown to interact with inflammatory pathways resulting in NF-kB activation. Further tests will evaluate the effect of CHOP deficiency on inflammatory, fibrotic and apoptotic response in our model. This study suggests that future findings could lead to the development of novel therapeutics to halt the progression of CKD.

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SA-PO458
Inhibition of TRPC6 Channels Protects against Renal Fibrosis
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Methods: Wildtype (WT) and TRPC6-null mice (129/SvJ) underwent unilateral ureteric obstruction (UUO) on left kidney and sham operation on contralateral kidney. Ten days after surgery, kidneys were harvested for fibrosis by trichrome staining and for measurement of mRNA expression by quantitative real-time PCR. In separate experiments, WT mice underwent UUO and received injection of TRPC6/3 inhibitor BTP2 (2 mg/kg) or saline by intraperitoneal injection for 7 days.

Results: UUO induced a >20-fold increase in mRNA for Trpc6 in UUO kidney vs contralateral sham kidney in WT mice. mRNA for collagen-1, vimentin, cTGF, TGF-β1, and matrix metalloproteinases MMP-2 and MMP-9 as well as area for fibrosis measured by trichrome staining were also markedly increased in UUO vs sham kidney. Deletion of Trpc6 resulted in less fibrosis and blunted the increase in mRNA expression of collagen-1, vimentin, cTGF, TGF-β1, MMP-2, and MMP-9 in UUO kidney relative to those in WT mice. Trpc6 deletion did not alter the basal gene expression in sham kidney. Compared to vehicle-treated mice, BTP2 treatment also markedly decreased the measured area of fibrosis and attenuated the increase in expression of fibrosis and pro-fibrotic genes markers in UUO kidney. As in results from Trpc6 deletion, inhibition of TRPC6 by BTP2 had no effect on sham kidney.

Conclusions: Activation of TRPC6 may be critical for myofibroblast transformation in fibrosis. TRPC6 may be a new potential pharmacologic target in treating renal fibrosis.

Funding: Pharmaceutical Company Support - Isis Pharmaceuticals, Inc.

SA-PO459
Histone Methyltransferase EZH2: A Novel Therapeutic Target for Renal Fibrosis
Xiaoxu Zhou, Murugavel Ponnusamy, Evelyn Tolbert, George P. Bayliss, Shougang Zhuang. Dept of Medicine, Rhode Island Hospital and Alpert Medical School, Brown Univ, Providence, RI.

Background: EZH2 (Enhancer of Zeste Homolog 2) is a histone methyltransferase that induces histone H3 lysine 27 trimethylation (H3K27me3) and functions as an oncogenic factor in many cancer types. However, its role in renal fibrogenesis remains to be explored. The purpose of this study was to determine the role of EZH2 in renal interstitial fibroblasts and development of renal fibrosis in a murine model of unilateral ureteral obstruction as well as mechanisms involved.

Results: Our results showed that EZH2 and H3K27me3 were highly expressed in the cultured renal fibroblasts from kidney tissue from mice with unilateral ureteral obstruction. Pharmacological inhibition of EZH2 with 3-deazaneplanocin A (3-DZNeP) and GSK126, or silencing of EZH2 with its specific siRNA, inhibited serum- and TGFβ1-induced activation of renal interstitial fibroblasts in vitro. Administration of 3-DZNeP attenuated the expression of extracellular matrix proteins and fibronectin in the obstructed kidney. Mechanistically, 3-DZNeP inhibited expression of type I TGFβ receptor and phosphorylation of Smad3, along with preservation of Smad7 expression. 3-DZNeP was also effective in blocking phosphorylation of the EGF and PDGFr receptors, and suppressing activation of STAT3 and ERK1/2 signaling pathways in the injured kidney. Moreover, 3-DZNeP treatment abolished injury-induced renal expression of avb6 integrin, Notch1 and Notch3. Finally, EZH2 inhibition increased expression of PTEN, a protein tyrosine phosphatase associated with dephosphorylation of multiple tyrosine kinase receptors, in the kidney after ureteral ligation.

Conclusions: This study has identified EZH2 as an important epigenetic regulator of renal fibrosis and suggested that it could be a novel target for therapeutic intervention in chronic kidney disease.

Funding: NIDDK Support

SA-PO460
Targeting PHD2 for the Treatment of Anemia and Interstitial Fibrosis in Chronic Kidney Disease

Background: Anemia is a common manifestation of chronic kidney disease (CKD) and is associated with cardiovascular disease. The predominant cause of anemia in CKD is erythropoietin (EPO) deficiency. EPO is a hormone produced primarily by adult kidneys and is essential for the production of red blood cells. It has been shown in many animal models that EPO protects the kidney against interstitial fibrosis. Prolyl hydroxylase domain protein 2 (PHD2) is an active regulator of hypoxia-inducible factors (HIFs) that regulate genes involved in cellular adaptation to reduced oxygen availability. When PHD2 is reduced, HIFα is stabilized and upregulates several genes to promote survival in low-oxygen conditions. Systemic PHD2 inactivation has been found to increase renal EPO production and stimulate red blood cell synthesis, which can improve anemia in CKD patients (Minamishima et al, Science 2010).

Results: Using antisense oligonucleotides (ASOs) designed against the PHD2 mRNA, we have demonstrated a 60% reduction of kidney PHD2 expression after 4 weeks of treatment (100 mg/kg, 50 mg/kg) compared to a saline group. In addition, we observed increases in EPO mRNA expression in the kidney interstitial fibroblasts by RT-PCR (~550-fold) and by in-situ analysis. We sought to demonstrate an improvement in anemia and renal fibrosis using our PHD2 ASO. We developed an adenine-induced mouse model of CKD that develops severe anemia and interstitial fibrosis. After simultaneous administration of the 0.2% adenine diet and the PHD2 ASO (100 mg/kg) for 12 weeks, we observed significant increases in kidney EPO mRNA (~35-fold) and plasma EPO levels (~12-fold) compared to the control ASO group. Histological analysis showed improved fibrosis based on reduced Sirius Red staining. There were also improvements in anemia based on whole blood analysis of hemoglobin and hematocrit levels.

Conclusions: These data indicate that reducing PHD2 with ASOs may be a viable option for treating CKD patients with severe anemia and renal fibrosis.

Funding: Pharmaceutical Company Support - Isis Pharmaceuticals, Inc.

SA-PO461
Fibronectin Assembly Mediates KIM-1 Induced TGFB-Dependent Kidney Fibrosis
Venkata Sabbisetti, Cuyian Xin, Sandhya Padmanabhan, Bhargavi Chandrasekar, Akinwande A. Akinfolarin, Joseph V. Bonventre. Dept of Cellular and Renal Div, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background: Cell-extracellular matrix interactions play a crucial role in kidney fibrosis. Localized activation of TGFβ is critical for exertion of its cellular effects. Kidney Injury Molecule-1 (KIM-1) is upregulated in dedifferentiated proximal tubular cells (PTECs) following kidney injury and has been shown to induce kidney fibrosis in vivo. Here, we report that KIM-1 mediates fibrosis by up-regulating the critical components of the TGFβ activation machinery including EGF and corresponding integrin receptors in vivo. Inhibition of fibronectin assembly reduces kidney fibrosis.

Methods: Full-length KIM-1 or the KIM-1 mutant was overexpressed in LLC-PK1 and HEK cell lines and fibronectin and integrin levels were evaluated. Active TGFβ was measured using a bioassay. Mice were subjected to ischemia/reperfusion injury (IRI) or...
unilateral ureteral obstruction (UUO). In the UUO model, mice were treated with fibronectin blocking peptide or control peptide to evaluate the effects of inhibition of fibronectin assembly on fibrosis.

Results: KIM-1 expressing PTECs produced significantly increased levels of fibronectin and fibronectin receptors. These increases were abrogated when phosphorytrosine-350 of KIM-1 was mutated or KIM-1 was deleted. KIM-1 expressing cells displayed higher levels of total and activated TGFβ as compared to control cells. In vivo, KIM-1 expressing tubular epithelial cells were characterized by high fibronectin staining after ischemia/reperfusion injury or UUO. Blocking fibronectin assembly with a blocking peptide decreased fibrosis in the UUO model.

Conclusions: KIM-1 induced localized activation of TGFβthrough up-regulation of TGFβI, fibronectin and integrin receptors. Blocking fibronectin assembly reduced fibrosis in response to UUO in vivo. This mechanism can contribute to the fibrosis associated with chronic kidney disease. Blocking fibronectin assembly may be therapeutically beneficial to prevent or reduce kidney fibrosis.

Funding: NIDDK Support

SA-PO462

Complement Modulation by C1-Inhibitor Hampered Pericyte (PC) to Myofibroblasts Trans-Differentiation (TDF) and Vascular Rarefaction in Ischemia/Reperfusion (I/R) Injury Giuseppe Castellano,1 Rossana Franzin,1 Chiara Divella,1 Alessandra Stasi,1 Angelica Intini,1 Margherita Gigante,1 Marco Fiorentino,1 G. Lucarelli,1 M. Battaglia,1 Giuseppe Grandaliano,1 Loreto Gesualdi,1 Nephrology and Urology Unit, Univ of Bari,2 Dept Medical and Surgical Science, Univ of Foggia, Italy.

Background: Preservation of endothelium-Pericyte (PC) interaction is critical to counteract renal fibrosis during chronic kidney disease; no data are available on PC involvement in AKI. We investigated whether Complement might modulate PC activation in I/R.

Methods: Ten pigs underwent to 30 min of renal warm I, followed by 24h of R. Five pigs were treated with C1-Inhibitor (C1-Inh, 500U/Kg). Biopsies were analyzed by IHC and IF for PDGFRβ, Caspase3 and aSMA. FACS, Acc-VIP and IF were performed on human PC (PDGFRβ) cells stimulated with C5a (1x10^−5 M) for 24h in vitro.

Results: I/R injury-induced PC to myofibroblasts TDF by reducing PDGFRβ without PC apoptosis (PDGFRβ/ Caspase3) in vivo. TDF was accompanied by a significant decrease in capillary lumens (Fig1 A %T0:11.3 ±2.1; T24:3.9 ±2.3; p<0.05) and aSMA up regulation (Fig1B). C1-Inh preserved PDGFRβ expression in PC and restored peritubular capillary area (T24C1-Inh: 12.06 ±3.5 vs T24). In accordance, C5a induced PC proliferation and Collagen I (T24C1-Inh: 12.06 ±3.5 vs T24). In accordance, C5a induced PC proliferation and Collagen I (T24C1-Inh: 12.06 ±3.5 vs T24). In accordance, C5a induced PC proliferation and Collagen I (T24C1-Inh: 12.06 ±3.5 vs T24).

Conclusions: Complement might contribute to PC to Myofibroblasts TDF in I/R injury, leading to vascular rarefaction and renal fibrosis. C1-Inh may be an effective strategy to prevent kidney development in transplanted kidney.

SA-PO463

Establishment of a Novel Mouse Strain to Trace Erythropoietin Producing Cells at Desired Time Points Keiichi Kaneke, Motoko Yanagita. Nephrology, Kyoto Univ, Kyoto, Japan.

Background: We previously reported that resident fibroblasts including Erythropoietin (Epo) producing cells were labeled with melanin proteoglycan and transdifferentiated into myofibroblasts during fibrosis with concomitant loss of Epo production. However, the previous method could not distinguish between Epo-producing cells and other resident fibroblasts and the behavior of Epo-producing cells remains unclear. Recently, Epo-Cre transare generated which enabled the lineage tracing of Epo-producing cells.

Results: Epo-Cre(WT) labeled cells were located in the interstitium of the cortical and corticomedullary region of the kidney, and the numbers were increased with the induction of anemia. Epo-Cre(KO) labeled cells expressed PDGFRβ and CD73, suggesting that Epo-Cre(KO) labeled cells are responsible for the production and deposition of the extracellular matrix, the origin of activated fibroblasts mediating renal fibrosis remains debatable. Recent studies have shown bone marrow-derived fibroblasts contributed significantly to the pathogenesis of renal fibrosis. We have previously shown that CXCL16 plays a critical role in recruiting bone marrow-derived fibroblasts into kidney. However, the signaling mechanisms are not known. In the present study, we examined the role of CXCL16 γ (PI3Kγ) in the recruitment of bone marrow-derived fibroblasts and development of renal fibrosis.

Conclusions: We generated a novel mouse strain and succeeded in labeling Epo-producing cells at desired time points. We demonstrated that Epo-producing cells transdifferentiated into myofibroblasts and were increased in fibrotic kidney. We aim to elucidate the mechanism of injury and repair of Epo-producing cells with this strain, Epo-Cre(WT) mice.

SA-PO464

Role of PI3K Kinase γ in Recruitment of Bone Marrow-Derived Fibroblasts and Development of Renal Fibrosis Yumuo Wu, Hua Liang, William E. Mitch, Yanlin Wang. Medicine, Baylor College of Medicine, Houston, TX.

Background: Renal fibrosis is a profound pathological feature of chronic kidney disease (CKD) leading to progressive loss of renal function. Although activated fibroblasts are responsible for the production and deposition of the extracellular matrix, the origin of activated fibroblasts mediating renal fibrosis remains debated. Recent studies have shown bone marrow-derived fibroblasts contributed significantly to the pathogenesis of renal fibrosis. We have previously shown that CXCL16 plays a critical role in recruiting bone marrow-derived fibroblasts into kidney. However, the signaling mechanisms are not known. In the present study, we examined the role of PI3K kinase γ (PI3Kγ) in the recruitment of bone marrow-derived fibroblasts and development of renal fibrosis.

Methods: We examined the role of PI3Kγ in the recruitment of bone marrow-derived fibroblasts and the development of fibrosis using a mouse model of folic acid-induced nephropathy in wild-type (WT) and PI3Kγ-knockout (KO) mice in vivo and migration of cultured mouse monocyte treated with CXCL16 in vitro.

Results: Compared with WT mice, PI3Kγ-KO mice exhibited significant preservation of kidney function as measured by serum urea nitrogen and displayed significantly fewer bone marrow-derived fibroblasts dual positive for CD45 and PDGFRβ in the kidney 2 weeks after folic acid cardinal treatment. Furthermore, PI3Kγ-KO mice exhibited fewer α-smooth muscle actin (α-SMA) positive monocytes and expressed less α-SMA protein in the kidney following folic acid treatment. Consistent with these findings, PI3Kγ-deficiency significantly reduced total collagen deposition and suppressed expression of extracellular matrix proteins (collagen 1 and fibronectin). In cultured mouse monocytes, CXCL16 activated PI3Kγ and induced the transwell migration, which was abolished in the absence of PI3Kγ.

Conclusions: These data indicate that PI3Kγ plays a pivotal role in recruiting bone marrow-derived fibroblasts into the kidney and developing renal fibrosis. Inhibition of PI3Kγ signaling may represent a novel therapeutic strategy for chronic kidney disease.

Funding: NIDDK Support

SA-PO465

Inhibition of K-Ras prior to Induction of Acute Kidney Reduces Long-Term Progression to Chronic Kidney Disease in a Murine Model of Aristolochic Acid Nephropathy Sujit Kumar Saha, Bruce M. Hendry, Claire C. Sharpe. Dept of Renal Sciences, King’s College London, London, United Kingdom.

Background: Acute kidney injury (AKI) is recognised to be an early harbinger of chronic kidney disease (CKD). We have previously shown that K-Ras expression and activation are up-regulated in renal fibrosis and reducing K-Ras expression can prevent scarring. In this study our aim was to test whether transiently reducing K-Ras expression in the peri-AKI period can reduce progression to CKD.

Methods: CD1 mice received i.p. injections of either 3.5mg/kg Aristolochic Acid (AA) or normal saline on Day 1 and on Day 5. A treatment group were also given a single

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

730A
subcutaneous injection of 100mg/kg of mouse K-Ras antisense oligonucleotide (ASO) 2 days prior to the first AA injection. A vehicle group was given a subcutaneous injection of saline 2 days prior to the first AA injection. Renal function at multiple time points was assessed through a blood urea nitrogen (BUN) assay. The degree of fibrosis was ascertained through Picrosirius Red (PSR) and Masson Trichrome (MT) staining to quantify collagen deposition. The expression of K-Ras was determined by Q-PCR.

Results: CD1 mice given AA suffered an AKI with a 4.6 fold rise in BUN at Day 12 that returned to baseline by Day 30. However by Day 80, the AA mice had a 57% higher BUN than control mice, demonstrating later onset CKD. AA mice treated with mouse K-Ras ASO pre-AKI suffered a similar AKI but BUN at Day 80 was 48% lower than untreated AA mice and was comparable with healthy controls. PSR and MT staining demonstrated a 5 fold increase in collagen deposition by Day 80 in AA mice which was reduced by 30% in ASO-treated animals. K-Ras expression was consistently unregulated in the untreated AA mice throughout the chronic phase but the transient treatment with ASO prior to the acute injury resulted in normalisation of K-Ras mRNA by Day 80.

Conclusions: Transiently reducing K-Ras expression in the peri-AKI period in a murine model of aristolochic acid nephropathy reduces downstream fibrosis and prevents the decline in renal secretory function. Targeting K-Ras may provide a future therapeutic option for preventing renal fibrosis and CKD following AKI.

SA-PO466
Non-Osmotic Sodium Storage Affects Glomerular Endothelial Cell Permeability
Rik He Olde Engberink,1 Peter Ochodnicky,2 Simon C. Satchell,2 Ed van Bavel,1 Liffert Vogt.1

Objective: The objective of this study is to investigate the interplay between Na+ and HS-GAGs and their effects on glomerular permeability.

Methods: Human glomerular endothelial cell (GEnCi) permeability to macromolecules was tested by measuring FITC-labeled albumin passage. Electrical resistance of a GEnCi monolayer, reflecting ESL Na+ content, was assessed with the ECIS8 system at 4000 Hz. We studied the expression of gene coding enzymes involved in heparan sulfate (HS-GAGs) in the endothelial surface layer (ESL) is of interest. The objective of this study is to investigate the interplay between Na+ and HS-GAGs and their effects on glomerular permeability.

Background: High dietary NaCl intake may affect glomerular permeability via pressure effects or via direct effects. In this respect, the Na+ buffering capacity of heparan sulfate glycosaminoglycans (HS-GAGs) in the endothelial surface layer (ESL) is of interest. The objective of this study is to investigate the interplay between Na+ and HS-GAGs and their effects on glomerular permeability.

Methods: Human glomerular endothelial cell (GEnCi) permeability to macromolecules was tested by measuring FITC-labeled albumin passage. Electrical resistance of a GEnCi monolayer, reflecting ESL Na+ content, was assessed with the ECIS8 system at 4000 Hz. We studied the expression of gene coding enzymes involved in heparan sulfate (HS-GAGs) in the endothelial surface layer (ESL) is of interest. The objective of this study is to investigate the interplay between Na+ and HS-GAGs and their effects on glomerular permeability.

Results: Relative to 125 mM, EXT-1 and EXT-2 expression was higher after stimulation with 150 mM NaCl while CHSY expression remained unchanged (Fig A). Albumin permeability decreased after 2 and 5-day stimulation with 150 and 175 mM NaCl (Fig B). ECIS experiments showed NaCl addition contributed to a concentration-dependent decrease in resistance (Fig C). NaCl did not alter resistance in the absence of cells. Heparanase increased resistance when added to 125 and 150 mM NaCl (Fig D). Mannitol did not alter permeability or resistance.

Conclusions: High NaCl stimulates HS-GAG synthesis of the glomerular endothelium, which may facilitate more Na+ binding. Subsequent higher ESL Na+ content may seal the glomerular barrier as suggested by both lower permeability and lower resistance.

SA-PO468
Centrality of Bone Marrow-Derived Fibroblasts in Magnetic Resonance Imaging Contrast-Induced Systemic Fibrosis
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Objective: So-called “nephrogenic” systemic fibrosis is a ghastly sclerotic condition that occurs only in conditions of low renal function (acute kidney injury or severe chronic kidney disease) and gadolinium–based contrast exposure. Nothing is known about the pathobiology.

Methods: Experiments were designed to test if bone marrow from magnetic resonance imaging contrast–treated donors is stimulated to induce fibrosis, and to what degree these cells can be primed to home to affected organs. Male Fisher 344 rats that express human placental alkaline phosphatase (hPAP) were divided into two groups; one served as control, the other treated with pharmacological-grade gadodiamide (Omniscan, General Electric) 2.5 mol/kg IV daily, aiming for 20 doses over 4 weeks or evidence of systemic fibrosis. Rats with 5/6 nephrectomies were lethally–irradiated (900 Rad) followed by salvage bone marrow transplant from the control or contrast–treated donors. After an engraftment period, bone marrow recipients were divided into control and contrast–treated groups. The recipients of marrow from contrast–treated donors is stimulated to induce fibrosis, and to what degree these cells can be primed to home to affected organs. Male Fisher 344 rats that express human placental alkaline phosphatase (hPAP) were divided into two groups; one served as control, the other treated with pharmacological-grade gadodiamide (Omniscan, General Electric) 2.5 mol/kg IV daily, aiming for 20 doses over 4 weeks or evidence of systemic fibrosis. Rats with 5/6 nephrectomies were lethally–irradiated (900 Rad) followed by salvage bone marrow transplant from the control or contrast–treated donors. After an engraftment period, bone marrow recipients were divided into control and contrast–treated groups. The recipients of marrow from contrast–treated donors is stimulated to induce fibrosis, and to what degree these cells can be primed to home to affected organs. Male Fisher 344 rats that express human placental alkaline phosphatase (hPAP) were divided into two groups; one served as control, the other treated with pharmacological-grade gadodiamide (Omniscan, General Electric) 2.5 mol/kg IV daily, aiming for 20 doses over 4 weeks or evidence of systemic fibrosis. Rats with 5/6 nephrectomies were lethally–irradiated (900 Rad) followed by salvage bone marrow transplant from the control or contrast–treated donors.

Results: Regardless of bone marrow source, contrast–treated recipients demonstrated severe skin fibrosis. Fibronectin was similarly increased by immunofluorescence and immunoblot, but a synergistic effect evident in recipients of contrast–treated animals. The fibroblast precursor (“fibrocyte”) markers, CD45RO and procollagen I, were increased in the contrast–treated recipients. Recipients of marrow from contrast–treated donors demonstrated greater dermal CD34 without histologic evidence of fibrosis.

Conclusions: Bone marrow from contrast–treated animals did not induce systemic fibrosis, therefore target organs (such as the skin) appear central to the process. However, given the synergistic effect, “primed” fibroblast precursors do have an increased affinity for diseased lesions. Clinically, this may explain why repeat administrations of gadolinium–based contrast correlate with chronicity.

Funding: NIDDK Support, Veterans Administration Support

Poster/Saturday

SA-PO469
SOCS2 Plays No Major Role in the Mouse Remnant Kidney Model of Fibrosis
Yael Segel,1 Muhamed Assadi,2 Ralph Rabkin,3 Daniel Landau,2 Medicine and Immunology, 1Gevaert Univ, Beer Sheva, Israel; 2Research Inst, Veterans Administration Hospital, Palo Alto, CA; 3Pediatrics B, Schneider Children’s Medical Center, Petach Tikva, Israel.

Background: SOCS2, a key negative regulator of GH stimulated JAK/STAT5 signaling, is overexpressed in muscle, bone and liver of uremic rats and is presumably a cause of uremic GH resistance and growth retardation. SOCS2 deficient mice are GH sensitive, exhibit gigantism and accumulate collagen in skin, trachea and lungs (Reiser K et al, AJP 2004). SOCS2/GH overexpression in mice causes renal fibrosis, we tested whether SOCS2 deletion, by decreasing GH sensitivity, accelerates remnant kidney fibrosis.

Conclusions: No difference in renal fibrosis was seen between SOCS2+/- and SOCS2-/- mice at 80 days post surgery. This suggests that SOCS2 plays no major role in renal fibrosis.

Funding: NIDDK Support, Veterans Administration Support
Methods: Four-week-old SOCS2 deficient mice (high growth - HG strain) and normal wild-type (N) underwent 5/6 nephrectomy (CRF) or sham operation (SO), forming 4 groups: SO-N, SO-HG, CRF-N, CRF-HG. Mice were sacrificed after 3 weeks. IP bovine GH was given 30 min before sacrifice.

Results: Weight gain was reduced significantly in CRF-N versus SO-N. In contrast, growth rate was similar in SO-HG versus both CRF-N and SO-N. Kidney SOCS2 mRNA, absent in HG mice, was significantly increased in CRF-N vs SO-N. The degree of renal insufficiency was similar in CRF-N and CRF-HG mice. TGF-β1 and type IV collagen mRNA levels were increased to the same extent in SO-HG, CRF-HG and CRF-N vs SO-N. Renal GH receptor mRNA levels were decreased in both CRF groups. GH stimulated STAT5 phosphorylation increased in SO-HG vs SO-N, decreased in CRF-N vs SO-N and increased in CRF-HG vs CRF-N. IL6, SOCS3 mRNA and phospho-STAT3 levels increased similarly in both CRF groups vs SO controls.

Conclusions: STAT5 signaling in depressed remnants of kidney CRF-N mice is but is increased in non-uremic and uremic SOCS2 deficient mutants. Levels of fibrosis-related genes rose similarly in CRF-HG and CRF-N, despite absence of SOCS2 expression in CRF-HG CRF-N mice. This suggests that SOCS2 does not play a central role in remnant kidney fibrosis. On the other hand, IL6 and its mediators phospho-STAT3 and SOCS3, were elevated in CRF-HG and CRF-N mice suggesting that inflammation may play a role in remnant kidney fibrosis.

Funding: Veterans Administration Support, Government Support - Non-U.S.

SA-PO470

β-arrestin2, Downstream of Angiotensin II Type I Receptor Biased Signaling Pathway, Plays an Important Role in Renal Fibrosis

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Background: Expect G protein signaling pathway, it is now considered that there is also a β-arrestin pathway in the downstream of G protein-coupled receptors (GPCRs); angiotensin II type 1 receptor (AT1R) belongs to GPCRs and angiotensin II (AngII) is a bimodal stimulus with G protein pathway and β-arrestin pathway; it is important to know which downstream pathway involving in AngII-AT1R-induced renal fibrosis. In this study, we used β-arrestin biased agonist SII ([1-19, 4, β-ile]-angiotensin II) to study β-arrestin pathway in renal fibrosis.

Methods: The model of unilateral ureteral obstruction (UUO) was used in vivo, and rat kidney fibroblast cell line (NRK-49F) was treated with SII in vitro.

Results: 1) SII induced the binding of β-arrestin2 with AT1R, not β-arrestin1. 2) SII increased the synthesis of collagen I and fibronectin in NRK-49F. Transfection of β-arrestin2 siRNA abolished the effect of SII on the accumulation of ECM. Overexpression of β-arrestin2 inhibited SII-induced ERK1/2 phosphorylation. Overexpression of β-arrestin2 siRNA abolished the effect of SII on the accumulation of ECM. Overexpression of β-arrestin2 in NRK-49F decreased TGF-β1-induced ERK phosphorylation. Overexpression of β-arrestin2 enhanced SII-induced ERK1/2 phosphorylation. 5) The mRNA and protein levels of β-arrestin2 were significantly upregulated in the UUO model.

Conclusions: Our results suggested that AT1R downstream β-arrestin2 pathway, not β-arrestin1, might play a key role in renal fibrosis by forming complexes of β-arrestin2 and AT1R, inducing ERK1/2 phosphorylation and increasing ECM accumulation.

Funding: Government Support - Non-U.S.

SA-PO471

Deletion of ATR, a Master Molecule of DNA Damage Response, in the Proximal Tubule Exacerbates Kidney Injury and Inhibits Fibrosis

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Background: Impaired response of cells to DNA damage can cause cellular senescence. We have previously implicated the DNA damage response of renal proximal tubule cell (RPTC) in progressive kidney injury and fibrosis. The purpose of this study was to investigate the role of Ataxia telangiectasia and Rad3-related (ATR), a master molecule of the DNA damage checkpoint, in kidney injury and fibrosis.

Methods: RPTC-specific conditional ATR knockout (ATR−/−) mice were generated by crossing ATR floxed (ATR+/−) mice, ATR−/− mice and tamoxifen-inducible (SCL34a1-CreERT2) mice. We evaluated the role of ATR in susceptibility to cisplatin nephrotoxicity, unilateral ureteral obstruction (UUO) and renal ischemia/reperfusion injury (IRI).

Results: Four days after cisplatin injection, ATR−/− mice had increased kidney histological damage, increased Kidney Injury Molecule-1 (KIM-1) expression and decreased renal function compared with wild-type mice. Within the first 5 days, 34% of ATR−/− mice died, while no WT mice died. Increased DNA damage and the number of apoptotic cells were also found in ATR−/− mice. At 7 days after UUO, when compared with wild-type mice, ATR−/− mice exhibited increased kidney histological damage, KIM-1 expression, DNA damage markers, and number of apoptotic cells.

Conclusions: ATR activation in the RPTC represents a protective response in acute and chronic kidney disease of various etiologies.

Funding: NIDDK Support

SA-PO472

Role of Heparanase in Renal Epithelial-Mesenchymal Transition Induced by Ischemia/Reperfusion

Valentina Masola,1 Gianluigi Zaza,1 Giovanni Gambaro,2 Maurizio Onisto,1 Gloria Bellin,1 Gisella Vischini,1 Iyad Khamaysi,4 Antonio Lupo,1 Israel Vlodavsky,3 Zaid Abbasis,1 Renal Unit, Dept of Medicine, Verona, Italy; 2Columbus-Gemelli Hospital Catholic Univ, Rome, Italy; 3Univ of Padova, Padova, Italy; 4Rambam Medical Center, Israel; 2Technion, Israel.

Background: Ischemia/reperfusion (IR) activates epithelial-mesenchymal transition (EMT) of tubular cells, thus leading to organ fibrosis. Heparanase (HPSE) controls the EMT induced by FGF2 and TGFβ. The aim of this study was to evaluate whether HPSE modulates the EMT induced by IR.

Methods: Tubular cells (HK-2) were stably silenced for HPSE were subjected to 24h of hypoxia and 24h of reoxygenation. The cells were also treated with SST0001 (Sigma-Tau Research Switzerland SA), an inhibitor of HPSE. The IR injury has been reproduced in vivo by clamping the renal arteries for 30 min in transgenic mice over-expressing HPSE (HPSE-tg) and their wt mice. Mice were sacrificed after 48 and 72 h. Gene and protein immunoactivity of EMT markers (α-SMA, VIM, FN and TGFβ) were evaluated by real-time PCR, WB and IIF; histology was assessed by PAS staining.

Results: In vitro, IR increased the expression of EMT-markers in wt tubular cells but not in HPSE-silenced cells. Similarly, the inhibition of HPSE with SST0001 (Sigma-Tau Research Switzerland SA) in wt cells prevented the development of IR-induced EMT. In vivo, FR induced acute tubular necrosis, which was more profound in HPSE-tg than their wt animals. In wt mice IR injury increased glomerular and tubular HPSE expression, but did not induce the EMT-markers. In contrast, in FR HPSE-tg mice remarkably induced the expression of EMT-markers already after 72h.

Conclusions: HPSE is a crucial factor for the development of EMT induced by IR. HPSE inhibition may therefore constitute a possible therapeutic approach for the prevention of fibrosis in organ transplantation.

Funding: Government Support - Non-U.S.

SA-PO473

Hydrogen Sulfide Deficiency in the Kidney and Brain in Aging Mice

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Background: Hydrogen sulfide (H2S) is constitutively synthesized by cystathionine β-lyase (CSE) and cystathionine β-synthase (CBS). It regulates GFR and tubular transport in the kidney and NMDA receptors in the brain. H2S activates AMPK to inhibit mTORC1 and abrogate matrix protein increment in high glucose treated renal cells (Lee, JBC, 2012). Since mTORC1 is implicated in aging, we surveyed the status of H2S relative to mTORC1 in organs of aging mice.

Methods: C57B6 mice, immunoblotting, H2S generation and content assays, histopathology, cell culture.

Results: The renal and cerebral CSE and CBS expression, H2S content and generation were reduced in old mice (26-32 mos old, n=6 mice) compared to young mice (4-6 mos old, n=6 mice); such changes were not seen in the heart or the skeletal muscle. Old mice showed increased renal collagens I, III, fibronectin, parenchymal fibrosis, albinumimia, and rose in serum cystatin C. Signaling analysis showed that aging was associated with renal and cerebral activation of Akt, reduced phosphorylation of AMPK, and activation of mTORC1 manifest as increase in the phosphorylation of p70S6 kinase and 4E-BP1. Since insulin has been implicated in the aging process, we examined insulin regulation of CSE and CBS in renal proximal tubular epithelial (MCT) cells; insulin rapidly reduced CSE and CBS expression and decreased H2S generation. Insulin also promoted the synthesis of fibronerin matrix protein in MCT cells.

Conclusions: Our data show for the first time that the aging kidney and cerebrum share similar changes in H2S metabolism associated with reduced AMPK activity leading

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Underline represents presenting author.
to mTORC1 activation; these pathways could be related to age related changes including fibrosis. Insulin may mediate reduction in CBS, CSE and H2S and contribute to matrix accumulation in the aging kidney. Funding: Other NIH Support - NIA, Veterans Administration Support

SA-PO474

The Role of Ergothioneine/OCTN1 in CKD

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Background: Chronic kidney disease (CKD) is a strong risk factor for end stage kidney disease, and closely complicates with other organ damages. Organic cation transporter 1 (OCTN1) is known as a specific transporter for ergothioneine (ERGO). ERGO is reported to have a strong antioxidative effect. We hypothesized that OCTN1 function and the reduction of ERGO were closely related to the progression of CKD.

Methods: To evaluate the effects of OCTN1 function in CKD, everted sac method was used in CKD model or control mice. Furthermore, the pathological changes and oxidative stress in the kidney of OCTN1−/− or OCTN1+/- were evaluated in the CKD model mice. Moreover, the amount of ERGO in red blood cells of was measured in CKD patients.

Results: The uptake of ERGO in everted sac significantly decreased in CKD mice compared to control mice. Interstitial fibrosis, that evaluated by azan stain, sirius red stain, and the concentration of ERGO in red blood cells decreased accompanied with CKD stage. Insulin may mediate reduction in CBS, CSE and H2S and contribute to matrix accumulation and progression of kidney injury. Funding: Other NIH Support - 1 F32 DK104475-0

SA-PO477

Delayed Administration of Suramin Attenuates Peritoneal Fibrosis in Rats

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Background: Peritoneal fibrosis is one of the most serious complications in patients with peritoneal dialysis (PD) and lacks effective treatments. Our recent study showed that treatment with suramin, a compound that inhibits the interaction of multiple cytokines and growth factors with their receptors, attenuated the development of peritoneal fibrosis in a model of peritoneal fibrosis induced by chlorhexidine gluconate (CG). In the current study, we further assessed the therapeutic effect of suramin on the progression of peritoneal fibrosis in this model.

Methods: Rats were given a daily intraperitoneal injection of chlorhexidine gluconate (CG) for 3 weeks to induce peritoneal fibrosis followed by weekly administration of suramin at 20mg/kg for an additional one or two weeks before kidneys were harvested.

Results: Delayed administration of suramin attenuated peritoneal membrane thickening and collagen fibril deposition occurred after CG exposure. Suramin was also effective in reducing CG-induced expression of a-smooth muscle actin, fibronectin and collagen I. Therefore, peritoneal mesothelial cells treated in increased phosphorylation of Smad-3, a prominent mediator in transforming growth factor-β signaling, and epithelial growth factor receptor (EGFR), a key tyrosine kinase receptor associated with peritoneal fibrosis; suramin treatment blocked their phosphorylation. Similarly, suramin reduced CG-induced phosphorylation of transducer and activator of transcription-3 (STAT3) and extracellular signal-regulated kinase 1 and 2 (ERK1/2), two molecules that mediate profibrotic signal transduction. Moreover, delayed application of suramin suppressed CG-induced expression of several inflammatory cytokines in fibrotic peritoneum.

Conclusions: Our results indicate that suramin treatment inhibits the progression of peritoneal fibrosis via a mechanism involved in suppression of TGF-β1 and EGFR signaling pathways, and suggest that suramin holds a therapeutic potential for treatment of peritoneal fibrosis.

SA-PO478

MDM2 Mediates Tubulointerstitial Fibrosis and Fibroblasts Activation via p53-Independent Pathway

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Background: MDM2 is an E3 ubiquitin ligase which plays essential roles in the classic MDM2-p53 pathway, is involved in fibroblast activation in an ubiquitination context-dependent manner, was reduced in cultured fibroblast treated with TGF-b1 which could be reversed by either genetic deletion of MDM2 or ubiquitin E1 activating enzyme inhibitor. Moreover, although pharmacologic or genetic blocking Notch1 signaling could trigger fibroblast activation it did not affect MDM2’s abundance.

Methods: Patients with TIF (secondary glomerulonephritis and interstitial nephritis were excluded) were enrolled in this study and Unilateral Ureteral Obstruction (UOO) animal model was constructed on B57CL6 mice. In vitro study cultured renal fibroblast cell line NRK-49F were employed. The expression of MDM2 and Notch1 was regulated by its pharmacologic inhibitors or transfection of Lentiviral shRNA.

Results: Compared with WT, cPLA2 KO animals had a 1.5-2.0 fold increase in mRNA for matrix proteins such as collagen and fibronectin, pro-fibrotic chemokines such as fractalkine, and inflammatory markers such as MCP-1 after UUO as compared with WT animals at 7 days. By flow cytometry, cPLA2 KO animals had significantly more infiltration of CD45+, CD11b positive Ly6C- negative cells than WT animals after UUO.

Conclusions: Deflection of cPLA2 and/or its products, predominantly from circulating myeloid cells, contribute to the development of experimental fibrosis using a UUO model in mice.

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SA-PO475

SIRT2-MDM2 Signaling Attributes to Fibroblasts Activation but Not Tubular Epithelial-Mesenchymal Transition During Tubulointerstitial Fibrosis

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Background: Renal resident fibroblasts and tubular epithelial cells are the main sources for extracellular matrix producing myofibroblasts during tubulointerstitial fibrosis (TIF). Histone deacetylases (HDAC) inhibitors are shown to have an antifibrotic effect in skin, liver and lung. Sirtuin 2 (SIRT2), belonging to class III HDAC, mediates p53 deacetylation and subsequent sensitizes the sequestration of p53 by MDM2, thereby resulting in a p53 reduction and cell cycle progression. Up to now it is unclear the role of SIRT2 and its association with MDM2 during renal fibrosis.

Methods: Unilateral Ureteral Obstruction (UOO) animal model was constructed on B57CL6 mice. In vitro study cultured tubular epithelial cell line NRK-52E (TEC) and renal fibroblast cell line NRK-49F were employed. The expression of SIRT2 and MDM2 was regulated by pharmacologic inhibitors or transfection of Lentiviral shRNA.

Results: It showed the protein level of SIRT2 was elevated markedly in UUO mice as well as the fibroblasts treated with TGF-b1. Nevertheless, in TECs the abundance of SIRT2 was not altered under TGF-b1 exposure. Additionally, AGK2, a specific SIRT2 inhibitor, attenuated the severity of TIF in UOO mice and the fibroblast activation triggered by TGF-b1. Next in fibroblast we found MDM2, a p53 inhibitor, was upregulated simultaneously under TGF-b1 stimulation. Interestingly, the increased MDM2 level can be minimized by pharmacologic or genetic blocking of SIRT2 which was not interfered by an MDM2 inhibitor of the interaction between MDM2 and p53. Thus, it indicated SIRT2 regulating MDM2 was p53 independent. Moreover, genetic deletion of MDM2 by shRNA transfection didn’t affect the expression of SIRT2, although which could alleviate fibroblast activation.

Conclusions: Our current study suggests that besides p53, SIRT2 also could modulate MDM2 during fibroblasts activation, and targeting SIRT2-MDM2 signaling may be a potential strategy for the treatment of renal fibrosis.

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SA-PO479
Biomarkers of Collagen Type III and V Turnover Can Predict Poor Recovery of Kidney Function in Kidney Transplant Recipients
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Background: Allograft dysfunction is a common complication after renal transplantation (Tx). The turnover of extracellular matrix proteins, collagen type III and type V, contributes to renal repair mechanisms which accompany allograft dysfunction. Distorted turnover may lead to progressive fibrosis and to loss of renal function. The objective of our study was to evaluate the role of specific collagen type III and type V cleavage fragments for early allograft dysfunction after kidney Tx.

Methods: 171 in-patient incident patients, receiving a kidney allograft were enrolled at Odense University Hospital. Plasma and urine samples were collected at the first postoperative days. CM and Pro-C6 were measured in samples using novel ELISAs. Early allograft dysfunction was defined as eGFR less than 30 ml per minute per 1.73m² 29 days after Tx. The difference of plasma creatinine (RCPC) is the difference between plasma creatinine (pCrea) on the preoperative and first postoperative day divided by preoperative pCrea. Follow-up data on pCrea from a subset of patients was available at 6- and 12 months.

Results: Plasma Pro-C6 ((pPro-C6) levels were significantly different in patients who received a deceased donor (DD), living donor (LD) and AB0 incompatible (AB0) donor kidney (p<0.001). pPro-C6 had a negative correlation with eGFR 29 days post Tx (p<0.0001, r=-0.35) and a positive correlation with pCrea at 6- (p<0.0001, r=0.31) and 12 months (p<0.0001, r=0.32). With a cut-off of 0.3 for the RCPC, ROC curves showed that pPro-C6 was a good predictor of allograft failure at 6- (p=0.0001, r=0.32) and 12 months post Tx (p=0.0001, r=-0.35). Plasma C3M was associated with plasma CRP levels showed a negative correlation with plasma creatinine at 6- (p<0.0001, r=-0.37) and 12 months post-Tx (p<0.001). pCrea. Follow-up data on pCrea from a subset of patients was available at 6- and 12 months.

Conclusions: pPro-C6 and C3M levels were associated with eGFR and pCrea. With a cut-off of 0.3 for the RCPC, ROC curves showed that pPro-C6 was a good predictor of allograft failure at 6- and 12 months post-Tx. Follow-up data on pCrea from a subset of patients was available at 6- and 12 months. Increased pCrea level blocks the progress of renal fibrosis. Increased C3M level and decreased pPro-C6 level is associated to early allograft dysfunction and predict poor recovery of kidney function in kidney transplant recipients.

SA-PO482
Endothelial Cell Thymosin β4 Knock Down Ameliorates Kidney Injury Induced by Reducing Endothelial to Mesenchymal Transition (EndoMT)
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Background: Thymosin β4 (Tβ4) is a G-actin sequestering protein with effects on angiogenesis, cell migration and matrix. Our previous data showed that exogenous Tβ4 treatment ameliorated matrix accumulation at day 14 after unilateral ureteral obstruction (UUO). In this study, we investigated whether knockdown of Tβ4 only on endothelial cells has effects on renal fibrosis.

Methods: We generated inducible endothelial cell Tβ4 knockdown mouse (Tβ4 KD) by mating Tβ4 sRNA lexp mouse with SCL Cre mice. SCL Cre negative mice were used as control (Cont). Tamoxifen was administrated to induce Tβ4 knockdown (+, qod, from-8d). Mice were sacrificed at 14 days after UUO.

Results: Peritubular capillary density, assessed by CD31 staining, was significantly decreased in Tβ4 KD mice (Tβ4 KD 2.39±0.11 vs. Cont 3.20±0.08 %, P<0.001). Peritubular capillary permeability, measured by injecting Evans blue dye in vivo and assessing extravasation of dye in the kidney, also was reduced in Tβ4 KD mice (Tβ4 KD 107.01±5.49 vs. Cont 161.85±16.32 mg/kg, P<0.05). Tβ4 KD had significantly decreased collagen I, I by IHC, vs Cont (Tβ4 KD 15.24±0.57 vs. Cont 17.68±0.71 %, P<0.05), but no significant change in Sirius red positive area (Tβ4 KD 0.91±0.03 vs. Cont 1.14±0.15 %). Tβ4 KD had less total collagen (Tβ4 KD 48.06±5.01 vs. Cont 53.50±2.34 mg/mg). Tβ4 KD had less EndoMT (α-SMA+ and CD31+ double positive cells/high power: Tβ4 KD 1.20±0.11 vs. Cont 1.74±0.17 P<0.05).

Conclusions: We conclude that endothelial cell thymosin β4 knockdown results in reduced peritubular capillary number and function, and reduced collagen in Tβ4 KD mice. We speculate that Tβ4 KD in endothelial cells may change endothelial function and modulate EndoMT.

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SA-PO483
Endostatin and Transglutaminase 2 Are Geroenic Proteins Involved in Fibrosis of Aging Kidney
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Background: Endostatin (EST), the C-terminal fragment of collagen XVIII and a potent anti-angiogenic factor, is highly enriched in aging kidneys. It has also been recently observed that peritubular capillary rarefaction is a result of mitochondrial dysfunction and extracellular matrix in tissue fibrosis. Mitochondrial dysfunction is an early event in renal fibrosis, but it leads to kidney fibrosis and how it is regulated is unclear. In this paper, we investigated the role of EST in renal fibrosis.

Methods: Primary renal proximal tubular cells (MRPTC) were cultured from Nrp-1+/lox mice. After infection of Nrp-1+/lox cells with adenovirus expressing Cre resulted in NRP1 knockout (NRP1-/-) in the primary cells. Human proximal tubular cell line HKC-8, MEF cells and 3T3-L1 cells were used in this study. TGF-β-driven promoter transcriptional activity was measured by luciferase assay.

Results: NRP-1 was down-regulated by TGF-β in HKC8 and up-regulated in MEF cells and 3T3-L1 cells, suggesting the different regulation mechanisms and functions of NRP-1 in proximal tubular cells and fibroblasts. Over-expression of TGF-β suppressed NRG1-β-induced phosphorylation of Smad3/2 and expression levels of fibronectin. HKC-8 cells over-expressing NRP-1 showed significantly decreased levels of both TGF-β receptor I and receptor II. The NRP1-/- cells showed higher TGF-β-induced Smad3/2 transcriptional activities and expression of TGF-β receptor in Nrp-1+/lox MRTC5 cells, compared with control adenovirus-infected Nrp-1+/lox MRTC5ts.

Conclusions: Proximal tubular cells-derived NRP1 inhibits the TGF beta signaling pathway. NRP1 functions are cell type-specific in the kidney.

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SA-PO484
The CAMP-epac Pathway Regulates Renal Fibrosis by Promoting Mitochondrial Biogenesis of Tubular Epithelial Cell
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Background: Distorted turnover may lead to progressive fibrosis and to loss of renal function. The cAMP-epac pathway is involved in renal fibrosis. Increased cAMP level could induce the downregulation of TGFb in PTC. Increasing the level of cAMP in PTC by rolipram, PDE 4b siRNA, epac activator or epac siRNA could reduce the damage of PTC under TGF-b1 stimulation; 6; Rolipram could restore PGC-1a expression, reduce the mtDNA damage and protect the mitochondrial function and structure of PTC under TGF-b1 stimulation.

Conclusions: cAMP-epac pathway is involved in renal fibrosis. Increased cAMP level blocks the progress of renal fibrosis. cAMP promotes mitochondrial biogenesis and restores mitochondrial structure and function of tubular epithelial cell.

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SA-PO485
Fibrosis of Aging Kidney
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Background: Endostatin (EST), the C-terminal fragment of collagen XVIII and a potent anti-angiogenic factor, is highly enriched in aging kidneys. It has also been recently observed that peritubular capillary rarefaction is a result of mitochondrial dysfunction and extracellular matrix in tissue fibrosis. Mitochondrial dysfunction is an early event in renal fibrosis, but it leads to kidney fibrosis and how it is regulated is unclear. In this paper, we investigated the role of EST in renal fibrosis.

Methods: Primary renal proximal tubular cells (MRPTC) were cultured from Nrp-1+/lox mice. After infection of Nrp-1+/lox cells with adenovirus expressing Cre resulted in NRP1 knockout (NRP1-/-) in the primary cells. Human proximal tubular cell line HKC-8, MEF cells and 3T3-L1 cells were used in this study. TGF-β-driven promoter transcriptional activity was measured by luciferase assay.

Results: NRP-1 was down-regulated by TGF-β in HKC8 and up-regulated in MEF cells and 3T3-L1 cells, suggesting the different regulation mechanisms and functions of NRP-1 in proximal tubular cells and fibroblasts. Over-expression of TGF-β suppressed NRG1-β-induced phosphorylation of Smad3/2 and expression levels of fibronectin. HKC-8 cells over-expressing NRP-1 showed significantly decreased levels of both TGF-β receptor I and receptor II. The NRP1-/- cells showed higher TGF-β-induced Smad3/2 transcriptional activities and expression of TGF-β receptor in Nrp-1+/lox MRTC5 cells, compared with control adenovirus-infected Nrp-1+/lox MRTC5ts.

Conclusions: Proximal tubular cells-derived NRP1 inhibits the TGF beta signaling pathway. NRP1 functions are cell type-specific in the kidney.

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SA-PO484

Angiopoietin-1 Deficiency Increases Tubulointerstitial Fibrosis

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Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function, independent of underlying disease. It is characterized by an increase in aSMA+ fibroblasts, myofibroblasts that produce collagen. Identification of factors that regulate the pro-fibrotic response are excellent candidate targets for treatment of kidney diseases. We previously showed that loss of Angiopoietin-1 (Ang1) in adult mice predisposes to fibrosis in wound healing and diabetic nephropathy. Ang1 acts through the Tie2 tyrosine kinase receptor expressed on endothelial cells and a subset of myofibroblasts. Here, we test the hypothesis that loss of Ang1-Tie2 signaling destabilizes endothelial cells and results in an increased fibrotic response.

Methods: To investigate the role of Ang1 in renal fibrosis we utilized Ang1-deficient conditional knockout mice in experimental models of renal fibrosis, including unilateral ureter obstruction (UUO) and ischemia/reperfusion injury. Gene and protein regulation of fibrotic markers were assessed at different time points. We also performed lineage tagging experiments using Tie2-Cre and LysM-Cre to better understand the contribution of Tie2+ cells and macrophages to the myofibroblast population in UUO.

Results: Ang1 deficient mice showed a significant (p<0.01) increase in fibrotic area 3 days after UUO, 9.7±0.45%, compared to controls, 7.9±0.24%. At the same time point, there was a trend (n) towards an increased number of myofibroblasts per field from 15.4±1.8 in controls 20.1±1.4 in Ang1 deficient mice. Ischemia/reperfusion experiments are ongoing. In our lineage tagging experiment we found that 18.5±3.0% of myofibroblasts came from the Tie2-lineage whereas the LysM lineage contributed minimally, 2.4±0.005%.

Conclusions: Our results suggest that loss of Ang1-Tie2 signaling increases tubulointerstitial fibrosis as seen by the increased expression of fibrosis markers in Ang1 deficient mice. Ongoing work is designed to use other models of fibrosis and to elucidate the mechanism(s).

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SA-PO485

Inter-Alpha-Inhibitor Heavy Chain5 Interactions Control Fibroblast: Myofibroblast Differentiation


Background: Fibroblasts are central to CKD through their Transforming Growth Factor-β (TGF-β1)-triggered phenotypic transition into contractile, α-smooth muscle actin (α-sma)-positive myofibroblasts. Transition is dependent on an increase in the synthesis and accumulation of a pericellular matrix of hyaluronan (HA) and the HA-dependent co-localisation of CD44 with EGFR. Interactions of HA with hyaluronidase, with intercellular-alpha-inhibitor (IαI) and the protein product of Tumour necrosis factor-stimulated gene 6 (TSG-6) and the assembly of this matrix and are also essential for the phenotypic activation of fibroblasts. The mechanisms controlling this effect, however, are not known and are the subject of this study.

Methods: Fibroblasts were incubated for 24 h with 10ng/ml TGF-β1 to become myofibroblasts. RT-PCR was used to assess mRNA, sRNA was used to knockdown mRNA expression and Western Blotting assessed protein levels. Results: Following TGF-β1 treatment, TSG-6 and α-sma, had different kinetics of induction. Using siCD44 or EGFR inhibitor AG1478 to interfere with the CD44/EGFR-dependent signal initiation prevented differentiation but had no effect on TSG6 expression. TSG-6, however, was essential for differentiation and using monoclonal antibody A3K, HA-oligosaccharides, Cobalt, or siBikunin to interfere with the activity of TSG6, all prevented phenotypic change. These results suggested that it was the TSG6/IαI heavy chain (HC) interaction that was necessary for the effect. HC5 was shown to be the principal HCs expressed in these cells. HC5 was released by hyaluronidase treatment of the fibroblast cell surface and siCD44, siTSG6 and siBikunin all inhibited the expression of HCs protein. Finally, HC5 could be deleted on the cell specific siRNA and this resulted in antagonism of phenotypic change, confirming its role in myofibroblast differentiation.

Conclusions: The mechanisms regulating TSG-6 and HA synthesis, during TGF-β1-dependent induction of myofibroblasts are distinct. TSG-6, however, contributes to the pro-fibrotic response through its catalytic transfer of IαI HC5 to HA leading to the β1-dependent induction of myofibroblasts. Identification of factors that regulate the pro-fibrotic response are excellent candidate targets for treatment of kidney diseases.

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SA-PO486

Role of IL-4 Receptor a in Bone Marrow-Derived Fibroblast Activation and Renal Fibrosis

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Background: Renal fibrosis is a common pathway leading to progression of chronic kidney diseases. We and others have shown that bone marrow-derived fibroblasts contribute significantly to the pathogenesis of renal fibrosis. However, the signaling pathways underlying the activation of bone marrow-derived fibroblasts in the kidney are incompletely understood. We have found that IL-4 and its receptor a (IL4Ra) are induced in the kidney during the development of renal fibrosis. However, little is known about the role of IL-4Ra in the activation of bone marrow-derived fibroblasts and the development of renal fibrosis.

Methods: We examined the role of IL-4Ra in the activation of bone marrow-derived fibroblasts in bone development using an IκBα-specific inhibitor to induce nephropathy and cultured bone marrow monocytes treated with IL-4.

Results: Compared with wild-type (WT) mice, IL-4Ra-deficient (KO) mice exhibited significant preservation of kidney function as measured by serum urea nitrogen and accumulated significantly fewer bone marrow-derived fibroblasts dual positive for CD45 and PDGFR-β in the kidney 2 weeks after folic acid treatment. Furthermore, IL-4Ra-KO mice exhibited fewer α-smooth muscle actin (α-SMA) positive myofibroblasts and expressed less α-SMA protein in the kidney following folic acid treatment. Consistent with these findings, infiltration of inflammatory cells was significantly reduced in IL-4Ra-KO mice. This suppression of extracellular matrix proteins (collagen 1 and fibronectin). In cultured bone marrow monocytes, IL-4 activated STAT6 and induced expression of α-SMA and extracellular matrix proteins, which was abolishes in the absence of IL-4Ra.

Conclusions: Our results demonstrate that IL-4Ra plays an important role in the activation of bone marrow-derived fibroblasts and the development of renal fibrosis. These results indicate that IL4Ra signaling may represent a novel therapeutic target for chronic kidney disease.

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SA-PO487

Role of Scaffolding Protein JLP in Preventing Renal Fibrosis in Obstructive Nephropathy

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Background: Renal fibrosis is a common pathological lesion in the end stage of various progressive kidney diseases, and is characterized by interstitial inflammation, proliferation of fibroblasts, and accumulation of extracellular matrix (ECM). The INK-associated leucine zipper protein (JLP) is a crucial scaffolding protein in signals transduction and molecular trafficking. JLP has been found expressed in mouse tissues of brain, lung, spleen, testis, and kidney. We reported here, for the first time, the effects of JLP deficiency on the progression of renal fibrosis in mice model of unilateral ureteral obstruction (UUO).

Methods: JLP Wild type (jlp+/+) and jlp deficient (jlp−/−) mice were divided into four groups: jlp+/+, jlp+/− and jlp−/− sham-operated groups, jlp−/− and jlp−/− unilateral ureteral obstruction (UUO)-operated groups (jlp−/− group) and jlp−/−- UUO group. Mice were sacrificed at the days of 7 and 14 to evaluate the fibrosis by Masson and H&E staining. The expression of transforming growth factor-b1 (TGF-b1), α-smooth muscle actin (α-SMA), collagen I (COL-I), and collagen III (COL-III) were assayed by immunohistochemistry staining.

Results: One week after the surgery, more collagen deposition was observed in the renal interstitial area in jlp−/− group than in jlp−/−- UUO group. Similar to that, the expression of COL-4 and COL-III were significantly increased in the kidney cortices in jlp−/−-UUO-operated groups. The expression of TGF-b1 and α-SMA was also significantly higher in jlp−/−- UUO-operated group than in jlp−/− group.

Conclusions: Scaffolding protein JLP is critical in preventing renal fibrosis through the mechanism of inhibition TGF-b1 expression and myo-fibroblast induction.

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SA-PO488

HGF-Producing Cell Sheet Suppress Renal Fibrosis Induced by Unilateral Ureteric Obstruction in a Rat

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Background: Tubulointerstitial fibrosis is a typical pathological finding in chronic kidney disease (CKD) and is associated with the progression of renal dysfunction. Recently several studies reported to suppress renal fibrosis by transplantation of cells expressing several growth factor, for example EGF, HGF. Cell sheet transplantation is a methodology of cell therapy for regenerative medicine. This technology demonstrated high effective therapy for diseases in other organs, such as cornea, periodontium, esophagus and heart. In this study, we performed to suppress renal fibrosis by local and sustained administration of hepatocyte growth factor (HGF) with HGF-producing cell sheet (HGF sheet) transplantation.

Methods: Human mesothelial cells transplanted human HGF gene by lipofection were cultured on temperature-responsive dish for 4 days. When temperature reduced, these HGF-producing cells were detached from dishes as cell sheet without enzyme-treated. We performed unilateral ureteric obstruction (UUO) in nude rat and transplanted the HGF sheet immediately. To compare HGF sheet transplantation with intermittent administration of HGF protein, we also injected HGF protein from tail vein every 24 hours for UUO rat (HGF i.v.). The kidney volume after operation measured with CT 7 days later. One week after operation, histologic examination and smooth muscle actin in kidney transplanted HGF sheet was significantly less compared to that in HGF i.v. kidney. Moreover, the kidney volume after treated HGF sheet with UUO rat was significantly less compared to control 4 weeks after operation and it maintained thick cortex in HGF i.v. kidney. We reported here, for the first time, the effects of JLP deficiency on the progression of renal fibrosis in mice model of unilateral ureteral obstruction (UUO).

Conclusions: Local and sustained HGF administration with HGF sheet strongly suppressed renal fibrosis induced by UUO in a rat. Our results suggested that cell sheet therapy may be a promising strategy for renal disease.

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SA-PO489
Extracellular Matrix Modulates Macrophage Phenotype Profile
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Background: It is known that macrophages play an important role in kidney damage and resolution. An increase in macrophages phenotype type 1 (M1) leads to pro-healing processes. However little is known on how the extracellular matrix (ECM) can direct macrophages toward a specific phenotype acquisition during development, tissue homeostasis and disease.

Methods: Using established protocols we decellularized human adult, healthy, diseased, and fetal kidneys; monocytes were seeded on the different ECMs and macrophage phenotype after 24hrs and 5 days was assessed. Macrophage maturation was tested by evaluating release of IL-10, IFN-γ, TNF-α and IL-4 in the culture media along with qRT-PCR and immunocytochemistry to evaluate expression of M1 (CD80 and CD86) and M2 (CD163, CD14, CD200 and CD200R) phenotypes.

Results: We observed that monocytes cultured on ECMs were able to mature into macrophages and present an increase in M1 marker (CD80) on diseased ECM, an increase in M2 markers (CD163, CD200R) on healthy ECM, and an increase in anti-inflammatory M2 marker (CD16) on fetal ECM, after 24hrs. After 5 days of co-culture there was an overall decrease in gene expression for all markers followed by an increase in media secretion of IL-10 on diseased ECM vs healthy and fetal ECM. Additionally after 5 days higher number of seeded monocytes appear to adhere onto the adult ECM vs the fetal ECM. IFN-γ, IL-4, IL-10 and CD46 expression was not detected during 24hrs and 5 days. Monocytes capacity to mature into macrophages was confirmed in vitro by administration of phorbol myristate acetate (PMA) and 1,25-dihydroxy vitamin D3 with LPS.

Conclusions: Our work suggests that the ECM has the capacity to modulate macrophage phenotype and might contribute to disease progression. Additionally, this model may be used to investigate mechanisms of ECM-dependent macrophage activation during renal disease and regeneration.

SA-PO490
High Salt Diet Induces Blood Pressure Independent Tubulointerstitial Remodeling and Lymphangiogenesis in Rat Kidney
Ryvane S. Hijmans, Saleh Yazdani, Gerjan Navis, Jacob van den Born.

Methods: Two groups (n=5) had a normal rat diet. After 2 weeks, one of the two groups on a high salt diet was sacrificed, and the other groups were sacrificed at 4 weeks. The kidneys were stained and quantified for lymphangiogenic, fibrotic and inflammatory markers.

Results: Rats with HS intake showed an increased number of lymph vessels compared to their controls at 2, 3 and 4 weeks.

Conclusions: This preliminary work suggests that the ECM has the capacity to modulate tubulointerstitial remodeling and lymphangiogenesis, inflammation and profibrotic changes in rat kidneys, even when the BP is not significantly different between the groups. This finding supports our hypothesis that the kidney intake has BP independent effects next to it’s well known BP dependent effects in CKD.

SA-PO491
Genetic and Epigenetic Analysis of the MicroRNA-200 Family for the Identification of Non-Invasive Biomarkers for Early Renal Disease
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Background: tubulointerstitial fibrosis (TIF) and lymphangiogenesis are key drivers of CKD progression. We aimed to measure, in preclinical models, the urinary and blood expression of microRNAs (miRNAs) associated with TIF, and lymphangiogenesis (LA). We assessed, in tubulointerstitial and lymphangiogenic models, the urinary and blood expression of miRNA-200 family members, by qRT-PCR.

Methods: We utilized two rat models of kidney disease, induced by administration of phorbol myristate acetate (PMA) and 1,25-dihydroxy vitamin D3 with LPS. We quantified for lymphangiogenic, fibrotic and inflammatory markers. We also assessed the blood expression of miRNA-200 family members in the aforementioned models.

Results: The urinary and blood expression of miRNA-200 family members was significantly upregulated in the kidney disease models. Additionally, we observed a significant increase in the urinary and blood expression of miRNA-200 family members in the lymphangiogenic model.

Conclusions: This preliminary work suggests that the ECM has the capacity to modulate tubulointerstitial remodeling and lymphangiogenesis, inflammation and profibrotic changes in rat kidneys, even when the BP is not significantly different between the groups. This finding supports our hypothesis that the kidney intake has BP independent effects next to it’s well known BP dependent effects in CKD.

SA-PO492
A MicroRNA Signature of Epithelial–Mesenchymal Transition in Progression of Chronic Renal Disease
Ali Ramezani, 1 Joseph M. Devaney, 2 Akshay Roy-Chaudhury, 1 Richard Scott, 3 Sara Karandish, 3 Susan Knoblach, 2 Gareth J. Ryanne Smyth. 1Univ of Southern California; 2Children’s Hospital Los Angeles; 3Wake Forest School of Medicine.

Background: The mechanisms of epithelial-mesenchymal transition (EMT) during renal disease and regeneration.

Methods: Using established protocols we decellularized human adult, healthy, diseased, and fetal kidneys; monocytes were seeded on the different ECMs and macrophage phenotype after 24hrs and 5 days was assessed. Macrophage maturation was tested by evaluating release of IL-10, IFN-γ, TNF-α and IL-4 in the culture media along with qRT-PCR and immunocytochemistry to evaluate expression of M1 (CD80 and CD86) and M2 (CD163, CD14, CD200 and CD200R) phenotypes.

Results: We observed that monocytes cultured on ECMs were able to mature into macrophages and present an increase in M1 marker (CD80) on diseased ECM, an increase in M2 markers (CD163, CD200R) on healthy ECM, and an increase in anti-inflammatory M2 marker (CD16) on fetal ECM, after 24hrs. After 5 days of co-culture there was an overall decrease in gene expression for all markers followed by an increase in media secretion of IL-10 on diseased ECM vs healthy and fetal ECM. Additionally after 5 days higher number of seeded monocytes appear to adhere onto the adult ECM vs the fetal ECM. IFN-γ, IL-4, IL-10 and CD46 expression was not detected during 24hrs and 5 days. Monocytes capacity to mature into macrophages was confirmed in vitro by administration of phorbol myristate acetate (PMA) and 1,25-dihydroxy vitamin D3 with LPS.

Conclusions: Our work suggests that the ECM has the capacity to modulate macrophage phenotype and might contribute to disease progression. Additionally, this model may be used to investigate mechanisms of ECM-dependent macrophage activation during renal disease and regeneration.

SA-PO493
The PR3 Receptor CD177 Is Controlled by Epigenetic Mechanisms
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Background: Proteinase 3 (PR3) is an ANCA antigen in granulomatosis with polyangiitis (GPA). PR3-ANCA binding to membrane-PR3 (mPR3) is a key event for neutrophil activation and vascular inflammation.

Methods: Haplotype analysis, genome-wide methylation analysis, chromatin immunoprecipitation (ChIP) analysis and CD177 expression studies were performed in neutrophils and HeLa cells.

Results: In determining its association with ESRD.

Conclusions: This preliminary work suggests that the ECM has the capacity to modulate tubulointerstitial remodeling and lymphangiogenesis, inflammation and profibrotic changes in rat kidneys, even when the BP is not significantly different between the groups. This finding supports our hypothesis that the kidney intake has BP independent effects next to it’s well known BP dependent effects in CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO494

Application of Human Kidney RNA-seq Expression Quantitative Trait Loci in Chronic Kidney Disease

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Background: There are more than 5 million sequenced variants in humans. Some genetic variants influence transcript levels and therefore have the ability to interfere with cell and organ function. Such genetic variants are called expression quantitative trait loci (eQTL). The goal of our study was to identify such functionally important genetic variants at the genome-wide level.

Methods: This analysis requires the collection of large number of human tissue samples with genotype and transcript level data. Here we used 99 human kidney samples of Central European descents RNAseq and genotype data was normalized and genotype data was imputed using 1,000 Genome reference data. The association between genotype and transcript levels was performed using Matrix eQTL software and was limited to cis-eQTL, where the genetic variant and transcript levels were within 2 megabases distance.

Results: We identified 164 significant target genes (we call these eGenes) and 7590 significant SNPs (eSNPs) that passed the threshold for statistical significance after multiple testing correction using adjusted p-values<1e-10. Next we compared variants that influence gene expression in the kidney to those that have been published for other organs using the publicly available Genotype-Tissue Expression project (GTEx). Of the 164 eGenes,103 were common between the kidney and other organs, indicating that there are cell type specific and cell type independent eGenes. Using kidney specific epigenome maps, we found that eSNPs were enriched on kidney specific regulatory elements, including promoters and enhancers. We also found a significantly greater overlap between kidney eGenes and polymorphisms that are associated with CKD development, compared to other tissues (digestive, nervous, immune system diseases, hematological measurement, cardiovascular, and metabolic disease).

Conclusions: We identified transcript level changes associated with genotypic variations. These results can highlight kidney specific regulatory elements and may also help to identify target genes for polymorphisms associated with kidney function related traits.

Funding: Other NIH Support - NIH Roadmap Epigenomics Program 5R01DK087655-02

SA-PO495

RNA Sequencing Reveals Tumor Necrosis Factor α Inducible Protein 6 (TNFAIP6) as a Potential Single Gene Classifier of Renal Cell Carcinoma Overxin Solhvere Fikrem,1 Christian Beisland,2 Andreas Scherer,2 Arnar Flatberg,3 Trude Skogstrøm,1 Lea Landbol,1 Sabine Leb,1 Karin Magrethje Hejle,1 Vidar Beisvag,3 Hans-Peter Marti.1 1Dept of Clinical Medicine, Univ of Bergen, Bergen, Norway; 2Dept of Cancer Research and Molecular Medicine, Univ of Science and Technology, Trondheim, Norway.

Background: The recent release of a new library preparation kit improved the cDNA library quality from formalin-fixed, paraffin-embedded (FFPE) tissues. In this study we demonstrate the feasibility of next generation sequencing (NGS) of RNA data from FFPE tissues as compared with RNA-sequenced (RNAseq) stored tissues.

Methods: Paired biopsies from tumors and adjacent non-tumorous tissue of 16 patients with ccRCC were either FFPE or stored in RNA-sequenced (RNAseq) tissue libraries. We used sequencing libraries were prepared using the TruSeq RNA Access Library Prep Kit (Illumina).

Results: The average expression of detected transcripts in both FFPE and RNA-sequenced datasets correlated with R²=0.97, and the log2 fold changes of the transcripts which are significantly altered in both datasets (n=1106) correlated with R²=0.94. A classifier model with TNFAIP6 was developed for the FFPE dataset with a specificity of 100% and sensitivity of 94%; ROC AUC=0.99 (Fig. 1A); only one normal sample was misclassified due to a small admixture of cancer tissue. Classifier validation in an Affymetrix microarray dataset of 94%; ROC AUC=0.99 (Fig. 1B); only one normal sample was misclassified due to a small admixture of cancer tissue. Classifier validation in an Affymetrix microarray dataset of 94%; ROC AUC=0.99 (Fig. 1B).

Figure 1: ROC of TNFAIP6 (A) present study, (B) validation in GSE53757 data set.

Conclusions: We describe a potential single gene classifier for ccRCC. Furthermore, NGS in FFPE tissues is feasible and correlates well with RNA-sequenced stored tissues. Thus, our study opens up novel diagnostic possibilities on archival renal biopsies.

Funding: Government Support - Non-U.S.

SA-PO496

Gene Expression Based Dissection of Chronic Kidney Disease Traits


Background: Chronic kidney disease (CKD) is a progressive decline in kidney function. There are several manifestations of CKD including glomerular function change, albuminuria, glomerulosclerosis, tubulointerstitial fibrosis and metabolic changes. These traits are strongly correlated but the question remains whether they are driven by identical mechanisms.

Methods: We conducted genome wide transcript level analysis of 95 microdissected human kidney tubule samples. We used transcript level changes as quantitative traits to dissect underlying mechanisms. These samples included subjects with normal eGFR with or without diabetes (DM) or hypertension (HTN) and diseased kidney samples with low eGFR, fibrosis and sclerosis, with or without DM or HTN.

Results: We identified 1430 transcripts with significant linear correlation with eGFR. Pathway analysis indicated significant enrichment for inflammation and metabolism related pathways. Subgroup analysis indicated enrichment for TGFβ and Wnt signaling and ECM receptor interactions only in earlier CKD stages. Our analysis identified 1606 transcripts that correlated with fibrosis and 1803 transcripts correlated with glomerulosclerosis. Similar to the clinical overlap between eGFR and fibrosis, we found that 78% of transcripts with identical. Transcripts that showed correlation with fibrosis but not with eGFR were enriched for inflammation related pathways. On the other hand, metabolism related genes correlated with eGFR but not with fibrosis. There were significant differences between male and female samples as well.

Conclusions: Our transcriptome-based dissection method highlights the relatedness of eGFR and kidney fibrosis, but also indicates potential differences in the underlying mechanisms of the two processes.

Funding: NIDDK Support

SA-PO497

Early-Onset, Severe Forms of Hypertension and Cardiovascular Complications Are Associated with APOL1 G1/G2 Susceptibility Alleles in African Americans


Background: APOL1 G1/G2 susceptibility alleles are associated with kidney disease progression and ESRD in hypertensive African Ancestry (AA) populations. We explored whether these APOL1 alleles are associated with blood pressure-related traits in AA enrolled in the electronic medical records and genomics (eMERGE) Network.

Methods: Study populations included the Mount Sinai BioMe biobank discovery(dis) cohort (n=5,213) and three EMR-linked biobank replication(rep) cohorts, including Vanderbilt BioVU (n=2,889), Northwestern NUgenome (n=613), and Mount Sinai BioMe (n=1,655). APOL1 single nucleotide polymorphisms (SNPs) rs73885319, rs71875313 and n69010145 were genotyped in BioMe samples and imputed in BioVU and NUgenome samples to determine APOL1 G1 and G2 risk alleles. Longitudinal phenotypic data were extracted from EMRs. Linear regression models & meta-analyses (METAL) were performed with age, sex, mean BMI, eGFR as covariates.

Results: Compared with carriers of [0 or 1] APOL1 G1/G2 risk alleles, carriers of [2] risk alleles were diagnosed with hypertension a mean of 2.5 years (95%CI 1.2-9.2 yrs) earlier in life (P=0.04, P<3x10-3); Cox hazard; manifest 2.3 mmHg higher systolic BP(SBP) in younger AA (age 20–39) (P dis=0.07, P rep =0.04); and were exposed to more antihypertensive medication classes (P=0.11; P<3x10-3). Carriers of [2] risk alleles were more likely to manifest. We determined that left ventricular hypertrophy by echocardiogram (OR [95%CI]=1.521 [1.14–2.02], P<0.01) and hemorrhagic cerebrovascular accidents (OR in 16C=2.42 [1.01–5.93], P=0.05)

Conclusions: APOL1 G1/G2 susceptibility alleles are associated with early-onset, more severe form(s) of hypertension & with hypertensive complications hemorrhagic stroke
and concentric LVH independent of kidney function & BMI. These results may warrant a shift from kidney-intrinsic to systemic vascular pathomechanisms attributable to **APOL1** G1/G2 susceptibility alleles.

**Funding:** Other NIH Support - NHGRI

### SA-PO498

**Apolipoprotein L1 (APOL1) Gene Variants and Incident Proteinuria: Results from the African American Study of Kidney Disease and Hypertension (AASK)**


**Nephrology, Johns Hopkins Univ; Nephrology, Univ of California San Francisco; Medicine, Johns Hopkins Univ.**

**Background:** APOL1 gene variants are associated with kidney function decline. Whether these same gene variants are associated with incident proteinuria in the context of pre-existing chronic kidney disease (CKD) is unknown.

**Methods:** Using the trial and cohort phases of AASK (median follow-up of 6.8 years, maximum follow-up of 12.2 years), we evaluated participants who had hypertension-attributed CKD and who did not have proteinuria at baseline. Cox proportional hazards models were used to estimate the relative hazard of incident proteinuria (defined as a doubling of urine protein-to-creatinine ratio and UP/Cr >0.22), comparing APOL1 high-risk genotype (2 risk alleles) vs. low-risk genotypes (0-1 risk alleles). We adjusted for age, gender, baseline GFR, percentage of European ancestry, randomized blood pressure goal (usual vs. low), and randomized blood pressure drug (ramipril vs. metprolol vs. amlopidine). Effect modification by randomized trial interventions and dietary sodium intake (as estimated by 24-hour sodium urine) was assessed.

**Results:** Of the 480 participants included in our study, 17% (n=82) had the APOL1 high-risk genotype. Individuals with the APOL1 high-risk genotype were 83% more likely to develop incident proteinuria compared to those with the low-risk genotypes (adjusted HR: 1.83; 95% CI: 1.36 to 2.47; p<0.001). The association between APOL1 and incident proteinuria was not modified by randomized pressure goal, randomized blood pressure drug, or dietary sodium intake (p-interaction 0.05 for each).

**Conclusions:** Among African-Americans with CKD attributed to hypertension but without baseline proteinuria, high-risk variants of APOL1 are associated with a greater risk of incident proteinuria.

**Funding:** NIDDK Support, Pharmaceutical Company Support - The AASK trial and cohort were also supported by the following pharmaceutical companies: King Pharmaceuticals, Pfizer, AstraZeneca, GlaxoSmithKline, Forest Laboratories, Pharmacia, and Upjohn.

### SA-PO499

**African Ancestry Specific Alleles Confer Chronic Kidney Disease Risk in U.S. Hispanics**


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**Background:** Hispanics are a heterogeneous group with varying genetic ancestry. African ancestry can differ in Hispanics by country of origin, and its proportion relates to the risk of chronic kidney disease (CKD).

**Methods:** We examined the association of African ancestry population-specific risk alleles (APOL1 and HBB rs334 related sickle cell anemia) with CKD in 11,921 Hispanics, aged 18-74 years, recruited in a community-based study in four US centers. APOL1 G1/2 alleles were genotyped and rs334 alleles were imputed (rsq=0.83). CKD was defined as an increased urine albumin to creatinine ratio (UACR) (>17 mg/g in men and >25 mg/g in women), reduced estimated glomerular filtration rate (eGFR) 60 ml/min/1.73 m² based on serum creatinine/ cystatin C CKD-EPI equation, or presence of reduced eGFR or an increased UACR. Analyses used generalized linear mixed models that accounted for the sampling strategy and family relatedness, age, sex, diabetes, systolic blood pressure and anti-hypertensive medications, and stratified by Hispanic background.

**Results:** There were 41% men, and mean age was 46 (SD =14). The prevalence of increased UACR was 13%, reduced eGFR was 4%, and combined CKD outcomes was 16%. Caribbean Hispanics (Cuban, Dominican, Puerto Rican, N=5348) had higher prevalence of 2 APOL1 risk alleles (1% vs 0.1%) and rs334 allele (2% vs. 0.7%) compared to Mainland Hispanics (Central American, Mexican, South American, N=6,539). APOL1 alleles were associated with increased UACR (p=10⁻⁷) and the composite CKD outcome (p=10⁻⁷), and rs334 was associated with same outcomes (UACR, p<10⁻³; CKD composite outcome, p<10⁻⁷) among Caribbeanans only.

**Conclusions:** African-specific alleles are associated with CKD in Hispanics, but associations vary by Hispanic background. Medical care providers should be aware of the impact of these genetic variants for CKD risk in Hispanics.

**Funding:** Other NIH Support - R21HL123677, IR01ES021367, IR01HL118305-01A1

### SA-PO500

**Role of Klotho Genetic Polymorphisms in Salt-Sensitivity: A Link Between Salt and Aging?**

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**Background:** Previous data in transgenic mice showed that one-half-klotho deficiency resulted in excessive premature aging, increased salt sensitivity and caused salt-sensitive hypertension. Recent gene expression study confirmed the expression of klotho in renal distal tubular cells. The aim of this study is to evaluate the role of klotho polymorphisms in salt sensitivity hypertension.

**Methods:** Design: study of pressure-natriuresis relationship in essential hypertensive patients, never treated before, naive (NHP) by Acute salt load (NaLoad: 310 mMol in 2 h iv) and low salt diet (Low SD: <100 mg/die for 15 days). Methods: 580 NHP underwent NaLoad whereas 137 NHP were compliant to low SD protocol (of 324 enrolled).

**Results:** GWA analysis identified 32 SNPs in Klotho gene (restricted to 15 with tagging r²>0.80). Six of these resulted significantly associated to BP variation after NaLoad and LowSD. The effect of intron 2 and 3 SNPs genotype on SBP variation after NaLoad and LowSD are reported in the (figure 1) confirming the similar effect in the two manoeuvres.

**Conclusions:** These results are the first demonstration of the role of Klotho gene in salt homeostasis and hypertension development and suggest that Klotho polymorphisms affect sodium renal tubular excretion. If confirmed these results propose Klotho as key gene in salt sensitivity and aging.

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

### SA-PO501

**Associations Between the Reticulon 1 Gene (RTN1) and End-Stage Kidney Disease**

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**Background:** RTN1 encodes endoplasmic reticulum stress proteins that have recently been associated with chronic kidney disease. We sought to determine if genetic variants within RTN1 were associated with end-stage renal disease (ESRD) in African Americans (AAs) and European Americans (EAs) with diabetic (T2D-ESRD) and non-diabetic forms of ESRD.

**Methods:** We examined the RTN1 gene region using a published AA T2D-ESRD genome-wide association study (Discovery study; n=922 cases, n=861 controls). Seven single nucleotide polymorphisms (SNPs) with p<0.05 were identified and genotyped in replication samples of AAs with T2D-ESRD (n=1,312) and controls (n=774), as well as...
EAs with T2D-ESRD (n=904) and controls (n=1030). SNPs were also investigated in AAs with renal disease in type 2 diabetes, including DN-ESRD (n=500 AAs, n=620 EAs). Data were adjusted for age, gender, admixture, and the APOL1 alleles, if applicable.

**Results:** The top 738A SNPs from the Discovery study underwent replication testing in independent case-control samples of AAs with T2D-ESRD. Replication was observed for rs3760106, but did not remain significant after correction for multiple comparisons. In combined data IMN, interaction analysis between IMN and DRB1*04:05 allele was assessed. In single locus analysis of AAs, no association with rs3760106 was observed when the risk allele was not present. For AAs with both risk alleles, no association was observed for any SNP. A combined AAs all-cause ESRD analysis (n=3,800 cases, n=1,803 controls) demonstrated associations with rs3760106 that remained significant after correction for multiple comparisons (OR=0.75, 95% CI, 0.67-0.87). The association was stronger for non-T2D ESRD in AAs (OR=0.77, 95% CI, 0.69-0.87).

**Conclusions:** This study demonstrated genetic evidence of association between 738A and ESRD in AAs and EAs. Further studies are needed to clarify the signal. **Funding:** NIDDK Support

**SA-PO502**

**Interaction of Risk Alleles in Japanese Idiopathic Membranous Nephropathy**

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**Background:** Recent studies have reported the association of risk alleles of PLA2R1 and HLA-DQ41 with idiopathic membranous nephropathy (IMN) in the European and Chinese populations. However, both close association of the risk alleles and interaction between risk alleles of PLA2R1 and HLA from high-resolution HLA typing among Japanese IMN patients has not been investigated.

**Methods:** Samples of Japanese biopsy-proven IMN patients (N = 183) and healthy controls (N = 620) were collected. Fifteen common variants were selected within PLA2R1 gene. High-resolution association analysis of single nucleotide polymorphisms (SNPs) within PLA2R1 and HLA alleles in HLA-A, B, C, DRB1, DQB1 and DPB1 were performed using 53 IMN cases and 420 controls. The significant associations discovered in the first sample set were validated by the second set that comprised of 130 IMN cases and 200 controls.

**Results:** The strong associations HLA-DRB1*15:01 (P = 7.7 x 10^(-9), OR = 2.9) and HLA-DQB1*06:02 (P = 5.1 x 10^(-4), OR = 2.6) were observed. Additionally, HLA-DRB1*07:04 (P = 2.1 x 10^(-4), OR = 2.2) and HLA-DQB1*04:05 (P = 1.2 x 10^(-4), OR = 2.1) were inversely associated with IMN. The associations did not remain significant after correction for multiple comparisons. In combined data analysis, HLA-DRB1*15:01 and HLA-DQB1*06:02 showed stronger association with IMN. In single locus analysis of PLA2R1, seven SNPs showed strong associations with IMN. Interaction analysis between HLA alleles and PLA2R1 variants revealed high odds ratio for IMN with both risk alleles.

**Conclusions:** The associations of PLA2R1 and HLA polymorphisms were identified in Japanese IMN patients. Moreover, PLA2R1 risk alleles and HLA risk haplotype showed additive effects that were stronger than individual odds ratios, indicating the importance of interaction of these two genes in the development of IMN.

**SA-PO503**

**Relationship Between rs3760106 Variation of PRKCB1 Gene and End-Stage Renal Disease in Type 2 Diabetes Mellitus in Chinese**

Limei Liu, 1 Xiaoxu Ge, 1 Langen Zhuang, 1 Ming Li, 2 Rong Zhang, 1 Feng Wang, 2 Niansong Wang, 2

**Background:** To explore the relationship between rs3760106 (C/T) variation of protein kinase C-β gene (PRKCB1) and end stage renal disease (ESRD) in type 2 Diabetes mellitus (T2DM) in Chinese.

**Methods:** 602 type 2 diabetes patients of Shanghai Han origin were recruited, which were divided into DN-ESRD group (n=274) with end stage renal disease (ESRD) of diabetic nephropathy (DN) and DN-0 group (n=328) without diabetic nephropathy (DN-0). Taqman PCR assay was used to detect the genotypes of rs3760106 variation of PRKCB1 gene. Genotypic and allelic frequencies and clinical characteristics were compared between two groups, including DN-0 and DN-ESRD groups as well as genotypic groups in DN-0 or DN-ESRD group.

**Results:** Three genotypes (CC, CT, and TT) of rs3760106 were detected. The distribution of the three genotypes of type 2 diabetes patients was in accordance with Hardy-Weinberg equilibrium. There were significant differences in both genotypic and allelic frequencies between DN-0 and DN-ESRD groups (p < 0.05 for each). The frequencies of CT/TT genotype and T allele in DN-ESRD group were significantly higher than those in DN-0 group (p < 0.05 for each). Patients with risk allele T (i.e. CT and TT genotypes) were at significantly higher risk of developing ESRD (OR = 2.14, 95% CI, 1.18-3.87, p < 0.05). After adjusting for confounding variables, i.e., sex, onset age of diabetes and BMI with multi-factorial logistic regression model, this odds ratio (OR) remained significant (OR=1.94 (95% CI, 1.04-3.64)). Moreover, compared with patients carrying CC genotype, those with CT+TT genotype had significantly higher fasting plasma glucose (FPG) level in DN-0 group (p < 0.05) or had an increasing tendency in DN-ESRD group (p < 0.05).
SA-PO506
Exome Sequencing as Diagnostic Tool in Daily Clinical Nephrology Practice
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Background: Next generation sequencing, e.g. exome sequencing (ES), is currently the state of the art technique to identify mutations in genetic diseases. We developed a workflow for implication of ES in daily clinical practice for patients with a suspected hereditary kidney disease. The aim of this study was to analyze the diagnostic yield of this approach in clinical practice.

Methods: We developed a two-tier analysis, in which the first step is a kidney disease gene panel to screen for pathogenic variants in 187 genes, minimizing the chance of coincidental findings. If causative mutations are not identified (first step), the complete exome data set was analyzed after additional written informed consent. We analyzed the diagnostic yield of this approach.

Results: From Jun. 2013 till Jan. 2015 we included 74 unrelated patients with kidney disease, defined as glomerular disease (n=34), cystic renal disease (n=16), electrolyte disorders (n=11), renal insufficiency of unknown cause (n=4) and other (n=9). The kidney disease gene panel revealed pathogenic mutations in 11 cases (15%), and likely pathogenic variants in 12 other cases (16%), necessitating follow-up studies. Further analysis of the complete exome data set in 19 patients, revealed candidate genes in 6 patients that are under investigation. In addition, copy number variation analysis revealed a pathogenic deletion in 2 patients (in one patient another pathogenic mutation was also identified in step one). There was 1 coincidental finding necessitating follow up for colon carcinoma. In 23 patients open exome analysis is currently ongoing. Nine patients refused further analysis.

Conclusions: Currently, in 30 out of 74 patients (41%) (likely) causative mutations or new candidate genes were identified. We conclude that diagnostic exome sequencing is a powerful tool for detecting causative mutations in daily clinical practice without having the limitations of other gene testing approaches (single gene testing/targeted sequencing).

SA-PO507
Atypical Hemolytic Uremic Syndrome Targeted Re-Sequencing in a South Italian Cohort of Patients
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Background: Atypical hemolytic uremic syndrome (aHUS) is a multifactorial disease due to autoimmune or genetic factors leading to deregulated alternative complement pathway activation. At present 12 genes are associated to aHUS, however 30-50% of patients lack mutations in these genes resulting in still partially obscure genotype-phenotype correlations.

Methods: We enrolled 20 aHUS patients and 2 relatives from Apulia Region, Italy. We performed targeted parallel re-sequencing of the 12 known genes plus ADAMTS13, identified in the aHUS diagnostic routine screening. We analyzed the genotypes investigating the overlapping with other alternative complement pathway disorders, such as C3 glomerulopathy, Age-related Macular Degeneration (AMD) and drusen. We selected patients for their history of sporadic aHUS. Target enrichment was performed using an Illumina TrueSeq Custom Amplicon panel. Sequencing was performed on Illumina MiSeq Desktop Sequencer. All variants were evaluated for their pathogenicity according to CADD, Sift and Polyphen algorithms.

Results: We identified 30 missense and one nonsense variants in known aHUS genes, plus seven missense variants in ADAMTS13. Several combined variants were identified which might explain the different phenotypic nuances of our patients, as well as, in some cases, their signs of other Complement-related diseases. We evidenced that different combination of variants together with different triggering factors result in a phenotypic spectrum encompassing all the Complement-related disease range. Additionally, in presence of some combinations, also other underlying pathologies can act as a triggering background for aHUS.

Conclusions: Our data suggest that (i) ADAMTS13 gene should be routinely sequenced for aHUS (ii) the overlapping with other complement-related diseases is considerable. Mutations should therefore be analyzed in combination, and the high-throughput strategy is the only feasible in this scenario.

SA-PO508
Whole Exome Sequencing (WES) Revealed Underlying Complexity in Genetic Studies of Familial IgA Nephropathy (fIgAN)
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Background: Diagnosis of familial glomerular diseases may be confounded by non-specific clinical (i.e. hematuria and proteinuria) and/or pathological findings. Indeed, a recent study of familial focal segmental glomerulosclerosis (FSGS) has identified COL4A3 and COL4A4 mutations in ~10% of study families [Kidney Int 86:1253-59, 2014]. In the course of studying a cohort of fIgAN, we unexpectedly identified pathogenic mutations in 13 families with non-IgA glomerular diseases.

Methods: We performed whole exome sequencing (WES) in 109 patients from 54 families, all with at least 2 biologically related cases.

Results: Our WES study identified heterozygous/hemizygous pathogenic COL4A3 (c.1504+1G>A; p.G291R; p.G695R; p.G1054E; p.G1286R), COL4A4 (p.Q970R; p.G1508A), and COL4A5 (p.G48R; p.G325R) mutations in 9 families with fIgAN. These mutations occurred at the canonical splice junction or conserved glycine residues and segregated in all affected subjects within family. In two multiplex families, co-existence of thin basement membrane disease (TBMD) with IgAN was also observed in the biopsied subjects in retrospect. Additionally, putative homozygous pathogenic variants were found in 3 families in the known genes for FSGS (ACTN4, c.398-2A>G), CFB57 nephropathy (CFHR5, p.C449S), and membranous nephropathy (PLA2R1, p.C192G) and homozygous mutation in one family in another known gene for FSGS (ADCK4, p.S246N).

Conclusions: The presence of other glomerular diseases may confound the diagnosis of fIgAN in some putatively affected subjects ascertained based on urinal findings or even kidney biopsy. Due to its high prevalence in the general population, TBMD may be an important cause of phenocopy that can confound genetic linkage studies in fIgAN.

SA-PO509
Disease Gene Discovery for Familial IgA Nephropathy (fIgAN) by Whole Exome Sequencing (WES)
Xuewen Song,1 Nicole M. Roslin,2 Meng Yi Xu,1 Kairong Wang,1 Jannel Liu,1 Bushra Joarder,2 Amirzea Haghighi,2 Melody Ren,1 Joseph C.K. Leung,1 Sydney C.W. Tang,1 Kar Neng Lai,1 Andrew D. Paterson,2 Florent Song,2 Florent Soubrier,4 York P. Pei,1 1Div of Nephrology, Univ of Hong Kong, Hong Kong, China; 2INSERM, Univ Pierre et Marie Curie Paris 06 (UPMC), Paris, France; 3Radboud Center Renal Disorders, RadboudUMC, Nijmegen, Netherlands; 4INSERM, Univ Pierre et Marie Curie Paris 06 (UPMC), Paris, France.

Background: IgaN is the most common primary glomerular disease worldwide. Genome-wide linkage scans have identified multiple susceptibility loci for fIgAN but no disease gene has yet been identified.

Methods: To identify susceptibility genes for fIgAN, we performed WES in 109 patients from 54 families all with ~2 biopsy-proven cases and putatively affected members ascertained with persistent hematuria/proteinuria. In 3 multiplex families each with ~5 affected cases, we also performed genome-wide linkage scans under a dominant model and focused WES on regions with suggestive linkage. Standard algorithms for sequence alignment, and QC filtering were applied to identify rare (MAF<1%) deleterious variants of high (i.e. protein-truncating) and moderate (i.e. inframe indels and nonsense) effect in all affected subjects. We initially tested 1,000 cases and identified 15 candidate genes using PolyPhen-2, Sift, Mutation Assessor, CADD phred, Phylopp,Distal and VPolytron (100) impact.

Conclusions: Overall, 99.8% of the targeted exome were covered with a mean depth of 100x. We examined 19 regions with LOD >1 in 3 multiplex families and ~3,000 immunologic candidate genes. We identified 26 candidate genes (i.e. IFIH1, CD33, MSHS, ERP2, FUT2, MMN1, MNA, OAS1, TLR1, RNASEL, MARCO, THADA, BTV1A1, PTPRK, RBLT, ERC6, ASB4, LCP1, HK3, ASH1L, LTBR, FES, MPO, GPIBA, BACH2, and EMP3), each with rare deleterious variants affecting 2 or unrelated families.

Conclusions: Our results suggest extensive genetic heterogeneity in fIgAN with many disease genes each contributing to a small proportion of cases. Future studies with expanded sample size will aid selection of the most promising candidate genes for functional studies. Identification of disease genes for fIgAN has the potential to improve diagnosis and treatment.

Funding: Government Support – Non-U.S.
Discovery of New Risk Gene LoCI in IgA Nephropathy: Genome-Wide Human Assay

**Background:** IgA nephropathy (IgAN) is the most common form of glomerulonephritis in Korea. The etiology of IgAN is complex with high genetic heterogeneity. Several genome-wide association studies (GWAS) suggested that specific polymorphisms of candidate genes were associated with susceptibility to IgAN. However, previous contents of GWAS DNA chip were fixed and did not cover SNPs in exonic region and promoter region.

**Methods:** We used the Axiom™ Genome-Wide Human Assay by Affymetrix. The contents of assay are useful to investigate association between several candidate SNPs and end-stage renal disease. We selected 47,777 genes of homo sapiens in NCBI gene database and searched the SNPs in dbSNP database. And the criteria for selection exonic promoter, and intron SNPs in each gene were following: SNPs with >10% minor allele frequency, >0.1 heterozygosity, known genotype frequencies of SNPs in Asians. SNPs studied in previous study, and unknown SNPs. Logistic regression models were performed to determine odds ratio (OR), 95% confidence interval (CI), and P value. The analysis was using Helix tree program.

**Results:** To investigate whether specific polymorphisms are involved in the development of IgAN, 182 biopsy confirmed IgAN patients and 455 healthy controls were studied. We selected 378,707 SNPs. We carried out genome wide genotyping on customized Axiom™ chip were fixed and did not cover SNPs in exonic region and promoter region.

**Conclusion:** We found a candidate mutation of ARHGAP32 gene for primary FSGS by combination with whole genome linkage analysis and whole exome sequencing.

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

Underline represents presenting author.
Premature Death in First Degree Relatives of End Stage Renal Disease Patients

Einar Svarstad, Anna Reisaeter, Hans-Petter Marti, Bjorn Egil Vike

Methods: The Norwegian Population Registry has since 1960 registered all Norwegian Citizens. Sifting data are complete for most individuals since 1953. The National Cause of Death Registry has registered causes of death since 1960 and the Norwegian Population Registry has registered all individuals with ESRD since 1980. The registries were linked. All citizens born in Norway with at least one registered first degree relative were included.

Results: Five thousand and 1 year earlier in individuals who died at age 70.

Conclusion: This study demonstrated higher death rates in first degree relatives of ESRD patients.

SA-P0515

Excluding known hereditary renal disease, aHR decreased to 1.12 (95% CI 1.09-1.16).

Genetic Variants in ANCA-Associated Vasculitis: A Meta-Analysis

Paul J. Phelan, Gianpiero Cavalleri, Peter J. Conlon

Methods: Relevant articles investigating the association between genetic markers and NODAT were identified by means of a database search of PubMed, Web of Science and Google Scholar from 1945 to 2015. Variants replicated in a minimum of three studies were included for analysis. Data was analysed using a random effects model in Review Manager 5.3. The association between identified variants and NODAT was calculated at the per-study allele level, where original studies were concordant with Hardy-Weinberg Equilibrium, to generate overall significance values and effect sizes.

Results: Our literature search returned 4,147 citations. Of the 36 eligible articles identified 31 genetic variants associated with NODAT following kidney transplantation. These meta-analyses examined the pooled effect of genetic variants associated with NODAT in kidney transplant populations.

Conclusions: These meta-analyses identified three genetic variants statistically associated with NODAT. Ideally, these variants should be assessed in less heterogeneous studies with larger numbers of kidney transplant recipients with a carefully defined NODAT phenotype.

Funding: Private Foundation Support

SA-P0516

Identifying Genetic Predictors of Skin Cancer in Renal Transplant Recipients

Caragh P. Stapleton, Mark Mccormack, Devla M. Connaughton, Paul J. Phelan, Gianpietro Cavalleri, Peter J. Conlon

Background: Skin cancer in non-transplant populations have been identified via large GWAS. These results have been validated via population registries. These strategies have identified variants associated with the development of skin cancer post-transplant in a candidate gene study design. The aim of this analysis was to search for genetic variants associated with skin cancer post kidney transplantation.
SA-PO520

Comparison of Genetic Associations with Different Definitions of CKD Progression in Children

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Background: The PediGFR Consortium aims to identify genetic factors associated with pediatric chronic kidney disease (CKD) progression. The optimal definition of CKD progression for testing is unclear. To address this question, we performed genome-wide association studies (GWAS) of two different definitions of CKD progression, slope and the annual change in estimated GFR (eGFR) versus time-to-event (TTE).

Methods: We genotyped 140 CKiD participants using the Illumina HumanExome BeadChip v2.0 comprising over 250,000 markers, including putative functional eQTL variants that were implicated in common metabolic disorders. 81,460 SNPs passed quality control and were tested for association with baseline proteinuria in 129 children with chronic kidney disease (CKD) stages 1-5. SNPs were adjusted for age, gender, and the first five eigenvectors from the population stratification analysis.

Results: We identified several genetic loci that were significantly associated with proteinuria (P<10^-4), as well as new candidate loci (P<10^-8). Among the top hits, notably revealed kidney-expressed genes that were previously associated with the TGFβ pathway, renal homeostasis, IgA nephropathy, congenital kidney disease, and vascular development and its mutations manifest two different types of glomerulopathies, Denys-Drash syndrome (DDS) and Frasier syndrome (FS). In this multi-center retrospective cohort study, genotype-phenotype correlations in Korean pediatric patients with WT1 mutations were analyzed.

Methods: During the period from 2001 to 2015, WT1 mutations were detected in a total of 14 patients by direct sequencing.

Results: The patients were grouped into FS (n=10, having a mutation in intron 9) and DDS (n=13, having an exon mutation). Nine (69%) DDS patients presented as congenital nephrotic syndrome (CNS) or infantile nephrotic syndrome (INS), while 7 (70%) FS patients presented as sporadic focal segmental glomerulosclerosis. Interestingly, monozygotic twin patients with DDS presented as end-stage renal disease (ESRD) without any previous history of glomerulopathy. Progression to ESRD was noted in 11 (85%) DDS patients at the median age of 0.22 (interquartile range [IQR], 0.07-1.65) years and in 5 (50%) FS patients at 0.25 (IQR, 0.16-5.0) years. Among DDS patients, 52 (97%) of 53 developed renal failure.

Conclusion: The clinical manifestations and disease course of the Korean patients with WT1 glomerulopathy were mostly the same as those of previous reports. Of note, patients with WT1 mutations can be manifested sporadically, i.e., chronic kidney disease without any preceding history of significant proteinuria and/or NS. DSD is common in both in FS and DDS and is a useful diagnostic clue. Genetic screening should be recommended.

SA-PO525

Age of the NPHS2 p. V260E Mutation, a Cause of Childhood Steroid Resistant Focal Segmental Glomerulosclerosis, in the Ancestral Population of Black Africans in Durban, South Africa

Yo Han Ahn,1 Hee Gyung Kang,1 Hye Won Limou,1 Rajendra Bhimma,2 Sophie Limou,1 Jeffrey B. Kopp,1 Cheryl Ann Winkler,1 FNLCR, NCI, Frederick, MD; 2Univ of KwaZulu-Natal, Durban, South Africa; NIDDK, NIH.

Background: A study of 44 children with sporadic steroid resistant nephrotic syndrome (SRNS) with focal segmental glomerulosclerosis (FSGS) histology, in Durban, South Africa, revealed 25% carried two copies of a missense mutation, p. V260E, in the podocin gene, NPHS2. This mutation has previously been reported as recessively associated with FSGS in consanguineous families in regions at one time in the Omani empire, suggesting spread with this empire. We speculated that the children in our study might be cryptically recessively common descent with an ancestral population.

Methods: Inheritance of the V260E mutation from two parents with a common ancestor will result in a region of homozygosity surrounding the locus, indicating the overlap of extended haplotypes preserved around the locus. To test for this we genotyped 10 individuals homozygous for the mutation, and 74 individuals homozygous for the wild type variant, with the Illumina exome chip v2.2 comprising over 250,000 markers, including putative functional eQTL variants that were implicated in common metabolic disorders. 81,460 SNPs passed quality control and were tested for association with baseline proteinuria in 129 children with chronic kidney disease (CKD) stages 1-5. SNPs were adjusted for age, gender, and the first five eigenvectors from the population stratification analysis.

Results: We identified several genetic loci that were significantly associated with proteinuria (P<10^-4), as well as new candidate loci (P<10^-8). Among the top hits, notably revealed kidney-expressed genes that were previously associated with the TGFβ pathway, renal homeostasis, IgA nephropathy, congenital kidney disease, and vascular development and its mutations manifest two different types of glomerulopathies, Denys-Drash syndrome (DDS) and Frasier syndrome (FS). In this multi-center retrospective cohort study, genotype-phenotype correlations in Korean pediatric patients with WT1 mutations were analyzed.

Methods: During the period from 2001 to 2015, WT1 mutations were detected in a total of 14 patients by direct sequencing.

Results: The patients were grouped into FS (n=10, having a mutation in intron 9) and DDS (n=13, having an exon mutation). Nine (69%) DDS patients presented as congenital nephrotic syndrome (CNS) or infantile nephrotic syndrome (INS), while 7 (70%) FS patients presented as sporadic focal segmental glomerulosclerosis. Interestingly, monozygotic twin patients with DDS presented as end-stage renal disease (ESRD) without any previous history of glomerulopathy. Progression to ESRD was noted in 11 (85%) DDS patients at the median age of 0.22 (interquartile range [IQR], 0.07-1.65) years and in 5 (50%) FS patients at 0.25 (IQR, 0.16-5.0) years. Among DDS patients, 52 (97%) of 53 developed renal failure.

Conclusion: The clinical manifestations and disease course of the Korean patients with WT1 glomerulopathy were mostly the same as those of previous reports. Of note, patients with WT1 mutations can be manifested sporadically, i.e., chronic kidney disease without any preceding history of significant proteinuria and/or NS. DSD is common in both in FS and DDS and is a useful diagnostic clue. Genetic screening should be recommended.
Conclusions: We confirmed the association of selected genetic variants with decline in Hgb in children with progressive CKD, with differential effects by ethnicity at specific loci. Clarification of the genes involved in susceptibility to anemia has the potential to identify new therapeutic targets.

Funding: NIDDK Support

SA-PO525

Cell-Free Hemoglobin and HMOX1 in Sickle Cell Nephropathy
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Background: Chronic kidney disease (CKD) is observed in over 50% of adults with sickle cell disease (SCD) and hemoglobinuria, a consequence of intravascular hemolysis, is independently associated with CKD stage and its progression. In this study we investigate the mechanistic role of hemoglobinuria and HMOX1, the rate limiting enzyme for heme metabolism, in SCD nephropathy.

Methods: Urinary tubular (kidney injury molecule-1, KIM-1) and glomerular (neprhin) biomarkers of injury were measured in 32 SCD patients by ELISA from the University of Illinois at Chicago (UIC). We then cultured human-kidney 2 (HK2) tubular cells with lyophilized hemoglobin (L-Hb) to determine biological responses and expression of candidate genes. We examined the association of KIM-1 with 11 tag SNPs and the GT-repeat polymorphism in HMOX1 in 247 UIC SCD patients and in a separate replication cohort (Walk-PhaSST) of 482 SCD patients.

Results: Urine KIM-1 correlated with increasing urine cell-free hemoglobin concentration (P=0.005), while urine neprhin levels did not. HK2 culture studies showed increasing KIM-1 concentrations in the culture medium (P=0.01), decreasing HK2 cell viability (P=0.01), increased HMOX1 expression (P=0.0001) and protein concentration (P=0.0001) with incremental concentrations of L-Hb. We identified a SNP in HMOX1 (rs7438111, MAF=0.14) that was significantly associated with CKD stage (OR 2.8, P=0.0093) and CKD stage 3 (OR 3.0, P=0.02) in the UIC cohort and with eGFR (OR 9.8, P=0.0004) and CKD stage 3 (OR 2.3, P=0.04) in our replication cohort. UIC SCD patients with L5 GT-repeats in the promoter region of HMOX1, known to be associated with increased HMOX1 inductability and activity, had higher estimated glomerular filtration rate (eGFR)(β=9.2, P=0.01).

Conclusions: Cell-free hemoglobin contributes to sickle cell nephropathy through renal tubular injury. A tag-SNP in HMOX1, rs7438111, was associated with kidney disease and the presence of shorter (GT)n repeats correlated with increasing eGFR, raising the possibility that altered HMOX1 activity has a critical role in SCD-nephropathy.

SA-PO527

Differences in Susceptibility to Cisplatin Nephrotoxicity Among 8 Mouse Strains
Gabor Bodonyi-Kovacs, Rosa Chan, Thu H. Le. Renal Div, Univ of Virginia, Charlottesville, VA.

Background: Cisplatin is a widely used chemotherapeutic agent with remarkable efficacy, but its use is limited by significant nephrotoxicity. Significant differences in susceptibility to nephrotoxicity among individual patients have been noted, but predicting those at risk remains a challenge. To begin to identify genes that play a role in susceptibility to cisplatin nephrotoxicity (CPN), we set out to determine differences in CPN among 8 genetically distinct founder mouse strains of the Collaborative Cross: A/J, C57BL/6J, 129S1/SvImJ, NOD/ShiLtJ, NZO/HILJCAST/EiJ, PWK/PhJ, and WSB/EiJ.

Methods: 10-14 week old male mice received ip. injection of 25 mg/kg cisplatin and serum was collected 72 hours later to sacrifice. Serum urea nitrogen (BUN) was measured for the 8 strains using a nonenzymatic, colorimetric kit (Arbor Assays) and analyzed by one way ANOVA and two sided t-test. Serum creatinine was measured using an enzymatic, colorimetric kit (Crystal Chem) and analyzed by a two sided t-test for the 2 strains that showed the largest difference in BUN.

Results: The 8 strains differed significantly in their serum BUN values (p=0.042). The number of animals in each group, and the mean and SD of BUN (mg/dl) were as follows: C57BL/6J (n=5) 188.6±9.2, CAST/EiJ (n=3) 207.9±32.7, NOD/ShiLtJ (n=5) 256.7±93.0, PWK/PhJ (n=4) 240.9±127.2, WSB/EiJ (n=5) 254.1±51.6, A/J (n=5) 267.6±62.3, NZO/HILJCAST/EiJ (n=5) 290.0±50.7, 129S1/SvImJ (n=6) 319.5 ±28.3. The biggest differences were seen between the C57BL/6J and 129S1/SvImJ strains, (p = 0.0001). In direct comparison the serum creatinine was significantly different between C57BL/6J (n=10) and 129S1/SvImJ (n=9) strains, (p=0.0047) (Figure 1).

Conclusions: Crosses from “susceptible” and “resistant” mouse strains may enable identification of novel genetic determinants governing individual susceptibility to CPN.

Funding: Other NIH Support - T32

SA-PO528

The PAX2-Related SNP rs11190739 Is Associated with Accelerated Loss of GFR in Diabetes Mellitus
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Background: In embryonic kidney, PAX2 is crucial for optimal branching of the ureteric bud and final nephron number. Previous studies show that common polymorphic variants of the PAX2 gene are associated with a 10% decrease in newborn kidney size. BRENNER proposed that individuals with suboptimal nephron number might have accelerated loss of GFR in the setting of acquired renal disease in adulthood.

Methods: We used PLINK software to test for an association between PAX2 SNPs and reduced GFR among Caucasians (N=225) entered into the FIND (“Family Investigation of Nephropathy and Diabetes”) cohort available through dbGaP. This cohort of adult diabetics consisted of 175 African-American, 225 European-American and 257 Mexican Americans with eGFR data 15-25 years after onset of diabetes. Association testing that incorporated the serum creatinine was significantly different between C57BL/6J (n=10) and 129S1/SvImJ (n=9) strains, (p=0.0047) (Figure 1).

Conclusions: Crosses from “susceptible” and “resistant” mouse strains may enable identification of novel genetic determinants governing individual susceptibility to CPN.

Funding: Other NIH Support - T32
Cefepime Dosing in Modeled Critically Ill Patients Receiving SHIFT Hemofiltration or Hemodialysis Renal Replacement Therapies

Katherine N. Gharibian, Susan J. Lewis, Bruce A. Mueller. College of Pharmacy, Univ of Michigan, Ann Arbor, MI.

Background: Cefepime is an antibiotic commonly used in the ICU where acute kidney injury (AKI) is prevalent. SHIFT therapy, a 6-12 hour renal replacement therapy (RRT), also referred to as Prolonged Intermittent Renal Replacement Therapy (PIRRT) or Slow Low Efficiency Daily Dialysis (SLEDD), is increasingly utilized to help treat AKI. However, dosing information for cefepime in critically ill patients receiving SHIFT therapy is currently lacking.

Methods: Using previously-published pharmacokinetic (PK) data and a PK model developed for critically ill patients receiving SHIFT RRT, a series of 5000-subject Monte Carlo simulations were performed for 18 cefepime regimens in 8 settings including duration (8 & 10 hr), effluent rate (4 & 5 L/hr), modality (HF/HD), and time of SHIFT relative to cefepime dosing. Cefepime regimens were evaluated on the probability of attaining a free drug concentration equal to at least the minimum inhibitory concentration (MIC) for ≥260% of the dosing interval during the first 48 hours of therapy. Optimal regimens yielded a probability of target attainment (PTA) >90% for MIC values ≤8 mg/L using the smallest total daily dose.

Results: Cefepime 1 g q6 hours with a 2 g loading dose was the only regimen to yield a PTA≥90% in all 8 SHIFT settings while limiting the total daily maintenance dose to 4 g. This dosing regimen resulted in 48-hour mean trough concentrations >32 mg/L in most subjects.

Conclusions: Published cefepime CRRT doses (2 g every 12 hours) yielded 90% PTA in modeled critically ill patients receiving 8 or 10 hours of SHIFT RRT. Results warrant clinical validation.

Funding: Pharmaceutical Company Support - NxStage Medical, Inc.

SA-PO530

Identification of Optimal Ceftazidime Dosing Regimens in Modeled Critically Ill Patients Receiving SHIFT Renal Replacement Therapy

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Background: Ceftazidime is an antibiotic commonly used in critically ill patients. Ceftazidime doses of 2 g every 12 hours have been recommended for continuous renal replacement therapies (CRRT), however, no studies have evaluated the optimal dose in patients receiving SHIFT Therapy (NxStage Medical), a 6-12 hr RRT commonly referred to as Prolonged Intermittent Renal Replacement Therapy (PIRRT) or Slow Low Efficiency Daily Dialysis (SLEDD).

Methods: Pharmacokinetic (PK) data compiled from previously-published studies were used to develop models for critically ill patients receiving intermittent hemofiltration (HF) or hemodialysis (HD). Eight models were developed to account for the variability in settings including duration (8 & 10 hr), effluent rate (4 & 5 L/hr), modality (HF/HD), and time of SHIFT relative to ceftazidime dose. Using a series of 5000-subject Monte Carlo simulations, 12 cefepime regimens were applied to each model and evaluated for the probability of attaining free drug concentrations equal to or greater than the minimum inhibitory concentration (MIC)=4 for ≥260% of the dosing interval during the first 48 hours of therapy. Optimal regimens yielded a probability of target attainment (PTA) >90% for MIC values ≤8 mg/L using the smallest total daily dose.

Results: Ceftazidime administered in 4 g total daily doses (2 g q12 hours; 1 g q6 hours) yielded a PTA≥90% in all 8 RRT models. Continuous infusion of the drug (3 g continuous infusion with a 2 g loading dose) achieved similar PTA values.

Conclusions: Published ceftazidime CRRT doses (2 g every 12 hours) yielded 90% PTA in modeled critically ill patients receiving 8 or 10 hours of SHIFT RRT. Future studies should validate these findings in the clinical setting.

Funding: Pharmaceutical Company Support - NxStage Medical, Inc.
**SA-PO532**

Evaluation of Piperacillin/Tazobactam Regimens in Patients with SHIFT Renal Replacement Therapy

Susan J. Lewis,1 Katherine N. Gharibian,1 Ashita J. Tolwani,2 William Henry Fissell,3 Bruce A. Mueller.1 College of Pharmacy, Univ of Michigan, MI;1 Univ of Alabama, AL; Vanderbilt Univ, TN.

**Background:** SHIFT Renal Replacement Therapy (RRT) is a prolonged intermittent RRT to treat critically ill patients with acute kidney injury, but lacks of antibiotic pharmacokinetic (PK) data in this RRT limits its utility. This study evaluated probability of target attainable PK of piperacillin/tazobactam regimens recommended in critically ill patients receiving SHIFT RRT, using Monte Carlo Simulations (MCS).

**Methods:** Mathematical PK models were constructed using literature-derived demographic/PK data with known variability. Four daily-SHIFT settings (hemofiltration or hemodialysis with effluent rates of 5L/hour x 8 hours or 4L/hour x 10 hours) occurring at 2 different times relative to drug dose were modeled. PTA of 13 piperacillin regimens (2-4g q6-h) and 3 tazobactam regimens (0.5g q6h) with intermittent or prolonged infusion (4-hour or continuous) were evaluated. MCS generated free drug concentration profiles for each regimen in the 5,000 virtual patients. Pharmacodynamic targets were > 90% of time free piperacillin concentrations above 4x the minimum inhibitory concentration (MIC) of Pseudomonas aeruginosa (16 µg/mL) and ≥ 50% of time free tazobactam concentrations above corresponding threshold (4 µg/mL) for the initial 48 hour-therapy. The optimal regimen required > 90% of PTA for both agents.

**Results:** The attainment of > 90% of PTA required piperacillin 16g/day and tazobactam 2g/day in all SHIFT settings. Prolonged infusion was not superior to intermittent infusion to yield better PTA in patients receiving SHIFT RRT.

**Conclusions:** Piperacillin/tazobactam 4.5g q6h is recommended for critically ill patients receiving 8 or 10 hour SHIFT RRT. These PK simulation results need to be clinically validated.

**Funding:** Pharmaceutical Company Support - NxStage Medical Inc.

**SA-PO533**

Beta-Blocker Dialyzability in Chronic Hemodialysis Patients

Alvin Tieu,1 Thomas Velenosi,1 Andrew S. Kucey,1 Laura Elizabeth Mccuaig,1 Matthew SA-PO533

**Background:** There is a paucity of data available to describe beta-blocker dialyzability. Of the available information, most were obtained prior to implementation of high-flux dialysis membranes. This study aims to characterize the dialyzability of four of the most commonly prescribed beta-blockers in patients undergoing conventional high-flux hemodialysis (HD). Based on physiochemical properties, we hypothesize atenolol and metoprolol to be extensively removed by HD, while bisoprolol and carvedilol to be poorly dialyzed.

**Methods:** HD patients from the London Health Sciences Centre were recruited for a pharmacokinetic, crossover study. Atenolol (50mg), bisoprolol (5mg), carvedilol (6.25mg) and metoprolol (50mg) were administered separately to each patient over four hemodialysis sessions. Arterial and venous blood samples and total spent dialysate were collected. Beta-blocker concentrations were measured by mass spectrometry, and dialytic clearance was determined by the dialyzer and recovery clearance methods.

**Results:** Following dialysis, 6.78 mg of atenolol, 0.66 mg of bisoprolol, 0.02 mg of carvedilol, and 1.53 mg of metoprolol were recovered in spent dialysate. These amounts of diazylated beta-blockers were applied in the recovery clearance method to produce dialytic clearances of 124.0, 91.5, 1.3, and 150.2 mL/min for atenolol, bisoprolol, carvedilol, and metoprolol, respectively.

**Conclusions:** Beta-blocker efficacy can be hindered if substantial dialytic clearance occurs. Accordingly, atenolol and metoprolol were extensively cleared by HD, while carvedilol displayed low dialyzability. Contrary to previous literature, our data suggests moderate dialyzability for bisoprolol. With reported studies indicating heightened recurrence risk in HD patients prescribed highly-dialyzable beta-blockers, drug dialyzability data is critically important to optimize pharmacotherapy in HD patients. Definitive characterization of beta-blocker dialyzability can allow for determination of post-dialysis supplemental drug doses in patients.

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

**SA-PO534**

Ritonavir Exhibits Altered Pharmacokinetics in Patients with Membranous Nephropathy

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**Background:** Ritonavir (RTX) is an anti-COD2 antibody used in the treatment of glomerular diseases including membranous nephropathy (MN). There is little information about the pharmacokinetics of therapeutic proteins, including RTX in patients with glomerular diseases. The study evaluated ritonavir pharmacokinetics in patients with MN from a pilot investigation (Fervenza et al., 2010).

**Methods:** Patients with MN (n=20) received 4 RTX weekly IV infusions (375mg/m²), with a repeat of the identical treatment at 6 months. Patient baseline characteristics were: gender (17M/3F), age (49±13 y), BSA (22.2±0.24 m²), urine protein excretion (11.3±4.1 g/d), creatinine clearance (72±33 mL/min). Pharmacokinetic analysis was performed using ritonavir-plasma concentration comparisons. Pharmacokinetic parameters of drug were measured between the MN patients and published data from other populations.

**Results:** The MN population had a favorable reduction in urinary protein excretion 3 months after each RTX treatment course (7339±1411 mg/day and 4131±3441 mg/day, respectively), while creatinine clearance values were similar to baseline (72±31 mL/min and 82±37 mL/min, respectively). Patients with MN exhibited a shortened half-life (T1/2), greater volume of distribution (Vd), and enhanced clearance of RTX vs. previous reports in other patient populations. These characteristics resulted in an exposure (AUC) that was significantly reduced in patients with MN.

**Conclusions:** The pharmacokinetics of RTX in patients with MN are significantly altered compared to published data from cancer and autoimmune populations. These results suggest shorter T1/2 and lower exposures to RTX in MN may necessitate higher doses or changes to dosing frequency in order to elicit an optimal therapeutic effect.

**Funding:** Pharmaceutical Company Support - NxStage Medical Inc.

**SA-PO535**

Eculizumab Treatment Effectively Prevents C5 Cleavage without C5a Generation In Vivo

Elena Volokhina,1 Grethe Bergseth,2 Nicole Van De Heuvel,3 Lambertus P.W.J. Van den Heuvel,1 Tom Eirik Mollnes.2 Radboud Univ Medical Center, Nijmegen, Netherlands; Nordland Hospital, Bodø, Norway.

**Background:** The C5 inhibitor eculizumab has been successfully used to treat atypical hemolytic uremic syndrome (aHUS), however, available data on pharmacodynamics of this medication are limited. Recently, increased generation of C5a in a single patient with HELLP syndrome treated with eculizumab has been reported. Since this observation was unexpected, we aimed to reproduce these data and search for possible explanations for the findings.

**Methods:** Levels of C5a were analyzed in EDTA plasma samples of aHUS (n=17) and HELLP (n=3) study patients using appropriate ELISA kits. C5a was measured by using another two commonly available commercial kits. When eculizumab was added in vitro to normal human serum prior to activation, no generation of C5a was measured by one of the commercial ELISA kits, increased significantly in all aHUS patients after the first eculizumab dose and then at various time points during treatment.

**Results:** In line with the report on HELLP patient, the C5a values, measured by one of the commercial ELISA kits, increased significantly in all aHUS patients after the first eculizumab dose as compared to the values obtained before treatment (p<0.016). C5a remained elevated throughout the treatment period. Such increase could not be reproduced by using another two commonly available commercial kits. When eculizumab was added in vitro to normal human serum prior to activation, no generation of C5a was measured by all used kits.

**Conclusions:** Our data indicate that existing commercial assays require validation for specificity before being used to monitor effect of eculizumab, especially in clinical laboratory practice. This example illustrates how false conclusions can be drawn when based on results from one single commercial assay not satisfactorily validated for the purpose it is used.

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

**SA-PO536**

Sensitive, Reliable and Easy-Performed Laboratory Monitoring of Eculizumab Therapy In Atypical Hemolytic Uremic Syndrome

Elena Volokhina,1 Grethe Bergseth,2 Thea J. van der Velden,1 Jack F. Wetzels,1 Lambertus P.W.J. Van den Heuvel,1 Tom Eirik Mollnes.2 Radboud Univ Medical Center, Nijmegen, Netherlands; Nordland Hospital, Bodø, Norway.

**Background:** Atypical hemolytic uremic syndrome is a severe renal illness caused by complement dysregulation. Treatment with the complement C5 inhibitor eculizumab is effective, but associated with high costs. Laboratory monitoring of these patients with an exposure (AUC) that was significantly reduced in patients with MN.

**Funding:** Government Support - Non-U.S.
respect to complement function has not been standardized. The aim of this study was to evaluate novel complement functional assays for their application in routine follow-up of eculizumab-treated patients.

Methods: Complement activity in serum samples was analyzed using Wieslab® complement screen assay. The presence of eculizumab-C3 complexes in serum, EDTA plasma samples and in urine was measured using ELISA. Levels of sC5b-9 in urine were measured using electroluminescent epitope assay.

Results: First, we documented that the Wieslab® complement screen assay showed a sensitivity of 1-2% of C5 activity by adding purified C5 or normal human serum to a C5 deficient serum. We found that all the patient samples obtained during the standard treatment course, were completely blocked for terminal complement pathway activity. Moreover, complement remained fully blocked when intervals between the eculizumab infusions were extended to four weeks. Levels of complexes between eculizumab and C5 were inversely correlated to the complement activity (p<0.01). Third, urinary sC5b-9 levels from eculizumab-treated patients into normal serum, revealed that eculizumab was present in excess up to four weeks after infusion. Finally, we showed that increased urine sC5b-9 disappeared after eculizumab treatment.

Conclusions: We demonstrate sensitive, reliable and easy-performed assays to monitor eculizumab-treated patients, which can be used to design individual dosage regimens.

Funding: Government Support - Non-U.S.

SA-PO537

Background: AKB-6548 is a novel, once-daily, oral hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) in development for the treatment of anemia in non-dialysis dependent (NDD) and dialysis dependent (DD) chronic kidney disease (CKD). Studies in NDD-CKD patients have shown AKB-6548 produces physiologic increases in erythropoietin, enhances iron mobilization, and produces a dose dependent increase in hemoglobin levels.

Methods: The pharmacokinetics (PK) of AKB-6548 have been evaluated in single and multiple dose studies in healthy volunteers and CKD patients (NDD-CKD and DD-CKD) over a broad range of dose levels. An analysis of results across studies was conducted to assess the potential impact of renal function on selecting the dose levels and dosing regimen in CKD patients. The analyses evaluated dose-linearity in drug exposure, clearance routes of AKB-6548 and its metabolites, as well as the impact of CKD severity and the hemodialysis procedure on drug disposition.

Results: In healthy volunteers, AKB-6548 demonstrated dose linearity and proportionality over single doses of 80-1200 mg and multiple doses of 500-900 mg/day. The PK parameters of AKB-6548 in healthy volunteers, NDD-CKD and DD-CKD patients were similar except for a slightly longer half-life with declining renal function (4.7 hr., 7.9 hr. and 9.1 hr., respectively). A mass balance study (using 14C-labeled drug) in healthy volunteers demonstrated both renal and fecal routes of parent drug and metabolite clearance, supporting use of AKB-6548 in CKD patients without significant differences in drug exposure. Moreover, AKB-6548 was minimally cleared by the hemodialysis procedure and the PK parameters were similar whether AKB-6548 was administered prior to or following dialysis.

Conclusions: The results demonstrate a linear dose-exposure relationship for AKB-6548 over a wide range of dose levels and support the utility of once-daily dosing and similar dose levels across the spectrum of CKD severity.

Funding: Pharmaceutical Company Support - Akebia Therapeutics

SA-PO538
Nonclinical Pharmacokinetics and Toxicokinetics of RG-012, an Inhibitor of MicroRNA-21 Being Investigated for Treatment of Alport Syndrome John Stewart Grundy,1 Kai Liu,2 Steven Neben,1 Cindy L. Berman,2 Deidre Mackenna,1 Neil W. Gibson.1 1Regulus Therapeutics, San Diego, CA; 2Berman Consulting, Wayland, MA.

Background: RG-012 is a single-stranded chemically modified oligonucleotide being developed to treat patients with Alport syndrome, which is characterized by loss of renal function associated with defects in specific collagen genes expressed in the kidney glomerulus filtration membrane. RG-012 inhibits miR-21, a microRNA target known to have increased expression in context of kidney stress and associated with renal dysfunction.

Methods: In vitro pharmacokinetic (PK) evaluations of RG-012 conducted during preclinical development included: plasma protein binding, metabolic stability in whole blood and liver lysates, and CYP3A4 inhibition/induction potential in cryopreserved human hepatocytes. In vivo PK and toxicokinetic (TK) properties of RG-012, and its major active metabolite (RG0005), were determined upon subcutaneous dosing of RG-012 in a set of nonclinical PK, pharmacology, and safety studies in CD-1, SV129, and COL4A3 mice (6.25–450 mg/kg) and cynomolgus monkeys (10–225 mg/kg/week).

Results: Both RG-012 and RG0005 were highly bound (≥98%) to proteins in plasma from mice, monkeys, and humans. RG0005 was the only major degradation product seen in whole blood and liver lysates from all three species. RG-012 exhibited little to no displacement from actively translating polysome complexes and subsequent derepression of messenger RNA targets. As levels of Let-7a, a control microRNA to which RG-012 has no complementarity, were efficacious in the Col4A3 mouse models. Loss of miR-21 from the polysomes was specific to or following dialysis.

Conclusions: RG-012 demonstrated dose dependent displacement of miR-21 from polysomes in both liver and kidney with a maximum effect reached at dose levels that are efficacious in the Col4A3 mouse models. Loss of miR-21 from the polysomes was specific as levels of Let-7a, a control microRNA to which RG-012 has no complementarity, were unaffected. In the liver, target engagement was also assessed using mRNA derepression of a set of confirmed miR-21 target genes. Here, target gene derepression strongly correlated with polysome displacement. This comparison was not possible in kidney, however, because target genes are not regulated in kidneys in the absence of stress.

Funding: Pharmaceutical Company Support - Regulus Therapeutics

SA-PO539
Novel Methodology for Assessing Inhibition of MicroRNA-21 by RG-012, a MicroRNA Therapeutic in Development for the Treatment of Kidney Dysfunction in Patients with Alport Syndrome John Rolf Androsavich, Xueqing Liu, Shweta Pandya, Deidre Mackenna. Regulus Therapeutics, San Diego, CA.

Background: microRNA-21 (miR-21) is upregulated in animals models with kidney dysfunction and also in patients with chronic kidney disease (CKD). RG-012 is a miR-21 inhibitor entering clinical development for treatment of CKD in Alport syndrome (AS) patients. RG-012 demonstrates activity both as a monootherapy and in combination with the ACE inhibitor ramipril in the Col4A3 deficient mutant mouse model of AS.

Methods: Two distinct methods have been developed to evaluate the ability of RG-012 to inhibit miR-21 in preclinical studies – the polysome shift assay (PSA) and alterations in the expression of miR-21 target mRNAs. The PSA measures direct target inhibition at the level of the physical interaction between microRNA and messenger RNA targets. C57Bl/6 mice were treated subcutaneously with RG-012 at doses ranging from 0.1 to 100 mg/kg. Tissue homogenates were separated using sucrose gradient ultracentrifugation, with microRNAs asociating with messenger RNA targets in the heavier polysome fraction. The ability of RG-012 to displace the target miR-21 from the polysome containing fraction was used to assess direct target engagement.

Results: RG-012 demonstrated dose dependent displacement of miR-21 from polysomes in both liver and kidney with a maximum effect reached at doses that are efficacious in the Col4A3 mouse models. Loss of miR-21 from the polysomes was specific as levels of Let-7a, a control microRNA to which RG-012 has no complementarity, were unaffected. In the liver, target engagement was also assessed using mRNA derepression of a set of confirmed miR-21 target genes. Here, target gene derepression strongly correlated with polysome displacement. This comparison was not possible in kidney, however, because target genes are not regulated in kidneys in the absence of stress.

Conclusions: RG-012 directly and specifically inhibits miR-21 resulting in its displacement from actively translating polysome complexes and subsequent derepression of messenger RNA targets.

Funding: Pharmaceutical Company Support - Regulus Therapeutics

SA-PO540
Tacrolimus Pharmacokinetics in Nephrotic Stage Mara Medeiros,1 Saul Valverde,1 Luis Velasquez-Jones,1 Ana M. Hernández,2 Gilberto Castañeda-Hernández,2 Guido Filler.1 1Hospital Infantil de México Federico Gómez, Mexico; 2CINVESTAV, IPN, Mexico; 3Children's Hospital, Univ of Western Ontario, Canada.

Background: While tacrolimus (Tac) therapy is not first-line therapy for childhood nephrotic syndrome, it is often used instead of cyclosporine to ameliorate the side effects. The pharmacokinetics of Tac can be influenced by many conditions, and it has a high plasma protein binding. The Tac pharmacokinetics during relapse and remission of childhood nephrotic syndrome have not been well described.

Methods: We performed 14 pharmacokinetic (PK) profiles (with measurements before and 0.5, 1, 2, 4 and 12 hours post intake) in 7 children with steroid-resistant nephrotic syndrome (SRNS) during relapse and in remission. These data were compared with historical PK data of 161 PK profiles in 87 pediatric renal transplant recipients with measurements before 0.5, 1, 5, 11, 15, 23, 48, 6, 8 and 12 hours post intake. Tac levels were measured using the Abbott Tacro II assay. We used descriptive statistics to generate percentiles and compared these with the SRNS patients. We also compared the PK profiles during relapse and remission.

Results: Median age of SRNS patients was 3.2 years. Tacrolimus dose, biochemical values and pharmacokinetics parameters are shown in Table 1. Values as median and interquartile range.

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747A
Clinical and Genetic Determinants of Longitudinal Dose-Corrected CNI Exposure in Children After Renal Transplantation

Background: Calcineurin-inhibitors (CNI) have a narrow therapeutic index and dosing is difficult due to inter- and intra-individual variation in pharmacokinetics (PK). Polymorphisms in genes involved in drug metabolism can play a critical role in individual exposure. Data concerning long-term CNI exposure in relation to dose in children are scarce and based in general upon trough levels. We present the longitudinal follow up of 12-hour CNI PK in relation to dose, clinical and genetic factors in a cohort pediatric renal allograft recipients.

Methods: Retrospective single center study in subjects after renal transplantation (age 0-20 yrs) with annual PK assessments (6-point AUC0-12hr) for tacrolimus (Tac) or cyclosporine (CsA). Clinical and laboratory data were retrieved. Analysis of polymorphisms CYP3A4, CYP3A5, CYP3A7, POR was performed.

Results: We collected 180 “full” AUCs for Tac, 56 for CsA in 51 kids. Mean age at Tx: 9.9 yrs(1-19); FU after Tx: 4.6 yrs (0-16). Dose-corr. exposure (AUC/Dose in mg/hr/ml) was demonstrated stable dose-corr. exposure for ages <15 yrs, and was higher only for >15 yrs (Tac: <5yrs-15 yrs: 44 (95%CI: 40-48) >15yrs: 73.4 ng hr/ml per mg/m2; CsA: 31 (26-38) ng hr/ml per mg/m2). Significant associations of TTT to Tac dose, CL and AUC/TBW were noted with sex sub-analysis and summarized as Phenotypic Mean with 95%CI of WT compared to variant  in table. These data suggest RTR with higher doses in AA (P<0.0001). Significant associations of TTT to Tac dose, CL and AUC/TBW were noted with sex sub-analysis and summarized as Phenotypic Mean with 95%CI of WT compared to variant  in table. These data suggest RTR with higher doses in AA (P<0.0001).

Conclusions: Sex-race differences in TAC PK contribute to differential dosing requirements in AA vs C. A more individualized approach to chronic TAC immunosuppression integrating sex-race with TDM and a standardized adverse effect assessment may benefit RTR.

Funding: NIDDK Support, Pharmaceutical Company Support - Astellas Scientific and Medical Affairs, Inc

SA-PO543

Sex and ABCB1 Haplotypes Associations with Tacrolimus Pharmacokinetics in Renal Transplant Recipients

Background: Tacrolimus (TAC) is the primary calcineurin inhibitor in immunosuppression in renal transplant recipients (RTR). TAC exhibits interpatient variability in pharmacokinetics (PK) attributed primarily to CYP 3A5 isoenzymes and P-glycoprotein (Pgp). Pgp is encoded by the ABCB1 gene. The common single nucleotide polymorphisms (SNPs): rs1045642 and rs2032582, have conflicting associations to TAC PK. This study objective evaluated these common SNP as haplotypes in relation to TAC PK.

Methods: During a 12-hr PK study, trough (C0), apparent clearance (CL) and lean body weight (LBW) normalized CL were determined in 29 female and 36 male African American (AA) and Caucasian (C) stable RTR greater than 6 months post-transplant receiving TAC and mycophenolic acid. TAC dosage was adjusted to C0 range of 4-9 ng/ml. The ABCB1 SNPs: c.1236C>T/rs1128501, c.2677G>T/rs2032582, and c.3435C>T/rs1045624 have conflicting associations to TAC PK. This study objective evaluated these common SNP as haplotypes in relation to TAC PK.

Results: The ABCB1 haplotypes have important impact into interpatient variability in TAC PK post renal transplant and the role of P-gp that is also influenced by sex. Results: The ABCB1 SNPs c.1236C>T/rs1128501, c.2677G>T/rs2032582, and c.3435C>T/rs1045624 have conflicting associations to TAC PK. This study objective evaluated these common SNP as haplotypes in relation to TAC PK.

Conclusions: The ABCB1 haplotypes provide important insight into interpatient variability in TAC PK post renal transplant and the role of P-gp that is also influenced by sex.

Funding: NIDDK Support, Pharmaceutical Company Support - Astellas Scientific and Medical Affairs, INC

SA-PO544

Pharmacokinetics and Pharmacodynamics of Tacrolimus, and NFAT Regulated Gene Expression in Kidney Transplant Patients

Background: Suppression of genes that are regulated by the nuclear factor of activated T-cells (NFAT) is an effect of calcineurin inhibitors. We correlated the pharmacodynamics to the pharmacokinetics of tacrolimus.

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478A
Methods: This study was undertaken in the University Hospitals of Ulm (Frieder Keller) and Heidelberg (Claudia Sommerer, Thomas Giese, Martin Zeier). Tacrolimus trough concentrations (Trough) and 1.5 – 2 hours later the peak concentrations (Cpeak) were measured by LCMS. Simultaneously, the NFAT trough effect (Trough) and the nadir effect (Enadir) were determined. The pharmacokinetic half-life (T1/2) was estimated from peak (Cpeak) and trough concentrations (Trough) considering the time distance between steady-state peak and troughs (10.5 – 10 hours). The pharmacodynamic concentration producing the half-maximum effect (CE50) and the Hill coefficient (H) were estimated from trough effect (Trough) at trough concentrations and from nadir effect (Enadir) at peak concentrations. The two equations were solved by numerical iteration for an estimate of the two unknown parameters (CE50, H).

Results: A total of 10 stable kidney transplant patients were included. The median age was 58 years and the median serum creatinine was 306 µmol/l. The pharmacokinetics of tacrolimus were estimated with T1/2 = 11 hours, CL/F = 64 l/h and Vd/F = 480 l. The median value for NFAT was 89% (Trough) of normal gene expression, and the nadir effect was 43% (Enadir) representing the strongest immunosuppression of basal gene expression. The pharmacodynamics of tacrolimus were estimated with CE50 = 7.7 ng/ml and the Hill coefficient with H = 4.6, respectively.

Conclusions: While on triple immunosuppression, the NFAT pharmacodynamics indicate a low concentration producing the half-maximum effect and a high Hill coefficient. These findings suggest a narrow trough-to-peak target concentration range of 4.0 to 9.5 ng/ml for tacrolimus.

SA-PO546
Renal Nitrate Clearance in Chronic Kidney Disease

Background: Endogenously synthesised nitric oxide (NO) is rapidly oxidised to nitrate and nitrite. These oxidation products can be recycled back into nitric oxide via a complex entero-salivary pathway, thus preserving NO activity. It has previously been shown that 60% of circulating nitrate is excreted in the urine in 48 hours with the fate of the remainder unknown. 24-hour urinary nitrate excretion is often used to estimate total body nitrite oxide synthesis rates. It is not known what effect declining GFR has on renal nitrate clearance.

Methods: 27 subjects, 14M,13F, median age 70 (range 27-74 years) with CKD-EPI eGFR between 9 and 89 were recruited. Following 24h low nitrate diet plasma nitrate concentration and 24 hour urinary nitrate excretion were measured to determine renal nitrate clearance using a microplate spectrophotometric method. We used a 1-compartment model to investigate nitrate clearance at lower eGFRs, we suggest that non-renal clearance is responsible for a greater proportion of nitrate elimination as GFR falls. We conclude that 24 hour urinary nitrate excretion cannot be considered a reliable measure of total body nitrite oxide synthesis in CKD. Elucidating the non-renal pathways of loss of the NO storage molecule, nitrate, may lead to novel therapeutic strategies in CKD and cardiovascular disease.

Conclusions: As plasma nitrate concentration is unchanged despite diminished renal nitrate clearance at lower eGFRs, we suggest that non-renal clearance is responsible for a greater proportion of nitrate elimination as GFR falls. We conclude that 24 hour urinary nitrate excretion cannot be considered a reliable measure of total body nitrite oxide synthesis in CKD. Elucidating the non-renal pathways of loss of the NO storage molecule, nitrate, may lead to novel therapeutic strategies in CKD and cardiovascular disease.

SA-PO545

2-Sample Iohexol Plasma Clearance: The Clear Choice for Measuring Kidney Function in Rats

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Background: The lack of simple and sensitive tools for longitudinal kidney function assessment in rodent models has impeded analysis of CKD onset and progression and the development of novel therapies. Two reference methods for pCl calculation were used: a 2-compartment model (2 COM) measured via the Jaffrey method, FITC-inulin via fluorometry, and iohexol via UPLC-MS. The pharmacodynamics of tacrolimus were estimated with CE50 = 7.7 ng/ml and the Hill coefficient (H) were estimated from trough effect and from nadir effect considering the time distance between steady-state peak and troughs (10.5 – 10 hours). The pharmacodynamic concentration producing the half-maximum effect (CE50) and the Hill coefficient (H) were estimated from trough effect (Trough) at trough concentrations and from nadir effect (Enadir) at peak concentrations. The two equations were solved by numerical iteration for an estimate of the two unknown parameters (CE50, H).

Methods: Progressive CKD was induced with a 0.25% adenine diet in male Sprague-Dawley rats (N=8). Following serial tail vein injections of iohexol (51.92 mg/kg) and a radio-contrast agent, compared to previously validated inulin pCl in rats to estimate GFR.

Results: Plasma creatinine was not significantly elevated and trapezoidal approximation (TRA) of area under the curve. Two reference methods for pCl calculation were used: a 2-compartment model (2 COM) measured via the Jaffrey method, FITC-inulin via fluorometry, and iohexol via UPLC-MS. The pharmacodynamics of tacrolimus were estimated with CE50 = 7.7 ng/ml and the Hill coefficient with H = 4.6, respectively.

Conclusions: While on triple immunosuppression, the NFAT pharmacodynamics indicate a low concentration producing the half-maximum effect and a high Hill coefficient. These findings suggest a narrow trough-to-peak target concentration range of 4.0 to 9.5 ng/ml for tacrolimus.

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749A
Conclusions: The pharmacodynamic effect of tenapanor, as judged by stool Na content, was greatest when tenapanor was taken before food. This supports taking tenapanor before meals in future trials.

Funding: Pharmaceutical Company Support - AstraZeneca

SA-PO548

Triferic Does Not Induce Non-Transferrin Bound Iron or Labile Plasma Iron: In-Vitro/In-Vitro Correlation

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Background: Triferic is a complex iron salt approved for administration via hemodialysis to maintain hemoglobin in patients with CKD HD. Triferic crosses the dialyzer membrane and binds to transferrin during hemodialysis replacing the obligatory iron losses in HD patients. Serum iron and transferrin saturation (TSAT) values rise after HD and return to the baseline by the start of the next dialysis session.

Methods: A pharmacokinetic (PK) study in healthy volunteers administered up to 10 mg of Triferic iron over 4 hours and up to 20 mg Triferic iron over 12 hours assessed the PK of serum total iron (sFe-total) and transferrin bound iron (TBI). An in-vitro study assessed labile plasma iron (LPI). Triferic iron was added to plasma like medium (40 mg/mL human serum albumin) at a concentration range of 0 to 112 mg/dL. In addition, Triferic was added to 5 different human plasma’s (TSAT, range 10 - 46%; total iron binding capacity (TIBC), mean 374 mg/dL, range: 342-446 mg/dL) across a concentration span up to and exceeding 100% TSAT. LPI was measured in the presence of 40 mM ascorbate using dihydrodorohadmine (DHR)-123 in the presence of 50 mM deferiprone (DFO) to detect iron-catalyzed radical generation.

Results: In the human PK study, sFe-total and TBI showed an identical PK profile. Non-transferrin bound iron (NTBI), calculated as the difference between sFe-total and TBI, showed no dose dependent increase up to a TSAT of 100%. In plasma like medium, LPI increased with increasing concentrations of Triferic iron. When Triferic was added to human plasma, there was a small increase in LPI observed when iron concentrations were less than 100% TSAT. The mean magnitude of LPI (expressed in concentration units) at approximately 100% TSAT was 5.35 mg/dL (mean 1.4% of the total iron concentration). Once 100% TSAT was exceeded, the LPI increased rapidly.

Conclusions: Triferic rapidly donates iron to transferrin in vivo and in vitro. In vivo, at TSAT less than 100%, NTBI was minimal. In vitro, the LPI results confirm the lack of redox active iron in plasma until the plasma TIBC is exceeded.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

SA-PO549

Impact of Tubular Luminal H+/Organic Cation Antiporter, MATE, on Imatinib-Induced Fluid Retention

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Background: A tyrosine kinase inhibitor, imatinib (IMA) is the first class agent against chronic myeloid leukemia. Although little is known about mechanism involved, more than 50% of imatinib-treated patients suffering from edema. In vitro study reported that clinical blood level of IMA inhibits multidrug and toxin extrusion (MATE, SLC47A)-mediated transport of metformine, a hypoglycemic drug. MATE is highly expressed in the brush border membrane of proximal tubular cells mediating the efflux of organic cations, such as metformin, monamines. The renal dopaminergic system is likely responsible for regulating >50% of net renal salt and water excretion when salt intake increases. In this study, we test a hypothesized that IMA prevents natriuresis by inhibiting MATE-mediated dopamine (DA) secretion into tubule lumen and consequently causes edema.

Methods: C57BL/6 wild type mice (WT) and Mate1 knockout mice (KO) were used. CYP3A4 and 3A5 expressed in HepG2s for 24 h, when cells were lysed. Underline represents presenting author.

Conclusions: More than 50% of imatinib-treated patients suffering from edema. In vitro study reported that clinical blood level of IMA inhibits multidrug and toxin extrusion (MATE, SLC47A)-mediated transport of metformine, a hypoglycemic drug. MATE is highly expressed in the brush border membrane of proximal tubular cells mediating the efflux of organic cations, such as metformin, monamines. The renal dopaminergic system is likely responsible for regulating >50% of net renal salt and water excretion when salt intake increases. In this study, we test a hypothesized that IMA prevents natriuresis by inhibiting MATE-mediated dopamine (DA) secretion into tubule lumen and consequently causes edema.

Funding: Government Support - Non-U.S.

SA-PO550

Optimizing Between-Patient Variability in Response to Renoprotective Drugs: Meta-Analysis of Rotation Trials

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Background: Individual response to albuminuria lowering intervention is highly variable between patients. To investigate whether up titrating the dose of drug, changing the mode of intervention (with similar or different drug classes), or lowering dietary sodium intake improves individual response variability, we meta-analyzed individual responses to different modes of anti-albuminuric intervention in non-diabetic and diabetic patients.

Methods: Randomized rotation trials were analyzed to assess correlation of patient-specific responses (n=216 patients) to anti-albuminuric interventions. Included studies (N=20) compared the anti-albuminuric effect of up titrating the dose of intervention in the RAS (RASi) (N=10 comparisons) and NSAIDS (N=1), rotation within the same class of RASi (e.g. ACEi to ARB; N=5) or NSAIDs (N=3), rotation between RASi and NSAIDs (N=2), and rotation from high to low sodium intake during RASi (N=1). A two stage meta-analysis was performed. First, deeming regression was conducted in each study to assess correlation in response. Individual study results were then meta-analyzed. Albuminuria was measured in 24-hr urine samples.

Results: The albuminuria response to one dose of RASi or NSAID positively correlated with the response to a higher dose of RASi or NSAID, rotation within the same class of RASi or NSAIDs, rotation between RASi and NSAIDs, and rotation from high to low salt intake. Correlations were consistent in diabetic and non-diabetic patients.

Conclusions: The correlations observed in this study indicate that patients poorly responding to one dose or mode of albuminuria lowering intervention also respond poorly to other doses or modes of intervention in the RAS. Whether other drugs targeting pathways beyond the RAS improve individual response variability requires further study.

SA-PO551

Acute Kidney Injury Serum Ureaplates Hepatic Transcription of Cytochrome P450 3A4 and 3A5

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Background: Hepatic drug metabolism by cytochrome P450 3A (CYP3A) is reduced in end stage kidney disease (ESKD) and acute kidney injury (AKI). The underlying mechanisms are uncertain. Previously we reported suppression of CYP3A4 mRNA transcription when human hepatocytes ( HepG2) were exposed to serum from ESKD patients compared to healthy adults. CYP3A4 and 5 protein concentrations were unchanged. We now investigate whether serum from patients with AKI elicits similar results.

Methods: Serum was collected from critically ill adults with varying AKI severity. Sera from 1KDGIO 0 (n=15) and KDIGO 3 (n=16) AKI patients were applied individually to HepG2s for 24 h, when cells were lysed. CYP3A4 and 3A5 gene expression was examined by RT-qPCR. CYP3A4 and CYP3A5 protein expression was examined by Western blotting. The sera were also applied to HepG2 in a pooled fashion, alongside pooled sera from adults with ESKD prior to hemodialysis (n=10) and healthy adults (n=6), to allow comparison with previous data.

Results: AKI serum exposure doubled CYP3A4 gene expression compared to No AKI serum (p=0.005 significant and p=0.003 pooled). AKI serum CYP3A5 mRNA increased approx. 25% compared to No AKI serum (p=0.11 individual and p=0.0098 pooled).

Comparison of Pooled Serum (10%) Effects on HepG2 CYP3A4 and CYP3A5

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Results: Indoxyl sulfate caused a concentration-dependent decrease in Huh7 CYP3A4 expression with an IC50 value of 179.8 ± 20.1 μM. In CKD rats, indoxyl uremic toxins: indoxyl sulfate, p-cresyl sulfate and hippuric acid levels significantly lower than CKD animals and similar to control animals. Hepatic CYP3A2 mRNA expression was significantly decreased by 90% in rats with CKD (P<0.05); however, rats with CKD given AST-120 had a 25% recovery in CYP3A2 mRNA expression. Rats with CKD had decreased AST-120 had indoxyl sulfate, p-cresyl sulfate and hippuric acid levels significantly lower than CKD animals and similar to control animals. Hepatic CYP3A2 mRNA expression was significantly decreased by 90% in rats with CKD (P<0.05); however, rats with CKD given AST-120 had a 25% recovery in CYP3A2 mRNA expression. Rats with CKD had decreased hepatic CYP2C11 mRNA expression that was not recovered by AST-120.

Conclusions: Uremic concentrations of indoxyl sulfate decreased CYP3A4 mRNA expression in Huh7 cells. AST-120 given to rats with CKD reduced indoxyl sulfate, p-cresyl sulfate and hippuric acid levels similar to control levels. Hepatic CYP3A2 mRNA expression was decreased in CKD and partially recovered by AST-120. AST-120 did not affect the downregulation of CYP2C11 in rats with CKD. Therefore, gut-derived uremic toxins may partially mediate the downregulation of hepatic CYP3A in CKD.

SA-PO555

The Effect of AST-120 on Hepatic and Intestinal Drug Transporter Expression in Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) is the progressive decline in renal function over time. There is a marked reduction in both renal and non-renal drug clearance in CKD. AST-120 is an oral absorbent that promotes the elimination of gut-derived toxins that accumulate in CKD due to impaired clearance. It is hypothesized that there will be a reduction in the expression of drug transporters in CKD conditions. AST-120 will help recover drug transporter expression in CKD by decreasing uremic toxins that accumulate in CKD.

Methods: In vivo: CKD was induced in Wistar rats by treatment with adenine (0.7%) in standard rodent chow for 7 weeks. Treatment groups received AST-120 in the final 3 weeks to decrease the concentration of uremic toxins. Expression of hepatic and intestinal transporters were determined by real-time PCR. In vitro: Using the human hepatoma cell line Huh7, specific uremic toxins (e.g. indoxyl sulfate, p-cresyl sulfate, CMPF) will be tested to see if they directly impair rosuvastatin transport. Rosuvastatin uptake will be measured with ultra-performance liquid chromatography coupled to mass spectrometry.

Results: Preliminary results have shown that OATP2 expression is decreased by 25% in CKD rat livers compared to control. Treatment with AST-120 causes a significant reduction in the plasma concentration of the uremic toxins indoxyl sulfate and p-cresyl sulfate. AST-120 treatment restores OATP2 expression to control levels.

Conclusions: Decreased hepatic OATP2 expression in CKD will result in reduced clearance of substrate drugs. This could lead to toxicity if a lowered dose is not administered. On average a CKD patient will be co-prescribed 10 different drugs. Clarifying the impact of CKD on drug transporter expression and activity will help guide dosing in this patient population.

SA-PO554

Patient Characteristics and Genetics Contribute to Kidney Function After Cisplatin Therapy

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Background: It is known that kidney function can decline after a single dose of cisplatin necessitating alternate chemotherapy regimens. The current study explored the contribution of patient characteristics and polymorphisms in drug metabolism and transport genes relevant to cisplatin kidney disposition on changes to renal function.

Methods: Blood (5mL) was obtained from patients (n=206) who received cisplatin. Genotyping assessments included candidate SNPs in kidney uptake and efflux transporters (SLC22A4, ABCB2, SLC47A1) and metabolism pathways (GSTA1, GSTP1, GGT1). Genotyping was performed using QuantStudio multiplex assays and coded [0( wt/ wt), 1( wt/var), or 2( var/var)]. Glomerular filtration rate (GFR, mL/min/1.73m2) and changes from baseline to 6 months after the time of cisplatin were calculated. Univariate and multivariate analyses were performed using patient characteristics and genotyping results.

Results: Patient demographics (mean±sd) included: age 55±14 y, weight 80±12 kg, BSA 1.9±0.3, Caucasian 90%, gender (50%M/50%F), and cisplatin dose (65±23 mg/m2). Specific patient characteristics that significantly (p<0.05) contributed to a beneficial effect on GFR were non-Caucasian race, baseline GFR, and non-fractonated cisplatin dosing. Genetic variant in GSTP1/GST pi-1 variant (rs1695) and wildtypes in SLC22A4/OCR2 (rs2279463 and rs3127573) significantly (p<0.05) contributed to a beneficial effect on GFR. Variables retained in the final model (R² 25.23%, P <0.0001) were: Change in GFR: 38.083 - 0.1714 (weight) – 0.3685 (baseline GFR) + 5.893 (GSTP1; rs1695).

Conclusions: The results from this study demonstrate the combined role of patient characteristics and genetic variants in drug disposition genes on changes to GFR secondary to cisplatin. Appropriate risk stratification based on patient characteristics and genetics may be used to simplify precision medicine to reduce the risk of kidney injury from cisplatin and potentially other nephrotoxins.

Funding: NIDDK Support
in LN patients. Pharmacokinetics of CTX and 4-hydroxycyclophosphamide (4OHCTX) were obtained from 22 patients randomly enrolled from 77 LN patients and applied to explore the mechanism.

Results: GSTA1, one of detoxification enzymes to CTX, gene polymorphism could greatly influence the therapeutic outcome to CTX treatment in these 77 LN patients. LN patients with a GSTA1*4 mutation (CT heterozygous) had a risk of none-response (P = 0.005).

Data suggest that FGF23 may directly suppress osteoblast maturation and mineralization, even when removed from the uremic milieu. We thus hypothesized that treatment response due to less exposure to activated 4OHCTX. A pharmacogenomic approach using the GSTA1 SNP may be useful for predicting clinical efficacy to CTX therapy in LN patients, and facilitating individualized therapy.

Pharmacokinetics data indicated that patients with a GSTA1*4 heterozygous variant had a lower exposure to 4OHCTX compared to wild-type patients (12.8(9.8, 19.5) μg/ml, P = 0.038), but not CTX. And clinical efficacy was significantly related to higher exposure to 4OHCTX, (P = 0.038).

Conclusions: LN patients with GSTA1*4 heterozygous genotypes had poor CTX treatment response due to less exposure to activated 4OHCTX. A pharmacogenomic approach using the GSTA1 SNP may be useful for predicting clinical efficacy to CTX therapy in LN patients, and facilitating individualized therapy.

SA-PO557

Effect of Growth Factors on Bone Mineralization in Health and CKD

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Background: Children with chronic kidney disease (CKD) develop unexplained resistance to PTH and GH. Moreover, bone expression of FGF23 is very high in CKD. Data suggest that FGF23 may directly suppress osteoblast maturation and mineralization in mice (Weng JBMR 2009); however, it is not known whether excess expression of this hormone has direct effects on bone cells in CKD. We have previously demonstrated that primary osteoblasts isolated from patients with CKD have altered proliferation, differentiation and mineralization characteristics, suggesting that CKD results in intrinsic changes to osteoblast biology, independent of circulating mineral ion and hormone concentrations.

Methods: To evaluate the interaction between CKD and 1,25D therapy on osteoblast maturation and mineralization, primary human osteoblasts from 3 healthy controls, 3 pediatric dialysis patients with low bone turnover (adynamic bone) and 3 pediatric patients with high bone turnover (2HPT) were cultured under pro-mineralizing conditions consisting of 10μM β-glycerolphosphate and 100 μg/ml ascorbic acid in the presence of 1,25D at 1, 2.5, and 4 weeks of growth under mineralizing conditions, cells were washed with PBS, fixed with 10% formalin, and stained with 2% Alizarin Red S. The amount of mineral content was assessed by measuring absorption of acetic acid-extracted Alizarin Red S dye (at 405 nm) normalized by live cell concentration (as assessed by absorption at 570 nm) of methanol-extracted Crystal Violet staining obtained from parallel cultures.

Results: Diminished mineralization is present in CKD; as previously demonstrated in pediatric patients. Further studies are required to assess whether PTH, IGF1 and FGF23 have an effect on mineralization of human osteoblasts.

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SA-PO558

CKD Induces Intrinsic Alterations in Osteoblast Response to 1,25D

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Background: Skeletal mineralization defects are common in pediatric CKD patients. In vivo 1,25(OH)2 vitamin D (1,25D), the only currently approved therapy for the treatment of 2HPT in children, fails to normalize skeletal mineralization in these patients. We have recently demonstrated that primary osteoblasts obtained from patients with CKD have altered proliferation, differentiation and mineralization characteristics, suggesting that CKD results in intrinsic changes to osteoblast biology, independent of circulating mineral ion and hormone concentrations.

Results: Diminished mineralization is present in CKD; as previously demonstrated in pediatric patients. Further studies are required to assess whether PTH, IGF1 and FGF23 have an effect on mineralization of human osteoblasts.

Conclusions: Children with chronic kidney disease develop unexplained resistance to PTH and GH. Moreover, bone expression of FGF23 is very high in CKD. Data suggest that FGF23 may directly suppress osteoblast maturation and mineralization in mice (Weng JBMR 2009); however, it is not known whether excess expression of this hormone has direct effects on bone cells in CKD. We have previously demonstrated that primary osteoblasts isolated from patients with CKD have defects in maturation and mineralization, even when removed from the uremic milieu. We thus hypothesized that CKD-mediated alterations in osteoblast maturation may contribute to a blunted response to growth factors in pediatric CKD.

Methods: Human osteoblasts isolated from 3 patients with CKD and 3 normal controls were grown to confluence and induced to mineralize. Cells were treated twice weekly with fresh media and 100 nm of PTH, 200ng/ml of IGF1 or 10ng/ml of FGF23 for 0, 2 and 4 weeks. Cell density and mineralization were assessed by staining parallel wells with crystal violet and alizarin red respectively and quantified using spectrophotometry.
Fourier Transform Infrared Spectroscopy Crystallinity Indices in Bone from Patients with ADPKD Renata C. Pereira, 1 Berenice Y. Gitomer, 1 Isidro B. Salusky, 1 Diana George, 2 Jason W. Stoneback, 2 Karen B. King, 3 Myles S. Wolf, 2 Michael Chonko, 2 1Pediatrics, UCLA, Los Angeles, CA; 2Medicine, University of Colorado, Aurora, CO; 3Orthopaedics, Univ of Colorado, Aurora, CO; 4Nephrology, Northwestern Univ, Chicago, IL.

Background: We have previously shown that patients with autosomal dominant polycystic kidney disease (ADPKD) and normal kidney function have a low bone turnover state. This is coupled with increased expression of fibroblast growth factor 23, dentin matrix protein 1 and osteopontin in bone compared to healthy controls. To further characterize the bone defect in ADPKD fourier transform infrared (FTIR) spectroscopy was undertaken.

Methods: With an average eGFR 111 ml/min/1.73m2 and normal parathyroid hormone levels underwent standard tetracycline double labeling prior to transilac crest bone biopsy. FTIR imaging was performed on bone sections from 6 ADPKD patients and 6 age and sex matched healthy historical controls.

Results: The mean eGFR of ADPKD patients were 29±4 yrs and 115 ml/min/1.73m2, respectively. The sex distribution was 5 males and 1 female. Crystallinity a measure of the size of mineral crystals and the degree of order within the crystals was obtained by FTIR and differed significantly between ADPKD and control samples. The differences were more pronounced in the cortices (1.22 vs. 1.19; p = 0.03) than in the trabeculae (1.19 vs. 1.17; p=0.48). There were no significant differences in heterogeneity of crystallinity, mineral/matrix, carbonate/mineral, collagen maturity (cross links) or acid phosphate substitution between ADPKD and historical control samples.

Conclusions: We describe for the first time a significant difference in the chemical composition of cortical bone measured by FTIR in patients with ADPKD when compared to historical control bone samples. Bone crystallinity has been associated with bone strength and stiffness, it is thus intriguing to hypothesize that the observed changes may impact bone quality and expression of bone proteins in ADPKD. Future studies that also assess bone strength and stiffness will be required to more fully investigate bone quality in ADPKD.

Funding: NIDDK Support

Late Onset Avascular Osteonecrosis in Renal Transplant Recipients Spyridon Arampatzis, Anita Maurer, Vasileios Devetzis, Uyen Huynh-do, Nephrology, Hypertension and Clinical Pharmacology, Uni. Hospital Bern, Inselpital, Bern, Switzerland.

Background: Avascular osteonecrosis (AO) after renal transplantation (RT) is a debilitating skeletal complication. In most studies patients with AO presented within the first 24 months after RT. In order to determine the prevalence and therapeutic outcome of late onset AO (24 months after RT) we conducted a single-center retrospective study based on radiological/histological confirmed cases.

Methods: We conducted a single-center retrospective study among our RTR with a clinical diagnosis of AO over the past two decades. We evaluated 70 cases with a AO. In 46 patients AO was radiological/histological confirmed and all relevant clinical, radiological and laboratory data were extracted and analyzed.

Results: The average follow-up time was 14 (±8) years after the first RT. The prevalence of AO was 5.4%. Overall, 41 patients showed AO of the femoral head, 23 bilateral AO of the femoral head 5 of the knee and 5 of other locations, while 43 patients were symptomatic at the time of diagnosis. The mean age at the time of onset (379 ± 124 months) of AO after RT. On average, AO was diagnosed 90 months after RT (SD±78). Furthermore, RTR with late onset were younger at the time of diagnosis. In our cohort 71% presented late onset (³24 months) AO after RT. AO of the femoral head was diagnosed in 34% of patients AO was radiological/histological confirmed and all relevant clinical, radiological and laboratory data were extracted and analyzed.

Conclusions: Late onset avascular necrosis represent a corticosteroid related complication, with a particularly high prevalence among young RTR and is associated with their first RT (48%) compared to the group of early onset (15%; p=0.038). Overall, 34% of patients AO was younger at the time of first RT (39 ± 18 years, HD duration; 14.3 ± 6.8 years ) were treated by total parathyroidectomy with immediate autotransplantation (parathyroidectomy) and received iliac bone biopsies before and at 1 week (n=4) and at 4 weeks (n=10) after parathyroidectomy. Adipocyte volume per marrow volume (Fa/Va/V), adipocyte number per marrow volume (N/Fa/Ma/V/mm3), and mean adipocyte volume (Fa/Va/V) (x 103 mm3/n) were obtained in the area away from bone surface. If there are so many artifacts in bone marrow, the bone samples were excluded from this research.

Funding: Private Foundation Support
mass and osteopenia cellularly with marrow adiposity, compromising dynamic parameters. MSCs differentiation is competitively balanced; mechanisms that promote one cell fate actively suppress mechanisms that include the alternative.

SA-PO564
High Marrow Adiposity Is Associated with Low Turnover Bone Disease in Peritonal Dialysis Patients

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Background: Marrow adiposity has been implicated in the pathogenesis of bone disorders, such as osteoporosis and bone fragility. We sought to investigate the relationship between marrow adiposity and renal osteodystrophy in peritoneal dialysis patients.

Methods: We analyzed transilic bone biopsy specimens from 41 peritoneal dialysis patients (age:50.3±10.2 yrs) by quantitative histomorphometry to assess bone and marrow adipocyte parameters. Selected biochemical parameters, such as serum markers of bone turnover and sclerosin, were measured.

Results: Adipocyte area (Ad.Ar), perimeter (Ad.Pm) and percentage of adipocyte volume per marrow volume (Ad.V/Ma.V) correlated positively with age. Diabetic patients had higher marrow adiposity than non diabetic patients (Ad.V/Ma.V: 50.14±39.12%, P=0.009; Ad.Ar:619.06±0.6 vs 51.05.05 mm², P=0.02). Ad.V/Ma.V demonstrated inverse association with bone specific alkaline phosphatase (r=−0.32;P=0.04) and direct relationship with sclerostin (r=0.38; P=0.01). No association was found between marrow adiposity and dynamic bone histomorphometric parameters. Interestingly, patients with Ad.V/Ma.V >41% (median) presented higher percentage of low turnover bone disease (P=0.04) as well as significantly lower bone specific alkaline phosphatase (39.5±23.7 vs 65.3±25.9 U/L; P=0.006) and higher sclerostin (2.3±0.97 vs 1.6±0.97 ng/mL; P=0.02) levels than patients below the median.

Conclusions: Increased marrow adiposity seems to be associated to lower osteoblast activity and to lower turnover bone disease in peritoneal dialysis patients. The higher marrow fat in diabetic and aged patients might expose them to an increased risk for fracture. Further studies are needed to understand the possible contribution of marrow adiposity to the pathogenesis of renal osteodystrophy.

Funding: Government Support - Non-U.S.

SA-PO565
Role of Wnt10b Signaling in Cinacalcet-Induced Bone Anabolic Effects

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Background: Chronic kidney disease-mineral bone disorders (CKD-MBD) is important for osteoporosis and bone fractures in CKD patients. Since calcium receptor plays an important role in osteostatic differentiation, we assume that calcimimetic agents (cinacalcet) might have a role in bone remodeling.

Methods: Bone marrow mononuclear cells isolated from rat femur and tibia were induced into osteoclasts by M-CSF and RANKL treatments. Osteoclasts were treated with different doses of cinacalcet. untreated osteoclasts used as control. The release of clastokines (i-PTH) levels decrease from 903.6 ± 503.0 to 212.7 ± 98.1 pg/ml after the treatment with cinacalcet HCL and received bone biopsies before and at 1 year after the treatment (Group II). Osteocyte number in micro-petrosis area (N.Ot/Mp.V; N/mm²) was not changed in both mictropetrosis area (100.1 ± 68.2 to 99.6 ± 76.1 N/mm²) and in the other area (from 240.1 ± 63.9 to 279.6 ± 88.6 N/mm²) after the treatment (Group II).

Conclusions: Cinacalcet HCL did not reduce osteocyte number in both micro-petrosis area and in the other area, suggesting that this agent improves bone quality by maintaining osteocytic pericellular/canalicul system. Parathyroidectomy reduces osteocyte number in only the micro-petrosis area.

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SA-PO567
Trabecular Bone Score in Kidney Transplant Recipients

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Background: Kidney transplant recipients have altered bone mineral metabolism and are at a higher risk of fracture compared to the general population. There is conflicting evidence regarding the ability of bone mineral density (BMD) to accurately predict fracture. Trabecular bone score (TBS) is a texture measure derived from dual energy x-ray absorptiometry (DXA) lumbar spine images which provides information independent of BMD. We assessed TBS in kidney transplant recipients.

Methods: We included 327 kidney transplant recipients from Manitoba, Canada, who received a post-transplant DXA (median 106 days post-transplant). We matched each kidney transplant recipient (mean age 45 years, 39% men) to three controls from the general population (matched on age, sex, and date of DXA). Lumbar spine (L-1-L-4) DXA images were used to derive TBS. Non-traumatic incident fracture (excluding hand, foot, and craniofacial) were assessed during a mean follow-up of 6.6 years. We used logistic regression to determine predictors of TBS and hazard ratios per standard deviation decrease in TBS to express the gradient of risk for fracture prediction using Cox proportional hazards regression.

Results: Compared to the general population, kidney transplant recipients had a significantly lower lumbar spine TBS (1.41 ± 0.13 versus 1.37 ± 0.13, P=0.001). Multiple logistic regression revealed reduced TBS (lowest versus highest tertile) in kidney transplant recipients compared to the general population (adjusted odds ratio, 2.13 95% confidence interval [CI] 1.47-3.07). TBS predicted fractures in kidney transplant recipients independent of the Fracture Risk Assessment (FRAX) score and spine BMD (adjusted hazard ratio per standard deviation decrease in TBS 1.57, 95% CI 1.07-2.9).

Conclusions: Kidney transplant recipients had abnormal bone texture as assessed by TBS. Lumbar spine TBS was able to predict incident fractures in kidney transplant recipients and may provide novel insights into skeletal fragility in this unique population.

SA-PO568
Low Bone Turnover Disease Is Prevalent 1 Year After Successful Renal Transplantation: A Cross-Sectional Bone Biopsy Study

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Transplantation: A Cross-Sectional Bone Biopsy Study

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

Underlines represents presenting author.

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hypocalcemic hyperparathyroidism (n=4, 7%) showed either low or normal bone turnover. Hypophosphatemia was present in 11%. Vitamin D stores were sufficient in 52% (median HydroxyvitaminD 32 ng/ml). Spearman correlation revealed significant correlations between bone formation rate and biomarkers of bone formation & resorption (direct: bAP: r0.36, p=0.01; TRAP: r0.40, p<0.01; NTX: r0.38, p<0.01) and inflammation (inverse: Il6: r-0.51, p<0.001), but not with mineral metabolism hormones (PTH, FGF23, sclerostin).

Conclusions: Low bone turnover disease is the most prevalent bone disease in renal transplant recipients 1 year after successful renal transplantation. Additional studies are required to clarify underlying pathophysiological mechanisms. PTH, FGF23 and sclerostin do not correlate with histomorphometric parameters and circulating biomarkers of bone turnover.

SA-PO569
Sclerostin Bone Expression and Blood Levels in Patients with Chronic Kidney Disease Stages 2-5

Background: Sclerostin (Scl) produced by osteocytes (ocy) was found to be increased in blood in early stages of CKD patients (pts) with renal osteodystrophy (ROD). The aim of this study was to establish when blood scl levels and bone expression are increased and how they progress with worsening CKD.

Methods: Fifty pts underwent anterior iliac crest biopsies and blood was drawn at time of biopsy. Kidney function was determined by creatinine clearance using MDRD calculation. There were: 11 CKD-2, 16 CKD-3, 9 CKD-4 5 pts, and 14 healthy age-matched controls. Scl concentrations in blood were determined by ELISA and scl expression in bone was determined in undecalcified bone sections by counting number of ocy exhibiting positive scl immunostaining. Measurements were done separately in cortical and cancellous bone. Bone sections were also evaluated by histomorphometry for turnover, mineralization and volume.

Results: Blood scl levels were significantly greater in CKD compared to controls with no differences between stages (P=0.01).

Bone scl expression was significantly higher in cortical bone of CKD 2-5 pts compared to controls (P<0.01). Scl expression was significantly greater in cortical than in cancellous bone in CKD. In cancellous bone scl expression was higher in CKD, this reached significance in CKD-3 (Figure 1).

Conclusions: Scl expression in cortical and cancellous bone correlated with serum scl (rho=0.30, 0.40, rsp; P<0.05). Serum scl correlated negatively with bone formation, activation frequency and osteoblast number (rho=-0.33, -0.38, -0.43, rps; P<0.05). Scl in bone correlated negatively with trabecular thickness (rho=-0.51; P<0.05), osteoblast and osteoclast surface, and erosion depth (rho=-0.50, -0.52, 0.55; rps; P<0.01).

Conclusions: These findings ascribe a potential role to scl in the pathogenesis and management of ROD.

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SA-PO570
Single Timepoint and Longitudinal Serum Sclerostin Levels as Mortality Predictors in Prevalent Dialysis Patients
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Background: Longitudinal serum sclerostin (sScl) levels, a 22kDa-sized glycoprotein inhibiting bone formation, are positively or negatively associated with mortality. Its concentration may change over time. Therefore, we investigated whether longitudinal sScl levels predict mortality better than a single measurement.

Methods: A post-hoc analysis on data from the CONTRAST study was performed, a RCT comparing online postdilution hemodiafiltration to hemodialysis in prevalent dialysis patients. sScl was measured in a subset of patients. Patients were eligible for analysis if a baseline (T0) and a 6 months (T6) sScl value were available. Hazard ratios (HRs) were calculated within quartiles for sScl level at T0, T6 and for Delta sScl. All-cause mortality was assessed as an end point. As the interaction between dialysis modality and Delta sScl was non-significant (p=0.1), pooled estimates are reported. To correct for multiple testing, a two-sided p-value <0.01 was considered statistically significant.

Results: Out of 714 patients, 341 were available for analysis. Baseline characteristics between the groups did not differ. Median sScl at T0, T6 and Delta sScl were 136.3 pmol/L (interquartile range [IQR] 98.7-186.1), 134.0 pmol/L (IQR 100.4-183.0) and 0 pmol/L (IQR -25 to 15), respectively. sScl values at baseline and T6 were negatively associated with mortality (adjusted HRs highest versus lowest quartile 0.49 [95% CI 0.30-0.81] and 0.48 [95% CI 0.29-0.82], respectively). However, we found no association between Delta sScl and mortality.

Conclusions: A single timepoint sScl is inversely associated with mortality in our cohort of dialysis patients. sScl change over a six month period does not predict mortality.

SA-PO571
Interleukin-1 Inhibition, Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), and Physical Function
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Background: In chronic kidney disease (CKD), physical function is associated with an increased risk of mortality. Interleukin-1 (IL-1) has been identified as an important player in the pathogenesis of CKD-MBD, and thus, the effect of IL-1 inhibition on physical function in CKD patients is of great interest.

Methods: In a two-site, double-blind trial, 42 patients with stage 3-4 CKD were randomized to receive either the IL-1 trap rilonacept (160 mg/week) or placebo for 12 weeks. The following CKD-MBD markers were assessed in serum before and after the intervention: calcium, phosphorus, 25-hydroxyvitamin D (25(OH)D), iPTH and FGF23. A battery of tests was also administered in a sub-group (n=22) to assess multiple domains of physical function (endurance, locomotion, dexterity, balance, strength, and fatigue).

Results: Participants were 63±11 years of age, 24% female, 29% Hispanic, mean eGFR 38±13 ml/min/1.73m2, and mean high sensitivity C-reactive protein (hsCRP) 4.7±4.2 mg/L. Rilonacept effectively reduced systemic inflammation, as evidenced by reduced hsCRP levels (p<0.01). There was no change in serum calcium, phosphorus, 25(OH)D, iPTH, or FGF23 levels (p>0.05) with IL-1 inhibition. Similarly, rilonacept did not alter locomotion, dexterity, balance, strength, or fatigue (p>0.02). However, endurance (400m walk time) tended to be reduced in the rilonacept (-29 sec) as compared to placebo (-6 sec; p=0.059).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: 12 weeks of IL-1 inhibition did not improve circulating markers of CKD-MBD or physical function (although it tended to improve endurance). These results support that inflammation does not directly mediate CKD-MBD or select domains of physical function.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Regeneron Pharmaceuticals, Inc., Private Foundation Support

SA-PO573

Serum Metabolomic Profiling and CKD-MBD: A New Tool for Bone Turnover Evaluation Aline Lourenço Baptista,1 Kallyanda Padilha,2 Pamela Araujo Malagrinho,2 Gabriela Venturini,2 Ana Carolina de Mattos Zeri,1 Janaina Silva Martins,4 Rodrigo Azevedo de Oliveira,4 Geusa Dutra,1 Luciene dos Reis,3 Vanda Jorgetti,1 Alexandre Costa Pereira,2 Rosa M.A. Moyses,1,2 *Neurology, USP; 2Molecular Cardiology, INCOR, USP; 3LNBio, CNPEM; 4UEM; 5UFRN; 6CEPID.

Background: Bone biopsy still is the gold standard to assess bone turnover in CKD patients and serum biomarkers are not able to replace histomorphometry. Recently, metabolomics has emerged as a new technique that could potentially improve disease diagnosis and the understanding of pathophysiology. However, as this approach has never been tested in the CKD-MBD scenario we investigated whether a serum metabolomic profile could help us to better predict bone turnover in CKD patients.

Methods: Serum and bone histomorphometry data from hemodialysis (HD, n=51) and peritoneal dialysis patients (PD, n=40) were analyzed. They were classified as high (HT), 49.4%) or low turnover (LT). Metabolomic analysis was done through MRI spectroscopy, followed by identification and quantification of metabolites and PLS-DA. As HD had a completely different metabolome of PD group, we analyzed them separately. In addition, we selected the main metabolites found in each group and searched for the metabolomic pathways involved.

Results: The difference between LT and HT was explained by 12 metabolites in HD and 8 in PD (p = 0.03 and 0.01, respectively). ROC curve analysis showed that parahormone and alkaline phosphatase were the best predictors for HT, whereas glyceroi and glucose were the best predictors for LT in HD and PD, respectively. The main canonical pathways involved were glycerine degradation, tyrosine biosynthesis IV and phenylalanine degradation I in HD and creatine-phosphate biosynthesis, pyruvate fermentation to lactate and AMPK signaling in PD group.

Conclusions: In this preliminary analysis, we identified new metabolites that might be used as biomarkers of bone turnover. Moreover, the differences in metabolome between the two dialysis modalities and the different metabolic pathways suggest that the pathophysiological mechanisms involved in the modulation of bone turnover in these patients might be different.

Funding: Government Support - Non-U.S.

SA-PO574

Deletion of the Gene Encoding the Transient Receptor Potential Canonical Type 1 (TRPC1) Channel Produces Hyperparathyroidism, Low Calcitonin (CaT), Hypercalcemia, but Hypocalcuria and Enhanced Bone Mass: Evidence for the Role of TRPC1 in Regulating Intracellular Ca (Ca2+i) in Target Cells Bonnie Eby,1 Alexander Lau,2 Lindsay J. Barron,1 Marybeth Humphrey,1 Leonidas Tsiokas,2 Kai Lau.1,3 *Medicine, Univ of Oklahoma, Oklahoma City, OK; 2Cell Biology, Univ of Oklahoma, Oklahoma City, OK; 3Medicine, VA Medical Center, Oklahoma City, OK.

Background: We recently showed that TRPC1 deficiency impairs store-operated Ca entry (SOCE), reduces [Ca 2+i], stimulates PTH and causes hypercalcemia. We here selected the main metabolites found in each group and searched for the metabolic pathways involved.

Methods: Serum and bone histomorphometry data from hemodialysis (HD, n=51) and peritoneal dialysis patients (PD, n=40) were analyzed. They were classified as high (HT), 49.4%) or low turnover (LT). Metabolomic analysis was done through MRI spectroscopy, followed by identification and quantification of metabolites and PLS-DA. As HD had a completely different metabolome of PD group, we analyzed them separately. In addition, we selected the main metabolites found in each group and searched for the metabolomic pathways involved.

Results: The difference between LT and HT was explained by 12 metabolites in HD and 8 in PD (p = 0.03 and 0.01, respectively). ROC curve analysis showed that parahormone and alkaline phosphatase were the best predictors for HT, whereas glyceroi and glucose were the best predictors for LT in HD and PD, respectively. The main canonical pathways involved were glycerine degradation, tyrosine biosynthesis IV and phenylalanine degradation I in HD and creatine-phosphate biosynthesis, pyruvate fermentation to lactate and AMPK signaling in PD group.

Conclusions: In this preliminary analysis, we identified new metabolites that might be used as biomarkers of bone turnover. Moreover, the differences in metabolome between the two dialysis modalities and the different metabolic pathways suggest that the pathophysiological mechanisms involved in the modulation of bone turnover in these patients might be different.

Funding: Government Support - Non-U.S.

SA-PO575

Role of the Sodium/Calcium Exchanger NCX1 in Osteoclasts Giuseppe Albanò,1,2,3 Candice Stoudmann,1,2 Willi Hofstetter,2 Olivier Bonny,2,3 Daniel G. Fuster.1,3,4 *Div of Nephrology, Hypertension and Clinical Pharmacology, Univ of Bern, Bern, Switzerland; 2Inst of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; 3Dept of Clinical Research, University Hospital Bern, Bern, Switzerland; 4NCCR Kidney.CH, Univ of Zürich, Zürich, Switzerland.

Background: Previous studies demonstrated that inhibition or siRNA-mediated knock-down of sodium/calcium exchanger 1 (NCX1) in osteoclasts decreases bone resorption in vitro, indicating a critical role of NCX1 in osteoclast-mediated bone resorption.

Methods: To test the role of NCX1 in osteoclasts in vivo, we generated mice with osteoclast-specific deletion of NCX1 (NCX1flox/flox). For this purpose, with a floxed exon 11 of NCX1 we crossed mice expressing Cre-recombinase under the influence of the osteoclast specific c窦phin K promoter.

Results: Osteoclasts differentiated from NCX1flox/flox mice displayed an 80-90 % reduction of NCX1 protein compared to wild-type mice. NCX1 expression was unaltered in extraosseous tissues in NCX1flox/flox mice. NCX2 and NCX3 were present at low levels in wild-type osteoclasts and not upregulated in NCX1flox/flox osteoclasts. In vitro RANKL stimulation of bone marrow cells isolated from wild-type and NCX1flox/flox mice yielded no differences in osteoclast development and resorptive activity. In addition, at 3 months of age, structural parameters of bone, quantified by high-resolution microcomputed tomography, were not different in NCX1flox/flox mice compared to wild-type littermates. To stimulate osteoclast-mediated bone resorption, we performed surgical ovariectomy (OVX) in 12 week old female mice, but OVX-induced bone loss over 12 weeks was similar in WT and NCX1flox/flox mice.

Interestingly, however, at 6 months of age, female NCX1flox/flox mice had significantly higher bone volume whereas male NCX1flox/flox mice displayed reduced bone volume compared to wild-type mice.

Conclusions: Our data indicate that genetically induced deficiency of NCX1 in osteoclast-precursors and mature osteoclasts does not affect osteoclast differentiation and bone resorption in vitro. However, NCX1flox/flox mice display an age- and sex-specific phenotype. Additional studies are needed to unveil the underlying mechanisms.

Funding: Government Support - Non-U.S.

SA-PO576


Background: The arteriovenous-fistula (AVF) of the distal radius often remain patent after transplantation. Distal radius is the typical site for peripheral DXA measurements in renal transplant recipients (RTR). Since no data exist concerning the impact of a previously created AVF on peripheral bone characteristics in RTR we evaluated the effect of AVF on bone mineral density (BMD) as mirrored by contralateral differences between forearms and explored the demetsocrit correlation of distal radius with the tibia as an alternative peripheral measurement site.

Methods: This cross sectional study included 40 renal transplant recipients (RTR) and 40 chronic kidney disease (CKD) patients matched for age, gender and BMI. In addition to relevant demographic, biochemical and clinical aspects we assessed bone characteristics of both forearms, femoral neck and tibia by DXA.

Results: The CKD patients without any AVF, displayed no significant discrepancies concerning BMD in both forearms. In RTR BMD was significantly lower in the AVF forearm compared to the contralateral non AVF forearm. This observation was evident at all measured subregions of the AVF radius sides, i.e. at the 1/3 radius (0.710±0.103 vs. 0.727±0.104, p=0.003), ultradistal radius (0.424±0.085 vs. 0.444±0.080, p=0.007) and total radius (0.571±0.090 vs. 0.589±0.090, p=0.001) as well. This significant side-to-side difference was 7.5% at the 1/3 radius, 7.2% at the total radius, and 7.0% at the ultradistal radius, respectively. The BMD intersite analysis between radius and distal site revealed a strong and highly significant correlation (r= 0.7346-0.875) between corresponding peripheral sites.

Conclusions: In conclusion, a previously placed AVF in RTR exerts a negative impact on the ipsilateral radius resulting in side-to-side BMD differences. A strong densitometric association exist between peripheral sites and thus DXA measurements at the tibia can be considered as a valuable alternative site to radius. Longitudinal studies are needed in order to replicated these findings by incorporating methods with higher bone density definition.

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

SA-PO577

Cortical Bone Analysis in Pre-Dialysis Patients: A Comparison with a Dialysis Population Catarina Carvalho,1 Juliana Magalhães,2 Ricardo Neto,1 Luciano Pereira,1 Teresa Adragão,2 João M. Frazao.1 *Nephrology and Infectiology Research and Development Group, INEB, Porto, Portugal; 2Nephrology, Hospital Santa Cruz, Lisboa, Portugal.

Background: ROD presents early in CKD pts. Bone biopsy is the gold-standard diagnostic tool. Cortical bone assesses 80% of human bone and is the major determinant of bone strength.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 756A
Methods: We evaluated cortical bone histomorphometry in 13 CKD stage 3 and 4 pts, (9 male, age 65.3±10.4, eGFR 23.8±3.3 ml/min/m², who underwent trans-diaphyseal bone biopsy and compared them to 13 dialysis pts (9 male, 11 on HD, age 52.1±10.2, 55.3±17.6 mo in RRT).

Results: Biochemical values and external cortical bone parameters of both groups shown in table

<table>
<thead>
<tr>
<th>External CORTICAL</th>
<th>Pre-dialysis</th>
<th>Dialysis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/ml)</td>
<td>157.8±85.9</td>
<td>283.2±187.5</td>
<td>0.038</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>9.6±0.4</td>
<td>9.0±0.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Pi (mg/dL)</td>
<td>3.6±0.8</td>
<td>4.8±2.2</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Dialysis pts compared to the pre-dialysis population showed more deranged cortical bone, with decreased cortical thickness, increased osteonal formation rate and decreased apposition rate. In this pre-dialysis population, external cortical porosity positively correlated with both trabecular bone volume and osteoid volume (respectively, r=0.70 and 0.76, p=0.016 and p=0.006). External cortical ostereal BFR correlated negatively with PTH effects. These findings were not observed in internal cortical suggesting that this is more stable to PTH effects.

Conclusions: In pre-dialysis pts, our findings support that PTH has a modulating effect on both trabecular and cortical bone. As renal disease progresses cortical thinning is more pronounced, eventually contributing to the higher fracture rate. Understanding cortical abnormalities may have implications in the treatment of CKD-MBD.

SA-PO579
Chronic Hypoponatremia Is a Novel Risk Factor for Hip Fracture in Chronic Kidney Disease-Mineral Bone Disease
Sagar U. Nipwekar,1 Andrew S. Allegretti, Julia Beth Wenger, Juan Carlos Ayus,2 Ravi R. Thadhani,1 Ishir Bhan.1
1Massachusetts General Hospital; 2Renal Consultants of Houston.

Background: Risk factors that make skeleton more fragile in chronic kidney disease (CKD) are uncertain. Considering recently reported direct effects of sodium depletion on bone health, we investigated chronic persistent hypoponatremia (CPH) as a novel risk factor for hip fractures caused by CKD-mineral bone disease (CKD-MBD).

Methods: Cases for this multi-center case-control study were elderly (>65 years) patients with CKD (eGFR <60 ml/min) with a new hip fracture. Controls (CKD patients with no hip fracture) were matched to cases on age, sex, race and comparative health.

Results: We analyzed 1,236 cases and 4,515 controls. Mean age of all patients was 84 ± 9 years, 87% were whites, and 39% were females. Serum calcium, phosphate, parathyroid hormone and 25-hydroxy vitamin D levels were similar between cases and controls. Prevalence of CPH (21.2 vs. 9.9%, P<0.001), CPH180 (15.5 vs. 6.5%, P<0.001) and H1 (52.7 vs. 41.1%, P<0.001) were higher in cases compared to controls. In analyses adjusted for falls, tobacco-use, osteoporosis, eGFR, body mass index, heart failure and medications, CPH90 and CPH180 were associated with increased risk of hip fracture but H1 was not.

Conclusions: CPH is a risk factor for hip fractures caused by CKD-MBD. Mechanistic studies are needed to investigate the effects of CPH on bone turnover, mineralization and volume in CKD.

Funding: Private Foundation Support

SA-PO580
Follicle Stimulating Hormone Is Associated with Low Bone Mineral Density in Women in Hemodialysis

Background: CKD-BMD associated to sexual hormonal status have not been well evaluated. Aim: Assess the association between female hormones (FSH and estradiol) and bone mineral density (BMD) in women in hemodialysis (HD).

Methods: Cross-sectional study in 46 women (20-60 years), at least 3 months in HD in a tertiary care setting between Jan-Jul 2014. Patients or with steroid medication were excluded. Physical examination and blood markers of sexual hormonal and mineral-bone status were done. A bone densitometry of lumbar spine and non-dominant femur was performed. The results were classified as normal, osteopenia and osteoporosis.

Results: 5 had osteoporosis and 5 had osteopenia in the lumbar spine. In the femur, 2 had osteopenia and 18 had osteopenia. Comparisons are shown in Table. BMD in lumbar spine was associated to FSH (R 2 0.27; P<0.001), FSH (OR -0.52 [-0.02 - -0.008]; P=0.001), on the other hand BMD in femur (R 2 0.30; P<0.001), FSH (OR -0.34 [-0.01 - -0.001]; P<0.02), and CRP were significantly associated (OR -0.32 [-0.02 - -0.001]; P<0.03)

Conclusions: This study highlights utility of BMD to predict fracture in CKD, underscores the burden of DM on outcomes, and reveals independent higher mortality after hip fracture in end stage kidney disease.
Background: Recent studies found the incidence of hip fractures has increased greatly in patients on dialysis. Most of the increase occurred in patients with characteristics typical of bone frailty, where oversuppression of intact parathyroid hormone (iPTH) could be harmful. Since recent studies have not addressed clinical risk factors, we studied time-varying risk factors for hip fractures in patients on dialysis.

Methods: 142,407 prevalent patients of Fresenius Medical Care had hip fractures identified by ICD-9 codes. Four cohorts were constructed: observation periods 2001-2003, 2004-2006, 2007-2009, 2010-2012. For each, the prior year was used to measure exposure. Models for risk adjustment were created: Case Mix CM-adjusted: age, gender, race, dialysis vintage, and diabetic status, CM+Lab adjusted and CM+Lab+Med adjusted.

Results: There were 16 (13.56%) fractures in 118 hemodialysis patients. Patients with fractures were significantly older and more osteoporosis. All BMD parameters at hip region (including femoral neck, femoral shaft, and total hip) were notably lower in fracture group than in non-fracture group (0.74: (0.65-0.87) vs 0.82: (0.74-0.96); 0.88: (0.77-1.01) vs 0.99: (0.86-1.14); 0.80: (0.66-0.88) vs 0.88: (0.78-1.00)). There was no difference in clinical characteristics or blood biochemistry levels between the two groups.

Conclusions: Among hemodialysis patients, age and BMD at hip are associated with fracture. FRAX performs better than BMD and OSTA at identifying patients with fractures (P < 0.05). But FRAX2 performed better than BMD and OSTA at identifying patients with fractures (P < 0.05). The best cutoff values were 0.91, 3, 7.2%, and 3.4%.

Background: Restless legs syndrome (RLS) is a movement sleep disorder that is common among patients on hemodialysis (HD) and is associated with cardiovascular morbidity and mortality. The physiopathology of this syndrome is not completely understood, and CKD-MBD may be implicated. We aimed to evaluate the prevalence of RLS in patients on hemodialysis, testing the relationship with CKD-MBD markers.

Conclusions: In conclusion, we found that lower time-averaged iPTH and calcium were associated with a greater risk for hip fracture in dialysis patients.

Funding: Clinical Revenue Support

SA-PO582
The Discriminative Ability of Three Fracture Risk Assessment Tools in Hemodialysis Patients Ying Qian, An jin Chang, Xiaonong Chen, Nan Chen. Dept of Nephrology, Ruijin Hospital Affiliated to Shanghai Jiaotong Univ School of Medicine, Shanghai, China.

Background: The present study aimed to explore factors associated with fractures among hemodialysis patients, and assess the ability of the World Health Organization’s fracture risk assessment tool (FRAX) compared with bone mineral density (BMD) and OSTa to discriminate fracture status.

Methods: We enrolled 118 hemodialysis patients in this cross-sectional study. Parameters including serum calcium, phosphate, intact parathyroid hormone, 25 hydroxy vitamin D, alkaline phosphatase were analyzed. Clinical characteristics were also collected. BMD values were at the lumbar spine and hip region. OSTa and FRAX scores were calculated using formula or through the FRAX website. Factors associated with fractures were examined. Discriminative ability of BMD, OSTa and FRAX (non-BMD model and BMD model) in fracture status was assessed with receiver operator characteristic (ROC) analysis.

Results: There were 16 (13.56%) fractures in 118 hemodialysis patients. Patients with fractures were significantly older and more osteoporosis. All BMD parameters at hip region (including femoral neck, femoral shaft, and total hip) were notably lower in fracture group than in non-fracture group (0.74: (0.65-0.87) vs 0.82: (0.74-0.96); 0.88: (0.77-1.01) vs 0.99: (0.86-1.14); 0.80: (0.66-0.88) vs 0.88: (0.78-1.00)). There was no difference in clinical characteristics or blood biochemistry levels between the two groups.

Conclusions: Among hemodialysis patients, age and BMD at hip are associated with fracture. FRAX performs better than BMD and OSTa in discriminating fracture status, suggesting its usefulness of fracture risk prediction in hemodialysis patients.

Funding: Government Support - Non-U.S.

SA-PO583
Teriparatide for Low Bone Mass in Hemodialysis Patients Rikako Hiramatani, Yoshihumi Ubara, Junichi Hosho, Kennrei Takaichi. Nephrology Center, Toranomon Hospital, Tokyo, Japan.

Background: Fracture rates in dialysis patients are extremely higher than general population. Recently the prevalence of low turnover has greatly increased in dialysis population. Teriparatide would be also beneficial for low turnover dialysis patients with low bone mass. However, there have been only a few reports describing the use of teriparatide in dialysis patients.

Methods: Design This was a prospective, single-center, observational study. Hemodialysis patients with low iPTH (iPTH<60 pg/ml) were the target population. BMD determined by lumbar spine (LS) and femoral neck (FN) T-score<-2.5 with DXA were eligible and subcutaneous recombinant human PTH1-34 (20 µg teriparatide; Forteo) was injected 3 times per week at the end of each hemodialysis sessions. We analyzed the following parameters, including serum Ca, P, albumin, ALP, iPTH and bone metabolic markers including i1NP, BAP, OC, and TRACP-5b at baseline and following teriparatide. BMD at LS and FN were measured at baseline, 6, 18 months after treatment. Pharmacokinetics After the 24th administration of teriparatide, we measured the serum teriparatide acetate concentrations.

Results: Five patients (median age: 72 years old,median hemodialysis periods; 24 months) were included. After teriparatide injection, BMD of LS as well as FN at 6 months significantly increased from 0.67±0.18 to 0.86±0.19 g/cm2 and from 0.44±0.08 to 0.48±0.07 g/cm2, respectively. Corrected Ca levels significantly decreased at 3 and 6 months with increases in endogenous iPTH in response to lowering of serum Ca. As for bone metabolic markers, percent changes of serum BAP and serum i1NP levels significantly increased at 3 and 6 months. Conversely, serum TRACP-5b decreased after injection. Throughout this study, there were no fractures. Pharmacokinetics result is shown in Figure 1. There was a peak at 30 minutes at 157.2 pg/ml, and then it rapidly decreased to undetectable level at 240 minutes.

Conclusions: In conclusion, treatment with teriparatide, the dose was 20 µg 3 times/week, which is smaller than suggested dose for non dialysis patients, led to increase of BMD at LS and FN. Our data on pharmacokinetic of teriparatide suggested that we can use this agent in normal dose in dialysis patients.

SA-PO584
Restless Leg Syndrome in Hemodialysis Patients: Possible Relationship with Mineral and Bone Metabolism Precil Diego Miranda de Menezes Neves,1 Ramaiane Aparecida Bridi,1 Rosa M.A. Moyes,2 Rosilene M. Elias,1,2 Nephrology Div, Univ of Sao Paulo, Sao Paulo, Brazil; 1Nephrology Div, Univ Nove de Julho - UNINOVE, Sao Paulo, Brazil.

Background: Restless legs syndrome (RLS) is a movement sleep disorder that is common among patients on hemodialysis (HD) and is associated with cardiovascular morbidity and mortality. The physiopathology of this syndrome is not completely understood, and CKD-MBD may be implicated. We aimed to evaluate the prevalence of RLS in patients on hemodialysis, testing the relationship with CKD-MBD markers.

Conclusions: In conclusion, treatment with teriparatide, the dose was 20 µg 3 times/week, which is smaller than suggested dose for non dialysis patients, led to increase of BMD at LS and FN. Our data on pharmacokinetic of teriparatide suggested that we can use this agent in normal dose in dialysis patients.
Methods: Prevalence and severity of RLS were assessed using the International RLS Study criteria (IRLS) in 1665 patients.

Results: Of the 101 patients (53.5% women) included, RLS was observed in 29 patients (28.7%), with mild, moderate, severe and very severe presentation in 1, 12, 3 and 3 patients, respectively. RLS was more frequent among women (62% vs 38%, p=0.04), and was associated with normal fasting glucose (OR=0.80, 95% CI 0.57-1.14, P=0.22). The expression of Nrf2 and HO-1, increased by P load, but the expression of Runx2-induced calcification was decreased gradually within incubation time after H2O2 or SFN + H2O2, pretreated.

Conclusions: The calcification in RASMCs is associated with the overexpression of endogenous ROS. Overexpression of Runx2 induced by endogenous ROS, but not exogenous ROS, may be inhibited or attenuated by the activated Nrf2/ HO-1 pathway.

SA-PO587
Matrix Vesicles from Calculating Vascular Smooth Muscle Cells (VSMC) Have Different MicroRNA (miRNA) Expression from Non-Calculating VSMC. Neal X Cheng,1 Sarath Chandra Janga,1 Kalishia O’Neill,2 Manjunath Shetty,3 and Chad A. Wang2,3,1

Methods: We added P of 1, 1.5, or 2.0 mM in the culture media (DMEM) of hVSMC with normal fasting or high glucose (HG) (100 or 450 mg/dl), although hVSMC are usually with normal fasting glucose at Day 7 and 14. At Day 7, the mRNA expression of Sox9, a chondrogenic differentiation marker, increased by P load and was higher with normal fasting glucose. The SOX9 mRNA expression at Day 7 correlated significantly with the content of calcification related to VSMC. The content of calcification was decreased significantly with the SOX9 mRNA expression at Day 7. At Day 1, the content of CPP increased by P load, and was higher with normal fasting glucose. The SOX9 mRNA expression at Day 7 correlated significantly with the content of CPP at Day 1. At Day 1, the mRNA expression of osteopontin (OPN), a calcification inhibitor, decreased by P load and was less with normal fasting glucose. The content of calcification was decreased significantly with the mRNA expression of OPN at Day 1.

Results: Regardless of P load amount, the degree of calcification was severer with normal fasting glucose at Day 7 and 14. At Day 7, the mRNA expression of Sox9, a chondrogenic differentiation marker, increased by P load and was higher with normal fasting glucose. The content of calcification was decreased significantly with the SOX9 mRNA expression at Day 7. At Day 1, the content of CPP increased by P load, and was higher with normal fasting glucose. The SOX9 mRNA expression at Day 7 correlated significantly with the content of CPP at Day 1. At Day 1, the mRNA expression of osteopontin (OPN), a calcification inhibitor, decreased by P load and was less with normal fasting glucose. The content of calcification was decreased significantly with the mRNA expression of OPN at Day 1.

Conclusions: In conclusion, P load with normal fasting glucose reduced OPN expression and induced the formation of CPP, followed by the chondrogenic differentiation and calcification in hVSMC.

Funding: Pharmaceutical Company Support - Kyowa Hakko Kirin, Government Support - Non-U.S.
SA-PO589

VCAM - 1 and TNF Alpha Induce Vascular Calcification In Vitro
Kevin Willy, Ralf Schindler, Daniel Zickler. Dept of Nephrology and Internal Intensive Care Medicine, Charité Univ Medicine, Berlin.

Background: VCAM, TNF alpha and soluble TNF alpha receptor 1 (sTNFR1) are elevated in patients with chronic kidney disease (CKD). In previous clinical trials with high cut-off dialysis plasma levels of these molecules and in vitro vascular calcification were lowered. Here we assessed the role of sTNFR 1 and VCAM on in vitro calcification.

Methods: In human vascular smooth muscle cells (VSMCs) vascular calcification was induced by osteogenic medium (OM). VCAM, TNF-α and sTNFR1 were added. Calcification was quantified by alkaline phosphatase staining and alizarin red staining. Calcification was then normalized to WST-8.

Results: VCAM enhances vascular calcification in vitro in a dose-dependent manner (p<0.001). TNF-α -induced calcification was effectively inhibited by sTNFR1 (50% reduction of the initial level; p<0.001). sTNFR1 alone does not promote vascular calcification.

Conclusions: VCAM and TNF alpha promote vascular calcification in vitro. Their elimination with high cut-off dialysis or their pharmacological blockade may be advantageous in regard to vascular calcification in CKD.


SA-PO590

The Tripeptide Collagen Analog (GPO)10 Affects Calcifications of Vascular Smooth Muscle Cells in a Concentration Dependent Manner
Uwe Querfeld, Nadja Kretzschmar, Christian Freise. Pediatric Nephrology, Charité, Berlin, Germany; Center for Cardiovascular Research, Charité, Berlin, Germany.

Background: Extensive remodeling of the extracellular matrix and the trans-differentiation of vascular smooth muscle cells (VSMC) contribute to the pathogenesis of vascular calcifications in patients with chronic kidney disease (CKD). Matrix metalloproteinases (MMPs) are proteolytic enzymes that impact on both of these processes and, thus, represent potential therapeutic targets. We have previously shown that the synthetic collagen analog (Gly-Pro-Hyp)10 -(GPO)10 –impacts the substrate binding and the enzymatic activity/stability of the gelatinases MMP-2 and -9 in a concentration dependent manner [1]. Aim of this study was therefore to investigate potential regulatory functions of (GPO)10 in an in-vitro model of atherosclerotic VSMC calcification.

Methods: Calciums of murine VSMC were induced by a calcification medium (CM) containing elevated concentrations of calcium and phosphorus with or without the presence of (GPO)10 -concentrations. VSMC calcifications were quantified by measuring calcium depositions and ALP-release in the cultures. Effects on MMP-activities were determined by specific substrate assays.

Results: CM-treated VSMC exhibit strong calcifications compared to control. Low (GPO)10 -concentrations (50-70 nM) massively enhanced calcifications of VSMC and were accompanied by elevated gelatinase activities in VSMC supernatants. In contrast, higher concentrations of (GPO)10 (680 nM) blocked CM-induced calcifications of VSMC and reduced gelatinolytic activities in culture supernatants.


Funding: Private Foundation Support

SA-PO591

Protective Effects of Epigallocatechin Gallate (EGCG) on Vascular Calcification In Vitro and In Vivo
Uwe Querfeld, Karoline Websky, Christian Freise, Kerstin Sommer, Ursula Schulz, Veronika Bobb. Pediatric Nephrology, Charité, Berlin, Germany; Center for Cardiovascular Research, Charité, Berlin, Germany.

Background: Vascular calcifications are common in patients with chronic kidney disease (CKD). Our preliminary studies indicate that inhibition of matrix metalloproteinases (MMP)-2 and -9 suppresses the development of arterial calcification in uremic rats. Epigallocatechin gallate (EGCG), a polyphenol ingredient of green tea, has strong antiinflammatory properties and inhibitory effects on MMPs. We therefore investigated potential protective effects of EGCG on calcification of vascular smooth muscle cells (VSMC) in vitro and in an animal model of uremia-associated arteriosclerosis in vivo.

Methods: In vitro, calcifications of murine VSMCs were induced by a high phosphate (HP)-medium and cells were treated with different EGCG-concentrations (20-100µg/ml). VSMC calcifications were quantified using the ortho-cresolphthalein-methode and proteolytic activities of MMP-2 and -9 in VSMC supernatants were determined by gelatin zymographies. C57BL/6 mice were 5/6-nephrectomized and arterial calcifications were induced by calcitriol (1µg/kg body weight) and a HP-diet (2% phosphate). One cohort (n=10) was additionally administrated 0.02% EGCG in drinking water. Animals were sacrificed after 2 weeks of treatment and aortic calcifications were quantified after von Kossa-staining.

Results: In-vitro, EGCG provoked a dose-dependent decrease of HP-induced calcification (up to 85%) of VSMCs and of proteolytic MMP-2 and -9 activities. In vivo, all calcitriol-treated mice had severe arterial calcifications, involving 50% of the arterial wall after only 2 weeks of treatment. EGCG had no significant inhibitory effect on the development of vascular calcifications.

Conclusions: In this “negative experimental trial”, EGCG had no beneficial effect in the chosen animal model, which (considering the rapid development of calcifications) may have been too aggressive, thus overriding potential protective effects of EGCG. Encouraged by the positive in vitro results, the effects of EGCG and other polyphenols should nonetheless be further investigated in other animal models of uremia-associated arteriosclerosis.

Funding: Private Foundation Support, Clinical Revenue Support
induced arterial dilatation in situ. Cell lineage tracing was performed in Rosa-ttd mice bred to obtain aortic smooth muscle cell lineage. Mice harboring Rosa-ttd express tomato red cells in rearing Cav2 recombinase.

Results: Circulating activin and Dkk1 levels were increased while aklotho levels were decreased by CKD. In diseased kidneys, activin was expressed in myofibroblasts, and activin signaling through Smad 3 was increased. An ActRIIA ligand trap, RAP-011, inhibited renal pSmad 3, ColA1 expression, urinary protein levels, and circulating free activin levels in adenine-preloaded rats, indicating that activin signaling is increased in CKD kidneys.

Conclusions: Reduced VSMC differentiation and function. The ActRIIA ligand trap increased VSMC differentiation and inhibited osteoblastic transition and atherosclerotic calcification. In the circulation, the ActRIIA ligand trap decreased Dkk1 levels. CKD induced expression of tomato red in cells of the adventia after two weeks of femoral artery injury in Tek-Cre/Rosa-ttd mice compared to Tek-Cre/Rosa-ttd mice with normal kidney function.

Funding: NIDDK Support, Pharmaceutical Company Support - Celgene

SA-PO594

Transient Azotemic Episode Exacerbates Vascular Calcification in Adenine-Induced Uremic Rats

Daisuke Mori,1 Isaio Matsui,1 Akhiro Shimomura,2 Yasuo Kusunoki,1 Sayoko Yonemoto,1 Masamitsu Senda,1 Yusuke Sakaguchi,1 Takayuki Hanno,1 Yoshitaka Isaka,2 Hiromi Rakugi.1

Background: Urea, the final metabolite of amino acids in the body, can carbamylate proteins at lysine residues, and thereby modifies characteristics of proteins irreversibly. Several studies have revealed that functions of proteins are impaired by carbamylation. In diseased kidneys, although AKI is not a perpetual condition, it is well-known that AKI follows a subsequent phase of cardiovascular diseases through yet-unknown mechanisms.

Methods: We evaluated the effects of transiently elevated serum urea on vascular calcification (VC). Male Sprague-Dawley rats at age 9 weeks were divided randomly into two groups: cellulose-preload + adenine diet (group C+A) and urea-preload + adenine diet (group U+A). Urea-preloaded group received 10% urea diet from 9 to 13 weeks of age. Controls were served as a control for urea. After one week of urea-washout period, all rats received 0.75% adenine-containing diet up to 19 weeks of age.

Results: Serum urea levels were 15.87 ± 2.96 mg/dl in cellulose-preloaded group and 39.20 ± 3.74 mg/dl in urea-preloaded group at the end of the preoad period. Serum urea levels in serum urea + preload group were normalized to 14.73 ± 1.28 mg/dl during the washout period. At age 19 weeks, rats in group U+A developed severe VC in comparison with the rats in group C+A. Serum creatinine, urea nitrogen, calcium, phosphorus, magnesium, albumin, and body weight were not different between the two groups at age 19 weeks. Western blot analysis of the aorta revealed that dietary preload of urea increased carbamylated protein.

Conclusions: Predialysis urea exacerbates VC in adenine-induced uremic rats. Protein carbamylation might link urea-preload to VC.

SA-PO595

SNF472 Inhibits Cardiovascular Calcification in Uremic Rats

Joan Perello,1,2 Carolina Salcedo,1 Ellen Neven,2 Geert J. Behets,3 Pieter H. Joubert,1 Patrick SNF472 Inhibits Cardiovascular Calcification in Uremic Rats

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Deoxycholic Acid (DCA), a Metabolite of Bile Acid Cycles, and Coronary Vascular Calcifications in Chronic Kidney Disease (CKD)

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Background: Our group has previously shown that DCA, a metabolite of circulating cholic acid, induces vascular mineralization and osteogenic differentiation in animal models and that circulating levels of DCA are elevated in patients with CKD. We investigated whether increased DCA serum levels are associated with an increase risk for higher coronary artery calcification (CAC) volumes and lower lumbar bone mineral density (BMD) in CKD patients.

Methods: We used stored baseline serum samples in 112 patients with moderate to advanced CKD (eGFR 20-45 mL/min/1.73m²) who participated in a randomized-controlled study to examine the effects of phosphate binders on vascular calcification. Circulating DCA levels were assayed using liquid-chromatography-tandem mass spectrometry (LC-MS/MS). CAC volume was obtained using GE-Imatron C150 scanner and lumbar BMD was determined using abdominal computed tomography scans with a calibrated phantom of known density. Linear regression models were used to examine the cross-sectional association between DCA with CAC volume and lumbar BMD.

Results: Participant characteristics were as follows: mean age, 68±11 years; 50% women; 10% black; mean eGFR, 32±8 mL/min/1.73m²; and median DCA 5.84 (Q29-112) ng/mL. After adjusting for demographics, co-existing illness, body mass index, eGFR and circulating markers of CKD-MBD including serum calcium, phosphorus, vitamin D, parathyroid hormone and fibroblast growth factor 23, an increase serum DCA level > 58 ng/mL positively associate with CAC volume (B = 4.94±3.28; p = 0.03) and negatively associated with BMD (B = -20.35± 9.56; p = 0.03).

Conclusions: Higher serum levels of DCA in patients with stage III and IV CKD is independently associated with higher CAC volume and lower lumbar BMD. Larger cohort studies are needed to confirm these findings.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO599

Fibroblast Growth Factor 23 and Fetuin-A Levels in Pre-Dialysis Stage 4-5 Chronic Kidney Disease Patients with Aortic Calcification: A Case Control Study

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Background: Vascular calcification (VC) contributes to the increased cardiovascular mortality seen in CKD. However, not everyone with advanced CKD develops VC, indicating that circulating levels of factors that modulate VC may play a role in determining individual susceptibility towards VC. We aimed to examine the hypothesis by measuring the levels of FGF-23 and Fetuin-A in a group of pre-dialysis CKD stage 4-5 patients who had documented abdominal aortic calcification (AAC) and an age, gender and eGFR matched group of patients who did not have AAC.

Methods: Out of a pre-existing cohort of 710 patients with CKD Stage 4-5, 28 patients with AAC (Group 1, cases) were compared with an equal number of age, gender and eGFR matched patients without AAC (Group 2, controls) with respect to their demographic and biochemical parameters, including FGF-23 and Fetuin-A. AAC was assessed by lateral abdominal X ray, while Fetuin-A and intact FGF-23 were estimated by ELISA in serum.

Results: Groups 1 and 2 were matched for age (mean 57.7 ± 57.6 years, respectively; p = 0.938), gender (84.6% males in both groups) and eGFR (median eGFR 14.5 ± 13.1 respectively, p = 0.826), and were not significantly different with respect to risk factors for AAC such as presence and duration of diabetes, hypertension, smoking, and obesity. Levels of calcium, phosphorus, PTH, 25 (OH) vitamin D, serum cholesterol, triglycerides, HDL and LDL were also comparable between the two groups. However, median FGF-23 levels were significantly higher in Group 1 [25.2, (Q1= 14, Q3=34.2)] compared to Group 2 [12.1 (Q1 = 6, Q3 = 14.1), p = 0.001]. Median Fetuin-A levels were also significantly higher in Group 1 [5.5 (Q1=4.4, Q3=6.5)] compared to Group 2 [4.1 (Q1 = 3.6, Q3 = 5.7, p = 0.034).

Conclusions: Pre-dialysis patients with Stage 4-5 CKD with AAC, had higher FGF-23 and Fetuin-A levels compared to age, gender and eGFR matched patients who did not have AAC. The nature and mechanism of this association between elevated FGF23 and Fetuin-A levels compared to age, gender and eGFR matched patients who did not have AAC.

SA-PO600

Lack of Association Between Serum Osteoprotegerin, Osteopontin and Fetuin-A Levels and the Longitudinal Changes in Arterial Stiffness in CKD Patients Undergoing Renin-Angiotensin System Blockade

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Background: Osteoprotein (OPG), osteopontin (OPN) and fetuin-A, have been suggested to participate in the accelerated development of arteriosclerosis seen in patients with chronic kidney disease (CKD). We have previously shown that measures of vascular stiffness were significantly reduced after 24 weeks of treatment with renin-angiotensin System (RAS) blocking agents. The aim of this longitudinal post hoc study was to investigate whether serum levels of OPG, OPN and fetuin-A were associated with these same changes in markers of arterial stiffness found in CKD patients treated with RAS blocking agents.

Methods: Serum OPG, OPN and fetuin-A levels were measured in 57 patients with CKD stage 3-5, mean eGFR 29 mL/min, as a post hoc analysis of data acquired during a 24-week placebo controlled trial in which patients were randomized to treatment with enalapril monotherapy with either enalapril or candesartan followed by 8 weeks of dual blockade. Serum levels were obtained upon study entry and after 16 and 24 weeks of RAS blocking therapy and compared to aortic pulse-wave velocity and augmentation index.

Results: Except for a significant correlation between OPN and central pulse pressure (p < 0.05), serum levels of OPG, OPN and fetuin-A did not correlate to markers of vascular stiffness. There were no significant changes in serum levels of OPG, OPN and fetuin-A when monotherapy with enalapril or candesartan was compared to dual blockade.

Conclusions: The present results do not corroborate the use of OPG, OPN and fetuin-A as surrogate markers for vascular stiffness in patients with CKD.

SA-PO601

Hyperuricemia Is Significantly Associated with Coronary Artery Calcification and Vascular Stiffness in Asymptomatic Subjects Undergoing General Health Examination

Arne Høj Nielsen,1 Allan Flyvbjerg,3 Mette Bjerre.3

Background: Recent studies suggest that hyperuricemia may be associated with increased adverse cardiovascular events even in healthy subjects. Quantity of coronary artery calcium (CAC) correlates with atherosclerotic plaque burden and increased cardiovascular events. This study aimed to determine the relationship between serum uric acid level (sUA) and coronary artery calcification score (CACS) as well as other traditional cardiovascular risk factors in asymptomatic subjects.

Methods: We consecutively enrolled 4,703 asymptomatic subjects who under-pBPM and coronary CT angiography as part of a general health examination. A high B-PWV was defined as having increased arterial stiffness. Hyperuricemia was defined as serum sUA greater than 497.5 μmol/L (75th percentile). The subjects were stratified into four groups according to sUA.

Results: Mean age of enrolled subject was 52.8 ± 9.4 years, 61 % of the study participants were male. Eight four percent of the study participants showed CACS greater than 100. The adjusted odds ratio (OR, 95% confidence interval) for the presence of high B-PWV in the second to fourth sUA quartile vs. first sUA quartile was 1.45 (1.137-1.840, P = 0.003), 1.42 (1.081-1.866; P = 0.012), 1.66 (1.246-2.218, P = 0.001), respectively, after adjusting for age, gender, diabetes, hypertension, smoking, body mass index (BMI), eGFR, serum total and low density lipoprotein cholesterol (eGFR), fasting blood sugar (FBS) and calculated LDL. Moreover, subjects with CACS greater than 100 also showed that fourth quartile of sUA was associated with high B-PWV compared with the first quartile of sUA [OR 2.4, (1.65-3.47, P = 0.001)]. Multivariate linear regression analysis demonstrated that old age, male, smoking, diabetes, BMI, FBS, eGFR and sUA were significantly associated with mean B-PWV and low transformed CACS.

Conclusions: Our results show that sUA is an independent risk factor for increased vascular stiffness and coronary atherosclerosis in asymptomatic adults undergoing health examination.
SA-PO603

Total Body multislice Computered Tomography as a Gold Standard of Vascular Calcification
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Background: Vascular calcification (VC) is a marker of cardiovascular risk in CKD patients. Imbalance of calcium-phosphate parameters and secondary hyperparathyroidism (sHP) has been proposed as indicators of VC. Traditionally VC has been evaluated with Kaupilla, Adragao and coronary Agatston scores but they are limited to restricted body areas and may underestimate total VC. We proposed a new method to assess VC in CKD patients with mild sHP based on total body multislice computered tomography (MSCT) without contrast.

Methods: Multicenter transversal study which included incident dialysis patients with mild sHP (PTH >150pg/dl) after signed informed consent. Kaupilla and Adragao scores were determined on abdominal and pelvic/hand X-ray, respectively. Total body area calcification (cm2) was measured by MSCT. Patients with a total calcified area of >150 cm2 were considered calcified. Sensibility and specificity of Kaupilla and Adragao scores were calculated considering total calcified body area > 150 cm2 as reference.

Results: We enrolled 22 patients (13 hemodialysis / 9 peritoneal dialysis), 45% diabetics, 62±15 years old. Mean±SD were: phosphorus 4.6±1.5mg/dl, calcium 9.2±1.04mg/dl and parathyroid hormone 278±132pg/dl. They presented mean Kaupilla score of 6.9±6.9, Adragao score of 2.3±3.7 and total calcified area of 112±61.96 cm2. 77% patients were calcified, considering positive if overall calcified area >150cm2. Diabetics and those with previous cardiovascular events had higher total body calcified area, whereas gender and type of dialysis didn’t demonstrate any influence on calcification. Sensibility of Kaupilla and Adragao scores were 70% and 30% respectively, whereas specificity of both of them was 100%.

Conclusions: It is possible to evaluate the overall body calcified area in patients with ESRD by multislice computered tomography, which could be considered as a potential gold standard of global vascular calcification in those patients.

SA-PO604

Comparison of Mineral Metabolic Markers and Therapy in Chronic Hemodialysis Patients with Different Degree of Abdominal Aortic Calcification Score
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Background: The correlations of vascular calcifications with different markers of CKD-MBD and also their therapy are not always consistent across the studies and cross-sectional associations are favoured over long-term analyses. We therefore aimed to evaluate laboratory markers and therapy load over a longer period in chronic hemodialysis patients with different severity of abdominal aortic calcification (AAC).

Methods: In hemodialysis patients AAC was determined by lateral lumbar radiography and quantified by Kaupilla score. Patients were divided in two groups according to median AAC score of the whole group. Mean active vitamin D and cinacalcet intake for last 4 years and calcium carbonate for last 10 years (or whole dialysis vintage for those on dialysis for shorter time) and mean mineral metabolism markers (Ca, P, iPTH, Ca×P product and alkaline phosphatase (AF) for last 4 years) were compared between the groups.

Results: With high AAC score were significantly older (72±5 vs. 59±15 years, p=0.003) and more often diabetic (15% vs. 2%, p=0.04) compared to 19 patients with low score, where there was no difference in dialysis vintage (6.4±4.8 vs. 5.3±4.2 years, p=0.44) or presence of cardiovascular disease. We found no difference in mean calcium carbonate dose (4.1±1.6 vs. 4.4±1.9 g/day, p=0.59) or mean cinacalcet dose (21.2±20 vs. 12±17 mg/day, p=0.18), but significantly higher mean calcium-equivalent dose of active vitamin D (1.7±0.8 vs. 0.9±0.8mg/wk, p=0.03). There was no significant difference in Ca, Ca×P product, iPTH or AF, but P was significantly higher (1.6±0.2 vs. 1.4±0.3 mmol/L, p=0.03) in group with high AAC score.

Conclusions: In patients with higher AAC score higher mean active vitamin D dose and higher phosphate levels over a long period of time were found in addition to older age and more diabetes. We find this retrospective analysis important because treatment and laboratory values were evaluated over a prolonged period.

SA-PO605

Influence of the Bone Mineral Disorder on Vascular Calcification Occurrence and Progression in Hemodialysis Patients
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Background: Cardiovascular disease is the main cause of death in hemodialysis patients; vascular calcification (VC) is common among them. The main objective of this study was to evaluate the influence of bone mineral disorders in VC and its progression in a prospective cohort of patients. Secondly, we intend to identify clinical, laboratory and medical predictors of the presence and progression of VC.

Methods: Adult patients undergoing HD for >90 days were included. At the beginning of and after 12 months Kaupilla and Adragao methods were used to determine the VC score.

SA-PO606

Low Bone Mineral Density of Lower Extremities Associates with Coroneary Calcification Score in End-Stage Renal Disease Patients
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Background: Kidney transplantation (RTx) corrects many abnormalities in uremia but mineral and bone disorders and cardiovascular disease often persevere. We investigated associations between low bone mineral density (BMD) and coronary artery calcification (CAC) in hemodialysis patients (pts) with end stage renal disease (ESRD) undergoing living donor RTx.

Methods: In 40 pts (aged 44 ± 13 years; 60% male) undergoing living donor RTx, BMD measurements were made before (n=19), close to (n=40) and after (n=13) RTx and CAC measurements (n=34) were also made close to RTx. BMD was assessed by dual-energy X-ray absorptiometry (DXA) and CAC by computed tomography. We investigated the associations between BMD and CAC (measured at the same time). Logistic regression models were adjusted for age, gender and diabetes.

Results: Altogether 32% (13/43) pts had CAC Agatston score ≥100. CAC associated with SBP (OR=0.46, p<0.01) and diabetes (OR=0.57, p<0.001). At baseline, there were significant associations between CAC and BMD of upper extremities (rho = -0.49, p<0.01), BMD of lower extremities (rho = -0.66, p<0.001) and BMD of femoral neck (rho = -0.58, p<0.001). In multivariate analysis adjusted for age, gender and diabetes, BMD of lower extremities remained as significantly lower in pts with CAC scores ≥ 100 (p< 0.05). No significant differences were seen between values of BMD obtained -2.0 [-4.4, -1.1] years before Rtx (n=19) as compared to BMD obtained close to Rtx at -0.1 [-0.7, 0.6] years (n=40) or 2.1 [1.1, 3.3] years after (n=13) Rtx. Sex-stratified analyses also showed no significant differences in BMD before, close to and after RTx.

Conclusions: BMD of lower extremities is associated with CAC in ESRD pts undergoing living donor RTx. No significant changes in BMD were found when comparing values before, close to and after RTx. Further studies are required to elucidate the mechanism(s) linking BMD to CAC score in ESRD pts.

Funding: Pharmaceutical Company Support - Baxter, Government Support - Non-U.S.
**Association of Vascular Calcification Biomarkers with Odds of PAD**

<table>
<thead>
<tr>
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<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPG, per 1 pmol/L higher</td>
<td>1.06 (1.02-1.11)</td>
<td>1.07 (1.01-1.13)</td>
</tr>
<tr>
<td>Fetuin A, per 1 g/L higher</td>
<td>0.88 (0.24-3.26)</td>
<td>1.25 (0.27-5.81)</td>
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<tr>
<td>MGP, per 1 log pM higher</td>
<td>0.98 (0.75-1.28)</td>
<td>0.91 (0.66-1.25)</td>
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**SA-PO608**

**Association of Metabolic Syndrome with Aortic Arch Calcification and Outcome in Non-Diabetic Peritoneal Dialysis Patients**

**Methods:** We enrolled 277 non-diabetic PD patients into this study. Posterior-anterior chest X-ray were assessed for the aortic arch calcification (AoAC). Frequency of different components and their constellation as MetS were determined according to the modified Adult Treatment Panel III criteria. Using multinomial logistic regression, the factors determining baseline AoAC were analyzed. We used Kaplan Meier analysis to assess the impact of MetS on both mortality and technique failure.

**Results:** Mean age was 48.4 ± 13 years and 43.1% (n=118) had metabolic syndrome. 179 patients were classified as no visible calcification (AoAC grade 0), 51 patients as mild calcification (AoAC grade 1), and 47 patients as moderate to severe calcification (AoAC grade 2-3). The adjusted odds ratio for AoAC grade 1 was 3.03 (95% CI: 1.34-6.84) and for AoAC grade 2-3 was 6.25 (95% CI: 2.26-17.27) among patients with MetS as compared to those without MetS. Multivariate linear regression analysis showed that the presence of MetS (P <0.001) was independent risk factor for higher inflammation, as denoted by high sensitivity C-reactive protein. Over a mean of 45.9 months of follow-up, 34 patients died. Kaplan Meier analysis demonstrated that the incidence of mortality and technique failure does not differ in patients with and without MetS.

**Conclusions:** MetS was independently associated with the presence and severity of AoAC but cannot predict mortality or technique failure in non-diabetic PD patients. Nevertheless, non-diabetic PD Patients with MetS warrant more aggressive risk factor management to reduce the risk of VC.

**SA-PO609**

**Increased Peripheral Arterial Calcification in Patients Receiving Warfarin**

**Methods:** A random sample from a computerized search of medical records yielded 430 patients with x-rays performed during or after warfarin therapy. Each was matched to a patient without warfarin exposure based on age and diabetes. Patients with warfarin exposure <1 month, history of ESRD, or serum creatinine > 2.0 were excluded. X-rays were reviewed visually for arterial calcification.

**Results:** Mean age was 66.9 ± 8.0, 41% were males, and 34% had diabetes. The indication for warfarin was atrial fibrillation in 45% and venous thrombosis or embolism in 44%, and mean duration of warfarin was 4.8 yrs (range: 1 month to 38 yrs). 68% were on warfarin at the time of the x-ray and the remainder had been off warfarin for a mean of 2.4 yrs (range: 1 day to 25 yrs). Serum calcium was slightly lower (9.04 +/- 0.03 vs. 9.17 +/- 0.02, p<0.0005) in the warfarin patient but serum creatinine and phosphorus did not differ. Prevalence of arterial calcification was 44% greater in warfarin patients (30.2% vs. 20.9%, p<0.0023) but not on x-rays performed prior to warfarin (26.4% vs. 22.4%, n=116), indicating that the increase was due specifically to the warfarin and not to underlying disease or other patient characteristics. The increase in calcification was seen only after >5 yrs of warfarin and only in the ankle and foot. It was similar in men and women and greatest (2.4-fold) in patients under age 60 (15% vs. 6.3%, p=0.04).

**Conclusions:** Warfarin use is associated with lower extremity arterial calcification in both men and women independent of age, diabetes, and other patient characteristics.

**SA-PO610**

**Matrix GlA Protein and Vascular Calcification in Patients with End Stage Renal Disease**

**Background:** Vascular calcification (VC) is a common and severe consequence of end-stage renal disease (ESRD). Matrix GlA protein (MGAP) is a calcification inhibitor expressed by the vasculature that counteracts the development of VC.

**Methods:** In 84 ESRD patients undergoing LD-Tx at Karolinska University Hospital, biopsies from the inferior epigastric artery were obtained during surgery. Vascular calcification was assessed by von Kossa staining both by manual scoring (0-3) and by semi-automated analysis (%). Total uncarboxylated MGP (uc-MGP) and diphospho-uncarboxylated MGP (dp-uc-MGP) were measured in plasma. Tissue MGP expression was quantified in arterial biopsies by TaqMan rPCR. DNA methylation of the MGP gene was assessed in peripheral blood from 12 ESRD patients and 12 healthy controls.

**Results:** 50 patients (59.5%) had low VC scores (0 and 1) and 34 (40.5%) patients had high VC scores (2 and 3). Plasma levels of dp-ucMGP were higher in patients with high VC scores compared to patients with low VC scores (2214 [1413-2995] vs. 1701 [1275-2233] pmol/L, p<0.05) and also associated with calcification (%)(Fig 1A). In addition, MGP expression was associated with arterial expression of MGP (Fig 1B: β [95%CI]: 0.04 [0.02 to 0.06] p<0.0001). uc-MGP levels were not associated with measures of DNA methylation of the MGP gene was significantly lower in patients with ESRD compared to healthy controls (adjusted p<0.01).

**Figure 1**

![Image](https://via.placeholder.com/150)

**Figure 1. The association between calcification % (as assessed by semi-automated analysis) and A) plasma dp-ucMGP levels, and B) tissue MGP expression.**

**Conclusions:** Tissue and plasma levels of dp-ucMGP were higher in patients with VC versus those without, possibly indicating a compensatory up-regulation of MGP to prevent further progression. The observation that the methylation of the MGP gene was lower in ESRD than in controls suggests that the altered expression could be due to epigenetic regulation.

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

**SA-PO611**

**A Nationally Representative Case Control Study of Calciphylaxis Risk Factors**

**Background:** Prior studies evaluating calciphylaxis risk factors suffer from sample size limitations and none examine whether characteristics at dialysis initiation predict calciphylaxis risk.

**Methods:** Data for this matched case control study were derived from hemodialysis (HD) population at the Fresenius Medical Care North America (FMCNA). Cases were identified from FMCNA calciphylaxis prospective database. Controls (HD patients without calciphylaxis) were matched to cases on age, sex, and race. Data on variables at HD initiation were abstracted. Variables for multivariable logistic regression analyses were identified using stepwise selection.

**Results:** We analyzed 1,025 calciphylaxis cases (52% biopsy-confirmed) and 2,050 controls. Body mass index, diabetes mellitus (DM), serum parathyroid hormone (PTH) level, use of warfarin and phosphate binders were higher whereas serum calcium and active vitamin D use were lower at HD initiation in cases compared to controls.
No significant differences were noted for serum phosphorous, diacylate calcium, use of statins and cinacalcet. In DM subgroup, insulin injection use was more common in males. In multivariable analyses, obesity (OR: 2.55, 95% CI: 1.82-3.59), DM (OR: 2.63, 95% CI: 1.83-3.69), use of warfarin (OR: 3.60, 95% CI: 2.40-5.41) and insulin injections (OR: 1.29, 95% CI: 1.07-1.89) were associated with higher risk. Similar results were noted in analyses restricted to biopsy-confirmed cases.

Conclusions: Obese, diabetic HD patients treated with insulin injections or warfarin are at high risk for calciphylaxis.

Funding: Private Foundation Support

SA-PO612 Calciphylaxis Quality Improvement Project and Case Series Rohan V. Mehta, Jean Luc Franck, Jason Cobb. Renal Div, Emory Univ, Atlanta, GA.

Background: Calciphylaxis (Calcific Uremic Arteriopathy) is a serious condition characterized by extended length of stays and multiple hospital admissions. The treatment of calciphylaxis can become a burden on the healthcare system especially with the demand on hospital systems to become more efficient. The lengths of stay & 30-day readmission rates are becoming a measure of hospital quality. We developed a multidisciplinary team including nephrologists, hospitalists, dermatologists, hospital administration, nurses, wound care staff, social workers, dieticians, and palliative care. The purpose of the team is to improve the quality of care of our calciphylaxis patients. In development of this quality improvement project we began by examining our baseline patient population. We are reporting our baseline data as a case-series.

Methods: Retrospective chart review of calciphylaxis patients from 2001-2014 in our single center hospital which includes academic and community physicians. Baseline data reported included age, calcium, phosphorus, PTH, albumin, hemoglobin, creatinine, BUN, and the use of warfarin. Treatment options, the length of stay, and number of admissions were reported.

Results: In 20 reported patients, 19 were African-American. Average age was 61 years old. Average calcium levels of 8.8 mg/dl and phosphorus of 5.5 mg/dl. The average PTH was 573, albumin 2.75 gm/dl, hemoglobin of 10.4 gm/dl, BUN of 42, and creatinine 6.5 mg/dl. 13 patients received hyperbaric oxygen treatment, 9 patients received sodium thiosulfate infusions and, 6 patients received cinacalcet. 11 patients were using warfarin for medical conditions including atrial fibrillation and deep venous thrombosis. The average length of stay was 45 days and 3 admissions per patient.

Conclusions: We reported one of the largest single center and predominant African-American calciphylaxis case series. In comparison to other reported calciphylaxis series our average PTH was lower and a high percentage of our patients were using warfarin at time of diagnosis. Future tasks include testing if the multidisciplinary quality improvement team interventions can improve our patient quality of care and hospital goals such as reductions in length of stay and 30-day readmission rates.

SA-PO614 The German Calciphylaxis Registry Vincent Brandenburg, Jürgen Floege, Joanna Korbiul, Markus Ketteler. 1Cardiology, RWTH Aachen Univ Hospital, Aachen, Germany; 2Nephrology, RWTH Aachen Univ Hospital, Aachen, Germany; 3Nephrology, Klinikum Coburg, Coburg, Germany.

Background: Calciphylaxis (CUA) is a rare disease and for patients a devastating condition associated with high morbidity and mortality. CUA is characterised by painful, ischemic, partly necrotic skin ulcerations. Pathomorphologically, media calcification of cutaneous arterioles and extracellular matrix remodelling are the hallmarks of CUA. Epidemiology and risk factors are incompletely understood. Referring patients to specialized units is limited due to high disease burden.

Methods: Therefore, we established an internet-based observational registry in 2006 (www.calciphylaxie.de) to allow online notification for pts with CUA. The registry includes a comprehensive data base with 71 parameters concerning patient and laboratory data, clinical background and presentation as well as therapeutic strategies. The diagnosis of CUA is made on clinical and/or histological grounds by the referring physician.

Results: Until Feb 2015 n=253 patients with CUA have been recorded (~30 pts/year at constant rate) with a median delay of 28 days after onset: 99% Caucasians, 60% females; 76% HD and 10% PD patients; median age 66 (IQR 59-76) years. Co-medication at the time of diagnosis: 75% ESA, 51% vitamin K antagonists (VKA). Skin biopsy was done in 45%, prior PEx in 12%; major skin lesion in 80% at the legs. Median lab data upon diagnosis of CUA: AK Phos 113 U/L (IQR 86-167); PT 173 mg/L (IQR 73-390); total calcium 2.20 mmol/L (IQR 2.04-2.36); phosphorus 1.62 mmol/L (IQR 1.28-2.00). Among the most frequently recorded therapeutic procedures were: surgical necrosectomy (plus antibiotics), intensifying dialysis modality, reduction of calcium supply, i.v. sodium-thiosulfate application. Survival was analyzed in a subgroup of 91 pts. Median survival time was 516 days after online notification.

Conclusions: CUA is a rare disease among ESRD pts with high mortality. Therapeutic strategies vary significantly among centers; EBM guidelines are absent. VKA usage appears to be a risk factor for CUA in ESRD pts. The German CUA registry is a valuable tool to collect data and may become a basis for a European registry (EuCalNet).

Funding: Pharmaceutical Company Support - Sanofi, Amgen

SA-PO615 Evaluation of the Effects of Sodium Thiosulfate Treatment on Calciphylaxis Pain Guillermo Ortiz, Joshua Wibecan, Julia Beth Wenger, Ravi I. Thadhani, Sagar U. Nigwekar. Nephrology Div, Massachusetts General Hospital, Boston, MA.

Background: Intravenous sodium thiosulfate (STS) is commonly prescribed to treat calciphylaxis, a highly fatal disease that presents with excruciating painful skin lesions. Anecdotal reports suggest that STS may improve calciphylaxis associated pain (CAP) within 2 weeks of initiation; however, systematic evaluation of effects of STS on CAP is lacking.

Methods: This observational study included 22 patients with biopsy-confirmed calciphylaxis who were hospitalized at our center for ≥ 2 weeks during 2012-2014 for newly diagnosed calciphylaxis and were treated with STS. Medical records were reviewed to abstract clinical data including CAP severity (0-10 scale) and analgesic use. CAP scores at baseline, 1-week, and 2-week time-points were noted and classified into mild (1-3), moderate (4-6), or severe (7-10) CAP.
moderate (4-6), and severe (7-10) categories. Responders were patients who reported ≥30% improvement in CAP severity score from baseline during the first 2 weeks of treatment. Predictors of response and association between CAP response during the first 2 weeks of STS treatment and 6-month outcomes (skin lesion status, mortality) were examined in univariate logistic regression analyses.

Results: Median age was 60 years (Range: 52-67). 59% were males, 95% were whites, 55% were on dialysis, 36% had chronic kidney disease not requiring dialysis, and 9% had normal kidney function. Median duration between lesion appearance and STS initiation was 12 weeks (Range: 6-19). There was a trend toward decrease in severe CAP from baseline to 2-weeks (figure 1) despite steady doses of opiate medications. No significant predictors of CAP response were observed and CAP improvement at 2-weeks did not predict 6-month outcomes.

Conclusions: A large prospective trial is needed to ascertain the effects of STS on CAP.

SA-PO616

Long-Term Impact of Strict Blood Pressure Control During CKD on Mortality Risk After ESRD

Evan Ku,1 Lawrence J. Appel,2 Jennifer J. Gassman,2 Miroslaw Smogorzewski,2 Mark J. Sarnak,3 David V. Glidden,1 Chi-yuan Hsu,1 UCSCF, 2AASK, 3Tufts.

Background: In extended follow-up of the Modification of Diet in Renal Disease (MDRD) study, we reported that strict BP control did not lower risk of ESRD but associated with lower mortality risk after ESRD (HR 0.72 [95% CI 0.58-0.89]) (Ku KI 2015). To further address this issue, we conducted parallel analyses in the African American Study of Kidney Disease (AASK) and post-hoc pooled analyses of AASK and MDRD.

Methods: AASK randomized 1094 persons with CKD attributed to hypertension to BP control targets (≤130/80 mmHg) vs usual care (≤140/90 mmHg). Median duration of follow-up was 6.2 years. We evaluated the effect of time-updated exposure to RAS blockade versus all other antihypertensive medications in obese, hypertensive, non-diabetic patients with normal or mildly reduced kidney function using a Cox proportional hazards model as estimated by pooled logistic regression to assess the hazards of developing a 50% reduction in estimated glomerular filtration rate (eGFR) or end stage renal disease. In addition to adjusting for baseline comorbidities including age, gender, socioeconomic status, cardiovascular disease, and body mass index (BMI), we adjusted for time-varying covariates including systolic blood pressure (SBP), number of antihypertensive medications, use of mineralocorticoid antagonists, and eGFR.

Results: There were 219,701 patients that met inclusion criteria, with a median 4.9 years of follow-up. Median baseline eGFR was 72.6 mL/min/1.73m², median SBP was 146 mmHg, and median BMI was 32.8 kg/m²; 59% of patients were on RAS blockade at baseline, and 60% of patients were on it for at least half the duration of follow-up. Taking into account time-updated exposure, there was a significantly reduced hazard of adverse renal outcomes in patients treated with RAS blockade compared to those treated with other antihypertensive medications (HR 0.93, p<0.01).

Conclusions: This study, conducted in a large real-world cohort of patients with detailed and time-updated data about blood pressure treatment, provides important evidence that RAS blockade may protect against deterioration in renal function among obese, hypertensive, non-diabetic patients.

Funding: NIDDK Support

SA-PO617

Obesity, Renin-Angiotensin System Blockade, and Chronic Kidney Disease: A Population-Based Cohort Study


Background: Obesity substantially increases the risk of the development and progression of chronic kidney disease. Adipose tissue expresses all of the components of the renin-angiotensin system (RAS), which is an important contributing factor to the high prevalence of hypertension in obese patients, and drives renal hyperfiltration and subsequent glomerular injury.

Methods: We performed a retrospective cohort study using the Health Improvement Network, a primary care database with comprehensive demographic, laboratory, and pharmacy data. We analyzed data from patients in the United Kingdom. We calculated the effect of time-updated exposure to RAS blockade versus all other antihypertensive medications in obese, hypertensive, non-diabetic patients with normal or mildly reduced kidney function using a Cox proportional hazards model as estimated by pooled logistic regression to assess the hazards of developing a 50% reduction in estimated glomerular filtration rate (eGFR) or end stage renal disease. In addition to adjusting for baseline comorbidities including age, gender, socioeconomic status, cardiovascular disease, and body mass index (BMI), we adjusted for time-varying covariates including systolic blood pressure (SBP), number of antihypertensive medications, use of mineralocorticoid antagonists, and eGFR.

Results: There were 219,701 patients that met inclusion criteria, with a median 4.9 years of follow-up. Median baseline eGFR was 72.6 mL/min/1.73m², median SBP was 146 mmHg, and median BMI was 32.8 kg/m²; 59% of patients were on RAS blockade at baseline, and 60% of patients were on it for at least half the duration of follow-up. Taking into account time-updated exposure, there was a significantly reduced hazard of adverse renal outcomes in patients treated with RAS blockade compared to those treated with other antihypertensive medications (HR 0.93, p<0.01).

Conclusions: This study, conducted in a large real-world cohort of patients with detailed and time-updated data about blood pressure treatment, provides important evidence that RAS blockade may protect against deterioration in renal function among obese, hypertensive, non-diabetic patients.

Funding: NIDDK Support

SA-PO618

Distribution and Prognostic Value of Central Blood Pressure in Chronic Kidney Disease

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Background: Central blood pressure (CBP) has been shown to be a better predictor for cardiovascular events and target organ damages than brachial blood pressure. However, little is known about comparative values of CBP and brachial BP in chronic kidney disease (CKD) population. We investigated the distribution of CBP and evaluated the comparative value of CBP and brachial BP for the prediction of renal progression in both CKD and non-CKD population.

Methods: We conducted this study using data from 868 subjects who underwent CBP measurement by the radial artery tonometric method between 2009 and 2013. Demographic and clinical characteristics were obtained from a review of the medical records at the time of CBP measurement. The outcome was renal progression defined as decline of estimated glomerular filtration rate greater than 30% of baseline during the follow-up.

Results: In overall, estimated central systolic BP (cSBP) was higher than brachial systolic BP (bSBP). The cSBP was significantly increased with age in non-CKD group, but such a correlation was not observed in CKD group. In CKD population, high cSBP group with greater than mean cSBP value (>130mmHg) had significantly increased probability of renal progression (P=0.016), while high bSBP (>140mmHg) group did not predict the outcome (P=0.370). In contrast, the predictor of renal progression was high bSBP but not cSBP in non-CKD population. In Cox analysis adjusted for covariates, high cSBP remained a predictor of renal progression in CKD population (HR 5.408; 95% CI 1.008-29.030; P=0.049), whereas high bSBP was not a significant predictor in non-CKD population (HR 2.891; 95% CI 0.786-10.650; P=0.110).

Conclusions: The CBP had different correlation with age and clinical significance according to presence or absence of CKD, and the high cSBP was strong independent predictor of kidney disease progression in CKD patients.

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766A
SA-PO619
Clinical Characteristics and Outcomes Associated with Resistant Hypertension in a Large Cohort of U.S. Veterans
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Background: The prevalence of true resistant hypertension (RH), the characteristics of patients with RH and its association with clinical outcomes is unclear.

Methods: From 2,398,778 patients with essential HTN, we identified 95,334 (4%) with RH, defined as: Failure to achieve BP<140/90 mmHg with >=3 antihypertensives (one being a thiazide diuretic) or success with >=4 drugs; excluding measurements when patient was <5, when interfering medications were prescribed and excluding those with confounding conditions (CKD, secondary HTN, sleep apnea, urinary obstruction, arterial, thyroid and parathyroid over-activity). We examined with mortality, incident CKD, ESRD, steeper slopes of eGFR, incident coronary heart disease (CHD) and stroke in Cox models and logistic regression models adjusted for demographic and socioeconomic factors, comorbidities, BP, and antihypertensives.

Results: The mean SBP,DBP in RH and non-RH patients were 148±22/81±14 vs. 137±19/78±12 mmHg. Compared to non-RH, patients with RH were older (64 ±11 vs. 60 ±13), more likely to be black (25 vs. 17%), and had a higher prevalence of DM and CVD.

The prevalence of true resistant hypertension (RH), the characteristics of patients with RH and its association with clinical outcomes is unclear. Therefore, methods were developed to identify patients with RH. This study aimed to assess the clinical characteristics and outcomes associated with RH.

Conclusions: RH is relatively infrequent (4%) among patients with essential HTN, and is associated with older age and a higher comorbidity burden. Patients with RH have a greater risk of incident CHD and stroke.

Funding: NIDDK Support, Veterans Administration Support

SA-PO620
Association of Components of Body Mass Index with Treatment-Resistant Hypertension in Men and Women with Chronic Kidney Disease
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Background: Treatment-resistant hypertension is a risk for cardiovascular disease and end-stage renal disease. However, the appropriate clinical management strategies remain unclear in patients with CKD. Our objective is to investigate the association of components of body mass index (BMI) with treatment-resistant hypertension in patients with CKD.

Methods: Body fluid composition was measured in 310 patients with CKD from 2005 to 2014, and BMI was separated into 3 components – (a) free water mass consisting of muscle, fat, and minerals, (b) intracellular water (ICW), and (c) extracellular water (ECW). Treatment-resistant hypertension was defined as an office BP of >130/80 mmHg, despite receiving >=3 antihypertensives including diuretics, or >=4 drugs usage. The main outcomes were adverse renal outcomes, as defined by a decline of 50% or more from baseline GFR or initiation of renal replacement therapy and cardiovascular events.

Results: The prevalence of treatment-resistant hypertension were 69 male patients (35.4%) and 19 females (16.5%). Patients with treatment-resistant hypertension were more likely to be diabetic, have a higher BMI, GFR, and proteinuria, and to be older especially in women. In the components of BMI, those in men and women tended to have higher ECW content and free water mass, respectively. Higher ECW contents in men and diabetes in relation to higher free water mass in men were independently caused treatment-resistant hypertension. Compared with patients with no treatment-resistant hypertension during a median 743-day follow-up, those with treatment-resistant hypertension had worse adverse renal outcomes (16.2 vs. 6.1 per 100 patient-years, P < 0.001) and cardiovascular events (5.0 vs. 1.6 per 100 patient-years, P < 0.001).

Conclusions: Treatment-resistant hypertension is associated with diabetes in relation to higher free water mass in men and higher ECW in men, which exhibits adverse renal outcomes and cardiovascular events. These findings emphasize the importance of adequate weight and volume status.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: 1. RDN leads to the temporary decrease of plasma reninase concentration in patients with HTN. 2. Lower plasma reninase concentrations seems to be a counteractive reaction to the antihypertensive effects of RDN.

Funding: Government Support - Non-U.S.

SA-PO623

A Non-Vascular Treatment for Resistant Hypertension Richard R. Heusser, Adam Gold. 1, 2
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Background: Systemic arterial hypertension remains the most common and important risk factor for cardiovascular and renal disease. A safe and effective medical device effecting a significant and immediate fall in arterial BP addresses an unmet clinical need. Early clinical experience with the Verve non-vascular device causes an immediate BP drop in patients with resistant hypertension.

Methods: In humans, there is a greater abundance of efferent compared with afferent nerve fibers and the afferent nerves are much less abundant in general and are much less abundant as one goes away from the aorta. In contrast to the widespread distribution of EFFERENT Sympathetic nerve fibers in the kidney, the majority of the AFFERENT Renal Sensory nerves are located in the renal pelvic area. With our first generation device, we treated patients with resistant hypertension. Four patients with resistant hypertension were treated. They had immediate blood pressure drop (Systolic Mean 44mmHg, Diastolic Mean 13mmHg), which was maintained for 3 months. Because of the possibility of calyceal damage noted in follow-up in our animal model, we have redesigned the probe and shortened the duration of therapy.

Results: In over two dozen animals, it appears that we get a similar histopathologic results with our first generation probe without late pelvic or calyceal damage. In our first clinical application of this helical probe, there also is an immediate blood pressure drop.

Conclusions: Unlike other renal derervation treatments, the Verve natural orifice approach appears to treat the afferent nerves and results in an immediate blood pressure drop. More patients will need to undergo treatment to confirm these encouraging results. We will present our first series of resistant hypertensive patients treated with the helical device.

SA-PO624


Background: Preeclampsia is a hypertensive disorder of pregnancy associated with high morbidity and mortality. Hallmarks of preeclampsia are endothelial damage and functional (e.g. proteinuria) and morphological renal aberrations. The only known remedy against this is the delivery of the placenta. Cell derived microparticles (MP) of different origins are elevated in preeclampsia but their mechanistic relevance is unknown. Preeclampsia is also associated with a pro-inflammatory condition but there are meager mechanistic insights into this as well.

Methods: To address these questions MP (endothelial or platelet derived) were injected into C57Bl/6 pregnant mice and the pregnancy outcome (embryonic survival and growth, placenta morphology) was studied. Morphology of the kidney was studied using PAS staining and electron microscopy. Proteinuria was studied as a measure of renal dysfunction. To address mechanistic questions, inflammasome activation by MP in placenta and trophoblast cells was studied using western blotting and immunohistochemistry. Human trophoblast derived cells and placentas from pregnancies complicated with preeclampsia were also studied for activation of inflammasome. NLRP3 and Casp-1 KO mice were used to rescue the mice from disease conditions and establish causality of the mechanism.

Results: MP caused preeclampsia associated with fetal loss and embryonic growth restriction in mice. This was associated with renal damage indicated by proteinuria, glomerular enlargement, thickness of glomerular basement membrane, and podocyte effacement in the kidney. Human and mouse placenta analysis indicated inflammasome activation seen by elevated expression of NLRP3, cleaved casp-1 and IL-1β. The pregnancy outcome and renal function was rescued in NLRP3 and Casp-1 KO mice.

Conclusions: The findings stress the importance of a close follow up to identify those women who need further care.

Mean follow up 172 days (+/-39.6) after delivery

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

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768A
SA-PO626
Preeclampsia: Long-Term Effects on Pediatric Neurologic Disability
Alberto Tejedor Jorge, Clara Nicolas, Patricinio Rodriguez Benitez, Olga Arroyo, Maria Silva, Laura Matesanz, Carmela Mercurio, Manuel Sánchez Luna. Hospital General Univ Gregorio Marañon.

Background: Preeclampsia affects up to 10% of pregnancies worldwide and is one of the main causes of fetal morbidity and mortality. Although it has been linked to developmental delay, its long-term effects on neurodevelopment in children have yet to be sufficiently quantified. Our aim is to evaluate whether the preeclampsia’s severity and the therapeutic options used to manage it correlate to the degree of developmental delay in these infants.

Methods: This is an observational and descriptive study performed on a population of 96 women who were diagnosed with preeclampsia at Hospital General Universitario Gregorio Marañón between 2007 and 2014, and their 111 children. To evaluate the mother, we gathered data pertaining to her medical history, renal function markers, and medical management of the preeclampsia. To assess the children, we collected fetal growth measurements, acute fetal distress markers and main diagnoses at birth. We used the Pediatric Disability Inventory in its computerized adaptive test version (PEDI-CAT) to study neurologic development, and the TNO-ASL Preschool children Quality of Life (TAQPOL) to estimate health-related quality of life.

Results: Early-onset and more severe preeclampsias were associated with higher preterm birth and perinatal mortality rates. Preeclampsias with a greater impact on maternal organ function showed a clear correlation to higher periventricular-intraventricular hemorrhage rates in the newborn. In terms of neurologic development, PEDI-CAT percentiles were consistently lower in the Social/Cognitive domain than in other areas. Lower Social/Cognitive percentiles were associated to both lower maternal IgG levels and lower Social/Cognitive percentiles were consistently lower in the Social/Cognitive domain than in other areas. Hemorrhage rates in the newborn. In terms of neurologic development, PEDI-CAT percentiles were consistently lower in the Social/Cognitive domain than in other areas. Lower Social/Cognitive percentiles were associated to both lower maternal IgG levels and lower Social/Cognitive percentiles were consistently lower in the Social/Cognitive domain than in other areas.

Conclusions: Lower Social/Cognitive percentiles were associated to both lower maternal IgG levels and poor social/cognitive outcomes exists that warrants further research, as does the possible link between preeclampsia, immaturity, and autistic features.

SA-PO627
Do Hypertension Providers Inquire About Hypertension in Pregnancy? 
Andrea G. Kattah, Vesna D. Garovic. Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Hypertensive pregnancy disorders are increasingly recognized as a risk factor for future hypertension and cardiovascular disease. However, knowledge of this risk may be inadequate among internal medicine providers.

Methods: We reviewed all new consults in a 2-month period in a hypertension subspeciality clinic. We determined the frequency with which providers documented a reproductive history, a history of hypertension in pregnancy and known cardiovascular risk factors. We also studied whether there were differences according to gender and level of training of the provider (consultants vs. residents/fellows) using the chi-square test.

Results: There were 102 consults for hypertension in the study period. The majority of consults were by consultants, 55/102 (53.9%), and 23/102 (22.6%) were by female providers. The most frequent questions were dietary issues, 29 (62%) 32 (58%) 0.72 for women and men respectively. Other questions included alcohol use, exercise, and family history of hypertension, 37 (79%) 36 (55%) 0.94 for men and women respectively. There was no significant difference between the two groups for illicit drug use, smoking, diabetes, dyslipidemia, renal disease, and hypertension in pregnancy.

Conclusions: Hypertension providers rarely document a reproductive history or a history of hypertension in pregnancy, irrespective of level of training. Female providers were more likely to document pregnancies.

SA-PO628
Accuracy of a Spot Urine Protein-to-Creatinine Ratio in Preeclampsia
Roshni Upadhyaya 1 Juliet Mushii, 2 Mary King, 2 Belinda Bun Jim, 1 Anjali Acharya.
1 Nephrology, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY; 2 Obstetrics, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY.

Background: Correlation between a 24 hour urinary protein excretion with a spot urine protein-to-creatinine (SP/Cr) ratio in patients with preeclampsia is unclear. Moreover, urinary creatinine excretion is greater in populations such as Africans and non-white Hispanics. We studied the correlation of the SP/Cr ratio with a 24 hour urine protein measurement in this minority population.

Methods: ICD-9 codes of 642.4, 642.5, 642.6, 642.7 representing mild pre-eclampsia to eclampsia were used for data collection. Only 110 women with both 24 urinary protein collection and (SP/Cr) were included in the analysis. Correlation between SP Cr and 24-hour protein excretion was assessed by Spearman correlation coefficient. The sensitivity and specificity of the SP/Cr ratio at various cut-offs for the prediction of significant proteinuria were estimated with a 95% confidence interval, using the 24-hour urine collection as gold standard. Receiver operating characteristic (ROC) curve analysis was used to determine the best discriminator values of the (SP/Cr) to predict proteinuria above 300 mg/24 hr. A value of 0.05 or less was significant.

Results: The median SP/Cr ratio was 0.30 (interquartile range (IQR) 0.3) while the median 24 hour urine protein was 316.5 mg (IQR 286.8). The overall Spearman correlation was 0.48 (P < 0.001), and 0.63 (P = 0.05), 0.59 (P = 0.1), and 0.45 (P = 0.001) for the 1st, 2nd, and 3rd trimesters respectively. At the cut-off value of 0.15 for SP/Cr, the sensitivity and specificity were 91.8% and 75.5% respectively. The cut-off SP/Cr ratio 0.25 was identified as the best threshold to detect a 24 hour protein excretion of 300 mg with a sensitivity and specificity of 75% and 59% respectively. The area under the curve (AUC) by the ROC curve analysis was found to be 0.69.

Conclusions: Even in a minority, inner city population we found significant correlation between the 24 hour protein excretion and the SP/Cr ratio, especially in the 2nd and 3rd trimesters of preeclampsia. Our findings are in line with the literature despite a minority patient population.

SA-PO629
Thiazide Diuretics for Hypertension in Kidney Transplant Recipients Using Tacrolimus
Arthur David Moes, Dennis Alexander Hesselinck, Anton H. Van den Meiracker, Robert Zietse, Ewout J. Hoorn. Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands.

Background: Hypertension after kidney transplantation is common and associated with poorer graft and recipient outcomes. Recently, we and others showed that tacrolimus activates the thiazide-sensitive sodium chloride cotransporter to cause hypertension. This suggests that thiazide diuretics may be especially effective drugs in this context, but prospective data are lacking.

Methods: We conducted a non-inferiority crossover trial to compare chlorthalidone (CT, 12.5-25 mg) with amlopidine (AML, 5-10 mg). Patients were invited for ambulatory blood pressure measurement (ABPM) if office BP >140/90 mmHg. Other criteria included eGFR >30 ml/min, proteinuria < 1 g, and no use of glucocorticoids. The treatment periods were randomized, last 8 weeks (allowing dose titration after 2 weeks), and were separated by a 2-week wash-out. Background anti-hypertensive drugs were allowed except for diuretics.

Results: 71 patients underwent initial ABPM of whom 45 patients (63%) with average wake SBP>140 mmHg were enrolled (median 2.6 years after transplantation). 38 patients completed the study (5 patients stopped during CT mainly due to electrolyte disorders vs. 2 during AML, p=0.4). CT and AML both markedly reduced ABPM after 8 weeks (151/85 ± 119/81 to 129/9 mmHg vs. 151/84 ± 13/9 to 138/79 ± 147 mmHg). There was no statistical difference in blood pressure response between the two drugs (p=0.3 by 2-way ANOVA). Dose titration rates were similar (42% for CT vs. 37% for AML, p=0.8). CT decreased eGFR (53 ± 17 to 46 ± 15 ml/min), whereas amlopidine increased it (50 ± 16 to 53 ± 17 ml/min, P<0.001). The first post-CT eGFR returned to baseline (51 ± 17 ml/min). Treatment with CT resulted in less proteinuria (median 14 vs. 19 mg/mmol, p=0.03) and less edema (8 vs. 31%, p=0.02). Regression analysis showed that a higher aldosterone to renin ratio, lower baseline serum potassium, and higher baseline serum bicarbonate predicted a better anti-hypertensive response to CT.

Conclusions: Thiazide diuretics effectively lower blood pressure in kidney transplant recipients using tacrolimus. Thiazides were especially effective in patients with more aldosterone effect.

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

SA-PO630
The Detrimental Effects of Beta-Blockers on Central Hemodynamic Parameters: A Propensity Score Analysis

Dominique Goupil,1  Dominique Dupuis,1  Stephan Troyanov,1  Francois Madore,1  Mohsen Agharazii,2

with decreased risk of development of dementia in comparison to treatment without CCBs. Results: In Model 1, the difference between peripheral and central systolic BP (DSBP) was 8.3 mmHg (OR 5.8, 11.6) with BB compared to 9.7 mmHg (7.1, 13.5) without (p<0.001), indicating that for any given peripheral BP, BB use resulted in higher central systolic BP. Pulse pressure amplification, augmentation index and augmented pressure were also less favorable with the use of BB. The different HR in Model 2 further increased the detrimental DSBP observed with BB to 7.9 (5.6, 11.0) vs. 10.6 (8.1, 14.3) without (p<0.001) and was associated with a higher central pulse pressure (46.5 ± 13.0 vs. 43.3 ± 11.3, p<0.001).

Conclusions: This study shows that the unfavorable central hemodynamic profile of BB has both a HR-dependent and a HR-independent component.

Funding: Government Support - Non-U.S.

SA-PO631
Risk of Development of Dementia During Treatment of Hypertension with Different Calcium Channel Blockers

Leonid Feldman,1  Shai Efrati,1  Ilia Beberashvili,2  Shlomo Vinker,2  Michal Shami,2

Background: Arterial hypertension (HTN) is proved to be a risk factor for development of dementia. Medical treatment of HTN may decrease the risk of dementia. Experimental study pointed to the possibility of difference between different calcium channel blockers (CCB) in their neuro-protective effect. The aim of our study was to evaluate the risk of dementia during treatment of HTN with one of three different CCBs.

Methods: This is a retrospective cohort study based on electronic database of Clalit Health Services, Central District. Study period was 11 years (2002-2012). Inclusion criteria: age 40-75, diagnosis of HTN without diagnosis of “Dementia” at the starting point, minimal duration of treatment >30 months with single specific CCB. New diagnosis of dementia was established according to appearance of its diagnostic code in the chronic diseases register or prescription of medication for its treatment – whatever occurred first. Results: 15,664 patients were included in the study: 3,884 were treated with amlodipine, 2,062 - with nifedipine, 609 - with lercanidipine and 9,109 never received CCBs. The mean age was 60.7 years, 52.9% were females and the mean baseline creatinine was 1.0 mg/dL. 13.4% of patients died during the study period. Dementia developed in 765 (4.9%) patients. Adjusted HR of dementia in patients treated with amlodipine, nifedipine and lercanidipine was 0.60 (p=0.001), 0.89 (NS) and 0.90 (NS).

Conclusions: Treatment of arterial hypertension with amlodipine may be associated with decreased risk of development of dementia in comparison to treatment without CCBs.

SA-PO632
The Association Between Antihypertensive Agents and Postural Blood Pressure Response Using Beat-to-Beat Data: Results from the Irish Longitudinal Study on Ageing

Mark N. Canney,1  Matthew D. O’Connell,1  Catriona M. Murphy,1  Mark Alan Little,1  Conall M. O’Seaghdha,2  Rose Anne M. Kenny,1

Background: Beat-to-beat blood pressure (BP) measurements provide a dynamic picture of BP behavior during postural change. Impaired BP stabilization after standing is associated with substantial morbidity and mortality. We aimed to define the relationship between class of antihypertensive drug and BP stabilization during an active stand.

Methods: Cross-sectional analysis from The Irish Longitudinal Study on Ageing, a nationally representative cohort study of 8175 adults ≥50 years. Beat-to-beat BP was recorded in participants undergoing an active stand test. We defined grade 1 hypertension according to European Society of Cardiology criteria (systolic BP [SBP] ≥140-159mmHg ≥ diastolic BP [DBP] 90-99mmHg). Orthostatic hypotension (OH) was defined as a drop in SBP ≥20mmHg ≥ DBP ≥10mmHg. Outcomes were sustained OH (OH throughout the test) and impaired BP stabilization (OH at each 10-second (s) interval during the test [total 110s]). Outcomes were assessed using logistic regression models adjusted for potential confounding variables.

Results: A total of 536 participants with self-report hypertension were receiving monotherapy with a renin-angiotensin-aldosterone-system inhibitor (317), betablocker (89), calcium channel blocker (89) or diuretic (41). Betablockers were associated with increased odds of sustained OH vs untreated grade 1 hypertension (OR 3.4, 95% CI 1.9-6.0). This was evident from 20s (OR 2.3, 95% CI 1.4-3.7) and remained statistically significant at 110s (OR 2.8, 95% CI 1.6-4.9). Multivariable adjustment did not attenuate the association. No significant association was detected among the other drug classes.

Conclusions: In older hypertensive adults betablocker monotherapy was associated with increased odds of increased odds of OH compared to subjects with untreated grade 1 hypertension. The effect was evident from 20s after standing and was sustained. This should inform decision-making regarding appropriate choice of antihypertensive agent in older adults.

Funding: NIDDK Support

SA-PO634
Effect of Vitamin D on 24 Hour Ambulatory Blood Pressure: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Ciaran Joseph McMullan,1  Lea Borgi,1  Gary C. Curhan,1  Naomi D.L. Fisher,1  John P. Forman.1

Background: Lower levels of 25-hydroxyvitamin D (25(OH)D) have been associated with an increased risk of hypertension in prospective cohort studies, suggesting that vitamin D might be a modifiable target for the prevention of hypertension. Vitamin D supplementation has also been shown to decrease clinic blood pressure (BP) in some studies.

Methods: We performed a randomized, double-blind, placebo-controlled trial of nonhypertensive participants with body mass index ≥25, and 25(OH)D<20ng/mL; subjects were randomized to receive either ergocalciferol 50,000 units or placebo, once a week for 8 weeks. Mean 24 hour BP was measured using 24 hour ABPM at baseline and 8 weeks after starting the study. Results: By the end of the trial, 29 and 27 participants randomized to receive vitamin D and placebo, respectively, had adequate 24 hour ABPM at both baseline and at 8 weeks. Mean vitamin D levels increased from 14.9 to 30.3 ng/mL in the intervention group and from 14.4 to 17.4 ng/mL in the placebo group. Vitamin D supplementation did not lower BP at 8 weeks; 24 hour systolic BP changed from 120±10 to 122±8 mmHg in the intervention group (p-value=0.29), and from 124±8 to 125±10mmHg in the placebo group (p-value=0.38), with a treatment effect p-value of 0.92.

Conclusions: In this randomized, double-blind, placebo-controlled trial of overweight/obese normotensive individuals, there was no improvement in mean 24 hour blood pressure after repletion of vitamin D. These findings are not consistent with vitamin D being a modifiable target for prevention of hypertension.

Funding: NIDDK Support

SA-PO635
Effect of Uric Acid Lowering on Intrinsic Renal and Systemic Renin Angiotensin System Activity: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Ciaran Joseph McMullan,1  Lea Borgi,1  Gary C. Curhan,1  John P. Forman.1

Background: The relationship between serum uric acid on RAS activity in humans is unknown. We performed a randomized, double-blind, placebo-controlled trial analyzing the Modifiable Effectors of Renin System Activation Treatment Evaluation (MODERATE). Normotensive individuals with body mass index (BMI) ≥25 and uric acid level ≥ 5.0 mg/dL.

Funding: Government Support - Non-U.S.
Comparison of Office Orthostatic Blood Pressure and 24-Hour Ambulatory Blood Pressure Measurements in the Prediction of Autonomic Dysfunction


Background: Evaluation of orthostatic hypotension (OH) may involve office orthostatic blood pressure (BP<sub>OP</sub>) measurements, 24-hour ambulatory BP (ABP) and autonomic reflex screen (ARS). We investigated the predictive performance of BP<sub>OP</sub> and the variables of ABP, i.e., reversal of circadian pattern (RCP), postprandial hypotension (PPH) and noncompensatory heart rate variability (HRV), to predict autonomic dysfunction as measured by the AUC of the ROC curves.

Methods: Data from previously published study were analyzed. Ninety-four patients were included for analysis. BP<sub>OP</sub>, RCP, PPH, HRV were investigated for the presence or absence of autonomic dysfunction. Autonomic dysfunction was defined as a CASS SA-PO636

Effect of Vitamin D Supplementation on Intrinsic Renal and Systemic Renin Angiotensin System Activity: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Clarian Joseph McMullan, Lea Borgi,1 Gary C. Curhan,2 Naomi D.L. Fisher,1 John P. Forman.1 1Pediatric Nephrology and Cardiology, Fondazione IRCCS Ca' Granda Policlinico, Milan, Italy; 2Pediatric Cardiology, Policlinico A. Ahsan Ejaz, 2 Patrizia Salice.1

Background: Disruption of vitamin D signalling in rodents causes activation of the renin angiotensin system (RAS). In humans lower circulating 25(OH)D is associated with increased renal specific RAS activity (measured using renal plasma flow [RPF]; in addition, a small, open label, uncontrolled study found that vitamin D supplementation decreased renal specific RAS activity. However, the effect of vitamin D supplementation on the RAS in humans with vitamin D deficiency has never been examined in a rigorous manner.

Methods: We performed a randomized, double-blind, placebo-controlled trial of normotensive individuals with body mass index <25 and vitamin D deficiency (25(OH)D £20ng/mL). subjects were assigned to receive either ergocalciferol 50,000 units or placebo, once a week for 8 weeks. Renal specific (assessed by RPF response to captopril in high sodium balance) and systemic RAS activity (plasma renin activity [PRA] and angiotensin II levels [AngII]) were measured at baseline and 8 weeks after starting the study.

Results: By the end of the trial, 43 and 41 participants allocated to receive vitamin D and placebo, completed the study with measurement of renal and systemic RAS activity. Mean vitamin D levels increased from 14.9 to 30.3 ng/mL in the ergocalciferol group and from 14.4 to 17.4 ng/mL in the placebo group. Renal specific D supplementation did not significantly change after vitamin D depletion: the RPF response to captopril was 33.9±56.1 mL/min at baseline and 35.7±87.7 mL/min at 8 weeks in the ergocalciferol group (p-value=0.26); and was 37.3±46.9 mL/min at baseline and 35.9±26.2 mL/min at 8 weeks in the placebo group (p-value=0.70), with a treatment effect p-value of 0.27. Similarly, vitamin D supplementation had no effect on PRA or AngII levels.

Conclusions: In contrast to animal experiments and observational studies, this randomized, double-blind, placebo-controlled trial found that lowering ionic acid had no effect on renal specific or systemic RAS activity.

Funding: NIDDK Support

SA-PO635

The diagnostic performance to predict autonomic dysfunction for HRV was superior to PPH. Both were superior to RCP. RCP was a better predictor of autonomic dysfunction than office BP<sub>OP</sub>.

Conclusions: Our data suggests that ABP is a reliable, simple and inexpensive predictor of autonomic dysfunction in routine clinical practice.

SA-PO637

Factors Predicting Long Term Renal Prognosis in Malignant Nephrosclerosis

Peng Xia, Jiaxin Lang, Yubing Wen, Mingxi Li, Hang Li, Xuewei Li, Limeng Chen. Nephrology, Peking Union Medical College Hospital, Beijing, China.

Background: This study investigated correlations between kidney pathology and Renin-Angiotensin System(RAS) activation, RAS inhibitor response and prognosis of malignant hypertensive nephrosclerosis(MHN) patients.

Methods: This retrospective cohort study included 82 essential MHN patients from Jan,2003 to Oct,2014 with renal biopsy followed up until May,2015. Pathology were evaluated by two pathologists independently. Localized renin expression and peritubular capillaritis(PTC) area were evaluated by IHC staining of renin and CD34. Renal replacement therapy, kidney transplant and death were defined as the primary end point.

Results: 87.8% of patients were male with mean age of 34.7±8.8 years. Clinical data showed highest blood pressure (BP) 226.6±25.7/152.2±22.0 mmHg, serum creatinine (Scr) 5.31±3.79 mg/dl, proteinuria 2.06±1.83 g/dl, eGFR 21.3±15.1 ml/min/1.73m<sup>2</sup>. Glomerular Sclerosis Index, tubular atrophy and interstitial fibrosis were 1.51±0.51, 63.7±18.3% and 64.0±18.3%. MHN patients has a lower PTC proportion (2.27±0.74%)<sub>(n=35)</sub>, 3.75±0.79%<sub>(n=17)</sub>, P<0.001) and a higher renin-positive juxtaglomerular apparatus ratio (35.1±17.8%<sub>(n=35)</sub>, 21.2±15.0%<sub>(n=17)</sub>, P<0.008) comparing with glomerular minimal lesion patients. Tubulointerstitial lesions correlated with Scr<sub>(r=-0.547,p<0.001)</sub>, eGFR<sub>(r=-0.574,p<0.001)</sub> and proteinuria<sub>(r=-0.447,p<0.001)</sub>. PTC area correlated with Scr<sub>(r=-0.675,p<0.001)</sub> and eGFR<sub>(r=0.648,p<0.001)</sub>. 90.4% patients received RAS inhibitors which was associated with improvements in BP (J Am Soc Nephrol 26: 2015) and kidney function (Kidney Int 87: 2013). However, the effect of vitamin D supplementation on the RAS in humans with vitamin D deficiency has never been examined in a rigorous manner.

Conclusion: MHN patients had localized activation of renin and less PTC area. RAS inhibitors benefited patients in BP control, eGFR improvements and long-term renal outcome.

Funding: Government Support - Non-U.S.

SA-PO638

Office Blood Pressure Monitoring: A Novel Tool for Evaluating Blood Pressure in Children (and Adults)

Gianluigi Ardissino,1 Paolo Marchetto,1 Francesca Tel,1 Sara Testa,1 Ilaria Possenti,1 Michela Perrone,1 Luciano Sangaletti,1 Amelia Ballarino,1 Stefani Rotondo,1 Silvia Ghiglia,1 Franco De Luca,1 Patrizia Salice.1 1Pediatric Nephrology and Cardiology, Fondazione IRCCS Ca' Granda Policlinico, Milan, Italy; 2Pediatric Cardiology, Policlinico Uni, Messina, Italy.

Background: Blood pressure measurement (BPM) is a common procedure in clinical practice but in children (C) obtaining reliable values can be challenging. Casual office BPM, the standard of care, is ill but accurate and ABPM may be difficult to perform or even misleading.

Methods: Office Blood Pressure Monitoring (OBPM) was developed at our Center in 2010 for evaluating BP in C with serial and automated BPM (³10 in at least 30 min)
with a standard oscillometric device. BP values are uploaded in a software to calculate the coefficient of variation (CV) after having excluded outlier values (<25 and >95th centiles of the recorded values).

Results: Since 2010 a total of 402 OBPMs have been performed but only the 282 in 110 C (59% Males) aged <18 yrs old (IQR 4.8-12.1) with a CV <10% for both syst and diast BP were considered for the analysis. The table compares BP as measured by OBPM with a single BPM (1st and 3rd) and with the mean of the 3 internal measurements (p<0.01 vs. others BPMs with student’s t test for paired data and c2).

Conclusions: OBPM provides significantly lower BP values, leading to a diagnosis of poor BP control in a smaller number of patients (10%). Given the lack of a gold standard, the present analysis doesn’t demonstrate that OBPM is more reliable than standard procedures however serial BPM have the potential of reducing measurement biases and white coat effect. We recommend the routine use of OBPM for measuring BP in C at risk of hypertension rather than relying upon few measurements.

SA-P0639
A Simple Prediction Score for Incident Hypertension in a Korean Population
Jong-Hwan Jung, Sung Kwang Park, Won Kim, Kyung Pyo Kang, Sik Lee.

Background: We aimed to develop a simple prediction model for incident hypertension that could help to prevent or delay the onset of hypertension for some patients who did not experience hypertension yet.

Methods: The Korean Genome and Epidemiology Study was used for the model development (n=3533) and validation (n=1698). Hypertension was defined when experiencing hypertension yet.

Results: That could help to prevent or delay the onset of hypertension for some patients who did not experience hypertension yet.

Conclusions: This prediction algorithm, weighted towards common modifiable variables, showed good performance characteristics in a Korean population.

SA-P0640
Hemodynamics and Cardiovascular Autonomic Efficiency During Blood Pressure Variations in Hemodialysis
Dan Sapoznikov, Rebecca Backenroth, Dvora Rubinger.

Background: Chronic hemodialysis (HD) is associated with hemodynamic instability and with reduced cardiovascular autonomic efficiency (Cae).

Methods: To define hemodynamic changes associated with intradialytic blood pressure variations, beat-to-beat systolic blood pressure (SBP) and interbeat interval (IBI) monitoring using Finometer device and Beatscope software was performed during HD sessions in 69 non-diabetic patients (Pts), age 56±15 y. Cardiac output (CO) and total peripheral resistance (TPR) were calculated using the Modelflow simulation method. Differences in variability indices during SBP periods, 10% above (high) or below (low) the mean SBP were considered representative of Cae.

Results: During low to high SBP periods, two patterns of changes were noted: increased CO and decreased TPR (18 Pts,TPR↓), and relatively stable CO with increased TPR (51 Pts, TPR↑). Low frequency (LF) range variability of SBP and IBI, CO and TPR (median and interquartile ranges) were:

![Table](https://example.com/table.png)

Conclusions: CT-Ps with intradialytic hypotension (56%) was significantly higher in TPR↑ than in TPR↓ (28%, p<0.036), while TPR changes were directly correlated with post dialysis SBP (r=0.45, p<0.001) and with sd IBI (r=0.35, p=0.001) in all Pts. There were no differences between groups in other variables.

Conclusions: 1.Cae resuming during HD may be associated with predominant CO and/or TPR variations; the latter are significantly correlated to sd IBI, a strong marker of autonomic activity. 2.Intradialytic hemodynamics may be different in hypotension-prone Pts. These observations are relevant to the pathogenesis of intradialytic hemodynamic instability and of postdialysis hypertension.

SA-P0641
Antihypertensive Medications and Blood Pressure Control in Chronic Kidney Disease: A Cross-Sectional Analysis from the German Chronic Kidney Disease (GCKD) Study

Background: We reported low rates of blood pressure (BP) control in a large German cohort of patients with chronic kidney disease (CKD). Here, we analyzed the antihypertensive drug therapy to assess the prevalence of resistant hypertension, and to determine associations with control of BP.

Methods: The German Chronic Kidney Disease (GCKD) study is a prospective observational cohort study which enrolled 5217 patients with CKD in Germany. Inclusion criteria were estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m2 or overt proteinuria. At enrollment, office BP was measured by trained study nurses, and antihypertensive drug therapy to assess the prevalence of resistant hypertension, and to determine associations with control of BP.

Conclusions: 1.Cae for resistant hypertension was present in 49.9% of CKD patients whose BP was uncontrolled hypertension, 49.9% met the definition of resistant hypertension (uncontrolled {140/90 mmHg and/or TPR variations; the latter are significantly correlated with sd IBI, a strong marker of autonomic activity. 2.Intradialytic hemodynamics may be different in hypotension-prone Pts. These observations are relevant to the pathogenesis of intradialytic hemodynamic instability and of postdialysis hypertension.

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

772A
Association Between Cystatin C Based eGFR, Ambulatory Blood Pressure Parameters, and In-Clinic versus Ambulatory Blood Pressure Agreement in Older Community-Living Adults

T佛山 Woodell, Jan M. Hughes-Austin, Tiffany Tran, Atul Malhotra, Joseph A. Abdelmalek, Dena E. Rifkin. UC San Diego.

Background: Although CKD IV-V has been associated with abnormal ambulatory blood pressure (ABPM) patterns, the associations with milder CKD have not been determined. We examined the relationship between mild chronic kidney disease (measured by cystatin C-based eGFR) and abnormal ABPM (including nocturnal dipping) in healthy older adults. Further, we assessed agreement between clinic and ambulatory blood pressure monitoring.

Methods: 334 older community-living adults had clinic BP and 24-hour ABPM measured. Serum cystatin C levels were used to calculate eGFRcys using the CKD-EPI equation. Multiple linear regression was performed to examine associations between eGFRcys < 60 ml/min/1.73m^2 (CKD stages) and ABPM parameters. Bland-Altman analysis was performed to evaluate agreement between clinic and ambulatory measurements.

Results: Average age was 72. Average eGFRcys was 78 ± 20, and 60 individuals with CKD stages. Compared to those without CKD, individuals with CKD stages were older, more likely to have clinic-based hypertension and less likely to be dippers. After multivariable analysis, the presence of CKD stages was significantly associated with lower mean ambulatory diastolic blood pressure (DBP) (-2 mm Hg, p = 0.048), but not with nocturnal dipping or other ABPM parameters. Analyses using creatinine-based eGFR yielded similar results. Cystatin c-based blood pressure (SBP) was significantly overestimated mean wake time ambulatory ABPM SBP; mean difference was 11 mmHg for those without CKD stages (95% limits of agreement -14 to 35 mmHg) and 14 mmHg for those with CKD stages (95% limits of agreement -13 to 41 mmHg); there was no statistically significant effect modification by CKD stage.

Conclusions: In older community-living adults, mild CKD as detected by cystatin C was associated with lower ambulatory DBP, but not with dipping status. This result is in contrast to findings with more advanced CKD in other studies and suggests that abnormal ABPM may only emerge at more advanced stages of CKD. The presence of CKD did not affect interpretation of clinic vs. ABPM pressures, although accuracy of clinic SBP was poor in this older cohort.

Funding: NIDDK Support

Serum MicroRNA Biomarkers for Obese Children with Hypertension

Scott Saint-Amour,1 Santosh Kumar Patnaik,2 Sudha Garimella.1 Pediatric Nephrology, Univ at Buffalo, Buffalo, NY; 2Cardiovascular Lab, RPCI, Buffalo, NY.

Background: Childhood obesity is a major health problem and 30% of obese children may develop hypertension. There is no clinical method to identify high risk obese children before they develop hypertension. MicroRNAs are non-coding RNAs that are implicated in pathways of inflammation and vascular injury. There has been no characterization of miRNA profiles of obese children with hypertension. This study aims to characterize miRNA profiles as a first step toward evaluating miRNAs as biomarkers for obesity-related hypertension.

Methods: 39 patients ages 3-21 were placed in four cohorts based on presence or absence of obesity and hypertension. Total serum RNA was isolated using miRCURY Biofluids kit Exiqon®, and examined for miRNAs by RT-PCR. Cq values were normalized by the global mean method. Rates of false discovery (FDR) arising from multiple testing were assessed using the Benjamini-Hochberg method.

Results: 69 of 179 examined miRNAs were detected in all samples. MiRNA measurements were globally reduced in sera of obese normotensive Vs. controls. Four miRNAs were identified as differentially expressed between these two groups at FDR < 0.1%, whereas no miRNA was identified as differentially expressed between controls and hypertensive obese. Tukey plots of miRNAs in the cohorts are shown.

Conclusions: Serum levels of four miRNAs appear to be reduced in patients with obesity alone, but not in those with obesity and hypertension. While it is possible that serum miRNA differences were because of variables such as serum lipid content and medications, our study suggests that serum miRNAs have utility in detecting hypertension risk in obese children. This should be validated in a larger study, and the biomarker value of the serum miRNAs correlated with ambulatory blood pressure monitoring data as well as left ventricular hypertrophy.

Funding: Pharmaceutical Company Support - Roswell Park Cancer Institute Support to Dr. Sai Yendamuri in the Cardiothoracic Lab at RPCI was used for this study.

Effect of Prenatal and Childhood Lead Exposure on Blood Pressure at 4 Years of Age Allison P. Sanders,1 Katherine Svensson,2 Chitra Amarasingirawana,2 Priyanka Basnet,1 Ivan Pantic,1 Adriana Mercado-Garcia,1 Lourdes Schnauss,3 Andrea A. Baccarelli,3 Martha M. Tellez-Rojo,4 Chris Gennings,5 Lisa M. Satlin,6 Robert O. Wright,1 1University of Medicine and Dentistry of New Jersey, 2Icahn School of Medicine at Mount Sinai, 3National Inst of Environmental Health Science, 4National Inst of Public Health, 5Harvard T.H. Chan School of Public Health.

Background: Prenatal lead (Pb) exposure occurs during a susceptible period of renal development and may program later life cardiovascular and renal disease.

Methods: Systolic and diastolic blood pressure (SBP and DBP) was obtained using an automated oscillometer from 397 children 4 years of age in the PROGRESS cohort located in Mexico City. Maternal blood samples were previously collected at the 2nd trimester (2T), 3rd trimester (3T), and at delivery and children’s blood samples were collected at birth (cord blood), 1 year, and 2 years of age. Blood lead levels (BLLs) were analyzed via inductively coupled plasma-mass spectrometry. We performed linear regression to examine the associations between longitudinal BLLs and children’s SBP, DBP, and pulse pressure (mSBP-mDBP) adjusting for child’s age, sex, body mass index, maternal education and environmental tobacco smoke.

Results: Maternal 2T BLLs ranged between 0.7 and 18.8 mg/dL, and 89 (22%) prenatal BLLs were above the CDC guideline level of 5 mg/dL. Increased 2T and 3T BLLs were associated with decreased pulse pressure (p<0.05) and modestly associated with increased DBP (p=0.1).

No significant associations were observed for childhood BLLs and BP. Stratification by sex showed that the effect of prenatal Pb (2T and 3T) on decreased pulse pressure was significant only among females.

Conclusions: Prenatal Pb exposure may contribute to subclinical changes in the developing kidney or cardiovascular system leading to elevated BP in childhood. Future studies will assess if the contributions of early life Pb exposure to BP outcomes persist at later life stages.

Figure 1. The effect of longitudinal lead exposure on childhood blood pressure at 4 yrs. Estimates (β) and 95% confidence intervals (βI) were adjusted for child’s age, sex, body mass index, as well as maternal education and environmental tobacco smoke.

SA-PO645

Smoking, Microalbuminuria and Renal Function in Essential Never Treated Hypertensive Patients

Dimitrios Petras,1 Vanessa Tzamou,2 Athanasios Bramos,3 Panagiota E. Giannou,1 Stella-Maria Kyvelou,1 Eva Karpanou,1 Gregory Vissoulis,1 1Nephrology Dept, Hippokration Hospital, Athens, Greece; 21st Cardiology Clinic, Onassis Cardiac Surgery Center, Athens, Greece; 3Hypertensive Unit, 1st Cardiology Clinic, Univ of Athens, Hippokration Hospital, Athens, Greece; 4Microbiology Dept, Hippokration Hospital, Athens, Greece.

Background: The aim of the present study was to identify possible differences depending on patient’s individual smoking history with renal function and microalbuminuria in essential never treated hypertensive patients.

Methods: The study included 6100 consecutive patients with essential hypertension. In each patient the smoking status has been assessed by means of a standard questionnaire. Each patient had renal profile work up including microalbumin levels, albumin creatinine ratio in 24h urine collection (ACR) and 24h creatinine clearance.

Results: The study population was divided according to the smoking status in three groups: Smokers (n=2350), Ex-smokers (n=663) and Non-smokers (n=3121). Microalbumin aCR was significantly higher in smokers compared to ex-smokers and non-smokers [(26.3±24.3 vs 23.6±21.7 vs 22.0±20.0, p<0.0001), (31.5±30.2 vs 28.8±29.3 vs 27.4±27.2, p<0.0001), respectively]. There was no significant difference in creatinine clearance among the three groups of smokers (p=NS)
### SA-PO646

**Comparison of Salt Taste Thresholds and Salty Usage Behaviors Between Myanmar and Korean Adults**

Hyungjin Cho, 1  Fridtjof Thomas, 1

**Background:** Excessive oral salt intake can induce hypertension. According to previous studies, prevalence of hypertension is higher in Myanmar than Korea. We postulated that National Univ Hospital, Jeju, Republic of Korea.

**Methods:** This cross sectional study enrolled the patients who visited volunteer medical service clinic at Ansong in Korea and Hpleu and Bago in Myanmar in August 2014. We measured vital signs, height and weight of each patient and evaluate detection threshold, recognition threshold, salt preference, salt usage behavior score and spot urine sodium.

**Results:** Out of 131 patients who were enrolled and 64 of them were Myanmarese and 67 were Koreans. Blood pressure was significantly higher in Myanmar adults than Koreans. Detection threshold, recognition threshold, salt preference, spot urine sodium and salt usage behavior score was also higher in Myanmar than Koreans.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Myanmar (n=64)</th>
<th>Korea (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection threshold (%)***</td>
<td>0.102±0.108</td>
<td>0.046±0.026</td>
</tr>
<tr>
<td>Recognition threshold (%)**</td>
<td>0.174±0.163</td>
<td>0.103±0.115</td>
</tr>
<tr>
<td>Salt preference (%)**</td>
<td>0.44±0.16</td>
<td>0.37±0.10</td>
</tr>
<tr>
<td>Spot urine sodium (mg/dL)**</td>
<td>157.8±84.3</td>
<td>117.0±62.1</td>
</tr>
<tr>
<td>Salt usage behavior score*</td>
<td>11.4±2.5</td>
<td>10.4±2.4</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001

We calculated correlation coefficient between spot urine Na and other parameters that related to salt intake. salt usage behavior score and detection threshold significantly correlated with the spot Urinal.

**Conclusions:** All parameters related to salt intake, such as detection thresholds, the recognition thresholds, salt preference, salt usage behavior score and spot urine sodium concentration, of Myanmarese were significantly higher than those of Korean.

### SA-PO647

**Relationship Between Circadian Rhythm of Blood Pressure and Intrarenal Arteriolar Occlusion**


**Background:** Hypertension (HT) is a common complication in chronic kidney disease (CKD) patients. CKD patients often have circadian rhythm disorder of blood pressure (BP). However, the relationship between circadian BP pattern and intrarenal damage remains unclear.

**Methods:** Ninety patients with glomerulonephritis were included in this study. Patients with diabetes mellitus and prescription for antihypertensive agents were excluded. Clinic BP (CBP) and 24-h ambulatory BP (ABP) measurements were performed in all the study patients, and who were divided into the following four groups; normotension (NT), white coat hypertension (WHT), masked HT (MHT) and sustained HT (SHT). As renal histological assessments, we evaluated the percents of sclerotic glomeruli (SG) and interstitial fibrosis (IF), and classified the degrees of intimal thickening of intra-lobular arteries (ILA) and arteriolar hyalinosis (AH) into four grades (none, mild, moderate, severe) in each biopsy specimen.

**Results:** The prevalence of NT, WHT, MHT and SHT was 60.0%, 3.3%, 23.3% and 13.4%, respectively. In comparison of circadian BP pattern, all-day HT was most prevalent in the SHT group, and nocturnal HT was most prevalent in the MHT group. SG and IF were significantly severe in the SHT group compared to the NT group. As for intrarenal vascular lesions, the MHT and SHT groups had more severe AH compared to the NT and WHT groups, whereas ILA was comparable between all the four groups. Furthermore, we investigated the relationship between intrarenal vascular lesions and clinical characteristics. ILA was significantly correlated with age and renal function, whereas AH was significantly correlated with age, sex, smoking, total cholesterol, HT based on ABP (ABPHT) and HT based on CBP (CBPHT). In multivariate analysis, ILA was significantly correlated with only AH and was significantly correlated with age and sex.

**Conclusions:** Our findings suggest that intrarenal AH was markedly severe not only in the SHT group, but also in the MHT group. Careful ABP monitoring should be recommended in patients with glomerulonephritis.

### SA-PO648

**Association of Inpatient versus Outpatient Systolic Blood Pressure with All-Cause Mortality in Patients with Normal Estimated Glomerular Filtration Rate**

Ostas W. Okechukwu, 1  Miklos Zsolt Molnar, 1  Praveen Kumar Potukuchi, 1  Jun Ling Lu, 1  Fridtjof Thomas, 1  Kamary Kalantar-Zadeh, 1  Csaba P. Kovesdy, 1 2 1  Univ of Tennessee Health Science Center, Memphis, TN; 2 Unif of California, Irvine, CA; 2 VA Medical Center, Memphis, TN.

**Background:** Hypertension is associated with worse outcomes, and its treatment improves mortality and cardiovascular disease. Hospitalized patients undergo frequent BP measurements, and hence hospitalization is an opportunity to diagnose and treat hypertension. However, it is unclear if BP measured as inpatient is associated with outcomes.  

**Methods:** From 3,499,271 US veterans with normal eGFR, we identified 1,113,515 patients with inpatient and outpatient SBP recordings. We examined the association of baseline outpatient SBP, and baseline inpatient SBP (defined as the SBP obtained on the first day of the first hospitalization following cohort entry) with all-cause mortality in Cox proportional hazards analyses. Models included both in- and outpatient SBP and their interactions, and were adjusted for age, gender, race, eGFR, comorbidities, socioeconomic factors, and antihypertensives.

**Results:** Low SBP was associated with higher mortality in both settings, but much more so inpatients (Figure). Outpatient SBP ≥140-149 mmHg was associated with linearly higher mortality (hazard ratio (95%CI) for SBP ≥170 mmHg: 1.22 (1.16-1.29), p<0.001), but with less increase in mortality in the inpatient setting, which was only present for SBP ≥170 mmHg (HR (95%CI) for SBP ≥170 mmHg: 1.08 (1.02-1.14)).

**Conclusions:** SBP shows markedly different associations in the outpatient vs inpatient setting, with higher blood pressures in the inpatient setting conferring less mortality risk compared to the outpatient setting. Until randomized controlled clinical trials are done, caution is warranted when treating hypertension in hospitalized patients.

**Funding:** NIDDK Support, Veterans Administration Support

### SA-PO649

**Fibroblast Growth Factor 23 and Sodium-Volume Regulation: FGF23-Response to Sodium Restriction in Essential Hypertensive Subjects and to Long Term Extracellular Volume Reduction in Hemodialysis Patients**


**Background:** Dietary sodium load causes volume expansion and hypertension in mouse models of FGF23 and αKlotho deficiency. FGF23 also associates with ultrafiltration in cross-sectional analyses in hemodialysis (HD) patients (pts) further implicating this bone hormone in extracellular volume regulation.

**Methods:** 32 uncomplicated essential hypertensives were randomized to a 2-weeks high-sodium diet (200mmol/day) or to 2-weeks low sodium diet (10-20 mmol/day). After 1 week wash out, these treatments were crossed-over. At the end of each diet-period, pts underwent 24h urine sodium, 24h ABPM and serum intact FGF23 measurements. The FGF23 response to UF intensification was assessed in hypo-tension HD pts. FGF23 and normalized BP measurements were performed at baseline and after 6 months of UF intensification.

**Results:** In essential hypertensives, PRA and aldosterone (*P<0.01*) rose during low sodium. However, FGF23 remained unmodified [low sodium: median 36.2 pg/mL, inter-quartile range (IQR) 32.4-44.0; high sodium: 33.9 pg/mL, IQR: 29.5-41.0; P=0.18]. Changes in FGF23 were unrelated to systolic and diastolic ABP, heart rate, PRA and aldosterone changes. In hypertensive HD pts, baseline FGF23 was 4062 pg/ml (IQR: 1381-12571). BP during the longitudinal study fell from 144 to 139 mmHg (P=0.02) along with a parallel increase in dry BW.

**Conclusions:** Changes in sodium intake that potently activate the renin-aldosterone system do not alter FGF23 in essential hypertensives. Similarly, extracellular volume...
Association of Urinary Albumin Excretion and Salt-Sensitivity of Blood Pressure: Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study

Jing Chen,1,2 L. Lee Hamm,1 Chung-shiuian Chen,2 Kevin K. Wu,2 L. Gabriel Navar,3 Jiang He,2 1Medicine, Tulane School of Medicine, New Orleans, LA; 2Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, LA.

Background: Albuminuria is a marker of early kidney injury and associated with risk of hypertension, cardiovascular disease, end-stage renal disease, and premature death. However, it is unknown whether urinary albumin excretion is associated with salt- and potassium-sensitivity.

Methods: We investigated the association between urinary albumin excretion and salt- and potassium-sensitivity of blood pressure (BP) among GenSalt study participants.

Results: Urinary albumin-to-creatinine ratio (Acr, mg/g) was significantly reduced during low-sodium and potassium-supplementation interventions to 2.26 (1.11, 4.61) and 2.10 (1.46, 4.26), respectively, from a baseline ratio of 2.97 (1.20, 6.40) and increased during the high-sodium intervention to 3.23 (2.15, 5.73) with P for group difference<0.005. One standard deviation higher of baseline log-transformed ACR (2.23 mg/g) was significantly associated with 1.5 (95% CI 0.3, 2.7) mm Hg higher in mean arterial BP (P<0.01) from low-sodium to high-sodium intervention (salt-sensitivity) but not statistically significantly associated with potassium-sensitivity after adjusting for confounding factors.

Conclusions: These data indicate that urinary albumin excretion may be associated with BP salt-sensitivity.

Effects of Nephrectomy on Blood Pressure and Its Circadian Rhythm

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Background: Intrarenal renin-angiotensin system (RAS) activation causes disturbance of sodium excretion from the kidney by increasing sodium reabsorption in the tubulus, with resultant blood pressure (BP) elevation and nocturnal hypertension. However, the effects of nephrectomy on BP and its circadian rhythm have not been clarified in the patients who have various renal functions.

Methods: We investigated 25 nephrectomized patients [17 men and 8 women, age: 61.3±14.7 years, chronic kidney disease stage 1 in 3 patients, stage 2 in 7, stage 3 in 5, stage 4 in 5 (nephrotic syndrome in 2 and peritoneal dialysis in 3), body weight (BW), circulating RAS [plasma renin activity (PRA) and plasma angiotensin II (AngII)] and 24-h ambulatory BP monitoring (ABPM) were examined before and after nephrectomy. We divided the daytime and nighttime for 24-h ABPM using sleep and waking times. Renal function [estimated glomerular filtration rate (eGFR)] was evaluated in non-dialysis patients.

Results: In non-dialysis patients, GBF after nephrectomy was significantly decreased compared with that before nephrectomy (67.8±23.1 ml/min/1.73m2 and after nephrectomy, 47.9±16.5 ml/min/1.73m2; p<0.01). There were no significant differences in the levels of BW, BP during daytime, nighttime and 24-h periods, and circulating RAS before and after nephrectomy. However, night-to-day (N/D) ratio of systolic BP (SBP) was significantly increased after nephrectomy compared with that before nephrectomy (before nephrectomy, 93.6±6.7% and after nephrectomy, 97.4±7.5%; p=0.032), and the patterns of circadian BP rhythm were also significantly changed before and after nephrectomy (p=0.021). Namely, dipper pattern decreased and non-dipper and riser patterns increased after nephrectomy. On the other hand, no significant findings were found in N/D ratio of SBP and the patterns of circadian BP rhythm in dialysis patients before and after nephrectomy.

Conclusions: Nephrectomy has effects on nocturnal hypertension due to the decrease of renal sodium filtration ability, but not absolute values of BP.

Association of Urinary Dopamine and Norepinephrine Excretion with Salt- and Potassium-Sensitivity of Blood Pressure

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Background: Dopamine and norepinephrine may play an important role in regulating sodium and potassium reabsorption in the proximal tubules. It is unknown, however, if urinary dopamine and norepinephrine excretion are associated with salt- and potassium-sensitivity of blood pressure (BP).

Methods: We investigated the association of urinary dopamine and norepinephrine with BP salt- and potassium-sensitivity among Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study participants. The GenSalt dietary intervention consisted of a 7-day low sodium diet (51.3 mmol sodium/day), 7-day high-sodium diet (307.8 mmol sodium/day), and 7-day high-sodium diet with potassium supplementation (307.8 mmol sodium/day and 60 mmol potassium/day). Twenty-four hour urinary dopamine and norepinephrine were estimated at baseline and at the end of each intervention in 100 randomly selected GenSalt participants.

Results: Urinary dopamine (µg/24h) was significantly reduced (p=0.01) from baseline (191.5±142.3) during high-sodium (457.2±142.3) and high-sodium and potassium supplementation (149.5±139.7) interventions. Likewise, urinary norepinephrine (µg/24h) was significantly (p<0.001) reduced from baseline (38.6±24.3) during high-sodium (24.5±21.4) and high-sodium and potassium supplementation (24.6±24.1) interventions. In addition, one standard deviation higher in urinary dopamine concentration (124.2 µg/24h) was associated with 1.5 (-2.5, -0.6) mm Hg of mean arterial BP reduction from high-sodium to high-sodium plus potassium supplementation (p=0.001). One standard deviation higher in urinary norepinephrine concentration (24.3 µg/24h) was associated with 1.4 (0.2, 2.6) mm Hg mean arterial BP increase from low-sodium to high-sodium (p=0.02) and 2.2 (-3.1, -1.3) mm Hg mean arterial BP reduction from high-sodium to high-sodium plus potassium supplementation (p=0.001).

Conclusions: These data indicate that urinary excretion of dopamine and norepinephrine may play a role in BP salt- and potassium-sensitivity.

Funding: Other NIH Support - NHLBI and the National Center for Research Resources, National Institutes of Health, Bethesda, MD.

Uric Acid Levels Are Associated with Peripheral but Not Central Blood Pressure Variables in Normotensive Individuals

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Background: Uric acid is increasing recognized as a risk factor for cardiovascular disease. Whether this could be explained by changes in peripheral or central blood pressure (BP) profiles remains controversial. The aim of this study was to assess the association of uric acid levels with peripheral and central hemodynamic parameters in untreated normotensive individuals.

Methods: Of 20,004 CARTAGENE participants, 8,420 were normotensive individuals not treated for hyperuricemia or hypertension with valid pulse wave analysis (46.9% male, 52.6 yr). The associations between uric acid levels and peripheral systolic BP (SBP), pulse pressure (PP) central systolic BP (cSBP), central PP (cPP), pulse pressure amplification (PPA), augmentation index (Alx) and increased pressure (AP) were tested with linear regression analysis.

Results: In univariate analyses, uric acid levels were significantly associated with all parameters. In contrast, in multivariate analyses, only SBP and cSBP remained independently associated with uric acid levels. As cSBP is usually highly dependent of SBP, it was further adjusted for peripheral BP, where it was not independently associated with uric acid levels (β coefficient -0.003, p=0.51).
Results: Mean age at 7th year was 78. Considering SBP or DBP separately, trajectory groups were primarily determined by baseline BP, and these were not independently associated with outcomes (all p<0.05). In contrast, three distinct groups were identified using joint SBP/DBP: (1) concordant increasing, (2) discordant (stable SBP and decreasing DBP), and (3) concordant decreasing. Compared with a concordant increasing, a concordant decreasing and discordant trajectory had increased risk of death. Concordant decreasing was associated with outcomes (all p>0.05). In contrast, three distinct groups were identified using joint SBP/DBP: (1) concordant increasing, (2) discordant (stable SBP and decreasing DBP), and (3) concordant decreasing. Compared with a concordant increasing, a concordant decreasing and discordant trajectory had increased risk of death. Concordant decreasing was also associated with increased risk for incident CVD and HF, compared with concordant increasing. Findings did not differ when we stratified by use of antihypertensives.

Among community-dwelling elders, distinct BP trajectories were identified integrating SBP and DBP. Decreasing BP is associated with higher risk for adverse outcomes. Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO656
Serum Uric Acid and Vascular Stiffness in African Americans with Hypertension
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Background: Elevated serum uric acid levels as well as vascular stiffness is associated with hypertension and cardiovascular (CV) disease. However, how uric acid affects vascular stiffness is not known. We examined the relationship between uric acid and vascular stiffness in a cohort of African American men and women with well-controlled hypertension.

Methods: 120 African-Americans with controlled hypertension were randomized in a double-blind, placebo controlled study to allopurinol (300mg/dl) or placebo for 4 weeks. Vascular stiffness was assessed by augmentation index at baseline and at 4 weeks after allopurinol therapy. Uric acid was characterized as low or high (>7 mg/dl in men and > 6 mg/dl in women).

Results: The mean age was 48.7 ± 8.73 years and majority of the participants were women (71%). Augmentation index was negatively correlated with uric acid at baseline (R= -0.24 ± p<0.009). The high uric group as compared to the low uric acid group, had a lower augmentation index (9.07 ± 5.52 vs. 11.22 ± 5.23 p=0.03) while the mean BP (119/75 vs 118/75), age (48.7 vs 48.6), and endothelial function as measured by endoPAT (22 vs. 22) were similar. With allopurinol therapy there was a drop in uric acid by 2.23 ± 1.4 mg/dl as compared to placebo ±0.15 ± 0.9 mg/dl but there were no significant changes in vascular stiffness or endothelial function.

Conclusions: In African Americans with hypertension uric acid is negatively associated with vascular stiffness and short-term therapy with allopurinol does not alter vascular stiffness. These changes are not explained by endothelial function. The mechanistic basis of how uric acid may be protective against vascular stiffness may explain the many conflicting studies on the contribution of uric acid to cardiovascular risk and merits further investigation.

Funding: Other NIH Support - NHLBI R01HL079352

SA-PO657
The Impact of Renin-Angiotensin System Blockers on Renal Sodium Handling: An Analysis of CARTaGENE
Catherine Delmas-Frenette, Stephanie Troyanov, Joscée Bouchard, François Madore, Remi Goupil. Nephrology, Hospital du Sacre-Coeur de Montreal, Montreal, QC, Canada.

Background: Renin-angiotensin system blockers (RASB) reduce the effects of angiotensin II, and subsequently aldosterone, leading to vasodilatation and natriuresis. The magnitude of the RASB-induced natriuresis compared to diuretics and other anti-hypertensive agents remains uncertain.

Methods: We identified patients treated for hypertension from the prospective CARTaGENE cohort, a random sample of the Quebec population aged 40 to 69, who had available urinary sodium levels. We compared the fractional excretion of sodium (FeNa) between patients on beta-blockers or calcium channel blockers without diuretics (Group 1), on RASB without diuretics (Group 2) and on diuretics (Group 3) with ANOVA and a general linear model adjusting for age, gender, estimated glomerular filtration rate (eGFR), diabetes and peripheral mean arterial pressure (pMAP).

Results: Of the 3828 individuals with treated self-declared hypertension, 155 had available urinary sodium levels. We compared the fractional excretion of sodium (FeNa) between patients on beta-blockers or calcium channel blockers without diuretics (Group 1), on RASB without diuretics (Group 2) and on diuretics (Group 3) with ANOVA and a general linear model adjusting for age, gender, estimated glomerular filtration rate (eGFR), diabetes and peripheral mean arterial pressure (pMAP).

Conclusions: After adjustment for important covariables, RASB therapy is associated with a natriuresis similar to diuretics and greater than other antihypertensive drugs in hypertensive patients. Whether the degree of natriuresis parallels the blood pressure response to these agents remains to be determined.
SA-PO668

Urine Mitochondrial-DNA Copy Number Identifies Renal Injury in Severe Renovascular Disease

Background: We have previously demonstrated that mitochondrial injury contributes to renal dysfunction in swine renovascular disease (RVD), but its implications in human RVD remain unknown. Fragments of the mitochondrial genome released from dying cells are considered surrogate markers of mitochondrial injury. We hypothesized that RVD would be associated with increased urine mitochondrial DNA (mtdNA) copy numbers.

Methods: We prospectively measured urine copy numbers of the mtdNA genes COX3 and ND1 by quantitative real-time PCR in essential hypertensive (EH), moderate RVD, and severe RVD patients (based on ultrasound criteria and evident loss of functional renal mass) (Figure). In RVD patients, urinary COX3 and ND1 directly correlated with RVD (R²=0.18, p<0.02 and R²=0.37, p=0.001), proteinuria (R²=0.33, p<0.01 and R²=0.53, p<0.001), and serum aldosterone (R²=0.27, p=0.002 and R²=0.16, p<0.02) levels, and inversely with eGFR (R²=0.15, p=0.05 and R²=0.09, p=0.04, respectively).

Conclusions: We found progressive increments in urine mitochondrial injury markers with increased severity of RVD, implicating mitochondrial injury in kidney damage in human RVD. Mitochondria might represent a novel therapeutic target in RVD.

Funding: NIDDK Support, Other NIH Support - DK100081

SA-PO659

Association Between Urinary Big Angiotensin-25 and Microalbuminuria in Hypertensive Patients

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Background: In hypertensive patients, albuminuria is a predictive factor for cardiovascular events. Recently, a newly glycylated angiotensin-related peptide, Big angiotensin-25 (Bang-25), was isolated from human urine (Nagata et al. Biochem Biophys Res Commun 2013), and it was localized to podocytes in kidney tissue. Bang-25 may be involved in the renin-independent pathway for localized angiotensin II generation, and can contribute to dysfunction in organ disorders. Using cross-sectional data, we investigated the relationship between urinary Bang-25 and albuminuria in hypertensive patients.

Methods: We examined the data of 408 hypertensive patients (male 50.5%; mean age 70±10 years, BMI 25.3±7.5 kg/m², diabetes mellitus 36.6%, and eGFR 72±17 ml/min/1.73m²). We evaluated urinary albumin to creatinine ratio (ACR) and we measured urinary Bang-25 by specific AlphaLISA immunoassay. The association between urinary Bang-25/creatinine ratio and albuminuria was analyzed by a multivariate logistic regression.

Results: Thirty patients were excluded because of macroalbuminuria (ACR³300 mg/gCr). Of 378 patients, 96 had microalbuminuria (30≤ACR<300 mg/gCr). Patients were then divided by quartiles of Bang-25/creatinine ratio. Older patients, females, lower hemoglobin, lower uric acid, and higher HDL were more prominent in higher Bang-25/creatinine quartiles. At adjusting for age, sex, eGFR, and presence of diabetes, the odds ratios (95% confidence intervals) for microalbuminuria per quartile, calculated using multiple logistic regression, were as follows: Q1, reference; Q2, 0.72 (0.33-1.54); Q3, 0.99 (0.49-2.01); and Q4, 2.05 (1.01-4.14).

Conclusions: Higher urinary Bang-25/creatinine quartile was significantly associated with microalbuminuria in hypertensive patients. As Bang-25 is localized to podocytes, it may play some role in the development of albuminuria.

Funding: NIDDK Support, Other NIH Support - DK100081

SA-PO660

Independent Association of Vitamin D on Endothelial Function: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Nephrology, Brigham and Women's Hospital, Boston, MA; Endocrinology, Brigham and Women's Hospital, Boston, MA.

Background: In nonhypertensive individuals, lower levels of 25-hydroxyvitamin D (25(OH)D) have been associated with increased risk of cardiovascula...

Conclusions: In this randomized, double-blind, placebo-controlled trial of nonhypertensive, nondiabetic overweight or obese individuals with vitamin D deficiency (body mass index [BMI] 25 and 25(OH)D<20ng/ml), we assigned subjects to receive either ergocalciferol (25,000 units) or matching placebo, once a week for 8 weeks. Our primary outcome was endothelial-dependent vasodilation (EDV) measured by brachial ultrasound at baseline and 8 weeks post-randomization.

Results: By the end of the trial, 46 and 47 participants were allocated to receive ergocalciferol and placebo, respectively. Mean 25(OH)D levels increased from 14.9 to 30.3 in the vitamin D group and from 14.4 to 17.4 in the placebo. EDV did not change significantly with either vitamin D repletion (from 6.3±1.6% at baseline to 6.1±1.6% at 8 weeks; p-value=0.78) or placebo (7.9±4.7% to 6.8±4.7%; p=0.17). The treatment effect p-value (comparing the 8-week change with ergocalciferol to the change with placebo) was 0.35.

Conclusions: In this randomized, double-blind, placebo-controlled trial, there was no improvement in endothelial function (measured as EDV) after repletion of vitamin D in overweight/obese non-hypertensive individuals.

Funding: NIDDK Support

SA-PO661

Secondary Hypertension, Primary Hyperaldosteronism, and Renal Cell Carcinoma
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Background: Primary hyperaldosteronism (PH) is the most common cause of secondary hypertension. Renal cell carcinoma (RCC) can cause secondary hypertension, but as a renin-mediated process. We describe 5 cases referred for evaluation of PH (uncontrolled hypertension and hypokalemia), incidentally diagnosed with RCC, and the potential role of RCC as a renin-independent mechanism for hypertension.

Methods: At the initial renal visit, average blood pressure (BP) was 167/87 mmHg, with an average of 4 BP meds (nonaldosterone blockers). Average serum levels of potassium, sodium and bicarbonate were 3.1, 143 and 30 mmol/L respectively. Average plasma renin activity (PRA) was 0.12 ng/ml/hr, average serum aldosterone (sAldo) was 16.6 ng/dL, with a mean sAldo:PRA of 143.6. In 24-hour urine analysis, aldosterone ranged from 11.8 to 30.2 ng/dL and sodium ranged 82-226 mmol/24 hours. All patients required 1 or 2 aldosterone blocking agents to achieve an average BP of 134/75 mmHg. Upon imaging, 4/5 had adrenal adenomas and all 5 patients had incidental solid renal masses with radiological characteristics of RCC. To date, 3/5 have had renal masses treated with partial/total nephrectomy or cryotherapy; all have confirmed pathology of RCC. All those undergoing RCC treatment were had improved BP with 2/3 having reduced therapy. At presentation these 3 patients had an average BP of 159/87 mmHg and were on an average of 4.6 BP meds; between 5 and 9 months after RCC treatment BP was 133/75 mmHg on an average of 4 BP meds (no aldosterone blockers). Average serum levels of potassium, sodium and bicarbonate were 3.1, 143 and 30 mmol/L respectively. Average plasma renin activity (PRA) was 0.12 ng/ml/hr, average serum aldosterone (sAldo) was 16.6 ng/dL, with a mean sAldo:PRA of 143.6. In 24-hour urine analysis, aldosterone ranged from 11.8 to 30.2 ng/dL and sodium ranged 82-226 mmol/24 hours. All patients required 1 or 2 aldosterone blocking agents to achieve an average BP of 134/75 mmHg. Upon imaging, 4/5 had adrenal adenomas and all 5 patients had incidental solid renal masses with radiological characteristics of RCC. To date, 3/5 have had renal masses treated with partial/total nephrectomy or cryotherapy; all have confirmed pathology of RCC. All those undergoing RCC treatment were had improved BP with 2/3 having reduced therapy. At presentation these 3 patients had an average BP of 159/87 mmHg and were on an average of 4.6 BP meds; between 5 and 9 months after RCC treatment BP was 133/75 mmHg on an average of 4 BP meds, 2/3 able to eliminate aldosterone blockade. 2/3 patients treated for RCC had follow-up biochemical assessment. sAldo:PRA normalized in the patient with partial nephrectomy; whereas it remained elevated in patient treated with cryotherapy.

Conclusions: To our knowledge this is the first case series describing a possible renin-independent, aldosterone-mediated mechanism for secondary hypertension associated with RCC. Although such cases are rare, if this association is confirmed, these cases describe a physiological link between the two. Whether RCC leads to maladaptive steroid pathways leading to an aldosterone-like action in mediating hypertension requires detailed analysis of RCC tumors.

SA-PO662

Effect of Uric Acid Lowering Agents on Endothelial Function: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Nephrology, Brigham and Women's Hospital, Boston, MA; Endocrinology, Brigham and Women's Hospital, Boston, MA.

Background: In nonhypertensive individuals, higher levels of serum uric acid have been associated with an increased risk of hypertension, and elevated serum uric acid has been associated with endothelial dysfunction in such individuals. However, the effect of lowering serum uric acid on endothelial dysfunction in nonhypertensive individuals has not been examined thoroughly.

Conclusions: Higher urinary Bang-25/creatinine quartile was significantly associated with microalbuminuria in hypertensive patients. As Bang-25 is localized to podocytes, it may play some role in the development of albuminuria.

Funding: NIDDK Support
Methods: In this randomized, double-blind, placebo-controlled trial of nonhypertensive, nondiabetic overweight or obese individuals with elevated serum uric acid (body mass index [BMI] ≥25 and serum uric acid ≥5 mg/dL), we assigned subjects to receive one of the following: allopurinol 300mg daily for 4 weeks followed by 600mg daily for 4 weeks; probenecid 500mg daily for 4 weeks, then 1000mg daily for 4 weeks, or matching placebo. Our primary outcome was endothelial-dependent vasodilation (EDV) measured by brachial artery ultrasound at baseline and 8 weeks post-randomization. Results: By the end of the trial, 43, 44, and 47 participants were allocated to receive probenecid, allopurinol and placebo, respectively. Mean serum uric acid levels decreased from 5.9 to 3.6 mg/dL in the probenecid group, from 5.6 to 2.9 mg/dL in the allopurinol group, and were unchanged in the placebo group (5.6 to 5.7 mg/dL). EDV did not change significantly with either probenecid (from 7.6±5.1% at baseline to 8.4±5.2% at 8 weeks; p-value=0.39), allopurinol (from 7.4±6.0% at baseline to 5.9±4.6% at 8 weeks; p-value=0.09) or placebo (6.8±3.8% at 7.1±4.9%; p=0.66). Conclusions: In this randomized, double-blind, placebo-controlled trial, there was no improvement in endothelial function (as measured as EDV) after lowering serum uric acid in overweight/obese non-hypertensive individuals. Funding: NIDDK Support

SA-PO663
Azelnidipine Can Restore the Deceleration Capacity of Heart Rate Variability (DC) In CKD Patients with Preceding Treatment with ARB Michio Fukuda, 1 Toshiyuki Miura, 1 Yoshiaki Ogiyama, 1 Ryo Sato, 1 Daisuke Fuwa, 1 Hiroyuki Ito, 1 Tetsuehi Matsuoka, 1 Yukako Isobe-Sasaki, 1 Ken Kiyono, 2 Hiddo Jan Lambers Heerspink, 2 Dick de Vries, 2 Osaka Univ; 2Tokyo Univ.

Background: Recently, we have hypothesized that DC, novel measure of cardiac vagal modulation, is also attributable to sympathetic nerve activities. Azelnidipine was reported to decrease non-Gaussianity index of HRV (l25s), which can serve as a marker of sympathetic cardiac overdrive.

Methods: In 43 hypertensive patients with CKD under treatment with an angiotensin receptor blocker (ARB), we tested whether 8-week add-on administration of azelnidipine can increase DC. DC was calculated by Bauer’s signal processing technique of phase-rectified signal averaging. For reference, the power of high frequency (HF, 0.15–0.40 Hz) obtained from frequency measure of HRV was examined as a conventional indicator of vagal activity. Results: DC increased (6.17 ± 1.84 to 6.55 ± 1.85, p=0.002) and l25s decreased (0.56 ± 0.15 to 0.50 ± 0.12, p=0.001), while no significant changes were observed in other HR variability measures including HF (p=0.9). Change in DC correlated inversely with the change in l25s (r=0.38, p=0.01), but not with the change in HF (p=0.8). Conclusions: Our findings are consistent with the thesis that DC is not a simple measure of vagal activity but a product of complex interplay between sympathetic and vagal nerve activities.

SA-PO664
Elevated Levels of Podocyte Derived Urinary Microparticles in Angiotensin II Induced Hypertension Uta Erdbruegge, Christine Rudy, Sylvia Cechova, Rosa Chan, Joseph C. Gigliotti, Thu H. Le. Div of Nephrology and HTN, Univ of Virginia Health System, Charlottesville.

Background: Early and non-invasive biomarkers of kidney damage are needed to identify hypertensive patients at risk for kidney damage. Urinary microparticles (uMPs) have gained significant attention as potential novel biomarkers for kidney damage, and have already been identified in pre-albuminuric diabetic glomerular injury. These vesicles are less than 1 micron in size and carry markers of the parent cell. We hypothesized that podocyte-derived uMPs are elevated in angiotensin II-induced hypertension (HTN).

Methods: Wild-type mice were treated with AII (400ng/kg/min) via mini-osmotic pumps. Untreated WT mice served as controls. Blood pressure was measured with tail-cuff manometry. 24 hour urine were collected after 5 days of all treatment. Enumeration and phenotyping of MPs was done of podocyte culture supernatant and urine. UMP levels were normalized to urinary creatinine concentration. Podocalyxin (Pcal), podoplanin (Ppla) and annexin 5 (AV) were used as surface markers.

Results: Pcal and Ppla positive MPs as well as AV positive and negative MPs were detectable in supernatant from primary podocyte cultures. Compared to untreated controls (n=3), all treated mice (n=2) had an increase in systolic blood pressure (SBP) by 33 mmHg (p=0.02). Despite similar urinary albumin/creatinine ratios between groups, there was a trend of higher levels of total numbers of Pcal and Ppla positive MPs in hypertensive mice compared to untreated (see Figure 1). In addition, AV negative but Ppla and AV positive MPs were also numerically higher in hypertensive mice compared to AV positive uMPs.

Conclusions: In conclusion, podocyte derived urinary MPs are detectable in all HTN. These findings need to be confirmed in a larger group of animals. Urinary MPs can be potential marker for kidney end-organ damage in HTN.

Funding: Clinical Revenue Support

SA-PO665
Blood Pressure Lowering Effects of Sulodexide Depend on Albuminuria Severity Rik Hg Olof Engberink, 1 Hiddo Jan Lambers Heerspink, 2 Dick de Zeeuw, 2 Lizlert Vogt. 1 Nephrology, AMC, Amsterdam, Netherlands; 2 Clinical Pharmacy and Pharmacology, UMC, Groningen, Netherlands.

Background: Diabetic patients have a thinner endothelial surface layer (ESL), especially when macroalbuminuria is present. Sulodexide, a mixture of glycaminoglycans (GAGs), increases ESL thickness. Previous data indicate that the ESL is pivotal for BP regulation. In this study, we assessed whether the BP reducing effect of sulodexide is modified by albuminuria severity (a surrogate for the ESL) in type II diabetic patients.

Methods: In a post-hoc analysis of the randomized, double-blind, placebo-controlled Sun-MACRO trial, including type 2 diabetic patients with macroalbuminuria and maximal angiotensin II receptor blocker therapy, we studied the BP effects of sulodexide 200 mg/d. We stratified patients in baseline urinary albumin-creatinine ratio (UACR) tertiles. We used ANCOVA to study whether baseline UACR modified the 3-month SBP changes of sulodexide.

Results: Of 843 patients were available for analysis. Baseline BP was 138/73 mmHg. At 3 months, mean (SEM) SBP change was -0.9 (±0.9) and +1.7 (±0.9) mmHg in the sulodexide and placebo arm, respectively (p=0.037). The SBP reduction was most pronounced in the highest UACR tertile (-1.6 [-1.5 to 2.9] vs 2.9 [±1.6] mmHg; p=0.042). Treatment (p=0.015), baseline SBP (p=0.001), heart rate (p=0.007) and UACR (p=0.007) were associated with SBP change. We found an interaction between treatment and UACR (p=0.047), indicating that sulodexide and placebo differently affected SBP at various UACR levels. Age, eGFR, BMI, HbA1c and lipid profile (i.e., factors influencing ESL thickness) did not modify the treatment effect. The BP differences persisted during the first year of follow-up (p=0.047).

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

SA-PO666
Under-Diagnosis of Hypertension in a Large Cohort of Overweight/Obese Adolescents Brian William Sykes, Divya G. Moodalbail, Christopher J. LaRosa, Joshua Zaritsky. Nephrology, Nemours/A.I. duPont Hospital, Wilmington, DE.

Background: The obesity epidemic in children is strongly associated with increasing prevalence of childhood hypertension (HTN) along with heightened risk for cardiovascular morbidity and mortality in adulthood. Therefore we assessed the identification of HTN in overweight/obese adolescents cared for by a large healthcare system utilizing an EMR system.

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

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Methods: We performed a retrospective study of patients (pts) in the Nemours Health Care System, aged 12-17 years, with a BMI >85%ile, and 3 documented BP values >120/80 in the outpatient setting, between 1/2010 and 12/2014. Pts with established diagnosis of htn (ICD-9 codes 401.XX – 405.XX), renal or heart disease were excluded.

Results: Of the 6604 distinct pts identified, only 253 (3.8%) received a diagnosis of htn during the study period, while 6,349 (96.2%) were undiagnosed. Pts who were undiagnosed had lower BMIs and BPs and were less likely to be African American or have Medicaid and were seen less by Nephrology, Cardiology or Weight management subspecialties compared with those diagnosed with htn (table). Additionally undiagnosed pts had fewer abnormal BPs and had a longer interval between their 1st and 3rd abnormal BP compared with those diagnosed with htn.

Conclusions: In this large cohort of overweight/obese adolescents with htn, the vast majority of pts were undiagnosed and not referred to subspecialists who manage BP monitoring and treatment. Thus it is crucial that future efforts focus on improving detection and early recognition of htn in order to reduce cardiovascular morbidity and mortality in this at-risk population.

SA-PO667 Multidisciplinary Selection of Angioplasty Indications in Atheromatous Renal Artery Stenosis Leads to an Improvement in Blood Pressure, Drug Sensitivity and Renal Function

Thomas Foumier,1 Florence Serei,2 Olivier Rouvière,2 Antoine Millon,3 Laurent Juillard,1 Gary L. Schwartz.1

Background: Angioplasty as treatment of atheromatous renal artery stenosis (ARAS) is controversial since 3 large randomised trials (CORAL, ASTRAL, STAR) failed to prove the superiority of percutaneous renal artery angioplasty and stenting (PTRAS) over medical treatment alone (MT). However, since population selection was questionable among other biases, the extrapolation of these results in clinical practice is uncertain.

Methods: ARAS cases were discussed during bi-monthly multidisciplinary meetings gathering nephrologists, radiologists and vascular surgeons from April 2013 to February 2015. For every patient, we compiled clinical, biological and radiological data. We then recorded blood pressure (BP), renal function and treatment evolution after a one-year follow-up.

Results: During 23 months, 52 cases were discussed. Mean age was 69 years. Two thirds of patients had at least 3 cardiovascular risk factors. Mean BP was 161/77 mmHg, despite the use of 2.5 ± 1.1 anti-hypertensive drugs. CKD-EPI was 55mL/min/1.73m². 31% of patients had a history of pulmonary edema. Collective decisions were PTRAS for 21 patients (40%), MT for 28 patients (54%) and surgery for 3 patients (6%). PTRAS and MT groups were initially comparable (blood pressure, renal function, treatment, comorbidities). In the PTRAS group, a significant improvement at 1 year was observed for clinic BP: -14.3/9.0 mmHg, P=0.0001 and 24h ABP: -9.0/4.8 mmHg, P=0.0001. The superiority of PTRAS over MT was also true for each racial subgroup: whites vs blacks: 22.5% vs 10.5% with the PTRAS strategy, and 41.1% for the other 2 strategies, P=0.08; in whites 63.5% with PTRAS strategy, 50.9% with A/R strategy, P=0.001 and 43.9% with TD strategy, P=0.001. This was also true for each racial subgroup: clinic BP: in whites: 50.3% with PTRAS strategy, 40.8% with A/R strategy (P=0.0004) and 31.7% with the TD strategy (P=0.0001); ABP: 61.3% with PTRAS strategy, 51.6% with A/R strategy (P=0.0001) and 43.9% with TD strategy (P=0.0001). It is uncertain which of these 3 strategies achieves the highest control rate with monotherapy in stage-I HTN.

Conclusions: Compared to TD and A/R, the PTRAS strategy for initial drug selection in stage-I HTN was associated with the highest control rate.

Funding: Other NIH Support - PEAR was supported by the National Institute of Health Pharmacogenomic Research Network grant (U01 GM074492) and the National Center for Advancing Translational Sciences under the award number UL1 TR000064 (University of Florida), UL1 TR000054 (Emory University), and UL1 TR000335 (Mayo Clinic). PEAR was also supported by funds from the Mayo Foundation.

SA-PO669 Primary Hyperaldosteronism: An Inner City Hypertension Clinic Experience

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Background: Primary Hyperaldosteronism (PA) has historically been regarded as a rare disorder. Recent studies have shown a widely variable prevalence. We screened for PA in the Hypertension(HTN) Clinic at Harlem Hospital in patients with predominantly African-American and Hispanic ethnicities.

Methods: Retrospective observational study of patients seen at Harlem HTN Clinic between January 2008 to November 2013. The inclusion criteria were patients seen with completed aldosterone and renin levels. The exclusion criteria were patients on spironolactone prior to the laboratory studies or with incomplete data. Prevalence was measured as number of patients with both an Aldosterone/Renin ratio >20 and an Aldosterone level >15ng/dl as a ratio of total number of patients tested.

Results: A total of 268 patients who had plasma aldosterone and renin activity obtained was reviewed. Of these, 8 patients had incomplete data and were excluded. 220 of the remaining patients in the final cohort of patients were black, while 48 were Hispanic. Overall, 33/260, or 16.5% of the patients were found to have met biochemical criteria for PA. About half, 22/43 or 51% of the patients had CAT Scans showing adrenal adenomas. Additionally, one patient had bilateral enlarged adrenal glands consistent with adrenal hyperplasia, 10 had CAT scans with no evidence of an adrenal mass, while the remaining 10 patients had no abdominal imaging. In the 43 patients who met biochemical criteria for PA, 34 patients were black, 16 of which (47%) had CT evidence of adrenal adenoma while 1 patient had bilateral hyperplasia. Of the 9 Hispanic patients, 6 (67%) had CT evidence of adrenal adenoma. Overall, the prevalence of PA was 34/220 (15.4%) in African-American patients and 9/40 (22.5%) in Hispanic patients.

Conclusions: Our study suggests a higher than anticipated prevalence of PA in African-American and Hispanic patients in Harlem, NY, based on selective screening with plasma aldosterone and renin activity and adrenal scans were present by CT scan in at least 50% of cases, potentially treatable with surgery. Thus, adequate screening of patients for PA is essential, especially in minorities.

SA-PO670 HIV-2 and Chronic Kidney Diseases (French HIV-2 Cohort ANRS CO5)

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Background: The link between HIV-2 and chronic kidney diseases (CKD) has not been studied. We describe the prevalence of CKD and their risk factors in people living with HIV-2.

Methods: All patients included in the HIV-2 French national cohort with 2 creatinine measurements at least 3 months apart were included. Glomerular filtration rate was estimated by MDRD formula and used to categorize CKD according to the NKF classification. Risk factors were determined by uni and multivariate analyses using a Cox model which included the main known risk factors for CKD and the main characteristics of HIV infection. A total of 1048 patients of which 917 had creatinine measurement. 69 patients were excluded because creatinine had not been measured at both points. Characteristics did not significantly differ from those of the total cohort: mean age (SD) was 50 (11) years, 62% of the patients were females, and 80.1% originated from sub-Saharan countries. On average, HIV-2 infection was diagnosed 12.8 (6.8) years before last creatinine measurement. Prevalence of CKD stage >2 was 39.8% and that of chronic kidney failure (stages >3) was 22.2%. In a multivariate analysis revealed that age (HR=1.06, p<0.01), HIV stage (HR=3.1, p<0.01 for CDC stage C), HIV-2 virus plasma viral load (HR=1.9 for each increment of log_{10}(copies/ml), p<0.10), and CD4 count (HR=3.12, p<10^(-1)/100 mm3) were risk factors for chronic
kidney failure. HIV stage A (HR=0.3, p<0.001) had a protective effect. Multivariate analysis revealed that age (HR=1.05, p=0.002) and CDC stage A (HR=0.35, p=0.01) were risk and protecting factors, respectively.

Conclusions: The prevalence of CKD in this very large cohort of people living with HIV-2 seems to be comparable to what is known in literature for people living with HIV-1. HIV-2 infection parameters determine most of the kidney risk. The role of ARV exposition remains to be taken into account.

Funding: Government Support - Non-U.S.

SA-PO671

Effect of Nephropathy on the Frequency of Cardiac Dysautonomia in HIV Patients

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Background: Dysfunction of autonomic nervous system including Cardiac Dysautonomia (CD) is seen in a variety of conditions like diabetes mellitus, adrenal insufficiency and renal failure. CD is well documented in patients with renal dysfunction. CKD. Prevalence of renal dysfunction (HIV Nephropathy) is high in our population of HIV positive patients, but the effect of HIV nephropathy on the frequency of CD has not been previously studied. We conducted this study to determine the effect of HIV nephropathy on the frequency of CD.

Methods: This cross sectional study was conducted at HIV Clinic in collaboration with the Department of Nephrology Jinnah Hospital Lahore. A total of 47 HIV positive patients were enrolled; 13 (28%) with nephropathy and 34 (72%) without nephropathy. Patients underwent 5 tests for cardiac autonomic dysfunction including resting tachycardia, abnormal heart rate response to deep breathing, abnormal Valsalva ratio, abnormal 30:15 ratio and postural hypotension. Patients with 2 or more abnormal tests were considered positive for CD.

Results: Of 47 patients, 39(83%) were male, 5(11%) female and 3(6%) were transgender with median age of 31 years (range 19-56 years). The median CD4 count was 339 (range 39-797) and 96% (n=45) patients were on highly active anti-retroviral therapy (HAART). The median duration of HIV was 12 months (range 1-56) and median duration of HAART was 11 months (range 0-49). CD was seen in 42 (89%) patients. Seventeen (36.2%) patients had 2, 18 (38.3%) had 3, 6 (12.8%) had 4 and 1 (2%) had 5 abnormal tests. The frequency of CD was comparable among patients with and without nephropathy [92% (12 out of 13) vs 88% (30 out of 34), respectively; p value=1]. The presence of CD had no correlation with CD4 count, degree of renal impairment, treatment regimen and duration on HAART.

Conclusions: There was high frequency of CD in our population of HIV patients and it was independent of presence or absence of nephropathy, CD count and duration of anti-retroviral therapy.

SA-PO672

Glomerular Filtration Rate Estimation Equations Using Beta-Trace Protein and Beta-2 Microglobulin in Chronic Kidney Disease


Background: Beta-trace protein (BTP) and beta-2-microglobulin (B2M), like cystatin C (Cys), are novel serum filtration markers that have stronger associations with adverse outcomes than serum creatinine (Cr). However, comparisons of BTP and B2M to Cr and Cys as filtration markers are limited by the absence of rigorously developed GFR estimation equations. Methods: Using a pooled database of three populations with CKD (N=3551, mean measured GFR using iothalamate [mGFR] 48 ml/min/1.73m 2 ), we developed equations estimating GFR from multiple biomarkers. Models: Using a pooled database of three populations with CKD (N=3551, mean measured GFR using iothalamate [mGFR] 48 ml/min/1.73m 2 ), we developed equations estimating GFR using Cys, BTP or B2M. Equations were developed in 2/3 of the population and tested in the remaining 1/3. Results: The table shows the coefficients included in each equation and the performance of the equations in the validation dataset compared to established CKD-EPI Cr-Cys equations.

Conclusions: BTP and B2M are less influenced by age, sex and race than Cr or Cys but did not improve precision (IQRF) or errors (1-P30), even when averaged with Cr-Cys equation. CKD-EPI BTP and B2M equations provide tools for future study in their associations with mGFR and risk and adverse outcomes, but further study is required before clinical use.

SA-PO673

Estimation of Glomerular Filtration Rate

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Background: Estimations of glomerular filtration rates (GFR) based on routine 24 hour urine collections have been replaced by relatively accurate equations derived from large epidemiological studies. Nonetheless, equations including Modification Diet in Renal disease-4 and 6 variables (MDRD-4, -6) and Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) are known to have wide variations in predicting GFR among patients with relatively good kidney function. As renal clearance of any solute is dependent on its presence in the plasma and not whole blood, we suspect that varying hemoglobin/ hematocrit (Hct) may play an important role in the actual clearance of solutes. We aim to determine if adding the plasma factor PF (1 - Hct/100) to MDRD-4, -6, or CKD-EPI equations can improve the accuracy of determining actual GFR.

Methods: This is a retrospective pilot study where the most recent 200 existing 24-hour urine collections obtained with creatinine concentrations as recorded by the Olive View-UCLA Medical laboratory are collected for analysis. Only 24-hour urine collections with concurrent measurements of complete blood count and chemistry 7 are included. To minimize poor 24 hour collections, only samples with urinary creatinine ranging between 15-25 mg/kg weight/day are used. PF is added as an inverse multiplication factor to MDRD-4 and 6-variables and CKD-EPI equations to assess for variations when correlated with actual 24 hour urine collections.
Results: 90 out 200 samples met inclusion criteria. Albeit small, when each of the aforementioned equation was adjusted for PF, R² variation improved. MDRD-4: unadjusted R²=0.836 to adjusted R²=0.853, MDRD-6, R²=0.811 to 0.813, CKD-epi, R²=0.746 to 0.747. Conclusions: Adding PF to MDRD-4, MDRD-6, and CKD-EPI equations reduced variations when correlated to 24 hour urine collections. Of interest, PF appears to improve MDRD (derived for CKD patients where anemia is prevalent) variations better than CKD-EPI. Large-scale reevaluation of eGFR estimates with consideration for PF is warranted.

SA-PO674
Interest of Cystatin C in the Evaluation of Glomerular Filtration Rate in Type 2 Cardio-Renal Syndrome Delphine Kervella,1,2,3 Sundrine Lemoine,2,3 Florence Lemoine,2,3, Denis Pouliquen,1,3 Laurence Dubourg,2,3 Fitsum Guebre
Background: In patients suffering from type 2 cardio-renal syndrome (CRS2), glomerular filtration rate (GFR) is overestimated with creatinine based formulae, leading to the misclassification of these patients in chronic kidney disease stages. As cystatin C is less dependent from muscle mass than creatinine, the aim of this study was to determine if estimation of GFR based on cystatin C offers a better evaluation of renal function than creatinine-based estimations in patients with CRS2.

Methods: GFR measured by Inulin clearance (measured GFR, mGFR) in 50 patients with CRS2 was compared to estimations of GFR (eGFR) with CKD EPI (Chronic Kidney Disease Epidemiology Collaboration) formulae based on creatinine (CKD EPI), cystatin (CKD EPIcyst) and cystatin and creatinine (CKD EPIcyst,cr) with the calculated absolute bias (eGFR-mGFR) and accuracy 30% for each formula.

Results: Mean mGFR is 26.5±11.5 mL/min/1.73 m². eGFR are 41.5±20, 35±14.5 mL/min/1.73 m² with CKD EPI, CKDEPICYST and CKD EPICYST-CREAT respectively.

Conclusions: Glomerular filtration rate is strongly overestimated with creatinine-based estimation in CRS2 patients as previously described. CKD EPI formula based on cystatin C offers a better evaluation of GFR in this population. The high prevalence of malnutrition in this population can explain these results.

SA-PO675
Cystatin C in Type 2 Cardio-Renal Syndrome
Delphine Kervella,1,2,3 Sundrine Lemoine,2,3 Florence Lemoine,2,3, Denis Pouliquen,1,3 Laurence Dubourg,2,3 Fitsum Guebre
Background: Serum creatinine is the most used endogenous marker to estimate glomerular filtration rate (GFR) in clinical practice. A handheld device (StatSensor®, Nova Biomedicals) allows to measure creatinine level in capillary blood. The aim of the study was to assess the accuracy of GFR values (eGFR) estimated from capillary blood creatinine level (cGFR), as compared with GFR values simultaneously measured by a gold standard method (mGFR) in patients with CKD.

Methods: The study included 79 adult patients (36 men, 43 women) who underwent renal function tests. The consent form contained information on the procedure and on the later use of the information for research. Inulin clearance was performed using a continuous infusion of inulin, and urine collections by periods of 30 min. Blood tests were done in the middle of each period of urine collection. Measurements of polyfructosan concentrations were performed using an enzymatic method. Inulin clearance was calculated in each period to obtain the average, and normalized to 1.73 m² body surface area. A drop of capillary blood was collected from a finger simultaneous to the first and the last blood sampling for inulin measurement. The drops were deposited on a test strip including enzyme reagents and inserted into the StatSensor® device. Reading was done at 30 sec. eGFR was calculated from CBCr with the CKD-EPI equation and the average of the 2 values was taken as eGFR. To assess the performance of CBCr-derived eGFR, the mean absolute bias (eGFR - mGFR) and the correlation coefficient (R²) were calculated.

Results: Mean age was 54.3±17 years, and mean BMI was 25.5±4.2 kg/m². Mean value of mGFR was 61.2±27 mL/min/1.73 m². Mean bias was -5.2 mL/min/1.73 m². On correlation analysis, there was no significant difference between the 2 methods (correlation coefficient 0.7,0.71).

Conclusions: Estimation of GFR using instant measurement of capillary blood creatinine level and CKD-EPI formula provides consistent results as compared with a gold standard method for GFR measurement, and could be used for screening and self-assessment purposes.

Funding: Clinical Revenue Support

SA-PO676
Renal Function Estimated with Different Formulae and Mortality in the INCIPE Cohort: Results After 8 Years Follow-up Pietro Manuel Ferrara,1 Antonio Lupo,2 Giovanni Gambaro,1,3 Div of Nephrology, Catholic Univ of the Sacred Heart, Rome, Italy; Div of Nephrology, Univ of Verona, Verona, Italy.

Background: Chronic kidney disease is a known risk factor for adverse outcomes. Its presence and severity is usually ascertained with formulae to estimate renal function based on serum creatinine and/or cystatin C. We analyzed whether renal function estimated with different formulae has a differential association with mortality.

Methods: The INCIPE is a sample of the Italian population enrolled in 2006-07, with follow-up data available up to 2014. CKD stages were defined as GFR ≥90, 89-60, 59-45 and <45 mL/min based on the following formulae: Cockcroft-Gault (CG), Cockcroft-Gault normalized to body surface area (nCG), abbreviated MDRD (MDRD), 6-variables MDRD (MDRD-6), CKD-EPI calculated with serum creatinine (EPI-Cr), with serum cystatin C (EPI-Cys), and with both serum creatinine and cystatin C (EPI-CrCys). CKD stage was then included in a Cox proportional hazards model together with age, body mass index, sex, high blood pressure, diabetes, dyslipidemia, previous cardiovascular disease, smoking status and albuminuria. Harrell’s c statistics with 95% confidence intervals (CI) were then calculated and compared for each formula.

Results: The final sample included 2,916 participants, all caucasians, 47.4% males, with an average age at enrollment of 59.9±11.4 years. Participants contributed a total of 22,514 person-years of follow-up (median follow-up 7.9 years) during which 198 death events occurred. Overall, the models were highly predictive of mortality.

The GFR-Cys model performed significantly better than MDRD-6 (difference in c-statistics of 0.008, 95% CI 0.001, 0.015; p=0.034), whereas all the other models performed similarly.

Conclusions: Our study suggests that CKD defined with the CKD-EPI cystatin C formula shows a better prediction of mortality after accounting for a large number of potential risk factors.

SA-PO677
Do the BIS Equations Better Predict Death in Older Women? Muna T. Canales,1,2 Terri L. Blackwell,3 Areef Ishani,1,2 Brent C. Taylor,4 Allyson Hart,2 Rebecca Blyth,2 Kristine E. Ensrud,4,5 Malcom-Randall FAMC; Univ of Florida; Minneapolis VA Health Care System; Univ of Minnesota; Hennepin County Medical Center, Minneapolis, MN.

Background: KDIGO 2012 guidelines recommend use of the CKD-EPI equations to estimate GFR except when there are alternate equations that may perform better in certain populations such as older adults. The BIS equations were specifically developed in an aged population, but their performance when compared to the CKD-EPI equations to predict mortality in older adults is unclear.

Methods: We conducted a prospective study of 1289 community-dwelling elderly women (≥72 years old) enrolled in the Study of Osteoporotic Fractures (SOF) who had both serum cystatin-C (cysC) and creatinineSCR measured at Year 10(1992-1994). We used Cox proportional hazards regression and net reclassification improvement(NRI) to compare the ability of the BIS2 (cysC & SCR-based), CKD-EPI_Cys, BIS1 (SCR-based), and CKD-EPI_Cys, expressed as 4 eGFR categories (27, 60-74, 45-59, <45) to predict death. For NRI analyses, reference equations were CKD-EPI_cys, for BIS2 and CKD-EPI_cys for BIS1.

Conclusions: Our study suggests that CKD defined with the CKD-EPI cystatin C formula shows a better prediction of mortality after accounting for a large number of potential risk factors.

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

781A
Results: The mean age was 79.5±4.6 years; 89% were white. Mean BMI was 27.5 kg/m². Mean follow-up time was 9.4 years. % eGFR<60 was: CKD-EPIcr 33%, BIS2 48%, CKD-EPI, 24% and BIS1 49%. When compared to eGFR<75 and after adjustment for age, race, BMI, HTN & DM, eGFR<45 by BIS2 was associated with a 2.1-fold greater risk of death (95% CI 1.5-3.0) vs 1.9-fold for eGFR <45 by CKD-EPIcr, (95% CI 1.5-2.5); BIS1 eGFR<45 was associated with a 1.6-fold greater risk of death (95% CI 1.1-2.1) vs 1.8-fold for eGFR <45 by CKD-EPI, (95% CI 1.2-4.4; p trend <0.001 across categories for each equation). In category-based NRI analyses neither of the BIS definitions materially changed discrimination of mortality risk when compared to CKD-EPI equations.

Conclusions: In this cohort of older community-dwelling women, the BIS equations identified a greater proportion of participants as having CKD. With respect to mortality risk prediction, the BIS equations did not perform better than current CKD-EPI equations recommended by KDIGO 2012.

Funding: Other NIH Support - NIA, Veterans Administration Support

SA-PO678

Canine Chronic Kidney Disease: New Protein Biomarkers and Treatment with Human Umbilical Cord Mesenchymal Stem Cells

Background: There are few strategies to prevent the progression of renal disease in humans or animals. In canine chronic kidney disease (cCKD), as in human CKD, proteinuria correlates with CKD progression, although there are no established urinary biomarkers. cCKD has become more common, dogs routinely being euthanized upon reaching the advanced stages. Mesenchymal stem cells (MSCs) have proven renoprotective in rodent CKD models. Here, we aim to characterize the roles that urinary excretion of albumin (Alb), Tamm-Horsfall protein (THP), vitamin D-binding protein (VDBP) and retinol-binding protein (RBP) play in cCKD and to determine whether human umbilical cord MSC (huMSC) administration slows its progression.

Methods: We performed Western blotting for urinary exosomal expression of Alb, THP, VDBP and RBP in cCKD stage 1-4 dogs (n=10/stage) and control dogs (n=10). We evaluated huMSC phenotypes with flow cytometry and immunocytochemistry. We randomized CKD stage 3 dogs to receive i.v.-injected placebo (n=5) or 10⁶ huMSC/kg (n=6).

Results: BIS has been analysed by immunonephelometry with N-Latex bTP Assay on a BN ProSpec ® System, Siemens, Germany. Analysis was done in 570 participants of the study.

Conclusions: Our findings broaden perspectives for CKD treatment. Supported by FAPESP.

SA-PO679

Validation of the Urine Total Protein-To-Creatinine Ratio-Based Chronic Kidney Disease Risk Classification: A Secondary Analysis

Background: The most recent Japanese chronic kidney disease (CKD) guideline states that patients without diabetes should be classified using the total urine protein-to-creatinine ratio (PCR) instead of the urine albumin-to-creatinine ratio (ACR); however, validation of the PCR is still required. This study was conducted to validate the PCR-based CKD risk classification compared with the ACR-based classification and to explore more accurate methods for classification, focusing on relatively early CKD patients.

Methods: We conducted a secondary analysis using two previous datasets with diabetic or cardiovascular patients who were classified into CKD stages A1-A2 and G1-G3b. We assessed the CKD stage and risk classification of each patient according to the estimated glomerular filtration rate and the ACR- or PCR-based classification method. Then, various candidate PCR values were utilized as the cut-off values between stages A1 and A2. Cohen’s kappa statistics were calculated to evaluate the agreement between each classification method.

Results: In total, 860 patients (131 from the diabetic clinic and 729 from the cardiovascular clinic) were enrolled. Using the cut-off value recommended in the current guideline (PCR 0.15 g/gCr), the misclassification rates in these populations were 26.0% and 16.6%, respectively; the misclassifications were primarily caused by underestimation. Cohen’s statistics achieved 0.56 (95% confidence interval, 0.45-0.69) and 0.72 (0.67-0.76), respectively. Using PCR values of 0.08-0.10 g/gCr as the cut-off value improved the misclassification rates and kappa values.

Conclusions: Current PCR-based CKD classification method leads to underestimation of risk classification in outpatient setting.

Funding: Private Foundation Support

SA-PO680

Beta-Trace Protein as Renal Marker in Older Adults – Results from the Berlin Initiative Study

Background: It has been shown that GFR estimation based on β-Trace Protein (BTP), a relatively novel biomarker, is reliable and might serve as an alternative in kidney transplant recipients. Whether BTP-based eGFR equations can be applied in older adults is not known.

Methods: BTP has been analysed by immunonephelometry with N-Latex® BT Assay on a BN ProSpec System. Siemens, Germany. Analysis was done in 570 participants of the Berlin Initiative Study (mean age: 78.5 yrs) who underwent iohexol clearance measurement (mean mgFR: 60.3 mL/min/1.73m²). The following 3 currently available eGFR equations were used: Pöge (BTP): GFR = 47.17 ×BTP -1.86 , Pöge (BTP/Crea): GFR = 974.31 × BTP -1.758 × creatinine-0.204 and White (BTP/Crea): GFR = 167.8 × BTP -0.758 × creatinine-0.204 × (0.871 if female). Comparison of BTP estimating equations with mgFR was done for determination of bias (mgFR-eGFR), precision (SD) and accuracy (P10, P30).

Results: The boxplot includes median and eGFR range calculated with the 3 GFR-equations. Mean eGFR was 100.3 for Pöge (BTP), 62.7 for Pöge (BTP/Crea) and 86.2 mL/min/1.73m² for White (BTP/Crea).

Funding: Private Foundation Support

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782A
SA-PO682

Chronic Kidney Disease: Long Term Prevalence Trends and Influence of Modifiable Risk Factors
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Background: Prevalence of chronic kidney disease (CKD) is high worldwide, and it has been increasing in the US. However, less strict treatment goals for hypertension have recently been suggested despite increasing prevalence of obesity and diabetes. We aimed to determine whether CKD prevalence is increasing in Norway, evaluating the influence of changing prevalence of CKD risk factors on CKD prevalence, and compared findings to corresponding US data.

Methods: We included general population based participants from the Nord-Trøndelag Health Studies (HUNT), Norway: 65237 from HUNT2 (1994-96) and and 50586 from HUNT3 (2006-08). eGFR and u-ACR based on fresh blood and 3 urine samples were used to diagnose CKD. Thorough quality-control and comparisons of methods over time excluded analytical drift. We used attendance weights used to avoid responder bias.

Results: Total CKD prevalence remained stable in Norway 1996-2007 (11.3%-11.1%, p=0.42) but increased in subjects >75 years (36.6%-39.3%, p=0.014). eGFR <60 ml/min/1.73m2 increased (4.5%-4.8%, p=0.033) while albuminuria >30mg/g decreased (7.9%-7.4%, p=0.034). The most important contributors were a strong blood pressure decline during this 10 years period, more physical activity and lower cholesterol; without these improvements 2.8, 0.7 and 0.6 percentage-point higher CKD prevalence would have been expected, respectively. In contrast, the prevalence of diabetes and obesity increased moderately, but diabetics received more intensive preventive therapy, and the proportion of diabetic patients with CKD decreased substantially (33.4%-28.6%, p=0.002). In contrast, published US data indicate a stronger increase in obesity and diabetes, and physical activity was low and not improving. Access to effective care was also suboptimal for a substantial group of the population.

Conclusions: In contrast to the US where CKD prevalence has been increasing, it remained stable over a 10 year period in Norway, likely due to substantial improvements in blood pressure, lipids and physical activity despite modestly increasing diabetes and obesity. Funding: NIDDK Support

SA-PO683

Natural Progression of Chronic Kidney Disease in Optimally Managed Patients on the Maximum Conservative Management Pathway
Suzanne H. Forbes, Kieran McCafferty, Muhammad M. Yaqoob, Nephrology, Royal London Hospital.

Background: The natural progression of advanced chronic kidney disease (CKD)/end-stage renal disease (ESRD) managed in a specialist palliative care nephrology clinic setting is unknown.

Methods: We conducted an observational study of all patients with advanced CKD undergoing predialysis counselling between 2009-2014 in a single UK center. All patients who opted for conservative management were followed up prospectively in a specialist conservative care clinic and their clinical phenotype and renal outcomes recorded. Change in eGFR was noted in those patients whose eGFR was<10, with 2 or more serum creatinine estimations taken more than 2 months apart.

Results: We prospectively studied 354 patients with median length of follow-up 452 days (165-769). Median eGFR at referral was 8ml/min (7-9). Demographics are shown.

| Age | 78 (73-84) |
| Gender | M - 62% F - 38% |
| Diabetes | Yes - 62% No - 38% |
| Ethnicity | Caucasian - 39% South Asian - 37% Black - 14% Other - 10% |
| Cause of CKD | Diabetes - 38% Renovascular (including hypertension) - 24% Urological - 9% GN - 5% Other - 4% Unknown - 20% |
| Previous Modality | Nephrolgy/Low Clearance Clinic - 92% Failing Transplant - 2% Unknown to Service - 6% |
| Death (n) | 209 |
| Cause of Death (n) | Cardiac - 16 (8) Sepsis - 13 (6) Stroke - 2 (1) Unknown - 38 (18) Other - 12 (6) |
| Age at Death | 80 (75 - 85) |
| Time to Death (days) | 276 (185 - 555) |

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SA-PO681

Galectin-3, Possible Useful Biomarker in Predicting Chronic Kidney Disease in Hepatitis C Positive Patients
Hany Refaat, Haitham Ezzat, Amir Mohab, Nephrology Dept, Ain Shams Univ, Cairo, Egypt.

Background: Galectin-3, a profibrotic mediator, is involved in mechanisms of tubulointerstitial fibrosis and CKD progression. Data regarding its predictive value of CKD development in Hepatitis C patients is scarce.

Methods: In this cohort study, we measured the level of Galectin-3 in the sera of 80 Hepatitis C positive patients. Patients levels were stratified into two groups: Forty hepatitis C positive patients with normal kidney function (Group I), and 40 hepatitis C positive patients with CKD (Group II). Galectin-3 concentration was also measured in 10 healthy individuals, as a control group (Group III). Other laboratory investigations were done which included hemoglobin level, serum creatinine, eGFR by MDRD equation, ALT, AST, INR, serum albumin, serum hirulbin and CRP titre. We correlated galectin-3 concentrations with demographic and biochemical parameters in all groups.

Results: 30 females (33.3%) and 60 males (66.7%) were included in the study with mean age 47.6±5.3 years. Plasma levels of Galectin-3 were highest in group II (22.1 ±5 ng/ml) when compared to group I (15 ±2.4 ng/ml) and group III (9.7 ±2.5 ng/ml) (p<0.001). Also CRP titre was highest in group II (10.1 ±1.5 mg/L), when compared to group I and III (2.5±0.9 mg/L and 2.3 ±1.1 mg/L respectively) (p<0.001). There was positive correlation between Galectin-3 level and CRP titre in both group I and II (p<0.001). Moreover, in group II, Galectin-3 level was positively correlated with serum creatinine (p<0.001), while inversely correlated with eGFR (p=0.001). There was no correlation between serum Galectin-3 level, and INR, ALT, AST and serum albumin in both group I and II.

Conclusions: In hepatitis C positive patients, galectin-3 concentrations increased with progressive renal impairment. Galectin-3 levels were not correlated with liver functions, suggesting the predictive value of galectin-3 for CKD development in hepatitis C positive patients.

Table 1 shows bias, precision and accuracy for all 3 equations compared to mGFR.

<table>
<thead>
<tr>
<th>Mean Bias (ml/ min/1.73m2)</th>
<th>SD of Differences</th>
<th>Mean Percentage Bias (%)</th>
<th>SD of prec. Bias</th>
<th>P10 (%)</th>
<th>P30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pöge, BTP</td>
<td>40.0</td>
<td>15.5</td>
<td>71.4</td>
<td>32.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Pöge, BTP/Crea</td>
<td>2.40</td>
<td>10.4</td>
<td>6.68</td>
<td>18.6</td>
<td>45.0</td>
</tr>
<tr>
<td>White, BTP/Crea</td>
<td>25.9</td>
<td>13.0</td>
<td>46.0</td>
<td>24.4</td>
<td>3.3</td>
</tr>
</tbody>
</table>
Fall in eGFR in ml/min/year was 3.9 (1.8-8). Neither baseline eGFR (p=0.13) nor presence of diabetes (p=0.72) affected this rate of decline. Time to death from eGFR 10ml/min was 276 days.

Conclusions: In this first longitudinal study of conservatively treated patients with advanced CKD, variable rate of decline of eGFR ranging between 1.8-8ml/year led to death of 55% of the cohort within the median follow up period of 15 months. Reassuringly the majority of patients died at their preferred place of terminal care (home/hospice) and were registered as deaths due to ESRD. Over 50% of patient’s eGFR decline was less than 4 ml/min per year which could translate into a life expectancy of >1 year without dialysis in these exceedingly frail individuals. Prospective study is ongoing to determine the quality of life of these patients treated conservatively.

SA-PO684
Estimating County-Level Prevalence of Chronic Kidney Disease (CKD) in the United States
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1Univ of Michigan, Ann Arbor, MI; 2Univ of California, San Francisco, CA; 3Centers for Disease Control and Prevention, Atlanta, GA.

Background: The prevalence of adult CKD in the US, estimated from 2005-2012 national survey data, is about 13%; however, those surveys are not designed to estimate rates for small regions. Applying a Bayesian multi-level model (BMLM), we estimated adult CKD prevalence in US counties using national and state surveys.

Methods: Data on self-reported CKD and risk-factors were obtained from (i) the National Health and Nutrition Examination Survey (NHANES 2005-2012; n=20,831), and (ii) the Behavior Risk Factor Surveillance System (BRFSS 2011; n=506,467); NHANES also provided CKD laboratory data. CKD was defined as estimated glomerular filtration rate 15-60 ml/min/m\(^2\) or urinary albumin-to-creatinine ratio >30mg/g. As BRFSS does not include laboratory data, CKD for each person in the BRFSS was multiply imputed using a logistic regression model trained on NHANES data. A BMLM that effectively combines information from neighboring counties was then fit to each imputed dataset to produce 10 sets of county-level estimates of CKD prevalence. These estimates were combined to obtain a final prevalence estimate for each county.

Results: Estimated county-level prevalence of CKD ranged from 12.3 to 27.8% (median: 18.8%) in 2011 (see map).

The standard deviation of these estimates ranged from 0.8 to 7%, and the coefficient of variation ranged from 5 to 32% of the estimate, suggesting good statistical precision.

Conclusions: We believe this is the first attempt to estimate CKD prevalence in U.S. counties. Our approach yields estimates with improved statistical precision for small counties, and is being used to study geographic variation in CKD burden across the U.S.

Funding: Other U.S. Government Support

SA-PO685
Overall CKD Prevalence in the U.S. Has Stabilized in Recent Years
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1UCSF [Drs. CY Hsu and NR Powe are Co-Senior Authors]; 2Univ of Michigan; 3CDC.

Background: ESRD incidence rates in the U.S. have stabilized recently. We sought to better understand trends in CKD prevalence in the U.S. between 2003 and 2004.

Methods: We examined data on adults from the National Health and Nutrition Examination Surveys from 1988 through 2012. We determined prevalence of stage 3-4 CKD (CKD-EPI equation eGFR 15-59 ml/min/1.73m\(^2\)) overall and by age, sex, race, and diabetes strata. We examined crude prevalence and adjusted prevalence for age, sex, race, and diabetes mellitus (diagnosed and undiagnosed). Restricted cubic splines were used to model trends. The years 2003-4 (last years with published literature) were compared to 2011-12 (most recent years of available data).

Results: Consistent with the published literature, we saw a rise in CKD prevalence from the late 1990s to the early 2000s. But since around 2003-4, adjusted and unadjusted prevalence of CKD have stabilized (Figure). This temporal trend was observed across age (p for interaction=0.11), sex (p=0.61) and racial-ethnic subgroups (p=0.07; although the trend in non-Hispanic blacks appeared to differ); and did not differ by diabetes status (p=0.17). There was no difference in overall stage 3-4 CKD prevalence comparing 2003-4 and 2011-12 (p=0.25). Similar results were seen with an expanded definition of CKD to include persons with higher eGFRs but albuminuria or used the MDRD equation.

Conclusions: Over the last decade in the U.S., there has been stabilization in the overall prevalence of stage 3-4 CKD, with a possible exception in blacks. This is contrast to what has been reported by prior studies analyzing older data but consistent with the observed stabilization of overall ESRD incidence. Efforts should be continued to implement reno-protective measures, especially in blacks.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

SA-PO686
Global Prevalence of Chronic Kidney Disease Categories 3-5 – A Systematic Review
Tazeen H. Jafar1, Priscley Nkouibert Assam,1,2 Fahad Javid Siddiqui,1 Shreyasee S. Pradhan,1 Edwin S.Y. Chan.2 1Duke-NUS Graduate Medical School, Singapore; 2Singapore Clinical Research Inst.

Background: Chronic kidney disease (CKD) has become a leading contributor to the global burden of disease. We performed a systematic review of published studies to estimate the global prevalence of CKD categories 3-5 defined by estimated glomerular filtration rate (eGFR) less than 60 ml/min/m\(^2\).

Methods: PubMed, EMBASE and Scopus were searched for studies published in English from 2003 to 2013 reporting prevalence of CKD categories 3-5 in the general population. Studies were included if they (1) sampled from the general adult population, (2) assessed CKD using CKD-EPI or MDRD Study equations; (3) not on renal replacement therapy.

Results: A total of 13,081 studies were considered, of which 566 studies from 54 countries assessed prevalence of CKD, and 284 studies were in unsellected general population. The global prevalence of CKD accounting for clustering among all adults aged 20 years or older are shown in table below

<table>
<thead>
<tr>
<th>CKD Category (C)</th>
<th>Countries</th>
<th>Studies</th>
<th>CKD Prevalence (95% CI)</th>
<th>Expected Number of Individuals with CKD (Millions) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 3 to 5 (eGFR &lt;60 ml/ min/1.73m(^2))</td>
<td>41</td>
<td>264</td>
<td>7.0 (5.2 to 9.3)</td>
<td>335.0 (249.0 to 446.0)</td>
</tr>
<tr>
<td>C 3 to 5 (20 to 65 yrs)</td>
<td>29</td>
<td>66</td>
<td>3.9 (2.1 to 7.2)</td>
<td>154.4 (80.0 to 289.0)</td>
</tr>
<tr>
<td>C 3 to 5 (65 + yrs)</td>
<td>25</td>
<td>58</td>
<td>28.9 (19.3 to 41.1)</td>
<td>229.6 (154.4 to 328.0)</td>
</tr>
<tr>
<td>C 3 only (eGFR 30-59 ml/m/1.73m(^2))</td>
<td>27</td>
<td>86</td>
<td>6.2 (4.2 to 9.3)</td>
<td>332.8 (220.9 to 446.0)</td>
</tr>
<tr>
<td>C 4 only (eGFR 15-29 ml/m/1.73m(^2))</td>
<td>18</td>
<td>50</td>
<td>0.3 (0.2 to 0.4)</td>
<td>14.4 (11.5 to 17.2)</td>
</tr>
<tr>
<td>C 5 only (eGFR&lt;15 ml/m/1.73m(^2))</td>
<td>15</td>
<td>29</td>
<td>0.1 (0.1 to 0.2)</td>
<td>5.2 (3.8 to 7.2)</td>
</tr>
</tbody>
</table>

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

784A
Prevalence of Chronic Kidney Disease with Diabetes and Glomerulonephritis in China

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Background: Diabetes is the leading cause of end stage kidney disease worldwide, while glomerulonephritis is thought to be the predominant cause in developing countries. However, the surging prevalence of diabetes in developing countries such as China may have substantial impact on the spectrum of chronic kidney disease.

Methods: A national in-patient database involving 19.5 million patient-records was used. Diagnoses of chronic kidney disease with diabetes (DM-CKD) as well as with glomerulonephritis (GN-CKD) were extracted from International Classification of Diseases-10 codes of the discharge diagnoses. Furthermore, a general population-based, national representative sample of 47 204 participants was used. Identification of DM-CKD and GN-CKD was based on laboratory tests and the questionnaire inquiring about medical history. Then the prevalence of DM-CKD and GN-CKD was compared among both hospitalized population and general population.

Results: Among 19.5 million hospitalized patients, 1.19% and 0.79% were identified as DM-CKD and with GN-CKD, respectively. Compared with GN-CKD, DM-CKD was associated with 7.2% (95% confidence interval [CI] 6.4-8.0%), 5.4% (95%CI 4.7-6.0%) and 59% (95%CI 46-73%) increase of costs, length-of-stay and in-hospital mortality, respectively. For general population, the prevalence of the GN-CKD is also exceeded by that of DM-CKD at 0.84% (95%CI 0.68-1.00%) and 1.23% (95% CI 1.06-1.41%), respectively. The estimated number of DM-CKD patients in China was 20.1 million.

Conclusions: Our study indicates that DM-CKD surpassed GN-CKD in both hospitalized population and general population, which marked a transition of kidney disease spectrum in China. Furthermore, DM-CKD is associated with substantial increased hospitalized population and general population, which marked a transition of kidney disease spectrum in China. Furthermore, DM-CKD is associated with substantial increased hospitalized population and general population.

Prevalence of Chronic Kidney Disease with Diabetes and Impaired Renal Function on the U.S.-Mexico Border: Role of Acculturation

Jonathan Michael Starkley, Kristina Vatcheva, Susan P. Fisher-Hoch, Joseph B. McCormick. Inst for Translational Sciences, Univ of Texas Medical Branch, Galveston, TX; Univ of Texas School of Public Health, Houston, TX.

Background: Mexican-Americans are the dominant Hispanic group in the US and face significant health disparities, including end-stage renal disease, diabetes and obesity. We characterize the quantity and associations of chronic kidney disease (CKD) in Cameron County, TX where almost 90% of the population is Hispanic and is predominantly zero or first generation Mexican-American.

Methods: The Cameron County Hispanic Cohort (CCHC) is a random sample of the Hispanic population on the southernmost point along the US-Mexico border. 1,777 participants with baseline serum creatinine measurements from 2003-2014 are included in this cross-sectional study. The glomerular filtration rate (eGFR) is estimated from serum creatinine and CKD is defined as eGFR < 60 ml/min/1.73 m². The weighted prevalence of CKD is estimated. A multivariate model of factors associated with CKD outcome.

Results: The prevalence of CKD is 6.0% in the CCHC and estimates the prevalence in Cameron County, TX. Stratified by gender, the prevalence in men and women is 6.9% and 4.0%, respectively. Multivariate analysis reveals significant associations of country of birth (OR 2.14, 95% CI [1.02, 4.46]) for those born in the US), hypertiglyceridemia (OR 2.72, 95% CI [1.41, 5.239]) and granulocyte count (OR 1.345, 95% CI [1.083, 1.708]) with CKD status after adjusting for age, gender, diabetes status, cardiovascular disease history, hypertension, smoking history, obesity, LDL and statin use.

Conclusions: The prevalence of CKD in the CCHC is higher than previous national estimates in Hispanics or Mexican-Americans. The data suggest that acculturation, triglycerides and inflammation are associated with CKD in Hispanics living on the US-Mexico border. More research is needed in Mexican-Americans to investigate CKD in this growing minority population.

Funding: Other NIH Support - K22 LM011869-01A1, National Library of Medicine (NLM) Starkey, Jonathan M (PI)

MD000170 P20 funded from the National Center on Minority Health and Health disparities (NCMHD) McCormick, Joseph (PI), and the Centers for Clinical and Translational Science Award U1L TR000371 from the National Center for Advancing Translational Science (NCATS)

Clinical and Translational Science Award (UL1TR000701)

SA-PO687

Validation of the Kidney Failure Risk Equation in Manitoba

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Background: Patients with chronic kidney disease (CKD) are at risk for progression to kidney failure. We previously developed the Kidney Failure Risk Equation (KFRE) to predict the progression of CKD to kidney failure in patients referred to nephrologists. This study aims to validate the KFRE in an unselected population in Manitoba, and to determine risk thresholds for clinical decision-making.

Methods: We included patients from the Diagnostic Services of Manitoba database with an eGFR < 60 ml/min/1.73 m² and a urinary albumin creatinine ratio measured between October 1, 2006 – March 31, 2007. Five year kidney failure risk was predicted using the 4-variable KFRE and compared with treated kidney failure events from the Manitoba Renal Program database. Sensitivity and specificity for KFRE thresholds (3% and 10% over 5 years) were then compared to eGFR thresholds (30 and 45 ml/min/1.73m²).

Results: 1,512 patients were included and 151 developed kidney failure over the 5-year follow-up period. The 4-variable KFRE more accurately predicted kidney failure when compared to eGFR alone (AUROCs 0.90 [95% confidence interval (CI) 0.88-0.92] for KFRE vs. 0.78 [95% CI 0.74-0.83] for eGFR). At a risk threshold of 3% over 5 years, the KFRE had a sensitivity of 97% and a specificity of 62%.

Conclusions: The KFRE is highly accurate at predicting 5-year risk of kidney failure in a population based sample of Manitobans with CKD Stages 3 to 5. Integration of the 4-variable KFRE into laboratory information systems should be considered.

Funding: Private Foundation Support

SA-PO690

A Risk Prediction Model of End-Stage Renal Disease in Type 1 Diabetes Using Urine MCP-1 as an Alternative Biomarker of ACR

Masayuki Yamamouchi, Monika A. Niewczas, Natalia Z. Nowak, Andrzej S. Krolewski. Genetics & Epidemiology, Joslin Diabetes Center, Boston, MA.

Background: There is a great need to develop risk prediction models to recruit patients at high risk of end-stage renal disease (ESRD) for clinical trials in patients with type 1 diabetes. We developed two models to predict progression of CKD 3 and 4 to ESRD in 5 years in patients with type 1 diabetes: “ACR model” that consists of patient’s age, eGFR, HbA1c and ACR, and “Urine MCP-1 model” that consists of the same markers but replacing ACR with urine MCP-1.

Methods: We identified 285 patients with type 1 diabetes and impaired renal function (eGFR < 60 ml/min/1.73 m²) from Joslin Proteinuria Cohort that was followed for 7 to 18 years to ascertain ESRD. We focused on the events within 5 years from enrollment. For the ACR model, the Cox model identified four baseline variables: age, eGFR, ACR, and HbA1c for the final model. For the urine MCP-1 model, urine MCP-1, age, eGFR and HbA1c were identified by the Cox model. Assigned point scores corresponded to each coefficient.

Results: 5-year risk of ESRD in the study group was 40.5%. In the ACR model, the variable with highest magnitude was eGFR<30, 4 points; followed by ACR<300, 2 points, HbA1c<7.5, 1 point; and age<45 years, 1 point, while in the urine MCP-1 model, the variable with highest magnitude was eGFR<30, 2 points; followed by urine MCP-1>545, 1 point; HbA1c<7.5, 1 point; and age<45 years, 1 point. The model with urine MCP-1 performed almost equal to the model with ACR (C statistic of 0.702 (0.556-0.831) vs. 0.719 (0.574-0.845)). Although the number of patients who developed ESRD in the high risk group in the urine MCP-1 model is smaller than in the ACR model, the incident rate of ESRD in the high risk group in the urine MCP-1 model was much higher than in the ACR model (291/1000 vs. 196/1000, p<0.001).

Conclusions: Using the risk score with urine MCP-1, we can identify a subgroup of patients at very high risk of ESRD.
SA-PO691
A Reliable Formula to Estimate 24-h Urine Sodium Excretion from Morning Fasting Urine in Patients with Chronic Kidney Disease
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Background: Estimated 24 hour urine sodium excretion based on spot urine has been proposed to replace 24 hour urine collection in epidemiologic studies. However, estimated sodium excretion has not been verified whether it is useful in patients with chronic kidney disease (CKD) as well as in interventional study. The aim is to evaluate the estimated sodium excretion in prospective low salt diet education study (ESPECIAL) cohort.

Methods: New formula was developed from baseline data of 228 CKD patients of ESPECIAL cohort using a multivariable linear regression and compared with previous three formulas from healthy population (Kawasaki, INTERSALT, Tanaka) and one from CKD patients (Nerbas) for the prediction of 24 hour sodium excretion after ARB treatment and low salt diet education.

Results: Among previous reported formulas, the estimation by Tanaka’s formula showed the smallest bias (estimated 144.3±46.5 vs. measured 154.1±69.6 mEq/day), but weak correlation (r=0.34). We developed new formula with improved bias (estimated 154.0±39.7 mEq/day) and correlation (r=0.56). New formula also showed the best correlation (r=0.57) with smallest bias (estimated ±3 mEq/day) even after ARB treatment, which did not show significant change of measured sodium excretion (156.3±70.6 mEq/day). Intensive low salt diet education elicited the significant decrease of measured sodium excretion (121.2±59.4 mEq/day). Although new formula also showed best correlation, any formula did not predict the amount of the decrease of measured sodium excretion.

Conclusions: We developed more reliable formula for estimating urine sodium excretion for CKD patients. However, our data suggests estimated sodium excretion could be applied for epidemiological study rather than low salt intervention study.

SA-PO692
Evaluation of Glycated Albumin for Glycemic Monitoring in Diabetic Nephropathy
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Background: Glycated albumin(GA) has been now widely used for the evaluation of blood glucose in diabetic nephropathy(DN) patients. However, the effect of proteinuria on GA should be taken into account, especially in patients with advanced DN.

Methods: A total of 621 diabetic nephropathy patients from year 2009 to 2014 were enrolled in the study. According to the 24h urinary protein(UP) output, subjects were divided into 3 groups defined as (1) microalbuminuria: UP=30-300mg/24h, (2) moderate albuminuria: UP=300-1000mg/24h, (3) macroalbuminuria: UP>1000mg/24h.

In all DN patients, the related factors of GA were fasting blood glucose(FBG), body mass index (BMI), 24 h UP. The multivariate regression equation was GA = 0.254FBG + 0.341BMI - 1.306UP (R2=0.375). There was no correlation between GA and 24h UP in patients with micro or moderate albuminuria. However, GA was found to be much lower and negatively correlated with 24h UP in DN patients with macroalbuminuria. Therefore, adjusted GA (adjGA) was applied for those subjects, taking 24h UP, serum albumin (SA) and the ratio of normal albumin metabolism days to total albumin metabolism days into account. adjGA= mGA×(1+3.75×UP/SA). As a result, GA value was increased after adjustment in DN macroalbuminuria group. The adjGA was also found only correlated with FBG and PBG, and had no relation with 24h UP and SA.

Conclusions: In diabetic nephropathy patients, blood glucose, serum albumin and 24h urinary protein output may serve as important factors for the evaluation of GA on glycemic level. GA tended to be underestimated in DN patients with macroalbuminuria. The adjGA may be a better way to objectively evaluate glycemic status in patients with advanced DN.
Discussions About CKD Between African Americans with High CKD Risks

Methods: As part of a baseline assessment for a randomized controlled trial, we characterized CKD awareness and perceived risk of CKD among AA patients with an eGFR<60 ml/min/1.73m2 and 60% had albuminuria alone. The majority (n=37, 71%) of patients were not aware of their CKD. Among these, 27% (n=10) considered themselves unlikely to develop CKD and 19% (n=7) were not concerned about developing CKD. CKD awareness was greater among patients with an eGFR<60 (vs. eGFR≥60) (adjusted percentages [95% CI]: 50% [19-81%] vs 35% [9-61%]). Conversely, patients with diabetes reported less CKD awareness than those without diabetes (AP [95% CI]: 53% [reference] and 10% [2-38%], respectively, p<0.0006). Perceived risk of CKD did not vary by patient characteristics.

Conclusions: Among AA patients with uncontrolled hypertension and CKD, awareness of CKD was low, with some patients unconcerned about developing CKD in the future. Strategies to improve recognition of CKD risks among AAs at high CKD risk are needed.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO696

Discussions About CKD Between African Americans with High CKD Risks and Their Primary Care Physicians

Methods: As part of a randomized controlled trial of African American (AA) patients with uncontrolled hypertension, we analyzed audio-recorded encounters between patients and their PCPs using the Roter Interaction Analysis System to characterize the occurrence of CKD discussions. Among 124 patients, the mean age was 58 years, 69% were female, 48% had diabetes, 35% had CKD (mean eGFR 83). The average visit length was 22 minutes. Patients and PCPs discussed CKD in 47% of visits and discussions more frequently occurred among patients with CKD (vs. without CKD) (66% vs. 36% respectively, p=0.002). Discussions were less common [Odds Ratio (95% CI) in visits of patients ≥ age 60 (vs. <60) (0.3 (0.1-0.8)], uncontrolled HTN (vs. controlled HTN): (0.75 [0.4-1.3]), male sex (vs. female): (0.6 [0.4-1.0]), and less common when visits were more (vs. less) patient-centered ([2.4 (1.0-5.8)] or when diabetes was (vs. was not) discussed [3.7 (1.5-9.4)]. Patient gender, comorbidity, and visit length did not predict discussions. Among patients with CKD (n=44), CKD discussions were also less common among patients ≥ age 60 ([1.0 (0.2-3.9)] or with higher eGFR [0.96 (0.92-1.0)].

Conclusions: AA patients at high risk of CKD and their PCPs discussed CKD in fewer than half of routine primary care visits. Efforts to improve the occurrence of CKD discussions during routine primary care encounters are needed.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO697

Primary Care Utilization Is Associated with Reduced Mortality Among Older Adults With CKD

Background: Routine primary care visits provide opportunities to identify and manage patients’ CKD risk factors and to provide preventative care. It is unclear how primary care utilization impacts clinical outcomes among older adults with CKD.

Methods: We quantified the association between primary care utilization and ESRD incidence or mortality among older US adults with CKD (in 2005-2006) using Medicare claims. We assessed (in 2006) patients’ primary care utilization (no visit at least one), other care utilization (nephrology care [no visit at least one], the total number of annual evaluation and management (E & M) visits with any type of provider), and patients’ comorbid conditions and sociodemographics. We used standard and cause-specific (accounting for competing risk of death) Cox proportional hazard models overall and stratified by age (65-74, 75-84, or ≥85 years) to estimate hazard ratios (HRs) for ESRD or mortality.

Results: Among 106,765 patients, most (79%) had at least one primary care visit in 2006, and 21% had at least one nephrology visit. The median number of ambulatory & E&M visits was 10. Compared to patients with no primary care visits, patients with at least one visit were younger (78 vs. 80 mean years, p<0.001), less likely African American (10 vs. 14%, p<0.001), and had a greater prevalence of diabetes (46 vs. 42%, p<0.001), hypertension (88 vs. 78%, p<0.001), or coronary artery disease (74 vs. 72%, p<0.001). Overall, we report 24.26 patients developed ESRD and 45.059 died. Primary care utilization was not associated with ESRD incidence. However, compared to patients with no primary care visits, patients with at least one visit had a lower risk of death [HR (95%CI): 0.73 (0.72-0.75)] overall and in age stratified models.

Conclusions: Primary care utilization was not associated with lower ESRD risk, but it was associated with a lower risk of death among older adults with CKD. Efforts to improve the engagement of primary care providers in the care of patients with CKD represent an important strategy to improve the health of this high risk population.

Funding: NIDDK Support

SA-PO698

Routine Use of Health Care Among High-Risk African Americans at Risk of CKD

Background: Engagement in routine health care (RHC) is a key strategy to decrease health inequities among African Americans (AAs) at high risk of developing CKD or CKD complications. We examined demographic, attitudinal and socio-cultural factors associated with RHC among high-risk AAs at risk of CKD incidence or progression.

Methods: We quantified the prevalence of RHC (physical exam ~1 year prior) use among AA Jackson Heart Study (JHS) baseline participants (from 2000-2004) with hypertension (HTN) or diabetes. We identified demographic, attitudinal (e.g., perceived discrimination, anger and hostility, stress, trust in health providers) and educational (i.e., CKD awareness) factors independently associated with RHC use. Those missing demographic or attitudinal data were excluded.

Results: Of 5301 JHS participants, 1152 met inclusion criteria. Most (n=999, 79%) reported RHC use. Rates of RHC were similar in those with and without CKD (22% vs. 23%). Participants not using RHC (vs. using) were more likely to be < 55 years of age (44 vs. 38%), not married (43% vs. 36%), male (45 vs. 38%), uncontrolled hypertension (HTN) (9% vs. 5%), and had a lower degree of trust in their health provider (80% vs. 95%), more frequently reported difficulty obtaining health services (17% vs. 8%), and less frequently reported provider satisfaction (91% vs. 98%), all p<0.05. In multivariable models, not using RHC was associated with age <55 OR 1.75 (95% CI 1.25-2.5), male sex (OR 1.55 [1.2-2.16]), Hispanic ethnicity (OR 1.63 [1.122-2.34]), no HTN (OR 2.14 [1.34-3.41]), lower provider trust (OR 3.27 [1.61-6.65]) and less anger and hostility (OR 1.55 [1.1-2.1]).

Conclusions: Among high-risk AAs in the JHS, younger participants and males were less likely to use RHC. Those with low trust were also less likely to use RHC. Efforts to address health risks among high-risk AAs should target those using less RHC and consider attitudinal barriers to RHC.

Funding: NIDDK Support

SA-PO699

Development of a Question Prompt Sheet for Patients with Chronic Kidney Disease

Background: Patients with chronic kidney disease (CKD) commonly have unmet information needs. Greater patient participation in healthcare discussions can address these needs, and is associated with improved health outcomes. A question prompt sheet (QPS), a list of questions to prompt discussion, has been shown to increase patient participation in other chronic disease discussions; however, no QPS has been developed for CKD patients.

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

787A
Methods: We conducted a 2-phase cross-sectional study involving semi-structured telephone interviews with an initial 67-item QPS targeted to patients with moderate CKD. Patients with an estimated glomerular filtration rate <60ml/min/1.73m2, on dialysis, or with a transplant were recruited from a single VA nephrology clinic. Phase 1 interviews included 17 open-ended questions assessing patients’ CKD information needs. Responses were quality coded into an initial 67-item QPS. Phase 2 participants reviewed pre-nailed QPS to rate the importance of asking each question on a 5-point Likert scale, provide open-ended feedback, and rate their willingness to use a CKD-QPS. Question item responses were refined and reduce QPS questions.

A total of 76 participants completed interviews (phase 1: n=32, phase 2: n=44). Most were male (96%), non-Hispanic white (68%), and mean age was 66 years. Patients desired more information about CKD, particularly regarding self-care techniques, dialysis/transplant, and CKD complications. The final QPS tool included 37-questions divided into 10 CKD subtopics (e.g., CKD definitions, causes, impact, monitoring, labs, self-care, treatment, dialysis, transplant, managing comorbid conditions). Most patients (91%) reported being ‘completely’ or ‘very’ willing to use a CKD-QPS in future doctor visits.

Conclusions: CKD patients have unmet information needs and wish to use a CKD-QPS. Further research is needed to assess whether our CKD-QPS effectively addresses patients’ information needs, enhances doctor-patient communication, and improves health outcomes.

Funding: Veterans Administration Support

SA-PO700

Medication Burden and Safety in Veterans with Chronic Kidney Disease

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Background: Veterans are at exceptionally high risk for chronic kidney disease (CKD) and other chronic health conditions. Pharmacologic treatments are a core aspect of CKD disease management. We characterized medication burden and safety and their relationship to CKD severity among elderly Veterans.

Methods: Using national VA databases, we included all female and a random 10% sample of male VA healthcare users who were <65 years old. We characterized the average number of medications, frequency of contraindicated medications, and occurrence of drug-drug interactions. CKD was defined by estimated glomerular filtration rate (eGFR) in 2008 and classified according to conventional eGFR-based severity groups. A non-CKD comparison was used (eGFR >=60 ml/min/1.73m2). Medications were identified in calendar year 2009 from VA utilization data and Medicare Part D claims.

Results: Among a final cohort of 96,317 Veterans, 47% had CKD (mean age=79.8, male 81%, non-black=93%, hypertension=90%, diabetes=33%). Mean medications increased with CKD severity: 8.5(eGFR =>60), 9.6 (eGFR 30-59), 11.7 (eGFR<15-29), 12.5 (eGFR <15). After adjusting for demographic characteristics, CKD stage 3, 4, and 5 took 1.3, 1.3, and 3.6 more medications, respectively, compared to the non-CKD group (p-value<0.0001). Contraindicated medications were often prescribed to patients with an eGFR<30ml/min/1.73m2 and included bisphosphonates (5%) and nonsteroidal anti-inflammatory drugs (4%). Concerning drug-drug interactions with an eGFR<60ml/min/1.73m2 included: sedatives/opioids (3.8%), ace inhibitor-angiotensin receptor blocker (1.6%), statins-diltiazem or verapamil (5.1%).

Conclusions: Greater severity of CKD was independently associated with an increasing number of medications among elderly Veterans. Medications that were contraindicated in CKD and concerning drug-drug interactions were commonly prescribed. Increased awareness and interventions are needed to improve medication management and safety in Veterans with CKD.

Funding: Veterans Administration Support

SA-PO701

Illicit Drug Use and Chronic Kidney Disease in an Urban Population

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Background: Opioid and cocaine use have been associated with risk of ESRD in retrospective studies, however, the association of illicit drug use with chronic kidney disease (CKD) has not been well-examined in prospective studies. Our objective was to determine the association of illicit drug use with reduced kidney function, albuminuria and rapid kidney function decline (KFD) among a cohort of urban-dwelling adults.

Methods: Our study included 2,286 Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study participants who are community-dwelling African American and white adults from 12 neighborhoods in Baltimore MD. We used logistic regression to examine whether opioid or cocaine use (defined as ≥ 5 lifetime uses of either drug) was associated with baseline reduced eGFR (<60 ml/min/1.73m2) by CKD-EPI), baseline albuminuria (albumin-to-creatinine ratio >30mg/g) or rapid KFD (eGFR decline of >5% per year over a median of 4.7 years of follow up).

Results: Participants’ mean age was 48 years, 57% were African American, 15% reported opioid use, and 22% reported cocaine use. Those reporting illicit drug use (opiod or cocaine) were more likely to be male, African American, living in poverty and/or uninsured, and tobacco use, problem drinking, and hepatitis C. The association of illicit drug use was not significant with any of the outcomes (P<0.01 for all variables). Our adjusted models included those variables above, and age, diabetes and hypertension. A total of 5.3% of illicit drug users had reduced eGFR compared to 5.0% of non-users (NS). A total of 5.9% of illicit drug users died during follow-up compared to 3.8% of non-users (P=0.03).

Conclusions: Illicit drug use was associated with prevalent reduced eGFR and albuminuria, but not rapid KFD. Illicit drug use may be an important risk factor for CKD in urban populations.

Funding: NIDDK Support, Other NIH Support - Intramural study of the National Institute on Aging

SA-PO702

A Tailored, Interactive Mobile Health Communication Application for Patients with Chronic Kidney Disease: Development and Feasibility Assessment

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Background: Chronic kidney disease (CKD) is an increasingly common chronic condition whose prognosis can be improved by patient involvement and self-management. Patient involvement can be fostered by web-based Interactive Mobile Health Communication Applications (IMHCAs) combining health information with decision support, social support and/or behavior change support. Tailoring content and tone of IMHCAs to the individual patient’s needs might improve their effectiveness.

Methods: A tailored, IMHCAs was developed by collaborative profession (nephrologist, nurse, research fellow, web developer). The effectiveness and usage of the tailored IMHCAs were tested against the control arm without access to this IMHA in a small-scale single-blinded randomized trial. The content covers information on CKD, its complications and sequelae, and its treatment options including health behavior and dietary guidance. In the intervention group the content is delivered in dialogue format, tailored to relevant patient characteristics (the stage of CKD and the Etiology). Eighty patients (forty patients at each arm) with stage 3-5 CKD were enrolled in the study. The data were collected directly after the first visit, and at 3-month follow-up.

Results: There were no difference between the two groups as to the age, gender, CKD stage and blood pressure. Three months after system use, participants using the tailored system displayed significantly more knowledge(P=0.001), better blood pressure compliance rate (P=0.02) and improved dietary behavior, mainly regarding low protein and enough calories (P=0.003).

Conclusions: This is the first tailored IMHCAs in China. Our data demonstrated that implementation of IMHCAs into standard practice is feasible. Suggested developments will augment reported strengths to inform ongoing testing in the wider China network of units.

Funding: Government Support - Non-U.S.

SA-PO703

Evaluation of Clinical Pharmacy Services in the Management of Kidney Disease

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Background: Chronic kidney disease (CKD) and end stage renal disease (ESRD) place a significant burden on healthcare systems and is the focus of national health initiatives. Management of CKD requires a multidisciplinary approach to maximize outcomes. Studies support the impact of clinical pharmacists (CP) in medication management, but studies demonstrating the significance of a CP as part of a multidisciplinary approach to management of AKI and CKD/ESRD are lacking. This study evaluates the effectiveness of pharmacy services in the setting of a multidisciplinary approach to the management of AKI and CKD/ESRD.

Methods: Interventions by a CP in the inpatient setting were collected from 12/1/2010 to 11/1/2011 as part of Nephrol Consults. Interventions were categorized as: drug interaction, dose/frequency adjustment, untreated diagnosis, adverse reactions, duplication of therapy, and other. Cost avoidance from these interventions were calculated. Outpatient pharmacy patient encounters were monitored from 1/1/2008 to 12/31/2014 as patient visits or interventions in hemodialysis (HD), peritoneal dialysis (PD), erythropoietin stimulating agent (ESA) clinic, and renal access clinic. CPs were involved in the management of anemia, hyperparathyroidism, renal bone disease, transplant, dialysis related infections, pharmacokinetic drug monitoring, medication reconciliation and patient counseling.

Results: Most of the 440 interventional interventions were dose adjustments for renal function and medication therapy for untreated diagnoses during AKI. Inpatient interventions by a CP resulted in $706,911 in cost avoidance. HD and PD encounters by a CP increased from 241 in 2008 to over 1,400 since 2011. Patient visits in the ESA/anaemia clinic increased from 185 in 2008 to near 300 in 2014. Encounters in the renal access clinic increased from 19 in 2008 to near 300 in 2014.

Conclusions: The expansion of pharmacy services in nephrology at Veterans Affairs San Diego Healthcare System has resulted in the improvement in the quality of care provided to patients with AKI, CKD or ESRD with significant cost avoidance. Clinical pharmacists play a significant role in the multidisciplinary approach to the management of CKD/ESRD.
SA-PO704
Views and Practice Patterns of Dialysis Medical Directors Towards End-of-Life Decision Making for Patients with End-Stage Renal Disease

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Background: Nephrologists frequently engage in end-of-life decision making for patients with end-stage renal disease (ESRD). Patients with ESRD report infrequent end-of-life discussions and nephrology trainees report feeling unprepared for end-of-life decision making, but the views of dialysis medical directors have not been studied. Our objective is to understand dialysis medical directors’ views and practice patterns on end-of-life decision making for patients with ESRD.

Methods: We administered questionnaires to dialysis medical directors during medical director meetings of three different dialysis organizations in 2013. Survey questions corresponded to recommendations from the Renal Physicians Association clinical practice guidelines on initiation and withdrawal of dialysis.

Results: There were 121 medical director respondents from 28 states. The majority of respondents felt “very prepared” (66%) or “somewhat prepared” (29%) to participate in end-of-life decisions and most (80%) endorsed a model of shared decision-making. If asked to do so, 70% of the respondents provided prognostic information “often” or “nearly always”. For patients with a poor prognosis, 36% of respondents would offer a time-limited trial of dialysis “often” or “nearly always”, while 56% of respondents would suggest withdrawal from dialysis “often” or “nearly always” for those with a poor prognosis currently receiving dialysis therapy. Patient resistance and fear of taking away hope were the most commonly cited barriers to end-of-life discussions.

Conclusions: Views and reported practice patterns of medical directors are consistent with clinical practice guidelines for end-of-life decision making for patients with ESRD but inconsistent with patient perceptions.

Funding: NIDDK Support

SA-PO705
Emergency Department Utilization Among United States ESRD Patients

Brendan P. Lovasik, Rebecca H. Zhang, Taylor A. Melanson, Stephen O. Pastan, Rachel E. Patzer. Emory Univ, Atlanta, GA.

Background: Single center studies suggest that ESRD patients have a high rate of emergency department (ED) utilization, with 0.9-2.4 ED visits/patient-year. Prior studies show that ESRD is a stronger risk factor for ED use than heart failure, lung disease, or cancer. However, ED utilization among a national ESRD patient population has not been examined.

Methods: We examined a cohort of 788,182 incident adult ESRD patients in the United States Renal Data System from 2005-2011. ED utilization was identified using CPT codes 99281-5 (Severity Levels 1-5) and 99291 (Critical Care) by American College of Emergency Physicians guidelines. ED and hospital admission, diagnosis, and procedures were obtained from the USRDS and Medicare Physician/Supplier and Inpatient databases for Medicare Part A/B claims.

Results: In the first year of ESRD diagnosis, 1,143,372 ED visits were observed for 480,176 unique ESRD patients. 77% of ESRD patients used the ED within the first year ED visits/patient-year. The national range was 1 to 172 ED visits per year with median 2 visits (interquartile range 1-4 visits) and 95th percentile 8 visits.

Conclusions: The top 5% of patients accounted for 80.4% of ED visits, and 7 patients utilized the ED over 100 times in their first ESRD year. Nearly half (46.0%) of ED visits were coded as a Severity Level 5, with 9.6% coded as Critical Care emergencies. 15.4% of ESRD patients over 100 times in their first ESRD year. Nearly half (46.0%) of ED visits were coded as a severity level 5, with 9.6% coded as critical care emergencies. 15.4% of ESRD patients over 100 times in their first ESRD year.

Funding: NIDDK Support

SA-PO706
Impact of Evidence-Based Clinical Care on Major Adverse Clinical Events in Patients with Clinically Significant Proteinuria: A Population-Based Retrospective Cohort Study

Julius Oluolu Oke,1 Bilal Qarni,2 Timothy Olusegun Olamirewa,2 Aminu K. Bello.1 1Univ of Alberta; 2Univ of Ilorin, Nigeria.

Background: Proteinuria is an important prognostic marker for cardiovascular (CV) and renal events. Most studies of quality of care (QoC) in chronic kidney disease (CKD) have focused on other markers for risk stratification and outcomes. We hypothesized that in proteinuric CKD, markers of good quality care will be associated with lower risk of adverse clinical outcomes (all-cause mortality, all-cause hospitalization, CV and renal outcomes).

Methods: We used a population-based cohort of patients with significant proteinuria (albumin:creatinine ratio (ACR) ≥60 mg/mmol, protein:creatinine ratio (PCR) ≥100 mg/mmol or protein + 3+ on dipstick) to evaluate current patterns of evidence-based care and association with outcomes. Markers of good quality care were defined as nephrology referral, relevant laboratory testing and appropriate medication use (ACEI/ARBs; statins).

Results: The cohort was followed from their index date until March 2009 for outcomes of all-cause mortality, hospitalization, CV and renal events. The associations between quality of care markers and outcomes were estimated using Cox proportional hazards models.

Results: Of the 71, 660 with at least 1 or 2 proteinuria measurements, 16,204 (22.6%) had significant proteinuria. At follow-up, receipt of good quality care (1) timely referral, (2) JHbA1c testing, (3) use of ACEI/ARBs, and (4) use of statins) was associated with reduced risk of mortality: 0.67 (0.59-0.75), 0.52 (0.46-0.59), 0.68 (0.60-0.74), and 0.63 (0.57-0.69), and all-cause hospitalization: 0.85 (0.80-0.93) 0.65 (0.59-0.72) 0.93 (0.87-0.99) and 0.82 (0.77-0.88) respectively. There were no statistically significant associations with the risk of CV and renal events.

Conclusions: This study examined the link between evidence-based treatment and clinical outcomes in an especially high-risk population with CKD. Good quality care impacts mortality risk and all-cause hospitalization, and reduced risk of hospitalization. The impact of QoC on renal and cardiovascular events is less clear. The findings would justify future interventions to increase uptake of such treatments in patients with proteinuric CKD.

Funding: NIDDK Support, Private Foundation Support

SA-PO707
APOL1 Risk Alleles and Risks of Cardiovascular Disease in Children with Focal Segmental Glomerulosclerosis (FGS)

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Background: APOL1 renal risk alleles are a major cause of glomerular disease in African Americans (AA). It is controversial as to whether individuals with high risk (HR) APOL1 genotypes (2 risk alleles) are at risk for atherosclerotic heart disease, and association with left ventricular hypertrophy (LVH) has not been explored. It is unclear whether children with focal segmental glomerulosclerosis (FSGS) and HR APOL1 are at increased cardiovascular risk.

Methods: Self-identified AA children with FSGS in CKD study cohort were genotyped for APOL1 renal risk variants: G1 (rs73858531, S342G) and G2 (rs71785313, Y388S-389 deletion), and compared to non-AA children with FSGS, none with HR.

Results: Of the 71 children with FSGS, 36 were non-AA, and 25 were AA with HR. APOL1 compared to non-AA, children with HR APOL1 developed FSGS at a later age, 11.5 (IQR: 9.5, 12.5) vs 6 (IQR: 2.5, 11) years, p=0.005. There were no differences in GFR, hemoglobin, iPTH, calcium-phosphate product, or CRP. HR APOL1 subjects had a higher prevalence of uncontrolled hypertension (52% vs 28%, p=0.06) and a lower prevalence of nephrotic range proteinuria (13% vs 43%, p=0.02). Subjects with HR APOL1 had higher left ventricular mass index (41 [28, 53] vs 30 [27, 33] g/m2.7, p=0.01) and a higher prevalence of LVH (53% vs 12%, p<0.009) compared to non-AA children with FSGS.

Conclusions: Children with FSGS and HR APOL1 have later onset kidney disease and are at higher risk for cardiovascular disease than non-AA.

Funding: NIDDK Support, Private Foundation Support

SA-PO708
Trends in Burden of Out-of-Pocket Expenses in United States Adults with Kidney Disease from 2002-2011

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Background: High out-of-pocket (OOP) burden negatively impacts health care access and outcomes. Studies examining high OOP burden in the general population exists however no studies have examined OOP healthcare burden in people with kidney disease (KD). This study examined trends in high OOP healthcare in people with KD while concurrently evaluating the impact of insurance status and income category on high OOP burden.

Methods: We analyzed 2,966 adults aged 18-64 years with kidney disease using the Medical Expenditure Panel Survey-MEPS. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157 - acute and unspecified renal failure; 158 - chronic renal failure; 160 - calculus or urinary tract and; 161

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

789A
SA-PO709 Health Disparities and Increased Risk of Developing End Stage Renal Disease in Patients With Chronic Kidney Disease Alejandro Ferrer, Ritika Sharma, Candace D. Grant, Ronak Patel, Monika Wadhwani, Vladimir Liberman, Shanza Mujeeb, Sairah Sharif, Shayan Shirazian, Nobuyuki (Bill) Liberman, Shanza Mujeeb, Sairah Sharif, Shayan Shirazian, Nobuyuki (Bill) Liberman, Shanza Mujeeb, Sairah Sharif, Shayan Shirazian, Nobuyuki (Bill) Liberman.

Background: Health disparities occur in groups of people that experience suboptimal care based on their social, economic, and/or environmental disadvantage. Identifying how these disparities affect the risk of chronic kidney disease (CKD) progression to end stage renal disease (ESRD) can hopefully lead to a reduction in these health inequities and improve clinical outcomes for all CKD patients. We examined health disparities and the risk of ESRD using patient-specific and community-specific variables.

Methods: We studied a cross-section of 623 patients with stage 3 and 4 CKD and estimated their 2- and 5-year risk of ESRD using the method of Tangri et al. (JAMA 2011; 305:1553–1559). The U.S. Census Bureau Community Survey was used to obtain patient zip code-specific data including percent foreign born, percent below the poverty level, median household income, and percentage graduating high school. We did a multivariable generalized linear analysis on the outcome variables of the 2 and 5 year risk of ESRD.

Results: Lower household income was associated with a higher risk of ESRD at 2 and 5 years (p<0.05). There was a trend towards a higher risk of ESRD amongst patients from zip codes with higher poverty rates and lower education levels. Being single, including by divorce and separation but not by being widowed, was associated with a significantly higher risk of ESRD. We also found that patients on Medicaid and patients with private insurance or self pay had a significantly higher risk of ESRD compared to those on Medicare.

Conclusions: Our findings suggest that there are substantial health disparities related to CKD and the risk of ESRD. Some of these disparities are patient-specific but others appear to be related to variables associated with the community where they reside. This suggests that evaluation of patient-specific as well as community-specific variables might help to better individualize CKD care and improve our ability to identify and treat the patient at increased risk of developing ESRD.

SA-PO710 Impact of Timely AV Fistula Placement on Resource Utilization After Initiation of Dialysis Edwin J Anand, 1 Kabir Jalal, 1 Laura L. Argauer, 2 Brian M. Murray, 1 Pradeep Arora, 3 Roco C. Venuto. 1 Medicine, SUNY at Buffalo, Buffalo, NY; 2Computer Task Group, Buffalo, NY; 3Epidemiology, SUNY at Buffalo, Buffalo, NY.

Background: Maintenance dialysis is ideally initiated in the outpatient setting with a permanent access. This requires advance planning and of care between nephrologists, and access surgeons. The costs associated with ‘crash’ initiation of dialysis is anticipated to be high. In this observational study, we studied the hospitalization rates and costs of care in the 12 months following dialysis initiation between patients who started dialysis in an ideal manner versus sub-optimally.

Methods: Claims and laboratory data from a large, regional insurance company covering half a million patients between January 2001 and May 2014 were reviewed. 32,121 patients were identified to have CKD (at least one eGFR <60 ml/min/1.73 m^3). Of these, 422 patients developed ESRD during the observed period. We defined a ‘crash’ if after the first instance of dialysis was in an inpatient setting, provided they had at least one eGFR value indicative of CKD before their first dialysis. Univariate and multivariate analyses were performed to analyze the effect of ‘crash’ on hospitalization and costs for 12 months following initial dialysis.

Results: 422 patients were started on dialysis in the above period. 257 patients (61%) had a crash start of dialysis. 86 patients (20%) had a fistula prior to dialysis. Compared to patients who did not crash, patients who crashed were older (p<0.0001), had a higher hospitalization rate in the one year period (p=0.0089). Multivariate analysis confirmed that patients who crashed had a significantly higher hospitalization rate in the one year period following dialysis (p=0.0067). Patients with a fistula in place prior to dialysis experienced fewer hospitalizations (p=0.0377). Cost in the first year was also higher in patients who had a ‘crash’ without a fistula (p=0.0181). The cost advantage of having a fistula decreased with increasing age (0.0402).

Conclusions: Dialysis ‘crash’ results in increased morbidity and resource utilization. Coordination of care and timely access creation should reduce hospitalization and costs.
Conclusions: Our study showed effectiveness of targeted interactive workshops to improve the recognition of CKD and its complications. Intelectualizing the taught concepts by residents did not translate to improved patient care. Declining retention of core concepts at 12-week testing indicates the need for ongoing reinforcement sessions. Continued education including online resources utilization is warranted as opposed to annual core-lectures provided by most training programs.

SA-PO713

Evaluating Progress of Healthy People 2020 Chronic Kidney Disease Objectives: Are We There Yet? Aseel Ryskulova,1 Lawrence Agodoa,2 Paul W. Eggers,3 Kevin C. Abbott.2 1NCHS, CDC, 2NIDDK, NIH.

Background: Chronic Kidney Disease (CKD) is a significant public health problem in the U.S. and a major source of disability, poor quality of life, and premature death for those afflicted. CKD and End-Stage Renal Disease (ESRD), the final stage of the CKD, exact a high economic price. In 2012 ESRD costs exceeded $49 billion dollars including 34 billion (about 20%) of total Medicare expenditures. An estimated 11.5% of adults ages 20 or older had physiological evidence of CKD determined from data collected through the 2001-06 National Health and Nutrition Examination Survey (NHANES). Each year in the United States, more than 115,000 people are diagnosed with ESRD.

Methods: Reflecting the importance of CKD, 24 CKD objectives area were included in the Healthy People 2020 (HP2020) national health goals to reduce new cases of CKD and related complications, disability, death, and economic costs. CKD objectives are focused on improving cardiovascular care in patients with CKD; increasing the proportion of patients with CKD and diabetes who received recommended treatment and evaluation; reducing death rate and percentage of U.S. population with CKD; and increasing CKD awareness in persons with impaired renal function. All CKD objectives are measurable, having at least one data point from national data systems including the NHANES, National Death Index, and U.S. Renal Data System.

Results: In 2015, 14 objectives had met their target (n=9) or showed improvement (n=5). Six objectives showed little or no significant change. Two objectives: increase the proportion of persons with diabetes and CKD who received recommended medical treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and increase the proportion of patients receiving a kidney transplant within 3 years of ESRD, moved away from the target. The remaining 2 objectives were not evaluated as they were informational with no target set. Disparities persisted by sex, race/ethnicity, and SES status.

Conclusions: The presentation will cover the most recent national and state data for selected CKD objectives and provide an overview of the HP2020 and data search using the HP2020 website.

SA-PO714

Telenephrology for the Remote Management of Chronic Kidney Disease (CKD): A Retrospective Cohort Study Rajeev Rohatgi,1 Judy K. Tan,2 Anitha Mehrrotta,3 Medicine, James J. Peters VAMC, Bronx, NY; 2Medicine, Icahn School of Medicine, New York, NY.

Background: Veterans with CKD who live in the Hudson Valley Veterans Affair Medical Center (HVVAMC) catchment area travel to the Bronx VAMC for nephrology care. Analysis of the no-show and cancellation frequencies for these renal appointments exceeded 50%, likely due to the distance between HVVAMC and the Bronx (60 miles).

Methods: We hypothesized that patients managed via a telenephrology service, where patients visit their local VA and are evaluated remotely via videoconference by a Bronx VA nephrologist, would exhibit comparable clinical outcomes and visit compliance as patients with CKD and diabetes who received recommended medical treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and increase the proportion of patients receiving a kidney transplant within 3 years of ESRD, moved away from the target. The remaining 2 objectives were not evaluated as they were informational with no target set. Disparities persisted by sex, race/ethnicity, and SES status.

Results: Characteristics of the groups were similar (initial creatinine [Cr], eGFR, distribution of CKD stage, urine protein) except for race and probable cause of CKD. Prior to the telenephrology service, 53.1% of scheduled visits of HVVAMC patients to the Bronx VAMC renal clinic were either cancelled or “no-shows” and this was reduced to nearly half (29.2%) after instituting telenephrology (p<0.001). Moreover, the frequency of attending appointments was greater in the telenephrology cohort (70.8%) vs. Bronx VA cohort (61.8%) which was driven by a greater frequency of cancelled visits in the Bronx VA (27.9%) vs. the telenephrology group (15.8%). The incidence of a composite outcome of doubling of Cr, ESRD and/or death was similar between both groups (Figure 1). The change in blood pressure and eGFR from baseline to 1 year was also similar.

Conclusions: Telenephrology is not inferior to in-person care for the management of CKD and may be superior for visit compliance. Application of this technology is a promising method to deliver care to CKD patients.

Funding: Veterans Administration Support

SA-PO715

Engaging Urban African Americans at Risk for CKD in Discussions About Their Diet Deidra C. Cressy,1 Debra L. Roter,1 Raquel C. Greer,1 Yang Liu,1 Patti Ephraim,1 Jessica M. Ameling,1 Kimberly Gudzune,1 Lisa A. Cooper,1 L. Ebony Boulware.2 1Johns Hopkins U., Baltimore, MD; 2Duke U., Durham, NC.

Background: Patient-physician discussions about diet are recommended in primary care to decrease patients’ health risks, including CKD. However, little is known about the frequency of diet discussions or factors influencing them among African Americans (AAs) at increased CKD risk.

Methods: In a randomized trial of urban AAs with uncontrolled hypertension, we audio-recorded patients’ routine visits with their primary care physicians (PCPs) at the first visit following enrollment. We transcribed audio recordings, and quantified the frequency of patient-physician discussions about diet during visits. We marked transcripts for discussions of 36 dietary terms (e.g. sodium, weight, sweets). We also assessed patterns of patient-physician communication, including patient centeredness (degree to which the discussion focused on the patient’s psychosocial and lifestyle context), during each encounter using the Roter Interaction Analysis System. We identified factors independently associated with discussions of diet using logistic regression.

Results: Among 127 participants, mean age was 58 years and 70% were female. Average PCP visit lasted 25 minutes. Diet was discussed in 73% of visits, but only included discussion of the Dietary Approaches to Stop Hypertension (DASH) diet in 12%, weight/obesity in 36%, and cholesterol in 39% of visits. Independent predictors of diet discussions (odds ratio, 95% confidence interval) were patient centeredness score ratio (7.5, 1.3-41.9), annual income (3.8, 1.4-10.5 comparing ≥$10k vs <$10k), and visit length (1.07, 1.02-1.1 for each minute increment). Patient age, gender, literacy, comorbid disease burden, obesity, diabetes nor CKD status predicted discussions.

Conclusions: Discussions of diet in primary care were frequent, and they were more likely to occur when visits were longer, were centered on patient priorities, and were attended by patients with incomes ≥$10k. Diet discussions focused on various topics, but infrequently on the recommended DASH diet or other key aspects of dietary modification. Improvements in the content of diet discussions among African Americans at risk for CKD may be needed.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO716


Background: The Miami VA Healthcare System serves veterans in three South Florida counties: Miami-Dade, Broward and Monroe, with an estimated veteran population of 175,000. To overcome geographical barriers and facilitate the access to nephrology evaluations, we implemented Provider-Patient Tele-Nephrology using secured videoconferencing.

Methods: A retrospective and descriptive study design was used to evaluate the effect of the Tele-Nephrology clinic intervention. Multiple clinical indicators were included in the analysis: blood pressure control, stabilization of the renal function and electrolyte/metabolic control. 101 patients that were evaluated in the clinic between 2013-2015 were included and the indicators were collected retrospectively.

Results: 101 patients were included, 95% male (n=96) and 5% female (n=5). The mean age was 65.5 years. 50 patients had Chronic Kidney Disease (CKD) stage III (69.5%), 14 patients had CKD stage IV (13%), 8 patients had CKD stage II (7.9%). A one-way analysis of variance analysis (ANOVA) between subjects was conducted and showed that the effect
of the Tele-Nephrology clinic intervention reducing blood pressure was statistically significant (systolic blood pressure P-value < 0.0001). Renal function stabilized but the creatinine changes over time were not statistically significant (P-value: 0.50).

Subgroup analysis of individuals with eGFR < 30 ml/min or on dialysis reduced the differences in age and SPPB between the groups, but demonstrated no significant difference to change in SPPB over time. HRQL did not change significantly between groups. Proportion of individuals with improved PA over 1-year was 36% and 38% in EC and CG, respectively (p = 0.82).

Conclusions: In this study, an exercise counseling clinic had no significant effect physical function as measured by SPPB at 1-year, suggesting that exercise counseling alone is inadequate to improve physical function in CKD.

SA-PO718

Ideal and Actual Support of Renal Replacement Therapy Modality Selection Patients with Chronic Kidney Disease: A Nationwide Survey in Japan

Shiho Kosaka,1 Shinichi Nishi,2 Yugo Shibagaki,3 Junichi Hoshino,4 Kazuo Takahashi,5 Yukiko Katagiri,6 Chika Murayama,7 Yuka Funaki.1 1Sophia Univ; Tokyo, Japan; 2Kobe Univ Graduate School of Medicine, Kobe, Japan; 3St. Marianna Univ Hospital, Kawasaki, Japan; 4Toranomon Hospital, Tokyo, Japan; 5Fujita Health Univ School of Medicine, Toyoake, Japan.

Background: Optimal renal replacement therapy (RRT) selection supports for chronic kidney disease (CKD) patients are essential to improve post-treatment outcomes. We aimed to investigate how and when modality selection supports for patients with CKD are used by nephrologists in Japan, through a nationwide questionnaire survey of nephrologists.

Methods: A questionnaire was mailed to 1903 board-certified nephrologists of Japanese Society of Nephrology. Questionnaire items targeting support for modality selection examined the following points: establishment of an RRT modality selection (RRT-MS) clinic, ideal and actual disease stage at which RRT-MS explanation is discussed, timing of RRT initiation, and type of specialist discussing RRT-MS with patients.

Results: The valid response rate was 12.3% (234/1903). Ninety-four out of 234 responding nephrologists (40.9%) had clinics dedicated to RRT-MS. Modality selection was most frequently discussed at CKD stage 4 (55.0%), stage 3b (22.8%), and stage 3a (13.4%). Nephrologists considered stage 3b (32.5%), stage 3a (19.5%), most ideal for discussing RRT-MS, a significant difference was therefore found between ideal and actual timing of RRT-MS discussion. Timing (by eGFR) of access placement of hemodialysis (HD) and peritoneal dialysis (PD) was significantly earlier in patients of RRT-MS clinics than in those of conventional clinics (HD, 12.3/14.1; PD, 12.6/14.9 ml/min/1.73 m²). Regarding types of specialists, nurses most frequently supported patients in RRT-MS (67.1%), however, this may be partly explained by the fact that nephrologists are required to commit more specialistismo supporting patients for RRT-MS.

Conclusions: A gap between ideal and actual timing of discussion of RRT-MS with patients in Japan was identified. To promote appropriate timing of RRT-MS among CKD patients, early and multidisciplinary support systems should be structured.

Funding: Government Support - Non-U.S.

SA-PO719

Primary Care Physicians’ Perceived Barriers and Facilitators to Care of Older Adults with Kidney Failure Not on Dialysis

Helen Tam-Tham, Brenda Hemmelgarn, Chandra Mary Thomas, Karen Fruetel, Robert R. Quinn, Kathryn M. King-Shier. Univ of Calgary, AB, Canada.

Background: Primary care physicians are important care providers for older adults with kidney failure, but how they perceive and practice conservative (non-dialysis) care has not been studied. We undertook a qualitative study to describe barriers, facilitators, possible enhancements of conservative care in the community for these older adults.

Methods: Semi-structured telephone interviews were conducted with primary care physicians from southern Alberta, Canada. Participants were identified by a snowball sampling strategy and purposefully sampled based on sex, age, and rural/urban location of clinical practice. All participants managed at least 1 patient ≥75 years with kidney failure (eGFR <15ml/min/1.73m² for at least 3 months, not on dialysis) over the past year. Transcripts were analyzed thematically by conventional content analysis.

Results: Twenty-seven primary care physicians participated in this study (55.6% of participants were male, 55.6% of participants were aged 40 to 60 years, and 51.9% of participants practiced in the primary care setting for greater than 20 years). Perceived barriers to conservative care included: managing expectations of kidney failure for patients and their families, optimizing medical management of conservative care, and negotiating provider roles and responsibilities of co-management. Facilities for care included: establishing patient and their family expectations of care early, preserving continuity of care, and utilizing a multidisciplinary team approach. Primary care physicians also identified suggestions for enhancement of conservative care in the community, including direct telephone access by primary care physicians to conservative care clinicians, treatment decision aids for patients and their families, and a conservative care clinical pathway for primary care providers.

Conclusions: We found important barriers and facilitators to conservative care by primary care physicians in the community. Further investigation of potential strategies that remove barriers and enable facilitators is required to improve the quality of conservative care in the community.

Funding: Government Support - Non-U.S.
SA-PO720


Background: Awareness of chronic kidney disease (CKD) is low, even among patients with advanced disease. Increasing awareness to 11.7% is a Healthy People 2020 goal. The National Health and Nutrition Examination Survey (NHANES) measures CKD awareness using the question “Have you ever been told by a doctor or other health professional that you had weak or failing kidneys (excluding kidney stones, bladder infections, or incontinence)?” The framing of this question may influence responses. We sought to compare its sensitivity/ specificity to different questions as well as to awareness of other chronic conditions.

Methods: We administered a questionnaire to 220 English, Spanish and Cantonese-speaking adults who received primary care in a public healthcare delivery system. We obtained demographic data, screened for health literacy and ascertained patient awareness about chronic health conditions, including CKD, diabetes, hypertension and hyperlipidemia. CKD awareness was measured using the NHANES question and additional ones, asking if patients had been told about “kidney disease,” “protein in the urine,” “kidney problem,” or “kidney damage”. Health conditions were verified by medical record review.

Results: In our diverse study population (9.6% White, 40.5% Black, 36.4% Hispanic, 12.0% Asian), mean age was 58, mean eGFR was 47 ml/min/1.73m2 and 47% had low health literacy. Sensitivities of each CKD awareness question were: 26.7% for “kidney damage”, 28.0% for “kidney disease”, 33.5% weak or failing kidneys” (NHANES), 36.2% for “protein in the urine” and 40.6% for “kidney problem”. Specificities ranged from 88.2% to 97.7%. Combining all 5 questions yielded a sensitivity of 61.1% and a specificity of 79.6%. This was comparable to awareness of hypertension (68.8%) but was lower than awareness for hypertension and diabetes (89.6% and 94.3% respectively). Sensitivities were lower in patients with low health literacy.

Conclusions: CKD awareness is low compared to other chronic diseases. Nevertheless, by using more sensitive combinations of questions to ascertain CKD awareness, we have likely reached the Healthy People 2020 goal.

Funding: NIDDK Support

SA-PO721

The Effects of Age and Symptoms on Recommendations to Initiate Dialysis Michael Walsh, Rajnish Mehrotra, Carmel M. Hawley, Marcello Tonelli, Clare I. Castledine, Stephen P. McDonald, Darin Treleaven, Vicki Levioditis, K. Scott Brimble. McMaster Univ.

Background: The extent to which patient characteristics influence Nephrologists’ recommendations regarding initiation is unclear. We conducted an international survey to examine the effect of country on recommendations to initiate dialysis.

Methods: Nephrologists from Australia, Canada, New Zealand, the UK and the US were surveyed by email. The survey included clinical vignettes that varied patient characteristics. The recipient scored the likelihood they would recommend initiating dialysis on an 8-point modified Likert scale anchored at 1 (definitely would not) and 8 (definitely would). Results were analysed using mixed-effects regression.

Results: 771 nephrologists were included. The degree to which patient age was associated with recommending dialysis varied by country (p<0.001 for interaction) (Figure 1). For a given level of GFR, only nephrologists from Canada (p<0.001) and the US (p<0.001) were more likely to recommend dialysis for patients 75 years old than those aged 45. Conversely, nephrologists from Australia (p<0.001), New Zealand (p=0.001) and the UK (p=0.003) were less likely to recommend dialysis for patients aged 90 than those aged 45. All nephrologists were more likely to recommend dialysis as symptoms increased but this association was less pronounced in the US and Australia (p<0.001 for interaction). Patient comorbidities, nephrologists’ years in practice, and practice type were not associated with recommendations.

Conclusions: For patients at a given eGFR, other characteristics such as age and symptom burden influence nephrologists’ recommendations to initiate dialysis but the extent of this influence differed substantially between nephrologists in different countries. Further research is required to understand the effect of these differences on patients and health systems.

SA-PO722

The Association of Community Health Indicators with Late Nephrology Referral in Patients Reaching End-Stage Renal Disease in the U.S. Jung-In Shin, Mari Palta, Micah R. Chan, Brad C. Astor. Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: Late nephrology referral in patients reaching end-stage renal disease (ESRD) is associated with inadequate preparation for dialysis and poorer clinical outcomes after renal replacement therapy (RRT). Previous studies have focused on individual-level factors to identify patients at higher risk of late nephrology referral. Environmental and socioeconomic conditions of communities in which patients live may also impact nephrology referral patterns.

Methods: We assessed the association of community health indicators with late nephrology referral in 587,574 patients reaching ESRD, using the data from United States Renal Data System (USRDS) from 2005-2012. An overall community health risk score was calculated using 35 community-level factors based on 1) health outcomes, 2) health behaviors, 3) access and quality of care, 4) socioeconomic factors, and 5) physical environment, using County Health Rankings data from University of Wisconsin Population Health Institute. Late nephrology referral was defined as the first encounter with a nephrologist occurring < 6 months before RRT initiation. Multilevel logistic regression models adjusted for individual characteristics, including demographics, cause of ESRD, body mass index, comorbidities, and insurance and employment status.

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

Underline represents presenting author.

793A
Results: The prevalence of late nephrology referral was 47.8%. A significant dose-response relationship of community risk score with late nephrology referral was found, with an adjusted odds ratio of 1.52 (95% CI: 1.36-1.71) for the highest versus lowest risk communities.

Conclusions: Higher community risk is significantly associated with late nephrology referral, independent of individual-level factors. Community risk may be an important consideration for developing interventions to improve access to pre-ESRD nephrology care.

SA-PO723
Assessment of Quality of Care Received by Patients with Predialytic CKD: Health Services, Disparities, and Prevention
Poster/Saturday

Background: In a country with limited access to dialysis and transplantation such as the Philippines, it is imperative to recognize patients with early stage CKD and aggressively intervene in a timely fashion to prevent ESRD and death. The objective of this study is to evaluate the quality of care (QoC) of patients with predialytic CKD seen at a general medicine clinic.

Methods: This was a retrospective study which reviewed the medical records of 276 patients with CKD Stages 3-4 who have at least 1 year of consult. Patients who were admitted for critical illness, and are on dialysis were excluded. For each QoC parameter, percentage of patients who received the appropriate care were reported. For the QoC study, all patients were seen at a medicine clinic.

Results: The mean QoC score for this study is 58.36% (± 23.7%) and the average annual GFR decline is 3.92 mL/min/1.73m².

Conclusions: Understanding of RRT options was poor among CKD patients participating in the US. Though the responses may not necessarily reflect information that was actually provided by their nephrology clinic teams, our results indicate that current educational strategies fail to adequately communicate key messages on RRT.

SA-PO724
Chronic Kidney Disease (CKD) Patients’ Understanding of Renal Replacement Therapy (RRT) Options: Early Findings from the U.S. CKD Outcomes and Practice Patterns Study (CKDopp)
Poster/Saturday

Background: Current KDIGO guidelines indicate that kidney failure patients should receive information on all RRT modalities, including conservative management. Even when education is provided, patients’ understanding of such a complex topic may be limited. We report the perspective of US participants in the first year of CKDopp.

Methods: CKDopp is a new international prospective cohort study that enrolls adult advanced CKD patients in national samples of nephrology clinics in the US, Brazil, France, and Germany and follows patients through the dialysis transition period. As of early 2015, 245 US participants with eGFR<30 mL/min/1.73m² completed a self-administered questionnaire including their understanding of, education on, and preferences for RRT options.

Results: The median age of patients was 71; 43% were male and 57% had diabetes. 66% of patients reported they received no education about treatment options for kidney failure; 20% said they received one-on-one education; and 14% participated in a class. 34% recalled that in-center hemodialysis (HD) was discussed as a treatment option, and less than 25% recalled their doctor discussing peritoneal dialysis, home HD, conservative management, or transplantation. 58% of participants reported they did not know if transplantation was an option for them. Nearly 3 out of 5 patients did not know what RRT option they would choose if their kidneys failed.

Conclusions: Understanding of RRT options was poor among CKD patients participating in the US. The responses may not necessarily reflect information that was actually provided by their nephrology clinic teams, our results indicate that current educational strategies fail to adequately communicate key messages on RRT.

SA-PO725
Chronic Kidney Disease (CKD) Patients’ Understanding of Renal Replacement Therapy (RRT) Options: Early Findings from the U.S. CKD Outcomes and Practice Patterns Study (CKDopp)
Poster/Saturday

Background: Current KDIGO guidelines indicate that kidney failure patients should receive information on all RRT modalities, including conservative management. Even when education is provided, patients’ understanding of such a complex topic may be limited. We report the perspective of US participants in the first year of CKDopp.

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Conclusions: Understanding of RRT options was poor among CKD patients participating in the US. Though the responses may not necessarily reflect information that was actually provided by their nephrology clinic teams, our results indicate that current educational strategies fail to adequately communicate key messages on RRT.

SA-PO726
Chronic Kidney Disease (CKD) Patients’ Understanding of Renal Replacement Therapy (RRT) Options: Early Findings from the U.S. CKD Outcomes and Practice Patterns Study (CKDopp)
Poster/Saturday

Background: Current KDIGO guidelines indicate that kidney failure patients should receive information on all RRT modalities, including conservative management. Even when education is provided, patients’ understanding of such a complex topic may be limited. We report the perspective of US participants in the first year of CKDopp.

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Conclusions: Understanding of RRT options was poor among CKD patients participating in the US. Though the responses may not necessarily reflect information that was actually provided by their nephrology clinic teams, our results indicate that current educational strategies fail to adequately communicate key messages on RRT.
Conclusion: These results suggest that the rate of prescription of statins in CKD patients is suboptimal and differs by the provider caring for the patient with CKD. Lack of CVD preventive care may impact overall CVD risk in patients with dialysis-dependent CKD.

SA-PO726

Patients’ Knowledge of Their Chronic Kidney Disease Stage and Education About Kidney Failure Prevention – The CKD-REIN Cohort

Benedicte Stengel, 1 Celine Lange, 2 Brian Con Serge, 2 Luc Frimat, 3 Denis Fouque, 4 Maurice Laville, 5 Christian Jacquelinet, 2 Bruce M. Robinson, 5 Ziad Fouque, 4 Maurice Laville, 5 Christian Jacquelinet, 2 Bruce M. Robinson, 5 Ziad Fouque, 4 Maurice Laville, 5 Christian Jacquelinet, 2 Bruce M. Robinson, 5 Ziad Fouque, 4 Maurice Laville, 5 Christian Jacquelinet, 2 Bruce M. Robinson, 5 Ziad Fouque, 4 Maurice Laville, 5 Christian Jacquelinet, 2 Bruce M. Robinson, 5 Ziad

Background: Patient knowledge about their CKD stage and how to prevent kidney failure is important to reduce ERSD risk through better adherence to treatment and lifestyle changes. We report preliminary findings about CKD knowledge among patients seen by nephrologists in France.

Methods: We used baseline data from the CKD-REIN study, a prospective cohort of patients with CKD stage 3 and 4 in a national sample of 40 nephrology clinics. Information was collected from patient interview and self-administered questionnaire. Comparisons between stages were adjusted for age and gender.

Results: Median age was 68 (59-76) and 56% were male. About 80% reported knowledge that their kidney function was low. Patients were more likely to know their creatinine level (40%) than GFR or CKD stage. For each question, knowledge increased slightly from stage 3 to stage 4. Education about how to prevent kidney failure was uncommon (10%).

SA-PO728

Getting a Diagnosis of Chronic Kidney Disease: Despite Fears, Patients Want to Know Early

Julie A. Wright Nunes, 1 Meghan Roney, 2 Eve Kerr, 3 Akinlolu O. Ojo, 1 Angela Fagerlin, 1,2 1 Internal Medicine, Univ of Michigan, Ann Arbor; MI; 2 Center for Bioethics and Social Sciences in Medicine, Univ of Michigan, Ann Arbor, MI; 3 Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, MI.

Background: Little is known about patient perspectives related to getting a diagnosis of chronic kidney disease (CKD). This information could help providers optimize diagnosis timing and the point of care.

Methods: Using root/cause analysis and quality function deployment we conducted semi-structured patient interviews. Adult patients with established non-dialysis CKD were interviewed between January-October 2014. Interviews were audiorecorded and transcribed. Content analysis was done with Dedoose, a qualitative software package.

Results: 49 patients completed interviews. Mean (SD) age was 63 (14) years, 50% were male, 80% were Caucasian and 84% had CKD Stage 3-5. Key themes emerged from a total of 786 statements: 1) Reaction to diagnosis (160 statements) 2) Barriers to accepting diagnosis (61 statements) and 3) Expectations of diagnosis communication (122 statements). 45% of patients felt fearful after getting a CKD diagnosis-most often related to perceived threats of future dialysis and death. Barriers to diagnosis acceptance included disbelief because of lack of symptoms and lack of prior familiarity with CKD. Despite fear and denial the majority of patients (63%) desired early diagnosis communication by their providers, i.e. at earliest stages of identification. Consistent terminology and disease explanations by providers across the care continuum were perceived as critical to effective communication and diagnosis delivery, yet patients expressed frustration at inconsistent terminology/explanations.

Conclusions: Our findings emphasize that patients learning of a CKD diagnosis can experience fear, but they also prefer early communication of diagnosis. More work is needed to set uniform diagnosis terminology for patients with CKD across the care continuum.

Funding: NIDDK Support

SA-PO729

The Cost-Effectiveness of Primary Screening for Chronic Kidney Disease in Rural and Remote First Nations

Thomas W. Ferguson, 1 Navdeep Tangri, 2 Matthew T. James, 2 Zhi Tan, 3 Claudio Rigatto, 2 Paul Komenda. 1, 2 Community Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; 3 Medicine, Univ of Manitoba, Winnipeg, MB, Canada; 4 Medicine, Univ of Calgary, Calgary, AL, Canada.

Background: Chronic Kidney Disease (CKD) is a risk factor for cardiovascular disease, early mortality, and kidney failure. We have shown that the burden of CKD in First Nations (FN) populations in Manitoba is similar to that in diabetic and hypertensive populations. The cost-effectiveness of screening for CKD and subsequent treatment in FN or other high-risk indigenous populations has not yet been described.

Methods: We constructed a Markov model comparing screening in adult FN (age ≥18) for CKD by both proteinuria and estimated glomerular filtration rate (eGFR) to usual care from the perspective of the publicly funded Canadian health care payer. Patients were assigned an initial risk classification based on urine albumin-to-creatinine ratio and eGFR using the Kidney Disease Improving Global Outcomes (KDIGO) heat map. We obtained screening tests results on 1346 adult participants from the First Nations Community Based Screening to Improve Kidney Health and Quality of Life (FINISHED) initiative. Our analysis was further stratified into communities accessible by road and communities accessed by air travel. Our primary outcome of interest was the incremental cost per quality-adjusted life-year (QALY).

Results: Overall crude prevalence of CKD in FN was 26.7%. Screening for CKD was associated with an ICER of $33,500/QALY in comparison to usual care. Restricting the model to screening in the remotest air access communities (prevalence of CKD 36.0%), this ratio fell to an ICER of $16,180/QALY. In less remote road access communities (CKD prevalence of 18.4%), the ICER was $63,780/QALY. Primary model drivers included the cost of dialysis, assumed treatment effectiveness, and rates of progression towards kidney failure.

Funding: Pharmaceutical Company Support - Amgen, Baxter, Fresenius, GSK, Lilly, MSD, Sanofi, Government Support - Non-U.S.

SA-PO727

The Cost-Effectiveness of Primary Screening for Chronic Kidney Disease


CKD: Health Services, Disparities, and Prevention

Poster/Saturday

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

Underline represents presenting author.

975A
Conclusions: Patients in advanced stages of CKD are at an increased risk of falling into financial hardship. Kidney transplantation may have a role in reducing the risks of household poverty due to CKD.

Funding: Government Support - Non-U.S.

SA-PO730

Healthcare Expenditures for Non-Dialysis Dependent Kidney Disease Compared to Other Chronic Diseases

Christina Small,1 Holly J. Kramer,1 Karen A. Griffin,1 David J. Leehey,1 Vinod K. Bansal,1 Kavitha Vellanki,1 Talar Markossian.1 1Loyola Univ Chicago; 2Hines VA Medical Center.

Background: There is a paucity of literature comparing the expenditures of kidney disease with other common costly chronic diseases in the United States. Our study compares the U.S. healthcare expenditures of non-dialysis dependent kidney diseases to several other chronic conditions.

Methods: This study used the 2012 Medical Conditions and Consolidated Data files from the Medical Expenditure Panel Survey administered by the Agency for Healthcare Research and Quality. Analyses included adults aged ≥ 21 years with one of the following conditions: kidney disease, stroke, cancer, or a combination of the three (multichronic). Non-dialysis dependent kidney disease included any ICD9 code for kidney related conditions while chronic kidney disease (CKD) included only ICD9 code “585.” Analyses of calculated healthcare expenditures accounted for the complex survey design and incorporated the sampling weights so that estimates represent healthcare expenditures for the 2012 adult U.S. population (~313.4 million). Out of pocket healthcare expenditure burden was defined as the ratio of out of pocket healthcare expenditure to total person-level income for the year 2012.

Results: The mean age for non-dialysis dependent kidney disease and CKD was 56.5 and 65.9 years, respectively. Table 1 shows the median total and out of pocket healthcare expenditure values and mean out of pocket healthcare burden for kidney disease, CKD and other chronic conditions.

<table>
<thead>
<tr>
<th>Chronic Condition</th>
<th>Median Out of Pocket Expenditures, $ (range)</th>
<th>Median Total Expenditures $ (range)</th>
<th>Mean Out of Pocket Healthcare Expenditure Burden %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>386 (38.3, 915)</td>
<td>22, 919 (1,782-189,893)</td>
<td>9.5</td>
</tr>
<tr>
<td>Any kidney disease</td>
<td>795 (0.02, 0.034)</td>
<td>6,351 (0.262, 189)</td>
<td>5.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>760 (0.54, 698)</td>
<td>8, 528 (0.147, 533)</td>
<td>5.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>790 (0.79, 313)</td>
<td>7,600 (0.212, 886)</td>
<td>5.2</td>
</tr>
<tr>
<td>Multiple Chronic Conditions</td>
<td>824 (2.5, 7.11)</td>
<td>16, 323 (992-276, 647)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Conclusions: Healthcare expenditures including out of pocket costs are higher for non-dialysis dependent CKD compared to other chronic medical conditions. Policy efforts should focus on reducing the healthcare cost burden for patients with kidney disease.

SA-PO731

Smartphone-Based Self-Management System for Chronic Kidney Disease: Results from a Single Centre Prospective Trial

Stephanie W. Ongh,1 Sarbjit Small,1,2 Holly J. Kramer,1 Karen A. Griffin,1 David J. Leehey,1 Vinod K. Bansal,1 Kavitha Vellanki,1 Talar Markossian.1 1Loyola Univ Chicago; 2Hines VA Medical Center.

Background: Following user-centric design principles we developed a smartphone-based self-management support system for patients with advanced CKD. The patient interface focuses on 4 behavioral elements over which they have direct control: monitoring BP at home, self-assessment of symptoms, managing medications and tracking laboratory results. The main objectives of this 6-month prospective study were to determine acceptability, measured by system adoption and adherence, and assess effectiveness by measuring pre and post changes in BP, medications, labs and self-management behaviors.

Methods: We tested the mobile app in 10 renal clinics at a single academic renal center in Toronto. The 47 enrolled patients were instructed at a regular clinic visit to use the mobile app. The clinical team independently received information on the mobile app system’s operation.

Results: 61% of participants were non-smartphone owners. All had more than one chronic condition and on average were on 10 to 15 medications. Most were over the age of 50 with the greatest representation in the age group 55-64. >80% of the users achieved more than the recommended 80% adherence rate to mobile app use.27% with normal clinic BP readings were discovered to have ‘masked’ hypertension on home BP monitoring. By the end of the study the SBP fell by 6.8 ± 20.4 mm Hg (p < 0.05) and DBP by 9.9 ± 9.1 mm Hg. Out of 250 medication reviews, 49% required intervention from the clinical team, such as altering drug dosing. Due to the short study duration and infrequency of lab testing, there were no changes in pre and post laboratory test results. On exit, patients and clinicians felt the mobile app helped engage and empower patients in their CKD care.

Conclusions: The mobile app was acceptable and suggests improvements in BP management and medication error prevention. This provides early evidence to supporting innovative use of mobile technology in CKD management and strongly support evaluating its use in a larger clinical.

SA-PO732

Potentially Preventable Hospitalization Among Patients with Chronic Kidney Disease and High Inpatient Use

Paul E. Ronksley, Braden J. Manns, Marcello Tonelli, James Wick, Brenda Hemmelgarn. 1Univ of Calgary, Calgary, AB, Canada.

Background: While prior studies have observed high rates of hospitalization among patients with chronic kidney disease (CKD), little attention has been given to those with high inpatient use. We explored clinical characteristics, patterns of hospital use, and potentially preventable acute care encounters among hospitalized patients with CKD.

Methods: We identified all adults (≥18 years) with an eGFR < 60 mL/min/1.73 m2 in Alberta, Canada between Jan 1 and Dec 31, 2009, excluding those with prior kidney failure. Patients with CKD were linked to administrative data to capture clinical characteristics and frequency of hospital encounters, and followed until death or end of study (Dec 31, 2012). Patients with 1 or more hospital encounters were categorized into 3 groups: persistent high use (upper 5% of inpatient use (≥3 encounters/yr) in 2 or more years), episodic high use (upper 5% in 1 year only), or non-high use (lower 95% in all years). Within each group we described patient characteristics and calculated the proportion of potentially preventable hospitalizations as defined by 4 CKD-specific ambulatory care sensitive conditions (ACSC); heart failure, hyperkalemia, volume overload, malignant hypertension.

Results: During a median follow-up of 3 years, 57007 patients had 118671 hospitalizations of which 1.7% of patients were persistent high users of hospital services, 12.3% episodic high users, and 86.0% non-high users. Persistent high users were often younger, male, First Nations, living in rural areas, and had higher levels of comorbidity compared to episodic and non-high use groups. Overall, 24804 (20.9%) CKD-related ACSC encounters were observed in the cohort. The proportion of ACSC encounters were higher in persistent high users (29.1%) compared to episodic (27.3%) and non-high users (17.3%) (p < 0.01). The majority of the encounters were attributed to heart failure and hyperkalemia in all groups.

Conclusions: A substantial proportion of hospitalizations among patients with CKD and high inpatient use are ACSC-related. These findings suggest opportunities to reduce inpatient use and cost by focusing on strategies to improve community-based care for this subset of patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO734

Rapid Post-Transplant Improvement of HRQOL in Older Kidney Recipients

Kristian Heldal,1,2 Kjersti Lonning,2 Tomm Bernklev,2 Nanna von der Lippe,2 Anna Reisaeter,3 Anders Hartmann,2 Marit Helen Andersen,3 Karsten Midveldt,1 1Clinic of Internal Medicine, Telemark Hospital, Skien, Norway; 2Inst of Clinical Medicine, Faculty of Medicine, Univ of Oslo, Oslo, Norway; 3Clinic of Surgery, Surgery and Transplantation, Oslo Univ Hospital, Rikshospitalet, Oslo, Norway; 4Research Unit, Telemark Hospital, Skien, Norway.

Background: It is widely accepted that health-related quality of life (HRQOL) is significantly compromised in patients with ESRD. In adults, kidney transplantation (KTx) is known to improve HRQOL. In older recipients there is a lack of studies measuring the effect of KTx on HRQOL. The aim of this study was to measure HRQOL longitudinally in enrolled patients ≥65 years of age, from pre-transplant and until 6 months after KTx.

Methods: Patients ≥65 years listed for transplantation at our centre were asked to complete the SF36 questionnaire at enlisting and thereafter every 6 months until KTx. Post-transplant, the patients received a new SF36 form after 10 weeks and 6 months.

Results: A total of 180 patients have been included from Jan 2013. Mean age at enlisting was 76.6 years (65.0-81.8) and 68% were male. By the end of May 2015, 100 patients were transplanted and 59 of them had completed both pre- and post-transplant questionnaires. While mean time from completing the first pre-tx questionnaire to transplantation was five months. When comparing the scores for the last SF36 pre-tx with 6 months post-tx, there was a significant statistical increase in the mean scores for GH (53.71), PF (68.74), BP (64.78), VT (53.71) and MH (79.85). There was also a tendency towards improved scores for RP and RE, while the SF score was unchanged.

Conclusions: Our preliminary findings indicate that older patients report a significant improved HRQOL measured by SF36 already 10 weeks after KTx and the status remains stable after 6 months. Longer follow-up is warranted.

Funding: Government Support - Non-U.S.

SA-PO735

L-Carnitine Improves Cognitive and Renal Functions in a Rat Model of Chronic Kidney Disease

Zaher Anis Armully,1 Adel Rafik Jabbour,2 Cheuk Yee Leung,1 Alpig childhood and associated metabolic abnormalities. L-Carnitine treatment of KTx rats significantly reduced Scr and BUN, attenuated renal hypertrophy and decreased renal tissue damage. In addition, in the two way shuffle avoidance learning, CKD animals showed cognitive impairment which recovered by the administration of L-Carnitine.

Methods: We studied 178 prevalence PD patients (103 males). Cognitive impairment was screened by the 10-item Abbreviated Mental Test (AMT) questionnaire. We also determined patients’ comorbidity load, dialysis adequacy, residual renal function, nutritional status, and degree of frailty.

Conclusions: The mean age was 60.7 ± 11.7 years; vintage of dialysis 42.5 ± 44.1 months. Average AMT score was 9.3 ± 1.3. The AMT score is closely associated with age (r –

SA-PO736

Being a Relative to Patients with Chronic Kidney Disease – Experiences of Participation in Care and Treatment

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Background: Studies concerning the lives of patients with chronic kidney disease have focused on the patients, and not the relatives. However, relatives share and are affected by the same consequences as the patient with regard to changes in everyday life, roles in the family and mutual relationship. The purpose of the study was to gain insight into and understanding of the needs of the relatives of patients with chronic kidney disease with regard to their ability to provide support in everyday life, and the expectations of the relatives of participation in care and treatment.

Methods: A qualitative study based on four focus group interviews with four to eight relatives in each group (in total 27 relatives). The groups were formed according to the age and gender of the relatives as well as their relation to the adult patient with chronic kidney disease.

Results: The study demonstrated how relatives provide substantial support to the patient both in everyday life and in care and treatment. In relation to the patient, it was a constant challenge for relatives to find the balance between supporting and taking over. They expressed a need for recognition by both the close relations and the health care professionals as well as a need for sharing their experiences with other relatives in the same situation.

Conclusions: When collaborating with the relatives with regard to care for patients with chronic kidney disease, the health care professionals should actively recognize the patient support that the relatives already provide in everyday life. Initiatives of participation in care and treatment should be based on collaboration and the needs, expectations and possibilities of both the patient and the relatives.

SA-PO737

CKD(3-5) Affects Endurance, Strength, Balance and Fine Motor Skills which Are Not Detectable by Questionnaire

Naomi D. Clvne,1 Matthias Hellberg,1 Peter Hoglund,2 1Clinical Sciences Lund, Nephrology, Lund Univ, Lund, Sweden; 2Laboratory Medicine, Clinical Pharmacology, Lund Univ, Lund, Sweden.

Background: Physical functions are impaired in dialysis patients. It is unclear which functions are affected and how they decline in the course of CKD. This study investigated the effects of declining GFR (CKD 3-5) on measured physical functions, self perceived physical functioning and well-being.

Methods: In this cross sectional analysis 101 patients (40 women, 61 men; mean age: 67.1±13 years, median GFR: 21 (9-41) ml/min/1.73m²) were tested with 6 Minutes Walk (6-MWT), Isometric Quadriceps Strength (IQS), Functional Reach (FR) and Picking-up (PUT). Self perceived physical functioning and well-being were assessed by KDQOL-SF. GFR was measured with iohexolclearance and comorbidity by Davies’ index. Multivariable linear regression analyses were employed including the following explanatory variables: GFR, age, sex, comorbidity and the interaction between sex and age.

Results: Significant associations were found between decline in GFR and endurance (6-MWT; p=0.039), strength (IQS; p=0.035), balance (FR; p=0.024) and fine motor skills (PUT; p=0.015) as well as by the patients’ perceived domains in the KDQOL-SF™ of effects (p<0.025) and burden (p=0.016) of kidney disease and social support (p=0.006) after having taken the explanatory variables into account. There were significant associations between the KDQOL-SF™ domains role physical and emotional well-being and 6-MWT (p=0.018; p=0.018, respectively) and IQS (p=0.005; p=0.045, respectively), but these were dependent on age, sex and comorbidity but not driven by GFR.

Conclusions: Physical functions comprising endurance, strength, balance and fine motor skills were impaired relatively early in the course of CKD (3b-5), seemed to progress with declining GFR and could be detected by easy to perform physical function tests. The relationship between self perceived physical functioning and well being, respectively, with measured endurance and strength, respectively, were driven by age, sex and comorbidity but not by decline in GFR. The only domains that discriminated for GFR associated influence were effects- and burden of kidney disease and social support.
Neurocognitive Functioning and Association with Clinical Outcomes in Adults with End-Stage Kidney Disease: The COGNITIVE-HD Study Giovanni F.M. Strippoli*

On behalf of the COGNITIVE-HD Study Investigators*, 1Duaveram Medical Scientific Office; 2Univ of Bari; 3Univ of Sydney.

Background: Cognitive impairment and neurocognitive disorder have been associated with increased mortality in the general population. Whether dialysis patients have specific patterns of cognitive dysfunction, or whether cognitive function is associated with activities of daily living and durability of dialysis treatment remain poorly understood.

Methods: The COGNITIVE-HD study will provide detailed neuropsychological assessments of cognitive function among hemodialysis patients to characterize age- and education-adjusted prevalence and patterns of cognitive impairment and the associations with physical and social functioning and clinical outcomes including cardiovascular events at 12 months. The COGNITIVE-HD study is a prospective, longitudinal, population study of 751 adults conducted in 20 dialysis centers in Italy. A detailed battery of comprehensive testing for executive function, visuospatial function, language, learning and memory, personality traits, and complex attention has been carried out by a trained psychologist at baseline to assess for presence of cognitive impairment and to evaluate the pattern of cognitive deficits, and any association between cognitive impairment and activities of daily living.

Results: Preliminary analyses have been conducted on the Mini Mental State Examination (MMSE) evaluation of cognitive function among 702 participants (mean age 68.2 years, 60% men). 50% had normal cognitive function (MMSE score 27-30), 22% had mild cognitive impairment (score 26-24), 198 patients (28%) had MMSE results compatible with dementia (score <24), of whom 51%, 48% and 1% had mild, moderate and severe impairment respectively.

Conclusions: The COGNITIVE-HD is a population-based study of cognitive function involving dialysis patients that has the potential to inform candidate interventions for treatment trials of cognitive impairment in the setting of advanced kidney disease. *List of study investigators: S Palmier, M Ruoppo, A Iurillo, V Saglimbene, P Natale, O Barulli, L Giargaro, AM Muro, +C.I. Cruz, DW Johnson, M Tonelli, J Heghrent, C Wollheim, G Logroscino and GFM Strippoli.

Lower Renal Function Predicts Poorer Performance in Specific Domains of Neurocognitive Function in Older Hypertensive Men

Stephen L. Seliger, 1 Jason Kissner, 2 Jamie Giffuni, 3 Leslie I. Katzel, 1 Shari R. Waldstein.

Background: Cognitive impairment and neurocognitive disorder have been associated with common cognitive risk factors. However, across a range of GFR, lower renal function is associated with worse performance in specific domains of cognitive function.

Methods: A total of 322 children (M:F 218:104) enrolled from seven major pediatric nephrology centers of Korea from July 2010 to December 2013 were the subject of this study. Neurocognitive function and psychiatric status of pediatric CKD patients were evaluated using Wechsler Intelligence Scale for children, Child Behavior Checklist, ADHD Rating Scale-IV, State-Trait Anxiety Inventory, Child Depression Inventory and Parental bonding instrument-Korean version.

Results: Verbal, performance and full scale IQ were lower in younger age and congenital anomalies of the kidney and urinary tract as a cause of CKD. More than 10 percent of school-age children with CKD presented significant emotional distress including somatization (15%), attention problems (15%) and anxiety (12%). Impact of progression of CKD on their neurocognitive function and psychiatric status will be investigated in KNOW-PedCKD cohort study in Korea.

Conclusions: We determined that pediatric chronic kidney disease (CKD) is associated with neurocognitive impairment and psychiatric disorder from the KNOW-PedCKD cohort study in Korea.

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

Adjusted associations (β) of estimated GFR with neurocognitive function

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Domainal Δ</th>
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<th>p-value</th>
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<tr>
<td>Logical Memory Immediate</td>
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</table>
Vitamin D Deficiency Is Significantly Associated with Depression in Chronic Kidney Disease Patients

Jung Hyeon Jhoo, Sul A. Lee, Hyung Jung Oh, Jung Tak Park, Seang Hyoeok Han, Shin-Wook Kang, Tae-Hyun Yoo. Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Recent studies have reported significant associations between vitamin D deficiency and depression in the general population. Although both vitamin D deficiency and depression are common features in chronic kidney disease (CKD) patients, the association between these two prevalent factors in this patient population remains poorly elucidated. Therefore, the association between vitamin D deficiency and depression in CKD patients was investigated.

Methods: The data from the Korean National Health and Nutrition Examination Survey between 2010 and 2012 were used. A total of 495 patients with estimated glomerular filtration rate ≤60 mL/min/1.73m² were enrolled. Vitamin D deficiency was defined as 25-hydroxyvitamin D3 [25(OH)D3] levels <10 ng/mL. Patients were dichotomized by the presence of vitamin D deficiency. Depression was determined by the EuroQOL-5D (EQ5D) questionnaire. Independent association between vitamin D deficiency and depression was evaluated by multivariate logistic regression analysis.

Results: The mean age was 71.2±9.3 years, and 257 patients (51.9%) were female. The median 25(OH)D3 levels were 17.9 (13.9-22.7) ng/mL. The prevalence of depression in CKD patients was higher compared to the general population (43.0% vs. 11.1%, P<0.01). In addition, the prevalence of depression was significantly higher in patients with vitamin D deficiency than those without vitamin D deficiency (27.9% vs. 13.3%, P<0.02). Multivariate logistic regression analysis showed that vitamin D deficiency was a significantly independent predictor of depression after adjusting for age, sex, alcohol, body mass index, hypertension, diabetes mellitus, anemia, suicidal idea, EQ5D index, and serum parathyroid hormone levels (odds ratio=6.27, 95% confidence interval=1.57-25.05, P=0.009).

Conclusions: Vitamin D deficiency was a significantly independent predictor of depression in CKD patients. Therefore, determining vitamin D levels might be helpful to predict depression in these patients.
Results: Phase 1 identified 13 common symptoms, and Phases 2 and 3 confirmed symptom selection and refined the wording used to describe them. The symptom descriptions finalised were: itching, sleep disturbance/insomnia, loss of appetite, feeling tired, pain in bones/joints, poor concentration/mental alertness, loss of libido/erectile dysfunction, loss of muscle strength/power, shortness of breath, cramp/muscle stiffness, restless legs/ difficulty keeping legs still, need to urinate more often, feeling cold. In Phase 4, 14 of 16 experts responded (87.5%). 10 of the 13 symptoms had “excellent” or “good” evaluation scores, and the content validity index of the whole questionnaire was 0.81, falling within the recommended threshold.

Conclusions: This work has provided a novel, validated symptom score for the early/pre-dialysis CKD population, which can be used as a patient reported outcome measure in both clinical management and research.

Funding: Private Foundation Support

SA-P0747


Background: Transplantation (Tx) is generally regarded as the best option for renal replacement therapy. However, few patients with CKD are listed for Tx when eligible. We examined the association between psychosocial factors in patients with advanced CKD and wait-listing for kidney Tx.

Methods: The study population includes 803 individuals with an eGFR of less than or equal to 20mL/min/1.73m² (advanced CKD) in the Chronic Renal Insufficiency Cohort study. The primary predictors were health related quality of life (HRQOL) and depressive symptoms assessed within 24 months prior to reaching the eGFR inclusion criteria using the Kidney Disease QOL (KDQOL)-56 survey and the Beck Depression Inventory (BDI), respectively. The primary composite outcome was wait-listing or transplantation (WLT). Cox proportional hazards models were used to examine the association between low HRQOL (1 SD below the cohort mean) and BDI (11) with WLT.

Results: Of the 803 subjects, 380 (47%) were wait-listed including 120 that proceeded to Tx. Compared to individuals who were not WLT, those in the WLT group were more likely to be younger, male, have no history of cardiovascular disease, and have proteinuria > 300mg/day (p < 0.01). After adjustment for demographic and clinical variables, a low Mental Component Summary (MCS) score was associated with a lower likelihood of WLT (Table). There was no association between the BDI or other QOL measures with WLT.

Conclusions: Lower MCS scores were associated with lower likelihood of WLT. Further work is needed to evaluate the impact of poor mental QOL in advanced CKD and how it might influence wait-listing.

Funding: NIDDK Support

SA-P0748

Perspectives on Pregnancy in Women with Chronic Kidney Disease Allison Tong,1 Mark A. Brown,2 Wolfgang C. Winkelmann,1 Jonathan C. Craig,3 Shilpa Jhawarson,1 1The Univ of Sydney; 2St. George Hospital; 3Baylor College of Medicine; 4Royal Adelaide Hospital.

Background: Women with chronic kidney disease (CKD) often have difficulty achieving pregnancy, and are at increased risk of adverse pregnancy outcomes. We aimed to describe the beliefs, values, and experiences of pregnancy in women with CKD, to inform pre-pregnancy counseling and pregnancy care.

Methods: Semi-structured interviews were conducted with 41 women aged 22-56 years with advanced chronic kidney disease, from two renal units in Australia. Transcripts were analyzed thematically.

Results: Six themes were identified: bodily failure (conscious of fragility, nosiness self, critical timing, suspended in limbo); devastating loss (denied motherhood, disempowered by medical catastrophizing, resolving grief, barriers to parenthood alternatives, social jealousy); intragentic guilt (disappointing partners, fear of genetic transmission, respecting donors); meaning sacrifice, medical judgment); rationalizing consequential risks (choosing survival, avoiding fetal harm, responding to family protectiveness, compromising health, decisional ownership, unjustifiable gamble); strengthening resolve (hope and opportunity, medical catastrophe, faith as determination, reticent hope); and reorientating focus (valuing life, gratitude in hindsight).

Conclusions: Decisions surrounding pregnancy in the context of chronic kidney disease require women to confront uncertainties about their own survival, disease progression, impact on their family and kidney donor, the outcomes of their offspring, and genetic transmission. Communicating the medical risks of pregnancy to women with chronic kidney disease must be carefully balanced with their values of autonomy, hope, security and family. Informed and shared decision making that is sensitive to women’s priorities as identified in this study can contribute to improved pregnancy, health and psychosocial outcomes in this vulnerable population.

SA-P0749

Nrf2 Activator, Resveratrol, Ameliorates Aging-Related Progressive Renal Injury in Mice Kim In Nam Kim, In Ae Yang, Ji Hee Lim, Min Young Kim, Buyung Ha Chung, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim, Yoonsik Chung, Bum Soon Choi. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: The senescence markers of kidney have been shown to cause many changes in the energy metabolism. Two important issues in aging kidney are mitochondria dysfunction and oxidative stress. Nrf2 activator, Resveratrol may prevent inflammation and oxidative stress by activating SIRT1 and Nrf2. We examined that Resveratrol can potentially ameliorate the cellular condition, such as renal injury due to cell oxidative stress and mitochondria dysfunction caused by aging.

Methods: Male 19-month-old C57BL/6 mice were used in this study. Resveratrol (0.04%) was provided to old mice for 6month. We compared histological change, oxidative stress, and aging-related protein expression in the kidneys between Resveratrol treated-old-mice group (RSV) and vehicle-old-mice group (VH).

Results: In our study, expression of Nrf2 in nuclear (1 ± 0.1 fold vs. 2 ± 0.4 fold; p < 0.01 vs. VH) was increased in RSV. Expression of SIRT1 (1 ± 0.2 fold vs. 1.31 ± 0.11 fold; p < 0.05 vs. VH) was increased in RSV, p-AMPK/Total AMPK ratio expression (1 ± 0.1 fold vs. 1.79 ± 0.2 fold; p < 0.01 vs. VH) was increased in RSV compared with VH. RSV group displayed decreased albuminuria and Creatinine clearance increased with RSV. There were decreases in mesangial volume, tubulointerstitial fibrosis and collagen IV in RSV. Immunohistochemistry of F4/80 expression in glomerulus and tubule were decreased in RSV compared with VH. Also, TGF-β was decreased in RSV. Urate isoprostane and 8-OHdGexcretion decreased with aging. Antioxidant enzyme, HO-1 (1 ± 0.8 fold vs. 1.6 ± 0.1 fold; p < 0.01 vs. VH) and NOQO-1 (1 ± 0.06 fold vs. 1.3 ± 0.1 fold; p < 0.01 vs. VH) were increased in RSV compared with VH.

Conclusions: These results suggest that activation of Nrf2 may benefit aging-related renal injury related with SIRT1 and AMPK activation by reducing oxidative stress. Pharmacologically targeting Nrf2 signaling molecules may reduce the pathologic changes of aging in the kidney.

SA-P0750

Dual Agonist of Nuclear Hormone Receptor Farnesoid X Receptor and G Protein Coupled Receptor TGR5 Exhibits Calorie Restriction Mimetic Efffects in Aging Mice Nawaon Wang,1 Evgenia Dobrinskikh,2 Yuhuan Townsend, Peter P. Reese, Meera Nair Harhay.

Background: Previous studies have shown that calorie restriction (CR) in mice and in rats prevent age-related proteinuria and glomerulosclerosis. We have observed an age-related decrease in renal nuclear hormone receptor farnesoid X receptor (FXR, NR1H4), and G protein-coupled receptor TGR5 (GPR130 or GPR131) expression. In contrast, renal FXR and TGR5 expression are increased by CR in the aging mice. FXR and TGR5 expression are also increased in the long-lived Ames dwarf mouse. The purpose of the present study was to determine if activation of FXR and TGR5 in the kidneys of ad lib fed aging mice have similar effects to CR.

Methods: We studied 5 month old ad lib fed, 24 month old ad lib fed, 22 months old ad lib fed mice treated with the dual FXR/TGR5 agonist INT-767 for 2 months, and compared them to lifelong 24 month old CR mice.

Results: Treatment of 22 month old ad lib fed aging mice with FXR/TGR5 dual agonist INT-767 for 2 months decreases albuminuria, TGF-β expression, and fibronectin accumulation in aging mice. INT-767 stimulates mitochondrial biogenesis, increases mitochondrial DNA content, and mitochondrial transcription factors Nrf-1 and Tfam in the aging kidney. INT-767 also increases the expression of SIRT1, PGC-1α, and ERRα mRNA expression. INT-767 activation of the mitochondrial NAD-dependent deacetylase SIRT3 restores its targets MCAD and acetyl-LDH to normal levels, which are important for regulation of mitochondrial fatty acid β-oxidation as well as mitochondrial redox status. Furthermore, INT-767 increased expression of NAMPT and Nk1, enzymes involved in synthesis of sirtuins substrate NAD.

Conclusions: Our results therefore indicate that activation of FXR and TGR5 in the aging kidney reverses most of the age-related changes and the effects of FXR and TGR5 are similar to beneficial effects achieved by lifelong CR.

Funding: NIDDK Support
SA-PO751
ESRD in Nonagenarians in the United States, 1995 Through 2010
Donald J. Sexton, Scott Reule, Robert N. Foley. Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Patients in their 90’s are increasingly being considered for maintenance dialysis, comprehensive epidemiological data could help with decision making.

Methods: We used US census data and data for patients who initiated maintenance dialysis between 1995 and 2010 (N=1,557,117) to examine trends in ESRD for those aged 90 to 99 years (N=14,289).

Results: The rate of ESRD in 1995-1996 was 0.6 per million per year in those aged 90-99 years respectively. Standardized incidence ratios (SIRs) rose between 1995 and 2010 both overall (SIR 2.8), and in individuals (males 2.89, females 2.7) white (3.1) African American (1.93) and other races (2.43).Median survival was 10.7 months.

Unspecified renal failure” was the most common reported cause of ESRD (62.6%), followed by “diabetes mellitus type 2” (15.8%), “ATN without recovery” 3.4%, “GN (not histologically examined)” 3.18%, “renal artery stenosis” 2.44% and other 12.44%.Causes of death included: Cardiac deaths 42.4%, Infection 12.07%, Withdrawal of dialysis/ uremia 10.16%, Stroke/ Intracranial Hemorrhage 3%, Cachexia 2.99%, Cancer 2.45%, Other 12.03% and Unknown 14.89%. Mortality fell over time, AHR (95% CI) 0.79 (0.72, 0.87) in 2009-2010 vs 1995-1996. Factors associated with a higher likelihood of death included: ischemic heart disease (AHR 1.13), AV graft (AHR 1.36 vs AV fistula), or venous catheter for hemodialysis vascular access (AHR 1.7 vs AV fistula), shorter pre-dialysis nephrology care (AHR 1.37), higher eGFR at dialysis initiation (AHR 1.13), serum albumin < 3.5 g/dl (AHR 1.34), cerebrovascular disease (AHR 1.21), peripheral vascular disease (AHR 1.14), cancer (AHR 1.08), inability to ambulate (1.43) or transfer (1.59), “ATN without recovery” as a primary cause of ESRD (AHR 1.11 vs “renal failure not specified”).

Conclusions: ESRD in nonagenarians has risen over the period of observation in the United States. Rising prevalence may be attributable not only to rising incidence but to falling mortality also.

SA-PO752
Impact of Geriatric Multi-Morbidity Versus Medical Multi-Morbidity on Quality of Life in Older CKD Patients
Christopher Lane, 1 2 Jason D. Fantus, 1 2 Kieran Reid, 1 2 Leslie I. Katzel, 1 Stephen L. Seliger, 1 Daniel E. Weiner, 1 Roger A. Fielding, 1 2
1Boston Univ, Boston, MA; 2Tufts Univ, Boston, MA; 3Univ of Maryland, Baltimore, MD.

Background: Geriatric conditions are constellations of signs and symptoms not always linked to a disease, such as cognitive impairment and fatigue; geriatric conditions are associated with worse quality of life (QoL). Older adults with CKD are likely to have geriatric multi-morbidity (GM), defined as ≥2 geriatric conditions. Medical multi-morbidity (MM) is also common in this population and affects QoL. We compared the impact of GM vs MM on QoL in older CKD patients.

Methods: We used baseline data from an ongoing trial of exercise in persons ≥55 years with stage 3b-4 CKD. For GM, persons were defined with 1) cognitive impairment or Montreal Cognitive Assessment ≤26, 2) poor physical function if Short Physical Performance Battery ≤7, 3) dizziness as reported by Memorial Symptom Assessment Scale; 4) fatigue if responded ≥‘good bit of time’ to feeling worn out on Short Form-36 (SF-36); and 5) chronic pain if ≥‘moderate’ pain on SF-36. For MM, hypertension, diabetes, CAD, and stroke were self-reported. Severe depression was defined as Beck Depression Inventory ≥15. QoL was measured with the SF-36. Linear regression adjusting for age, sex, race, site, BMI, and eGFR was utilized.

Results: Of 72 persons (31% women, mean age 68.6±7.8 years, mean eGFR 33.3±9.8 ml/min/1.73m²), 49% (35) had GM and 76% (55) had MM. GM was associated with lower scores in all SF-36 subscales (all p<0.05). MM was associated with lower scores in two SF-36 subscales (both p<0.05).

Conclusions: In older adults with CKD, geriatric multi-morbidity is common and likely affects QoL.

<table>
<thead>
<tr>
<th>SF-36 Subdomain</th>
<th>Geriatric Multi-Morbidity</th>
<th>P value</th>
<th>Medical Multi-Morbidity</th>
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</tr>
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<td>Role-physical</td>
<td>-0.489</td>
<td>&lt;0.001</td>
<td>-0.060</td>
<td>0.61</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-0.650</td>
<td>&lt;0.001</td>
<td>-0.025</td>
<td>0.81</td>
</tr>
<tr>
<td>General health</td>
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<td>&lt;0.001</td>
<td>-0.259</td>
<td>0.02</td>
</tr>
<tr>
<td>Vitality</td>
<td>-0.524</td>
<td>&lt;0.001</td>
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<td>Social functioning</td>
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<td>&lt;0.001</td>
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<tr>
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<td>0.02</td>
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</tr>
<tr>
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<td>0.07</td>
<td>-0.106</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Funding: Private Foundation Support

SA-PO753
A Survey of Provider Knowledge, Attitude, and Practices Surrounding Conservative Management for Patients with Advanced Chronic Kidney Disease
Sanah Parvez, 1 Khaled Abdel-Kader, 1 V. Shane Pankratz, 1 Mi-Kyung Song, 1 Mark L. Unruh, 1 2
1Div of Nephrology, Univ of New Mexico; 2Div of Nephrology, Vanderbilt Univ; 3Adult and Geriatric Health Div; School of Nursing, Univ of North Carolina.

Background: Despite the potential benefits of conservative management (CM), discussing CM as a viable treatment option rarely occurs. Several factors might contribute to this but no studies in the U.S. have described them. The purpose of this survey was to describe nephrologists’ (NEPHs) and primary care providers’ (PCPs) knowledge, attitudes, and practices of CM for patients with advanced CKD.

Methods: We developed a survey based on the relevant literature to include items assessing knowledge, attitudes, and self-reported practices of CM for patients with advanced CKD. We then conducted a web-based cross-sectional survey between April and May 2015. We used the American Medical Association’s Physician Masterfile to identify NEPH and PCPs practicing in the U.S.

Results: 431 (67.6% NEPHs, 32.4% PCPs) providers completed the survey. The respondents were, on average, white, predominantly male, and in their 30s and 40s. A majority of both PCP (83.5%) and NEPH respondents (78.2%) reported that they were likely to discuss CM with their older advanced CKD patients. Self-reported number of patients managed conservatively was at least >11 patients for 30.6% NEPHs and 49.2% of PCPs. As shown in the figure where a higher percent demonstrates a lower barrier, the major barriers to CM discussions identified by NEPHs and PCPs significantly differed.

There were significant differences in knowledge across the groups with PCPs reporting significantly more uncertainty about survival rates with CM.

Conclusions: Both NEPH and PCP are comfortable with discussing CM with their patients. PCPs have less certainty regarding patient selection for CM and report feeling less informed about outcomes of CM.

Funding: Pharmaceutical Company Support - DCI Inc

SA-PO754
Which Therapeutic Project for Elderly Reaching ESRD? Patient’s Characteristics and Outcomes
Corinne Fafin, 1 2 Cecile Couchoud, 1 2 Cecile M. Vigneau, 1 Olivier Moranne, 1 2 3Nephrology, CHU Nice, Nice, France; 2REIN Registry, Agence de Biomédecine, St. Denis La Plaine, France; 3Nephrology, CHU Pontchaillon, Rennes, France.

Background: The KDIGO guidelines recommend referral for planning RRT in people at risk of kidney failure. Treatment without dialysis in ESRD patient is another therapeutic option especially in elderly. The objective of our study is to describe the therapeutic projects declared by nephrologist and associated patient’s characteristics and outcomes in a prospective design.

Methods: 573 patients over 75 y/o (82±5 y/o) with eGFR below 20 (14 ± 4) were included by nephrologists in 2009 and followed 4 years (Moranne et al 2012). At baseline, we recorded social, clinical characteristics and therapeutic project declared by nephrologist and associated patient’s characteristics and outcomes of these patients according to the therapeutic projects.

Results: The therapeutic project was STAB in 234 patients (41%), DIAL in 216 pts (38%), NDne in 66 (12%) and NDpt in 55 (10%). Patients were older in ND group, with more women for NDpt and more comorbidities for NDne (dementia, active malignancy,
CVD, less physical autonomy). After 4 years follow-up, the number of death before dialysis and during the first dialysis month were 10%/85% for DIAL, 42%/34% for STAB, 67%/20% for NDpt and 95%/2% for NDN respectively. There was significantly more emergency start for the NDpt group starting nevertheless dialysis. In all groups, the main reasons declared by nephrologist to start dialysis were: eGFR level, fluid overload and weight lost.

Conclusions: In this study, we observed many patients with stable conditions and high risk mortality which anyway raises the issue of dialysis options and care organization. Although some patients expressed their willingness not to start dialysis at one point or another, it could nonetheless occur but with worst condition. On the contrary, if the dialysis options exist and retain by the nephrologists, it will not occur.

Funding: Pharmaceutical Company Support - Roche, Baxter, Amgen, Fresenius, MSD, Shire
Agence de Biomédecine; Société Francophone de Dialyse, Government Support - Non-U.S.

SA-PO755
Specific Prognosis Factors of Death and Dialysis Start for Elderly Patients Reaching ESRD in the Prospective PSPA Cohort Study
Hwa Liu,1 Yeda Aparecida Oliveira Souza,1 Emmanuel A. Burdmann,1 Cécile Couchoud,2 Cécile M. Vigneau,3 Olivier Moranne.1
Nephrology, CHU Nice, Nice, France; 2Agence de Biomédecine, REIN, St Denis de la Plaine, France; 3Nephrology, CHU Pontchaillon, Rennes, France.

Background: The death before dialysis start is high in elderly patients reaching ESRD and the treatment without dialysis is another option. We need to better predict the outcomes of this specific population and identify prognosis factors to improve strategies of care. The objective of our study is the identification of prognosis factors of dialysis start or death before dialysis in a multicenter prospective cohort of elderly reaching ESRD.

Methods: 573 patients over 75 yrs ([82,5] yrs) and with eGFR below 20 (eGFR14 ≥ 4 mL/min/1.73m²) were included by nephrologist in 2009-10 (Moranne et al 2012). At baseline, we recorded social and clinical characteristics, laboratory test and medications. Information about death or dialysis status is available for all patients after 4 years follow-up. Prognosis factors for dialysis start or death before dialysis were quantified with subdistribution hazard ratios using proportional hazard regression models constructed according to Fine and Gray to take account competiting risks.

Results: After 4 yrs follow-up, 274 patients (48%) started dialysis and 223 (39%) died. Compared to patients without dialysis, the patients independently associated with higher risk of death prior to dialysis are: higher age, male, diabetes, lower eGFR, behavioural disorder, less mobility, cerebrovascular disease, cardiac heart failure, active malignancy and anemia. The variables associated to higher probability of dialysis start are: lower age, male, lower eGFR, high blood pressure, hyperphosphatemia, higher proteinuria, chronic respiratory disease, cerebrovascular disease and less behaviour disorder or active malignancy.

Conclusions: We observed a higher probability of dialysis start than death before dialysis in this population. The results exclude changes independently associated by the different characteristics according to the study. We identified specific prognosis factors that could discriminate the risk of starting dialysis or died before dialysis to help organisation of the CKD 5 care in elderly patients.

Funding: Pharmaceutical Company Support - roche bucher amgen fresenius msd shire

SA-PO756
Ageing and Decreased GFR: A 1,249,388 Elderly Population-Based Study
Regina C.R.M. Abdulka1der,2 Mario Lucia Lebrão,1 Dirce M.T. Zanetta.1
1Div of Nephrology, Univ of Sao Paulo Medical School, Sao Paulo, SP, Brazil; 2Epidemiology, School of Public Health of the Univ of Sao Paulo, Sao Paulo, SP, Brazil.

Background: GFR decreases with ageing and so a low GFR in old people might occur due to a physiologic process instead of being a mark of a disease. However, comorbidities can superimpose on this process, and reduce GFR by a pathologic course. This study aims to assess the frequency of isolated low GFR without coincident diseases in a geriatric population in a developing country megalopolis.

Methods: A multistage cluster sampling (1,353 inhabitants) was used in order to obtain a sample representative of the elderly population of São Paulo megalopolis (1,249,388 inhabitants aged ≥50 years). Participants answered a survey on socio-demographic factors and health and had urine and blood samples collected. GFR < 60 mL/min/1.73m² (estimated by the abbreviated MDRD equation) was defined as low and presence of hematuria or proteinuria as kidney damage. Data are presented as weighted proportion or means and standard errors. Comparisons were made by chi-square with Rao-Scott correction or t-test.

Results: Individuals with GFR < 60 (19.8%) were older (75 ± 1 vs. 69 ± 1 y, p<0.001), had lower education level, more hypertension, diabetes and cardio-vascular disease and more kidney damage (35% vs 15%, p<0.001), when compared with the group with GFR ≥ 60. In the low GFR group only 25% of the individuals had no simultaneous diseases and no kidney damage.

Conclusions: Low GFR was associated with kidney damage and/or coincident chronic diseases that might affect the kidneys in this population. These data strongly suggest that in this group of geriatric individuals low GFR is indicative of renal damage. Funding: Government Support - Non-U.S (FAPESP, Ministério da Saúde, Brasil). Funding: Government Support - Non-U.S.

SA-PO757
Indoxyl Sulfate, a Representative Uremic Toxic, Suppresses Myogenic Differentiation: Implication in Uremic Sarcopenia
Chih-Kang Chang,1,2 Un Jong Ao,1 Yuan-Siao Chen,1 Shing-Hwa Liu.1 Inst of Toxicology, College of Medicine, National Taiwan Univ, Taipei, Taiwan; 2Dept of Integrated Diagnostics and Therapeutics and Internal Medicine, College of Medicine, National Taiwan Univ, Taipei, Taiwan.

Background: Sarcopenia (or muscle wasting) is a common feature of the uremic phenotype and retards the process of sarcopenia progression. Myogenic differentiation is disturbed by the uremic toxins and contribute to sarcopenia and frailty. We hypothesized that indoxyl sulfate (IS), a representative protein-bound uremic toxin, might disturb skeletal myobute differentiation and contribute to sarcopenia and frailty.

Methods: The mouse myoblast cell C2C12 was applied to evaluate myobute differentiation and signaling. Cell viability evaluated by MIT assay. Cell morphology was observed by microscope. Hematoxylin and eosin staining morphologically analyzed the multinucleated myobute formation. The expressions of myogenic differentiation markers and related signaling proteins were determined by Western blotting.

Results: We first investigated the non-lethal concentration of IS by MTT assay, and found IS level less than 1mM without significant cellular toxicity as compared with control group. In order to development the protocol, we confirmed myobutes were visibly formed throughout 4 days of differentiation first. IS significantly attenuated the number of myobutes and the percentage of mature myobutes. Furthermore, IS significantly and dose-dependently decreased the expression of MyoD, Myogenin and myosin heavy chain, which is the representative markers of slow and fast myobute phenotype, both in translational and transcriptional level. The molecular signals of myobute differentiation were also disturbed by IS treatment.

Conclusions: These findings suggest that IS, a uremic toxic, dysregulates myobute differentiation in C2C12 cells. This is the first time to provide additional evidence that IS might contribute to the development of sarcopenia in uremic patients. Further explore would give the light to provide potential therapeutics in uremic sarcopenia.

Funding: Other NIH Support - MOST in Taiwan

SA-PO758
Attitudes, Experiences and Perspectives of Elderly Kidney Transplant Recipients: Thematic Synthesis of Qualitative Research
Jule Pinter,1 Camilla Sara Hanson,1 Jonathan C. Craig,1 Jeremy R. Chapman,1 Klemens Buddke,2 Fabian Halleck,2 Allison Tong.1
1Univ of Sydney; 2Charité - Universitätsmedizin Berlin.

Background: Kidney transplantation offers improved survival and quality of life in an increasing number of elderly patients with end-stage kidney disease. However, elderly kidney transplant recipients may face unique challenges due to a higher burden of comorbidity, greater cumulative risk of immunosuppression-related complications, and increasing frailty. We aimed to describe the perspectives of elderly kidney transplant recipients.

Methods: Electronic databases were searched to April 2015. Thematic synthesis was used to analyze the findings.

Results: 41 studies involving more than 120 kidney transplant recipients aged 60 yrs and over were included (29 studies did not specify number of patients aged ≥ 60 yrs). We identified 6 themes. Regaining strength and vitality meant valuing the marked physical and psychosocial improvements in daily functioning and life participation. Extending life was the willingness to accept an organ, including an extended criteria kidney, to prolong survival. Debt of gratitude entailed a need to be consciously appreciative towards their donor knowing they were unable to repay their sacrifice. Moral responsibility of maintaining health motivated adherence to medication and lifestyle recommendations out of an ethical duty to protect their gift and prolong graft survival. Disillusionsment with transplant reflected disappointment and exasperation at having to contend with side effects and adverse events such as cancer, and residual physical limitations. Finality of treatment option reflected an acute awareness that their current transplant may be their last and some would not return to dialysis if the transplant failed.

Conclusions: Kidney transplantation reverses deterioration of functioning and well-being that patients experienced whilst on dialysis. However, elderly transplant recipients may have anxieties about debilitating adverse events, comorbidities, and a sense of vulnerability that the current transplant may be their last. Addressing these concerns in the care of elderly kidney transplant recipients may improve treatment outcomes in this growing population.

SA-PO759
New Perspectives on the Evolution of Quality of Life and Depression Among Hemodialysis Patients
Christiane Hegedus Karam, Nadia Guimaraes-Souza, Adriano Luiz Ammirati, Maria C.C. Andréoli, Thais Nemoto Matsui, Fabiana Dias Carreira, Rosana Andrade, Maria Amâncio, Gean Mezzalira, Bento C. Santoso. Nephrology, Hospital Albert Einstein, São Paulo, Brazil.

Background: Hemodialysis is the most common treatment for patients with chronic kidney disease. Five to 22% of these patients have a psychiatric condition. The objective of this study was to evaluate the quality of life perception and depression symptoms in three groups of age (<65, 65-75, >65 y.o.).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: This was a retrospective observational study. Clinical and social demographic data were collected from clinical records. The Kidney Disease Quality of Life and Depression inventory were used to assess quality of life and depression symptoms.

Results: 104 patients were included. 68.3% were men, 71.2% married, 91.3% Caucasian and 44.2% were in productive life period. A relation between quality of life score and time in dialysis was observed (p=0.0118, CI -0.023; 0.0003). Patients younger than 65 y.o. showed more favorable results, such as general health perceptions, emotional well-being, fatigue, pain, and dialysis staff encouragement. Patients between 65 to 75 y.o. showed lower energy/fatigue index (11.98; CI -22.92; -1.02) and a reduction of 18.97 points (IC: -33.97; -3.98) for emotional well-being. A 15.04-point (CI -27.21; -2.87) and a 14.78-point (p<0.001; -26.46; -1.10) reduction, for patients between 65-75 y.o. and for older than 75 years, respectively, was observed in physical function. Burden of kidney disease had a reduction of 13.29 (-25.46, -1.18) and sexual function reduced 69% (27%; 87%) in 65-75 y.o. patients. Patients older than 75 years had a significant increase in quality of social interaction (17%; CI: 1%;36%) and an increase of 16% (CI 3% -30%) in social support. Depression correlated with time in hemodialysis (p = 0.0007; CI 0.14%; 0.55%). For each month an increase of 0.35% on depression symptoms was found.

Conclusions: For patients younger than 65 years hemodialysis treatment represents a rehabilitation possibility. Patients over 75 years had significant increase on social support and social interaction. Patients 65 to 75 y.o. had worse perception of quality of life.

SA-PO760
Fibroblast Growth Factor 23 and the Risk of Infection-Related Hospitalization in Older Adults: The Cardiovascular Health Study

Kristen L. Nowak,1 Traci M. Bartz,2 Lorien S. Dalrymple,1 Joachim H. Ix,1 Ian H. De Boer,3 Bryan R. Kestenbaum,2 Michael Shlipak,4 Pranav S. Gariianna,1 Michel Chonchol.1 1Univ of Colorado Denver; 2Washington University; 3Univ of California Davis; 4Univ of California San Diego; 5Univ of California San Francisco; 6Tufts Medical Center.

Background: Fibroblast growth factor 23 (FGF23) may inhibit 25-hydroxyvitamin-D-1α-hydroxylase (CYP27B1) in monocytes. We hypothesized that higher circulating FGF23 levels might lead to an increase in serious infection risk because FGF23 decreases the intracrine production of 1,25-dihydroxyvitamin D (1,25(OH)2 D), which consequently reduces production of cathelicidins.

Methods: Plasma C-terminal FGF23 concentrations were measured in 3141 Caucasian and 44.2% were in productive life period. A relation between quality of life score and time in dialysis was observed (p=0.0118, CI -0.023; 0.0003). Patients younger than 65 y.o. showed more favorable results, such as general health perceptions, emotional well-being, fatigue, pain, and dialysis staff encouragement. Patients between 65 to 75 y.o. showed lower energy/fatigue index (11.98; CI -22.92; -1.02) and a reduction of 18.97 points (IC: -33.97; -3.98) for emotional well-being. A 15.04-point (CI -27.21; -2.87) and a 14.78-point (p<0.001; -26.46; -1.10) reduction, for patients between 65-75 y.o. and for older than 75 years, respectively, was observed in physical function. Burden of kidney disease had a reduction of 13.29 (-25.46, -1.18) and sexual function reduced 69% (27%; 87%) in 65-75 y.o. patients. Patients older than 75 years had a significant increase in quality of social interaction (17%; CI: 1%;36%) and an increase of 16% (CI 3% -30%) in social support. Depression correlated with time in hemodialysis (p = 0.0007; CI 0.14%; 0.55%). For each month an increase of 0.35% on depression symptoms was found.

Conclusions: For patients younger than 65 years hemodialysis treatment represents a rehabilitation possibility. Patients over 75 years had significant increase on social support and social interaction. Patients 65 to 75 y.o. had worse perception of quality of life.

SA-PO761
Characteristic of the Elderly Patients in the Chronic Renal Insufficiency Standards Implementation Study (CRISIS) Cohort Compared to Their Younger Cohort A Descriptive Analysis

Maharajan Raman, Darren Green, James Ritchie, Thilini Nishani Abeygunaratne, Smeeta Sinha, Philip A. Kalra. Renal Medicine, Salford Royal NHS Foundation Trust, Salford, Manchester; United Kingdom.

Background: CKD in the Elderly is associated with high mortality and slower rate of progression to ESRD. Identifying the characteristics of this phenotype and modifying their risk may reduce the burden of death but this can be challenging due to the heterogeneity of the disease in this group.

Methods: The CRISIS cohort of 2706 participants was divided into four groups based on their age. Descriptive statistical analysis was performed using SPSS and in between group significance was calculated using one way ANOVA or Chi-Square test.

Results: Essential characteristics of the cohort are shown in the table below.

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;55years</th>
<th>55-&lt;65years</th>
<th>65-&lt;75years</th>
<th>&gt;75years</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
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<td>507</td>
<td>823</td>
<td>732</td>
<td>0.000</td>
</tr>
<tr>
<td>Age(years)</td>
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<td>60.5± 2.8</td>
<td>70± 2.8</td>
<td>80± 3.7</td>
<td>64.5</td>
</tr>
<tr>
<td>Male(%)</td>
<td>56.4</td>
<td>63.9</td>
<td>64</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td>Current Smoker(%)</td>
<td>19.7</td>
<td>15</td>
<td>12.2</td>
<td>5.2</td>
<td>-</td>
</tr>
<tr>
<td>Systolic Blood Pressure*</td>
<td>131.6± 22.9</td>
<td>138.2± 22</td>
<td>141.2± 23.6</td>
<td>141.59± 25.7</td>
<td>0.000</td>
</tr>
<tr>
<td>eGFR(ml/min/1.73m2)*</td>
<td>35.9± 19.0</td>
<td>119.4± 201.5</td>
<td>34.6± 17.7</td>
<td>32± 16.4</td>
<td>28.7± 13.2</td>
</tr>
<tr>
<td>Primary Renal Disease(%)</td>
<td>Hypertension</td>
<td>5.3</td>
<td>10.1</td>
<td>14.1</td>
<td>19.9</td>
</tr>
<tr>
<td>APVD</td>
<td>3</td>
<td>7.5</td>
<td>14.8</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>14.8</td>
<td>20.1</td>
<td>19.9</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Obstructive Uropathy</td>
<td>0.8</td>
<td>1.4</td>
<td>1.3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Gliomerulonephritis</td>
<td>25.8</td>
<td>20.7</td>
<td>12.4</td>
<td>7.5</td>
<td></td>
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<tr>
<td>Pyelonephritis</td>
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<td>5.1</td>
<td>2.6</td>
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<td></td>
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<tr>
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<tr>
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<td>12.4</td>
<td>14.8</td>
<td>20.5</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: The group aged >75 years had the highest incidence of death and accumulation of co-morbidities. We aim to develop a risk prediction model to identify the characteristics of this phenotype, which may help in modifying their risk.

SA-PO762
Muscle Strength Rather Than Muscle Mass Is More Important in Evaluating Physical Function in Elderly Patients with Predialysis Chronic Kidney Disease

Yasuhiro Taki, Koji Hiraki, Keita Uehara, Hiro Kawarazaki, Tsutomu Sakurada, Yugo Shibagaki.1 1Dept of Nephrology and Hypertension, St. Marianna School of Medicine, Kawasaki, Kanagawa, Japan; 2Dept of Rehabilitation Medicine, St. Marianna School of Medicine, Kawasaki, Kanagawa, Japan.

Background: Recently, physical function has been reported to be strongly associated with prognosis of patients with chronic kidney disease (CKD). Sarcoopenia is well described in CKD patients on dialysis especially of the elderly and is known to be associated with reduced physical function, but whether this is the case in elderly predialysis CKD is undetermined.

Methods: We enrolled consecutive 85 elderly patients (age over 60) with predialysis CKD (estimated GFR< 60 ml/min/1.73m2) in outpatient nephrology clinic at St Marianna University Hospital. We evaluated kidney functional parameters, muscle mass by bioimpedance, muscle strength by dynamometer (hand grip, knee extension) and 4-meter walking speed in these participants.

Results: Average age was 74 years old, 76% were men, 33% had diabetes mellitus (DM) and average eGFR was 28.6ml/min/1.73m2. Patients were divided into those with eGFR<30 or >30. After adjustment for age, gender and history of DM, hand grip strength (<4.36, 95%CI: -0.85–7.85), knee extension strength (-5.62, 95%CI: -2.28–8.97) and 4-meter walking speed (>0.12, 95%CI: -0.02–0.22) were significantly reduced in those with eGFR<30. However, there was no difference in muscle mass (-0.23, 95%CI: -0.68–0.23).

Conclusions: In conclusion, muscle strength and walking speed but not muscle mass decreased along with progression of CKD. Thus, it seemed more important to check muscle strength and walking speed rather than muscle mass when evaluating physical function in elderly patients with predialysis CKD.

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

803A
SA-PO763

Lower Muscle Endurance, Strength and Quality Are Associated with Greater Risk of Functional Limitations in Older Adults with CKD


**Background:** Chronic kidney disease is associated with inflammation and insulin resistance contributing to fatigue and muscle weakness. The association of muscle endurance, strength, and quality with functional limitation among persons with CKD is unknown.

**Methods:** We studied 186 participants with eGFR<60 at the year 3 Health ABC visit. Participants were excluded if unable to complete >90% of quadriceps isokinetic fatigue testing. Quadriceps endurance was defined by total work using isokinetic dynamometer. Quadriceps strength was measuring by isometric torque. Lean leg mass (legml) was measured using DXA. Muscle quality was defined by specific work (work/legml) and specific torque (torque/legml). Outcome was incident persistent severe lower extremity limitation (PSLL) based on 2 consecutive reports of having a lot of difficulty or inability to walk 1/4 mile or climb 10 steps without resting. We used competing risks regression.

**Results:** Participants had a mean age 76.2 ±3yrs, eGFR<60 of 49.2 ±10. None had mobility disability. There were 82 PSLL events over a median 6 years. After adjustment each 1-SD lower quadriceps isokinetic work and isometric maximal torque were associated with mobility disability. There were 82 PSLL events over a median 6 years. After adjustment each 1-SD lower quadriceps isokinetic work and isometric maximal torque were associated with functional limitation among persons with CKD. The association of muscle endurance, strength, and quality with functional limitation among persons with CKD is unknown. Adjusted SHR Adjusted SHR

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Standardized β</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isokinetic Work (Joules)</td>
<td>1.26 (0.99, 1.61)</td>
<td>1.38 (1.04, 1.85)*</td>
</tr>
<tr>
<td>Specific work (Joules/kg)</td>
<td>1.32 (1.06, 1.64)</td>
<td>1.38 (1.09, 1.76)*</td>
</tr>
<tr>
<td>Isometric Torque (N*m)</td>
<td>1.37 (1.01, 1.79)*</td>
<td>1.43 (1.01, 2.03)*</td>
</tr>
<tr>
<td>Specific Torque (N*m/kg)</td>
<td>1.46 (1.10, 1.94)*</td>
<td>1.42 (1.04, 1.93)*</td>
</tr>
</tbody>
</table>

**Conclusions:** Among older adults with CKD free of mobility disability, lower muscle endurance, strength, and quality are independently associated with greater risk of severe lower extremity limitation. 

**Funding:** NIDDK Support, Other NIH Support - NIDDK K23DK099442 Health ABC study funded by NIA

SA-PO764

Efficacy and Safety of Exercise Training in Patients with Predialysis Chronic Kidney Disease

Yuho Shibagaki, Koji Hiraki, Takashi Yasuda, Kenjiro Kimura. Div of Nephrology and Hypertension, St. Marianna Univ; Div of Rehabilitation, St. Marianna Univ.

**Background:** Efficacy and safety of exercise training has not been well studied in patients with predialysis chronic kidney disease (CKD). Since we have reported in elderly patients with predialysis CKD that there was a significant reduction in muscle strength and short-term exercise did not damage kidney, we conducted a randomized controlled trial to elucidate the long-term efficacy and safety of exercise in this population.

**Methods:** Study design was a randomized controlled trial. Thirty six male elderly patients with CKD stage 3-4 were studied. Patients with eGFR<60 of 49.2 ±10. None had mobility disability. There were 82 PSLL events over a median 6 years. After adjustment each 1-SD lower quadriceps isokinetic work and isometric maximal torque were associated with functional limitation among persons with CKD. The association of muscle endurance, strength, and quality with functional limitation among persons with CKD is unknown. Adjusted SHR Adjusted SHR

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Standardized β</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.25</td>
<td>0.005</td>
</tr>
<tr>
<td>African-American</td>
<td>0.08</td>
<td>0.3</td>
</tr>
<tr>
<td>Male</td>
<td>0.41</td>
<td>&lt;.001</td>
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<tr>
<td>Diabetes</td>
<td>0.01</td>
<td>0.9</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>-0.25</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>-0.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GFR</td>
<td>0.09</td>
<td>0.3</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.19</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Estimated METS: Mean achieved METS was 5.6±1.8. Although there was low bias for estimated vs. achieved METS (mean difference, -0.45), precision and accuracy were poor, with only 35% of predicted values within 1 MET of achieved values, and nearly one third of estimated values >30% different from achieved.

**Conclusions:** Among older adults with CKD stage, CRF as reflected by VO2peak is markedly impaired. Lower hemoglobin, obesity, and prevalent cardiac disease are associated with worse aerobic capacity. The use of estimated METS during treadmill testing poorly estimates actual aerobic capacity. 

**Funding:** NIDDK Support, Veterans Administration Support

SA-PO765

Determinants of Impaired Cardiorespiratory Fitness in Older Adults with CKD

Stephen L. Seliger, Jamie Giffuni, Roger A. Fielding, Eamon F. Fleming, Christine Liu, Leslie I. Katzel, Kieran Reid, Sushrut S. Waikar, Andrew M. Well, Daniel E. Weiner. Medicine, U Maryland Sch of Medicine; GRECC, VA Maryland Healthcare System; Tufts Univ Sch of Medicine; Boston Univ Sch of Medicine; Brigham and Women's Hospital; Emory Univ School of Medicine.

**Background:** Chronic Kidney Disease (CKD) may be associated with impaired cardiorespiratory fitness (CRF). We examined methods of estimating CRF in CKD and identified factors associated with CRF.

**Methods:** We measured peak aerobic capacity (VO2peak) using a modified Graded Exercise Treadmill Test (GXT) in 71 older adults with CKD stage 3b-4 in an ongoing exercise clinical trial. GFR was estimated with the CKD-Epi equation. Linear regression was used to examine factors associated with VO2peak. Resting VO2 was measured prior to GXT in seated position. Metabolic Equivalents of Task (MET, oxygen consumption during exercise relative to rest) was estimated at peak exercise based on GXT stage and compared to actual achieved METS.

**Results:** Mean age was 68.4±7.7 years; 61% African-Americans; 30% women; mean eGFR was 33±11 ml/min/1.73m² and mean Hb was 12.3±1.6 g/dL. Mean VO2peak was 17.4±5.4 ml/kg/min, which was 31±17% lower than expected based on normative values (p<0.001). In a multivariate model including demographics and co-morbidity, lower hemoglobin - but not GFR - was associated with lower VO2peak (Table). Albuminuria did not correlate with VO2peak.

SA-PO766

Access to Kidney Transplantation and Outcomes of Those Listed for Kidney Transplant in Elderly

Pritika Shrivastava, Ankit Sakhuja, Diane M. Cibrik, Abhijit S. Naik. Div of Transplant Nephrology, U Michigan, Ann Arbor, MI.

**Background:** Data suggests that patients above 70 years of age (>70 y.o.) with ESRD derive a benefit from kidney transplant (KT). We report our single center experience of access to transplant and outcomes for those >70 y.o. listed for KT. We used the number of evaluations in a year and rate of acceptance after evaluation as surrogate markers for KT access in elderly.

**Methods:** We assessed the rate of acceptance for KT and its trends over the years for those >70 y.o. between 2000-2014. Linear regression was used to assess trends over time. Differences in rates of listing stratified by diabetes status, KT rates among those approved for listing by diabetes status and mortality among those transplanted vs waitlisted was assessed.

**Results:** Over 15 year period, we evaluated 612 elderly patients (pts). 25.3% of those evaluated were approved to list for transplant. There were 9 patients who were evaluated twice of those 5 were approved for listing the second time and two got transplanted. There was 300% increase in annual evaluation of the elderly from year 2000 to 2014 and trend towards increased acceptance rate of those evaluated (slope=0.82, p=0.12).

**Conclusions:** Only the advice on exercise training could increase the physical activity and muscle strength without compromising kidney function in the elderly patients with predialysis CKD.
The acceptance rate was lower in diabetics compared to non-diabetics (18.2% vs 32.0%; p<0.001). 38.0% of listed pts have been transplanted and the rate of transplant did not differ by diabetes status. Of those transplanted 59.3% had living donors. Mortality among those transplanted was 64.4% in comparison to 87.3% of those Waitlisted (p<0.001).

Conclusions: Only a fourth of those ≥70 evaluated for KT were accepted for listing, though there has been some improvement in the acceptance rate over time. Acceptance rate was significantly lower among elderly diabetics. Mortality though improved remains significantly high for transplant vs waitlisted patients.

SA-PO767

P-Cystatin C Improves GFR Estimation in Older People  
Karin Werner,1 Anders G. Christensson,2 Mats Pihlsgård,1 Söolve Elmståhl,1 1Dept of Geriatrics, Lund Univ, Malmo, Sweden; 2Dept of Nephrology and Transplantation, Lund Univ, Malmo, Sweden.

Background: There is a need for validation of commonly used cystatin C and creatinine based formulas for eGFR (estimated glomerular filtration rate) in the older segment of the general population for all levels of kidney function.

Methods: Markers used for eGFR estimation were P-Cystatin C and P-Creatinine. Measured GFR (mGFR) adjusted to body surface area was performed by a single sample iohexol clearance in 112 participants, aged 70-100 years old from the population-based cohort “Good Aging in Skåne”. The participants were selected to cover a wide range of kidney function and to obtain an even distribution regarding sex and age. The timing of the sample depended on eGFR (eGFR >50, 25-50, and >25 at 4, 7, and 24 hours respectively). Formulas using both markers (CKD EPI combined, Lund-Malmö combined, BIS2), only creatinine (CKD EPI creatinine, MDRD) and only cystatin C (CKD EPI cystatin C) were compared. The analysis included bias (median difference: mGFR-eGFR), precision (IQR: interquartile range of the differences), accuracy (P30: percentage of estimates ±30% of mGFR) as well as accuracy (P30) above and below mGFR 45.

Results: There were 57 women and 55 men. Mean age was 82 years and mean GFR 55 ml/min per 1.73m². Results are presented in the table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 1 year increase</td>
<td>1.05 (1.03, 1.07)</td>
</tr>
<tr>
<td>Male sex vs. female</td>
<td>1.16 (0.87, 1.55)</td>
</tr>
<tr>
<td>African American vs. not</td>
<td>0.82 (0.58, 1.16)</td>
</tr>
<tr>
<td>Smoke</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>1.15 (0.64, 2.07)</td>
</tr>
<tr>
<td>Missing</td>
<td>1.26 (0.67, 2.36)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>2.22 (0.85, 5.76)</td>
</tr>
<tr>
<td>18.5-25 kg/m²</td>
<td>Ref</td>
</tr>
<tr>
<td>25-29.9 kg/m²</td>
<td>0.74 (0.52, 1.06)</td>
</tr>
<tr>
<td>30+ kg/m²</td>
<td>0.87 (0.60, 1.27)</td>
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<td>Diabetes mellitus</td>
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<tr>
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<tr>
<td>Cerebrovascular disease</td>
<td>0.96 (0.64, 1.42)</td>
</tr>
<tr>
<td>COPD</td>
<td>0.82 (0.44, 1.53)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.76 (1.27, 2.45)</td>
</tr>
<tr>
<td>CAD</td>
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<tr>
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</tr>
<tr>
<td>Alcohol use</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>0.73 (0.52, 1.04)</td>
</tr>
<tr>
<td>missing</td>
<td>0.98 (0.57, 1.69)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.69 (0.37, 1.30)</td>
</tr>
<tr>
<td>Albumin (g/dl) per 1 unit increase</td>
<td>0.75 (0.59, 0.96)</td>
</tr>
<tr>
<td>Potassium (meq/l) per 1 unit increase</td>
<td>0.92 (0.74, 1.13)</td>
</tr>
<tr>
<td>AVF access</td>
<td></td>
</tr>
<tr>
<td>No AVF</td>
<td>Ref</td>
</tr>
<tr>
<td>AVF present</td>
<td>0.35 (0.20, 0.61)</td>
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<tr>
<td>Missing</td>
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</tr>
</tbody>
</table>

Conclusions: All the formulas that include cystatin C performed well in this Swedish cohort with a mean age above 80. This confirms that it is safe to use either of those formulas in our older patients across a wide spectrum of kidney function. However, the formulas based solely on creatinine are not reliable enough below GFR 45. Further sub-analysis can demonstrate detailed performance for males and females respectively, for all CKD-stages and for smaller age-intervals.

Funding: Government Support - Non-U.S.

SA-PO768

Factors Associated with Early Death After Dialysis Initiation Among Elderly CKD Patients  
Fahad Saeed, Susana Arrigain, Jesse D. Schold, Joseph V. Nally, Sankar D. Navaneethan. Nephrology, Cleveland Clinic.

Background: There are limited studies examining prognosis for elderly CKD patients following dialysis initiation. Herein, we evaluated the factors associated with poor one year survival after dialysis initiation among elderly CKD patients at our institution.

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

SA-PO769

Differential Significance of Prognostic Factors for 6-Month and 3-Year Mortality in Elderly Patients on Hemodialysis  
Koji Harada,1 Azusa Izumiya,1 Tomohiro Kawamura,2 Juri Tsukahara,1 Koichi Sumida,3 Yukinari Yamaguchi,4 Yasuhiko Akai,5 1Dept of Nephrology, Rakunakai-Otsu Hospital, Yamashina, Kyoto, Japan; 2Center for Postgraduate Training, Nara Medical Univ, Kashihara, Nara, Japan.

Background: As the population of elderly people has been growing, the number of older chronic kidney disease patients commencing renal replacement therapy (RRT) is increasing. The survival advantage of RRT may be counterbalanced by the burden of treatment and its negative effect on quality of life in the elderly, and old age is no longer seen as a contraindication to RRT. Therefore, it is important to evaluate survival factors in this population. We conducted this study to investigate prognostic factors for mortality in elderly patients starting hemodialysis (HD) for end-stage renal disease (ESRD).

Methods: We studied 621 CKD patients≥65 years from an EMR based CKD registry linked to the USRDS data. We retrospectively analyzed factors associated with one year mortality after dialysis initiation including: age, sex, race, presence of diabetes, hypertension, BMI, stroke, CHF, COPD, malignancy, peripheral vascular disease, depression, alcohol use, smoking, presence of AVF, pre-dialysis serum albumin and potassium.

Results: In our study, 224 (36%) patients died within the first year of dialysis initiation. Results from the Cox proportional model showed that older age and CHF were associated with early deaths, while higher albumin, presence of AVF and HTN were associated with a lower hazard of early death.

Conclusions: CHF and older age in the pre-dialysis setting are associated with higher 1-year mortality after dialysis initiation. These prognostic data need to be presented to geriatric CKD patients while discussing renal replacement therapy options.

Table. Multivariable Cox model of 1 year mortality among elderly CKD patients

<table>
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</tr>
</tbody>
</table>
Methods: This is a single-center, retrospective cohort study from January 2009 to December 2014. In total, 90 ESRD patients commencing HD were enrolled. All the patients were aged 65 years or older. Six-month and 3-year survival rates and prognostic factors for mortality were evaluated.

Results: The mean follow-up period was 21.7±18.3 months. The 6-month and 3-year survival rate were 94.0% and 66.9%, respectively. Age, unplanned initiation of HD, presence of heart failure, high value of estimated GFR on starting HD, Charlson comorbidity index (CCI), and Eastern Cooperative Oncology Group Performance Status scale (ECOG-PS) were associated with 3-year mortality, whereas only the presence of heart failure and ECOG-PS were significant predictors of 6-month mortality. There was no significant difference in 6-month mortality rate between patients aged ≥ 80 and < 80. On the other hand, 3-year mortality rate of ≥ 80 year-old patients was significantly higher than that of < 80 (p: 53.3% vs: 80: 14.2%, p = 0.0004).

Conclusions: There is a variation of significance among different prognostic factors according to the duration of life after starting hemodialysis. The presence of heart failure and ECOG-PS predicted short-term mortality among elderly ESRD patients starting HD. These results might help clinical decision making when nephrologists considering commencing HD for elderly ESRD patients.

SA-PO770
Cumulative Cardiovascular Polypharmacy Is Associated With the Risk of Geriatric Acute Kidney Injury
Chia-Ter Chao,1 Hung-Bin Tsai.1, 2
1Dept of Medicine, National Taiwan Univ Hospital Jin-Shan Branch, New Taipei City, Taiwan; 2Department of Nephrology, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Polypharmacy is common in the elderly due to multiple morbidities. However, the effect of polypharmacy on renal outcomes is rarely recognized. We investigated the effect of cardiovascular polypharmacy on acute kidney injury (AKI) in elderly patients.

Methods: We used the Taiwan National Health Insurance PharmaCloud system to investigate the relationship between cumulative cardiovascular medications in the 3 months prior to admission and risk of AKI in the elderly at admission to general wards. Community-dwelling elderly patients (>60 years) were prospectively enrolled and classified according to the number of pre-admission cardiovascular medications. Cardiovascular polypharmacy was defined as use of 2 or more relevant medications.

Results: We enrolled 152 patients, 48% with AKI (based upon Kidney Disease Improving Global Outcomes [KDIGO] classification) and 64% with cardiovascular polypharmacy. The incidence of AKI was higher in patients taking more cardiovascular medications (0 drugs: 33%; 1 drug: 50%; 2 drugs: 57%; 3 or more: 60%; p = 0.048). Patients with higher KDIGO grades also took more cardiovascular medications (p = 0.04).

Conclusions: We found that elderly patients taking more cardiovascular medications had increased risk for adverse renal events. Interventions that reduce polypharmacy may be able to reduce the incidence of geriatric AKI.

SA-PO771
Low Bicarbonate Associates with Higher Mortality Independent of pH in Healthy Older Individuals: The Health, Aging, and Body Composition Study
Kalani L. Raphael,1 Rachel A. Murphy,1 Michael Shipkai,1 Suzanne Satterfield,3 Hunter K. Huston,1 Anthony Sebastain,1 Deborah Sellmeyer,1 Kushang V. Patel,1 Anne B. Newman,2 Mark J. Sarnak,3 Joachim H. Ix,4 Linda F. Fried.7
1Dept of Medicine, Univ Medical Center Groningen, Groningen, Netherlands; 2Univ of California San Francisco, San Francisco, CA; 3Univ of Tennessee; Johns Hopkins Univ; Univ of Washington; Univ of Pittsburgh; Tufts Medical Center; Univ of California San Diego.

Background: Low serum [HCO₃⁻] associates with higher mortality in CKD. The purpose of this study is to determine if [HCO₃⁻] associates with all-cause mortality independent of systemic pH in healthy older persons.

Methods: Data were analyzed from the Health, Aging, and Body Composition Study, an observational study of black and white adults aged 70-79 years followed from 1997-2014. Arterialized venous blood gas measurements were obtained in 2,287 individuals. Participants were grouped into one of 3 [HCO₃⁻] categories: <23.0 (low), 23.0-27.9 (reference group), and ≥28.0 mEq/L (high). Mortality hazard ratios (HR) in the low and high [HCO₃⁻] groups were compared to the reference group using Cox models adjusted for demographics, eGFR, albuminuria, COPD, smoking, and pH. Multiplicative interaction terms tested whether CKD status modified the relationship between [HCO₃⁻] categories and mortality.

Results: The mean age was 76 years, 51% were female, and 38% were black. The mean pH was 7.41, mean [HCO₃⁻] was 25.1 mEq/L, 11% had low and 10% had high [HCO₃⁻]. The mean eGFR was 82.1 ml/min/1.73m²; 12% had CKD. During follow-up (mean 10.3 years), 1,326 (58%) participants died. The adjusted all-cause mortality HR was 1.24 (95% CI, 1.02-1.49) in the low [HCO₃⁻] category and 1.03 (95% CI, 0.84-1.26) in the high [HCO₃⁻] category compared to the reference group. CKD status did not modify the association between [HCO₃⁻] and mortality (p=0.74).

Conclusions: Healthy older persons with low [HCO₃⁻] have higher mortality risk than those with normal [HCO₃⁻] independent of pH and potential confounders. High [HCO₃⁻] does not associate with higher mortality. The potential health benefits of normalizing low [HCO₃⁻] in generally healthy older persons should be investigated.

Funding: Other NIH Support - National Institutes on Aging and National Institute of Nursing Research, Veterans Administration Support, Private Foundation Support

SA-PO772
Low Urinary Creatinine Excretion Is a Valid Surrogate for Frailty in Patients with Advanced Chronic Kidney Disease
Harmke Polinder-Bos,1 Hakan Nacak,2 Friedo W. Dekker,2 Stephan J.L. Bakker,1 Carlo A. Gaillard,1 Ron T. Gansevoort.1
1Dept of Internal Medicine, Univ Medical Center Groningen, Groningen, Netherlands; 2Epidemiology, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Muscle wasting is a key component of frailty, which is highly prevalent in advanced stages of chronic kidney disease (CKD). Whether low urinary creatinine excretion (UCrE), a marker of low muscle mass, is a valid surrogate for frailty in this population is unknown. We studied cross-sectional associations between frailty and a low UCrE in patients with CKD stages 4 and 5 (not on dialysis).

Methods: 2748 healthy individuals of the general population were included to define low UCrE. Low UCrE was defined as height-indexed UCrE below the age- and sex-specific 5th percentile. In a CKD population including 320 and 967 participants of the prepARE-2 and NECOSAD studies, associations of frailty, the individual components that define frailty, and frailty-associated variables with low UCrE were evaluated using multivariable logistic and linear regression models. Frailty was defined as a composite construct including self-reported poor physical functioning, exhaustion, low physical activity, and underweight.

Results: In the general population with a median age of 46 years, median UCrE was 9.8 mmol/day for women and 14.3 mmol/day for men, compared to 7.0 mmol/day and 9.5 mmol/day in CKD patients, respectively. In the CKD patients with a median age of 63 years, low UCrE was found in 38%. Frailty, and the individual components that define frailty, were associated with a low UCrE, independent of comorbidities (OR frailty = 2.19 [1.28-3.77], p=0.005). Of the frailty-associated variables, lower hemoglobin and albumin levels, and higher parathyroid hormone levels were associated with low UCrE. Adjustment for GFR attenuated the associations of frailty, and the individual components that define frailty with low UCrE, except for underweight.

Conclusions: Low UCrE is a valid surrogate for frailty, independent of comorbidities. Low UCrE is strongly determined by a lower kidney function, suggesting that reduced kidney function induces changes in muscle mass and performance leading to frailty.

SA-PO773
Oral Anticoagulation and Kidney Function in Elderly
Antonios Dousou,1 Elke Schaeffer,2 Olga Jakob,1 Reinhold Kreutz,1 Natalie Ebert.2
1Clinical Pharmacology, Charité; 2Nephrology, Charité; 3Clinical Epidemiology, Charité.

Background: In the past years new oral anticoagulants (NOACs) were approved expanding our pharmacological arsenal. Data on their utilization in elderly compared to vitamin K antagonists (VKA) are scarce and the impact of kidney function (KF) on NOAC use in a population with declining glomerular filtration rate (GFR) is of great interest. The present study investigates anticoagulant use and KF in people ≥ 70 years. Medication was assessed through personal interviews and coded using the Anatomical Therapeutic Chemical Classification System. For GFR estimation we used the CKD-EPI Cr equation. Predictor analysis was conducted via logistic regression.

Results: Figure 1 illustrates the percentage of drug use for the three NOACs and phenprocoumon, the most common VKA in Germany, over the course of 4 years.
Can Morbidity Predict Mortality in Dialysis Patients? Kathryn Dressard,1 Vijaya Sundararajan,2 Nuala Barker,1 Jodie L. Burchell,2 Robyn G. Langham.1
1Dept of Nephrology, St. Vincent’s Hospital, Fitzroy, Victoria, Australia; 2Dept of Medicine, Melbourne Univ, Fitzroy, Victoria, Australia.

Background: Symptom management and quality of life (QOL) in dialysis patients is increasingly important in determining treatment approach and outcome research. This study identified symptoms, QOL, functional status in dialysis patients, determining if symptom burden had an impact on mortality.

Methods: A single-centre cross-sectional study was undertaken in dialysis patients with median follow up time 10 months. Patients completed surveys incorporating POS-S (n=153), Phenprocoumon (n=14), Dabigatran (n=46), Rivaroxaban (n=12), Apixaban (n=12).

Results: 112 patients were recruited; 67 hemodialysis, 10 home/nocturnal hemodialysis (n=153). Pain (82%) at a rate of 10.56% was found. Poor mobility and skin changes on survival was found. Symptom burden (median POS-S score 13 (inter-quartile range (IQR 9, 22)) and reduced QOL 4 (IQR 3,4), health satisfaction 3 (IQR 2,4) and performance status 60 (IQR 50,70). A log rank analysis was performed on 104 POS-S renal responses with 8 deaths total.

Conclusions: Our data show that also in the elderly NOAC use increased over the past years. Characteristics such as age, sex or KF had an impact on the choice of oral anticoagulation.

Funding: Other NIH Support - Kuratorium für Dialyse und Nierentransplantation (KfH Foundation of Preventive Medicine)

SA-PO774

Outcomes of Cardiopulmonary Resuscitation in Maintenance Dialysis Patients Based on CPR Characteristics Haris Farooq Murad, Fahad Saeed. Cleveland Clinic Foundation.

Background: Cardiopulmonary resuscitation (CPR) is associated with high rates of mortality, especially in patients with end stage renal disease (ESRD). Previous studies have reported an in-hospital mortality rate of up to 75% in ESRD patients undergoing CPR. There are no large studies to date on how individual CPR characteristics relate to the long term outcomes in these patients. Herein, we aimed to answer this question.

Methods: By an EMR inquiry, we identified all the adult patients (>18years) who had undergone CPR from January 2006 to December 2014, and then selected patients who were on maintenance dialysis. We conducted a chart review of CPR characteristics and its association with the hospital discharge survival. We studied following variables: initial rhythm, duration of CPR, in-hospital versus out of hospital CPR and the use of hypothermia protocol.

Results: We studied a total of 497 ESRD who had undergone CPR. Sixty eight percent of our patients had expired in the hospital post-CPR. Pulseless electrical activity (PEA) was the most common initial rhythm (51.4%), followed by ventricular arrhythmias (19.6%) and asystole (19.2%). In-hospital mortality was the highest (76.8%) for patients with asystole as the initial rhythm, duration of CPR, in-hospital versus out of hospital CPR and the use of hypothermia protocol.

Conclusions: This study demonstrated high symptom burden, reduced functional status and QOL in dialysis patients. Patients with severe pain, weakness, shortness of breath, nausea, mouth problems, drowsiness, poor mobility and skin changes were more likely associated with higher mortality risk. Symptom identification and management may help predict and improve patient QOL outcomes in dialysis patients.

SA-PO775

End of Life Care Preferences in Maintenance Dialysis Patients based on CPR Characteristics Haris Farooq Murad, Fahad Saeed. Cleveland Clinic Foundation.

Background: Dialysis patients have an annual mortality rate of 20-25%. A previous Canadian study comprising mainly of Caucasian patients has shown that patients are interested in active involvement in end of life care discussions and majority would want to know their prognosis on dialysis. In this Caucasian predominant cohort, approximately 50% chose to be DNR. It is not known if patients’ preferences on end of life care are any different in a racially more diverse cohort of patients in the U.S.

Conclusions: CPR in dialysis patients is associated with high mortality rates. It is possible to predict hospital discharge survival of patients with cardio-pulmonary arrest based on the CPR characteristics.

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

Underline represents presenting author.

807A
Methods: We collected data on 423 out of 440 dialysis patients from 7 dialysis facilities in the U.S. using self-reported questionnaires. 

Results: Our study included 28.1% Caucasian and 66.7% African American patients. Eighty-three percent of the patients felt that their QOL was an important determinant in their end-of-life care. We sought to introduce ACP and increase documentation of AD in older outpatient nephrology patients.

Conclusions: Multiple treatments are available to older patients with advanced chronic kidney disease. However, poor communication about available treatment options may result in a mismatch between patient preferences and treatment choice.

SA-PO777 

“So I had No Choice”: Perceptions of Dialysis Decision-Making Among Older Adults

Keren Ladin,1 Daniel E. Weiner.2 (1Occupational Therapy, Tufts Univ, Medford, MA; 2Medicine, Tufts Univ Medical School, Boston, MA.

Background: Many US dialysis patients undergo intensive procedures intended to prolong life such as mechanical ventilation, cardiopulmonary resuscitation or feeding tube placement at the very end of life. Little is known about trends over time in use of intensive procedures in this population.

Methods: We examined temporal trends in receipt of inpatient intensive procedures in the last 6 months of life by age and race among 601,942 adult Medicare beneficiaries treated with maintenance dialysis who died between January 1, 2000 and December 31, 2011.

Results: From 2000 to 2011, inpatient admissions during the last six months of life increased slightly from 89% to 90%. Among those admitted, there was a marked increase in the use of intensive procedures ranging from 38% in 2000 to 44% in 2011. Intensive procedures at the end of life were more common among black vs. white patients (50% to 57% vs. 34% to 39%) and among younger vs. older patients (50% to 61% for those < 55 years vs. 27% to 26% for those > 85 years).

Conclusions: These procedures were most common and increased most dramatically in younger patients while racial differences were most pronounced in older patients.

Funding: NIDDK Support

SA-PO780 

Will Nephrologists Implement an Advance Directives Program in Their Patients? (Quality Improvement Program)

Ali Mohammed Habeeb, Sheldon W. Tobe. Nephrology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.

Background: Mortality remains high among patients on dialysis. Advanced age and multiple co-morbidities are the major predictors for increasing mortality. ADs extend patients’ autonomy and are the best tool to inform patients about their preferences for health care decisions when they become unable to make such decisions. Chronic dialysis patients have been shown to want to discuss ADs in the past.

Methods: We reviewed 215 chronic in-center hemodialysis patients at Sunnybrook Health Sciences Centre from March to April 2015 by the dialysis unit social workers for any documents related to ADs (like Living wills, Substitute Decision Maker (SDM) and CPR forms). Only 2 patients had ADs in their charts (1%). When this data has presented to the Nephrologists they agreed that ADs should be discussed with their patients and that this was a quality improvement project and they started discussing ADs with their patients.

Results: As part of the process to discuss ADs, the unit’s social workers distributed a pamphlet for the patients with simple and explicit definitions and advantages of AD and also pamphlets explaining about the contents of the form pamphlets. The Staff Nephrologists were educated about the importance and advantages of ADs in their patients and were asked to start discussing the issues with their patients. The Nephrologists will also be educated about how an AD discussion might go and how to document the results of the discussion. In 3 months, a review of the patients’ charts will again look for any documented ADs. We will also study the response of individual dialysis staff and their participation in completing and discussing the ADs. We will assess the potential barriers for not completing ADs by the dialysis unit staff and by patients and attempt to address these barriers.

Conclusions: Expected Outcome: Based on the Prochaska model we are anticipating the dialysis staff are now in the contemplation stage and we are aiming to observe the progression in their behavior to more advanced stages of behavior and try to find out what are the barriers that prevent the progression.

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

Underline represents presenting author.

808A
SA-P0781

Current Practice of Advance Care Planning in New Zealand

Background: Recent guidelines emphasise the need to improve advance care planning (ACP) for patients with chronic kidney disease (CKD). Little is known about current ACP practice in Australian/New Zealand renal centres. We aimed to describe current practice and barriers to ACP from the perspective of renal clinicians.

Methods: A cross-sectional survey was administered online to nephrology nurses, nephrologists, and social workers between 30th June and 1st January 2015. Survey questions covered the topics of experience, skills, comfort and knowledge regarding ACP, workplace policies and procedures concerning ACP, perceived barriers and facilitators to ACP, and perceived need for new CKD-specific ACP programs and materials.

Results: The 487 respondents included 41 nephrologists, 152 nurses/physician assistants, 199 social workers, and 95 dialysis center administrators. There was a significant difference by discipline in reported unmet palliative care needs for symptom management, care coordination, and family bereavement support, with administrators least likely to view these barriers (all p <.05). For example, 86% of nephrologists, 79% of nurses, and 71% of social workers reported having 4 or more symptom treatment barriers, compared to 56% of administrators. Furthermore, 71% of nephrologists, 61% of nurses, and 59% of social workers reported having 4 or more care coordination barriers, compared to 49% of administrators. In contrast, 81% of nephrologists, 75% of nurses, and 74% of social workers reported having 4 or more barriers to bereavement support, compared to 55% of administrators.

Conclusions: ACP in Australian/New Zealand renal centres is subject to health system, provider and patient related barriers. Given the volunteer effect associated with online surveys, our study may underestimate the need for ACP support. Targeted interventions are needed to improve ACP in Australian and New Zealand renal centres.

Funding: Private Foundation Support

SA-P0782

Nephrology Leadership Required to Address Unmet Palliative Care Needs in Dialysis Centers

Background: Because of high symptom burden, numerous comorbidities, and shortened life expectancy, dialysis patients are increasingly recognized as appropriate candidates for early and continuous palliative care.

Methods: In 2013 the Coalition for Supportive Care of Kidney Patients conducted an online survey of dialysis professionals and administrators using ESRD Network and Renal Physicians Association email lists to determine perceptions about how well patient palliative care needs are met. Differences among disciplines were assessed by chi-squared testing and one-way ANOVA.

Results: The 487 respondents included 41 nephrologists, 152 nurses/physician assistants, 199 social workers, and 95 dialysis center administrators. There was a significant difference by discipline in reported unmet palliative care needs for symptom management, care coordination, and family bereavement support, with administrators least likely to view these barriers (all p <.05). For example, 86% of nephrologists, 79% of nurses, and 71% of social workers reported having 4 or more symptom treatment barriers, compared to 56% of administrators. Furthermore, 71% of nephrologists, 61% of nurses, and 69% of social workers reported having 4 or more care coordination barriers, compared to 49% of administrators. In contrast, 81% of nephrologists, 75% of nurses, and 74% of social workers reported having 4 or more barriers to bereavement support, compared to 55% of administrators.

Conclusions: Nephrologists report more unmet palliative care needs, barriers, and resources than the administrators who oversee dialysis centers. Because the respondents were self-selected, a study limitation, the results likely underestimate unmet palliative care needs. To better address palliative care needs, nephrologists need to lead interdisciplinary collaborations, including administrators, to implement palliative care pathways already established in evidence-based clinical practice guidelines.

SA-P0783

Hospice and Race for End-Of-Life Care in U.S. Dialysis Patients

Background: While hospice use is increasingly used for end-of-life care in dialysis patients, we hypothesized that important racial disparities may be present.

Methods: To address this hypothesis, we examined USRDS files to characterize end-of-life care for deaths occurring between 2006 and 2011.

Results: During this 5-year period, the proportion of deaths in hospice increased from 14.7% to 24.2%; grouped by age at death, the following trends were observed: 65 years-11.5% to 15.0%; 65 to 79 years-19.1% to 26.1%; 80-89 years-24.9% to 34.3%; ≥ 90 years-25.9% to 39.6%. As shown in the accompanying Table, associations of hospice use among decedents included more recent calendar year, older age and female sex. Hospice use varied substantially with race: compared to whites, adjusted odds ratios of hospice use were 0.56, 0.56 and 0.57, respectively, in patients of African American, Native American and Asian race.

Conclusions: While end-of-life care in hospice settings is growing rapidly in the US, substantial, unexplained racial disparities exist.

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SA-P0784

Palliative Care Perspectives of Latinos with End-Stage Renal Disease

Background: Latinos are the fastest growing minority and have a nearly 2-fold faster progression from chronic kidney disease to end-stage renal disease (ESRD). Despite the high symptom burden and mortality suffered by patients with ESRD, there is limited palliative care research and Latinos are underrepresented in existing palliative care studies. The purpose of our study is to provide the first description of the Latino palliative care perspective.

Methods: Observational descriptive survey of adult English and Spanish speaking Latinos with ESRD from a safety-net hospital and two private dialysis centers. We modified Davison’s 2010 End of Life Care Preferences and Needs Survey to include known barriers to palliative care in the Latino community. The survey was translated to 3rd grade Spanish and then back-translated to English.

Results: Participants (n=61) had a mean age of 59 years ± 12, mean Charlson Comorbidity Index of 6.5 ± 2.5, and a dialysis vintage mean of 43.3 months ±44.8. The majority (77%) spoke Spanish and reported limited understanding of hospice and palliative care. We found that 60 (98%) want to be informed about their prognosis and 55 (90%) want to be prepared and plan ahead; however, only 16 (26%) had discussed prognosis and only 10 (16%) had discussed end-of-life care with their nephrologist. The majority of participants stated that it was their doctor’s choice (68.8%) to start dialysis, however, few (14.7%) regret the decision to start dialysis. Participants reported a preference to have advance care planning conversations on a routine basis (86.8%), after starting dialysis but before becoming ill (85.2%), and while receiving dialysis (47.5%) or at home (37.7%). Participants want their family to have a central role in medical decision-making (93.4%) and care giving (95%).

Conclusions: Our findings provide the first description of the palliative care perspectives of a predominantly Mexican Latino population with ESRD. By understanding the palliative care perspectives and barriers experienced by Latino patients with ESRD, we can move toward a value-based and patient-centered model of palliative care.

Funding: Private Foundation Support

SA-P0785

Symptom Burden Amongst Latinos with End-Stage Renal Disease

Background: All patients with end-stage renal disease (ESRD) experience a high symptom burden. Although Latinos represent 19% of the US ESRD community, little research is available on their symptom burden. The purpose of our study was to provide the first description of symptom burden prevalence and severity amongst Latinos with ESRD.

Methods: Observational descriptive survey of adult English and Spanish speaking Latinos with ESRD from a safety-net hospital and two private dialysis centers. We used Davison’s ESRA-8: renal tool which measures physical and psychological symptom distress and contains 11 symptom items on a Likert scale of 0-10. Moderate = 4-6 and severe = 7-10. We asked three questions about symptom treatment preferences.

Results: Participants (n=61) had a mean age of 59 ±12 years, mean Charlson Comorbidity Index of 6.5 ± 2.5, and a dialysis vintage mean of 43.3 ±44.8 months. The majority were born in Mexico (90.2%), spoke Spanish only (77%), and had a less than high school education (72.2%). Overall, Latinos experience a substantial symptom burden with a mean of 6.8 ± 2.9 symptoms of which 5.1 ± 2.8 are moderate or severe symptoms. Tiredness Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only.
was experienced by 83.5% of patients and reported as moderate or severe by 67.2%. Pain was present in 66.5% and moderate or severe in 40.1%. Depression was reported by 55.7% and anxiety by 49.1% and moderate or severe in 49.2% and 39.3%, respectively. The majority (78.6%) of patients reported lack of well-being and feeling dizzy (70.5%). With respect to medication preferences, our cohort prefers Western Medicine (77.1%) over traditional curandero (22.9%) medicine and is agreeable (77.1%) to taking a few more medications if it meant all symptoms could be controlled. Our Latino cohort prefers (88.5%) to have their physical symptoms (e.g. pain, nausea) treated by nephrology staff.

Conclusions: Latinos with ESRD suffer from a debilitating symptom burden and over half of the symptoms are amenable to symptoms directed therapy. Our findings support the early identification and treatment of physical symptoms by nephrology staff.

Funding: Private Foundation Support

SA-PO786

Care of the ‘Failing HD Patient’: Role of a Supportive Care Register

Tracy Maryan, Maria Da Silva-Gane, Suresh Mathavakannan. Renal Unit, Lister Hospital, Stevenage, Hertfordshire, United Kingdom.

Background: Older dialysis patients (>70) often have significant comorbidities, that worsen with duration on HD. Continuation of dialysis often occurs at the expense of frequent illness episodes. There is a progressive decline in cognitive and physical function that exacerbates dialysis. We had introduced a Supportive Care Register (SCR) in 2012 to identify ‘failing dialysis patients’ based on their physical performance scores. We attempted to understand whether being on the SCR enabled better patient care when these patients were admitted with inter-current illnesses.

Methods: Data was collected from Patient Administration System (PAS) and Renal IT database in a large Tertiary (non-transplanting) Renal Unit serving a catchment population of 1.2 million. Data maintained in the SCR was reviewed. Total number of HD patient database in a large Tertiary (non-transplanting) Renal Unit serving a catchment population of 1.2 million. Data maintained in the SCR was reviewed. Total number of HD patient admissions to the acute renal service in 2013 were obtained with analysis of demographics, length of stay (LoS) and outcomes at discharge. Patients who were admitted were checked against the SCR entries.

Results: 287 out of the 409 total HD patients were admitted (123 F, median age 68 years, 590 episodes) with 137 of these patients being admitted more than once. The LoS was 9 days. 49 patients died in 2013 (28M; 76±16 yr; vintage 60 m; LoS 18 ±12 p<0.05). 28 patients died in hospital or at home/hospital following withdrawal of dialysis and institution of palliative care. 16 patients had died following severe acute illness. Five patients died at home. 18/28 patients were on the SCR and had discussions relating to ongoing and future dialysis therapy and advanced and preferred place of care planning prior to their last admission in the clinic setting. Seven patients had proceeded to discussions regarding resuscitation.

Conclusions: In conclusion, establishment of a SCR for dialysis patients with declining functional capacity and significant comorbidities allows for an early identification of patients at risk of physical and functional decapitation. Once identified, establishing a dialogue in the OP dialysis setting about future care needs and expectations allows for a more integrated care approach when patients decompensate to the point of being unable to continue dialysis.

Funding: Government Support - Non-U.S.

SA-PO787

A Descriptive Study of Home Palliative Service Utilization and Care Trajectory Among Patients Dying on Dialysis

Dixion, Marnie MacKinnon, Sarah E. Bota, Jade S. Hayward, Erin Arthurs, Sara N. Davidson. 1Nephrology Program, Humber River Hospital, Toronto, ON, Canada; 2Inst for Clinical Evaluative Sciences, London, ON, Canada; 3Ontario Renal Network, Toronto, ON, Canada; 4Ottawa Health Research Inst, Ottawa, ON, Canada; 5Faculty of Medicine, Univ of Alberta, Edmonton, AB, Canada.

Background: Palliative care service use and outcomes among Ontario’s dialysis recipients remain uncharacterized.

Methods: We conducted a descriptive, retrospective, cohort study of 5,507 patients who died while receiving or withdrawing from chronic dialysis (hemodialysis or peritoneal dialysis) in Ontario, between January 1, 2010 and December 31, 2012. Data sources included the Ontario Renal Reporting System, the Canadian Organ Replacement Register, the Home Care database, and other linked administrative health datasets. The date of death served as the index date, and we examined patterns of service use in the prior 365 days. We present selected measures of health service use and outcomes.

Results: Cohort characteristics at death, expressed as median (IQR) or percent of cohort included: 75 (16) yrs old, 3.0 (5) yrs on dialysis, 42% female, 65% had diabetes, 14 (4) Johns Hopkins ACG (comorbidity score). Final dialysis modality was 85% centre HD, 1% home HD, 4% PD, 10% missing. During the last year of life, 11.3% received at least one palliative care service in the home, and 17.5% withdrew from dialysis in the last 30 days of life. In the last 14 days of life, 44% of patients had an emergency department (ED) visit and 65.6% an ICU visit. ED and ICU visits were less frequent among patients who had received home palliative services in the last year of life. Place of death was ICU in 33%, and acute care hospital (without ICU) in 32%, while only 3.6% of patients died at home. Patients with home palliative care services in the last year of life had a greater frequency of death at home (15 vs. 2%) compared with those who died at other places.

Conclusions: Home palliative care services may not be used optimally by dialysis patients in Ontario. Further studies are needed to understand barriers to accessing palliative care services and to improve service planning and delivery.

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

SA-PO788

Ventilator Dependent Dialysis Patients

Jack Rubin, Los Angeles.

Background: We have started treating ventilator dependent patients at our dialysis unit and wish to share our results.

Methods: Chart review was done on all ventilator dependent patients treated at our unit.

Results: All data are shown mean ± sd. To date we have treated 19 patients (8F/11M) aged 71 ± 14 years with a mean time on dialysis of 90 ± 102 days. These patients were on dialysis prior to coming to us a mean 741 ± 1046 days. Seven were started within 2 months of their catastrophic event. Mean last available Kt/V 1.5 ± 0.3, weight 152 ± 41 pounds, dialysis time 194 ± 21 minutes, bun 90 ± 20, creatinine 4.5 ± 1.5 Hemoglobin 9 ± 1.2, albumin 3 ± 0.5 gm%, pre-albumin 18 ± 9 mg%, calcium 9.2 ± 0.6 mg% and phosphorus 3.4 ± 1.3 mg%. Four patients were transferred a mean of 71 ± 54 days because of insurance issues. 7 are on dialysis 97 ± 137 days and 8 have died after 94 ± 95 days on dialysis. There were no apparent differences in the parameters listed above between those transferred for insurance reasons, those who died and those still receiving treatment.

Conclusions: These non verbal non communicative patients are receiving aggressive end-of-life care fostered in some cases by Unrealistic family expectations and in other instances by state conservators who prefer treatment until death so that outpatient withdrawal of dialysis and comfort care is not a realistic option. There are two groups - vintage patients and new to dialysis patients with a catastrophic event. The goal should be to educate families on the consequences of dialysis for the patient so that they do not start or allow withdrawal of dialysis after a defined trial. Upon taking on treatment of this group of patients the dialysis unit should anticipate a lower star rating in the benchmarks as most are on catheters and are frequently admitted for infection, bedsores or pulmonary complications. To sustain these selected patients requires a dedicated staff of nurses, respiratory technicians and ambulance services.

SA-PO789

External Validation of a Prediction Model for 6-Months Mortality Risk

Adeera Levin, Brian Forzley, Helen Chiu, Lee Er, Ogjenka Djurdjev, Mohamud A. Karim, Rachel C. Carson, Gaylene M. Hargrove, Dan J. Martinussen. 1Dept of Medicine, Faculty of Medicine, UBC; 2BC Provincial Renal Agency; 3Island Health Authority, BC, Canada.

Background: End-Stage Renal Disease (ESRD) is associated with poor prognosis. Clinicians must be prepared to address end-of-life issues; hence, identifying patients at higher MR is recommended. We aimed to validate a 6-month MR prediction model for prevalent hemodialysis patients derived by Cohen et al. (2010) in a Canadian cohort and assess its clinical utility.

Methods: 375 prevalent dialysis patients in two regions of BC, Canada, were followed for 6 months. Data including serum albumin (ALB), age, peripheral vascular disease and dementia captured when the surprise question (SQ) was asked were used to validate the 6-month MR model. Model performance was evaluated through discrimination, calibration and decision-curve analysis.

Results: The observed mortality was 13.3% at 6-months. The model had reasonable discrimination (c-stat=0.67) but poor calibration (slope=0.64 [95% CI: 0.35, 0.72]) in our data. Decision curve showed added value of the model for threshold probabilities of 8%-20% (~ 12-42% fewer false-positive death), but no more beneficial to “treat-all” for probability >8% and “treat-none” for probability >20%.
SA-PO792
Charcoal Hemoperfusion in the Treatment of Pruritus in Cholestatic Liver Disease
Nephrology, Mayo Clinic, Rochester, MN.

Background: Pruritus is a distressing symptom in a considerable proportion of cholestatic patients and few of them do not respond to conventional treatment. Charcoal hemoperfusion (CH) is an extracorporeal technique to eliminate albumin-bound substances that are accumulated during cholestasis by the passage of blood through a column containing activated charcoal. Several case reports have shown significant reduction of bilirubin in mechanical jaundice and neonatal hemolytic jaundice. However, the published data of CH for the treatment of resistant pruritus in cholestatic patients is scarce.

Methods: Procedure code “Charcoal hemoperfusion” was used to identify patients who received charcoal hemoperfusion at Mayo Clinic, Rochester from 1/1/2000 to 5/1/2015.

Results: Thirty patients were identified. All patients had failed conservative treatment and 2 of them had not responded to plasmapheresis. A median of 3 (IQR 1-9) sessions for a total of 20(1-33) hours were performed. CH resulted in a significant decrease of pruritus in 19 patients (69%). 2 patients did not have significant relief and 2 patients did not pursue further treatments after having adverse reaction during the first session. Median pruritic score significantly decreased from 9/9 (10-10) to 4/10 (0-0) posttreatment (p=0.004). Duration of symptom free period ranged from 8 to 46 days (median 18 days) in 6 patients who returned for follow up. 6 patients (46%) experienced adverse reactions described in Table 1.

Conclusions: Charcoal hemoperfusion is an effective therapy for refractory cholestatic pruritus. However, the improvement is not sustainable and the short benefit should be balanced with the invasive nature of the therapy and the relatively common adverse reactions.

SA-PO793
Strict Adherence to Medicaid InterQual® Criteria Increases Adverse Events and Health Care Utilization in Undocumented Dialysis Patients
Medicine, Indiana Univ, Indianapolis, IN.

Background: Current estimates suggest there are 6000 undocumented ESRD patients in the US that may be ineligible for scheduled hemodialysis. To meet emergency Medicaid requirements, hospitals have sought creative ways to treat undocumented patients. We present data from an undocumented cohort as it progressed through a succession of three periods with different dialysis criterion.

Methods: “Renady’s” a sybiotic dietary supplement was studied in randomized clinical trials in CKD 3 and 4 and ESRD patients. Other oral therapies for removal of uremic toxins include the use of keto acids and charcoal sorbents.

Results: Our studies using Renady for “Enteric Dialysis” showed reduction in levels of various uremic toxins like lactic and indoxyl glucuronide. Levels of CRP also decreased with improved quality of life. This demonstrates the potential restoration of the gut microbiome dysisbosis with the use of specific strains of probiotics.

Conclusions: The use of a well-researched, clinically documented and safe probiotic/ prebiotic dietary supplement formulation has the potential to safely perform continuous 24h/7d uremic toxin removal and thus stabilize the gut Microbiome and its dysbiosis. Hence, the concept of “Enteric Dialysis” with continuous removal of uremic toxins may be the future key to providing an alternative HOPE for renal failure population.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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associated with increased adverse events with a composite OR for intubation, bacteremia, NSTEMI, ICU admit, and death of 48 (5.9-391.2) compared to P1. P2 charge estimates increased from P1 ($357,501 v $202,326 per person per year, P=0.0001).

Fig. 1 – Hospital utilization per patient per month. * = P < 0.05.

Conclusions: Strict adherence to InterQual® Criteria increases adverse events and healthcare cost per patient. We must determine better alternatives to emergent dialysis which minimize cost, while maintaining dignity, safety, and quality of life.

SA-PO794

Factors Associated with Withdrawal of Care (WOC) in Maintenance Dialysis Patients Fahad Saeed, Robert Butler, Jesse D. Schold. Nephrology, Cleveland Clinic.

Background: There is paucity of data on factors leading to WOC in dialysis patients. We studied this question by using the NIS dataset, 2005-2011.

Methods: We studied the following six major primary diagnoses: MI, cardiogenic shock, sepsis, stroke, CPR and coma. Effect of age, sex, race, hospitals’ profit status and comorbidities were assessed on WOC status. We studied 836563 dialysis patients’ admissions, and WOC occurred in 68152 patients.

Results: Male sex, African American and Latino races, smoking, obesity, psychosis and anemia carried lower odds of WOC. Primary diagnoses of CPR, coma, MI, cardiogenic shock, and sepsis; and co-morbidities such as CHF, dementia, HTN, CA, liver disease, paralysis, chronic lung disease, DM, weight loss were associated with higher odds of WOC. Odds of WOC were increased by approximately 6 % per year of patient age. Teaching hospitals had higher odds while private hospitals carried lower odds of WOC status.

Conclusions: Age, non-profit hospital status, coma, metastatic malignancy and weight loss are the most significant factors associated with WOC among dialysis patients. These prognostic data should be considered while treating such patients.

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<td>CHF</td>
<td>1.225</td>
<td>1.163-1.291</td>
<td>&lt;.0001</td>
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</tr>
<tr>
<td>DM</td>
<td>0.614</td>
<td>0.575-0.656</td>
<td>&lt;.0001</td>
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</tr>
<tr>
<td>HTN</td>
<td>0.673</td>
<td>0.634-0.714</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.430</td>
<td>1.279-1.599</td>
<td>&lt;.0001</td>
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</tr>
<tr>
<td>Metastatic cancer</td>
<td>3.334</td>
<td>2.988-3.719</td>
<td>&lt;.0001</td>
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<tr>
<td>Obesity</td>
<td>0.777</td>
<td>0.708-0.851</td>
<td>&lt;.0001</td>
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<tr>
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<td>1.096-1.346</td>
<td>0.0002</td>
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<tr>
<td>Psychosis</td>
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<td>0.763-0.976</td>
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</tr>
<tr>
<td>Cancer</td>
<td>2.323</td>
<td>2.095-2.576</td>
<td>&lt;.0001</td>
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<tr>
<td>Weight loss</td>
<td>2.154</td>
<td>1.819-2.551</td>
<td>&lt;.0001</td>
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</tr>
<tr>
<td>Teaching hospital status</td>
<td>1.263</td>
<td>1.048-1.522</td>
<td>0.0140</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Higher RDW is associated with higher mortality risk in HD patients. It is unclear whether RDW is a risk factor for mortality or an epiphenomenon of underlying biological and metabolic imbalances across RDW categories. Further studies are needed to confirm the findings generated from our study and to determine the mechanisms underlying the RDW-mortality association.

Funding: NIDDK Support

SA-PO795

Red Cell Distribution Width and Mortality in Incident Hemodialysis Patients Tania Vashistha, Elon Streja, Miklos Zsolt Molnar, Conni Rhee, Steven M. Brunelli, Hamid Moradi, Tae Hee Kim, Vanessa A. Ravel, Melissa Soohoo, Csaba P. Kovesdy, Kamyar Kalantar-Zadeh. UC Irvine; UTHSC; DaVita Clinical Research.

Background: Red cell distribution width (RDW) is a measure of red blood cell size and variability that is often used as an indicator of iron-deficiency anemia. Although RDW has recently been found to be associated with mortality in the general population, few studies have examined this association in hemodialysis (HD) patients.

Methods: We examined the association of RDW with all-cause mortality in a cohort of 109,675 incident HD patients from a large dialysis organization during 2007-2011 using Cox proportional hazards regression with adjustment for case-mix (demographics, comorbidities covariates) and markers of malnutrition and inflammation (MICS). RDW was divided into 5 categories <14.5, 14.5-<15.5, 15.5-<16.5, 16.5-<17.5, and >17.5 %.

Results: The mean age (mean/SD) of the cohort was 63.1 ±15 years old and included 44% females, 58% diabetics, and 31% African Americans. Higher baseline RDW was linearly associated with higher all-cause mortality risk in both unadjusted and fully adjusted models.

Conclusions: Higher RDW is associated with higher mortality risk in HD patients. It is unclear whether RDW is a risk factor for mortality or an epiphenomenon of underlying biological and metabolic imbalances across RDW categories. Further studies are needed to confirm the findings generated from our study and to determine the mechanisms underlying the RDW-mortality association.

Funding: NIDDK Support

SA-PO796

Association of Pre-ESRD Hemoglobin with Early Post-ESRD Mortality Among U.S. Veterans: A Transition of Care in CKD Study Melissa Soohoo, Connie Rhee, Vanessa A. Ravel, Elon Streja, Jennie Jing, Danh V. Nguyen, Csaba P. Kovesdy, Kamyar Kalantar-Zadeh. UC Irvine; UTHSC.

Background: Patients with chronic kidney disease (CKD) are often afflicted with anemia. Previous studies have shown that low hemoglobin (HGB) is associated with pre-dialysis mortality in non-dialysis dependent CKD patients, yet the association of HGB levels in the immediate period preceding dialysis (prelude) and early post-dialysis mortality remains unknown. We hypothesized that lower HGB levels are associated with higher post-transition survival in comparison to higher HGB levels.

Methods: We investigated 18,555 US veterans who initiated dialysis between 10/2007-9/2011 and had at least 1 HGB measurement during the 6 month prelude period before dialysis transition. 6 month averaged HGB was used as a continuous predictor of early post-dialysis all-cause mortality occurring in the first 3 months after initiation using restricted cubic spline models and Cox proportional hazard regressions. The models were adjusted for age, gender, race, ethnicity, region and primary cause of ESRD.

Results: The analytic cohort was a mean±SD age of 68±11 yrs, among whom 30% were African-American, 7% Hispanic and 30% had diabetes as the cause of ESRD. The 6 month prelude HGB average was 10.9±1.6 g/dL. Prelude HGB exhibited a U-shaped association with 3-month post-ESRD all-cause mortality; patients with a 6 month prelude HGB average of 11-15.5 g/dL had better survival, whereas patients with HGB measurements <9 g/dL or >13 g/dL had higher mortality (Figure).

Conclusions: The analytic cohort was a mean±SD age of 68±11 yrs, among whom 30% were African-American, 7% Hispanic and 30% had diabetes as the cause of ESRD. The 6 month prelude HGB average was 10.9±1.6 g/dL. Prelude HGB exhibited a U-shaped association with 3-month post-ESRD all-cause mortality; patients with a 6 month prelude HGB average of 10-11.5 g/dL had better survival, whereas patients with HGB measurements >13 g/dL had higher mortality (Figure).

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

812A
SA-PO797

Higher Serum Ferritin Levels Are Associated with Better Survival in the HEMO Study

Anna Jeannette Kovanyovich, 1 Eugene J. Nuccio, 2 Alfred K. Stockler 3, 4 Tom Greene, 2 Michel Chonchol, 2 Denver VA Medical Center; 2VA Salt Lake City; 4Univ of Colorado Denver; 2VA Salt Lake City; 4Univ of Utah.

Background: Ferritin is an important indicator of total body iron stores and has been shown to prevent ox-LDL induced oxidative injury in endothelial cells. Studies regarding the relationship between serum ferritin levels and all-cause mortality in chronic hemodialysis patients are conflicting. The purpose of this study was to determine the relationship between higher serum ferritin levels and death among participants in the Effect of Dialysis and Membrane Flux in Maintenance Hemodialysis (HEMO) trial.

Methods: We studied the association of serum ferritin and iron levels with all-cause mortality among 1799 subjects from the HEMO trial. Cox regression models adjusted for important confounding variables including demographics, comorbidities, treatment assignment, smoking, and albumin.

Results: Mean age was 58±14 years, 56% were female, and 63% were black. Median (IQR) ferritin and iron levels were 249 (2-497) ng/ml and 50 (5-78) µg/dl, respectively. Over a mean follow-up of 2.84 years, there were 582 deaths. Among subjects with levels in the highest quartile compared to the lowest quartile, both ferritin and iron were significantly associated with reduced all-cause mortality in adjusted analyses, odds ratio (OR) 0.67 (95% CI, 0.46-0.97) and OR 0.60 (95% CI, 0.42-0.85), respectively.

Conclusions: Among subjects participating in the HEMO trial higher serum ferritin and iron levels were associated with reduced mortality. We hypothesize that ferritin may play an important role in protecting the endothelium from oxidative stress-induced damage. Funding: NIDDK Support, Veterans Administration Support.

SA-PO798

Anemia in Chronic Kidney Disease Patients Could BeLinked to Indoxyl Sulfate Levels

Denise Mafra, 1 Natalia Alvarenga Borges, 1 Milena Barcza Stockler-Pinto, 2 Amanda F. Barros. 1 Medical Sciences Graduate Program, Federal Univ Fluminense, Brazil; 2Cardiovascular Sciences Graduate Program, Federal Univ Fluminense, Brazil.

Background: Indoxyl sulfate (IS) is a uremic toxin derived from the action of colon bacteria in dietary tryptophan. This toxin is related to many complications for chronic kidney disease (CKD) patients, including anemia. The aim of this study was to verify the relationship between IS plasma levels and anemia in hemodialysis (HD) patients.

Methods: This transversal study included 18 HD patients (50% men, 54.2 ± 11.6 yrs, BMI 26.3 ± 4.7kg/m², time on dialysis 51 (30-52) months, all patients received the same dose erythropoietin per week). Routine laboratory parameters were measured, the total IS plasma levels were quantified with high-performance liquid chromatography (HPLC) and protein C reactive (CRP) levels analyzed by Immunoenzymatic Assay. Statistical analyses were performed with SPSS version 19.0.

Results: The mean of hemoglobin was 11.0 ± 1.28 g/dL and hematocrit of 34.2 ± 3.0%. The mean of IS plasma levels was 23.9 (10.3 - 100.9) mg/L and CRP 3.1 (1.3 - 8.6) mg/dL. Multivariate linear regression analysis adjusted for age, sex, time on HD, albumin, BMI, CRP revealed that serum hemoglobin (β = -0.62; p = 0.01) was independently and negatively associated with IS levels.

Conclusions: This study provided evidence that IS seems be associate with anemia in HD patients and therapeutic strategies in the clinical care to reduce uremic toxins levels may be effective to management of anemia in HD patients. Funding: Government Support - Non-U.S.
Initially, mean Hb level was approximately 1 g/dL lower among ESA-only patients and remained 0.4 g/dL lower throughout the study. During follow-up, ESA was associated with a greater adjusted risk of mortality vs no ESA (control referent). Incidence rate ratios (95% confidence interval) ranged from 2.24 (1.93-2.60) in the 2nd quarter to 1.48 (1.18-1.84) in the 8th quarter.

Conclusions: Using a contemporarily relevant definition, ESA at a single point in time is potently and persistently associated with greater ESA utilization, lower Hb levels, and higher mortality risk.

Funding: Pharmaceutical Company Support - Akebia Therapeutics

SA-PO801
Impact of ESAs and Iron on Survival in Hemodialysis Patients: Which Is the Best, Which Is the Worth? Jacques B. Rottbourm,1 Alain Guerin.2 1Dept of Nephrology, Hôpital de la Pitié, Paris, France; 2Hemodialysis Units, Diaverium, Paris, France.

Background: Appropriate anemia management for Hemodialysis (HD) patients (Pts) is still challenging. Intravenous (IV) iron and erythropoiesis-stimulating agents (ESAs) are the main therapies, with conflicting outcomes. In the unit, pts were treated over the last seven years, cumulative doses of ESAs (darbepoetin alfa [DA]), converted in µg per session, and IV iron (iron-sucrose [IS]), converted in mg per session, were exactly constantly reported. Survival depending on the cumulative dose of each product and both products together was calculated using the Kaplan Meier methodology.

Methods: 300 incident HD pts (67% male) mean [M] (SD) age at start 59.7(16.3) years, were treated for 100,430 dialysis sessions [S], receiving all over 1,192,250 µg of DA, and 1,794,050 mg of IS. M Hb level was 11.55(0.77) g/dL, MT SAT 37.1(8.5)%, and Ms ferritin 562(322) µg/L. The M DA dose injected was 12.91(9.99) µg per S. The M IS dose injected was 20.91(11.57) mg per S. Expressing the separate doses of DA and IS received by the pts in three categories for each product, we obtained 9 categories of pts, depending on whether they received low, middle, or high doses of ESA and IS per S: M doses were [5.4(2.6), 10.8(3.4), 25.1(14.8)]/µg for ESA, [12.5(4.5), 18.4(3.4), 32.3(11.9)] mg for IV iron respectively.

Results: Survival was expressed at 1000, 2000, and 3000 days (d):

The better survival was obtained in the group of low ESA and low IV iron, the worst was high ESA and high IV iron. Survival is better with low ESA, whatever is the IV iron dose injected. High ESA dose, whatever IV iron dose is injected, seems to be worth.

Conclusions: Because the majority of patients on HD receives ESA and IS, rigorously conducted and adequately powered clinical trials studying the cumulative doses of ESA and IV iron, reflective of present-day practice, are greatly needed.

SA-PO802
Relation between Statin Prescription and Erythropoietin Stimulating Agent (ESA) Hyporesponsiveness in Hemodialysis (HD) Patients: Results from the Japan Dialysis Outcomes and Practice Patterns Study (JDOPPS) Takeshi Hasegawa,1+ Junhui Zhao,2 Douglas S. Fuller,3 Brian Bieber,4 Yun Lin,5 Jarcy Zee,5 Hal Morgenstem,6 Masami Nangaku,7 Bruce M. Robinson,8 Norio Hanafusa,9,10 Fukushima Medical Univ Hospital, Fukushima City, Fukushima, Japan; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Univ of Michigan, Ann Arbor, MI; 4Univ of Tokyo, Tokyo, Japan; 5Anemia Working Group of JDOPPS, Japan.

Background: Statins are widely used in HD patients and have pleiotropic anti-inflammatory and anti-oxidative effects, but the latest guideline is advising against starting its use in this population. Hypothesizing that statins could be used as adjuvant treatment for renal anemia, we examined the association between statin prescription and ESA hyporesponsiveness (ESAHYPO) in Japanese HD patients (pts) prescribed ESAs.

Methods: We included 3208 pts in 178 HD facilities dialyzed 3x/week for ≥4 months from JDOPPS phases 3-5. Statin Rx was reported at baseline. ESAHYPO was defined in patients on maintenance hemodialysis (MHD) as having an erythropoietin resistance index (ERI) of ≥25 U/kg/week/g/dl. Logistic regression was used to evaluate the key variables which might be independently associated with erythropoietin hyporesponsiveness in MHD patients.

Results: Mean erythropoietin resistance index (ERI) for the entire study population was 16±5 U/kg/week/g/dl. 26% patients were erythropoietin hyporesponsive. Patients were divided into two groups according to ERI: ERI<25±U/kg/week/g/dl and ERI≥25±U/kg/week/g/dl. In ERI 125±U/kg/week/g/dl cases, the proportion of female gender was higher, hemoglobin and 25(OH)D were significantly lower than that of patients with ERI <25±U/kg/week/g/dl. In addition, comparing with ERI<25±U/kg/week/g/dl patients, body mass index (BMI) and serum cholesterol were slightly lower in ERI≥25±U/kg/week/g/dl patients (p=0.05). Logistic regression study adjusted gender, dialysis periods, BMI, Kt/v, serum cholesterol, serum albumin, and alkaline phosphatase, indicating an independent association between 25(OH)D deficiency and the erythropoietin hyporesponsiveness (HR:4.590, 95%CI:1.277~16.503).

Conclusions: Erythropoietin hyporesponsiveness is prevalent among MHD patients. Female gender and malnutrition are associated with erythropoietin hyporesponsiveness. 25(OH)D deficiency is the main risk factor for erythropoietin hyporesponsiveness. Improving 25(OH)D deficiency and malnutrition may increase the response to erythropoietin treatment in MHD patients.

SA-PO803
25(OH)D Deficiency Contributes to the Erythropoietin Hyporesponsiveness in Patients on Maintenance Hemodialysis Pu Lei, Daqing Hong, Fei Deng, Li Wang, Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: The aim of this study was to identify the factors that contribute to erythropoietin hyporesponsiveness in patients on maintenance hemodialysis (MHD).

Methods: demographic data, hemoglobin, dose of erythropoietin, biochemical indicators and other related indicators of 80 MHD patients were collected and retrospectively analyzed. They were followed up for 12 months. Erythropoietin resistance index (ERI) was used to evaluate the response to erythropoietin in patients on MHD. The ERI was calculated dividing the weekly weight-adjusted (kg) dose of ESA (IU) by the hemoglobin level (g/dL). Logistic regression study was used to determine the key variables which might be independently associated with erythropoietin hyporesponsiveness in MHD patients.

Results: Mean erythropoietin resistance index (ERI) for the entire study population was 16±5 U/kg/week/g/dl. 26% patients were erythropoietin hyporesponsive. Patients were divided into two groups according to ERI: ERI<25±U/kg/week/g/dl and ERI≥25±U/kg/week/g/dl. In ERI 125±U/kg/week/g/dl cases, the proportion of female gender was higher, hemoglobin and 25(OH)D were significantly lower than that of patients with ERI <25±U/kg/week/g/dl. In addition, comparing with ERI<25±U/kg/week/g/dl patients, body mass index (BMI) and serum cholesterol were slightly lower in ERI≥25±U/kg/week/g/dl patients (p=0.05). Logistic regression study adjusted gender, dialysis periods, BMI, Kt/v, serum cholesterol, serum albumin, and alkaline phosphatase, indicating an independent association between 25(OH)D deficiency and the erythropoietin hyporesponsiveness (HR:4.590, 95%CI:1.277~16.503).

Conclusions: 25(OH)D deficiency and malnutrition may increase the response to erythropoietin treatment in MHD patients.

SA-PO804
Incidental Findings on 15 Fluorodeoxyglucose Positron Emission Tomography Along with Low Dose Computerized Tomography (FDG PET CT) Scans Among Clinically Stable Haemodialysis with Erythropoietin Stimulating Agent (ESA) Hyporesponsive Patients Kaushik V. Y. Pujari,1 Haua A. C. Fung,2 Stanley Fan,3 Neringa Vilimiene,4 Muhammad M. Yaqoob. 1Pharmaceutical Company Support - Akebia Therapeutics, 2Hasegawa Medical Hospital, J Funayama, Tokyo, Japan; 3Barts Health NHS Trust, United Kingdom.

Background: Burden of comorbidities is high among hemodialysis (HD) patient. Underlying infective focus or occult malignancy is always of concern when clinically stable patients have ESA-R (ESA resistance index of ≥6.5 U/kg body weight/mean Hgb). We started expanding malignancy to be suspected and assigned from on going living donor kidney transplant work up. 4 patients needed antibiotics and 1 had anti TB therapy. 7 patients needed appropriate invasive investigations for confirmatory diagnosis. There was no association between elevated CRP around time of scan and pathological tracer uptake (P=0.468).
SA-PO807
Oral Vitamin C Supplementation Reduces Erythropoietin Requirement in Hemodialysis Patients with Functional Iron Deficiency

Tamini Sultan, Maria V. DeVita, Michael F. Michielis. Medicine, Lenox Hill Hospital, New York, NY.

Background: Functional iron deficiency (FID) is a major cause of erythropoietin (Epo) hyporesponsiveness and persistent anemia in dialysis patients. Vitamin C acts as a reducing agent and enhances mobilization of the ferrous form of iron to transferrin thus increasing its bioavailability. High dose intravenous vitamin C has been shown to decrease the Epo requirement and improve hemoglobin levels in previous studies. This route has its downside regarding difficulty of use, higher cost and associations with increased oxalate levels and inflammatory markers. Use of oral vitamin C has been limited due to the concerns of low bioavailability and patients compliance to medication. This study assessed the effect of low dose oral vitamin C on Epo dose requirements in stable hemodialysis patients with functional iron deficiency.

Methods: This prospective study included 22 stable hemodialysis patients with functional iron deficiency defined as transferrin saturation (Tsat) <30 % and ferritin levels of >100 mcg/L with Epo requirement of ≥ 4000 u/HD. Patients received oral vitamin C 250 mg daily for three months. Epo dose was adjusted according to unit protocol depending on the hemoglobin level. Hemoglobin, iron and Tsat levels were recorded monthly. None of these participants received iron or renal vitamin supplementation during the study period.

Results: The mean Epo dose was reduced in fifteen participants by 867±1356u/HD (p=0.03). In seven responders there was 33 % reduction in Epo dose from their base line. No ill effects of oral vitamin C were observed. Despite adjustment of Epo dose, hemoglobin level significantly increased from 10±1.6 mg/dl to 10.7±0.6 mg/dl (p=0.03). There were no significant change in Tsat and ferritin levels.

Conclusions: Low dose oral vitamin C supplementation reduced Epo dose requirements in hemodialysis patients with functional iron deficiency. Despite concerns regarding oral vitamin C absorption in dialysis patients this study indicates Vitamin C is well tolerated and effective.

SA-PO808
The Greatly Misunderstood Erythropoietin Resistance Index

Yossi Chait, Sahir Kalam, Joseph Horovitz, Christopher V. Hollo, Elizabeth D. Ankens, Michael J. Germain, Ravi I. Thadhani. 1UMass; 2WNE Renal & Transplant Assoc; 3MGH.

Background: The use of erythropoiesis stimulating agents (ESAs) to treat anemia in end stage renal disease remains controversial due to reported associations with adverse events. Many studies introduce so-called ESA resistance indices (ERIs) to characterize a patient’s resistance to ESA.

Methods: We use retrospective data from a cohort study of incident hemodialysis patients (n=8924). ERI is defined as average weekly erythropoietin (EPO) dose (IU) per kg body weight (EPOwt) per average hemoglobin (Hgb) (g/dl) over a 3-month period. Linear regression was used to describe the relationship between ERI and EPOwt. Logistic (Cox proportional hazards) regression modelled the relationship between 1-year mortality (survival time) and albumin, age, and either ERI or EPOwt.

Results: ERIs were strongly linearly related with EPOwt (r=0.98) but weakly correlated with 1/Hgb (r=0.44). Associations between covariates and mortality based on two logistic regression models differing only by a single covariate, EPOwt or ERI, were almost identical (figure 1); the same was found for Cox proportional hazards models (Table 2).

Table 1: Linear regression of death on covariates albumin, age, and X, where X = log(Eري) (Model A) or log(EPOwt) (Model B). OR, odds ratio; Sens, sensitivity; Spec, specificity.

<table>
<thead>
<tr>
<th>Model</th>
<th>B</th>
<th>P-value</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>0.530 (0.578-0.586)</td>
<td>&lt;2e-16</td>
<td>1.032 (1.029-1.035)</td>
<td>&lt;2e-16</td>
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<tr>
<td>Age</td>
<td>1.035 (1.029-1.040)</td>
<td>&lt;2e-16</td>
<td>1.034 (1.029-1.040)</td>
<td>&lt;2e-16</td>
</tr>
<tr>
<td>X</td>
<td>1.380 (1.316-1.369)</td>
<td>4.56e-09</td>
<td>1.380 (1.316-1.418)</td>
<td>7.62e-07</td>
</tr>
<tr>
<td>AUC</td>
<td>0.73</td>
<td>Sens=0.65, Spec=0.67</td>
<td>Sens=0.64, Spec=0.68</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Cox proportional hazard regression results with covariates albumin, age, and X, where X = log(Eري) (Model A) or log(EPOwt) (Model B). HR, hazard ratio.

<table>
<thead>
<tr>
<th>Model</th>
<th>B</th>
<th>P-value</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>0.657 (0.577-0.701)</td>
<td>&lt;2e-16</td>
<td>1.02 (1.027-1.037)</td>
<td>&lt;2e-16</td>
</tr>
<tr>
<td>Age</td>
<td>1.012 (1.013-1.017)</td>
<td>&lt;2e-16</td>
<td>1.012 (1.012-1.017)</td>
<td>&lt;2e-16</td>
</tr>
<tr>
<td>X</td>
<td>1.248 (1.219-1.279)</td>
<td>2.17e-09</td>
<td>1.201 (1.175-1.411)</td>
<td>4.29e-07</td>
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</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The area under the ROC curve (AUC) was changed by <1% when covariates ERI or EPOwt were removed from the logistic regression model (AUC = 0.71, sensitivity = 0.66, specificity = 0.65).

Conclusions: ERIs are strongly linearly related to weight-adjusted EPO doses by a “universal” (i.e., not patient specific) formula, hence are merely surrogates of EPO dose. Because true resistance must depend on both the input, (EPO) and its effect (Hb increase over endogenous Hgb level), ERI appears to be a poor marker of resistance. EPO dose itself, even though a statistically significant covariate, does not substantially strengthen the association between mortality and albumin and age as assessed by logistic or Cox regression. Funding: NIDDK Support

SA-PO809
Evaluation of Iron Deposition by MRI in the Heart and Liver in End Stage Renal Disease Patients on Hemodialysis
Rhea Bhargava,1 Ibrahim Saeed,1 Joseph S. Soltys,2 Omkar U. Vaidya,3 1Dept of Internal Medicine, Univ of Missouri- Kansas City, Kansas City, MO; 2Dept of Nephrology and Hypertension, Univ of Missouri- Kansas City, Kansas City, MO; 3Dept of Cardiovascular Diseases, Mid America Heart Inst, Saint Luke’s Hospital, Kansas City, MO; 4Dept of Cardiovascular Imaging, Cardiovascular Imaging Technologies, LLC, Kansas City, MO.

Background: Anemia is highly prevalent in patients with chronic kidney disease and its management is one of the key components of treatment in this population. 2011 introduced the bundling system which led to increased use of parental iron to treat anemia in this population. There has been significant controversy regarding our current model of iron and whether this leads to iron overload and increased mortality.

Methods: Retrospective evaluation of patients with end-stage renal disease on hemodialysis who had a cardiac MRI for clinical reasons to evaluate for iron deposition in the heart and liver. Exclusion criteria: Porphyria cutanea tarda, chronic liver disease, hemochromatosis,sideroblastic anemia , thalassemia. Inclusion criteria: End stage renal disease and received a cardiac MRI after 3-5 years of hemodialysis.

Results: Average total dose of venofer dose before cardiac MRI was 3500 mg. Average ferritin level: 695 ng/mL. Average iron saturation: 34%. All patients receiving IV iron had hepatic iron deposition. No correlation was seen between ferritin or iron saturation and hepatic iron deposition. A weak relationship was noted between the total iron dose and hepatic iron deposition.

Conclusions: These data suggest that even though we still use iron markers like ferritin and iron saturation for treatment of anemia in ESRD patients, this may not have a correlation with iron deposition in the liver. Significant iron deposition was not noted in the myocardium. MRI can be a useful modality to evaluate iron overload in this population.

Funding: Private Foundation Support

SA-PO811
Paricalcitol, Klotho and Renal Anemia in Hemodialysis Patients
Miguel Uriol Riveras,1 Sheila Caballo Pelegrin,2 Gonzalez Gómez Marqués,3 Manuel Luque-Ramírez,2 1Nephrology, Son Espases Univ Hospital, Palma de Mallorca, Islas Baleares, Spain; 2Endocrinology, Ramón y Cajal Univ Hospital, Madrid, Spain.

Background: Low Klotho levels, a protein linked to aging, is associated with an increase in the etioprotein process (programmed cell death). Chronic Kidney Disease is considered as a state of Klotho deficiency. We evaluate the association between plasma sKlotho levels with iron and hematologic parameters, and the influence of paricalcitol on these.

Methods: Data were obtained from the MIR-EPO study (EudraCT: 2009-015511-40). Chronic hemodialysis patients were stratified as a function of paricalcitol use (Group A) or not (Group B). Erythropoietin-stimulating agents (ESA) and iron supplementation were administered in order to maintain hemoglobin (Hb) between 10.5 and 12.0 g/dL and transferrin saturation (TSAT) ≥ 20%. After a 3-month observation period, sKlotho was measured(month 3 and 6 of follow-up) by ELISA. The changes in sKlotho from month 3 to 6 (A) and their associations with iron metabolism and hematologic parameters as a function of paricalcitol use were assessed.

Results: A total of 31 patients were evaluated (Group A: 23; Group B: 8). Intact parathyroid hormone (iPTH) levels and ESA doses did not change during the study. Mean sKlotho levels decreased at month 6 compared to month 3 in the whole group of patients (527 vs 474 pg/ml, P<0.001). After adjustment for iPTH and globular sedimentation rate, mean sKlotho levels in the Group A were higher than those observed in the Group B throughout the study (537 versus 401 pg/ml, P=0.005). A sKlotho correlated with Δ serum iron (r:0.42, P=0.020) in the Group A of patients. A cubic regression model showed that Δ sKlotho strongly explained Δ serum iron in these subjects (F:9.5, R²:0.64, P<0.001). A sKlotho were also associated with changes in iron supplementation (r: -0.47, P = 0.030) in the Group A of patients. In the Group B, a direct correlation between Δ sKlotho and Δ red blood cell count was found (r:0.73, P = 0.030).

Conclusions: Soluble Klotho is associated with iron metabolism in hemodialysis patients. Higher soluble Klotho levels may be a novel beneficial effect of paricalcitol use on renal anemia.

Funding: Private Foundation Support

SA-PO812
Influence of the Paricalcitol on Iron Metabolism in Hemodialysis Patients
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Background: Interleukin-6 (IL-6) and hepcidin may play a role in the pathogenesis of iron functional deficiency (IFD). The influence of the Paricalcitol in IFD is not known.

Methods: Data were obtained from the MIR-EPO study (EudraCT:2009-015511-40). Chronic hemodialysis patients were stratified as a function of paricalcitol use (Group A) or not (Group B). Erythropoietin-stimulating agents (ESA) and iron supplements were administered in order to maintain hemoglobin (Hb) between 10.5 and 12.0 g/dL and transferrin saturation (TSAT) ≥ 20%. After a 3-month observation period, plasma IL-6 and hepcidin were measured(month 3 and 6 of follow-up) by ELISA. The changes in IL-6 and hepcidin levels from month 3 to 6 (Δ) and their associations with iron metabolism and hematologic parameters as a function of paricalcitol use were assessed.

Results: A total of 31 patients were evaluated (Group A: 23; Group B: 8). Intact parathyroid hormone (iPTH) and ESA doses did not change throughout the study. We found no correlation between ΔIL-6 and Δhepcidin (r:0.10, P=0.640). However, ΔIL-6 correlated with DTSAT (r:0.40, P=0.030). After adjustment for iPTH and globular sedimentation rate, mean IL-6 levels in Group A were lower than in Group B (8 versus 22 pg/ml, P=0.010). IL-6 levels decreased in the whole group of patients throughout the study, but these changes correlated with an increase in serum iron and TSAT only in the Group A. Hecidin decreased in the whole group of patients throughout the study as well. Correlation between ΔHepcidin

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and ΔHb(-0.49, P=0.010) was found in the whole group of patients. Interestingly, mean hepcidin levels were higher in Group A than in Group B (992 vs 494 pg/ml, P=0.050) during the study. In the Group A, Δhepcidin correlated with ΔHb(-r=-0.55, P=0.030).

**Conclusions:** IL-6 and hepcidin are likely related to different iron pools (functional and storage, respectively) since no correlations between their changes were found. Paricalcitol therapy showed an unexpected increase in iron availability for erythropoiesis that might be associated with changes in IL-6 and hepcidin levels.

**Funding:** Private Foundation Support

**SA-PO813**

**48 Week Open Label Safety Extension Study with Ferric Citrate Demonstrates Favorable Safety Profile in Subjects Not on Intravenous Iron: A Post-Hoc Analysis**  

**Background:** Ferric citrate (FC) is an iron-based phosphate binder approved for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis. The Phase 3 pivotal trial in subjects with ESRD demonstrated FC to effectively control serum phosphorus but also significantly increased serum iron parameters. This 48-week open-label extension study to the Phase 3 pivotal trial was conducted to demonstrate long-term safety of ferric citrate. The primary data have been reported previously.

**Methods:** Subjects from the pivotal FC RCT (NCT01191255) who completed the active control period and, if eligible, the placebo control period were eligible to enroll in the safety extension trial. 79% had a time lag between participation in the RCT and this trial. The primary outcome was safety as assessed by lab data and adverse events (AE): 168 subjects enrolled. 166 received a dose of FC. The data presented are a post-hoc analysis of 98 of the 166 subjects that did not receive IV iron for the duration of the 48-week trial. Safety data regarding changes in serum iron parameters and treatment emerging AEs by system organ class are presented.

**Results:** Of the 98 subjects included in this analysis, 71 subjects were randomized to FC in the previous Phase 3 trial and 27 to the AC group. Table below shows the changes in TSAT and serum ferritin over the 48 wk period. Data presented as mean (SD).

<table>
<thead>
<tr>
<th>Time (wk)</th>
<th>TSAT (%)</th>
<th>Serum ferritin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>34.5 (14.1)</td>
<td>772 (378)</td>
</tr>
<tr>
<td>12</td>
<td>37.9 (16)</td>
<td>891 (458)</td>
</tr>
<tr>
<td>24</td>
<td>38.1 (15.9)</td>
<td>904 (450)</td>
</tr>
<tr>
<td>36</td>
<td>41.7 (19.1)</td>
<td>961 (517)</td>
</tr>
<tr>
<td>48</td>
<td>40.9 (19)</td>
<td>872 (417)</td>
</tr>
</tbody>
</table>

83% of subjects experienced at least one treatment emergent adverse event with the most common being gastrointestinal disorders (40%) and infections and infestations (37%).

**Conclusions:** Subjects receiving ferric citrate and no IV iron demonstrated serum phosphorus control over the 48 wk study period, and an increase in TSAT and serum ferritin. The increase in TSAT did not exceed 45% in subjects receiving ferric citrate and no IV iron, which might suggest that ferric citrate is absorbed but the risk of excessive iron absorption is low.

**Funding:** Pharmaceutical Company Support - Keryx Biopharmaceuticals

**SA-PO814**

**Iron Isomaltoside: A Novel Intravenous Iron Preparation for Hemodialysis**  
David Jackson, Christopher Brown, Grant Sugiuira, Rachel S. Ashcroft, Ashraf I. Mikhail. Nephrology, ABM Univ Health Board, United Kingdom.

**Background:** Diäfer® (iron isomaltoside) is newly licensed in Europe for iron deficiency anemia in CKD patients on dialysis. It is thought the controlled-release matrix minimises free iron, possibly reducing side effects. Little is known about the efficacy & safety of Diäfer in clinical practice. This study aims to assess the impact of this novel formulation on anemia parameters in prevalent hemodialysis (HD) patients previously maintained on iron sucrose.

**Methods:** Data was collected for 13 months; 6 month pre-switch (iron sucrose), 1 month crossover, & 6 month post-switch (iron isomaltoside). All patients received dialysis for ≥3 months before evaluation, excluding potential bias of iron loading doses. For both preparations, patients received intradialytic bolus doses of 100mg at frequencies dependent on individual requirements as per current practice.

**Results:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mth -6 to -1</th>
<th>Mth 0</th>
<th>Mth 1 to +6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/l)</td>
<td>Mean</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>Feritin (ng/ml)</td>
<td>449</td>
<td>447</td>
<td>477</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>19.5</td>
<td>19.0</td>
<td>20.4</td>
</tr>
<tr>
<td>ESA (U/wk)</td>
<td>7680</td>
<td>6000</td>
<td>7980</td>
</tr>
<tr>
<td>Iron (mg/d)</td>
<td>202</td>
<td>200</td>
<td>186</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>14</td>
<td>7</td>
<td>15</td>
</tr>
</tbody>
</table>

The percentage of patients maintaining Hb target (100-120g/L) was 71% with iron sucrose & 70% with iron isomaltoside. No adverse drug reactions were observed. No metallic tastes were reported with Diäfer administration. The CRP rise during months 1-6 was imparted by 2 infections & 1 amputation.

**Conclusions:** Iron isomaltoside maintains Hb stability & adequate iron status in HD patients when incorporated into current practice. While these data suggest Diäfer may reduce ESA & iron requirements, further analyses are necessary to validate these findings. Whether the potential to reduce labile iron with iron isomaltoside impacts on clinical outcomes is yet to be determined.

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

**SA-PO815**

**Low Iron Availability May Influence on Second Patency Rates of Vascular Access in Patients on Hemodialysis**  
Yukiko Hasu- suke, Wataru Fukao, Takeshi Nakamichi. Div of Kidney and Dialysis, Dept of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.

**Background:** Vascular access (VA) is essential for the patients on HD. However, VA failure is often occurred even after percutaneous-transluminal angioplasty (PTA). Iron is important for normal vascular physiology, and insufficient iron availability can lead to various vascular dysfunction. The purpose of this study was to examine the factors affecting VA patency after PTA, including iron availability and oxidative stress.

**Methods:** Blood samples were taken from 281 HD patients at the PTA. Routine blood chemistries and factors related to iron metabolism (transferrin saturation rate (TST), ferritin), oxidative stress (advanced oxidation protein products (AOPP), 8OHdG, GSH/GSSG), and inflammation (high-sensitive CRP, interleukin-6, tumor necrosis factor-a, pentraxin-3) were measured. The end point of study was the re-vascularization or re-operation of VA during the observational period after PTA. Cox proportional hazards models for the end point was used.

**Results:** 133 patients (47.3%) had native arteriovenous fistula. During follow-up period, re-vascularization was performed in 34 patients and re-operation in 31 patients. The patients with VA failure had higher numbers of leukocytes and platelet, significantly lower TST, and a tendency of higher AOPP compared with the patients without VA failure. There was no significant difference in other factors between the patients with and without VA failure. The Kaplan-Meier analysis showed lower TST (~20%) was associated with VA failure (<0.0010, (figure 1)).

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

**Underline represents presenting author.**
Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

SA-PO818
Proton Pump Inhibitors and CYP2C19 Are Associated with Iron-Deficiency Anemia in Hemodialysis Patients: A Cross-Sectional Study

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Background: Hyporesponsiveness to erythropoiesis stimulating agents (ESA) is an important phenomenon in dialysis patients. As chronic proton pump inhibitor (PPI) use reduces gastric acid secretion, it seems possible that chronic PPI use might lead to iron malabsorption and anemia. In addition, PPI is mainly metabolized by cytochrome P450 enzymes, particularly CYP2C19, in the liver. The genotypes of CYP2C19 affect the pharmacokinetics and pharmacodynamics of PPI. However, there is no study investigating the relationship between PPI use and anemia status that includes the effect of CYP2C19 genotype in hemodialysis patients.

Methods: This cross-sectional cohort study analyzed 1350 hemodialysis patients. DNA was isolated from leukocytes in peripheral blood. We used polymerase chain reactions and direct sequencing to analyze CYP2C19 genotypes. We analyzed anemia status with and without PPI usage, including the association with CYP2C19 genotypes.

Results: PPI use was associated with a significantly lower mean serum hemoglobin concentration. Iron and TSAT were also lower in PPI users. ESA dosage was significantly higher in patients receiving PPIs(mean [SD] PPI): 5685 [3288] IU/week; non-PPI: 2899 [2734] IU/week; P=0.001), and multiple regression analysis indicated a significant relationship between PPI use and ESA dosage(β: 494.1 P=0.011). CYP2C19 genotypes were significantly associated with iron status and anemia. Multiple regression analysis demonstrated that CYP2C19 poor metabolizer (PM) type was significantly associated with ESA dosage in PPI users (β: 901.1 P=0.036).

Conclusions: In this study, we found that PPI use is associated with iron status and anemia in hemodialysis patients. Among the dialysis patients receiving PPIs, CYP2C19 genotype was associated with hemoglobin levels, ESA dosage, and iron status.

SA-PO819
A 4-Week Dose Response Study of the Hypoxia Inducible Factor-Prolyl Hydroxylase Inhibitor GSK1278863 in Japanese Anemic Hemodialysis Subjects

Yukihiro Endo, Tomoko Kohno, Yukiko Imai, Natsumi Kawase, Katsutoshi Hara, John J. Lepore, Alexander Ralph Cobitz.

Endo Katsutoshi Hara, 1 John J. Lepore, 2 Alexander Ralph Cobitz. 2

1Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan; 2Univ Massachusetts, Lowell, MA.

Background: Hyporesponsiveness to erythropoiesis stimulating agents (ESA) is an important phenomenon in dialysis patients. As chronic proton pump inhibitor (PPI) use reduces gastric acid secretion, it seems possible that chronic PPI use might lead to iron malabsorption and anemia. In addition, PPI is mainly metabolized by cytochrome P450 enzymes, particularly CYP2C19, in the liver. The genotypes of CYP2C19 affect the pharmacokinetics and pharmacodynamics of PPI. However, there is no study investigating the relationship between PPI use and anemia status that includes the effect of CYP2C19 genotype in hemodialysis patients.

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Conclusions: In this study, we found that PPI use is associated with iron status and anemia in hemodialysis patients. Among the dialysis patients receiving PPIs, CYP2C19 genotype was associated with hemoglobin levels, ESA dosage, and iron status.
erythropoiesis stimulating agent for at least 2 weeks were randomized to placebo or to 4 mg, 6 mg, 8 mg, 10 mg GSK1278863 once daily. The primary endpoint was Hgb from baseline at Week 4. Other endpoints included circulating levels of erythropoietin (EPO), vascular endothelial growth factor (VEGF) and hepcidin.

**Results:** A total of 97 subjects were randomized, and 88 subjects completed the study. Mean Hgb at baseline ranged from 9.68 g/dL to 9.92 g/dL across the treatment groups. After 4-week treatment, GSK1278863 produced dose-dependent increases in mean Hgb from baseline (placebo: -1.41 g/dL; 4 mg: -0.28 g/dL; 6 mg: -0.01 g/dL; 8 mg: 0.54 g/dL; 10 mg: 0.97 g/dL). A posteriori distribution from Bayesian four parameter Enamx model estimated that 2.0 mg, 3.9 mg and 8.7 mg doses would, on average, lead to achieve placebo-corrected increases in Hgb over 4 weeks of 0.5 g/dL, 1.0 g/dL and 2.0 g/dL, respectively. Dose-dependent increases in EPO and decreases in hepcidin were observed across the GSK1278863 groups, while no trends of increase in VEGF were observed in any groups. All AEs were reported as single instances in any treatment groups except nasopharyngitis, and no trends in AEs were noted. There were no deaths in the study.

**Conclusions:** This study demonstrated that GSK1278863 produced dose-dependent elevations in Hgb correction in Japanese HDD subjects across the dose range tested.

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**SA-PO828**

A Three-Year Study of an ESA Treatment Algorithm for Patients with Renal Anemia: Stable Hb Levels Obtained with Twice-Monthly Administration of CERA (Second Report)  
Tatuhiko Mue, Shigeru Owada. Internal Medicine, Asao Kidney Clinic, Kawasaki, Japan.

**Background:** Treatment of renal anemia in hemodialysis (HD) patients requires an adequate ESA dosage to maintain stable Hb levels. Guidelines in Japan recommend determining the ESA dosage based on Hb levels measured twice a month. An algorithm for the administration of continuous erythropoietin receptor activator (CERA) has been prepared and implemented to treat patients on HD. The 2-year study results were previously reported during the ASN Kidney Week 2014 (TH-P0 820).

**Methods:** Based on the algorithm, CERA was administered for 1 year to 102 HD patients being treated with rHuEPO. After the first year, the algorithm was reviewed, and some cases of fluctuating Hb levels because of terminating and restarting CERA administration were found. Therefore, the algorithm was revised. Consequently, CERA administration was continued for another 2 years. The target Hb level was 10.5–11.0 g/dL, and Hb levels, CERA dosage, Erythropoietin Resistance Index (ERI), and iron dosage were investigated. CERA was administered once every 2 weeks, and the dosages were changed within a range of 25 g/dose based on Hb levels. The standard iron dosage was not changed during the evaluation period.

**Results:** Hb levels at baseline and 1, 2, and 3 years after the baseline measurement were 10.9 and 11.1, 11.2, and 11.2 g/dL, respectively. The corresponding CERA dosages, administered every 2 weeks, were 62 ± 13, 38 ± 25, 36 ± 23, and 33 ± 21 mg, respectively, and ERI values were 0.11 ± 0.04, 0.06 ± 0.05, 0.06 ± 0.04, and 0.06 ± 0.04, respectively. To reduce fluctuations in Hb levels to a possible extent, terminating CERA administration was avoided. Serum ferritin levels gradually decreased from 147.9 ± 122.1 at the baseline to 112 ± 95, 88 ± 67, and 67 ± 47 ng/ml in the 1st, 2nd, and 3rd years, respectively, and weekly iron dosage decreased from 13 ± 2 at the baseline to 11 ± 2.6 and 11 ± 2.4 mg in the 1st, 2nd and 3rd years, respectively.

**Conclusions:** Three years of twice-monthly CERA administration, based on the algorithm, could maintain stable Hb levels, improve ERI, and reduce iron dosage. Twice-monthly CERA administration based on the algorithm effectively controlled anemia in HD patients.

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**SA-PO821**

Continuous Erythropoiesis Receptor Activator (CERA) for the Anemia of Chronic Kidney Disease (CKD): A Meta-Analysis of Randomized Controlled Trials  
Valeria M. Saigliahbone,1 Suzetia Palmore,1 Giovanni F.M. Strippoli,1,3  
1Diaverum Medical Scientific Office; 2Univ of Otago Christchurch; 3Cochrane Kidney and Transplant.

**Background:** Targeting high hemoglobin levels with erythropoiesis-stimulating agents (ESA) leads to adverse effects in people with chronic kidney disease (CKD). Whether there are treatment differences between different ESA agents is uncertain.

**Methods:** We did a systematic review of randomized controlled trials evaluating treatment with CERA compared with other epoetins (darbepoetin alfa and epoetin alfa or beta) or placebo/no treatment, in people with CKD of any severity. We systematically searched Cochrane databases. Results were expressed as risk ratios (RR) and their 95% confidence intervals that CERA was associated with lower mortality, cardiovascular outcomes, and better cardiovascular risk factors than other ESAs.**

**Results:** 17 studies involving 5397 participants were eligible. Studies compared CERA with epoetin (n=8 studies), darbepoetin (n=5), differing frequency (n=2) and dose (n=4). Compared to epoetin and darbepoetin, CERA had similar effects on mortality, hypertension, need for blood transfusion and iron therapy.

**Conclusions:** Two studies of low-moderate risk of bias, CERA significantly improved quality of life as measured by SF-36. Data were sparse for differing frequency of administration and dose. Evidence for treatment effects of CERA was absent among children and particularly limited for kidney transplant recipients. Studies included in this review were generally at high or unclear risk of bias.

**In summary:** There is no evidence that CERA has different effects on patients-centered outcomes compared to epoetin or darbepoetin among adults with CKD. CERA may improve health-related quality of life, but further high quality trials are needed. Its effects in children with CKD and kidney transplant recipients remains poorly understood.

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**SA-PO823**

**Risks of Long-Term Management for Anemia, Cardiovascular Disease (CVD) Death and Risk Factors for Heart Failure in Maintenance Hemodialysis**  
Hajime Hirano,1 Haruhito Azuma,1 Hideaki Shima.1  
1Blood Purification Center, Osaka Medical College, Takatsuki, Japan; 2Nephrology, Osaka Medical College, Takatsuki, Japan.

**Background:** In this study, we evaluated the various outcome factors, the effects of improvement in anemia in patients treated with hemodialysis on the vital prognosis were evaluated focusing on changes after enrollment.

**Methods:** This retrospective study was conducted with 201 outpatients with hemodialysis at our Blood Purification Therapy Center and our other related hemodialysis facilities from March 2005 to February 2007 (24 months, 136 males and 65 females, age: male: 59.4 years old, female: 59.8 years old; overall: 59.5 years old). Using CVD death and hospitalization due to heart failure as outcomes, 2-year risk of CVD death was analyzed by logistic regression model with surviving patients. In addition, we assess anemia, changes over a long time after start of observation were evaluated.

**Results:** The multivariate analysis revealed 3 factors for CVD death risk including smoking history (OR: 9.06 [95%CI: 1.86–44.0, p=0.006]), history of ischemic heart disease (OR: 3.82 [95%CI: 1.19–12.25, p=0.024]) and hypercalcaemia. (OR: 1.77 [95%CI: 1.00–3.13, p=0.049]). Similarly, the risk factors for heart failure were smoking (OR:3.11 [95%CI:0.78–12.36, p=0.101]) and history of ischemic heart disease (OR: 5.03 [95%CI: 1.46–17.33, p=0.010]), and history of ischemic heart disease was the only significant variable in the final step.

**Conclusions:** The factors that influence the risk of CVD death included smoking, history of ischemic heart disease and hypercalcaemia. The risk factors occurring heart failure included history of IHD, and it was shown that the effects of smoking and history of IHD on prognosis were stronger than the effects of anemia. The evaluation of changes in Hb over time revealed that the low Hb sustained for a long time would increase the risk. In addition, the risk of death was high in the high-dose rHuEPO group suggesting the risk in the low HbEPO response patients.

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**SA-PO825**

**Anemia Management in ESRD Patients Admitted to the Hospital Priyanka Govindan, Arjun V. Sharma. Dept of Nephrology, Univ of Washington Medical Center, Seattle, WA.**

**Background:** Anemia was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5. Anemia can be managed successfully with appropriate investigations and therapy in the ESRD population. The aim of the study was to see how appropriate the management of anemia was in our hospital in patients on dialysis and to identify areas for improvement.

**Methods:** Selected patients were those with ESRD on hemodialysis and peritoneal dialysis that underwent in-hospital dialysis at the University of Washington Medical Center from July 1st 2014 to Sep 30th 2014. The patients who had been undergoing dialysis for less than 12 weeks were considered to have AKI and were excluded from the analysis. In addition, the patients who underwent dialysis only in the Intensive Care units were excluded. The data was collected from the electronic medical records of the individual patient charts.

**Gender, Age, Anemia status, Lowest Hemoglobin, Iron panel, Reticulocyte count were noted in addition to treatment with iron, blood transfusions and ESA.**

**Results:** A total 145 dialysis patients were identified and 65 of them had both ESRD and anemia. 73.86% of these patients were found to be anemic by KDIGO. Patients in the 66-69 age range had the largest number of anemia with a total of 20 falling in this category. 18 patients had anemia with a Hemoglobin <7.0. Among the anemic patients 48.5% did not have an iron panel checked and 86.4% did not have a reticulocyte count checked. 40% of those with a Hb < 6 mg/dl had an iron panel checked. In patients with Hemoglobin of less than 11 31% were treated with ESA at least once during their hospital stay. 36.36% received transfusions. 50% of the patients who received blood transfusions did not have an iron panel checked.

**Conclusions:** Routine investigations for the management of anemia are being missed regularly. Worse anemia was associated with fewer investigations. We suspect that the management of anemia in patients with ESRD can be improved with more comprehensive labs and therapy. We intend to follow up with an intervention involving the EMR making it easier to work up anemia in the hospital.
SA-PO824

Variability in Hemoglobin (Hb) Levels in Hemodialysis (HD) Patients in the Current Era

**Background:** Hb variability in dialysis patients has been characterized using a number of methods. The majority of this work occurred prior to the 2011 change in CMS reimbursement policy and ESA labels. We therefore examined Hb variability and patient demographics from current data and compared the results to those obtained prior to implementation of these policy changes.

**Methods:** We used CMS ESRD data to define a cohort of chronic HD patients who were alive from Apr 1 through Dec 31, 2012. Using a method from Ebben et al. (CJASN 1:205-1210, 2006), monthly Hb values were categorized as low (L), intermediate (I), and high (H), where L and H were based on monthly Hb values below or above the 25th and 75th percentiles, respectively. Variability was then classified based on the Hb categories during a 6-month period, resulting in 6 categories of variability (see figure legend).

**Results:** This figure compares the percentage (%) of patients in each Hb variability group in 2004 compared to 2012. The 25th and 75th percentiles in the 2012 data were 10.2 and 11.5. Corresponding 2004 values were 11 and 12.5. Similar % of patients were observed in 2004 and 2012 for the LL and LH categories. A higher % of patients was consistently intermediate (II) in 2012 than 2004 (9.5% vs. 6.0%), whereas a larger % was observed for LL and a smaller % for LH. Compared to the overall 2012 cohort, II patients were older (mean=65.2), and LL or LH patients were younger (mean=58.2 and 57.8). LH had the highest % who were black (48.8%).

**Conclusions:** While Hb levels have decreased during the last few years, Hb variability is still present. The lower % of patients in the LH group is consistent with a narrowing of the overall Hb distribution. Further studies are needed to assess the association of variability with outcomes in the current era.

**Funding:** Pharmaceutical Company Support - Akebia Therapeutics, Inc.

SA-PO825

Prevalence and Predictors of Naturally Occurring Normal Hemoglobin Concentration in Hemodialysis Patients

**Background:** Pre-dialysis laboratory measurements of hemoglobin (Hb) are generally used for anemia management. In some clinics, bi-weekly or even weekly Hb measurements are performed for this purpose. The Crit-Line® Monitor (CLM) provides Hb non-invasively and continuously during hemodialysis (HD), but initial readings early during HD are systematically lower than pre-HD laboratory values due to hemodilution caused by the priming fluid. We present a method of correcting CLM Hb for hemodilution.

**Methods:** Pre-HD reference Hb (Hb_Spec) was measured by Spectra East Laboratories. Hb obtained by CLM (Hb_CLM) was averaged between minutes 4 and 6 after start of the HD treatment. The difference between the two (Hb_Spec - Hb_CLM) was estimated as ΔHb = (V_sal * 0.5 * (t_CLM/1.2_1_sal - V_sal) * Hb_CLM/BV, with V_sal = amount of priming fluid (saline) infused at start of HD, t_clm = time point of Hb_CLM measurement (5 min into HD), t_1/2_sal = plasma half life of infused saline (20 min, adapted from ATC Consensus Statement, 2004), VUF = cumulative ultrafiltration volume up until time point of Hb_CLM measurement, BV = pre-HD blood volume (obtained by estimating post-HD BV via Nadler equation (using post-HD weight, sex, height), then dividing by end-HD relative blood volume and subtracting V_sal). Corrected Hb_CLM was calculated as Hb_corr = Hb_CLM + ΔHb.

**Results:** 5,731 HD treatments from 952 chronic HD patients in the USA were analyzed. Without correction, Hb_CLM was found to be systematically lower than Hb_Spec by on average 0.425 g/dL (SD 0.59 g/dL). After correction for hemodilution, the difference (Hb_corr - Hb_Spec) was reduced to ~0.068 g/dL (SD 0.59 g/dL).

**Conclusions:** When applying a correction for the hemodilution caused by infusion of the priming fluid at the start of HD, the Crit-Line® Hb is nearly identical on average to the pre-HD Hb measured by a reference laboratory. More and more clinicians are employing Crit-Line® Monitors for fluid and anaemia management. Crit-Line® Hb corrected in this way may be used for anemia management, which could reduce blood draws and costs.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO826

Evaluation of Pre-Dialysis Hemoglobin Concentration Using the Crit-Line® Monitor

**Background:** Pre-dialysis laboratory measurements of hemoglobin (Hb) are generally used for anemia management. In some clinics, bi-weekly or even weekly Hb measurements are performed for this purpose. The Crit-Line® Monitor (CLM) provides Hb non-invasively and continuously during hemodialysis (HD), but initial readings early during HD are systematically lower than pre-HD laboratory values due to hemodilution caused by the priming fluid. We present a method of correcting CLM Hb for hemodilution.

**Methods:** Pre-HD reference Hb (Hb_Spec) was measured by Spectra East Laboratories. Hb obtained by CLM (Hb_CLM) was averaged between minutes 4 and 6 after start of the HD treatment. The difference between the two (Hb_Spec - Hb_CLM) was estimated as ΔHb = (V_sal * 0.5 * (t_CLM/1.2_1_sal - V_sal) * Hb_CLM/BV, with V_sal = amount of priming fluid (saline) infused at start of HD, t_clm = time point of Hb_CLM measurement (5 min into HD), t_1/2_sal = plasma half life of infused saline (20 min, adapted from ATC Consensus Statement, 2004), VUF = cumulative ultrafiltration volume up until time point of Hb_CLM measurement, BV = pre-HD blood volume (obtained by estimating post-HD BV via Nadler equation (using post-HD weight, sex, height), then dividing by end-HD relative blood volume and subtracting V_sal). Corrected Hb_CLM was calculated as Hb_corr = Hb_CLM + ΔHb.

**Results:** 5,731 HD treatments from 952 chronic HD patients in the USA were analyzed. Without correction, Hb_CLM was found to be systematically lower than Hb_Spec by on average 0.425 g/dL (SD 0.59 g/dL). After correction for hemodilution, the difference (Hb_corr - Hb_Spec) was reduced to ~0.068 g/dL (SD 0.59 g/dL).

**Conclusions:** When applying a correction for the hemodilution caused by infusion of the priming fluid at the start of HD, the Crit-Line® Hb is nearly identical on average to the pre-HD Hb measured by a reference laboratory. More and more clinicians are employing Crit-Line® Monitors for fluid and anaemia management. Crit-Line® Hb corrected in this way may be used for anemia management, which could reduce blood draws and costs.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO827

Hemodialysis (HD) Patients Who Can Maintain Fair Hb Level (>10g/dl) without Iron or Erythropoietin (Epo) Administration Showed Higher Serum Soluble Transferrin Receptor(sTfR) and Normal Epo, Vitamin C (VC) Levels

**Background:** HD patients have severe anemia and their Hb levels were recommended to be maintained at greater than 10g/dl using iron and Epo supplementation. Certain HD patients showed Hb level >10g/dl without iron or Epo. HD patients with fair Hb level revealed higher sTfR, %HypoHe and erythropoietic activity, of G1(30.0(22.1-36.5)nmol/L) was significantly higher than those of GN and G2. 2. MCV values were not significantly different in all three groups. 3. sTfR level, %HypoHe and VC(6.8(2.8-23.4)µg/mL) of G1 were not significantly different from those of GN, whereas significantly higher than those of G2, respectively. 4. Epo level(7.3(5.1-15.2)mIU/mL), reticulocytes(12(9-15)‰) was revealed between %HypoHe and sTfR(r=0.816, p<0.001). By multivariate analysis, %HypoHe was a predictor of sTfR(β=0.834, p<0.001).

**Results:** 1. In G1, ferritin(20(14-36) ng/ml), transferrin saturation(14(8-19)%), HPC(0/7.0(2.5-4.5)mg/ml) were significantly lower than those in both GN and G2, respectively. The percentage of hypochromic RBCs(%HypoHe) increased from (2.7(1.5-4.8)%) was higher than those of GN and G2. 2. MCV values were not significantly different in all three groups. 3. sTfR level, a marker of erythropoietic activity, of G1(30.0(22.1-36.5)nmol/L) was significantly higher than those of GN and G2. 4. Epo level(7.3(5.1-15.2)µmol/L), reticulocytes(12(9-15)%), %HypoHe and VC(6.8(2.8-23.4)µg/mL) of G1 were not significantly different from those of GN, whereas significantly higher than those of G2, respectively. 5. In G1, negative correlation was revealed between VC and %HypoHe(r=-0.437, p=0.048), whereas positive correlation was revealed between %HypoHe and sTfR(r=0.816, p<0.001). By multivariate analysis, %HypoHe was the predictor of sTfR(β=-0.834, p<0.001).

**Conclusions:** HD patients with fair Hb level revealed higher sTfR, %HypoHe and normal Epo, MCV, VC and low HPC levels. These results indicated that iron utilization of these patients was upregulated and this may participate in the maintenance of erythropoiesis.

**Funding:** Private Foundation Support
SA-PO828

Acute Effects of Erythropoietin Administration on Blood Pressure in Dialysis Patients
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Nephrology, Massachusetts General Hospital, Boston, MA.

Background: Erythropoiesis-stimulating agent (ESA) doses are often held in patients with end stage renal disease (ESRD) because of hypertention. However, missed doses may exacerbate anemia of chronic disease. The acute effects of ESA on blood pressure are unknown. We hypothesized that ESA administration during dialysis would not be associated with a significant change in blood pressure.

Methods: With institutional review board approval, we retrospectively reviewed the medical records of 100 hemodialysis patients who were admitted to our hospital between 1/2013-4/2015. All patients in this study were prescribed, and received, ESA's during dialysis. Patients were excluded if dialyzed in the ICU, received vasoppressors, were treated for hypertensive urgency (>180/110 mmHg), initiated on hemodialysis, or only underwent ultrafiltration without dialysis. Blood pressure just prior to and 2 hours after ESA were compared using a paired t-test.

Results: The mean age was 61.6 years (±12.8), 42% were male, 66% were Caucasian, 16% African-American, and 10% Asian. Mean change in blood pressures immediately prior to ESA administration and 2 hours after are summarized.

<table>
<thead>
<tr>
<th>Pre-Dialysis</th>
<th>Just Prior to ESA</th>
<th>2 Hours Post ESA</th>
<th>Mean Change (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP 136±25</td>
<td>SBP 132±27</td>
<td>SBP 128±25</td>
<td>-4.5 (1.74)</td>
<td>p=0.008</td>
</tr>
<tr>
<td>DBP 68±11</td>
<td>DBP 67±10</td>
<td>DBP 66±11</td>
<td>-1.2 (0.25)</td>
<td>p=0.18</td>
</tr>
</tbody>
</table>

No statistically significant increase in SBP or DBP was noted. In fact, we observed a significantly lower SBP 2 hours after ESA dosing. In a subgroup analysis of patients with an SBP > 160 immediately prior to ESA administration, an even greater decrease in SBP was noted 2 hours after ESA compared to a subgroup with an SBP < 160 (p=0.004). No significant relationship existed between dose of ESA and effect on blood pressure (SBP, p=0.52; DBP, p=0.95).

Conclusions: We demonstrated a decrease in systolic blood pressure 2 hours after ESA administration with no significant change in diastolic blood pressure. Withholding ESA during dialysis due to hypertention may be unnecessary.

SA-PO829

Serum Ferritin Predicts Mortality Regardless of Inflammatory and Nutritional Status in Incident Peritoneal Dialysis Patients
Meiyun Wu,1 Kyoung Sook Park,2 Hyung Jung Oh,2 Jung Tak Park,2 Seung Hyeok Han,2 Tae-Hyun Yoo,3 Shin-Wook Kang.1,2 1Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea; 2Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Serum ferritin levels have been proposed as a prognostic factor in hemodialysis (HD) patients, due to its close relationship with inflammation and malnutrition. Since iron supplementation methods and factors affecting nutritional status are somewhat different from those of HD patients, the impact of serum ferritin on clinical outcomes was investigated in incident peritoneal dialysis (PD) patients.

Methods: A prospective cohort of 408 PD patients from the Clinical Research Center for End-Stage Renal Disease was selected. Patients were divided into three groups according to tertiles of Ln ferritin concentrations (group 1: <4.69 ng/mL, group 2: 4.69-5.58 ng/mL, group 3: >5.58 ng/mL). Cox proportional hazard analysis was performed to determine the independent prognostic value of serum ferritin levels for all-cause mortality.

Results: The mean age was 52.1±13.2 years and 236 (57.8%) were male. During a median follow-up of 25 months, 46 (11.3%) patients died. Univariate Cox analysis revealed that the mortality risk was significantly higher in group 2 [hazard ratio (HR)=2.65, 95% CI=1.31-5.42, p=0.009] compared to group 1. Moreover, multivariate Cox proportional hazard models that the mortality risk was significantly higher in group 2 [HR=1.94, 95% CI=1.31-2.88, p=0.001], even after adjustment for variables representing inflammatory and nutritional status.

Conclusions: Higher serum ferritin level was a significant independent risk factor for all-cause mortality regardless of systemic inflammation and nutritional status. Therefore, determining serum ferritin levels could be a useful marker to predict clinical outcomes in incident PD patients.

SA-PO830

Improving Anemia Therapy in Hemodialysis Patients: Interim Results
Pablo Gublan,1 Hamad Al-Gublan,2 Kristin M. Corapi,3 Ishir Bhan,4 Erika Schumann,3 Thomas Ryzlewicz,4 Franz Ferdinand Becker,4 Amelia Macdougall1
1Renal Unit, King's College Hospital, London, United Kingdom; 2Via Medis, Riesa, Germany; 3Oxyless Ltd, London, United Kingdom.

Background: An earlier pilot audit (ASN 2013, PUB200) suggested that the use of a novel bloodline (Oxylens), which reduces the contact between blood and air, could improve the efficiency of Erythropoietin Stimulating Agent (ESA) therapy by prolonging red cell survival. The aim of this investigation was to explore this effect in a larger population.

Methods: Patients (n=110; >18 years, HD ≥ 3 months via AV fistulae) were entered into an 8-month open label, single crossover audit following a 3 month Run-In. Patients reverted to control bloodlines (Nikkiso/Gambro) in the crossover phase after treatment with Oxylens. Hemoglobin (Hb) levels, IV iron sucrose and ESA doses were reported.

Results: Data analysis was conducted on 66 patients from two clinics. Twenty six patients dropped out due to transplantation and intercurrent events, death (n=14) and clinic transfers (n=4). Hb was maintained over the Treatment phase (11.22-11.34 g/dL). Mean ESA doses reduced by 34% (p=0.01) at month 8, equal to 1.09 IU/week/patient. IV iron dose did not change significantly during the audit.

Conclusions: The reduction in ESA doses observed during Treatment, and the initial reversal in the crossover, support that this novel bloodline can improve anemia therapy in HD patients. The audit design increases the confidence in the data validity. These results could have clinical and financial benefits for HD service delivery.

Funding: Pharmaceutical Company Support - Oxyless Ltd
SA-PO832
The Big Red Kidney Bus: Mobile Holiday Dialysis Peter G. Kerr,1 Lesley Ross,1 Jo M. Fairbairn,2 Anne C. Wilson,2 ‘Nephrology, Monash Health, Clayton, Vic, Australia; 2Kidney Health Australia, South Melbourne, Vic, Australia.

Background: The availability of hospital based hemodialysis for those wishing to travel is scarce and often results in restricted opportunities for patients on dialysis to have a holiday. The Kidney Health Australia (KHA) and Monash Health (MH) Big Red Kidney Bus Project (BRKB) offers patients the ability to dialyse on the BRKB whilst on holiday at one of a range of Victorian tourist destinations.

Methods: The aim of the BRKB Project is to provide safe, fully staffed mobile haemodialysis care, to enable people, their families and carers to take a break. KHA owns the bus, manages the bookings and markets the BRKB nationally. MH, a regional health care provider oversees the clinical assessment and treatment and provides medical supervision, dialysis nurses and renal technicians.

The BRKB is a modified bus accommodating 3 hemodialysis machines, dialysis chairs and complete water treatment. Typically, holiday dialysis on the BRKB operates across 2 sessions per day, 6 days per week duplicating the dialysis parameters of the patients’ home unit. The bus is driven to and parked at caravan parks around Victoria for 6-week periods, during which time patients may book in for dialysis sessions. Their accommodation is up to them to decide on – with the option of using cabins in the parks or local motels (or their own caravans).

Results: Since its inaugural visit in October 2014, 148 different patients have taken advantage of the BRKB. The bus has visited 6 sites around the State and has site bookings for the next 10 months. Participating holidaymakers were overwhelmingly positive about the service. They found the booking system easy to use. The dialysis service on the bus was delivered to the standard of care experienced at their home units. The professionalism of the nursing staff and friendliness was commended and all participants would recommend the service to others.

Conclusions: The BRKB is a unique project that provides patients with the opportunity to dialyse on the bus while taking a much-needed holiday.

Funding: Private Foundation Support

SA-PO833
Patient and Caregiver Values, Beliefs and Experiences when Considering Home Dialysis as a Treatment Option: A Semi-Structured Interview Study Rachael C. Walker,1 Kirsten Howard,2 Rachael L. Morton,1 Suettania Palmer,2 Mark R. Marshall,3 Allison Tong,4 ‘Univ of Sydney; ‘Univ of Otago; ‘Middledore Hospital, New Zealand; ‘Univ of South Australia.

Background: Home dialysis is associated with higher quality of life and economic benefits to health care systems compared with facility dialysis. However, little is known about the decision-making process of patients when considering home dialysis as a treatment option.

Methods: This semi-structured interview study aimed to describe patient and caregiver values, beliefs and experiences when considering home dialysis, to inform policy and practice strategies that align with patient preferences. We conducted semi-structured interviews with adults with CKD Stage 4-5D (on dialysis <1 year) and their caregivers, treated in 3 nephrology centers in New Zealand. Transcripts were analyzed thematically.

Results: 43 patients (18 pre-dialysis, 13 peritoneal dialysis, 4 home hemodialysis and 9 facility hemodialysis) and 9 caregivers participated. We identified 5 themes related to decision-making when considering home dialysis; lacking decisional power (complexity of information, limited exposure to home dialysis, feeling disempowered, deprived of choice, pressure to choose); sustaining relationships (maintaining cultural involvement, family influence, trusting clinicians, minimizing social isolation); reducing lifestyle disruption (sustaining employment, avoiding relocation, considering additional expenses, seeking flexible schedules, creating free time); gaining confidence in choice (guarantee of safety, depending on professional certainty, reassurance of peers, overcoming fears); and maximizing survival.

Conclusions: Patients feel disempowered when choosing home dialysis and make decisions that sustain their relationships, maintain lifestyle values and maximize survival. Confidence in their modality decision is gained by medical professional and peer support combined with overcoming safety concerns. Pre-dialysis programs that address this patient experiences may support home dialysis as a treatment option.

Funding: Pharmaceutical Company Support - Baxter Clinical Evidence Council research program

SA-PO834
Patient Experiences of Training and Transition to Home Hemodialysis: A Longitudinal Mixed Methods Study Camilla Sara Hansen,1,2 Jeremy R. Chapman,1 Jonathan C. Craig,1 David C. Harris,3 Lukas K. Kairaitis,4 Mary Ann Nicdao,3 Mary Mikhaeel,1 Allison Tong,1,3 ‘School of Public Health, The Univ of Sydney, Sydney, NSW, Australia; ‘Centre for Kidney Research, The Children’s Hospital at Westmead, Sydney, NSW, Australia; ‘Centre for Transplant and Renal Research, Westmead Hospital, Sydney, NSW, Australia; ‘Dept of Renal Medicine, Westmead Hospital, Sydney, NSW, Australia.

Background: Home hemodialysis (HD) can offer better survival and quality of life outcomes compared with in-centre HD. However, psychosocial barriers such as fears of needles and medical isolation may limit home HD uptake. This study aims to describe patients’ perspectives on training and transition to home HD; to inform strategies to optimize home HD programs.

Methods: Three semi-structured interviews were conducted prospectively with 20 patients before, during and after home HD training at an Australian renal unit. The CHOICE satisfaction survey was administered during the first and final interview. Transcripts were analyzed thematically.

Results: We identified six themes: persevering despite trepidations (intimidation of machinery, acquiring to fatal risks, reconciling censure fears, dispensing concerns of neglect, tolerating concessions); optimizing learning pathway (practicing problem solving, learning from mistakes, grasping technical complexity, minimizing cognitive overload); developing confidence (believing in own abilities, depending on caregiver partnership, faith in crisis support); interrupted transition momentum (lacking individual attention, language barriers, installation delays, illness and complications, acclimatizing to new conditions); noticing immediate gains (reclaiming normality, satisfying self-sufficiency, personalizing treatment regime); depleting resources and energy (exhaustion, draining financial reserves, imposing caregiver burden). There was no significant change in satisfaction with care after commencing home HD.

Conclusions: Individualized home HD training fosters confidence and competency in patients; however patients may face anxiety and exhaustion with medical responsibilities. Ensuring access to respite, medical assistance, and psychosocial support may alleviate treatment burdens for patients commencing home HD.

Funding: Private Foundation Support

SA-PO835
Incremental Hemodialysis, Residual Kidney Function, and Mortality Risk in Incident Hemodialysis Patients Yoshitsugu Obi,1 Elani Streja,2 Connie Rhee,1 Vanessa A. Ravel,1 Alpesh Amin,1 Csaba P. Kovesdy,2 Rajnish Mehrotra,3 Kamyar Kalantar-Zadeh,1 ’UC Irvine, ’UTHSC, ’UW.

Background: We have previously reported that an incremental hemodialysis regimen (e.g., dialysis initiation at twice weekly) was associated with more preserved residual kidney function over a year of dialysis therapy (WCN 2015, Cape Town). Here, we compared survival between the incremental vs. conventional regimen.

Methods: In a longitudinal cohort of 33,277 patients who initiated maintenance hemodialysis over four years (1/2007-12/2010) and survived the first year, 364 patients treated with the incremental regimen were matched to 4,797 patients treated with the conventional regimen on age, gender, race, the use of central venous catheter as blood access, and a history of congestive heart failure at the initiation of dialysis. The incremental hemodialysis regimen was associated with ~20% higher residual renal urea clearance (KRU) and 24-hr urine volume (UV) after 1 year of dialysis initiation. We then examined survival after the first year.

Results: Patients were 69±12 years old, 39% female, 13% non-Hispanic Black, and 66% diabetic. Median KRU and UV were 4.74 (IQR, 3.23-6.65) mL/min/1.73m² and 1,150 (IQR, 800-1,650) mL/day, respectively. Baseline KRU and UV modified the association between the incremental regimen and mortality; the incremental regimen was associated with higher mortality in patients with KRU <3.0 mL/min/1.73m² or UV <600 mL/day, but not in those with higher levels of KRU and UV.

Funding: NIDDK Support

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

822A
SA-PO836
Seasonal Trends in Dialysis Initiation and Rising Home Dialysis: Results from the USRDS
Hui Liu,1 Yang Jiao,2 Douglas Lehmann,2 Richard Hirth,3 Yi Li,1 Rajiv Saran.1 1Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI; 2Dept of Biostatistics, Univ of Michigan, Ann Arbor, MI; 3Dept of Health Management and Policy, Univ of Michigan, Ann Arbor, MI.

Background: Motivated by increasing interest in home dialysis and incentive for it in the bundled payment system, we examined incident trends in home dialysis use in the United States Renal Data System (USRDS).

Methods: Using USRDS data (2007-2013), monthly counts of all new ESRD cases in the US, as well as incident home hemodialysis (HHD) and incident peritoneal dialysis (PD) patients were tracked. Incident HHD patients were those who started HHD within 90 days of entry into an ESRD program and incident PD patients who started PD as their initial modality.

Results: In 2013, over 55% of US facilities offered only in-center HD, 24.7% both HD and PD and 13.5% offered HD, PD and HHD. Figure 1 shows trends in monthly ESRD and PD utilization in the US during 2007-2013. The incidence rate of ESRD has been stable since 2010, but the number of new PD starts has risen steadily since 2009 and has somewhat further accelerated since 2011. Figure 1 also shows a seasonal trend for new ESRD and PD starts: incident ESRD cases tend to peak in the first 3 months of the year, while new PD starts tend to peak by mid-year. Rising HHD use is evident since 2007, without seasonal variation. A substantial variation in the annual growth rate of PD is notable across the states.

Conclusions: We report steadily rising home dialysis use in the US, both HHD and PD, since 2007 and 2009, respectively. This rise predates the implementation of the bundled payment system in 2011, although PD use seems to be rising faster since 2011. Research into this seasonality in ESRD incidence and the impact of rising home dialysis use are warranted.

Funding: NIDDK Support SA-PO837 Understanding Barriers to Home-Based and Self-Care In-Center Hemodialysis May L. You,1 Luis Alvarez,2 Michelle Carver,1 Geoffrey A. Block,2 Glenn Matthew Chertow.4 1Outset Medical, Inc, San Jose, CA; 2Sutter Health, Mendlo Park, CA; 4Denver Nephrology, Denver, CO; 3Stanford School of Med, Palo Alto, CA.

Background: Despite superior outcomes and lower associated costs, few patients with end stage renal disease undergo selfcare (SC) or home hemodialysis (HHD). Few studies have examined patient and physician barriers to SC and HHD and the degree which innovative technology might facilitate adoption.

Methods: We surveyed 250 in-center patients (pts) receiving hemodialysis and 51 board-certified nephrologists to identify key barriers to adoption of SC and HHD.

Results: Overall, 172 (69%) pts reported that they were “likely” or “very likely” (figure 1) to consider SC hemodialysis if they were properly trained on a new hemodialysis system designed for SC.

Patients that would consider performing self-care on a novel, patient-centered hemodialysis system

Conclusions: Nephrologists believed that pts were capable of performing dialysis-relevant tasks, including: weighing themselves (98%), wiping down the chair and machine (84%), clearing alarms during treatment (53%), taking vital signs (46%), and cannulating vascular access (41%), but thought that patients would not be willing to do the same.

Reasons that nephrologists believe pts are hesitant to pursue SC do not correspond to reasons reported by patients.

Conclusions: SC and HHD offer several advantages to patients and dialysis providers. Overcoming real and perceived barriers with new technology, and education will be required for these modalities to gain traction in the coming years.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.
SA-PO839
Wessex Kidney Centre Experience of Nocturnal Home Haemodialysis Using the NxStage System One Venkat Gangaram, Amanda Jane Laird, Laura Hignell, Natalie L. Borman. Renal Medicine, Wessex Kidney Centre, Queen Alexandra Hospital, Portsmouth, United Kingdom.

Background: Wessex Kidney Centre (WKC) Portsmouth established Home Haemodialysis (HHDH) programme in 2009. In the absence of an in-house technician and limited capital the programme was set up using NxStage system one (NSO). WKC has now established a rapidly growing HHD programme using exclusively NSO, trained 97 patients to date includes nocturnal therapy.

Results: A total of 18 patients have received NHHD with mean time of 12.3 months (range 1 to 31). All patients dialyse alternate nights processing 40-60 litres using dual needleling access and a single bolus of Enoxaparin Sodium. Patients have regular transonic monitoring of their access and home visits. Two NHHD patients successfully dialyse alone. The mean age is 47.7 years (range 26 to 80), 78% male, 94% Caucasian with mean BMI 26.9. The Access used was A V fistula 56%, A V graft 22% and CVC 22% of patients. 14 patients changed from short daily HHD (SDHHD), 3 patients from in centre Haemodialysis and 1 from Peritoneal dialysis. Laboratory parameters have been favourable as shown below.

<table>
<thead>
<tr>
<th></th>
<th>C.Ca Mmol/L</th>
<th>PO4 Mmol/L</th>
<th>K Mmol/L</th>
<th>Hb g/l</th>
<th>Alb g/l</th>
<th>Ca-PO4 g/mol/L</th>
<th>2sKt/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-NHHD (n=18)</td>
<td>2.4</td>
<td>1.6</td>
<td>4.9</td>
<td>11.3</td>
<td>35</td>
<td>3.8</td>
<td>2.44</td>
</tr>
<tr>
<td>6 months (n=14)</td>
<td>2.4</td>
<td>1.4</td>
<td>4.7</td>
<td>12.3</td>
<td>36</td>
<td>3.3</td>
<td>2.57</td>
</tr>
<tr>
<td>12 months (n=10)</td>
<td>2.4</td>
<td>1.36</td>
<td>4.6</td>
<td>12.3</td>
<td>36</td>
<td>3.0</td>
<td>2.50</td>
</tr>
</tbody>
</table>

Retention has been excellent with one patient returning to in-centre HD after 25 months of HHD. Two patients switched to SD HHD as it more suited to their lifestyle and five patients have been transplanted. Pill burden has reduced, with less or no phosphorus binders (mean number of binders reduced from 6 to 2) and a 40 % reduction in antihypertensive medication.

Conclusions: Patients experience excellent, with high quality of life and with less pill burden, flexibility and more opportunity to engage in social activities.

SA-PO840
Current and Future Training of Home Haemodialysis Nurses Ruth Silvertown, 1 Philippa Catherine Brown, 1 Paul Laboi, 1 Nicola Thomas. 2 1 Department of Renal Medicine, York Hospital, United Kingdom; 2School of Health and Social Care, London South Bank Univ, United Kingdom.

Background: The UK National Institute for Health and Care Excellence recommend that >10% of dialysis patients be treated by home haemodialysis (HHHD), however only 4.1% of patients in the UK are undergoing this modality. Success with HHHD can be attributed to a supportive health policy, formal infrastructure, committed individuals and home dialysis experience; providing a patient-centred approach. Lack of nursing expertise is reported as a barrier to home dialysis for 30% of units. A 2010 survey by the Australian HOME network revealed insufficient resources in dialysis units to provide support and education to patients. A potential barrier to HHD in the UK is specific training for renal nurses on the facilitation of shared or self-care.

Methods: The extent of current training provision for dialysis nurses in order to educate patients in home therapies/shared care was evaluated via an online survey. A link to the survey was sent to the British Renal Society database and the survey was available online for 1 month. There were 63 respondents.

Results: Over 76% of respondents (n=48) had worked in renal care for >10 years, with a third (n=21) receiving more than 5 days of structured training in how to teach self care. The majority of this training (51%) was as part of an ‘in-service programme’, with just over half (53%) of all nurses surveyed feeling adequately prepared for educating patients. The preferred mode of further training was face to face at a national event (38%), with a quarter (n=14) citing e-learning as the preferred option.

Conclusions: Data from the survey highlights a lack of adequate, standardised training for HHD nurses, demonstrating the need for a structured programme that ensures up-to-date best practice. As a result, we plan to pilot a specific HHD training scheme that involves patients and carers in curriculum planning and delivery, with content including; assessment of patients’ learning styles, how to facilitate shared decision-making with patients, and how to evaluate effectiveness of the HHD programme.

SA-PO841
Daily Hemodialysis in France: Patient’s Characteristics, Trajectories, and Treatment Modalities Adelaide Pladys, 1,2 Sahar Bayat, 1 Cécile Couchoud, 1 Cécile M. Vigneau, 1,4 1French School of Public Health, Rennes, France; 2‘Univ Rennes 1, Rennes, France; 3French Biomedicine Agency, Saint Denis La Plaine, France; 4CHU Pontchaillou, Rennes, France.

Background: Increased weekly frequency of hemodialysis (HD) sessions should have positive effects on the control of several biological data of end stage renal disease patients. However, a recent study observed contradicting results in terms of survival compared to previous ones. Patients included in this study came mainly from France where knowledge about daily hemodialysis (DHD) practices is poor. In this context, the aim of this study was to describe the characteristics of French patients in DHD, the treatment modalities and the individual trajectory before starting such a program.

Methods: We included all patients >18 y/o who started DHD between 2003 and 2012 in France. Bioclinical and treatment characteristics were extracted from the French Renal Epidemiology and Information Network (REIN) registry then described and compared by groups using Chi-square tests.

Results: 753 patients were included in the study. According to the median age (64 years), two groups of patients were distinguished: old group (≥64 years) characterized by lots of comorbidities such as diabetes (48% vs 29%, p<0.0001), active malignancy (17% vs 10%, p=0.008), 1 cardiovascular disease (80% vs 41%, p<0.0001) compared to the younger one (<64 years). At the 31/12/2013, 30.4% of the young patients underwent renal transplantation and 69% of the old ones were died. The main regimen observed was HD 6x/week with sessions’ duration of 3 hours. Among these patients, 496 started with other dialysis modality before switching to DHD (dDHD) and 257 started directly with DHD (dDHD). Before starting DHD, 81% of dDHD patients were in HD 3x/week and 5.4% had 1x1 modality change. dDHD patients initiated DHD in urgent condition for 57% of them and 92.6% underwent DHD in centre.

Conclusions: DHD in France is addressed both to old patients with lots of comorbidities who died rapidly and to young patients in better medical conditions who accessed more to renal transplantation. DHD regimens are various and depend of patients’ characteristics and previous trajectories.

SA-PO842
In Vivo Urea Removal by Electro-Oxidation in a Wearable Dialysis Device Maarten Wester, 1 Frank Simonis, 1 Diënty Haenbrink, 1 Jaap A. Joles, 1 Karin G. Gerritsen. 1 1Nephrology and Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands; 2Nanodialysis BV, Oirschot, Netherlands.

Background: In EU consortium NEPHRON+ a wearable dialysis device is being developed that can offer prolonged dialysis by continuous regeneration of a small volume of dialysate. A major challenge is the removal of urea, since the daily urea production is high and removal by adsorption difficult. Electro-oxidation (EO) seems attractive since electrodes are durable, small and inexpensive. Here, we studied in vivo urea removal by EO in a hemodialysis model in goats.

Methods: An EO-unit containing 10 graphite electrodes for EO and sorbent beads for K+ and PO4- removal was incorporated in a dialysate circuit in series with activated carbon (AC;25g/unit). 3 Ampère (A) was applied using 1 EO-unit (1x3A,N=7) or 2 EO-units in parallel (2x3A,N=7). Healthy goats were instrumented with a CVC, heparinized blood was pumped (110mL/min) during 3hrs over a 0.2m2 Polyflux dialyzer and dialysate was recirculated over the EO unit in counter current direction (40mL/min for 1x3A; 2x40mL/ min and 2x70mL/min for 2x3A; total dialysate volume 100mL (1 EO-unit) or 150mL (2 EO-units)). Urea was infused to achieve higher urea concentrations.

Results: Urea removal and clearance were 8.4±1.5mmol/h and 11.9±1.6 mL/min, respectively, using 1 EO unit (Fig. A,B) and remained stable during consecutive hours. Use of 2 units in parallel doubled the removal of urea and caused a 1.6-fold increase in urea.
clearance. Increase of the dialysate flow did not further increase urea removal. Urea removal was dependent on urea plasma concentrations (loglinear). Limited release of ammonia-umol was observed (0.16±0.03 mole per removed mole of urea).

Conclusions: By electro-photocatalytic reactors combined with AC showing promising urea removal in vivo. Research aimed at increasing the efficacy and biocompatibility testing is warranted.

SA-PO843
Unplanned “Crash” Home Dialysis Starts: Single Center Experience from a University Hospital in the United States
Kristen P. Tamura, 1 Jose A. Morfin, 2 Nephrology, UC Davis Medical Center, Sacramento, CA; 1Nephrology, UC Davis Medical Center, Sacramento, CA.

Background: There is a high incidence of starting dialysis from the hospital to the in-center unit, and frequently these starts are unplanned and unexpected (“crash”). To this end, we sought to implement an educational program to identify patients suitable for a home dialysis modality, unplanned home hemodialysis (UHHD) and unplanned peritoneal dialysis (UPD).

Methods: We performed an retrospective observational analyses on patients who were started on dialysis from January 2013 to April 2015 in a diverse patient population admitted to UC Davis Medical Center in Sacramento, CA. We devised a systematic and comprehensive screening educational program to provide all modality options. We identified patients suitable UHHD, and UPD, both which were transitioned to a home dialysis training program upon discharge. Clinical characteristics and outcomes were compared to groups who had a standard start home dialysis (SHHD, SPD) during the study period. Our measured outcomes include the following: average training days, interval of technique failure (patient drop out) access status and complications, infections, hospitalizations and mortality in the first 90 days.

Results: Preliminary results reveal the groups tended to have similar demographic profiles with the average age for patients starting an unplanned home dialysis 51.5 years of age, 66% non-white race, but with a trend toward more males at 59% compared to standard starts.

Conclusions: In this small representative sample, UHHD and UPD was a viable option for programs to consider for the transition of new dialysis patients from the hospital to the outpatient setting. We found similar outcomes in comparison to patients starting home dialysis training in a traditional standard way. Education and screening of home dialysis therapies should be promoted in the hospital setting.

SA-PO844
Quality of Life After 1 Year of Nocturnal Home Hemodialysis Is Comparable to Quality of Life After Renal Transplantation
Anna A. Bonenkamp, 1 Franka E. Van Reekum, 1 Marianne C. Verhaar, 2 Brigid C. van Jaarsveld. 2 Nephrology & Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands; 1Nephrology, VU Univ Medical Center, Amsterdam, Netherlands.

Background: Quality of life (QOL) is an important outcome measure for pts with ESRD. Several studies found improved QOL in Nocturnal Home Hemodialysis (NHHHD) compared to conventional HD (CHD). There are no studies comparing QOL in NHHHD vs Tx. Therefore, some pts on NHHHD hesitate whether or not to apply for a place on the renal transplant (Tx) waiting list. The aim of this study is to assess the difference in QOL between NHHHD and Tx after 1 yr of follow up.

Methods: Data were obtained from the ongoing NOCTX-study, which evaluates the 3-yr progression of coronary atherosclerosis in pts treated with CHD, PD, NHHHD and Tx. In this study, QOL was measured with the Kidney Disease-QOL SF questionnaire at baseline (<3 mo after start) and after 1 yr in NHHHD (n=22; 5:76/cr, 6-8 HD per day; all Tx-waitlisted) and Tx (n=30). Composite scores (Physical = PCS, Mental = MCS) and disease related domains were used. One yr results were analyzed with an unpaired t-test.

Results: Pts (n=52) were 50.12 yr, 67% male and median duration of RRT was 37:31mo. Baseline characteristics were comparable between the groups. PCS was 46.9 in NHHHD and 44:8 in Tx group at baseline; follow up PCS was 44:7 and 47:9 respectively (p=0.13). MCS at baseline was 53:9 vs 53:8 and 50:12 vs 52:9 after 1 yr (NS). Compared to NHHHD, Tx pts scored better on the domain “Effects of kidney disease” (75:18 vs 86:14 p=0.01). Sexual function had a remarkably good response rate (90%) and equal scores between NHHHD and Tx (69:34 vs 75:27 p=0.55). In other KQDOL domains no significance was observed.

Conclusions: This is the first study to compare QOL between Tx pts and wait-listed NHHHD patients. Physical and Mental Composite Scores were similar. In disease specific domains, Tx and NHHHD scored not significantly different except for the domain ‘Effects’. These data support an important role for NHHHD as an alternative to renal transplantation.

Funding: Pharmaceutical Company Support - The NOCTX study is performed with unrestricted grants from Bayer Netherlands B.V. Roche Nederland BV Amgen Nederland BV Fresenius Medical Care Nederland Shire Pharmaceuticals Benelux Novartis B.V. Wellerdieck de Goede funds, UM Utrecht.

SA-PO845
Association of Vascular Access Type with Mortality, Hospitalization, and Transfer to In-Center Hemodialysis in Patients Undergoing Home Hemodialysis
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Background: In individuals undergoing in-center hemodialysis (HD), use of central venous catheters (CVCs) is associated with worse clinical outcomes compared to use of arteriovenous access. However, it is unclear whether a similar difference in vascular access type risk is present in patients undergoing home HD, as these patients have higher dialysis treatment frequency and lower rates of exposure to sources of nosocomial infection.

Methods: We examined the associations of vascular access type with all-cause mortality, hospitalization, and transfer to in-center HD in patients who started home HD from 2007-2011 in 464 facilities in 43 states in the United States. We analyzed the data using competing-risks hazard regression with vascular access type as the start of home HD as the primary exposure in a propensity score-matched cohort (1052 patients; 526 with CVC, 526 with arteriovenous access).

Results: Compared to arteriovenous access, CVC use was associated with increased risk for mortality (hazard ratio [HR] 1.78; 95% confidence interval [95% CI] 1.21 to 2.61) and hospitalization (HR 1.38; 95% CI 1.19 to 1.59). CVC use was not associated with increased risk for transfer to in-center HD (HR 1.07; 95% CI 0.81 to 1.40). The results of analyses in the entire unmatched cohort (2481 patients), with vascular access type modeled as baseline exposure at start of home HD or as a time-varying exposure, were similar.

Conclusions: In a large nationally representative cohort of home HD patients, CVC use was associated with increased risk for mortality and hospitalization.

Funding: NIDDK Support

SA-PO846
Time to Transplant Associates with Home Dialysis Modality
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Background: We recently showed that prevalent end-stage renal disease patients starting home dialysis (HDH) have reduced cardiovascular and infection-related hospitalization risk compared to those starting peritoneal dialysis (PD). As current hospitalization precludes being active on the transplant wait-list, we investigated whether HDH patients receiving home HDH would be more likely to be transplanted than those receiving PD.

Methods: We matched 2997 adults starting home dialysis (HDH) in a single US dialysis provider’s facilities from 2004-2011, to 2997 contemporaneous USRDS patients starting PD (US state and center matched scores. Demographic & insurance status, co-morbidities, complications, and outcomes were ascertained from USRDS. We used Cox regression stratified on matched sets censoring for death, and competing risk analysis using Fine’s approach for stratified data, to compare times to transplantation between groups.

Results: Baseline variables were balanced between groups after matching, with standardized differences <10%. During 12,558 years of follow-up (mean 2.1±1.4 yrs), 514 HDH and 428 PD patients were transplanted. HDH patients were 19% more likely to be transplanted than PD patients (HDH 8.2 vs PD 6.8 per 100 patient-yrs; HR 1.19, 95%CI 1.05-1.35, p=0.012). Competing risk analysis accounting for death and follow-up losses yielded a HR of 1.18 (95%CI 1.04-1.33, p=0.010). Time to waiting-list did not differ between groups (HR 0.97, 95% CI 0.90-1.06, p=0.54), but once waitlisted, PD patients were significantly more likely to be permanently removed from the wait-list (PD 14.2% vs HDH 10.2%, RR 1.39 [95%CI 1.09-1.78], p<0.008).

Conclusions: In this prevalent cohort, home HDH patients were more likely to be transplanted than matched PD patients, and less likely to be permanently removed from the wait-list during follow-up. Mean times to wait-listing were similar, suggesting that the groups were well-matched at baseline. Further study needs to determine the factors responsible for the differential transplantation rates observed in home HDH and PD patients.

Funding: Private Foundation Support.
SA-PO847
Spectrum of Mutations in PKD1 and PKD2 Genes in 100 Unrelated Italian Pedigrees with ADPKD – Sanger Sequencing versus Next Generation Sequencing (NGS) Madalena Gigante,1 S. Diella,1 Matteo Accetturo;2 Paola Pontrelli;2 Giovanni Stailone;1 Giuseppe Grandaliano;1 Loreto Gesualdo.1 1 Univ of Foggia, Foggia, Italy; 2 DETO, Univ of Bari, Bari, Italy.
Background: ADPKD is caused by mutations in PKD1 or PKD2 genes. Although, clinical studies and case reports describing one or few ADPKD families have been reported in Italian population, to date a comprehensive molecular study is still lacking.
Methods: PKD1 and PKD2 genes were analyzed in 150 Italian ADPKD patients from 100 unrelated pedigrees - the largest Italian cohort analyzed to date in a single study - using Sanger sequencing and NGS. The potential pathogenicity of the newly identified variants was evaluated by combining different in silico methods.
Results: We identified the largest number of definitively and probable pathogenic mutations (n=78) reported in a single study in Italian population, achieving an overall detection rate of 90%. 55 mutations (52 PKD1 and 3 PKD2) have not been previously described, expanding the spectrum of known ADPKD mutations. We identified 12 de novo PKD1 mutations in sporadic patients without family history, providing a definitive diagnosis of ADPKD. We found the largest number of de novo mutations reported in a single study (15%) demonstrating, for the first time, that the prevalence of PKD1 de novo mutations may be underestimated. 4/32 PKD2 mutations were found in 2 unrelated Italian patients, a sign of founder effect. 20 patients were analyzed by NGS: we confirm the presence of a nonsense PKD1 mutation and the lacking of clear pathogenic mutations in 3 patients previously analyzed by Sanger, and the presence of definitively/probable pathogenic mutations in the 17 not previously genotyped patients. All NGS results have been confirmed by Sanger sequencing, achieving sensitivity and specificity of 100%.
Conclusions: Our data provide important new advances in the molecular diagnostics of ADPKD: (i) describe for the first time new potential founder mutations in Italy; (ii) report the largest number of de novo mutations identified in a single study and (iii) provide a new NGS method with a detection rate comparable to Sanger sequencing but with significantly lower cost and reduced turnaround time.
Funding: Government Support - Non-U.S.
SA-PO848
The Use of Screening MR Angiography in Patient with ADPKD Claudine Christiansen, Ruben Poensen, Dirk R. Kuypers, Bert Bammens, Bjorn Meijers. Nephrology, Univ Hospitals Leuven, Belgium.
Background: Autosomal dominant polycystic kidney disease (ADPKD) is associated with the development of intracranial aneurysms and an elevated risk of hemorrhagic stroke (HIS). It is suggested that screening MR angiography reduces the incidence of hemorrhagic stroke. Current screening criteria include positive aneurysm history in relatives, neurological symptoms and planned major surgery. The efficacy of these screening criteria has, however, not been fully evaluated.
Methods: We performed a single-center retrospective analysis of all ADPKD patients followed at the University Hospitals Leuven, between January 1990 (date of the first MR angiography) and August 2014. Baseline demographics and occurrence of screening criteria, screening MR angiography, intracranial aneurysm and hemorrhagic stroke were evaluated.
Results: We identified 865 patients with ADPKD. Those who were seen at least three times (median age 51y, 49% males) were included for analysis. Mean duration of follow up was 11.6 years. In this cohort, current screening criteria were met in 183 ADPKD patients (29.2%). Of these, 136 (74.3%) had screening MR angiography. In patients with no MR angiography, presence of screening criteria was associated with an elevated risk of hemorrhagic stroke (12.8% vs. 4.0%, P=0.02). Use of MR angiography in patients with screening criteria was related with a lower risk of hemorrhagic stroke during follow-up (2.2% vs. 12.8%, P=0.01).
Conclusions: In patients with ADPKD, current screening criteria for intracranial aneurysm are associated with an 3-fold elevated risk for future hemorrhagic stroke and performing MR angiography seems effective in reducing this risk.
SA-PO849
Influence of Genotype on ADPKD Progression in the HALT PKD Cohort Christina M. Heyer,1 Kaleab Z. Abebe,1 Vicente E. Torres,2 Ronald D. Perrone,4 Marie C. Hogan,7 William E. Braun,5 Godela M. Brosnahan,2 Peter G. Czarnecki,1 Charity G. Moore,2 Peter C. Harris,1 Dana Miskulin,2 The HALT PKD Investigators.1 1 Mayo Clinic, Rochester, MN; 2 U of Pittsburgh, Pittsburgh, PA; 3 U of Colorado, Denver, CO; 4 Tufts, Boston, MA; 5 Cleveland Clinic, Cleveland, OH; 6 Brigham and Women’s Hospital, Boston, MA; 7 Carolina’s Health Care System, Charlotte, NC; 8 Sites.
Background: We assayed here the influence of the ADPKD disease gene (PKD1 or PKD3) or PKD1 mutation type (truncating or non-truncating) on the rates of renal disease progression over 5 years in the HALT PKD cohort.
Methods: PKD1 mutation type was divided into strength groups: truncating (MSG1), and more or less penetrant non-truncating (MSG2 and MSG3). Correlations were made between gene type/MSG and changes in eGFR or height adjusted total kidney volume (htTKV).
Results: PKD1 patients had a faster eGFR decline than PKD2 (3.3 vs. 1.87 ml/ min/1.73m2/yr; P=0.0001) but the rate of htTKV increase did not differ (6.44 vs. 6.81%/ yr; P=0.42). Baseline PKD1 htTKV was larger than PKD2 (733, 557 ml/m2; P=0.0001) and so PKD1 kidneys expanded to a greater extent (268, 217 ml/m2/yr; P=0.0001). Rates of change in eGFR or htTKV did not differ between PKD1 MSG2 and MSG3 (P=0.15 and 0.70), but MSG3 baseline kidneys were smaller relative to MSG1 and MSG2 (611, 753, 777 ml/m2; P<0.004) and so the volume increase was less (221, 262, 277 ml/yr; P<0.004). PKD2 patients were less likely to reach a study endpoint (death, ESRD or 50% eGFR decline; P=0.003), but there was no difference between PKD1 MSG1, 2, 3 (P=0.61). Patients with no mutation detected, had a slower increase in htTKV (4.84%/yr; P=0.008 vs. PKD1). The study showed a difference in TKV increase between the low and standard blood pressure groups (5.6 vs. 6.6%/yr; P<0.006).
Conclusions: PKD1 MSG3 kidneys are smaller but not because they grow more slowly; possibly because they have less early cysts, similar to PKD2 vs. PKD1. Since genic and allelic effects do not alter progression rates, restricting analysis by genetic factors did not improve significance.
Funding: Clinical Revenue Support
SA-PO850
Climate Temperature Affects the Age of End-Stage Kidney Disease in Autosomal Dominant Polycystic Kidney Disease (PKD) Marwan M. Abbas,1 Michael E. Bleyer,2 Elizabeth Swain,1 Kendra O. Kidd,1 Gregory B. Russell,2 Anthony J. Bleyer.1 Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC; Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC.
Background: Vasopressin receptor 2 antagonists decrease cyst size in PKD. We postulated that patients in hotter climates would have more concentrated urine, and this would affect the age of ESRD in PKD.
Methods: We obtained demographic data and cause of ESRD on 1,332,402 individuals who had their first occurrence of ESRD between ages 30 and 90 between 1971 and 2012 from the US Renal Data system (USRDS). We obtained annual mean temperatures from 1990 to 2010 for US weather stations and linked a participant’s zip code to the nearest weather center. We correlated the mean age of onset of ESRD for PKD and other causes of ESRD with 5 degree temperature intervals. We created a multivariate model for PKD patients, with the dependent variable age of ESRD and independent variables race, gender, year starting dialysis, residual GFR at start of ESRD, annual median income by patient zip code, and temperature as discrete variables in 5 degree intervals.
Results: Figure 1 shows the mean age of onset of ESRD by disease. Cold and warm temperature extremes were associated with increasing age of ESRD for PKD, but other diseases.

The multivariate model showed that temperature had a minimal effect on age of ESRD compared to other variables in the model.

Conclusions: There was a U-shaped relationship for age of ESRD according to temperature that was present in PKD and other diseases. However, in a multivariate model, climate temperature had a minimal effect on age of ESRD in PKD.
Funding: Clinical Revenue Support

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

826A
SA-PO851
Urinary Biomarkers and Prediction of Disease Progression in Autosomal Dominant Polycystic Kidney Disease

Background: The variable disease course of ADPKD underlines the importance of predicting disease progression especially since therapeutic options are now available. Conventional risk markers (age, gender, GFR, total kidney volume (TKV)) lack sensitivity, are expensive or time-consuming to measure. We therefore investigated whether easy to measure urinary markers can predict disease progression and have additional value to conventional risk markers.

Methods: At baseline tubular damage and inflammatory markers were measured in 24-hour urine: albumin, IgG, IgM, 192mg, H-FABP, MIF, NGAL and MCP-1. Patient function was estimated (eGFR by CKD-EPI) and measured (mGFR by (125)I-iothalamate), and TKV by MRI. Disease progression was expressed as annual change in eGFR, mGFR, and height-adjusted (ht)TKV. Multivariate linear regression was used to assess the predictive ability of the markers above conventional risk markers.

Results: Included were 104 ADPKD patients, 40±11yrs, 39% female, eGFR 77±30 ml/min/1.73m², mGFR 79±29 ml/min/1.73m² and htTKV 852 (510-1243) mL/m². During a follow-up of 3.8±1.2 yrs, annual change in eGFR was -5.3±3.0, in mGFR -5.0±3.0 ml/min/1.73m² and in htTKV 0.2±5.9 yrs. B2MG and MCP-1 were associated with annual change in eGFR (Spearman β = -0.23, p = 0.02; Sβ = -0.38, p = 0.001 resp.) and mGFR (Sβ = -0.24, p = 0.03; Sβ = -0.24, p = 0.03 resp.), even when adjusted for conventional risk markers, but not with annual change in htTKV. Similar results were obtained when patients with an eGFR>60 mL/min/1.73m² were selected. Combined B2MG and MCP-1 had an added predictive ability for annual change in eGFR (R² = 0.178 vs. 0.324, p = 0.008) and in mGFR (R² = 0.134 vs 0.217, p = 0.07). The best predictive model for annual change in eGFR included age, htTKV, MIF, b2MG and MCP-1 (R² = 0.343, p = 0.025), and for annual change in mGFR, gender, b2MG, NGAL and mGFR (R² =0.411, p = 0.021).

Conclusions: Significant urinary markers can predict disease progression and had an added predictive value on top of conventional risk markers. These markers have therefore potential to serve as a predictive tool for clinical practice.

SA-PO852
The Novel Surrogate Marker of Autosomal Dominant Polycystic Kidney Disease (ADPKD) – Urinary Copeptin
Satoru Mutô1, Yu Lan1, Haruna Kawano,2 Shigeo Horie.2 1Urology, Teikyo Univ School of Medicine, Tokyo, Japan; 2Urology, Juntendo Univ, Graduate School of Medicine, Tokyo, Japan.

Background: Experimental studies suggest a detrimental role for Arginine vasopressin (AVP) in the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). Copeptin consists of the C-terminal portion of Pro-AVP and has been shown to be a reliable and stable substitute for circulating AVP concentration. In contrast to serum or plasma, urinary proteins do not undergo detectable degradation by endogenous proteases after voiding. It is unknown, however, whether urinary copeptin concentration are associated with disease severity in patients with ADPKD.

Methods: Serum and Urinary copeptin concentration were measured by immunoassay in ADPKD patients with CKD stage ≤ 4. We compared our measurements with clinical parameters including estimated Glomerular Filtration Rate (eGFR), Total Kidney Volume (TKV) and height-adjusted TKV (htTKV). Logarithmic transformation of all variables was performed to fulfill the requirement of equal distribution of the residuals.

Results: We included 50 patients in this study (24 females and 26 males; mean age: 49.3±8.2 years). The median eGFR and TKV were 55.2 ml/min/1.73 m² (interquartile range: IQR 24.9 - 68.0) and 1138.1 ml (IQR 814.7 - 2065.0), respectively. The median urinary copeptin level was 12.19 (IQR 6.91 - 22.32) pg/ml. We could show the positive-correlation between u-copeptin and plasma copeptin but without significant relationship (p = 0.198). Although there are no significant correlations between plasma copeptin and eGFR (R = -0.245, p = 0.227), there are significant correlations between plasma copeptin and htTKV (R = -0.458, p = 0.019) and TKV (R = -0.465, p = 0.017). On the other hand, Urinary copeptin/ u-Cr was statistically associated with the various markers of disease severity in ADPKD (positively with TKV (R = 0.351, p = 0.014), htTKV (R = 0.383, p = 0.008) and negatively with eGFR (R = -0.304, p = 0.036).

Conclusions: In ADPKD subjects, a higher urinary copeptin concentration is associated with disease progression, suggesting that urinary copeptin may be a surrogate marker to detect disease severity renal prognosis in ADPKD.

SA-PO853
The Burden of Tolvaptan Treatment for Autosomal Dominant Polycystic Kidney Disease (ADPKD) – Satoru Mutô1, Haruna Kawano,2 Masaki Kimura,2 Shigeo Horie.2 1Urology, Teikyo Univ School of Medicine, Tokyo, Japan; 2Urology, Juntendo Univ, Graduate School of Medicine, Tokyo, Japan.

Background: Last year, Japan became the first country in the world to approve tolvaptan for the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Because tolvaptan has powerful diuretic effect, patients have to take huge amount of water and suffer from dehydration. We evaluated the burden of tolvaptan treatment on patients with ADPKD.

Methods: This study targeted Japanese patients with ADPKD on tolvaptan. An initial dose of tolvaptan was 60 mg. Estimated glomerular filtration rate (eGFR) and total kidney volume (TKV) were measured at regular intervals. The burden of tolvaptan treatment was evaluated by using clinical and laboratory analyses performed using analysis of variance.

Results: We included 40 patients (male: 28, female: 12). The median age was 46.5 ± 6.5 years (interquartile range: IQR 26.9 – 58.8) and the median baseline TKV was 1.917 mlQ (IQR 1.378 - 2.905). The median starting dosage of tolvaptan was 60 mg (IQR: 30 – 60) and the median treatment period was 8 months (IQR: 6 - 11). We observed no statistical variations in eGFR (p = 0.787) and TKV (p = 0.561) during treatment. There were no significant changes in SAP scores for general fatigue (p = 0.817), anorexia (p = 0.393), back pain (p = 0.682), and abdominal distention (p = 0.607) during treatment. Although analysis of variance demonstrated that aquaretic burden including thirst and dry skin were significantly increased after Tolvaptan treatment (P<0.003), 35% of patients did not completely sense thirst at al during treatment, and 42% (n=17) of patients spontaneously improved without any additional treatment or tolvaptan withdrawal.

Conclusions: Although analysis of variance demonstrated that aquaretic burden including thirst and dry skin were significantly increased after Tolvaptan treatment, almost third of the patients did not completely sense thirst at al from beginning of treatment, and the remaining third part of patients spontaneously improved.
Conclusions: We present the first use of texture analysis for PKD assessment. Results are promising in terms of identifying new imaging biomarkers that correlate with disease progression. This approach could function as a surrogate to more difficult imaging methods (e.g., quantitative MRI) and costly analysis (e.g., cyst segmentation). It is likely that combining texture analysis with other patient data will allow for substantial improvements to PKD prognosis.

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SA-PO856

Accuracy of Traditional and Novel Renal Filtration Markers for Estimating GFR in ADPKD Patients

Stephen L. Seliger, Charalee D. Digs, MSN, Thomas C. Dowling, Robert Christenson, Terry J. Wannick, Medicine, U Maryland Sch Medicine, Baltimore; Ferris State Univ, Pathology, U Maryland Sch Medicine, Baltimore.

Background: The best method for estimating GFR in ADPKD is unclear. Changes in tubular handling of filtration markers may affect estimating equation accuracy.

Methods: Among 51 adults with ADPKD and eGFR >20 cc/min/1.73 m², we measured GFR using iohexol plasma clearance (iGFR), serum creatinine (SCr), IDMS-traceable assay), Cystatin C (CysC, Dimension VISTA assay) and beta-trace protein (BTP, immunonephelometric assay, Siemens). We estimated GFR (eGFR) using validated equations based on SCr (CKD-Epi Cr, MDRD), Cystatin C (CKD-Epi cys, both CysC and SCr (BTP, immunonephelometric assay, Siemens). We estimated GFR (eGFR) using validated equations based on SCr (CKD-Epi Cr, MDRD), Cystatin C (CKD-Epi cys, both CysC and SCr (BTP, immunonephelometric assay, Siemens).

Results: Mean age was 51 ±12 years, 71% were female, 84% Caucasian, and mean eGFR was 68.4+/-34.2 cc/min/1.73 m². Of the 5 equations, the CKD-Epi cys was most accurate, and classification for iGFR-60 cc/min/1.73 m²) of each estimating equation.

Conclusions: Older patients with more advanced and/or severe ADPKD are more likely to be treated with statins. Placebo patients using statins progressed faster; tolvaptan slowed progression and annulled the effects of statin use.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical

SA-PO858

Systems Biology of Polycystic Kidney Disease

Kelly A. George, Herve Husson, Ramya Kalyana Kumar, Vishal S. Vaidya, Jagesh V. Shah, Laboratory of Systems Pharmacology, Harvard Medical School, Boston, MA; 2 Renal Div, Brigham and Women’s Hospital, Boston, MA; 3 Genzyme Corp, Framingham, MA.

Background: Polycystic kidney disease (PKD) is a group of hereditary disease states characterized by cystic kidneys and often accompanied by other manifestations such as cystic liver and hypertension. PKD occurs in 1 in 500 people, usually resulting from a dominant mutation in one of two genes, PKD1 or PKD2. There are no treatments for PKD and it is the leading genetic cause of renal failure. Numerous studies have identified pathways that are misregulated in PKD but targeting these individual pathways has not led to a successful therapeutic intervention or molecular biomarker.

Methods: To identify potential biomarkers and develop a systems-level understanding of PKD, we are using transcriptomics, and quantitative proteomics and phospho-proteomics to evaluate the state of cystic and normal kidneys in a mouse model of PKD. Kidney cysts also induce injury to the surrounding tissues, confounding any analysis of the “cystic state”. In an effort to separate the injury signature from the cystic signature, we are also evaluating the state of the injured kidney using a folate model of acute kidney injury and fibrosis. The multi-kinase inhibitor Roscovitine has been shown to prevent cystogenesis in mouse models of PKD but its mechanism of action remains unknown. To gain insight into the mechanism(s) of Roscovitine and to identify biomarkers that change with treatment, we are also using the above “omic” strategies using kidneys from mice following treatment.

Results: From the transcriptomic experiments, we have a list of potential biomarker candidates that are currently being tested by qPCR in mouse tissue at various stages of disease progression. Phosphorylation at motifs for CK1, CK1, CaMK, and other drugs are reduced in kidneys treated with Roscovitine. The primary transcription factor family found to be suppressed with Roscovitine treatment is the E2Fs, likely a result of the loss of CDK signaling.

Conclusions: In ADPKD patients, cystatin-based GFR equations may over-estimate true GFR in contrast to the lower bias observed in the general CKD population. The SCr-based CKD-Epi equation performed best overall among 5 equations. The utility of equations utilizing beta-trace protein deserves further investigation.

Funding: NIDDK Support

SA-PO857

Statins, ADPKD Severity and Progression in the TEMPO 3:4 ADPKD Clinical Trial


Background: In ADPKD, low HDL and high LDL cholesterol are associated with faster total kidney volume (TKV) increase and eGFR decline. A randomized controlled trial (RCT) of pravastatin in children showed lower TKV expansion without effect on renal function.

Methods: Exploratory post-hoc analysis of TEMPO 3:4 (3-year RCT of tolvaptan in relatively early but progressive ADPKD, age 18-50 yrs, TKV >750 ml, cSCr >60 ml per minute) to examine whether use of statins might have affected ADPKD progression. Linear mixed-effect models that adjust for gender, age and baseline TKV and eGFR were used to compare TKV and eGFR slopes between groups.

Results: Patients randomized to placebo using statins were older, had larger TKV and lower eGFR at baseline, and their TKV and eGFR slopes were steeper compared to statin users (Table). Similarly, patients randomized to tolvaptan and statins were older and had lower eGFR, with a non-significant trend to larger TKV compared to statin non-users; however, there was no difference between TKV or eGFR slopes of statin users and nonusers randomized to tolvaptan. Statin use did not affect a composite end point of clinically relevant ADPKD events in the placebo (HR=1.013, P=0.91) or tolvaptan (HR=0.954, P=0.65) group.

Conclusions: In ADPKD patients, cystatin-based GFR equations may over-estimate true GFR in contrast to the lower bias observed in the general CKD population. The SCr-based CKD-Epi equation performed best overall among 5 equations. The utility of equations utilizing beta-trace protein deserves further investigation.

Funding: NIDDK Support

SA-PO858

Systems Biology of Polycystic Kidney Disease

Kelly A. George, Herve Husson, Ramya Kalyana Kumar, Vishal S. Vaidya, Jagesh V. Shah, Laboratory of Systems Pharmacology, Harvard Medical School, Boston, MA; Renal Div, Brigham and Women’s Hospital, Boston, MA; Genzyme Corp, Framingham, MA.

Background: Polycystic kidney disease (PKD) is a group of hereditary disease states characterized by cystic kidneys and often accompanied by other manifestations such as cystic liver and hypertension. PKD occurs in 1 in 500 people, usually resulting from a dominant mutation in one of two genes, PKD1 or PKD2. There are no treatments for PKD and it is the leading genetic cause of renal failure. Numerous studies have identified pathways that are misregulated in PKD but targeting these individual pathways has not led to a successful therapeutic intervention or molecular biomarker.

Methods: To identify potential biomarkers and develop a systems-level understanding of PKD, we are using transcriptomics, and quantitative proteomics and phospho-proteomics to evaluate the state of cystic and normal kidneys in a mouse model of PKD. Kidney cysts also induce injury to the surrounding tissues, confounding any analysis of the “cystic state”. In an effort to separate the injury signature from the cystic signature, we are also evaluating the state of the injured kidney using a folate model of acute kidney injury and fibrosis. The multi-kinase inhibitor Roscovitine has been shown to prevent cystogenesis in mouse models of PKD but its mechanism of action remains unknown. To gain insight into the mechanism(s) of Roscovitine and to identify biomarkers that change with treatment, we are also using the above “omic” strategies using kidneys from mice following treatment.

Results: From the transcriptomic experiments, we have a list of potential biomarker candidates that are currently being tested by qPCR in mouse tissue at various stages of disease progression. Phosphorylation at motifs for CK1, CK1, CaMK, and other drugs are reduced in kidneys treated with Roscovitine. The primary transcription factor family found to be suppressed with Roscovitine treatment is the E2Fs, likely a result of the loss of CDK signaling.

Conclusions: In ADPKD patients, cystatin-based GFR equations may over-estimate true GFR in contrast to the lower bias observed in the general CKD population. The SCr-based CKD-Epi equation performed best overall among 5 equations. The utility of equations utilizing beta-trace protein deserves further investigation.

Funding: NIDDK Support
Conclusions: These experiments will not only provide candidate biomarkers for PKD progression, but will also yield a deeper understanding of the state of the cystic kidney. Funding: Pharmaceutical Company Support - Sanofi Genzyme, Private Foundation Support

SA-PO859
Prognostic Enrichment Strategies in the TEMPO 3:4 ADPKD Clinical Trial
Maria V. Irazabal,1 Jaime Blais,2 Ronald D. Perrone,3 Ron T. Gansevoort,4 Arlene B. Chapman,5 Olivier Devuyst,6 Eiji Higashihara,7 Wen Zhou,8 John Ouyang,9 Frank S. Czerwiec,2 Vicente E. Torres,1 Mayo Clinic; 2Osaka PDC; 3Tufts MC; 4UMC Groningen; 5U. Chicago; 6U. Zurich; Kyorin U.

Background: An image classification of ADPKD based on diffuse (class 1) vs. asymmetric (class 2) cyst distribution along with estimated cyst growth determined by age and height-adjusted total kidney volume (htTKV, subclaus A-E) has been proposed for prognostic enrichment by excluding patients with a lesser risk for progression (classes 1A-B and 2).

Methods: This enrichment strategy was compared, post-hoc, to exclusion criteria used for TEMPO3:4 to examine tolvaptan effects on ADPKD progression in patients with early but progressive renal disease (38-50 year-old, TKV >750 mL, eGCL >60 mL/min).

Results: 1436 TEMPO 3:4 subjects with baseline MRIs were classified, finding only 10% class 2 or 1B and no 1A subjects. TEMPO3:4 enriched categories 1C-E (90%) compared to the published cohorts (62%, Irazabal 2014 JASN). TKV and eGFR slopes steepened from class 1B to 1E (both P<0.001, Table).

Conclusion: Tolvaptan effects on TKV and eGFR slopes was greater in classes 1C to E. Originally, tolvaptan blunted TKV and eGFR slopes from 5.51% to 2.80% and from -3.70 to -2.78 mL/min/1.73m² per year (both P<0.001), and lowered the risk for a composite endpoint (CE) of clinical progression events (hazard ratio [HR] 0.87, p=0.0095, Torres 2012 NEJM).

Methods: Removing class 1A-B and class 2 patients from the trial, marginally improved estimates of tolvaptan effects on TKV and eGFR slopes 5.78% to 2.91% and -3.93 to -2.82 mL/min/1.73 m² per year (both P<0.001), and the CE endpoint (HR 0.84, p=0.0032).

Conclusions: Prognostic enrichment strategies using kidney morphology can enhance ADPKD trials for rapidly progressing patients, increasing power and reducing costs. Refinements of imaging criteria can improve the probability of success of future clinical trials. Funding: NIDDK Support

SA-PO860
Prognostic Enrichment Design in Clinical Trials for ADPKD: The HALT PKD A Trial
Maria V. Irazabal,1 Kaleab Z. Abebe,2 Kyongtae Ty Bae,2 Ronald D. Perrone,3 Arlene B. Chapman,5 Robert W. Schrier,7 Alan S.L. Yu,4 William E. Braun,8 Theodore I. Steinman,9 Michael F. Flessner,9 Vicente E. Torres,1-5 Mayo Clinic; 2U of Pittsburgh; 3Tufts U.; 4U of Chicago; 5U of Colorado; 6Kans U.; 7Cleveland Clinic; 8Beth Israel Deaconess; NIH-NIDDK.

Background: Patients with mild ADPKD phenotype are less likely to be informative in clinical trials. An image classification into typical (diffuse cyst distribution) class 1A and atypical (asymmetric cyst distribution) class 2 has been proposed for prognostic enrichment design in clinical trials with recommendations to exclude class 1A-B and follow-up class 1B (asymmetric cyst distribution) class 2 has been proposed for prognostic enrichment design.

Methods: Post-hoc analysis of HLTK-PKD A, RCT of rigorous vs standard BP control on TKV increase and eGFR decline; eGFR=60 mL/min/1.73 m² to investigate the performance of this classification for prognostic enrichment design.

Results: 551 participants were classified by 2 raters (98.2% agreement) into class 1A (6.2%), IB (20.3%), IC (34.1%), 1D (22.1%), IE (11.8%), and 2 (5.4%). TKV increase and eGFR decline became steeper from class 1A → 1E (both P<0.0001). HALT PKD A showed slower TKV increase, faster eGFR decline in the first four months (FO-5) and marginally slower eGFR thereafter (FO-80), without a significant overall (FO-80) effect with rigorous BP control. To ascertain the ability to detect an effect of rigorous BP control on TKV increase and eGFR decline; eGFR>60 mL/min/1.73m² per year (both P<0.001), and lowered the risk for a composite endpoint (CE) to investigate the performance of this classification for prognostic enrichment design.

Methods: Examine adverse drug reactions (ADRs) of tolvaptan for up to 3 years after TEMPO in Japanese ADPKD patients.

Methods: This open-label study was conducted in 135 patients participating in the preceding TEMPO. Doses of tolvaptan were adjusted from 60 to 120 mg/day.

Results: Main ADRs, thirst (77%), polyuria (57%), polydipsia (38%), and hyperuricemia (15%) were noted during up to 3 years. In TEMPO, hepatic function-related ADRs were observed more frequently for tolvaptan than for placebo early during treatment. In this study, 8 patients (6%) experienced >3-fold increases above upper limits of normal sodium (˚SNa) >160 mmol/1, AST 3 to 9 months after tolvaptan initiation, but all recovered after tolvaptan cessation. Of these 8 patients, 7 had been allocated to placebo in TEMPO. However, the residual one patient allocated to tolvaptan similarly had shown increased serum ALT in TEMPO. None of the 8 patients met Hy’s Law criteria. No ADRs besides those seen in TEMPO were newly observed in this study.

Conclusions: Hepatic function-related ADRs occurred early during treatment and were reversible. Tolvaptan was thus indicated to be a promising drug for treatment of ADPKD for up to 6 years while carefully monitoring ADRs including hepatic function abnormalities. Funding: Pharmaceutical Company Support - Osuka Pharmaceutical Co., Ltd.

SA-PO861
Long-Term Safety Profile of Tolvaptan in Japanese ADPKD Patients
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Background: Tolvaptan was first approved in Japan for autosomal dominant polycystic kidney disease (ADPKD) based on results of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3-4 trial (TEMPO) to examine adverse drug reactions (ADRs) of tolvaptan for up to 3 years after TEMPO in Japanese ADPKD patients.

Methods: This open-label study was conducted in 135 patients participating in the preceding TEMPO. Doses of tolvaptan were adjusted from 60 to 120 mg/day.

Results: Main ADRs, thirst (77%), polyuria (57%), polydipsia (38%), and hyperuricemia (15%) were noted during up to 3 years. In TEMPO, hepatic function-related ADRs were observed more frequently for tolvaptan than for placebo early during treatment. In this study, 8 patients (6%) experienced >3-fold increases above upper limits of normal sodium (˚SNa) >160 mmol/1, AST 3 to 9 months after tolvaptan initiation, but all recovered after tolvaptan cessation. Of these 8 patients, 7 had been allocated to placebo in TEMPO. However, the residual one patient allocated to tolvaptan similarly had shown increased serum ALT in TEMPO. None of the 8 patients met Hy’s Law criteria. No ADRs besides those seen in TEMPO were newly observed in this study.

Conclusions: Hepatic function-related ADRs occurred early during treatment and were reversible. Tolvaptan was thus indicated to be a promising drug for treatment of ADPKD for up to 6 years while carefully monitoring ADRs including hepatic function abnormalities. Funding: Pharmaceutical Company Support - Osuka Pharmaceutical Co., Ltd.

SA-PO862
Pregnancy Outcome in Participants in the HALT PKD Clinical Trials
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Background: ADPKD is the most common hereditary disease. Fertility rates are not impaired in ADPKD women, however, preexisting hypertension and proteinuria associate with increased maternal and fetal complications. In the HALT PKD trials, 38 pregnancies occurred despite counseling and review with participants. We now present maternal and fetal outcomes from these pregnancies.

Methods: In a secondary analysis, data regarding maternal and fetal outcomes and complications of reported pregnancies were obtained including spontaneous abortions, delivery types and still births. Data collection relied on completion of protocol case report forms, followup of hospital discharge summaries and patient based reports if available.

Results: In Study A, 102 of 128 (80%) women were premenopausal. In all pregnancies, study medications were stopped immediately or before the pregnancy began. 36 pregnancies occurred in 30 women with experiencing 2 pregnancies. 26 women experienced 32 pregnancies in Study A (12.8%) and 4 occurred in 4 women in Study B (4.5%). In Study A, baseline TKV was 871.5+502.9 mls, and GFR was 104.3+17.5 mL/min. In Study B, baseline GFR was 51.6+9.3 mL/min. Information on pregnancy outcome was not available in 3 pregnancies (2 LTFU and 1 pregnant at the end of study). In 33 pregnancies, 58% resulted in a live birth (100% in Halt B). In the remainder, 7 spontaneous and 2 therapeutic abortions, 1 ectopic and 1 stillbirth occurred. Two C-sections, one for pre-eclampsia and one pre-term delivery was reported.

Conclusions: In this secondary analysis of HALT Study A and B, 10.3% of studied pregnancies evolved. Strategies for prognostic enrichment such as the image classification should be used in the design of RCTs for ADPKD to increase their power and reduce their cost. Funding: NIDDK Support
Renal Concentrating Capacity and Copeptin Concentration in Patients with ADPKD and IgA Nephropathy with Impaired Renal Function


**Background:** ADPKD patients have an impaired maximal urinary concentrating capacity (Unmax). This may be specific for ADPKD or may be associated with reduced renal function. Intraabdominal organ growth in ADPKD may affect Unmax. Whether this is an aspecific effect of renal function impairment, or specific for ADPKD is yet unknown. We hypothesized that ADPKD patients have a more severely impaired Unmax in comparison with non-ADPKD renal disease patients, which leads to an exaggerated vasopressin (AVP) response that may be damaging to the kidney.

**Methods:** 15 ADPKD (eGFR>60) and 15 IgA patients, matched for age, sex and eGFR underwent a water deprivation test to determine Unmax. Urine and plasma osmolality (Uosm and Posm), albuminuria (ACR) and plasma copeptin (surrogate marker for AVP in pmol/L), were measured at baseline and after water deprivation (average 17 hours). Height adjusted total kidney volume (htTKV) was measured by MRI.

**Results:** Unmax was lower in ADPKD compared with IgA patients. Upon water deprivation Posm increased in ADPKD (p=0.003), but not in IgA (p=0.1), whereas copeptin increased in both groups similarly (ADPKD: p=0.001; IgA: p=0.02). Copeptin after water deprivation was negatively associated with Unmax in both groups (ADPKD: R=-0.72, p=0.002; IgA: R=-0.70, p=0.004). In ADPKD, copeptin and albuminuria were correlated after water deprivation (R=-0.71, p=0.003), independently of eGFR or htTKV. Furthermore, htTKV in ADPKD was associated after water deprivation with Posm (R=0.52, p=0.048), copeptin (R=0.58, p=0.03) and Unmax (R=0.34, p=0.04).

**Conclusions:** ADPKD patients have a lower Unmax compared with IgA patients with similar renal function. Remarkably, this is not accompanied with an exaggerated increase in AVP. Notwithstanding, ADPKD severity was associated with stronger increases in Posm, copeptin and albuminuria during water deprivation. This suggests that in ADPKD water deprivation may be deleterious and should be avoided.

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

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Tyrosine Kinase Inhibitor Tesevatinib for Patients with Autosomal Dominant Polycystic Kidney Disease

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**Background:** Tesevatinib (formerly KD019) inhibits both epidermal growth factor receptor (EGFR) and SRC. It decreases cyst growth and slows the decline in renal function in BPK mouse & PCK rat PKD models. In oncology trials the most common adverse events (AEs) were EGFR inhibitor AEs of acneiform rash and diarrhea. The 1:2:1 of approx. 60 hrs allows for schedules other than daily dosing.

**Methods:** This study evaluated the safety and tolerability of tesevatinib at several doses and schedules. Eligibility used Ravine criteria for autosomal dominant polycystic kidney disease (ADPKD) in patients (pts) aged 18-55 years with eGFR ≥ 50 mL/min/1.73 m².

**Results:** 46 ADPKD pts were enrolled into 5 dose/schedule cohorts. At 150 mg/day, 3/5 pts had moderate rash occurring during the first 28 days that was not tolerated and led to study discontinuation for 2. The tolerability of intermittent dosing schedules using 150 mg (Mon, Wed, Fri or Mon, Thu) was improved over 150 mg/day, but 1 case of severe rash occurred. QTC prolongation >485 ms occurred in 2 pts on 100 mg/day, and 1 pt on 150 mg MWF. The most common AEs overall in preclinical safety data were diarrhea (36%), rash (33%), nausea (29%), and asymptomatic CPK increase (24%). Other AEs included asymptomatic mild amylase elevations (21%).

**Conclusions:** Tesevatinib 150 mg in various schedules was associated with skin rash that was not well tolerated. A rate of QTC prolongation not acceptable for chronic use was associated with tesevatinib 100 mg/day. Tesevatinib 50 mg/day appears to be a well tolerated dose in patients with ADPKD, although some acneiform rash occurs. In order to confirm the safety profile at 50 mg/day, an additional 20 pts are being enrolled.

**Funding:** Pharmaceutical Company Support - Kadmon Corporation

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Total Abdominal Organ Volume Is a Major Risk Factor for Malnutrition in Ambulatory Patients with Autosomal Dominant Polycystic Kidney Disease

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**Background:** In Autosomal dominant polycystic kidney disease (ADPKD), malnutrition may develop as renal function decreases and abdominal organ volume enlarged. In this study, we evaluated the nutritional status of outpatient ADPKD patients by using subjective global assessment (SGA) and investigated the risk factors for malnutrition.

**Methods:** In this single center, cross sectional study, anthropometric and laboratory data including serum creatinine (scr), albumin, and cholesterol were collected, and total kidney and liver volume were measured. Total abdominal organ volume was defined as the sum of total kidney and liver volume and adjusted by height (htTV).

**Results:** A total of 296 patients (47.9%) were included and mean age was 48±12 years. Mean estimated glomerular filtration rate (eGFR) was 65.3 ± 25.3 mL/min/1.73m². Mean SGA score was 6±0.6. 186 patients (53.8%) were in chronic kidney disease stage 1 or 2, 94 (31.4%) stage 3 and 21 (7.3%) stage 4. Total 21 patients (7.3%) were mild to moderately malnourished (SGA 4–5) and 63 patients(21.7%) were at risk of malnutrition (SGA 6). There was no difference in SGA score distribution with sex. Physical scores related to nutritional status in total and male were age, height, weight and body mass index. However none of these parameters were related in female. Lower hemoglobin level and relatively preserved renal function. Intraabdominal organ growth in ADPKD may affect the nutritional status independently from the renal deterioration.

**Conclusions:** The prevalence of malnutrition in this PKD population is high, and risk factors for malnutrition include low hemoglobin and relatively preserved renal function. Intraabdominal organ growth in ADPKD may affect the nutritional status independently from the renal deterioration.

**Funding:** Government Support - Non-U.S.
Renal function did not change significantly during the period that patients were on metformin. We will continue to observe these patients and accumulate more patients with PKD and diabetes but not on metformin to see if metformin is beneficial in PKD patients.

SA-PO867

11Beta-Dichloro Inhibits Cyst Progression in an Adult ADPKD Model

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Background: ADPKD is the most common monogenic disorder for which no effective therapy exists. We have previously shown that the novel antitumor agent 11β-dichloro specifically induced apoptosis in Pkd1 null cells (ASN 2013 FR-OR100). Administration of 11β-dichloro resulted in amelioration of cystic disease in the Pkd1fl/fl;Pkd1-Cre neonatal ADPKD model. In the current work we explored the pathways involved in the pro-apoptotic effect of 11β-dichloro and investigated whether the beneficial effect seen in the early model is also present in an adult inducible Pax8rtTA;TetO-cre; Pkd1fl/fl model which is more akin to the human disease.

Methods: Pax8rtTA;TetO-cre; Pkd1fl mice were induced with doxycycline for 2 weeks beginning at P28. 11β-dichloro was administered by IP injection at a dose of 10 mg/kg, 3 times a week for 12 weeks beginning from P42; At the end of treatment the kidneys were harvested for analysis.

Results: 11β-dichloro treated adult mice resulted in a decrease in KW/BW ratio as compared to vehicle injected controls (2.6 ±0.1 vs. 6.1 ±0.4); There was no difference in body weight between treated and control. These changes were accompanied by a decrease in the cystic index (29%±1.5 vs. 49%±1.4), BUN (41±2.4 vs. 83±2.7), and creatinine (0.18±0.007 vs. 0.37 ±0.02). 11β-dichloro specifically increased apoptosis in cyst-lining cells but not in wild-type. UPR and ROS have been implicated as potential drivers of the 11β-dichloro-dependent pro-apoptotic phenotype. We found that upregulation of the UPR marker BiP and its transcriptional targets BiP and Erdf4 was specific to the Pkd1 null cells compared with wild-type, in vitro and in vivo. Treatment with 11β-dichloro increased mRNA levels of the antioxidant genes catalase and SOD1 specifically in the Pkd1 cystic kidneys and not in vehicle-treated kidneys.

Conclusions: 11β-dichloro specifically induces UPR, ROS, and apoptosis in cystic vs. wild-type kidneys. In an adult inducible cystic model, the compound ameliorates polycystic disease progression and improves kidney function.

Funding: Other U.S. Government Support, Private Foundation Support

SA-PO868

Outcomes of Combined Partial Hepatectomy and Cyst Fenestration for Massive Polycystic Liver Disease

Fouda T. Chebib, Yeon Soon Jung, Christina M. Heyer, Maria V. Irazabal, Marie C. Hogan, Patrick S. Kamath, Vicente E. Torres, Ziad El-Zoghby. 1 Div of Nephrology, Mayo Clinic, Rochester, MN; 2 Kosin U.

Background: PLD is the most common extrarenal manifestation in pts with ADPKD. Here we analyzed the influence of genotype and gender on the severity of PLD.

Methods: Clinical data was retrieved from electronic records in a large cohort of pts who were mutation screened, determined to be PKD1 or PKD2 and had available CT or MR liver imaging during 2000-2014 at the Mayo Clinic (n=445). Liver volumes (LV) were measured by stereoreo on axial images and adjusted to height (HxLV).

Results: Among the 445 pts, 220 (49.5%) had truncating PKD1, 153 (34.4%) nontruncating PKD1 and 72 (16.1%) PKD2 mutations. Compared to nontruncating PKD1 and PKD2, pts with truncating PKD1 were younger at time of first imaging (43.6 vs 47.6 and 50.4; p<.001), had lower median survival time to ESRD (62.4 vs 66.9 and 81.4; p<.001), had larger kidney volumes (785 vs 614 and 548 ml/m; p<.001). LV in pts with PKD1 truncating, PKD1 nontruncating and PKD2 were not different (HxLV 1039, 1076 and 1058 ml/m, respectively; p=0.53). Females had larger HxLV compared to males (1104 vs 1019 ml/m; p<.001). Annualized median liver growth rates were 1.65, 1.74 and 1.2% for truncating PKD1, nontruncating PKD1 and PKD2, respectively (p<.05). Females younger than 48 had higher annualized median growth rates compared to those older than 48 (2.65 vs 0.09%;p<.001). When adjusting for age, gender and baseline LV, growth rate remained unaffected by the ADPKD genotype.

At follow-up (mean 7.8 years), median LV was 2500 ml. Interestingly, 29 out of 61 patients with available LV2 and LV3 showed further regression in LV upon follow up (median -4.988%); while the rest showed mild growth of 9.5%. Overall volumetric comparison of preoperative to follow-up liver imaging showed sustained liver volume reduction (median 66%)

Conclusions: Sustained long-term reductions in LV in after PHCF can be achieved in selected patients with severe, highly symptomatic PLD. In our experience, liver-related death and subsequent liver transplantation are infrequent after PHCF.

SA-PO869

Effect of Genotype on the Severity and Volume Progression of Polycystic Liver Disease (PLD) in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Fouda T. Chebib, Yeon Soon Jung, Christina M. Heyer, Maria V. Irazabal, Marie C. Hogan, Peter C. Harris, Vicente E. Torres, Ziad El-Zoghby. 1 Div of Nephrology, Mayo Clinic, Rochester, MN; 2 Kosin U.

Background: PLD is the most common extrarenal manifestation in pts with ADPKD. Here we analyzed the influence of genotype and gender on the severity of PLD.

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At follow-up (mean 7.8 years), median LV was 2500 ml. Interestingly, 29 out of 61 patients with available LV2 and LV3 showed further regression in LV upon follow up (median -4.988%); while the rest showed mild growth of 9.5%. Overall volumetric comparison of preoperative to follow-up liver imaging showed sustained liver volume reduction (median 66%)

Conclusions: Sustained long-term reductions in LV in after PHCF can be achieved in selected patients with severe, highly symptomatic PLD. In our experience, liver-related death and subsequent liver transplantation are infrequent after PHCF.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: In contrast to the renal phenotype, ADPKD gene type or PKD1 mutation type were not significantly associated with the severity or growth rate of PLD in ADPKD pts. This finding, along with the demonstrated gender influence, indicates that modifiers beyond the disease gene significantly influence this phenotype.

SA-PO870

Eligibility for Renal Transcatheter Arterial Embolization in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: In patients with ADPKD, massive renal enlargement is a serious problem. Renal transcatheter arterial embolization (TAE) is effective for reducing renal volume, but there is large variation of its effectiveness and the reasons remain unclear. We investigated factors influencing the renal volume reduction rate (RVRR) for one year after TAE.

Methods: All patients with ADPKD who received renal TAE at Toranomon Hospital from 2006 to 2013 were enrolled. We calculated RVRR by the calculation formula (1 - renal volume at each time after TAE/renal volume before TAE)*100, and analyzed factors affecting RVRR. We also compared sequential change of large cysts (>5cm), by classified them into four groups as cysts with wall thickening (>4mm), cyst with acute hemorrhage, normal cysts, and the others.

Results: 449 patients (228 men, 221 women, mean age: 57.0 ± 9.1 years) were enrolled. The RVRR at 1 year after TAE ranged from 3.9 to 84.8%, and the least squares mean RVRR calculated using mixed model was 45.73% (95% confidence interval [95% CI]: 44.36 to 47.10%). Multivariate analysis using mixed model revealed that large cysts with wall thickening (regression coefficient: -5.830, 95% CI: -9.410 to -2.250, p<0.0006), age (5 years): -0.847, -1.073 to -0.621, p<0.0001), dialysis duration (12 months): -0.115, -0.193 to -0.037, p<0.0009), systolic blood pressure (10mmHg): 0.283, 0.065 to 0.501, p<0.0109), and number of microcysts used for renal TAE (1.333, 0.784 to 1.882, p<0.0001) had a significant influence on the RVRR. Among large cysts, only cysts with wall thickening did not decrease in volume. Significantly more microcysts were needed to achieve complete renal artery occlusion in patients with younger age and less dialysis duration.

Conclusions: Cyst wall thickening had an important influence on cyst volume reduction. Renal TAE was more effective in patients who were younger, had shorter dialysis duration, or had hypertension, parameters that might be associated with cyst wall stiffness. Renal artery narrowing may occur in older patients or those on longer dialysis, which might contribute to renal TAE being less effective in these patients.

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

SA-PO871

Patient Reported Health Related Quality of Life in ADPKD: Analysis from OUTVERTE

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Background: Although hepatomegaly in polycystic liver disease (PLD) is common, few studies have evaluated natural history & factors associated with progression. Goal: Examine change in height adjusted liver volume (htLV) & factors influencing progression in participants in HALT-PKD-A randomized clinical trial.

Methods: Baseline PLD group (mild (htLV<1000ml;n=240) moderate (1000-1800ml; n=180; 74% female) & severe (>1800ml; n=28; 81% female)) & follow up htLVs, quality of life (QOL;SF-36), influence of telmisartan (T) vs placebo (P) on progression were assessed (n=558, age 15-49y, eGFR > 60 ml/min). We assessed factors influencing htLVs such as treatment group, age, gender, genotype (in separate models) & factors influencing progression over time were examined using linear mixed models.

Results: Annual htLV growth rates were 0.76, 0.91 & 1.08% (P<NS) in the mild, moderate & severe groups, respectively (figure 1). Neither baseline age or genotype associated with annual htLV increase. There were strong negative relationships of eGFR (p<0.02) & serum albumin (p<0.0003) with htLV. Prior pregnancy & higher parity (both age adjusted) associated with htLV but not with progression over time. Increases in BLV were associated with increased rates of fatigued/weakness (p=0.003) and declines in SF-36 physical functioning over time (p=0.02). Progression was independent of drug assignment (T 0.09% vs P 1.07% p=NS) & BP target (low 0.81 vs std. 1.15% p=NS).

**SA-PO874**

**Towards Personalised Medicine – Treating a Renal Ciliopathy**

Shalabh Srivastava, 1 Simon Ramsbottom, 2 Sophie Saunier, 1 Colin Miles, 1 John Andrew Sayer. 1

1Nephrology, Inst of Genetic Medicine, Newcastle Univ, Newcastle upon Tyne, United Kingdom; 2Laboratory of Inherited Kidney Diseases, Imagine Inst, Paris, France.

**Background:** Renal ciliopathies are genetic disorders presenting with nephronophthisis, cystic kidneys or cystic dysplasia. Pathogenesis of ciliopathies may include altered signalling or defective DNA damage response. Due to the huge genetic/phenotypic variability in ciliopathies it is pertinent to explore the most important contributor to individual phenotypes. We investigated disease mechanisms of a patient with Joubert Syndrome aiming to provide a personalised medicine approach to treatment.

**Methods:** We identified a family with 2 affected siblings with a ciliopathy phenotype. Ciliopathy gene panel sequencing followed by Sanger sequencing and segregation analysis was undertaken to provide a molecular genetic diagnosis. We established Human Urine Derived Renal Epithelial Cell (HUREC) cultures from one sibling and a control. Cultured cells where characterised and their response to therapeutic agents quantified.

**Results:** The siblings exhibited a cerebro-retinal-ciliary phenotype with renal corticomedullary cyst formation and progressive renal failure. Panel sequencing followed by Sanger sequencing confirmed a likely mutation in HURC1. Using HURECSC we have characterised, at a personalised medicine scale, the cellular defect. This data suggests that renal ciliopathies may have potential therapeutic targets and investigation through individual HUREC based model is an exciting new development.

**SA-PO875**

**Effect of Metformin on the Progression of Autosomal Dominant Polycystic Kidney Disease**

Godela M. Brosnahan, 1 Michel Chonchol, 1 John R. Holmen, 2 Eugene J. Nuccio, 3 Berenice Y. Gitomer. 1

1Univ of Colorado; 3Intermountain Healthcare, Salt Lake City, UT.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder resulting in end-stage renal disease (ESRD), without an approved treatment. In an animal model of ADPKD metformin therapy resulted in amelioration of cystic renal growth. We sought to determine whether patients with ADPKD and type 2 diabetes treated with metformin had slower progression to ESRD than similar patients treated with other antidiabetic drugs.

**Methods:** We conducted a population-based cohort study of adult patients with ADPKD and type 2 diabetes between January 1/2000 and December 31/2014. We identified 322 adults with ADPKD and type 2 diabetes, of whom 119 were treated with metformin only and 203 with other antidiabetic agents. Among these we identified 31 subjects treated with metformin only, who could be matched for age, sex, race, history of hypertension and coronary artery disease, and baseline renal function to 31 subjects not treated with metformin. The primary outcomes were incident ESRD and all-cause mortality.

**Results:** The median age of the enrolled patients was 61 years, 45% were women. Approximately 74% and 26% had a history of hypertension and myocardial infarction, respectively. The baseline MDRD-eGFR in patients receiving and not receiving metformin was 49±12 and 47±14 mL/min/1.73m2 (p=0.70). After a median follow-up of 4.5 years, incident ESRD occurred in 29% and 16% of those not exposed and exposed to metformin, respectively, with a OR of 2.13 (95% CI 1.10-3.46; p=0.02). Deaths occurred in 32% and 26% of those not exposed and exposed to metformin, with a OR of 1.37 (95% CI 0.5-2.47; p=0.60).

**Conclusions:** Metformin therapy may slow progression to ESRD in ADPKD adults with type 2 diabetes compared to other antidiabetic drugs. Because metformin has an excellent safety record, a trial to slow the progression of ADPKD in the absence of diabetes is warranted.

**Funding:** NIDDK Support, Other NIH Support - Supported by grants from the NIDDK (DK62402 to Dr. Schrier, DK62411 to Dr. Perrone, DK08230 to Dr. Moore, DK62408 to Dr. Chapman, and DK62401 to Washington University in St. Louis) and the National Center for Research Resources General Clinical Research Centers (RR000039 to Emory University, RR0000S3 to the Mayo Clinic, RR000054 to Tufts Medical Center, RR000051 to the University of Colorado, RR023940 to the University of Kansas Medical Center, and RR010032 to Beth Israel Deaconess Medical Center), National Center for Advancing Translational Sciences Clinical and Translational Science Awards (RR025008 and TR000454 to Emory University, RR024150 and TR00135 to the Mayo Clinic, RR027752 and TR010064 to Tufts University, RR027580 and TR001082 to the University of Colorado, RR025758 and TR01102 to Beth Israel Deaconess Medical Center, RR033179 and TR000001 to the University of Kansas Medical Center, and RR024999 and TR000439 to Cleveland Clinic), Private Foundation Support.

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**Figure 1:** Mean (±SE) htTLV, parenchymal volume (htLPV) & total liver cyst volume (htTVCV) at month in study by baseline htTLV group (<1000, 1000-1800, >1800ml).

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**Conclusions:** BetalVxs increased in HALT-A participants over time, correlated with fatigue/ weakness and were associated with measurable continued declines in SF36 QOL subdomains.

**Funding:** NIDDK Support, Other NIH Support - Supported by grants from the NIDDK (DK62402 to Dr. Schrier, DK62411 to Dr. Perrone, DK08230 to Dr. Moore, DK62408 to Dr. Chapman, and DK62401 to Washington University in St. Louis) and the National Center for Research Resources General Clinical Research Centers (RR000039 to Emory University, RR0000S3 to the Mayo Clinic, RR000054 to Tufts Medical Center, RR000051 to the University of Colorado, RR023940 to the University of Kansas Medical Center, and RR010032 to Beth Israel Deaconess Medical Center), National Center for Advancing Translational Sciences Clinical and Translational Science Awards (RR025008 and TR000454 to Emory University, RR024150 and TR00135 to the Mayo Clinic, RR027752 and TR010064 to Tufts University, RR027580 and TR001082 to the University of Colorado, RR025758 and TR01102 to Beth Israel Deaconess Medical Center, RR033179 and TR000001 to the University of Kansas Medical Center, and RR024999 and TR000439 to Cleveland Clinic), Private Foundation Support.

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**SA-PO876**

**Frequency and Reasons for Hospitalization Among ADPKD Patients with GFR >25 mls/min**

Dana Miskulin, 1 Kaleab Z. Abeebe, 1 Ronald D. Perrone, 1 Marie C. Hogan, 1 Frederic F. Rahbari-Oskoui, 1 Peter G. Czarniecki, 2 Susan Spillane, 1 Arlene B. Chapman, 1 Robert W. Schrier, 1 Vicente E. Torres, 1 Charity G. Moore. 1

1Tufts Medical Center, Boston, 2Mayo Clinic, Rochester; 3Emory Univ, Atlanta; 4Brigham and Women’s Hospital, Boston; 5Univ of Pittsburgh; 6Univ of Chicago; 7Univ of Colorado.

**Background:** There is a paucity of data about the frequency and causes of hospitalization in Autosomal Dominant Polycystic Kidney Disease (ADPKD).

**Methods:** We investigated disease mechanisms of a patient with Joubert Syndrome aiming to provide a personalised medicine approach to treatment.

**Results:** The siblings exhibited a cerebro-retinal-ciliary phenotype with renal corticomedullary cyst formation and progressive renal failure. Panel sequencing followed by Sanger sequencing and segregation analysis was undertaken to provide a molecular genetic diagnosis. We established Human Urine Derived Renal Epithelial Cell (HUREC) cultures from one sibling and a control. Cultured cells where characterised and their response to therapeutic agents quantified.

**Conclusions:** Metformin therapy may slow progression to ESRD in ADPKD adults with type 2 diabetes compared to other antidiabetic drugs. Because metformin has an excellent safety record, a trial to slow the progression of ADPKD in the absence of diabetes is warranted.

**Funding:** NIDDK Support
Methods: Information about hospitalizations was prospectively collected in the HALT-PKD Studies, 2 multi-center trials involving people with ADPKD and GFR 60-ml/min (Study A) and GFR 25-60 ml/min (Study B). The primary diagnosis was designated after review of discharge summaries and independently adjudicated by a committee.

Results: Total patient years (ptyrs) of follow-up in the 558 Study A patients and 486 Study B patients were 23,142 and 21,806. The incidence rates (IR) of all-cause hospitalization, in Study A and B, respectively, was 67.7 and 123.3 per 1000 ptyrs, which compares to 80.3 and 118.0, in respective age-matched general populations (CDC/NHIS National Hospital Discharge Survey, 2010). The IRs in Study A and B, respectively, for cardiovascular-related hospitalization per 1000 ptyrs were 10.5 and 11.2. For ADPKD-related hospitalization (primary diagnosis kidney or liver cyst pain, infection or hemorrhage, pyelonephritis, kidney stones or cerebral aneurysm) were 12.7 and 26.7 per 1000 ptyrs. The most common primary diagnoses are listed in the table.

Conclusions: As compared with the respective age-matched general US populations, hospitalization rates were lower in ADPKD patients with GFR 60-ml/min and higher in patients with GFR 25-60 ml/min. PKD-related complications were more common than cardiovascular related diagnoses as the primary reason for hospitalization in both Study A and B.

Funding: NIDDK Support, Private Foundation Support

SA-PO877

Effect of Statins on the Progression of Autosomal Dominant Polycystic Kidney Disease (the HALT PKD Investigators) Godela M. Brosnahan,1 Kaleab Z. Abebe,2 Frederic F. Rahbari-Oskoui,3 Charity G. Moore,4 Kyongtae Ty Baec,5 Robert W. Schrier,6 Jared J. Grantham.7,8 1Univ of Colorado; 2Univ of Pittsburgh; 3Emory Univ; 4Univ of Kansas.

Background: ADPKD is the most common hereditary disease resulting in end-stage renal failure (ESRD), without an approved treatment. In a small randomized trial comparing pravastatin for 3 years (n=55) against placebo, 50 ADPKD patients age 8-22 yr, the study group experienced a slower rate of renal enlargement. No large trial has tested the effect of statins in ADPKD adults.

Methods: We performed a secondary analysis of the HALT-PKD trials, categorizing participants into 3 groups based on statin use: 1) never users, 2) less than 3 y, and 3) at least 3 y of use. For subjects in Study A (n=558, age 15-49 y, eGFR > 60 ml/min/1.73 m2) we compared the percent change in height-adjusted total kidney volume (htTKV), in height-adjusted total liver volume (htTLV) and the rate of decline in eGFR between the 3 statin use groups. For participants in Study B (n=486, age 18-64 y, eGFR 25-60 ml/min/1.73 m2) we compared time to composite endpoint of death, ESRD or 50% decline in eGFR.

Results: In HALT Study A only 59 subjects used statins for > 3y and 37 for < 3y. There was no difference in the rate of annual htTKV increase (6.41%, 7.11%, 5.97%; p=NS) or htTLV growth (1.02%, 1.15%, 0.65%; p<NS) between the 3 groups, after controlling for sex, age, and treatment arms. The rate of eGFR decline was faster in group 2 (4.07 ml/min/yr) than in groups 1 and 3 (2.93 and 2.82 ml/min/yr; p=0.015), after adjusting for the more favorable baseline characteristics of group 1 (more females, younger age, higher baseline eGFR).

In Study B 118 subjects used statins for > 3y and 76 for 3y. There was no difference in time to endpoint between the 3 groups.

Conclusions: In this secondary analysis of the HALT-PKD trials, statin therapy for 3 years did not slow the rate of renal or liver enlargement or of eGFR decline in ADPKD adults, but these results are limited by the small numbers of statin users in Study A, different statin drugs and doses, and non-randomized allocation to groups.

Funding: NIDDK Support, Other NIH Support - cooperative agreements (grants DK2408, DK62401, DK62410, DK2402, and DK62230) with the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, the National Center for Research Resources General Clinical Research Centers (RR000039 Emory University, RR00585 Mayo Clinic, RR000054 Tufts University, RR000051 University of Colorado, RR23940 Kansas University, and RR024296 Beth Israel Deaconess Medical Center), and the Centers for Translational Science Activities at the participating institutions (RR02508 Emory University, RR024150 Mayo Clinic, RR02575 Tufts University, RR025780 University of Colorado, and RR024989 Cleveland Clinic.), Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals Inc donated telmisartan and matched placebo, Merck & Co Inc donated lisinopril, Private Foundation Support

SA-PO878

Assessment of a Dosage-Sensitive Mutational Network for PKD in a Large Cohort of Patients with Early and Severe Forms of Polycystic Kidney Disease Carmen Bergmann,1,2 John Devane,3 Steffen Neuber,4 Eva Decker,4 Uyen Tran,4 Oliver Wessely,3 Elisabeth B. Ott. 1Center for Human Genetics, Bioscientia, Ingelheim, Germany; 2Renal Div, Univ Hospital, Freiburg, Germany; 3Cellular & Molecular Medicine, Cleveland Clinic.

Background: ADPKD patients with early and severe disease manifestations only make up a minor proportion, but are crucial for a better understanding of PKD. Affected families have a high recurrence risk for babies with a severe clinical course often resulting in perinatal death. Especially in prenatal cases the diagnostic distinction between different forms of PKD and other ciliopathies can be difficult and illustrates the need for more comprehensive genetic testing.

Methods: An accurate genetic diagnosis is crucial for genetic counselling, prenatal diagnostics and the clinical management of patients. To this end, we established a sequence capture based NGS approach targeting 95 genes for cystic and polycystic kidney disease. This includes PKD1, which - due to the presence of pseudogenes - is difficult to test. As an additional advantage over conventional Sanger sequencing we were able to detect copy number variations. The biological significance of some of the detected alleles were subsequently tested in vitro and in vivo studies using a range of animal models including zebrafish, Xenopus and mice to validate some of our findings in terms of a functionally proven dosage-sensitive network.

Conclusions: This study is the most comprehensive analysis performed so far and points towards a general and underestimated concept for the modification of disease gene expression.

SA-PO879

Determinants of Progression in Early Autosomal Dominant Polycystic Kidney Disease - Is It Blood Pressure or Renin-Angiotensin-System Blockade? The HALT PKD Trial Godela M. Brosnahan,1 Kaleab Z. Abebe,2 Charity G. Moore,3 Theodore I. Steinman,4 Frederic F. Rahbari-Oskoui,5 Susan Spillanc,6 Kyongtae Ty Baec,5 Robert W. Schrier.7 1Univ of Colorado; 2Univ of Pittsburgh; 3Beth Israel Deaconess; 4Emory Univ. Medical Center.

Background: The HALT PKD Study A (558 subjects age 15-49 years, eGFR > 60 ml/min/1.73 m2) showed that intensive control of systolic blood pressure (SBP) to 95-110 mmHg was associated with a slower rate of kidney volume growth compared to standard control (SBP 120-130 mmHg). It is unclear whether this result was due to lower BP per se or to greater blockade of the renin-angiotensin-aldosterone system (RAAS) by allowing higher drug doses in the low BP group.

Methods: In this secondary analysis of HALT PKD Study A categorizing participants into 3 groups based on losartan (L) and telmisartan (T) dosage at 4 months, after initial dose titration: 1) high, defined as ≤ 140 mg + T 80 mg daily, 2) middle (everyone not high or low) and 3) low, defined as ≤ 120 mg + T < 80 mg daily. We compared the percent change in height-adjusted total kidney volume (htTKV) and the rate of eGFR decline between the 3 groups during follow-up for 5-8 years.

Results: Participants in the high dose group (n=51) were more likely male and assigned to the low BP arm; they had higher baseline BP and lower eGFR at 4 months than subjects in the mid- (n=272) and low-dose (n=165) groups. After adjustment for age, sex, genotype, target BP (low or standard), and eGFR at 4 months, there was no significant difference in the rate of kidney growth (5.63, 6.40 and 5.83% yr) or eGFR decline (3.00, 2.94 and 3.29 ml/min/1.73 m2) between the low, middle and high dosage groups.

Conclusions: In this secondary analysis of HALT Study A in young ADPKD adults, a higher dosage of RAAS blocking drugs was not associated with a slower rate of htTKV growth or of eGFR decline, after adjustment for allocation to intensive BP control. Low BP appears to be the main determinant for reducing kidney volume growth.

Funding: NIDDK Support, Other NIH Support - cooperative agreements (grants DK2408, DK62401, DK62410, DK62402, and DK62230) with the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, the National Center for Research Resources General Clinical Research Centers (RR000039 Emory University, RR00585 Mayo Clinic, RR000054 Tufts University, RR000051 University of Colorado, RR23940 Kansas University, and RR024296 Beth Israel Deaconess Medical Center), and the Centers for Translational Science Activities at the participating institutions (RR02508 Emory University, RR024150 Mayo Clinic, RR02575 Tufts University, RR025780 University of Colorado, and RR024989 Cleveland Clinic.), Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals Inc donated telmisartan and matched placebo, Merck & Co Inc donated lisinopril, Private Foundation Support

Poster/Saturday
SA-PO880
The Short Term Effect of Tolvaptan for CKD Stage4 Autosomal Dominant Polycystic Kidney Disease Haruna Kawano,1,2 Satoru Muto,1,2 Shigeto Horie.1,2 1Urology, Juntendo Univ Graduate School of Medicine, Tokyo, Japan; 2Urology, Teikyo Univ, Tokyo, Japan; 3Endowed Course for the Study of Polycystic Kidney Disease, Juntendo Univ Graduate School of Medicine, Tokyo, Japan.

Background: In Japan, the treatment of tolvaptan, a V2 receptor antagonist, started from March 2014. Indication criteria of tolvaptan for ADPKD treatment in Japan is adult patient with more than 750ml total kidney volume (TKV) and more than about 5%year increasing rate of TKV. It is contradiction to use tolvaptan for patients with eGFR<15ml/min/1.73m². It is recommended to reduce dose of tolvaptan for patients with CCR<30ml/min. However, the treatment effect for patients with CKD stage 4 is still unknown. So, we evaluated the short time efficacy of tolvaptan treatment for patients with CKD stage 4.

Methods: Thirteen patients (5 females and 8 males, mean age; 52.5 years) with ADPKD who started tolvaptan at our hospitals from April 2014 to April 2015 were analyzed in this study. Although our standard starting dose of tolvaptan for patients with good renal function is 60mg/day, we administered 15mg/day for patients with eGFR<25ml/min/1.73m² patients. Patients were measured eGFR and TKV at the commencement of treatment and at 1.5 and 6 months later.

Results: The baseline median eGFR and TKV were 21.8 ml/min/1.73m² (range; 17.1-28.9) and 2810ml (range; 1031-5847), respectively. The change of median eGFR from baseline at 1.5 months and at 6 months were -0.36 ml/min/1.73m² (p=0.39) and -1.80 ml/min/1.73m² (p=0.04), respectively. The change of median TKV from baseline at 1.5 months and at 6 months were -132ml (p=0.39) and +12ml (p=0.93), respectively. One female patient and one male patient temporarily stopped their treatment at 3 months and at 6months because of their eGFR decreased to lower than 15 ml/min/1.73m². Hepatic toxicity, hypernatremia, and the other severe adverse events were not detected.

Conclusions: No severe adverse events were occurred and 85% of CKD stage4 patients could keep treatment for 6 months without CKD progression. Tolvaptan was safe and tolerable for ADPKD patients with CKD stage 4 in lower dose.


SA-PO881
Estimation of Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease Edwin M. Spithoven,1 Maatje D.A. van Gastel,1 A. Lianne Escobar,2 Katharina Hopp,3 Cynthia J. Sieben,4 Peter C. Harris,5 S.L. Yu,6 Jareed L. Grantham,7 Arlene B. Chapman,1 Jared J. Grantham,1 Kyongtae L. Oskoui,8 Alan L. White,9 Thomas M. Bennett,4 Edwin M. Spithoven,1 Ron T. Gansevoort,1 1Internal Medicine, Nephrology, UMC Groningen; 2On behalf of the DIPAK Consortium, Netherlands.

Background: Measuring total kidney volume (TKV) in autosomal dominant polycystic kidney disease (ADPKD) by magnetic resonance image (MRI) and manual tracing is time consuming. Two alternative MRI methods have recently been proposed to estimate TKV (eTKV ELLIPSOID and eTKV PANK) which require less time.

Methods: ADPKD patients with a wide range of kidney function were included, if they had an approved T2 weighted MRI. A test set of 10 MRI was used for assessing reproducibility, 220 for cross-sectional analyses and 48 for longitudinal analyses with a follow-up of three years. mTKV was used to assess Irazabal risk categories, reclassification was calculated for eTKV ELLIPSOID and eTKV PANK. Measured TKV (mTKV) was manually traced, eTKV ELLIPSOID was calculated as advised in literature as π/6 * (length + width + depth)/2 * length * width * depth/1000 and eTKV PANK as midslice x number of slices covering the kidney x 0.624 or 0.657 for the left and right kidney, respectively.

Results: In the test set, intra- and inter-coefficients of variation were low: mTKV 1.8% and 2.3%, eTKV ELLIPSOID 3.9% and 6.3%, and eTKV PANK 3.0% and 3.4%. Duration of analyses were respectively 55, 5 and 15 minutes. In cross-sectional analyses baseline kidney volumes (liters) were 1.96 (1.28-2.92) for mTKV, 1.93 (1.25-2.82) for eTKV ELLIPSOID and 1.81 (1.17-2.62) for eTKV PANK. The latter both significantly different from mTKV (p<0.004 and p<0.001 respectively). Bias was low and precision high for repeated mTKV (0.2%±3.2%), eTKV ELLIPSOID (1.4%±9.2%) as well as eTKV PANK (4.6±7.6%). In longitudinal analyses, no significant differences were observed between percentage change in mTKV (16±7.1%) compared to change in eTKV ELLIPSOID (19±3.1%) and eTKV PANK (17.8±16.1%). Both methods resulted in limited reclassification in Irazabal risk categories; 6.7% for eTKV ELLIPSOID and 9.8% for eTKV PANK.

Conclusions: Both methods to estimate TKV perform relatively well compared to mTKV, and detect similar changes in TKV over time. Since eTKV ELLIPSOID requires less time than eTKV PANK, we suggest this method should be preferred in clinical care.

Funding: Private Foundation Support

SA-PO882
Genetic Background Radically Alters Disease Progression in the Pkd1<sup>RC/RC</sup> Model Diana L. Escobar,1 Katharina Hopp, Cynthia J. Sieben, Peter C. Harris, Mayo Clinic, Rochester, MN.

Background: Studies in ADPKD patients and PKD mouse models have shown that genetic background influences the disease phenotype. Here, we evaluated the phenotype of the inbred homozygous Pkd1: p.R3277C (RC) model in three new backgrounds: BalbC, 129S6, and F1 (C57BL6 X BalbC) and compared them to C57BL6.

Methods: To characterize the cystic disease burden, Pkd1<sup>RC/RC</sup> animals were inbred into three different strains and aged to 3 months (m). At this time point %Kidney Weight/Body W, BUN levels, kidney cyst index were used to compare disease severity.

Results: At this early stage of cyst progression (3m) genetic background significantly affects the severity of the disease in the Pkd1<sup>RC/RC</sup> model with %KW/Body significantly higher in the BalbC (3.31) and 129S6 (3.12) backgrounds compared with F1 (1.92; P<0.001). C57BL6 was 1.74; both P<0.001). However, BUN levels did not deviate from the physiological norm at this early stage of the disease in any of the backgrounds. In respect to cyst index, 129S6 (21.87%) and BalbC (19.47%) animals had a greater disease burden compared to F1 (3.71%; both P<0.001) and C57BL6 (5.24%; both P<0.001) animals. No significant difference was found between 129S6 and BalbC mice (P=0.47). Histological analysis showed a distribution of various sized cysts in the medulla and cortex in BalbC and large cysts mainly in the medulla in 129S6, which contrasted with small cysts mainly in the cortex in F1 and C57BL6 (figure 1). Immunofluorescence at 3m in all backgrounds showed the majority of cyst had a collecting duct (CD) origin, however some cysts were negative for the nephron markers LTA-AQP1 (PT), AQP2-DBA (CD).

Conclusions: This study highlights the role of genetic background in cystic disease progression in the Pkd1<sup>RC/RC</sup> model. Due to the more rapid progression and severe cystic burden, the BalbC and 129S6 models may be more suitable for PKD pre-clinical testing.

Funding: NIDDK Support
SA-PO884
Therapeutic Effects of the Fibrokinase Inhibitor ANG3070 in Polycystic Kidney Disease
Prakash Narayan, Liming Zhang, Bin Duan, Jingsong Li, Frederic F. Rahbari, Soo Ha, Oskoui, Jessay Gopuran Devassy, Md Monirujjaman, Tamio Mayo Clinic; 7National Insts of Health; 8Legacy Good Samaritan Hospital.

Background: Aberrant receptor tyrosine kinase signaling has been implicated in cyst expansion, renal interstitial fibrosis, increased kidney volume and reduced renal function in polycystic kidney disease (PKD). We investigated the effects of a novel, orally bioavailable, small molecule fibrokinase inhibitor, ANG3070, in experimental PKD.

Methods: Male PCK rats (PCK/CrljCrl-pkhd1pck/Crl) were randomized to vehicle or ANG3070 (25 mg/kg, BID, PO) at 6.5 weeks of age following confirmation of frank disease and sacrificed at 13.5 weeks. Age-matched male Sprague-Dawley rats served as wild-type controls.

Results: ANG3070 has no effect on mean arterial pressure. In PCK rats with diseased kidneys (figure1), randomization to ANG3070 treatment was therapeutic, reducing cystic index, renal interstitial fibrosis (hydroxyproline (HYP), albuminuria and other urine biomarkers of renal injury and serum creatinine (* p<0.05).

Conclusions: ANG3070 reduces renal cyst burden and renal interstitial fibrosis in PCK rats. This oral fibrokinase inhibitor is promising as a potential therapeutic agent in human polycystic kidney disease.

SA-PO886
Alterations in Renal Oxylipins in Models of Polycystic Kidney Disease: Potential for Cyclooxygenase Inhibition for Disease Treatment
Harold M. Aukema, Jessy Gopuran Devassy, Md Monirujjaman, Tamio Yamaguchi, Amir Ravandi. Human Nutritional Sciences, Univ of Manitoba, Winnipeg, MB, Canada; CCARM, St. Boniface Research Hospital Research Centre, Winnipeg, MB, Canada; Inst for Cardiovascular Sciences, St. Boniface Research Hospital Research Centre, Winnipeg, MB, Canada.

Background: The Han:SPRD-Cy rat and the pcy mouse, prostanoid forms via the cyclooxygenase (COX) pathway are elevated, while oxylipins produced via the lipoxigenase (LOX) and cytochrome P450 (CYP) pathways are reduced. Importantly, inhibiting the formation of the elevated COX oxylipins with selective (NS-398) or unselective (aspirin) COX inhibitors reduces the progression of disease in the Han:SPRD-Cy rat, suggesting their potential use in the treatment of nephronophthisis. It is not known, however, whether renal oxylipins are altered in orthologous models of human polycystic kidney disease (PKD).

Methods: Renal oxylipins were analyzed by LC/MS/MS.

Results: The elevated renal COX oxylipins in these PKD models are consistent with the cystic kidney disease models. This suggests that COX inhibition with common drugs such as aspirin or selective COX inhibitors may be beneficial in PKD, as it is in other models of cystic kidney diseases.

Conclusions: Funding: NIDDK Support

SA-PO887
Hepatorenal Fibrocystic Diseases in Children
Ruvin Park, Yo Han Ahn, Hee Gyung Kang, Hye Won Park, Il-Soo Ha, Jae Il Cheong. Dept of Pediatrics, Seoul National Univ Children’s Hospital, Seoul, Korea; Research Coordination Center for Rare Diseases, Seoul National Univ Hospital, Seoul, Korea; Dept of Pediatrics, Seoul National Univ Bundang Hospital, Seongnam, Korea.

Background: Hepatorenal fibrocystic diseases (HRFCDs) are a group of monogenic disorders characterized by developmental abnormalities involving the liver and kidney. In this study, we performed genotype and phenotype analyses of children with HRFCDs to determine the distribution of underlying disease.

Methods: A total of 36 children with HRFCDs were recruited, with genetic tests performed in 22 patients and 14 patients diagnosed clinically as having autosomal recessive polycystic kidney disease (ARPKD).

Results: In Mx1Cre Pkd1floxflox mice with disease, renal levels of the COX metabolites, prostaglandin (PG)E2 and 6-keto-PGF1α were elevated by 35 and 59%, respectively. In Pkd2−/− mice, 11β-PGE2, PGE2, PGF2α and 6-keto-PGF1α were elevated in diseased kidneys by 43, 49, 46, 67 and 136%, respectively. In the PCK rat model of ARPKD, PGE2 and 6-keto-PGF1α were elevated by 38 and 50%, respectively. In all three models, although not as consistent as the COX oxylipins changes, LOX and CYP oxylipins were generally lower, which is similar to findings in the Han:SPRD-Cy rat and pcy mouse.

Conclusions: The elevated renal COX oxylipins in these PKD models are consistent with other cystic kidney disease models. This suggests that COX inhibition with common drugs such as aspirin or selective COX inhibitors may be beneficial in PKD, as it is in other models of cystic kidney diseases.

Funding: Government Support - Non-U.S.

SA-PO888
Extended Follow-Up of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP III): The Predictive Value of Height Corrected Total Kidney Volume (hTKV) for the Future Development of CKD Stages 3a, 3b, 4 and 5 After Ten Years Follow-Up in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Arlene B. Chapman, Chengli Shen, Alan S.L. Yu, Michal Murg, Frederic F. Rahbari-Oskou, Vicente E. Torres, Jared J. Grantham, Michael F. Flessner, Kyongtae Ty Bae, Doug Landsittel, Peter C. Harris, William M. Bennett, U of Chicago; U of Pittsburgh; U of Kansas; Univ of Alabama Birmingham; Emory Univ; Mayo Clinic; National Insts of Health; Legacy Good Samaritan Hospital.

Background: CRISP III is a longitudinal observational cohort study of 241 ADPKD individuals now extending beyond 10 years. Measures of cyst burden by magnetic resonance imaging (MRI) provide an accurate assessment through measures of htTKV. We have shown previously that baseline htTKV predicted CKD stage 3 after 8 years. We now evaluate whether baseline htTKV can predict CKD Stage 3a, 3b, 4 and 5 after 10 years of followup.

Methods: Participants underwent protocol visits including MR imaging, iothalamate clearances and serum creatinine measurements. Baseline htTKV was evaluated in its capacity to predict later CKD stages both individually and in a multivariable model that includes age, race, gender, and baseline iothalamate clearance. Receiver operator characteristic area under the curves (AUROC) were developed for reaching CKD stage 3a, 3b, 4 or 5 after a minimum of 10 years of followup.

Results: At 10 years, 59.8%, 32.1% and 21.6% of patients had reached CKD stage 3, 4 or 5. Baseline htTKV alone predicts CKD stage 3 in 10 years with a ROC of 0.85 and an optimal TKV cut point of 470 ml/m2. Multivariable analysis assessing future CKD Stage 3a, 3b, 4 and 5 at 10 years demonstrated a ROC of 0.89, 0.87, 0.90, and 0.89 respectively.

Conclusions: HTKV is a powerful predictor of the development of all advanced stages of CKD within 10 years with an optimal htTKV of 470 ml/m2 for CKD Stage 3.

Funding: NIDDK Support

SA-PO889
Diagnostic and Therapeutic Advances in PKD
Poster/Saturday
Identifying Genetic Modifiers in Severe Polycystic Liver Disease (PLD) by Whole Exome Sequencing (WES) 

Gema Ariceta, Carsten Young, William C. Nahas, Luiz F. Onuchic. 1

Background: PLD (sPLD) is a rare and poorly understood phenotype seen in ADPKD and ADPLD. Mutations of POLR2A or SEC63 in ADPLD reduce functional polycystin-1 dosage by decreasing endoplasmic reticulum (ER) protein-processing and aggravates cystic disease severity in vivo (Nait Genet 43: 639-647, 2011). We hypothesize that rare mutations in ER pathway genes may modify PLD.

Methods: We performed WES using Illumina HiSeq2000/2500 with SSV4/5 capture kit in 88 patients (24 affected discordant sib-pairs and 7 affected concordant sib-pairs for sPLD and 27 sporadic cases). All sPLD patients had a liver span >25 cm by CT/MRI or >5x normal liver volume. In addition to genome-wide analysis, we performed focused analysis on 168 ER genes. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare deleterious variants of high and moderate impact as predicted by PolyPhen-2, Sift, Mutation Assessor, Mammalian and Vertebrate nucleotide-level conservation, and Combined Annotation Dependent Depletion.

Results: Overall, we achieved a mean target coverage of 108X with 90% of targeted exomes having >30X read depth. We identified 4,696 rare deleterious variants that segregated with PLD disease severity in at least one family. From them, we found 7 non ER genes (TNN, DNAH10, DNAH14, HMCN2, NEB, OBSCN and ADAMTS28) with rare variants that segregate in 4 to 6 families each and 8 ER genes (WFS1, SEC63, SEC61Q, T, ATPLF, DNAH5, DNAI1, and DNAI3) with rare variants that segregate in at least one family and 3-4 sporadic sPLD cases.

Conclusions: Our results suggest extensive genetic heterogeneity with no single gene accounting for a large proportion of sPLD cases. Future studies with expanded sample size will help to identify promising candidate genes for follow-up functional studies. Identification of genetic modifiers of sPLD has the potential to improve risk prediction and treatment of this unusual complication.

Funding: Private Foundation Support

TOSCA – Tuberous Sclerosis Registry to Increase Disease Awareness: Renal Manifestations of Tuberous Sclerosis Complex

John C. Kingswood, Anna C. Jensen, 1

Sussex Kidney Unit, Royal Sussex County Hospital, Brighton, United Kingdom; 2Pediatric Neurology Unit, UZ Brussel, Brussels, Belgium.

Background: Renal manifestations are the most common cause of morbidity and mortality in adult patients with tuberous sclerosis complex (TSC). The aim of the Tuberous Sclerosis Registry to increase disease Awareness (TOSCA) is to understand the various manifestations of TSC. The baseline data of renal manifestations in the overall TOSCA cohort are presented here.

Methods: Patients diagnosed with TSC were enrolled in TOSCA from 170 sites across 31 countries worldwide. Patients will be followed up for 5 up to 5 years with interim analysis performed every year.

Results: Baseline core data from 2093 patients were entered in the registry as of September 30, 2014 (cut-off date for the 2nd interim analysis). Median age at consent was 13 years (range: 0.5 – 89.5 years). 578 renal anomalies were reported in 987 (47.2%) patients. Median age at diagnosis of angiomyolipoma was 13 years (0-67). Of the 946 (95.8%) patients with ongoing renal angiomyolipomas, 396 (41.9%) had multiple and bilateral lesions, 329 (34.8%) had lesions > 3 cm, and 204 (21.6%) had growing lesions. Symptoms/signs associated with renal angiomyolipomas were reported either individually or in combination with others, were elevated blood pressure (48 [5.1%]), microscopic hematuria (35 [3.7%]), hemorrhage (47 [5.0%]), impaired renal function (36 [3.8%]), and pain (51 [5.4%]). Renal angiomyolipomas were treated in 274 (27.8%) patients; major treatment modalities included embolization in 98 (35.8%) and mammalian target of rapamycin (mTOR) inhibitors in 78 (28.5%) patients. Other renal features reported were renal malignancy (24 [1.1%]), renal cysts (477 [22.8%]), polycystic kidneys (73 [3.5%]), and impaired renal function (43 [2.1%]).

Conclusions: The prevalence of renal angiomyolipomas of 47.2% in our cohort compares with 30-85% in the literature probably reflects their young mean age. Despite this the intervention rate was high, emphasizing the need for active surveillance. This is the largest cohort of patients with TSC ever reported, thus TOSCA is a powerful tool to delineate the natural history of TSC.

Funding: Pharmaceutical Company Support - Novartis Pharma AG

Siroliimus Reduces Fundamentally the Vascular and/or Muscular Components of Angiomyolipomas and Can Be Neoadjuvant to Partial Nephrectomy in Tuberous Sclerosis Complex

Eliyahu Y. Yarouch, Robert Johnson, Agnieszka Kaczka, Jochen Bergmann. 1

Heiko Billing, 2 Reinhard Buettner, 3 Ali Duzova, 4 Heike Goebel, 5 Dieter Haffner, 6 Thomas Illig, 7 Augustinowa Jankauskien, 8 Djilalia Mekahli, 9 Bruno Ranchin, 10 Anja Christine Sander, 11 Sara Testa, 12 Lutz Thorsten Weber, 13 Dorota Wicher, 14 Elke Wuehl, 15 Franz S. Schafer, 16 Mix Liebau. 17

Univ Hospital of Cologne, Germany; 2Univ Hospital Vall d’Hebron, Barcelona, Spain; 3Bioscientia Center for Human Genetics, Ingelheim, Germany; 4Univ Hospital of Freiburg, Germany; 5Univ Hospital of Tuebingen, Germany; 6Hacettepe Univ, Ankara, Turkey; 7Hanover Medical School, Germany; 8Center for Pediatrics, Univ Hospital of Vila, Lithuania; 9Univ Hospital of Leuven, Belgium; 10Univ de Lyon, Bron, France; 11Univ of Heidelberg, Germany; 12Fondazione IRCCS Ca Granda Ospedale Maggiore Polic, Milan, Italy; 13The Children’s Memorial Health Inst, Warsaw, Poland; 14Univ Hospital of Heidelberg, Heidelberg, Germany.

Background: Autosomal recessive polycystic kidney disease (ARPKD) is the rare form of polycystic kidney disease presenting in early childhood. There is unexplained phenotypic heterogeneity. Current therapeutic approaches continue to be largely opinion-based and symptomatic.

Methods: ARegPKD is an international, mostly European, pro- and retrospective, observational study in both pediatric and adult ARPKD patients to generate a deeply-characterized ARPKD cohort. Using web-based questionnaires regarding patients’ clinical data in combination with associated biobanking and reference histology ARegPKD will characterize long-term ARPKD courses and set roots for future translational research.

Results: In June 2015 63 centers have registered and more than 130 patients have been included (67.6 % male; mean age at inclusion 7.6 ±2.4 years; number of follow-up visits up to 17). Here we present data on general patient characteristics, genetics, testing, renal and hepatic phenotype putting a special focus on the peri- and postnatal period (perinatal findings, ventilation modalities, sonographical findings, laboratory values).

Conclusions: ARegPKD aims to deeply characterize ARPKD patients in order to provide evidence base for clinical treatment decisions and contribute to the understanding of this severe renal disorder of early childhood.

Funding: Private Foundation Support

The Effect of Sodium Nitrite on Central and Peripheral Hemodynamics, Vasoactive Hormones, GFR and Sodium Excretion in Healthy Subjects

Jeppe B. Hansen, Aasleiv Nielsen, Matthias H. Christensen, Frank H. Mose, Erling B. Pedersen, Jesper N. Bech. Univ Clinic in Nephrology and Hypertension, Holstebro Hospital and Aarhus Univ, Denmark.

Background: Recent research has shown that sodium nitrite is readily converted to nitric oxide (NO) by enzymes in vivo and exerts vasodilatory effects. Previous studies based on nitric oxide synthase inhibition indicates a natriuretic effect of nitrite. The purpose of the present study was to examine the effects of sodium nitrite on central and peripheral blood pressure, heart rate, fractional sodium excretion and GFR.

Methods: In a single blinded, placebo controlled dose-response study 12 healthy subjects were treated, in a randomized order, with placebo (isotonic NaCl) or one of three doses of sodium nitrite 40, 120 or 240 mg/kg/hour for two hours. Each examination was preceded by 4 days standardized diet. Subjects were supine and water loaded throughout the day. Before, during and after sodium nitrite administration we measured diastolic, systolic and mean arterial blood pressure (DBP, SBP and MAP), heart rate, plasma renin, angiotensin II and aldosterone, GFR by creatinine-creatinine clearance, fractional sodium excretion and urinary excretion rate of nitrite and nitrate (NOx).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO093
The Spatial Distribution of Metabolites Determined by Imaging Mass Spectrometry in the Kidneys of Rats Treated with Furosemide

Background: In the kidney, metabolic processes vary among the cortex (COR), outer medulla (OM), and inner medulla (IM), and the concentrations of metabolites are different according to the kidney zones. We aimed to examine the regional differences of the significantly changed metabolites in the kidneys of rats treated with loop diuretics by exploiting the matrix-assisted laser desorption/ionization (MALDI) and imaging mass spectrometry (IMS).

Methods: Omnipine minipumps were implanted in male Sprague-Dawley rats to deliver 12 mg/day of furosemide (s.c.). Vehicle-treated control rats (n = 15) and furosemide-treated rats (furosemide rats, n = 15) were maintained in metabolic cages for 6 d on a fixed daily dose, 0.24% (±0.2) by the intermediate dose and 0.32% (0.06;0.59) by the highest dose compared to placebo. The highest dose of sodium nitrate reduced SBP by 4.5 mmHg (0.5,8.5), DBP by 3.8 mmHg (0.6,6.7), MAP by 4.0 mmHg (1.2,6.8) and increased Pr-creatinin concentration by 17.6% (2.3,32.2), P-angiotensin II by 21.8% (4.6,38.9) and urinary creatinine excretion rate by 95% (59,132) compared to placebo. There was no effect on heart rate, GFR or aldosterone

Conclusions: In supine, water loaded subjects a two hour infusion of 240 mg/kg/hour sodium nitrite exerts an antinatriuretic and BP lowering effect. The rise in urinary excretion rate of NOx suggests an increased bioavailability. The activation of the renin-angiotensin-aldosterone system (RAAS) could either be mediated directly by nitrite/NO or by baroreceptor reflex. The antinatriuretic effect might, at least partially, be mediated by the RAAS.

Funding: Government Support - Non-U.S.

SA-PO094
Bicarbonate Supplementation Improves Vascular Function in Patients with Chronic Kidney Disease: A Pilot Study

Background: Metabolic acidosis, as reflected by a low serum bicarbonate level, is associated with increased risks of endothelial dysfunction, hypertension and death. Metabolic acidosis induces inflammation and endothelin-1, both of which contribute to vascular dysfunction. Whether alkali therapy improves vascular function in patients with chronic kidney disease (CKD) is unknown.

Methods: Seven subjects (5 men and 2 women) with stage III/IV CKD and serum bicarbonate level of less than 21 mmol/L. A total of 1500 mg of sodium bicarbonate (8.3mEq) was added to three meals per day for goal serum bicarbonate of ≥ 23 mEq/L.

Results: Fractional sodium excretion were reduced by 0.25% 95%CI (0.02;0.47) by the lowest dose, 0.24% (±0.12;0.59) by the intermediate dose and 0.32% (0.06;0.59) by the highest dose compared to placebo. The highest dose of sodium nitrate reduced SBP by 4.5 mmHg (0.5,8.5), DBP by 3.8 mmHg (0.6,6.7), MAP by 4.0 mmHg (1.2,6.8) and increased Pr-creatinin concentration by 17.6% (2.3,32.2), P-angiotensin II by 21.8% (4.6,38.9) and urinary creatinine excretion rate by 95% (59,132) compared to placebo. There was no effect on heart rate, GFR or aldosterone

Conclusions: In supine, water loaded subjects a two hour infusion of 240 mg/kg/hour sodium nitrite exerts an antinatriuretic and BP lowering effect. The rise in urinary excretion rate of NOx suggests an increased bioavailability. The activation of the renin-angiotensin-aldosterone system (RAAS) could either be mediated directly by nitrite/NO or by baroreceptor reflex. The antinatriuretic effect might, at least partially, be mediated by the RAAS.

Funding: Government Support - Non-U.S.

SA-PO095
Tenofovir-Related Distal Tubular Disorders in HIV Infected Patients

Background: Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse transcriptase inhibitor extensively used worldwide and is now the most prescribed drug on Highly Active Antiretroviral Therapy (HAART). TDF toxicity is mainly targeted at the proximal tubule, and less often, the distal tubule. TDF toxicity may cause Fanconi Syndrome or acute kidney injury. Despite this, there are no studies evaluating other types of tubular toxicity. This study evaluated the presence of distal renal tubular acidosis (dRTA) in HIV patients on HAART.

Methods: Sixty one HIV patients older than 18 years on treatment with HAART for more than 12 months and GFR estimated by CKD-EPI equation greater than 45 ml/min/1.73m2 were evaluated. They were divided into two groups: 31 used HAART that included TDF and 30 used HAART with no current or previous use of TDF. They were submitted to fluid restriction for 12 hours and received 40mg of furosemide and 0.1mg of dDAVP subcutaneously, following a 1-hour test procedure previously described by Alkhouri et al (2007). We measured serum bicarbonate and the following parameters: hourly urine pH (4h) by potentiometry, urinary ammonium (uNH4+) by spectrophotometry and urinary titratable acidity (uTA) by NaOH (0h and 4h). The diagnosis of dRTA was established when the urinary pH was higher than 5.3 in all measurements.

Results: There was no significant difference between the groups in terms of age, gender, ethnicity, CD4 count or cGFR. The prevalence of dRTA was 6% in the group without TDF and 26% in TDF group (p<0.04). In both groups, patients without dRTA showed increase in uNH4+ (p=0.05 and p=0.009, respectively) and in uTA (p=0.06 and p=0.05, respectively), unlike patients with dRTA, who did not show increase neither in uNH4+ (p=0.44 and p=0.34, respectively) nor in uTA (p=0.52 and p=0.11, respectively). In all cases with dRTA, the serum bicarbonate was normal, featuring an incomplete presentation.

Conclusions: The prevalence of incomplete dRTA in patients using TDF was significantly higher than the group not using the drug. This is the first study suggesting a possible association between TDF and dRTA. Subsequent studies will be necessary to corroborate this hypothesis.

SA-PO096
Comparison of Acid-Base Disorder Between Patients Undergoing Ileal Neobladder and Ileal Conduit

Background: Since the 1980s, the orthotopic ileal neobladder(INB) has been as an new option by eliminating the need for a cutaneous stoma and urinary diversion appliances of ileal conduit(IC). Although this method has improved patients’ quality of life, frequent incidence of metabolic acidosis(MA) have been reported. We compared occurrence of MA in INB group to IC group, and searched for risk factors affecting MA.

Methods: We conducted a retrospective study in 95 patients who underwent radical cystectomy and urinary diversion from January 2001 to December 2014 at Hallym University Medical Center. Patients who have any illness such as severe pulmonary disorder, take any medication that could lead to MA and sepsis were excluded. Acid-base balance and renal function were measured at first hospital stay. Serum bicarbonate and the following parameters: hourly urinary pH (0h to 4h) were measured serum bicarbonate and the following parameters: hourly urinary pH (0h to 4h) were measured serum bicarbonate and the following parameters: hourly urinary pH (0h to 4h)

Results: MA was detected in 74.2% and 69.7% within 7 days(p=0.64), and in 31% and 14.8% at 1 month(p=0.1) after operation in INB and IC group. But cases on bicarbonate therapy were significantly more in INB group(p<0.02). Serum HC03 levels(p=0.05) and base excess(p=0.02) were significantly lower in INB group in spite of more cases on bicarbonate therapy. Acute kidney injury(AKI) at 1 month was higher in INB group(p<0.008). Serum creatinine concentrations were significantly correlated with bicarbonate levels. Multivariate logistic analysis showed that 1 mg/dl increase of serum creatinine level result in a 5.38-fold higher risk of MA (95% confidence interval, 1.14-25.3; P = 0.03). Patients without AKI, MA was detected in 13.5% in INB group, 12% in IC group at 1 month(p<1.0).

Conclusions: Despite there being no statistical difference, INB group may more easily develop MA compared with IC group especially in patients with elevated serum creatinine concentrations. In addition, a close association between the serum creatinine level and the degree of MA was observed in both groups.

Funding: Private Foundation Support

SA-PO097
Screening for Hyperlactatemia: Relationship Between the Anion Gap and Serum Lactate in Hypovolemic Shock

Background: In lactic acidosis (LA), a discrepancy between the increase in serum anion gap (AG) and serum lactate concentration has been noted. Previous studies evaluated patients in the Intensive Care Unit with established LA. No study has examined the relationship between AG and serum lactate within the first hour of the development of LA, specifically the sensitivity and specificity of an elevated AG for predicting hyperlactemia.

Methods: We conducted a retrospective study in 95 patients who underwent radical cystectomy and urinary diversion from January 2001 to December 2014 at Hallym University Medical Center. Patients who have any illness such as severe pulmonary disorder, take any medication that could lead to MA and sepsis were excluded. Acid-base balance and renal function were measured at first hospital stay. Serum bicarbonate and the following parameters: hourly urinary pH (0h to 4h) were measured serum bicarbonate and the following parameters: hourly urinary pH (0h to 4h)

Results: MA was detected in 74.2% and 69.7% within 7 days(p=0.64), and in 31% and 14.8% at 1 month(p=0.1) after operation in INB and IC group. But cases on bicarbonate therapy were significantly more in INB group(p<0.02). Serum HC03 levels(p=0.05) and base excess(p=0.02) were significantly lower in INB group in spite of more cases on bicarbonate therapy. Acute kidney injury(AKI) at 1 month was higher in INB group(p<0.008). Serum creatinine concentrations were significantly correlated with bicarbonate levels. Multivariate logistic analysis showed that 1 mg/dl increase of serum creatinine level result in a 5.38-fold higher risk of MA (95% confidence interval, 1.14-25.3; P = 0.03). Patients without AKI, MA was detected in 13.5% in INB group, 12% in IC group at 1 month(p<1.0).

Conclusions: Despite there being no statistical difference, INB group may more easily develop MA compared with IC group especially in patients with elevated serum creatinine concentrations. In addition, a close association between the serum creatinine level and the degree of MA was observed in both groups.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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838A
Methods: Data were obtained prospectively from adult trauma patients at a single level 1 trauma center. Venous samples were drawn prior to initiation of intravenous fluid resuscitation.

Results: 117 patients with elevated serum lactate levels (>2.1 mmol/L) were included. The sensitivity of an elevated AG (≥ 10) to reveal hyperlactatemia was only 43% whereas specificity was 84%. Sensitivity improved if the upper limit of normal AG was lowered and with increasing levels of serum lactate. (Table 1). The correlation between the AG and serum lactate level yielded an R² of 0.30 (p < 0.001) and the slope of this relationship was 0.29 ± 0.58 (95% confidence interval 0.23–0.35).

Table 1: Sensitivity and specificity from use of the AG as an indicator of hyperlactatemia for specific AG and lactate level thresholds

<table>
<thead>
<tr>
<th>Threshold for increased lactate concentration</th>
<th>Sensitivity/Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>0.92/0.25</td>
</tr>
<tr>
<td>&gt;8</td>
<td>0.74/0.57</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0.83/0.68</td>
</tr>
<tr>
<td>&gt;12</td>
<td>0.86/0.80</td>
</tr>
</tbody>
</table>

Conclusions: Within the first hour of the development of LA due to hypovolemic shock, the AG was not a sensitive indicator of an elevated serum lactate level, but it was fairly specific. The sensitivity and specificity of the AG as an indicator of hyperlactatemia is consistent with prior studies examining later stages of LA. The AG increased to a greater extent than the serum lactate and approximately 70% of the change in AG could not be explained by increases in serum lactate. Our results suggest that other anions contribute to the AG in LA.

SA-PO899

The Δ Anion Gap/Δ Bicarbonate Ratio in Early Lactic Acidosis: Time for Another Delta?

Background: The ratio of Δ anion gap and Δ bicarbonate (ΔAG/ΔHCO₃⁻) is used to detect co-existing acid-base disorders in patients with high AG metabolic acidosis. Classic teaching holds that in lactic acidosis (LA), the ΔAG/ΔHCO₃⁻ is 1:1 within the first 60 minutes of onset (despite limited human data) and subsequently rises to 1.8:1. This study examined the ΔAG/ΔHCO₃⁻ for all patients with elevated serum lactate levels (>2.1 mM) with a mean AG of 7.1, the value used to calculate subsequent ΔAG values. ΔAG/ΔHCO₃⁻ was calculated for 45 patients who had elevated serum lactate levels (>2.1 mM). The mean ΔAG/ΔHCO₃⁻ for all patients with elevated serum lactate levels was 1.36 (SD 1.40). The correlation between ΔHCO₃⁻ and AG showed a 95% prediction interval of ±6.15 (Figure 1).

Figure 1: Correlation between ΔHCO₃⁻ and ΔAG

Conclusions: The mean ΔAG/ΔHCO₃⁻ was 1.86 within the first hour of the development of LA due to hypovolemic shock, confirming a small prior human study. This contradicts the traditional belief that in LA the ΔAG/ΔHCO₃⁻ is 1:1 within the first 60 minutes. The classic 1:1 stoichiometry is based on animal models (in which lactic acid is infused into the extracellular [EC] space, facilitating EC buffering of protons by bicarbonate), while our results demonstrate a higher initial ΔAG/ΔHCO₃⁻ ratio in early endogenous LA in humans (which originates intracellularly, resulting in intracellular buffering of protons while lactate is predominantly distributed in the EC fluid). The wide 95% prediction interval suggests that ΔAG/ΔHCO₃⁻ should be used cautiously in the diagnosis of mixed acid-base disorders.

SA-PO900

Blood Lactate as a Predictor for Mortality in Sepsis Patients with Lactic Acidosis Treated Sodium Bicarbonate: A Retrospective Analysis

Methods: We conducted a single center analysis from May 2011 through April 2014. We retrospectively analyzed 109 sepsis patients with lactic acidosis treated with sodium bicarbonate.

Results: Among the 230 patients with lactic acidosis treated with sodium bicarbonate, we finally included 109 patients (47.4%) with lactic acidosis caused by sepsis. The non-survivors had lower albumin levels (P=0.009), higher SOFA and APACHE II scores (P=0.002, P=0.047, respectively), and higher blood lactate level at 6 hours, 24 hours, and 48 hours after checking the initial lactate level (P=0.002, P=0.001, P=0.001, respectively). In particular, decrement of at least 10% in lactate clearance for the first 6 hours, 24 hours, and 48 hours of treatment were more dominant in non-survivors than survivors. Lactate clearance at 6 hours, 24 hours, and 48 hours was significantly associated with mortality after adjustment for confounding variables, including age, gender, CRP, albumin, SOFA and APACHE II scores, ventilator care, CRRT, and use of inotropic (HR: 2.201, 95% CI: 1.197–4.046, P=0.011; HR: 3.948, 95% CI: 1.269–12.281, P=0.018; HR: 4.970, 95% CI: 1.679–14.710, P=0.004, respectively).

Conclusions: Serial blood lactate levels monitoring is useful in terms of predicting mortality, which is consistent with prior studies examining later stages of LA.

SA-PO901

D-Lactate: It’s All in the Gut

Background: D-Lactic acidosis is a rare form of lactic acidosis that can occur in patients with short bowel syndrome.

Methods: 88 yo M with PMH significant for HTN and small bowel obstruction s/p subtotal small bowel resection presented to the ED with complaints of nausea, vomiting, constipation, loss of appetite, altered mental status and decreased urinary output.

On admission:

- Vitals: Blood pressure: 115/68 mmHg, Pulse: 80/min, Temperature: 98.5 F and SpO₂: 92%
- Examination: Distended abdomen with no peripheral edema.
- Imaging: CT abdomen revealed dilated bowel loops but no bowel obstruction or free air in the abdomen/pelvis.

Labs: Na: 134mmol/L, K: 4.5mmol/L, Cl: 108mmol/L, CO₂: 16mmol/L, BUN: 45mg/dL, Creatine: 1.6mg/dL and Albumin 2.3g/dL. ABGs: pH: 7.42, pCO₂: 31mmHg, HCO₃⁻: 19mEq/L. He was found to have anion gap metabolic acidosis with a non-metabolizable gap metabolic acidosis. Venous lactate: 1.11 mmol/L (Normal 0.5-2.2 mmol/L). Serum D-lactate was drawn revealing an elevation at 4.15mmol/L – thus confirming the diagnosis of D-lactic acidosis.

Treatment: Patient received IV fluids with bicarb. PO Flagyl was started and constipation was also treated. He had a normal mental status along with his acidosis subsequently improved. Diagnoses of anion gap metabolic acidosis in the setting of D-Lactic acidosis was made due to bacterial over growth because of his past history of small bowel resection.

Conclusions: The diagnosis of D-lactic acidosis should be promptly considered in patients with malabsorptive disorder such as short bowel syndrome or following a jejunocolic bypass especially when no other cause of anion gap metabolic acidosis is found. Diagnosis is confirmed by a special enzymatic test measuring serum D-Lactate. Treatment involves a low carbohydrate diet, sodium bicarbonate infusion to correct acidemia and antibiotics to minimize D-lactate producing bacteria.

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

Underline represents presenting author.

839A
Methods: Theoretical modeling has been performed using Mathematica software to determine equilibrium ion concentrations in mixed strong-weak base solutions. If these solutions have a significant proportion of strong base yet lower concentration, they are predicted to raise blood pH without generating CO₂ or producing large osmotic stress. Strong bases examined include disodium carbonate (Na₂CO₃) and sodium hydroxide (NaOH); these were mixed with NaHCO₃. Acid-base parameters were measured in acidified canine blood mixed with the base solutions in a closed system using a blood gas analyzer. Treated blood was examined using an optical microscope.

Results: A near-isotonic base solution containing Na₂CO₃;NaHCO₃, at a ratio of 3:1 is predicted to raise blood pH without increasing CO₂ or causing osmotic stress. Addition of this base to acidified blood raised blood pH while reducing CO₂. By contrast, NaHCO₃ raised blood pH, but also generated CO₂. Examination of red blood cells exposed to the former solution revealed no evidence of osmotic stress. Mixed base solutions of NaOH and NaHCO₃ are also promising as a lower sodium alternative.

Conclusions: Mixed strong-weak base solutions, rather than hyper tonic NaHCO₃, can raise blood pH and serum bicarbonate levels, minimize osmotic stress, and limit CO₂ generation. A 3:1 mixture of Na₂CO₃;NaHCO₃ well below 1 M concentration appears to be effective in this regard.

SA-PO902
Chloride Alterations in Hospitalized Patients: Prevalence and Outcome Significance Qi Oian, Charat Thongprayoon, Wisit Cheungpasitporn. Medicine/ Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Chloride (Cl⁻) plays a fundamental role in the maintenance of serum osmotic pressure, acid-base balance, and cellular health. Cl⁻ channels are expressed in almost all cells in the body. Dysfunctions in the Cl⁻ channel result in a broad spectrum of diseases. Cl⁻ alterations in hospitalized patients have not been comprehensively studied in recent years.

Methods: We conducted a retrospective study of adult (≥18 years old) hospital admissions at Mayo Clinic over a period of three years (2011 to 2013). Patients without admission Cl⁻ measurement were excluded. Outcome measures included all-cause mortality, length of hospital stay and discharge disposition.

Results: 76,719 unique patients from a total of 147,358 hospital admissions were enrolled. 55,523 (72.4%) had repeat Cl⁻ measurements within 48 hours. Admission serum Cl⁻ (£24 hr of admission) were excluded. Outcome measures included all-cause mortality, length of hospital stay and discharge disposition.

Conclusions: Mixed strong-weak base solutions, rather than hyper tonic NaHCO₃, can raise blood pH and serum bicarbonate levels, minimize osmotic stress, and limit CO₂ generation. A 3:1 mixture of Na₂CO₃;NaHCO₃ well below 1 M concentration appears to be effective in this regard.

SA-PO903
A Retrospective Review of Paediatric Patients with Bartter and Gitelman Syndrome Patrick Walsh, Marc Bienias, Detlef Bockenhauer. ICH, UCL, London, United Kingdom.

Background: Bartter and Gitelman syndrome are rare autosomal recessive disorders of renal salt handling. They are characterized by disturbed electrolyte and acid-base homeostasis with potentially severe complications. Currently little is known about the long-term disease course and best treatment is controversial. We performed a retrospective case review to investigate the long-term disease course of patients with a diagnosis of Bartter/Gitelman syndrome.

Methods: Demographic and Laboratory data was recorded at presentation, and ages 1,2,3,4,5,10 and 15.

Results: 42 patients with a genetic diagnosis of Bartter/Gitelman were reviewed with a median follow up of 7.85 years (Range 0 -18 Years).

Conclusions: The overall prognosis during childhood was good. Final heights were within the normal range and no child developed ESRD. Albuninuria was common in Bartter 3, indicating the need for long-term monitoring of renal function. Interestingly, hypomagnesemia is often absent at presentation and develops over time in both Bartter 3 and Gitelman.

SA-PO904
Urinary Calcium to Magnesium Ratio Aids to Diagnose Gitelman’s Syndrome without Hypocalciuria and Receiving Intraavenous Magnesium Administration Chih-Jen Cheng,1,2,3 Shih-Hua P. Lin,1,2 Ming-Tso Yan,1,2 1Tri-Service General Hospital; 2National Defense Medical Center; 3Cathay General Hospital.

Background: Although hypocalciuria is widely used to distinguish Gitelman’s syndrome (GS) from Bartter syndrome (BS), several patients with GS actually have not hypocalciuria and may be clinically misdiagnosed as BS. Intraavenous magnesium administration to correct hypocalciurna, another distinct finding in GS can significantly enhance urine calcium excretion and unmask the preexisting hypocalciuria. Because renal Mg²⁺ wasting is characteristic in GS, we hypothesize that urine Ca²⁺/Mg²⁺ ratio may be superior in diagnosing GS.

Methods: One hundred forty three Taiwanese GS patients (M:F = 87:56, age ≥25 ± 10) with definite SLC12A3 mutations was enrolled. Nine BS patients with CLCNKB mutations and 15 healthy subjects were enrolled as disease and normal control, respectively. Intraavenous MgSO₄, was administered (elemental Mg 0.35 mmol/kg) in 8 GS patients with hypocalciuria. Relevant blood laboratory and at least two urine collection for all electrolytes excretion were determined. Hypocalciuria was defined as urine Ca²⁺/Cr ratio less than 0.1 mmol/mmol.

Results: Fourteen (9.8%) of 143 GS patients did not have hypocalciuria (Ca²⁺/Cr ratio 0.28 ± 0.09 mmol/mmol) and exhibited no significant difference in blood parameters compared with GS patients without hypocalciuria. Although their urine Ca²⁺/Cr ratio was significantly lower than that in BS (0.51 ± 0.18 mmol/mmol), there was still overlapping between them. Notably, urine Ca²⁺/Mg²⁺ ratio was significantly lower in GS than BS without overlap (0.46 ± 0.12 vs 1.57 ± 0.53 mmol/mmol, p<0.001). Acute MgSO₄ administration in GS patients markedly enhanced urine Ca²⁺ excretion (Ca²⁺/Cr ratio 0.05 ± 0.1 to 0.64 ± 0.01 mmol/mmol, p <0.001). However, urine Ca²⁺/Mg²⁺ ratio (0.21 ± 0.01 mmol/mmol) remained much lower than healthy subjects (1.35 ± 0.63 mmol/mmol, p<0.001) and BS.

Conclusions: Urine Ca²⁺/Mg²⁺ ratio may be a good index to help diagnose GS without hypocalciuria and even receiving intraavenous Mg²⁺ administration.

SA-PO905
A Blunted Response to Thiazide Diuretics Is Not Specific for Patients with Gitelman Syndrome Anneke Bech, Jack F. Wetzels, Tom Nijenhuis. Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: In Gitelman syndrome (GS), a defective sodium-chloride co-transporter (NCC) in the distal tubule classically leads to hypocalcaemia and hypomagnesemia. A challenge with thiazide diuretics, testing the functional presence of NCC, has been shown to differentiate GS from Bartter syndrome (BS) and normal controls. However, the performance of the thiazide test in renal magnesium wasting disorders other than GS and BS has not been studied.

Methods: Eleven patients who presented to our clinic between 2010-2014 with renal magnesium wasting and in whom a thiazide test was performed were included. An abnormal test result is defined as a maximal change of fractional chloride excretion (ΔFeCl) < 2.3% [Colussi 2007]. The thiazide test in eight volunteers in our clinic showed a mean maximal ΔFeCl 3.12 ± 0.48% with the lowest value being higher than 2.3%. Additional DNA mutation analyses were performed.

Results: Three patients had a mutation in SLC12A3 (GS), one patient had a compound mutation in CLCNKB and KCNJ1 (BS), 1 patient had a mutation in FXYD2 and five patients had a deletion of one HNF1β allele. The patients with GS showed a blunted thiazide test and the patient with BS showed a normal response, the patient with a FXYD2 mutation showed a blunted response and the patients with HNF1β mutations showed different responses to thiazide diuretics.

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

840A
Impact of Hydration Status, Assessed by Bioelectrical Impedance Vector Analysis, on Mortality in Critically Ill Patients

**Background:** Clinical trials have shown a positive correlation between fluid overload and adverse outcomes in pts admitted to intensive care unit (ICU). Currently, there is not a non-invasive method that can provide an accurate and timely assessment of whole body hydration status.

**Objectives:** To evaluate if bioelectrical impedance vector analysis (BIVA), an ICU mortality in critically ill pts.

**Methods:** A prospective, dual-center study included 272 ICU pts with an ICU stay of 72 hrs or more. An anthropometric, medical history, and laboratory data were collected. Assessment of hydration status was performed by BIVA, using a single frequency analyzer at the baseline and daily for a period of 72-120 hrs.

**Results:** We found a significant correlation between BIVA hydration status and ICU mortality.

**Conclusions:** Further studies are needed to validate the clinical usefulness of BIVA in the general ICU setting.

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**SA-PO097**

Assessment of Hydration Status by Bioimpedance Spectroscopy in Peritoneal and Hemodialysis Patients from a Single Center

**Background:** Peritoneal and hemodialysis (PD and HD) patients are at risk of fluid overload and hyperhydration. Bioimpedance spectroscopy (BIS) can be used to assess hydration status.

**Objectives:** To evaluate the hydration status of PD and HD patients using BIS.

**Methods:** We enrolled 188 pts, 120 PD and 68 HD patients. BIS was performed to assess hydration status.

**Results:** We found that measurement of SBP is not sensitive to assess the HYD in PD and HD pts. We also found that PD pts with NSBP tend to be more HH than HD pts. We suggest that SBP should not be used alone as a marker for HYD in PD and HD pts, it should always be accompanied by other tools.

**Conclusions:** The hydration status of PD and HD patients can be accurately assessed using BIS. Further studies are needed to validate its clinical usefulness.

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**SA-PO098**

Sleep-Disordered Breathing Is Not Associated with Body Fluid Volume in Chronic Hemodialysis Patients

**Background:** Sleep-disordered breathing (SDB) is common in chronic hemodialysis (CHD) patients. Fluid retention may promote SDB in these patients. However, the relationship between SDB and body fluid volume is not well understood.

**Objectives:** To evaluate the relationship between SDB and body fluid volume in CHD patients.

**Methods:** Eighty-eight CHD patients in Nasu-Minami Hospital and Japanese Red Cross Koga Hospital were included in this study. SDB was assessed using overnight pulse oximetry.

**Results:** We found that SDB was not associated with body fluid volume in CHD patients.

**Conclusions:** Our findings confirm the hypothesis that SDB is not associated with body fluid volume in CHD patients.
Conclusions: SDB is associated with increased fat mass, but not body fluid volume in CHD patients. Further studies are needed to evaluate some factors that can explain the high frequency of SDB in CHD.

Funding: Private Foundation Support

SA-PO909
Association Between Brain Natriuretic Peptide and Fluid Volume Imbalance Between Intra- and Extracellular Water in Patients with Chronic Kidney Disease
Yasushi Ohashi, Reibin Tai, Toshiyuki Aoki, Shizuka Kobayashi, Atsushi Aikawa, Ken Sakai. Dept of Nephrology, School of Medicine, Faculty of Medicine, Toho Univ; Tokyo, Japan.

Background: Malignant and elderly patients with chronic kidney disease (CKD) may be susceptible to an extracellular fluid volume overload due to a decreased intracellular fluid volume capacity. We assume that excessive fluid volume is redistributed on the basis of the baseline fluid volume balance when they are exposed to fluid accumulation.

Methods: Using bioimpedance analysis, body fluid composition was measured in 129 patients with CKD from 2013 to 2015 and was separated into three components—(a) free water mass consisting of muscle, fat, and minerals, (b) intracellular water (ICW) content, and (c) extracellular water (ECW) content. Participants were also measured brain natriuretic peptide levels at the time of the body fluid composition measurement. The relationship between the ratio of ECW to ICW and brain natriuretic peptide was examined.

Results: Patients with higher log-transformed plasma level of brain natriuretic peptide were more likely to be older and have lower body mass index (BMI), glomerular filtration rate (GFR), and serum albumin levels and higher proteinuria. In body fluid composition analysis, the brain natriuretic peptide levels increased along with a decrease in all components of free water mass consisting of muscle, fat, and mineral (r = -0.49, P < 0.001), ICW content (r = -0.34, P < 0.001), and ECW content (r = -0.25, P < 0.01). By the steeper decreased free water mass and ICW content than the decreased ECW content in those patients, the percentage of ECW in body weight increased, and the ratio of ECW to ICW had a positive correlation with the brain natriuretic peptide levels (r = -0.58, P < 0.001). Multivariate analysis, age, BMI, GFR, and ECW/ICW ratio remained independently associated with the brain natriuretic peptide levels.

Conclusions: Brain natriuretic peptide is elevated in leaner and elderly patients with fluid volume imbalance between intracellular- and extracellular water. Fluid volume imbalance between intracellular- and extracellular water may express a reserve capacity for fluid volume overload and impact on cardiac preload.

SA-PO910
Blood Volume Estimation in Hemodialysis Patients
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Background: Anthropometric formulas used to estimate absolute blood volume (ABV) are generally derived from healthy subjects. Most hemodialysis (HD) patients have an expanded ABV prior to HD, rendering these formulas inappropriate for estimation of pre-HD ABV (pre-ABV). Here, we compare the performance of several ABV formulas, used in conjunction with Crit-Line data, for assessment of pre-ABV.

Methods: We assume that post-HD ABV is closer to normal ABV, which we calculated based on height, sex and post-HD weight using several published formulas. Pre-ABV was then calculated from post-HD blood volume using pre- and post-HD HDct measured by Crit-Line®. The calculated pre-ABV was then compared to pre-ABV measured immediately before HD using 18F-labeled albumin dilution.

Results: We compared 27 formulas for ABV estimation in 21 patients (1/3; mean ± SD: age 59 ± 14.7 years, height: 170.7 ± 10 cm, post-HD weight: 82.2 ± 16.7 kg). None of the equations showed good agreement with the measured data. The Nadler formula yielded the most accurate results (Fig 1). As exemplified in Fig 1, the equations yield a systematic trend in bias, with reasonable accuracy for ABV between 5-6 L but progressive underestimation and increasing heteroscedasticity towards higher ABV (caused by fluid overload).

Conclusions: Anthropometric equations such as the Nadler formula show reasonable accuracy (unsatisfactory precision) for patients close to normal end-HD ABV, but they fail in non-euvolemic patients. Their validity in HD patients depends on the patients’ fluid status, which varies widely; hence their undifferentiated use in this population should be discouraged. More accurate and precise estimates of ABV would require a more sophisticated approach incorporating fluid status information, e.g. from bioimpedance.

Funding: Pharmaceutical Company Support - Daxor Corporation

SA-PO911
Impact of Hospital-Associated Hypernatremia on Outcomes in an Unselected Patient Population: A Retrospective Cohort Study
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Background: Although hypernatremia has been associated with an increased risk of adverse outcomes, the majority of available studies have examined selected populations questioning the generalizability of their results to unselected patients.

Methods: The discharge data of 20,072 unselected adult patients admitted to a tertiary care facility over a 7-year period were analyzed. Based on the crude relationship between [Na+] and mortality, hypernatremia was defined as [Na+] > 142 mEq/L. Patients with community-acquired hypernatremia (CAH) and those with hospital-acquired hypernatremia (HAH) were compared to patients with normonatremia at presentation ([Na+] 138-142 mEq/L) in terms of in-hospital mortality, length of stay (LOS), and discharge disposition. Furthermore, patients with CAH in whom hypernatremia was associated with a greater increase in serum osmolality (HAggH) were compared to those without aggravation. Multivariable logistic and negative binomial regression analyses were conducted.

Results: CAH occurred in 20% of hospitalized patients and was associated with an adjusted odds ratio (OR) of 1.67 (95% confidence interval [CI] 1.38, 2.01) for in-hospital mortality, and 1.44 (95% CI 1.32, 1.56) for discharge to a short-/long-term care facility, and an adjusted 10% (95% CI, 7%-13%) increase in LOS. HAH developed in 25.9% of hospitalized patients and was associated with an adjusted OR of 3.17 (95% CI 2.45, 4.09) for in-hospital mortality, and 1.45 (95% CI 1.32, 1.59) for discharge to a facility, and an adjusted 49% (95% CI 44%, 53%) increase in LOS. HAggH developed in 8.9% of patients with CAH. Compared to patients with CAH and no further increase in [Na+]s, HAggH was associated with greater risk of in-hospital mortality (adjusted OR 1.84, 95% CI 1.32, 2.54) and discharge to a facility (adjusted OR 1.90, 95% CI 1.49, 2.41), and an adjusted 13% (95% CI 4%-23%) increase in LOS.

Conclusions: All forms of hypernatremia encountered in unselected hospitalized patients are independently associated with increased in-hospital mortality and heightened resource consumption.

SA-PO912
Utility of Urine/Plasma Osmolality Ratio for Assessing Volume Status in Hyponatremic Patients
Sho Hasegawa, Maki Shibata, Takehiro Sugiyama, Fumihiko Hinoshita. National Center for Global Health and Medicine, Tokyo, Japan.

Background: Assessing volume status is critical for managing hyponatremia. Physical examination (P/E) and laboratory data are often used for the assessment, but the utility of each parameter has not been validated in hyponatremic patients. A body composition monitor (BCM) uses bioimpedance spectroscopy and can quantify extracellular water (ECW) and volume excess or deficiency. Here, we examined which parameter is superior in assessing volume status of hyponatremic patients, using BCM data as the reference standard.

Methods: We enrolled hospitalized patients (n=41) with hyponatremia (<130 mEq/L) at our institution and conducted P/E, laboratory tests and BCM measurement. Patients with high plasma osmolality (>255 mOsm/kg) were excluded (n=5). We used %ECW/ ratio (volume excess or deficiency to ECW) derived from BCM data as the reference standard of volume status. First, patients were divided into overhydration (%ECW<0%, n=29) and dehydration (%ECW<0%, n=7) groups. Clinical signs obtained from P/E and parameters of volume status such as serum albumin (Alb), serum uric acid (UA), urine chloride, urine/plasma osmolality ratio (U/P Osm), U/NUN/BUN, U/BUN/creatinine, U/P creatinine, FENA, FEUN and FEUA were compared between the groups by Fisher’s exact test or Mann-Whitney U-test. Next, we performed univariate and multiple linear regression analyses to identify associations between each parameter and %ECW.

Results: U/P Osm was significantly higher in dehydration than in overhydration (median: 1.10 vs. 1.3, p=0.01) and carbohydrate loading case showed no significant differences. Univariate regression analysis showed that Alb (β=−7.1±3.2, p=0.04), U/P Osm (β=−11.4±3.1, p=0.001), U/NUN/BUN (β=−0.3±0.1, p=0.001) and U/P creatinine (β=−0.1±0.05, p=0.001) were associated with %ECW. Since U/NUN/BUN and U/P creatinine strongly correlated with U/P Osm, we conducted multiple regression analysis using only Alb and U/P Osm. Results showed that compared with Alb (β=−7.7±2.7, p=0.007), U/P Osm (β=−12.0±2.9, p=0.002) was more strongly associated with %ECW.

Conclusions: U/P Osm is superior to other commonly used parameters and clinical signs for assessing volume status in hyponatremic patients.

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

842A
Sodium Concentrations of Body Fluid Losses: A Systematic Review

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Background: Unexplained wide ranges and discrepancies of sodium concentrations [Na+] have been noted for different body fluids. This has led to use of “cumulative fluid balance” regardless of composition, which cannot account for specific water and sodium requirements. Appropriate water and volume management may be facilitated by an accurate and detailed knowledge of water and sodium composition of body fluid losses and gains.

Methods: We performed a systematic review of [Na+] of body fluids lost in adult humans. Particular attention was paid to gastric fluid with high and low acid states, diarrhea due to different mechanisms, and peritoneal, pleural and wound fluids. Inclusion criteria were met for 106 full-text articles.

Results: [Na+] are fluid-specific and consistent. Mean [Na+] were statistically lower for acidic (mean=SD+44+21mEq/L) than for alkaline (55+31mEq/L) gastric fluid; the difference is not clinically relevant. [Na+] are higher for bile (184+24mEq/L) or pancreatic fluid (156+3mEq/L) than all other body fluids, and similar for intact small bowel (119±4mEq/L) and ileostomy outputs (116+25mEq/L). Specific mechanisms for diarrhea are associated with different Na+. [Na+] were significantly greater for cholera (128±18mEq/L) and lower for osmotic-induced (28±16mEq/L) than all other causes. Among osmotic diarrheas, sorbitol-induced [Na+] was higher (63+17mEq/L) than for carbohydrate malabsorption (43+20mEq/L), lactulose (26+9mEq/L), Idolax (16+13mEq/L) and polyethylene glycol (13±7mEq/L). Among secretory diarrheas [Na+] for idiopathic causes (53+22mEq/L) was lower than for neuroendocrine and villous tumors (75+13mEq/L) or non-osmotic laxatives (88+33mEq/L). Pleural, peritoneal, and edema fluid had [Na+] (137±13mEq/L) similar to plasma. [Na+] for sweat was 44±17mEq/L.

Conclusions: This is the first in-depth review of verifiable sodium concentrations of body fluids most commonly lost in hospitalized patients. We propose that these losses be replaced with appropriate water and sodium content of enteral and parenteral fluids to correct and avoid dysnatremias and perturbations of volume status.

Hyponatremia in CKD: The Prevalence and Risk Factors

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Background: Kidney is a vital organ regulating water and sodium homeostasis, and it is plausible that patients with CKD are more prone to develop hyponatremia due to diminished urinary dilution ability, reduced solute intake, and/or medication which affects free water clearance. However, the prevalence and risk factors of hyponatremia among CKD patients have not been elucidated. The aim of the present study is to clarify the prevalence and risk factors contributing to hyponatremia in CKD patients.

Methods: Among 32,438 patients who visited our outpatient clinic between 2011 and 2014, 9,388 patients met the criteria of CKD, which is defined as either eGFR ≤60 ml/min/1.73m2 or proteinuria >300mg/day. We performed a systematic review of [Na+] of body fluids lost in adult humans. Particular attention was paid to gastric fluid with high and low acid states, diarrhea due to different mechanisms, and peritoneal, pleural and wound fluids. Inclusion criteria were met for 106 full-text articles.

Results: [Na+] of body fluids lost in adult humans. Particular attention was paid to gastric fluid with high and low acid states, diarrhea due to different mechanisms, and peritoneal, pleural and wound fluids. Inclusion criteria were met for 106 full-text articles.

Conclusions: The present study shows that the prevalence of hyponatremia was 8% in CKD patients, and development of hyponatremia is correlated with progression of CKD in moderate and severe CKD. Worsening CKD and Diabetes are risk factors, while RAS inhibitors are protective for hyponatremia in CKD.

SA-PO915

Mild Hyponatremia on Admission Is Associated with Sepsis and Increased Mortality in Patients Presenting with a Hip Fracture

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Background: Hyponatremia is associated with an increased risk of falls and hip fractures in the elderly (JAMA 281: 2299-2304, 1999). Moreover, sepsis is a frequent etiology in patients with hyponatremia (AJKD 65:135-142, 2015). We assessed if hyponatremia on admission was associated with sepsis and increased mortality in patients presenting with a hip fracture.

Methods: A cohort study in adult patients admitted with a traumatic hip fracture and at least one serum Na measured at admission. Hyponatremia (H): Na <135 mEq/L, and normonatremic (N) patients were evaluated for complications occurring within 30 days of surgery, length of hospital stay, readmission rate, in-hospital mortality and mortality during 1 year follow-up. An unadjusted and adjusted odds ratio (OR) and hazard ratio (HR) were calculated for in-hospital mortality and 1 year mortality. Adjustments were made for age, gender, propensity score for hyponatremia, CVA, CHF, ischemic heart disease, arthriticms, thromboembolic disease, sepsis and dementia.

Results: 1571 patients were included of whom 366 (23.2%) were hyponatremic ( Na <124 mEq/L vs 138±3 mEq/L, <0.001). Length of stay was 8 days in H vs 7 days in N (p<0.053). There was in increased incidence of sepsis in hyponatremic patient, 9.8% in H vs. 6% in N (p<0.01) OR 1.7 (95%: 1.3-2.6). In-hospital mortality was significantly higher in H vs N patients (19 vs 14.7%; p=0.016), with an un-adjusted OR of 1.45 (95% CI 1.07-1.90) and an adjusted OR of 1.15 (95% CI 0.84-1.6). Readmissions were 15.8% for H vs 12.9% for N (p=0.14). One-year mortality was greater in H vs N patients (15.4 vs. 6.6%; p<0.001), with an un-adjusted HR of 1.8 (95% CI 1.4-2.35) and an adjusted HR of 1.45 (95% CI 1.1-1.9).

Conclusions: Mild hyponatremia on admission is associated with sepsis and increased in-hospital and late mortality in patients presenting with a hip fracture.

SA-PO916

Characteristics of Tolvaptan Trial in Korean Patients with SIADH


Background: This clinical study, a multicenter trial in 8 tertiary hospitals in Korea, was carried out to evaluate changes in serum sodium (Na) during 11 days on tolvaptan (TЛV) daily and at the 7th day after stopping TЛV in SIADH patients (pts) (<135 mEq/L). TЛV was given daily to a total of 39 pts(MF: 23/ age, 71±11.3 yrs) without neurologic symptoms were studied from Jun 1, 2013 to Dec 31, 2014. All pts received 15 mg of TЛV as the initial dose and then further increased to 60 mg/d as needed in the hospital.

Results: Serum Na (mEq/L) increased predominantly from baseline during first 24 hrs (127±13 to 131±4 mEq/L, p<0.001). It increased to day 4 (134±3.8 to 136±3.6, p<0.001), and then maintained a plateau until discontinuation of TЛV at day 11 (137±4.5). The changes in serum sodium (DNa) from the baseline were 2.8±3.3 in 4 hrs, 5.9±4.1 in 8 hrs, and 6.8±4.2 in 24 hrs, respectively. The correlation between DNa in 24 hrs and baseline Na was significant (r=-0.613, p<0.01). When hyponatremia was stratified into 3 groups, mild (I, 130-134, n=12), moderate (II, 125-129, n=18), and severe, (III, ≤124, n=9) groups, DNa in II (11.1±4.8) during first 24 hrs was significantly higher than I (6.4±2.5, p<0.05) and I (4.3±3.3, p<0.01). Also, those of DNa in 24 hrs (mEq/L) ranged from <8 to ≥21 had significantly lower baseline serum creatinine (0.56 vs. 0.73 mG/dL), Wt (53 vs 60 Kg), BMI (21 vs 23), and body surface area (1.54 vs 1.63) (all p<0.05). Then, serum Na after discontinuation of TЛV for 1 wk was similar to the baseline (127±4.3 vs 129±6.8, p=NS). All pts underwent successfully this trial more than 24 hrs, but 4 pts were withdrawn due to hypotension (1) and recurrent infection (3).

Conclusions: Tolvaptan is effective and well tolerated in Korean with SIADH. However, Korean patients, particularly those with smaller frame and severe hyponatremia (<125 mEq/L), could be vulnerable to rapid correction by usual initial dose of Tolvaptan 15 mg.

Funding: Pharmaceutical Company Support - Korea Otsuka Pharmaceutical Co., Ltd.
Persistent Hyponatremia at 72 Hours in Cancer Patients with Severe Hyponatremia Is Associated with Mortality Independent of Cancer Stage

Vesh Srivastava, 1 Xian Wu, 2 Edgar A. Jaimies, 2 Ilya Glezerman, 2 Lenar T. Yessayan, 2 Balazs Szamosfalvi, 2

Background: Hyponatremia is a common problem and a known independent risk factor for mortality in cancer patients. The impact of rate of correction of sodium on mortality is unknown. The study aim was to determine if the rate of correction in cancer patients with severe hyponatremia (Na < 120 mEq/L) is linked to 90 day mortality.

Methods: Patients with Na < 120 mEq/L were identified from the Memorial Sloan Kettering Cancer Center database from June 1, 2009 until June 30, 2014. 195 patients were identified. 55 patients were excluded from analysis because less than 72 hours after admission they either died (4), had no follow up data (16), were discharged (21), or made comfort care (14). The final cohort consisted of 140 patients who stayed in the hospital for at least 72 hours and had serial measurements of serum Na.

Results: The mean initial serum Na was 116.7 ± 3.0 mEq/L. The median rate of correction was 6 mEq/L with interquartile range 3.9-9 mEq/L in the first 24 hours, and the overall 90 day mortality was 32.4%. No patients with Na correction <8 mEq/L in the first 24 hours (n=54) developed osmotic demyelination syndrome. In patients who died within 90 days, the mean serum Na at 72 hrs was 128.3 ± 4.4 mEq/L compared to 130.5 ± 4.9 mEq/L in survivors (p<0.01). When adjusting for cancer stage and rate of correction in a multivariate Cox model, serum Na ≤ 130 mEq/L at 72 hrs was independently associated with 90 day mortality with adjusted HR 2.62 (1.47-4.64, p<0.001).

Conclusions: Cancer patients with severe hyponatremia are at heightened risk for 90-day mortality independent of cancer stage and rate of Na correction if their serum Na at 72 hrs is < 130 mEq/L. Based on this finding we recommend that cancer patients with severe hyponatremia should be corrected to >130 mEq/L at 72 hrs.

SA-PO919

Hyponatremia Correction Using CRRT: Does Kinetic Modeling Avoid Overcorrection? Saurabh Dassgupta, 1 Lenar T. Yessayan, 2 Balazs Szamosfalvi, 2 Suvag Demirjian, 1 Nephrology, Cleveland Clinic, Cleveland, OH 1 Nephrology, Henry Ford Hospital, Detroit, MI.

Background: Hyponatremia is the most common electrolyte abnormality in inpatients. It must be corrected at a gradual rate of 8 mEq/L in 24 hrs to minimize the risk of central pontine myelinolysis, which can be effectively achieved in patients with renal failure by CRRT. Sodium (Na) kinetic models can predict end dialysis water. A simplified single pool fixed volume kinetic model may be applicable when net Na generation (G) is ~0 mEq/h. Our goal was to measure the correlation of predicted rate of correction by the formula to that observed in ICU patients with hyponatremia treated with CRRT.

Methods: 66 critically ill subjects with serum Na <130 at time of CRRT initiation were retrospectively identified. Median age was 60, and 52% were male. The predominant CRRT modality was CVVHD (97%), using dialysate Na of 140 mmol/L in most patients (92%) with average cumulative dose of 6L1, delivered over median duration of 23.2 hrs. Predicted Na correction in the first 24 hours was calculated using a single pool fixed volume kinetic model. The values were then compared to actual measured serum Na using simple correlation, and Bland-Altman plot.

Results: The correlation factor was calculated to be 0.49 with a p value <0.001. The Bland Altman plot (figure) showed a mean difference of 2 mmol/L between the observed and predicted delta Na values, with a trend for overestimation of Na correction as delta sodium levels increased.

Conclusions: Increasing Hb spuriously decreases dNa and increases dNa. A linear correction for this artifact can reduce the discordance between iNa and dNa, promoting their interchangeable use.

Funding: Veterans Administration Support

SA-PO921

HHV-6 Encephalitis Resulting in Cerebral Salt Wasting and Hyponatremia Jonathan A. Ducastel, Uday S. Nori. Internal Medicine and Nephrology, Ohio State Univ, Columbus, OH.

Background: Hyponatremia is a common electrolyte abnormality that can be associated with hypo-, hyper-, or euolemic states. Low circulating volumes secondary to extra-renal losses, fluid overload states, and syndrome of inappropriate ADH are some of the more common causes of hyponatremia. One consideration that is uncommon and often overlooked is cerebral salt wasting (CSW). CSW is defined as “renal loss of sodium during intracranial disorders leading to hyponatremia and a decrease in the extracellular fluid volume.” It occurs in the setting of cerebral injury, most commonly associated with subarachnoid hemorrhage.

Hb Category Hb mean N ANa, unadjusted ANa, adjusted
-6 5 17 1.4±0.4 1.2±0.5
-6.7-9.7 7.2 43 1.8±0.3 1.5±0.3
8.9-9.9 9.1 166 2.3±0.2 1.9±0.2
10.1-11.9 11 240 2.4±0.1 2.4±0.1
12.1-13.9 12.9 185 2.4±0.2 2.6±0.2
14.1-15.9 14.8 82 2.5±0.3 2.8±0.2
≥16 17 39 2.6±0.3 3.1±0.3

Conclusions: Increasing Hb spuriously decreases dNa and increases dNa. A linear correction for this artifact can reduce the discordance between iNa and dNa, promoting their interchangeable use.

Funding: Veterans Administration Support
hemorrhage, but also documented with other disorders of central nervous system. The mechanism of CSW is not completely understood, but is believed that a cerebral injury can lead to impairment of the sympathetic outflow causing primary natriuresis leading to hypovolemia and sodium depletion.

**Methods:** Here we describe a case of CSW in a patient with human herpes virus-6 (HHV-6) encephalitis. The patient was a 29 year old male with a history of AML who was continued on IV saline with the addition of oral salt supplements and started on foscarnet with normalization of the serum and CSF PCR within 10 days.

**Conclusions:** This case is important because the diagnosis of CSW is often confused with SIADH, as both share similar diagnostic criteria such as elevated urine sodium concentration and urine osmolality. The important clinical distinction is the patient, despite having a hypovolemic state would have polyuria and renal sodium wasting.

**SA-PO922**

**Association of 6-Month Pre-ESRD Potassium with Immediate Post-ESRD Survival: A Transition to CKD Study.** Melissa Sooho,$^1$ Connie Rhee,$^1$ Vanessa A. Ravel,$^1$ Elani Streja,$^1$ Jennie Jing,$^1$ Rajiv Saran,$^2$ Bruce M. Robinson,$^3$ Yi Li,$^2$ Danh V. Nguyen,$^2$ Csaba P. Kovessy,$^2$ Kamyar Kalantar-Zadeh.$^1$

**Background:** Previous studies of the association between serum potassium level and mortality in dialysis patients have suggested that a range of 4.6-5.3 mEq/L portends greatest survival in this population. However, the optimal potassium range in the immediate pre-ESRD period before ESRD transition (6 month-prelude) is not known. We hypothesized that a similar pre-ESRD serum potassium range is also associated with higher survival in this population.

**Methods:** We investigated a cohort of 20,404 US veterans who initiated dialysis between 10/2007-9/2011 and had at least 1 potassium measurement during the last 6 month period before ESRD transition (6 month-prelude). We examined the association of 6 month averaged potassium as a continuous predictor of all-cause mortality and early post dialysis episode of severe hyperkalemia. Among the different classes of antihypertensives, K-sparing diuretics had the strongest associations with both mild and severe hyperkalemia, followed by ACEis and then beta blockers, which were associated only with mild hyperkalemia (Figure).

**Results:** Potassium levels were checked ≥1 time/year in 53% of the cohort; 4% had levels checked >5 times/year. Overall, 7.4% had >1 episode of mild hyperkalemia; 0.4% had an episode of severe hyperkalemia. Among the different classes of antihypertensives, potassium sparing diuretics were protective against mild hyperkalemia but not severe hyperkalemia. There were no consistent interactions between types of antihypertensive medication for risk of hyperkalemia.

**Conclusions:** Mild hyperkalemia is relatively common and associated with the use of ACEis and K-sparing diuretics but not ARBs in this single healthcare system.

**SA-PO923**

**Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Healthcare System.** Alex R. Chang,$^1$ Yingying Sang,$^2$ H. Lester Kirchner,$^1$ Kunhiro Matsushita,$^2$ Shoshana Ballew,$^2$ Jose Corisb,$^3$ Morgan Grams,$^2$ Gessinger Health System; Johns Hopkins Bloomberg School of Public Health.

**Background:** The association of outpatient medication use with patterns and prevalence of hyperkalemia has not been rigorously examined.

**Methods:** We evaluated the association between baseline antihypertensive medications [angiotensin converting enzyme-inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, loop/thiazide diuretics, and K-sparing diuretics] with the frequency and pattern of mild (K<5-5 mEq/L) and severe hyperkalemia (>6 mEq/L) over a 2 year window in 342,342 outpatients in the Gessinger Health System based on medication prescription orders. Orders of hyperkalemia were classified as: never, transient (1-time), intermittent (>1-time but ≤50% of the time), and persistent (≥50% of the time). Analyses were adjusted for demographics, eGFR, systolic blood pressure, diabetes, and history of cardiovascular disease. Interactions between medication types with hyperkalemia risk were also tested.

**Results:** There were no consistent interactions between types of antihypertensive medication for risk of hyperkalemia.

**Conclusions:** Mild hyperkalemia is relatively common and associated with the use of ACEis and K-sparing diuretics but not ARBs in this single healthcare system.

**SA-PO924**

**Wide Range in Variation in Serum Potassium in Hyperkalemic Patients with CKD, Response to a Fixed 60 mEq Potassium Diet.** David A. Bushinsky,$^1$ Martha Mayo,$^2$ Dahlia Garza,$^2$ Yuri Stavis,$^2$ Daniel J. Wilson,$^3$ Charles Dumond,$^2$ Lance Berman,$^2$ Murray Epstein,$^2$ Univ of Rochester; Relypsa, Inc; Univ of Miami.

**Background:** A wide range of inter-individual variation in s-K+ (maximum-minimum) in s-K+ at each time point for the remaining observation period to determine variation in s-K+.

**Methods:** A total of 27 pts with s-K+ ≥5.5 to ≤6.2 mEq/L were monitored in a clinical research unit. At baseline pts were fed a 60 mEq K+ diet with CKD (stage 2-4) on stable doses of RAASi, during the run-in phase of a treatment trial.

**Results:** There were no consistent interactions between types of antihypertensive medication for risk of hyperkalemia.

**Conclusions:** Mild hyperkalemia is relatively common and associated with the use of ACEis and K-sparing diuretics but not ARBs in this single healthcare system.

**SA-PO925**

**Funding:** Private Foundation Support

**SA-PO926**

**Funding:** NIDDK Support
**Table Variation in s-K+ (max-min) over 72 h during run-in on a 60 mg k+ diet, n=27**

<table>
<thead>
<tr>
<th>Time</th>
<th>baseline</th>
<th>+10 h</th>
<th>+24 h</th>
<th>+36 h</th>
<th>+48 h</th>
<th>+62 h</th>
<th>+71 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>A in s-K+</td>
<td>0.44±</td>
<td>0.24±</td>
<td>0.36±</td>
<td>0.23±</td>
<td>0.37±</td>
<td>0.21±</td>
</tr>
<tr>
<td></td>
<td>mEq/L</td>
<td>0.24±</td>
<td>0.24±</td>
<td>0.24±</td>
<td>0.24±</td>
<td>0.24±</td>
<td>0.09±</td>
</tr>
<tr>
<td>P-value*</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Comparing values from baseline to values at +10, +24, +36, +48, +62 and +71 h via paired t-test with Bonferroni correction (α=0.05; P<0.0083 is significant).

**Funding:** Pharmaceutical Company Support - Relypsia, Inc.

**SA-PO0925**

Best EKG Criteria for Hyperkalemia in Chronic Hemodialysis Patients

**Background:** To the date effects of hyperkalemia(HK) on the EKG of chronic hemodialysis(CHD) patients(pts) is inconsistent. We studied the EKGs of 128 consecutive CHD pts with clotted grafts or fistulas. EKGs from 46 HK pts > 5.5 mEq/L were compared to 82 pts with normal potassium (NK) levels < 5.5 mEq/L. Pts with RBBB or LBBB or cardiac events within 3 months were already excluded. There were no differences between NK and HK pts for dialysis duration, causes for ESRD, cardiac disease or serum levels of Na, Ca, HCO3, or phosphorus.

**Methods:** EKG analysis included: the height & width of the P waves, the T waves in V4 & the T waves in Lead 2, the time intervals of PR, QRS, QTc, PR/QT, PR/QTc, & slopes of ascending & descending T waves in Lead 2 & V4. For the first time ever in HK CHD pts, the EKG measurements in 32 NK pts with complete data were compared to their NK EKGs obtained 3 to 6 months from the HK EKG

**Results:** Univariate stats between the 46 HK & 82 NK pts showed 4 differences in mean values: V4 T wave height 4.0 vs 2.9 mm, Lead 2 T wave height 2.7 vs 2.0 mm, & the V4 T wave ascending (0.3 vs 0.2) and descending slopes (1.6 vs 0.3). Multivariate analysis for all clinical & EKG findings between HK & NK pts found only the increased height of the T wave in V4 was significant, p<0.05. In contrast, the EKG analysis of the HK pts to their NK EKGs revealed more differences: higher T wave height in V4, 5.0 vs 3.7 mm, higher T wave height in Lead 2, 4.0 vs 2.7 mm, shorter width of T wave in V4, 2.4 vs 4.1 ms or Lead 2, 2.1 vs 4.1 ms , longer PR 188 vs 167 ms , & steeper slopes in the T waves in Lead 2 and V4. Regression analysis of the change in potassium from NK to HK to each EKG measurement showed that the only significant correlation was the width of T wave in V4, r = 0.33, p<0.05. In these HK CHD pts T wave trending in V4 was now present in 56%.

**Conclusions:** We conclude: 1) Comparison of a NK EKG to a HK EKG in CHD pts significantly helps to confirm HK EKG changes in CHD pts. 2) A shortened width and an increased height of the T wave in V4 are the most important HK EKG changes in CHD pts.

**SA-PO0926**

Sodium Polystyrene Sulfonate for the Treatment of Mild Hyperkalemia in Chronic Kidney Disease: A Randomized Clinical Trial

**Background:** Hyperkalemia affects up to 10% of patients with chronic kidney disease (CKD). Sodium polystyrene sulfonate (SPS) has long been prescribed for this condition even though evidence is lacking on its efficacy for the treatment of mild hyperkalemia (5.0 to 5.9 mmol/L) in pre-dialysis outpatients. We randomly assigned 33 patients on stable medication to receive either SPS or placebo 30g orally once a day for 7 days. Patients had to be on stable medication to be eligible for the trial.

**Results:** SPS is superior to placebo in the treatment of mild hyperkalemia over several days.

**Methods:** The aim of this double-blind, randomized trial was to evaluate the efficacy of SPS in the treatment of mild hyperkalemia (5.0 to 5.9 mmol/L) in pre-dialysis outpatients. We randomly assigned 33 patients on stable medication to either receive SPS or placebo orally once a day for 7 days. Patients had to be on stable medication to be eligible for the trial. The primary outcome was the comparison between study groups of the mean difference of serum potassium levels between the day following the last dose of treatment and baseline.

**Results:** The mean duration of treatment was 6.9 days. SPS was superior to placebo in the reduction of serum potassium levels (mean difference between groups of -1.04 mmol/L; 95%CI: -1.37 to -0.71). A higher proportion of patients in the SPS group tended to attain normokalemia (defined as a serum potassium level of at least 3.5 mmol/L and less than 5.0 mmol/L) at the end of their treatment compared to the placebo group (73% vs 38%, P=0.07). Patients in the group treated with SPS had an increase in hyperkalemia, hypocalcemia, constipation and nausea compared to the control group.

**Conclusions:** SPS is superior to placebo in the treatment of mild hyperkalemia over seven days in CKD patients. Its use was generally well tolerated in our study population, but does require monitoring of gastrointestinal side effects and electrolytic disorders.
Conclusions: Patients with SIRS and hypoMg (<1.5 mg/dL) at the time of admission had increased risk of developing septic shock during hospitalization.

SA-PO929
Risk Factors for Calcium-Alkali Syndrome in Post-Surgical Hypoparathyroidism
Sayaka Kuroya, Masahiko Yazawa, Naoto Tominaga, Kalyani Perumal, Masanori Abe,

Background: Post-surgical hypoparathyroidism is a common complication of total thyroidectomy. Patients complicated by permanent hypoparathyroidism often require either both calcium or vitamin D supplement therapy to maintain serum calcium levels, and long-term therapy can lead to calcium-alkali syndrome (CAS). We examined the incidence rate, magnitude, and risk factors of CAS in patients being treated for post-surgical hypoparathyroidism.

Methods: We retrospectively observed 27 patients with neck tumors who had undergone total thyroidectomy with total parathyroidectomy without autotransplantation between January 2010 and October 2013 at St. Marianna University Hospital. All patients received calcium lactate and alfalcacidol. Medical records were reviewed for historical, clinical, laboratory, and imaging data. Definitions were as follows: hypercalcemia, corrected serum calcium ([cCa] >10.0 mg/dL); acute kidney disease (AKD), either or both >50% increase in serum creatinine (sCr) or >35% decrease in estimated glomerular filtration rate (eGFR); and metabolic alkalosis, difference in serum sodium (Na+) and serum chloride (Cl–) >38. Data were expressed as mean ± standard deviation (SD). For statistical analysis, the paired t-test, Student’s t-test, and chi-square test were used to compare two matched variables.

Results: Average duration between surgery and reaching peak cCa level was 392.7 ± 403.8 days, with levels peaking at 11.1 ± 0.2876 (P = 0.0033; P < 0.01). Nineteen patients (70.3%) had hypercalcemia, 9 (33.3%) had AKD, and 7 (36.9%) had metabolic alkalosis. The incidence rate was 0.2876; P = 0.244) was no obvious correlation between the body temperature rise. On the other hand, respectively in the TP concentration and the ALB concentration of 0.5 mg/dL. It was found correlated with body temperature rise after intravenous injection. In particular, a strong correlation between the ALB concentration and the increase in body temperature was observed (r = 0.8033; P < 0.01).

Conclusions: The correlation of body temperature rise after intravenous injection and IL-6 is weak, while the correlation between the corrected ALB concentration and the body temperature rise was very strong. From these results, we considered that any substance bound to the ALB or ALB itself are associated with elevated body temperature.
SA-PO933
Effect of NBCe1 Deletion on Renal Ammonia Metabolism
J. David Weiner,1,2 Mary E. Handlogten,1 Gunars Osis,1 Hyun-Wook Lee,1 Jill W. Verlander.1 1Renal Div, Univ of Florida, Gainesville, FL; 2Nephropathy Section, NF/SVGH, Gainesville, FL.

Background: Metabolic acidosis typically increases renal ammonia excretion, but people with proximal renal tubular acidosis (pRTA), despite the associated metabolic acidosis, do not have increased ammonia excretion. Genetic forms of human pRTA typically involve the proximal tubule bicarbonate transporter, NBCe1. Based on these observations, we postulated that NBCe1 has a role in renal ammonia metabolism that is in addition to its role in bicarbonate reabsorption.

Methods: We used previously reported mice with NBCe1 deletion. Because <~5% mice have 100% mortality by d10-21, we studied mice at d8. Wild-type (WT), heterozygous (Het) and homozygous knock-out (KO) mice were generated by breeding HET male and female mice.

Results: Serum HCO3 was 26.4±1.0 mEq/L in WT, 19.8±1.9 in HET, and 10.3±0.6 mEq/L in KO mice (P<0.05). Thus, NBCe1 deletion causes metabolic acidosis at d8. Although acidosis normally increases ammonia excretion, NBCe1 deletion decreased spontaneous ammonia excretion: 275±44, 212±11 and 94±69 mmol/g creatinine in WT, HET and KO mice, respectively (P<0.01). Serum Na and K were unchanged. Urine pH was 5.3±0.2, 4.8±0.1 and 4.2±0.1 in WT, HET and KO mice, respectively (P<0.01), indicating intact urine acidification and no ongoing HCO3 loss. NBCe1 deletion did not alter urine osmolality significantly (WT, 596±74; HET, 693±51; and, KO, 726±34 mOsm/kg H2O; P=NS), which, in combination with intact urine acidification, suggests intact collecting duct function. The regulation of multiple proteins involved in ammonia metabolism was atypical of acidosis. NBCe1 deletion decreased expression of PDG and PEPCk and increased expression of the ammonia recycling enzyme, glutamine synthetase. This pattern is the exact opposite of that expected with acidosis. Expression of the TAL ammonia transporter, NKCC2, and the collecting duct ammonia transporters, RHbg and RHcg, was unchanged.

Conclusions: We conclude: 1) NBCe1 deletion significantly alters proximal tubule ammonia metabolism, leading to decreased urinary ammonia excretion; and, 2) NBCe1, in addition to its role in HCO3 transport, may have an important role in ammonia metabolism.

Funding: NIDDK Support, Veterans Administration Support

SA-PO934
Assessing Urine Ammonium Concentration by Urine Osmolal Gap in Chronic Kidney Disease
Takuya Fujimaru, Yasuhiro Komatsu, Takuya Shuo. Nephrology, St. Luke’s International Hospital, Tokyo, Japan.

Background: Acidemia is one of the risk factor for end stage kidney disease and mortality for patients with chronic kidney disease (CKD). Although ammonium is the crucial component of renal acid excretion, measurement of urine ammonium concentration (NH4) is not routinely available in most hospital laboratories. To estimate NH4, urine osmolal gap (UOG = urine osmolality - [2(Na + K) + urea + glucose]) is calculated and the formula (NH4 = UOG/2) has traditionally been used. However, studies evaluating it in CKD patients are scarce. The present study aims to assess the relationship between NH4 and UOG in CKD patients.

Methods: Spot urine samples were collected from 36 patients with CKD in our hospital (24 males, age 41-96 years, serum creatinine 0.9-12.4 mg/dl). We measured urine pH, Na, K, Cl, urea, glucose and NH4. NH4 was measured by colorimetric assay (modified Fujii-Okuda method). The Bland-Altman plot was used to evaluate the agreement between NH4 and UOG/2.

Results: NH4 ranged from 0.3-45.8 mmol/l (median, 6.2 mmol/l). UOG/2 correlated positively and significantly with NH4 (r=0.92, p<0.0001).

Conclusions: UOG is an accurate method to estimate NH4 in CKD patients and can be used to assess urinary acidification ability in CKD patients.

SA-PO935
Vascular H+-ATPase Regulation by 14-3-3 Proteins
M. Soline Bourgeois, Carsten A. Wagner. Inst of Physiology, Univ of Zurich, Zurich, Switzerland.

Background: The vascular proton-ATPase (V-ATPase) is highly expressed at the apical membrane of type A intercalated cells (ICs) in the collecting duct. This pump mediates proton transport across a membrane often against a gradient. Defects in V-ATPase function can lead to renal tubular acidosis. In kidney cells we showed that the metabolic sensor AMP-activated protein kinase (AMPK) phosphorylates the V-ATPase A subunit at Ser-384. AMPK regulates some transport proteins by inhibiting their function and promoting their ubiquitination and degradation. These mechanisms are likely important for inhibition of membrane transport during cellular metabolic stress. We noticed that Ser-384 exists within a 14–3-3 binding motif. Dimeric 14–3-3 bind to phosphorylated sites on target proteins and modulate protein function. We hypothesized that phosphorylation by AMPK and an additional kinase modulate A subunit binding to 14-3-3 proteins and A subunit ubiquitination.

Methods: We used transient transfections of V-ATPase A subunit mutants in Clone C ICs, followed by immunoprecipitation and immunoblotting.

Results: We have preliminary evidence that phosphorylation at Ser-384 and a new “Site III” in the V-ATPase A subunit are required for 14-3-3 binding. For example, 14-3-3 binding to the A subunit increased when we used a phosphomimetic mutant (Ser-to-Asp) at Site III compared to the WT sequence at that site, and this binding was not dependent on the presence of the AMPK A subunit partner AICAR. Furthermore, AICAR increased A subunit ubiquitination as compared to untreated controls.

Conclusions: We propose that V-ATPase A subunit binding to 14-3-3-3s promotes its ubiquitination and degradation. These pathways are downstream of phosphorylation of the subunit at Ser-384 by AMPK and at Site III by another unidentified kinase. Our results link downregulation of the V-ATPase to metabolic depletion in kidney epithelial cells.

Funding: NIDDK Support

SA-PO936
Albuminuria Enhances Renal NHE3 Expression via the Activation of Mitochondrial Oxidative Stress/RAS Axis
Soline Bourgeois,1,2 Yibo Zhang,1 Guixia Ding,1 Songming Huang,1 Zhanjun Jia,1,2 Nephrology Dept, Nanjing Children Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China; 2Nanjing Key Laboratory of Pediatrics.

Background: Renal sodium–hydrogen exchanger 3 (NHE3) plays a known role in the reabsorption of bicarbonate and fluid. As a result, NHE3 is thought to be important in acid base balance and vascular volume homeostasis. The present study was to investigate the role albuminuria in regulating renal NHE3 expression as well as the underlying mechanisms.

Methods: An albumin overload mouse model was established by i.p injection of albumin. The mouse kidney tissues and kidney biopsy specimens from proteinuric patients were analyzed.

Results: Following 12-day albumin overload, we found that albuminuria increased NHE3 expression by 2-fold in mouse kidneys determined by Western blotting and qRT-PCR. Considering the known role of renin-angiotensin system (RAS) in modulating renal sodium handling, we examined key components of RAS and found a striking elevation of angiotensinogen (AGT, +2.1 folds), angiotensin converting enzyme (ACE, +3.3 folds), and urinary angiotensin II (Ang II, +70%) output determined by Western blotting or ELISA. In proteinuric patients, we detected a 1.9-fold upregulation of NHE3 and 3-fold increase of ACE by immunohistochemistry in line with a 2-fold increment of urinary Ang II excretion. To further investigate the role of RAS in upregulating NHE3, we performed primary cultures of renal tubular cells and observed that albumin directly enhanced NHE3 accompanied by stimulated AGT/ACE/Ang II cascade, which was entirely abolished by ACE inhibitor captopril, indicating a key role of RAS in mediating albuminuria effect on NHE3 upregulation. More interestingly, albumin load significantly induced mitochondrial oxidative stress evidenced by reduced mitochondrial superoxide dismutase (SOD2, -60%) and elevated ROS production. Notably, a SOD2 mimic (MnTBAP) completely normalized NHE3 upregulation and activated AGT/ACE/Ang II cascade in mice with albumin overload.

Conclusions: These results suggest that albuminuria is of vital importance in upregulating renal NHE3 expression in proteinuric patients via mitochondrial oxidative stress-initiated stimulation of AGT/ACE/Ang II cascade.

Funding: Government Support - Non-U.S.

SA-PO937
ATP6v1b1 Haploinsufficiency Lead to a Mild Incomplete Renal Tubular Acidosis (RTA) in Mice
Soline Bourgeois, Carsten A. Wagner. Inst of Physiology, Univ of Zurich, Zurich, Switzerland.

Background: Mutations in ATP6v1b1 gene in man is considered as an autosomal recessive disease and lead to distal RTA by dysfunction of the B1 subunit of H-ATPase in type A intercalated cells. In some transgenic models in mouse, renal failure and also distal RTA and a decrease in ammonium and alkaline urine pH.

Methods: Here we investigated on littermate mice whether ATP6v1b1+/- mice also develop acid-base disturbances during an acute and chronic acid challenge performed by 0.2 M HCl added to powdered standard food.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: ATP6v1b1+/+ (WT) and +/- (HET) mice exhibited no difference in their blood and urine parameters under baseline conditions. During the acid challenge, while ATP6v1b1+/+ mice (KO) developed alkaline pH and low ammoniuria with hypercalcemia, HET mice showed no difference in their urine data over the whole acid load compared to WT mice. However, even though, HET mice did not exhibit low blood pH, as KO mice, they had a lower bicarbonatemia, higher chloride, and lower pCO2 compared to WT mice at the end of the acid challenge. Both KO and HET mice drank more than WT mice over the acid load with a tendency to urinate more. After 4 days of acid load, subcellular localization of the a4 and B2 subunits of H-ATPase were not different within the 3 strains of mice and WT and HET mice exhibited the same localization of B1 subunit. However, western blot analysis of B1 and B2 expression in renal membrane fractions revealed a 2-fold decrease of B1 and B2 protein expression in HET mice compared to WT mice and no difference in the expression of B2 protein in KO mice compared to WT mice while B1 protein was totally absent from KO kidneys.

Conclusions: In conclusion, 1) HET mice developed a mild incomplete RTA during an acid challenge, undetectable regarding urine parameters. The RTA is partly compensated by the respiration and an increase in water consumption. 2) B2 subunit does not compensate for the decrease in B1 expression both in HET kidney tissues and seems to be inhibited by acid load.

Funding: Government Support - Non-U.S.

SA-PO938
Bedside Rule (pCO2=HCO3+15) Is Reliable in Predicting Respiratory Response in Metabolic Acidosis with Bicarbonate Levels of More Than 7 meq/L
Mohammad Kazem Fallahzadeh, Michael Emmett. Dept of Internal Medicine, Baylor Univ Medical Center, Dallas, TX.

Background: There is controversy about the reliability of the bedside rule (pCO2=HCO3+15) in prediction of respiratory response in metabolic acidosis. The aim of our study was to compare the accuracy of the bedside rule with Winter’s equation in predicting respiratory response in metabolic acidosis.

Methods: We extracted the measured bicarbonate and pCO2 levels of 382 patients with metabolic acidosis from the previously published articles evaluating the respiratory response to metabolic acidosis. We calculated the predicted levels of CO2 by bedside rule and Winter’s equation for each patient. Then we compared the accuracy of these formulas in predicting the respiratory response to metabolic acidosis.

Results: As demonstrated in the figure 1, the values calculated by bedside equation (pCO2=HCO3+15) appear to be a reliable predictor of respiratory response in HCO3 levels of more than 7 meq/L, as compared with the line of best fit and Winter’s equation.

Conclusions: Our results show that bedside rule (pCO2=HCO3+15) is reliable in predicting respiratory response in metabolic acidosis with HCO3 levels of more than 7 meq/L.

SA-PO939
TSS-Seq Analysis of Low pH-Induced Gene Transcripts in the Intercalated Cells of the Collecting Ducts
Yukihiro Izumi, Koji Eguchi, Kazem Kazem, Terumasa Kumamoto, Koji Eguchi, 1  Terumasa Kumamoto, 1  Koji Eguchi, 1  Michael Emmett.

Background: Metabolic acidosis is caused by acute and chronic kidney disease due to the decrease of acid excretion in the intercalated cells of the collecting duct in the kidney. Although the effect of acidosis on renal function has been examined in vivo, direct effect of low pH on the intercalated cells has not been investigated.

Methods: We employed Transcription Start Site-sequencing (TSS-Seq) to provide low pH-2.47s differentially expressed transcripts in an intercalated cell line (IN-IC cells). Two biological replicates were used for the analysis. Cells were grown in a FBS-free DMEM/F12 overnight and incubated in an isotonic solution for 24h in which pH was adjusted either to 7.4 or 7.0, then total RNA was extracted. cDNA library for CAGE (Cap Analysis Gene Expression) was constructed and deep sequencing was performed. Reads were identified. 261 transcripts were upregulated and 17 were downregulated. Among them, 225 upregulated and 13 downregulated transcripts were corresponded to known protein products. GO analysis of Biological Processes and Molecular Functions showed 9 clusters of the GO terms with high enrichment score (>1.5) in the expressed transcripts were identified. The software was used to map TSS-Seq reads. ReCLU was used to identify differentially expressed transcripts. Gene Ontology (GO) analysis was carried out using the Database for Annotation, Visualization and Integrated Discovery (DAVID).

Results: Deep sequencing of low pH-exposed IN-IC cells was carried out. The reads were mapped to the genome and gene loci were identified. The number of valid reads was 261, corresponding to 150 distinct transcripts. The GO enrichment analysis of the upregulated genes showed that they were involved in the regulation of transcription, cell cycle, and enzyme-linked receptor protein signaling pathway. The downregulated transcripts included Jak2, Pten, and Gsk3a, that are involved in renal fibrosis and urine concentration mechanism.

Conclusions: The results suggest that metabolic acidosis could regulate the function of intercalated cells and further exacerbate the renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO940
Narrowing the Gap Between the Anion Gap and the Strong Ion Gap
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Background: Despite its importance in understanding acid-base pathophysiology, many physicians do not understand the concept of the strong anion gap. The core of the Stewart acid-base approach is the “strong ion gap” (SIG). The concept of SIG is similar to the AG, but the main difference is that Stewart uses more strong ions and the contribution of albumin and phosphate are adjusted for the pH. Because SIG gives a more precise picture of the acid-base status than the AG, one may postulate that it provides a more accurate analysis of acid-base disturbances. The exact differences, however, are not established. This paper will give insight into the difference between the anion gap and the strong anion gap and provide an adjusted formula for the anion gap to replace the need for the strong gap.

Methods: The change of the strong ion gap (SIG) and the albumin-corrected anion gap (AG) were calculated at a wide range of albumin, phosphate and pH levels.

Results: At a low albumin level of 1 to 3 g/dl and decreased pH from 6.9 to 7.3, the contribution difference of albumin in AG, and SIG will be maximally <0.97 to 0.51 meq/L. In normal human plasma (pH up to 7.6) and hypocalciuricemic (1 to 3 g/dl), the AG differs less than 2 meq/L with SIG. There is a linear relationship of the serum phosphate and the ionic contribution of SIG: at a pH of 6.9, the phosphateAg is 1.66 times higher and at a pH of 7.6, 1.86 higher. In metabolic alkalosis and moderate hyperphosphatemia, the ionic contribution to the anion gap will increase, but less than 1 meq/L.

Conclusions: SIG and AG are almost identical across a wide range of values, particularly when albumin and phosphate levels are low. The pH adjusted serum phosphate level in the SIG is about 1.76 higher, with a confidence interval of +0.5 mmol/L. The anion gap will be more precise and incorporate the major components of the SIG when using the equation: [Na+] - [CT] - [HCO3-] - 2.5 [albumin, in g/dl] – 1.76 [phosphate], with an arbitrarily set reference range of 1+5 meq/L.

SA-PO941
V-ATPase in Luminal Membrane of Renal Proximal Tubule Requires B2 Subunit and CLC-5 for Its Full Functional Activity
Nobuhiko Sato,1 Motonobu Nakamura,1 Atsushi Suzuki,1 Masashi Suzuki,1 George Seki,2 Shoko Horita,1 Nephrology, The Univ of Tokyo Hospital, Tokyo, Japan; 2Tiazu City Hospital, Shizuoka, Japan.

Background: Using an isolated rat proximal tubule (PT) primary culture system, we have previously shown that the activity of basolateral Na/H+ cotransporter (NBCc1) was preserved for 36 hours. Furthermore, gene silencing with siRNA enabled us to identify the signaling pathways involved in insulin-mediated NBCc1 stimulation (Nakamura M, Kidney Int, 2015). However, it remains unknown whether this technique is applicable to analysis of PT luminal transporters.

Methods: Freshly isolated mouse PT was attached to a glass coverslip with Cell-Tak glue and the lumen was exposed with a broken glass capillary. BCECF was used to measure intracellular pH (pHi). While the cariporide-insensitive luminal NHE activity was determined by the rates of pH decrease in response to Na removal, the bath-luminal-sensitive V-ATPase activity Na-dependent NHE activity was measured. The uncoupler 2,4-dinitrophenol (DNP) was added to the PT cultures to separate the Na-dependent from Na-independent NHE activity.

Results: The luminal NHE activity was at least partially preserved in isolated PT primary cultures (0.09+/−0.08 vs 0.89+/−0.08 pmol/min/mg protein). V-ATPase activity determined by the rates of pHi decrease in Na-dependent Na-independent NHE activity was also confirmed in the presence of Na-free solution. The experiments were also performed after PTs were cultured overnight in the presence of siRNA against V-ATPase B2 subunit or CLC-5.

Conclusions: The luminal NHE activity was at least partially preserved in isolated PT primary cultures. The mechanism behind this preservation is not clear, but it could be due to the expression of basolateral NBCc1 and CLC-5. V-ATPase activity was preserved for 36 hours. Furthermore, gene silencing with siRNA enabled us to identify the signaling pathways involved in insulin-mediated NBCc1 stimulation (Nakamura M, Kidney Int, 2015). However, it remains unknown whether this technique is applicable to analysis of PT luminal transporters.

Funding: N. Sato (PhD course) was supported by a Grant-in-Aid for JSPS Research Fellowships for Young Scientists (19J20420).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
The Mechanistic Target of Rapamycin Regulates Solute Transport in Renal Tubules Nasir A. Shah, Davide Pietro Cina, Tuncer Onay, Vera Eremina, Robert A. Fenton, Timo Rieg, Sharon L. Barone, Kamyar A. Zahedi, Manoocher Soleimani, Thampi George, David W. Basolateral Na+/H+ Exchange Medullary Thick Ascending Limb (MTAL) Through Receptor for Advanced by inhibition of Rho. Addition of a direct Rho activator reduced basal HCO3− transporters in the renal tubular epithelium. The RAGE-Rho-ROCK1 pathway is driven, tubule-specific Mtor knockout mouse (Mtor−/−). Results: Loss of Mtor in the renal tubular epithelium resulted in increased 24-hour urine volume, diminished urine osmolality, and renal failure. Despite elevated 24-hour urinary albumin, Ca2+, and Mg2+ Mtor−/− mice were both hypercalcemic and hyperglycemic. Histologically, Mtor−/− mice exhibited generalized tubular atrophy with focal cystic dilations of the distal and cortical collecting tubules, and interstitial fibrosis. Immunohistochemistry showed decreased expression of aquaporin-2 (Aqp2), Calbindin D 28k (Cbdl), and the sodium-potassium-chloride cotransporter (Ncc2). Increased expression of the transient receptor potential cation channel subfamily V member 5 (Trpv5) was also noted. Conclusions: Taken together, our results suggest that Mtor is a key player in maintaining electrolyte balance by modifying the expression, and function of solute transporters in the renal tubular epithelium.

High Mobility Group Box 1 (HMGB1) Inhibits HCO3− Absorption in Medullary Thick Ascending Limb (MTAL) Through Receptor for Advanced Glycation End Product (RAGE)-Rho–ROCK-Mediated Inhibition of Basolateral Na+/H+ Exchange. Bruce A. Watts, Thampi George, David W. Good. Univ TX Med Branch, Galveston, TX.

Background: HMGB1 is a damage-associated molecule that is released extracellularly in response to infection or injury and plays a role in mediating kidney dysfunction in sepsis and sterile inflammatory disorders. Recently we showed that basolateral HMGB1 inhibits HCO3− absorption in perfused rat MTALs through a RAGE-dependent pathway additive to TLR4-ERK-mediated inhibition by LPS. Here we examined signaling and transport mechanisms involved in inhibition by HMGB1.

Results: Inhibition of HCO3− absorption by HMGB1 was eliminated by the Rho-associated kinase (ROCK) inhibitor Y27632 and by a specific inhibitor of Rho, the direct activator of ROCK. HMGB1 increased ROCK1 activity in dissected inner stripe of outer medulla, a preparation that accurately reproduces changes in MTAL signaling proteins. Activation of ROCK1 by HMGB1 was eliminated by the RAGE antagonist FSP-ZM1 and by inhibition of Rho. Addition of a direct Rho activator reduced basal HCO3− absorption rate and prevented inhibition by HMGB1. The Rho and ROCK inhibitors had no effect on inhibition by bath LPS. The Rho-ROCK1 pathway regulates NHE3 and we have shown that inhibition of NHE1 decreases MTAL HCO3− absorption secondary through cytoskeleton-dependent inhibition of apical NHE3. Inhibition of HCO3− absorption by HMGB1 was eliminated by bath amiloride, 0 Na+ bath, and the F-actin stabilizer jasplakinolide, three maneuvers that selectively prevent inhibition of HCO3− absorption mediated through NHE1. Bath amiloride and jasplakinolide did not affect inhibition by bath LPS.

Conclusions: We conclude: 1) HMGB1 inhibits HCO3− absorption in the MTAL through a RAGE-Rho–ROCK1 pathway coupled to inhibition of NHE1; 2) this pathway functions in parallel with the bath LPS-ERK pathway to impair MTAL HCO3− absorption. Thus, during sepsis, endogenous damage-associated molecules and exogenous bacteria-associated molecules act directly and independently to inhibit MTAL HCO3− absorption through different receptor signaling and transport pathways. The RAGE-Rho–ROCK1 pathway is a potential target to attenuate sepsis-induced renal tubule dysfunction.


Background: Identification of networks interacting proteins is crucial for all levels of cellular function. The Slc26 family of anion transporters [Slc26a3 (DRA), Slc26a5 (proxim.), Slc26a6 (PAT-1), and Slc26a9] form multi-protein complexes with cytoskeleton, anchoring proteins, PDZ adaptor proteins, CTR and/or protein kinases, which impart regulatory signals on these isoforms. No information is available on proteins that interact with pendrin (Slc26a4).

Methods: A yeast two hybrid system was employed to screen a mouse kidney cDNA library with a pendrin C-terminal fragment as bait. A total of 6 × 106 interacting clones were identified, out of which 14 clones were confirmed to be positive when screened for β-gal expression. Plasmids from these clones were purified and their interaction with pendrin was confirmed.

Results: Our experiments identified IQGAP-1 as a pendrin C-terminus binding partner. IQGAP-1 is a scaffolding protein that binds and/or stabilizes ezrin, CDC42 and RAC1, and interacts with cytoskeletal and cell adhesion molecules. In the kidney, IQGAP-1 is strongly expressed in the DCT, CNT, CCD and podocytes. IQGAP-1 has also been shown to control tight junction formation through recruitment of claudin. Our results indicate that IQGAP-1 co-localizes with pendrin on the apical membrane of B-intercalated cells. IQGAP-1 is also detected on the basolateral membrane of A-intercalated cells in CCD. Functional studies in HEK293 cells demonstrated that the co-transfection of IQGAP-1 and pendrin increased pendrin-mediated CI/HCO3− exchange activity by more than 60%. Confocal microscopy showed more abundant plasma membrane expression of pendrin in the presence of IQGAP-1.

Conclusions: These studies demonstrate the interaction of IQGAP-1 and pendrin in B-intercalated cells, as well as the stimulatory role of IQGAP-1 on pendrin activity. We propose that pendrin interaction with IQGAP-1 is important in the regulation of CED function and physiology, and that disruption of this interaction contributes to altered pendrin trafficking and/or activity in pathophysiologic states.

Regulation of Rhcg by Aldosterone in Intercalated Cells of the Collecting Ducts Koji Eguchi, Yuichiro Izumi, Terumasa Nakagawa, Yushi Nakayama, Hikedi Inoue, Yutaka Kakizoe, Takashige Kuwabara, Masashi Mukoyama. Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Acid-base balance is regulated by aldosterone which stimulates acid secretion in the intercalated cells of the collecting ducts of the kidney. Rhesus blood group C glycoprotein (Rhcg) is an ammonia transporter which cooperates with H^+/ATPase to secrete H^+ in the intercalated cells. In vivo experiments have shown that metabolic acidosis and hypokalemia, that change plasma aldosterone level, increases and decreases the expression of Rhcg, respectively. Direct effect of aldosterone on the regulation of Rhcg has not been examined.

Methods: We examined the effect of aldosterone on the regulation of Rhcg. Membrane fraction of the whole kidney was extracted from mice that were continuously administered aldosterone (20μg body/day) for a week. To further examine the effect of aldosterone on the regulation of Rhcg in the intercalated cells, mRNA, whole cell protein, and membrane fraction were extracted from IN-IC cells (a rat intercalated cell line) after the treatment with aldosterone (10^-4 M) for 24h. The Rhcg mRNA and protein expressions were measured by real-time PCR and Western blotting, respectively. The expression of serum and glucocorticoid-regulated kinase 1 (Sgk1) mRNA was also measured in IN-IC cells.

Results: Administration of aldosterone increased the expression of Rhcg protein in membrane fraction of the whole kidney. In IN-IC cells the expressions of Rhcg and Sgk1 mRNA were 1.3- and 3.2-fold greater, respectively, in cells treated with aldosterone (10^-4 M) than in cells with vehicle. The expression of Rhcg protein in whole cell extract was not changed by the treatment with aldosterone. However, the expression of Rhcg protein in membrane fraction was 3.2-fold greater in cells treated with aldosterone than in cells with vehicle.

Conclusions: The results suggest that aldosterone regulates membrane accumulation of Rhcg possibly through the activation of Sgk1.
Impact of Hypothermic Machine Perfusion on Outcomes following Kidney Transplantation

**Background:** Patient and allograft outcomes following deceased donor kidney transplantation (DDKT) are thought to be influenced by the intrinsic quality of the organ at procurement and any superimposed subsequent injury that occurs during cold preservation (CP). Hypothermic machine perfusion (HMP) is used in an attempt to decrease injury from CP especially for organs that have extended periods of cold ischemia. We analyzed the impact of complete, partial or no HMP use during CP on patient and graft survival following DDKT.

**Methods:** We identified 75,660 first-time adult renal transplant recipients, who received a DD kidney from 2000-2011 in SRTR. Pearson’s chi-square tests of independence and Kruskal-Wallis tests were performed to test for association between HMP and mortality, graft failure, and delayed graft function (DGF). Cox analyses, adjusting for donor factors (age, gender, creatinine, cause of death), recipient factors (age, dialysis duration, PRA, HLA mismatch), CP time, and specified effect measure modifiers, were performed to estimate the hazard of either graft failure, or DGF occurring given HMP.

**Results:** On unadjusted analyses, compared to no HMP use, kidneys that received HMP performed better (OR=0.82, p<0.001 & OR=0.77, p<0.0001) but more likely to experience allograft failure (HR=1.19, p<0.001 & HR=1.20, p<0.0001, figure 1). On multivariable analyses, the use of HMP was associated with a lower incidence of DGF(OR=0.70, p<0.001 & OR=0.59, p<0.0001) but continued to be associated with a higher risk of allograft failure even after adjusting for CIT and the lower DGF (HR=1.11, p=0.023 & HR=1.26, p=0.002).

**Conclusions:** HMP improves short term outcomes by lowering rates of DGF but is associated with reduced long-term allograft survival.

**SA-PO949**
Impact of Remote Ischaemic Preconditioning (RIPC) on the Inflammatory Response following Live Donor Kidney Transplantation
Kristin Vibeke Veyoug, Madhur P. Motwani, Jennifer Nicholas, Raymond Macallister. Weisse Kidney Unit, Portsmouth Hospitals NHS Trust, United Kingdom; UCL Centre for Clinical Pharmacology & Therapeutics, Unv College London, United Kingdom; Clinical Trials Unit, London School of Hygiene and Tropical Medicine, United Kingdom.

**Background:** Ischaemia reperfusion injury (IR) at transplantation contributes to organ damage that limits allograft longevity. Animal studies have demonstrated a reduction in circulating proinflammatory cytokines following RIPC, which may contribute to tissue protective effects. REPAIR demonstrated a trend towards improved live donor kidney function following RIPC. We investigated the effects of RIPC on serum and urinary cytokines in this study.

**Methods:** 406 adult live donor/patient pairs were recruited. Pairs were randomised using a factorial design to either: sham RIPC, early RIPC (immediately pre-surgery), late RIPC (24 hours pre-surgery) or dual RIPC. Donor and recipient received the same interventions (active or sham RIPC). Serum from donor and recipient and urine from recipients were analysed at baseline and on day 2 for pro-inflammatory cytokines IL-1β, IL-6, IFN-γ and TNFα, using multiplex ELISA. All analyses were conducted using linear regression adjusted for baseline (pre-treatment) values of the cytokine and indicator variables for early and late treatment group. Cytokine values were log transformed before analysis to account for skewed distribution.

**Results:** There was no difference in the expression of serum cytokines in donor serum or recipient serum and urinary protein baseline pre-surgery and day 2 post surgery.

**Conclusions:**
SA-PO952

Low Expression of the Messenger RNA TLRs 2-4,9 from Peripheral Blood Mononuclear Cells of the Kidney Recipients May Indicate Previous Delayed Graft Function


**Background:** The Toll-like receptors (TLR) 2-4,9 are engaged in the pathogenesis of acute renal injury. Earlier studies demonstrated that 24 hrs. after transplantation (KT), the expression of the messenger RNA (mRNA) TLR4 of peripheral blood mononuclear cells (PBMC) from patients (pts) with delayed graft function (DGF+) was lower than in recipients of kidneys without DGF (DGF-). The aim of study was to examine whether the reduced expression of TLR2,4-9 mRNA is a more permanent phenomenon associated with DGF.

**Methods:** Each of the 151 KT pts was more than 1 month after KT (from 1 to 128 months). Within this group: in 117 pts blood sample was taken for more than 3 months after KT, 45 pts experienced DGF, 13 DGF+ pts was HBcAb positive (DGF+HBc+). Control group (Con.) included 38 healthy volunteers. TLR-2,4-9 mRNA expression (expr.) from PBMC was assessed by polymerase chain reaction (real-time PCR) and analyzed in terms of DGF and clinical course.

**Results:**
- KTG+ pts had generally lower TLR2,4-9 mRNA expr. than KTG- pts (TLR2: p=0.06; TLR3: p=0.02; TLR4: p=0.07; TLR 9, p=0.027) TLR3 mRNA of DGF+HBc+ pts was: lower (p=0.046) than DGF+HBc, lower (p=0.013) than DGF-ATN- and lower (p=0.008) than Con. TLR9 mRNA of DGF+HBc+ was lower (p=0.002) than Con. In multiple regression analysis low expr. of TLR mRNA 2,4-9 was associated with the occurrence of DGF in the past.

**Conclusions:** Lower than typical expression of TLR 2-4,9 mRNA seems to be a permanent feature of peripheral blood mononuclear cells of the recipient of the transplanted kidney who experienced delayed graft function. Hepatitis B seems may be associated with additional decline of TLR3 and TLR9 mRNA expression. TLR3,4,9 mRNA expression could potentially be used as an indicator of the likelihood of delayed graft function.

**Funding:** Clinical Revenue Support

**SA-PO953**

**BB3, a Hepatocyte Growth Factor-Like Small Molecule, Improves Outcome in Kidney Transplant Recipients with Delayed Graft Function**

Jonathan Bromberg, 1 Matthew R. Weir, 2 A. Osama Gaber, 3 Matthew Cooper, 4 Mark Laflavi, 5 Barry Browne, 6 Bo Zhang, 7 Prakash Narayan, 8 Michael A. Yamin, 9 Izthak D. Goldberg, 7 Weizhong Cai. 7 Div of Transplant Surgery, Univ of Maryland School of Medicine, Baltimore, MD; 3 Div of Nephrology, Univ of Maryland School of Medicine, Baltimore, MD; 7 The Methodist Hospital, Houston, TX; 8 MedStar Georgetown Univ Hospital, Washington, DC; 7 Transplant Center at Erie County Medical Center, Buffalo, NY; 9 BMGC, San Diego, CA; 9 Anjion Biomedica Corp, Uniondale, NY.

**Background:** Duration of delayed graft function (DGF) portends poor short- and long-term renal function and graft survival. We studied the safety and efficacy of BB3, a small molecule with HGF-like activities, dosed starting 24 hr post-transplant (Tx) in patients with reduced urine output (UO) in a double-blind Phase 2 study.

**Methods:** Patients producing <50 cc urine/hr over 6-8 h post-Tx were randomized (2:1) to BB3 (2 mg/kg IV QD X 3 d) or placebo (PBO). An interim analysis was performed on 12 BB3- and 7 PBO-treated patients.

**Results:** BB3 was safe and well-tolerated. BB3 reduced the median time to produce 1.2L UO/24 hr from >28 d to 7.5 d, increased the % of patients reaching this UO within 28 d from 43% to 83%, increased cumulative UO (figure), decreased median duration of dialysis (figure), decreased % on-dialysis days during Days 7-28 (14.2% to 7.1%) and during Days 14-28 (10.9% to 3.6%), reduced median SCR, reduced BUN, and shortened median hospital stay (7 d to 5.5 d). BB3 reduced serum CRP and NGAL.

**Conclusions:** BB3 administered ~24 hours post-Tx significantly reduced severity of DGF in patients presenting with reduced UO. Confirmation of these results in a Phase 3 trial may translate to improved long-term outcome, decreased Tx costs, increased use of marginal organs, and a shorter waitlist.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Angion Biomedica Corp.
SA-PO954

DSA Monitoring and Treatment in Kidney Transplant Recipients
Monica Grafals,1 Alexander Gilbert,1 Olga A. Timofeeva.2

Background: The development of DSA monitoring is a new technique to detect antibodies in kidney transplant recipients. We previously showed that patients who developed de novo DSA (dnDSA) suffer a 35% graft loss. Because of this we have developed a protocol for treating patients who have developed dnDSA post kidney transplant.

Methods: Since the implementation of this treatment protocol on September 12, 2014, there have been 9 patients that have developed dnDSA after renal transplantation.

Results: Four of the patients that developed dnDSA were in the low risk category and in 3 of them the DSA has cleared. The 4th patient has a DSA against DP1 with an MFI of 1587 that has remained stable. All of these patients have a GFR>45 cc/min. Three patients were in the intermediate risk category. One of them has a creatinine of 3, BK viremia and he has a DSA against A1 with an MFI of 3150 which has been stable. Another patient in this group developed CMV viremia and his DSA became negative after treatment. The third patient just received treatment for DSA this past month and follow up DSA is not available at this time. Two patients were in the high risk category and both of them received treatment and their GFRs are >45 cc/min and their DSAs have become undetectable and weak respectively.

Conclusions: Since the development of dnDSA post kidney transplant is associated with worse graft outcomes, implementation of treatment protocols is necessary for kidney transplant patients. This preliminary data shows that treatment for dnDSA with this protocol seems to success fully treat the antibodies.

SA-PO955

On the Patterns of Early De Novo DSA Development in Kidney Transplant Recipients in the First 6 Months After Alemtuzumab Induction
Cheelesa Estrada, Yezina T Nigatu, Hecesuck Suh, Frank Darras, Mersema Abate, Edward P. Nord. Nephrology and Transplantation, Stony Brook Medicine, New York.

Background: The presence of de novo DSA (dnDSA) is associated with antibody mediated rejection and suboptimal graft outcomes. The incidence of dnDSA post renal transplantation varies according to immunosuppression protocols, screening, and detection methods, and ranges from 5-25%. A higher incidence of dnDSA after alemtuzumab (AL) has been observed. We sought to characterize the expression of early dnDSA development after AL induction in renal transplant recipients.

Methods: Consecutive kidney transplant recipients were screened for dnDSA from 7/1/14 to 4/30/15. DnDSA was detected by single antigen beads and luminex technology at months 1, 2, 3, and 6. Mean Fluorescent Intensity (mfi) >500 was considered high level. Acute ABMR and TG histology met Banff 2013 criteria. In this cohort, induction was with alemtuzumab and rapid steroid withdrawal, and maintenance immunosuppression was with tacrolimus and mycophenolate mofetil. Chi square analysis was used to assess the association between low and high levels of DSA and biopsy findings of antibody mediated injury.

Results: Fifty-three consecutive indication kidney transplant biopsies were performed from 7/1/14– 5/21/15. Of these 12 had evidence of ABMR (2 acute, 8 TG and 2 both). Six of the 8 patients with TG alone did not have DSA. At the time of biopsy, 12 class I (6 low and 6 high level) and 13 class II (3 low and 10 high level) were detected.

Conclusions: 1. The presence of high level class II DSA was significantly associated with the concurrent biopsy finding of antibody mediated injury. 2. Of greater significance, the presence of class I DSA or low level class II DSA did not correlate with pathologic findings.

SA-PO957

Characteristics of Kidney Transplant Candidates with and without Antibody against Angiotensin II Type 1 Receptor (AT1R-Ab)
Mary Carmelle Philogene, S.M. Bagnasco,2 Annette M. Jackson,1 Mary S. Leffell,1 Andrea A. Zachary.1

1Medicine, Johns Hopkins Univ, Baltimore, MD. 2Pathology, Johns Hopkins Univ, Baltimore, MD.

Background: In this study we sought to determine whether baseline characteristics of kidney transplant candidates when correlated with presence of AT1R-Ab are predictive of transplant outcomes.

Methods: 122 renal transplant recipients were tested for presence of AT1R-Ab using quantitative ELISA (CellTrend GmbH, Germany). Patient demographics were obtained from the hospital electronic record under an approved IRB.

Results: Patients were categorized according to AT1R-Ab levels: positive >17 Units/ml (30%); borderline 10-17 Units/ml (34%), negative <10 Units/ml (36%). There were fewer females (33% versus 61%, 55%) and African Americans (14% versus 24%, 16%) in the AT1R-Ab >17 Units/ml group compared to the other two groups. The presence of AT1R-Ab has been associated with development of hypertension and fibrosis; therefore, we examined AT1R-Ab among patients categorized by the following diseases: IgA nephropathy, glomerulonephritis, lupus nephritis, FSGS, and membranoproliferative glomerulonephritis. We found no correlation between these diseases and AT1R-Ab levels (38%, 29% and 30%, respectively; p=0.7). We also found no association with diagnosis of hypertension and AT1R-Ab levels (16%, 17%, 18%). The most significant difference between the three groups was a higher percentage of positive patients among those who received more than one kidney transplant (78%, 22%, 45%; p=0.001). Post transplantation, sixty-one patients were biopsied to investigate graft dysfunction. There were more patients in the borderline and positive AT1R-Ab groups who were evaluated for graft dysfunction compared to the negative group (>55%, 54% versus 34%) although this did not reach statistical significance.

Conclusions: The only pre-transplant characteristic linked to presence of AT1R-Ab in patients who are being evaluated for kidney transplantation is the incidence of previous transplant.

Funding: Clinical Revenue Support
Effect of B-Cell Activating Factor (BAFF) Inhibition (LY2127399; Tabalumab) on Highly Sensitized Patients with End Stage Renal Disease awaiting Transplantation
Nephrology, Univ of Texas Medical Branch, Galveston, TX; 1Transplant Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; 2Bio-Medicines, Eli Lilly and Company, Indianapolis, IN; 3Nephrology, Univ of Michigan Health System, Ann Arbor, MI.

Background: B cell activation factor (BAFF) is critical in B-cell maturation. Inhibition of BAFF represents an appealing target for desensitization of highly sensitized end stage kidney disease patients.

Methods: We conducted a Phase 2a, single-arm, open-label exploratory study investigating the effect of tabalumab (BAFF inhibitor) in ESRD patients with cPRAs >50%. The treatment period had a total duration of 24 weeks. Eighteen patients received tabalumab, at a dose of 240-mg subcutaneous (SC) at Week 0 followed by 120-mg SC at 4-week intervals for 5 more months. Patients were then followed for an additional 52 weeks. Blood samples were analyzed for HLA antibodies, BAFF levels, serum immunoglobulins, T and B cell subsets at specified time intervals during the treatment and follow-up periods. Pre and post treatment tonsil and bone marrow biopsies were also performed.

Results: Significant reductions in cPRAs were observed at week 16 (p=0.043) and at week 36 (p=0.004), however the absolute reductions were small (<5%). Overall factor effect at week 76 compared to baseline was significant (p=0.04). Mean BAFF levels increased during treatment, reflecting binding to tabalumab and decreased in the follow-up period remaining slightly above baseline at week 76. Expected changes in B cell subsets and reductions in immunoglobulins were observed. Two tabalumab-related serious adverse events occurred (pneumonia and worsening of peripheral neuropathy) while the most common other adverse events were injection-site pain and hypotension. Three patients received a matched donor cadaveric transplant during the study follow up.

Conclusions: The results resulted in statistically significant, but not clinically meaningful reduction in the cPRAs from baseline. Funding: Pharmaceutical Company Support - Eli Lilly

Behavior and Impact of Donor-Specific Antibodies Before and After Kidney Transplant

Background: Pre- and post-transplant DSA increases the risk for acute rejection, humoral rejection and graft loss. Every year a 5% of patients will develop DSA but other patients turn negative. It is unclear how the behavior of pre-transplant DSA under immunosuppression and their clinical impact. This study evaluate the relationship between de novo DSA and the outcome of kidney transplantation, and whether the development of these antibodies is related to pre-transplant DSA status.

Methods: Prospective cohort study. From Jan/2004-Dec/2014 a total of 519 kidney transplant were performed. For analysis we include 412 with DSA determination plus these antibodies is related to pre-transplant DSA status.

Results: From 412 patients, 58 patients (14.1%) had pre-transplant DSA. Patients with Pos/Pos or Pos/De Novo DSA had higher and earlier AR and AMR rate, followed by Neg/De Novo-Variable and Neg/De Novo, as you can see in the figure A) and B) respectively. For graft loss only those with Pos/De Novo was higher than Neg/Neg (Figure C). Interestingly, those who are Pos/Neg had similar outcomes than Neg/Neg.

Conclusions: Staying with the same DSA or developing De Novo-DSA after transplantation, regardless what the pretransplant condition was, were associated with development of AR, AMR, and graft loss.

Course of Anti-HLA Antibodies After Induction Therapy with Rituximab in Renal Transplantation
Luuk Hilbrands, Wil Allebes, Marij W. F. van den Hoogen, Irma Joosten, Marije C. Baas.

Background: Rituximab is used to desensitize highly sensitized patients awaiting kidney transplantation. T or B cell depleting agents are known to be associated with a delayed onset of anti-HLA Ab development.

Methods: We conducted a Phase 2a, single-arm, open-label exploratory study investigating the effect of rituximab in ESRD patients with cPRAs >50%. The treatment period had a total duration of 24 weeks. Eighteen patients received rituximab, at a dose of 375-mg subcutaneous (SC) at Week 0 followed by 375-mg SC at 4-week intervals for 5 more months. Patients were then followed for an additional 52 weeks. Blood samples were analyzed for HLA antibodies, BAFF levels, serum immunoglobulins, T and B cell subsets at specified time intervals during the treatment and follow-up periods. Pre and post treatment tonsil and bone marrow biopsies were also performed.

Results: Significant reductions in cPRAs were observed at week 16 (p=0.043) and at week 36 (p=0.004), however the absolute reductions were small (<5%). Overall factor effect at week 76 compared to baseline was significant (p=0.04). Mean BAFF levels increased during treatment, reflecting binding to tabalumab and decreased in the follow-up period remaining slightly above baseline at week 76. Expected changes in B cell subsets and reductions in immunoglobulins were observed. Two tabalumab-related serious adverse events occurred (pneumonia and worsening of peripheral neuropathy) while the most common other adverse events were injection-site pain and hypotension. Three patients received a matched donor cadaveric transplant during the study follow up.

Conclusions: The results resulted in statistically significant, but not clinically meaningful reduction in the cPRAs from baseline. Funding: Pharmaceutical Company Support - Eli Lilly

Benefit of Desensitization with Rituximab from the Viewpoint of Anti-A/B Antibody Titer and Pathological Findings in ABO-Incompatible Kidney Transplantation

Background: We conducted a multicenter prospective clinical study in ABO-incompatible kidney transplantation (ABOi-KT) without splenectomy (UMIN000006635). To evaluate the benefit of desensitization with rituximab (R), we investigated the data of this study from the time course change of anti-A/B antibody (ab) titer and sequential pathological findings.

Methods: Desensitization protocol included low dose MMF and steroid started 28 days before and CNI started a few days before surgery. R 375 mg/m² was administered at day -14 and day -1. Minimum 2 sessions of plasma exchange were done for anti-A/B ab removal before transplant, and basiliximab was administered on day 0 and day 4. Anti-A/B
ab titer and eGFR were sequentially evaluated, 0 hr, 1 hr and protocol biopsies (4 weeks after transplant) were also sequentially performed as possible. Pathological specimens were centrally diagnosed by 3 pathologists.

Results: 18 pts received ABOi-KT. One-year pts and grafts survival were both 100%. The desensitization with R was well tolerated. Average anti-A/B ab (IgG) titer at baseline was 15.4x and decreased to 19.7x immediately before surgery, maintaining until the end of the study. In pts whose sequential pathological specimen available showed positive C4d deposition in 1/13 at 1 hr and 11/16(69%) at protocol biopsy. No pts developed AMR related to anti-A/B abs except for one who experienced AMR with anti-HLA ab (Banff07 type II). Her anti-A/B ab titers were slightly higher than the others (4x-32x). Pathological findings included arteriosclerosis in 8, nephrocalcinosis in 1, IF/TA (grade 1) in 1 and suspicious CNI acute nephrotoxicity in 1. Two pts showed C4d+ without other pathological signs.

Conclusions: In this series, anti-A/B ab titer were successfully decreased and no AMR occurred other than 1 caused by anti-HLA ab, whereas C4d deposition was detected in 6/13 of pts by protocol biopsy. Our desensitization protocol was confirmed both pathologically and clinically safe and effective for ABOi-KT.


SA-PO962
Post-Transplant BAFF Levels Do Not Predict the Development of Anti-HLA Antibody in Kidney Transplant Recipients. Ji Won Min,1,2 Burn Soon Choi,1,2 Cheol Whae Park,1,2 Chul Woo Yang,1,2 Yong-Soo Kim,1,2 Byung Ha Chung.1,2

Background: It is well known that pre-transplant B cell activating factor (BAFF) levels are associated with the development of de novo anti-HLA antibodies and also antibody mediated rejection post-transplant. However, the clinical significance of BAFF values at alloreactive rejection has not been determined. In this study, we investigated the clinical significance of pre- and post-transplant BAFF levels measured when indication biopsy was done.

Methods: In 130 kidney transplant (KT) recipients who required alloreactive biopsy due to an increase in serum creatinine, we checked for anti-HLA antibodies using Luminex single antigen assay, and measured BAFF levels using ELISA kits. In 78 of these patients we also measured pre-transplant BAFF and anti-HLA antibody levels. We investigated the relationship between pre-transplant, post-transplant and delta BAFF levels and the occurrence of anti-HLA antibodies.

Results: Pre-transplant BAFF levels showed significant association with pre-transplant sensitization, represented by positive PRA, high PRA, and presence of HLA-DSA. They also showed positive association with early rejection (rejection within 6 months from KT). Post-transplant BAFF levels showed significant association with post-transplant sensitization, but did not show association with anti-HLA antibodies and positive donor-specific antibodies at the time of biopsy. We did not find any association between post-transplant BAFF levels and cumulative alloreactive rejection, alloreactive biopsy results, Banff scores and microvascular inflammation scores.

Conclusions: In conclusion, pre-transplant BAFF levels are associated with pre-transplant sensitization and are useful in predicting alloreactive rejection. But post-transplant BAFF levels measured at the time of indicated biopsy are not associated with the appearance of de novo HLA-DSA, alloreactive rejection, biopsy findings and other alloreactive outcomes.

SA-PO963
Effectiveness of Bortezomib (BT) in the Treatment of Antibody Mediated Rejection (AMR) Among Pediatric Kidney Transplant Recipients (pKTx). Sarah J. Kizilbash,1 Donna J. Claes,1 Isla Ashoor,1 Ashton Chen,4 Sara E. Jandeska,1 Raed Bou Matar,1 Jason Misurac,7 Katherine Twombley,8 Priya Verghese1,3 Pediatric Nephrology, Univ of Minnesota; 2Cincinnati Children’s Hospital; 3Children’s Hospital New Orleans; 4Wake Forest Univ; 5Rush Univ; 6Cleveland Clinic; 7Indiana Univ; 8Medical Univ of South Carolina.

Background: AMR has a poor prognosis despite a number of therapeutic options. BT is increasingly being utilized in adults but there are limited data on its safety and efficacy in pKTx with AMR.

Methods: Multicenter retrospective case series including all pKTx who received BT for biopsy proven AMR, from 2008-2015, at 8 centers within Midwest Pediatric Nephrology Consortium.

Results: Twenty-four pKTx from 8 centers were treated with BT for AMR. In addition to BT, 75% were treated with rituximab, 79.2% with plasmapheresis and 91.7% with IVIG. 62.5% were males, 45.8% were white, and 41.7% were African American. Two-thirds were deceased donor recipients, and mean age at transplant was 11.1 years (SD 5.19). Obstructive urethropathy and dysplasia comprised 50% of the underlying diseases. At the time of transplant, 82.2% of patients had 0.0% panel reactive antibodies. Mean estimated GFR (eGFR) prior to AMR was 49.6 (SD 12.1). Prevalence of donor specific antibodies (DSA) and changes in eGFR are shown in table 1.

Conclusions: Even though limited by small patient numbers, this trial suggests efficacy of IA in the treatment of late AMBR.

SA-PO965
Pre-Transplant Phospholipase A2 Receptor Autoantibody Concentration Is Associated with Recurrence of Membranous Nephropathy Post-Kidney Transplantation. Hasan Fattahi,1 Gaurav Gupta,1 Dhiren Kumar,1 Luis F. Quintana,2 Anne L. King,1 Rivka Ayalon,1 Laurence H. Beck,3 Nephrology, Virginia Commonwealth Univ; Richmond, VA; 2Nephrology, Hospital Clinic de Barcelona, Barcelona, Spain; 3Nephrology, Boston Univ, Boston, MA.

Background: Idiopathic membranous nephropathy (mN) has been associated with anti phospholipase A2 receptor autoantibody (PLA2R-Ab) both in the native kidneys as well as in the setting of recurrence (rMN) post-kidney transplant (txp). Previous studies that have assessed pre-txp PLA2R-Ab for the prediction of rMN have yielded variable results. Many of these studies have been limited by the use of variable immunosuppressive regiments among patients, different ELISA assays as well as method of diagnoses (surveillance vs indication biopsies).

Results: Tubulointerstitial scarring (ci+ct) (p=0.81), microcirculation inflammation (g+p+c) (p=0.38) and transplant glomerulopathy (cg) (p=0.21) scores were similar. However, the mean total inflammation (ti) score of IA group (2.60±0.55) was significantly higher than PE (1.69±0.70) and DFPP (1.79±0.71). The rates of graft loss were as follows; PE; 13/16 (81.3%), DFPP; 10/19 (52.6%) and IA; 1/5 (25%) (p=0.03). The graft survival was significantly higher for IA than PE (p=0.01). There was a tendency of better graft survival in DFPP compared to PE group (p=0.07). Kaplan-Meier survival analysis revealed better overall survival for IA than for PE and DFPP (p=0.03).

Conclusions: Although limited by small patient numbers, this trial suggests efficiency of IA in the treatment of late ABMR.
**SA-PO966**

Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio Predict Acute Allograft Rejection

**Methods:** Sixteen consecutive test patients with a history of IMN were tested for per-protocol PLA2R-Ab. ELISA titers (Euroimmun, NJ, USA) > 14 RU/ml were considered positive, as per manufacturer instructions. All patients received similar post-transplant immunosuppression. A receiver operating characteristic (ROC) analysis was performed after combining data from Quintana et al. (n=21; Transplantation Feb 2015) to determine a PLA2R-Ab concentration which could predict rMN.

**Results:** Six (out of 16; 37%) patients had biopsy-proven rMN at a median of 3.2 years post-txp. Of these, 5/6 (83%) had a positive PLA2R-Ab pre-txp with a median of 82 RU/ml (range=31-1500). The only patient who had rMN with a negative PLA2R-Ab was later diagnosed with non-Hodgkin’s lymphoma. 100% (n=10) patients with no evidence of rMN had a PLA2R-Ab concentration which could predict rMN.

**Conclusions:** Pre-transplant PLA2R-Ab could be a useful tool for the prediction of rMN. Patients with rMN in the absence of PLA2R-Ab should be screened for occult malignancy.

**SA-PO968**

The Pre-Transplant Ratio of T Regulatory Cells to Effector/Memory CDB+ T Cells Is Correlated with the Development of Acute Rejection

**Methods:** Single center retrospective case-control study examined all kidney transplant biopsies conducted at Einstein Medical Center from Jan 2013 through Dec 2014. Biopsies were stratified for rejection (acute cellular, borderline, negative). The NLR and PLR were calculated from routine laboratory studies obtained at various time points preceding the biopsy.

**Results:** Of the 102 “cause” biopsies, 37.3% showed clear evidence of acute rejection and 18.6% were borderline. NLR and PLR obtained within the week prior to the biopsy showed a significant reduction in NLR (p<0.001) and PLR (p<0.04) in patients with acute rejection. The AUC for NLR in NLR and PLR preceded the biopsy by 2-4 weeks suggesting a rejection prodrome. Interestingly, NLR at the time of borderline rejection accurately predicted rejection status on subsequent biopsy conducted within 8 weeks.

**Conclusions:** NLR and PLR are highly sensitive biomarkers for acute rejection which become positive prior to other clinical manifestations. Furthermore, in cases of borderline biopsies NLR accurately predict the result of subsequent biopsies. The inclusion of NLR and PLR could revolutionize allograft rejection evaluation by reducing the need for biopsies and providing additional insight in cases where the biopsy is non-diagnostic.
SA-PO970

Quantitative Characterization of T Cell Repertoires in Kidney Transplant Patients

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Background: Acute and chronic T cell mediated rejection remains a major cause of kidney graft failure. Despite the significant decrease in early acute rejection due to current potent immunosuppressions, long-term graft survival remains unsatisfactory. Thus, characterization of the T cell repertoire and the kinetic of the expanded clones in transplant (Tx) patients may shed a light on our understanding of the T cells' role in graft rejection.

Methods: We collected blood and urine samples from (46) patients before Tx, and at sequential time points post Tx and at time of T cell mediated rejection. We utilized next generation sequencing approach to characterize T cell receptor (TCR) repertoire. Sequencing using the illumina miSeq was performed on DNA synthesized from RNA extracted from patients' samples. This approach enables to track each expanded TCR clone in the graft at 3 months post Tx, back to their first appearance in blood and urine samples obtained pre or 1 month post Tx. We also measured the RNA expression levels of CD8, CD4, FOXP3, Granzyme and Perforin in blood samples (N=43).

Results: Only patients with acute T cell mediated rejection (n=2) had TCR repertoires defined by the top 10 TCR clones appeared at any time point in blood, showed significant expansion in blood at 3 month post Tx compared with that at 1 month post Tx (P<0.01 and 0.02). CD8, FOXP3, Granzyme and perform RNA levels were significantly higher in samples obtained from patients with rejection compared to that in patients with no rejection (P<0.02).

Conclusions: Our study provides valuable comprehensive longitudinal analyses that define the kinetics of each TCR beta clone, and the changes in diversity of CDR3. This approach allows for identification of the expanded T cell clones that are possibly associated with graft rejection.

SA-PO971

Critical Appraisal of the New Banff Criteria for Chronic Antibody-Mediated Rejection in the Real Life Setting

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Background: Significant changes in the criteria for chronic active antibody-mediated rejection (CAABMR) were made at the 2013 meeting, which is of major concern for clinical management. Here we compared the 2007 vs. 2013 criteria with regards to clinical outcomes.

Methods: Single-center, observational retrospective cohort study of all patients who received an indication biopsy between January 2006 and October 2014, during which EM evaluation, ptc scoring and C4d scoring by IH and IF was routinely performed. Patients were included if they met the criterion 1 for CAABMR: score cg1a>0, cg1b>0 or severe peritubular capillary basement membrane multilayering. GN, immune deposits, HCV+ status or suspicion of TTP-HUS were excluded. The endpoint was a composite of doubling of serum creatinine and death-censored graft loss.

Results: 123 patients were included. 18% met the full 2007 criteria, whereas an additional 18% fulfilled the full 2013 criteria. Only 25% of patients met the 2007 criterion #2-C4d, in contrast to 82% for the 2013 criterion #2-microvascular injury (MVI). 67% were C4d-positive and 55% were g’ptc positive, with substantial overlap. 45 patients experienced the endpoint at a median of 22mo post-biopsy. Overall, only a 2013 diagnosis of CAABMR was associated with the endpoint (adjusted HR=2.5 [1.2-5.0] for 2013 vs. HR=1.6 [0.7-3.8] for 2007 diagnosis). Adjusted Cox modelling revealed that the 2013 criterion #2-MVI was more strongly associated with the endpoint than the 2007 criterion #2-C4d (HR=4.0 [1.1-14.1] vs. HR=2.3 [1.0-5.3]). When the 2013 criterion #2 was dissected by component, the C4d-component was significant (HR=2.5 [1.1-5.4]), but the g’ptc (HR=1.0 [0.5-2.3]).

Conclusions: Compared to the 2007 criteria, applying the 2013 criteria here doubled the proportion of patients with CAABMR. Importantly, it improved the association with clinical outcomes.

SA-PO972

Tissue Expression of Aquaporine 2 Is Correlated to Urine Output and Allograft Function in Sensitized Kidney Transplant Patients

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Background: Salt and water disturbances often occur during acute kidney allograft dysfunction contributing to graft failure, but this condition has still been poorly investigated in the setting of allograft rejection. We evaluated the tissue expression of aquaporins (AQP1, AQP2) and of the epithelial sodium channel (ENaC) in kidney allograft biopsies from transplant patients with high immunological risk.

Methods: Eighty-six kidney transplant biopsies from thirty-three sensitized patients were divided into three groups according to the clinical context a possible pathological correlates as follows: time-zero/tx biopsy (N=9), protocol (N=9) and indication (N=68) biopsies. The indication biopsies were further divided into three subgroups, according to the presence or absence of acute tubular necrosis or acute rejection. Normal kidney tissue samples (N=6) served as controls. Immunohistochemical expression of AQP1, AQP2 and ENaC was analyzed with assistance of an image software.

Results: We observed a significantly lower AQP1 expression in time-zero and indication biopsies with rejection compared to controls (7.7±2.0% and 9.1±0.6% vs. 14.3±2.9% of area positively stained; P=0.03 and P=0.04 respectively). AQP2 expression was significantly lower in patients with an indication biopsy when compared to controls and protocol biopsies (21.0±2.9% vs. 4.4±0.7 and 4.0±0.5% of area positively stained, P=0.05 and P=0.005, respectively). For ENaC, a lower expression in indication biopsies compared to controls was seen (P=0.04). Both AQP1 and AQP2 tissue expressions were significantly correlated to the urine output (r=0.45 and r=0.32; P=0.001 and P=0.02, respectively), and AQP2 was correlated to the MDRD-glomerular filtration rate at the time of biopsy (r=0.23; P=0.05).

Conclusions: Our findings can partially confirm previous experimental data showing downregulation of AQP1 expression after ischemia-reperfusion injury and during rejection. AQP2 downregulation seems to be rejection-independent occurring during deteriorating or poor kidney graft function.

SA-PO973

The Utility of Protocol Biopsy in Renal Recipients: Meta Analysis and Systematic Review


Background: To evaluate the value of protocol biopsy in patients after renal transplantation.

Methods: Searches were applied to the following electronic database: Medline, Embase Database, Cochrane Library, Randomized controlled trials evaluating the value of protocol biopsy for renal allograft recipients were included. Data were extracted independently by two reviewers. The risk of bias of included studies was assessed by the Cochrane collaboration’s tool for assessing risk of bias.

Results: 5 RCTs were included. Long term graft loss was significantly reduced (RR 0.40, 95% CI 0.25 to 0.65, P=0.001 (figure 1) by protocol biopsy after renal transplantation.

Conclusions: Protocol biopsy may reduce the long term serum creatinine (WMD 38.21, 95% CI 54.83 to 21.60, p<0.00001). For renal recipients whose basal immunosuppression is CNI (tacrolimus or cyclosporine), protocol biopsy can significantly improve the long term eGFR (SMD 0.78, 95% CI 0.51 to 1.05, P=0.00001). However, for those whose basal immunosuppression is tacrolimus, this effect is not notable. Protocol biopsy seems to have no significant beneficial effect of reducing clinical acute rejection episodes.

SA-PO974

Longitudinal Biopsy Findings Among Children, Adolescents, and Young Adult Renal Transplant Recipients from a Southeastern USA Cohort

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Background: Longitudinal procedure history in children, adolescent, and young adult renal transplant recipients needs to be characterized based on their primary cause of end-stage renal disease (ESRD). It is known that pediatric patients are a high risk group for transplant failure. Elucidating potential factors for transplant failure in this group is important for protecting vulnerable patients.

Methods: Clinical, demographic and pathological records of patients who received a renal transplant at age ≤ 30 years of age and who underwent transplant biopsies between 2000 and 2014 at the UNC Hospitals were analyzed. This cohort was classified based on
the primary cause of ESRD as either glomerular or non-glomerular. Demographics, number of biopsies (total and adjusted for graft failure), and transplant failure (rates and cause) were compared between the two groups.

Results: We enrolled 179 patients; 105 (58.7%) were male; 67 (38.3%) African American, 92 (51%) Caucasian, and 20 (11%) other race. Their mean age at transplant was 18.7 ± 8.2 years and 98 (55%) had a glomerular cause of ESRD. This cohort underwent a total of 505 graft biopsies. Comparing patients with glomerular vs. non-glomerular conditions, we found no significant differences in cellular or humoral rejections (p=0.430); mean number of biopsies (3.0 ± 1.9 glomerular; 2.7±1.9 non-glomerular; p=0.289); mean number of biopsies per year for failed transplants (p=0.702), current functioning grafts (p=0.090); time to a failed transplant (p=0.476); or age at time of transplant (p=0.136).

Conclusions: In this single institution cohort of children, adolescents and young adults, we found no statistical differences in renal biopsy findings regarding number of biopsies and transplant failure. This high risk age group shows no different longitudinal graft survival based on primary cause of ESRD. More analysis will follow.

Funding: Private Foundation Support

SA-PO975

Prospective Study of Risk Factors and Impact of Subclinical Rejection (SCR) and Acute Clinical Rejection (ACR) in Renal Transplant Recipients

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Background: The long term outcomes of subclinical rejection (SCR) remain unclear. The current study evaluated the risk factors for SCR at 3 mths and followed up renal function upto 1 year in pts with SCR, ACR and no rejection.

Methods: We prospectively followed 340 pts who underwent an ABO compatible kidney transplant between Jan 2013 and Sep 2014. Eight pts were excluded. All patients received induction therapy with either thymoglobulin (95%) or Basiliximab for induction, CNIs/MPA for maintenance therapy and rapid steroid withdrawal by day 7. Protocol biopsies were performed 3 months post transplant. Based on this, they were divided into 4 groups. Grp 1 - pts with SCR, Grp 2 - pts with normal biopsy; Grp 3 - pts with ACR; Grp 4 - pts with no biopsy. Banff classification was followed for biopsy grading. Steroids, thymoglobulin and PPI IVG were used as indicated for the treatment of rejection.

Results:

<table>
<thead>
<tr>
<th>Grp 1 (SCR)</th>
<th>Grp 2 (Normal Bi)</th>
<th>Grp 3 (ACR)</th>
<th>Grp 4 (No Bi)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>50±16</td>
<td>52±15</td>
<td>48±15</td>
<td>55±12</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>28/16</td>
<td>100/59</td>
<td>15/18</td>
<td>52/44</td>
</tr>
<tr>
<td>Race (W/O)</td>
<td>34/10</td>
<td>126/33</td>
<td>25/8</td>
<td>80/16</td>
</tr>
<tr>
<td>CIT (mins)</td>
<td>474±327</td>
<td>409±386</td>
<td>396±316</td>
<td>510±380</td>
</tr>
<tr>
<td>DGF (Y/N)</td>
<td>13/31</td>
<td>17/142</td>
<td>15/28</td>
<td>21/75</td>
</tr>
<tr>
<td>HLA mm</td>
<td>4.1±1.5</td>
<td>3.9±1.7</td>
<td>4.25±2.3</td>
<td>3.96±1.8</td>
</tr>
<tr>
<td>HLA DR mm</td>
<td>1.23±0.7</td>
<td>1.12±0.7</td>
<td>1.41±0.7</td>
<td>1.31±0.7</td>
</tr>
<tr>
<td>DSA (Y/N)</td>
<td>11/27</td>
<td>23/109</td>
<td>9/24</td>
<td>13/73</td>
</tr>
<tr>
<td>PRA I</td>
<td>6.7±17</td>
<td>6.5±19</td>
<td>7.9±19</td>
<td>14±37</td>
</tr>
<tr>
<td>PRA II</td>
<td>10.8±26</td>
<td>14.8±29</td>
<td>7.1±22</td>
<td>12.6±27</td>
</tr>
<tr>
<td>Cr 3m</td>
<td>1.52±0.4</td>
<td>1.42±0.5</td>
<td>1.69±0.48</td>
<td>1.33±0.46</td>
</tr>
<tr>
<td>Cr 6m</td>
<td>1.52±0.5</td>
<td>1.46±0.5</td>
<td>1.54±0.57</td>
<td>1.26±0.42</td>
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<tr>
<td>Cr 1yr</td>
<td>1.6±0.46</td>
<td>1.5±0.77</td>
<td>1.66±0.48</td>
<td>1.38±0.63</td>
</tr>
<tr>
<td>Banff Gr</td>
<td>25/75</td>
<td>NA</td>
<td>27/73</td>
<td>NA</td>
</tr>
</tbody>
</table>

Conclusions: 1. Incidence of SCR and ACR around 3 mths was 18.6% and 9.9% respectively 2. Significant risk variables for SCR/ACR were female recipients and DGF 3. No difference in renal function was noted between the groups at 1 year.

SA-PO976

Histological Scoring System Predicts Renal Outcome of Post Transplantation Acute Tubular Necrosis: A Single-Center Experience in Japan

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Background: Acute Tubular Necrosis (ATN) is a common cause of Delayed Graft Function (DGF) after renal transplantation (RTX). Currently no histological model is available to predict renal outcome. Recovery of ATN is the result of the balance between regeneration and repair. In this study we evaluated the predictive value of immunohistochemical parameters of renal damage and regeneration and compared these to an accepted clinical prediction model for cadaveric renal transplantation.

Methods: We included 25 patients that underwent cadaveric RTX with DGF caused by ATN only, as shown in a renal biopsy 1 week after RTX. Biopsies were evaluated for histological tubular damage (atrophy, edema, casts, vacuolization), DNA damage (γH2AX staining) and apoptosis (cC3 staining). Regeneration was assessed by staining for stem cell marker CD133 and proliferation marker Ki67. Clinical parameters for renal outcome were collected as previously described in the Deceased Donor Score (DDS). The relation between these parameters and renal outcome, defined as eGFR at 6 months, was assessed using regression or one-way ANOVA. A correct analysis for regenerative markers was performed to eliminate potential confounding by the amount of renal damage.

Results: The histological damage score significantly predicted renal outcome (R= 0.52 P<0.01), whereas the DDS only tended to correlate with renal outcome (F:3.12 R: P=0.05). Neither staining for DNA damage, nor for apoptosis could predict renal outcome (R= 0.24 P=0.91 and R= 0.16 P=0.44 respectively). In addition, the investigated parameters for regeneration (CD133 and Ki67) did not predict renal outcome (R= 0.25 P=0.23 and R= 0.10 P=0.63 respectively), also not after correction for renal damage.

Conclusions: We are the first to show that histological parameters can predict renal outcome of post transplantation ATN. Importantly, our histological damage score correlated better with renal outcome than the DDS. Despite the crucial role of regeneration in recovery after ATN, no relation was found between stem cell marker CD133, proliferation marker Ki67 and renal outcome.

Funding: Pharmaceutical Company Support - Dutch Kidney Foundation

The Netherlands Institute for Regenerative Medicine

SA-PO977

Histopathological Changes and Graft Survival of Long-Term Kidney Allograft in Alport Syndrome: A Single-Center Experience in Japan

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Background: Patients with Alport syndrome (AS) commonly develop progressive kidney dysfunction due to a hereditary type IV collagen deficiency, which results in an abnormality in the glomerular basement membrane (GBM). Recurrent glomerulonephritis does not occur in transplanted kidneys, and the allograft survival rate in these patients is similar to that in patients with other renal diseases. Several studies have shown that the type IV collagen of the GBM originates from the recipient’s bone marrow–derived cells. Therefore, we postulated that recurrent glomerulonephritis could occur locally and should influence the long-term allograft survival. In this study, we investigated graft survival and histopathological changes in renal allograft recipients with AS, focusing particularly on whether the expression of GBM type IV collagen is altered.

Methods: We collected data on the clinical characteristics of 19 renal allograft recipients who had been diagnosed with AS. All data were obtained from a database at the Department of Urology, Tokyo Women’s Medical University. Graft survival was evaluated using the Kaplan–Meier method and compared with a control group (n = 18). We assessed the double staining of a2 and a5 using frozen specimens obtained from long-term allograft survival samples.

Results: The graft survival rate was not statistically different between patients with AS and controls (log-rank p = 0.2240). Immunoreactivity to a5 antibody in four patients exhibiting long-term allograft survival showed strong linear positivity and no GBM abnormalities. In the case of chronic active antibody-mediated rejection, the immunoreactivity to a2 antibodies increased in the mesangium and subendothelial space.

Conclusions: These results suggest that the GBM type IV collagen structure was histopathologically maintained for the long term after kidney transplantation, indicating better kidney graft survival in patients with AS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
A clinical need exists for a noninvasive method for diagnosing AMR. Endothelial cells (HMEC-1) and a monoclonal murine antibody against human HLA class II molecules were used to explore endothelial microvesicles in vitro to explore endothelial microvesicles in vitro and to explore endothelial microvesicles in vitro and to explore endothelial microvesicles in vitro and to explore endothelial microvesicles in vitro and to explore endothelial microvesicles in vitro.

**Results:**

Total number (n) and mean n of biopsies per patient performed are overall similar in both groups until mo60. N of pts with at least one rejection (as per final clinical diagnosis) was slightly higher in CNI group vs EVR group. N of pts with IFTA was higher in the EVR group especially due to mild, early acute rejections (mostly BANFF IA and IB). N of pts with histological evidence of chronic allograft nephropathy was similar in both groups (10%). CNI staining positivity was found slightly higher in the EVR group (11% EVR vs 7% CNI), however, pts with evidence of antibody mediated rejection was higher in the CNI group (2% EVR vs 4% CNI), same for CNI-induced toxicity lesions (16% EVR vs 23% CNI). The diagnosis of AMR is dependent upon pathologic examination of renal biopsy tissue. HLA on the endothelial cells activate the complement system via the classical pathway. This leads to deposition of complement split products on the cell surface (analogous to C4d deposition in biopsies from patients with AMR) and increased release of endothelial microvesicles. Consequently, Dual LCA/C4d BIC aided the evaluation quantification of inflammatory infiltrate in renal allograft rejection, possibly allowing finer and more reproducible discrimination between ptc and i scores and identifying the extent of glomerulitis. Annular detection of tubulointerstitial inflammation is unclear. We aimed the study to determine the role of CD3+CD8+Gzm-B+ cell-mediated rejection in renal transplant recipients. We evaluated a dual pan-leukocyte marker (LCA) and a vascular endothelial cell marker (CD34) immunohistochemistry and flow cytometry. Microvesicle analysis was performed using flow cytometry.

**Results:**

We have shown that W6/32 antibody binds HMEC-I cells and activates the classical complement pathway upon exposure to normal human serum. This leads to deposition of complement split products on the cell surface (analogous to C4d deposition in biopsies from patients with AMR) and increased release of endothelial microvesicles. Furthermore, anti-HLA antibody (W6/32), C3, and C4 were deposited on the surface of the microvesicles.

**Conclusions:**

Our results suggest that AMR will lead to an increase in production of microvesicles by the renal endothelium, and AMR-associated microvesicles will have surface-bound IgG and C4d. We have obtained human plasma samples from renal transplant recipients with AMR and healthy controls, and we are currently examining the potential of endothelial microvesicles as a biomarker of AMR.

**Funding:** NIDDK Support
Methods: We identified 15 normal transplant kidney biopsies without leukocyturia (Group 1) and 33 biopsies with non-specific interstitial fibrosis/tubular atrophy (IFTA) for gene expression profiling. Of the 33 biopsies with IFPTA, 24 patients had no sterile leukocyturia (Group 2) and 9 patients had sterile leukocyturia (Group 3). Biopsies with a diagnosis of acute or chronic rejection, recurrent or de novo glomerular disease, or polypoma nephropathy were excluded. Leukocyturia was defined by the presence of more than 10 leukocytes in the urine (>10/L) without bacterial growth in urine culture. The urinalysis was done within 1 month before or after the biopsy. The gene expression profiles were studied by Affymetrix HuGene 1.0 ST expression arrays.

Results: There was no significant difference in age, race, and sex, type of transplant, previous history of transplantation or acute rejection, donor characteristics, panel reactive antibody levels and immunosuppressive treatment between the Groups 2 and 3. Both groups also had similar acute and chronic Banff leukocyturia injury scores. There was a statistically significant decrease in gene expression profiles between the Group 1 and 2. When Group 3 biopsies were compared to the Group 1 and 2 biopsies, significantly increased gene transcripts were associated with cytotoxic and regulatory T cells, and macrophages (P-value for significance <0.05). There was a trend towards increased interferon-gamma and rejection associated transcripts but no statistically significant difference in expression of B-cell or natural killer cell associated transcripts.

Conclusions: The biopsies of the patients with sterile leukocyturia showed increased expression of gene transcripts associated with T cells indicating heightened inflammatory immune activity. Those patients might require close monitoring of their allograft function.

SA-PO983
Elevated Glomerular Mechano-Growth Factor and Vascular Endothelial Growth Factor in Chronic Allograft Nephropathy Is Associated with Activation of Erk1/2
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Background: We previously identified increased GLUT1 glucose transporter, Mechano-Growth Factor (MGF) and Vascular Endothelial Growth Factor (VEGF) in human Chronic Allograft Nephropathy (CAN) kidneys which demonstrate glomerulosclerosis. Here we investigated a glomerular signaling pathway, Erk1/2, with potential to mediate effects of MGF and VEGF on extracellular matrix (ECM) genes. We employed IHC with specific antibodies to assess protein expression for MGF, VEGF and phospho-Erk1/2 (active Erk1/2) in human CAN kidneys vs Normal Control kidneys.

Methods: This study involving examination of archived renal biopsy samples was approved by the Institutional IRB. N = 6 for each group of renal transplant - and native kidney specimens. Immunolabelling of human CAN and Normal Control paraﬃn-embedded kidney sections was performed for assessment of selected proteins with specific antibodies, by use of immunoperoxidase stain. Scoring of glomerular immunolabelling for individual proteins was 0 – 4. Data was normalized to open glomerular tuft area. P < 0.05 was considered significant in statistical analysis.

Results: Glomerular MGF protein was increased 3.9-fold in CAN kidneys vs Normal Control kidneys, P < 0.001. Glomerular VEGF was elevated 3.0-fold in CAN vs Normal Control kidneys, P = 0.009. Both of these growth factors have potential to signal via Erk1/2 to ECM expression. Glomerular Erk1/2 activation (i.e. phospho-Erk1/2) was examined and found to be increased 4.3-fold in CAN vs Control, P < 0.0001.

Conclusions: Human CAN, characterized by excessive glomerular MGF and VEGF expression, involved enhanced activation of Erk1/2 in the glomeruli. This provides a mechanism which might induce ECM production and glomerulosclerosis. Therefore, MGF and VEGF activation of Erk1/2 may contribute to progressive glomerulosclerosis and renal failure in CAN.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO984
Microarray Analysis of Interstitial Fibrosis/Tubular Atrophy in Kidney Transplant Recipients Using Formalin-Fixed, Paraffin-Embedded Renal Biopsy Tissue
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Background: Interstitial fibrosis/tubular atrophy (IFTA) is a common and complex feature of renal allograft dysfunction that is difficult to predict. Early identification of progressive IFTA (pIFTA) may lead to alternative therapies that may attenuate irreversible injury. In this study, we used formalin-fixed, paraffin-embedded (FFPE) renal biopsy specimens with microarrays to conduct differential gene expression studies to identify predictors of IFTA in kidney transplant recipients.

Methods: We identified 22 individuals with multiple protocol biopsies within the first 3 years after transplant. Glomeruli and blood vessels were removed using laser capture microdissection and the remaining tissue was used for mRNA extraction. Affymetrix PrimaGene arrays were used following standard protocols. IFTA was defined by histological image masking in Histolab to quantify the cortical interstitial fraction. pIFTA was defined as a 0.5% absolute increase in the interstitial fraction per month between serial biopsies. Data analysis was conducted using R 3.0.2 and Bioconductor 2.22. Significance was defined as an unadjusted p<5 x 10^-6.

Results: Of the 22 subjects in this study, 9 had pIFTA while the remaining 13 were considered stable IFTA (sIFTA). At baseline, the eGFR was 60.5 vs 58.5mL/min/1.73m2 (p=0.79) and log(Urine Albumin) was 3.44 vs 3.17 (p=0.072) for the sIFTA and pIFTA groups, respectively. The baseline fibrosis was higher in the sIFTA group (18%) compared to the pIFTA group (13%); p=0.04. Using linear modeling, 3 of the top 6 differentially expressed genes were metallothionein (MT1A and MT1X) and RASA1. Paired analysis of serial biopsies did not reveal any significant differences between sIFTA and pIFTA.

Conclusions: Microarray analysis of FFPE specimens show that pIFTA is associated with the differential expression of multiple genes prior to phenotypic changes. Prospective investigation of these genes is needed to determine if these are predictive of pIFTA.

Funding: Private Foundation Support

SA-PO985
Pathological Analysis for Transplant Nephropathy - 124 Consecutive Cases in a Single Center Study Over 10 Years
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Background: Transplant nephropathy (TNx) is performed for several indications. This study evaluates in depth histological analysis of TNx specimen.

Methods: We identified all cases at the Royal London Hospital between 2004 and 2014. The indication for TNx was divided into four groups: 47 cases with acute graft loss without significant blood flow (AGL); 44 cases of suspected ongoing rejection or graft intolerance syndrome (Rej/GIS); 24 cases with infection (INF); and 9 miscellaneous reasons (MIS). We examined the histological changes in detail and specifically looked at the artery, vein and ureter.

Results: AGL was less likely to have tubulointerstitial changes, but 74.5% had necrosis. In the AGL group, the majority of cases scored zero for t, 1, c1 and c2. Neutrophil rich arteritis at renal and small arteries was observed in 29.8% and 19.2%. Venous thrombosis was found in 61.7%. All cases in the Rej/GIS group showed c1 and c2 and 49.0% showed c3 and c4. Glomerulitis was observed in 52.3% and c2 was detected in 75.1%. Arteritis of small and renal arteries was detected in 70.5% and 59.1%. C4d expression was present in 54.1%. Nearly 70% showed ureteric inflammation. Variable cellular infiltrate comprising of lymphocytes, plasma cells and eosinophil were seen in all cases. In the INF group, 66.7% (i1-3) and 79.2% (i1-3) were observed, and c3 and c1 were detected in 66.7%. Glomerulitis was rare although allograft nephropathy was detected in 62.5%. All cases had intimal thickening of small and renal arteries but arteritis was unusual. Lymphocyte and plasma cell were common at interstitium and corticalis. In the MIS group, histological changes were minor, t3, i1-3, arteritis and venulets were not detected.

Conclusions: The histological changes were similar and specific within the TNx groups but different between the groups. A failed graft often showed substantial immunological response. In depth histological analysis may aid management of subsequent grafts.

SA-PO986
miRNAs as Novel Biomarkers for Transplant Patient’s Evolution
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Background: Transplanted patients evolution and outcome is dependent on many factors including allograft function, vascular homeostasis and immunogenity. Up to this moments, apart from creatinine renal biopsy, there are no quantifiable and accurate biomarkers to predict the evolution of the allograft and the receptor, what would enable clinicians to improve the transplanted patient’s management. Our group has validated a combination of serum miRNAs as accurate biomarkers for AKI from ischemic aetiology, including: miR-127, miR-101, miR-210, miR-146a, miR-20b, miR-29a, miR-10a, miR-93 and miR-27a. Here we have determine the expression of these miRNA in serum from kidney donors and receptors and correlate this expression with clinical parameters of allograft evolution, including ATN development, delayed graft function, rejection and vascular complications.

Methods: For this purpose, serum sample from brain death donors and receptors along post-transplantation period (6h, 1, 2, 3, 4, 5, 6 and 7days and 1,3,6 months) in 30 transplanted patients form our Hospital. After RNA extraction from serum, the combination of miRNAs has been determined by qRT-PCR and correlation with clinical data has been established using SPSS.

Results: The expression of these 10 miRNAs in serum samples from donors did not exhibited significant differences among them. This combination neither correlate with immediate delay graft function because NTA or immunological rejection. However, some of the miRNAs correlate with long term evolution of transplanted patients in terms of non-optimal graft function and they also discriminate patients with also exhibited renal allograft alterations.

Conclusions: In summary we have identified miRNAs that correlates with long term evolution of transplanted patients. These information could be useful for improve transplanted patient’s evolution differentiating patients with potential renal allograft function and they also discriminate patients with also exhibited renal allograft alterations.

Funding: Other NIH Support - Fundación Mutua Madrileñ as de Investigación
Plasma MicroRNA 17 Host Gene Protein level Cluster and Tumor Necrosis Factor-Alpha (TNF-α) in Patients with Renal Transplantation: Relation to Allograft Function and Survival

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Background: Chronic allograft dysfunction (CAD) remains the leading cause of late graft loss after kidney transplantation. MicroRNAs (miR) are small (19-25 nucleotides) noncoding RNAs that regulate gene expression of diverse biological processes. The polycistronic miR-17~92 cluster is comprised of six miRs and its primary transcript may also encode for a polypeptide of 70 amino acids designated as the miR-17 host gene (MIR17HG) protein. So the aim of this work was to evaluate the plasma levels of MIR17HG protein and TNF-α levels in patients with renal transplantation in relation to renal allograft function and survival.

Methods: This study included 45 subjects; they were divided into three groups each 15, renal transplant patients with stable renal function (Group I), with CAD (Group II) and healthy subjects as controls (Group III). Quantitative determination of plasma levels of MIR17HG protein and TNF-α were performed using enzyme linked immunoassay (ELISA). Blood urea, serum creatinine and estimated glomerular filtration rate (eGFR), urinary albumin/urinary creatinine ratio and C-reactive protein (CRP) were done. Resistive index (RI) was calculated. Renal biopsy was done in patients with CAD.

Results: MIR17HG protein and TNF-α levels were significantly higher in renal transplant especially patients with CAD than the controls. In patients with renal transplantation, MIR17HG levels and TNF-α were positively correlated with each other and with serum creatinine, urinary albumin/creatinine ratio and CRP and was negatively correlated with e-GFR. The degree of fibrosis in renal biopsy was positively correlated with MIR17HG protein, TNF-α and resistive index (P<0.05).

Conclusion: MIR17HG Protein and TNF-α plasma levels can be served as circulating biomarkers for early detection of renal allograft dysfunction and follow up of patients with renal transplantation. They can act as a pro-fibrotic factor and denoting with MIR17HG protein, TNF-α levels and RI (P<0.05).

SA-PO988
Polyorphism of IL-17 and CXCL9 Genes, but Not AIF1 Gene, Affect Early Kidney Allograft Function After Transplantation

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Background: Kidney transplantation outcome is determined by immunological and non-immunological factors, both the donor and the recipient dependent. There are reports suggesting that AIF1, IL-17 and CXCL9 genes polymorphisms might influence the post-transplant immune response, and thus kidney function. Therefore the aim of this study was analysis of association between 8 AIF1, IL-17 and CXCL9 polymorphisms and creatinine concentrations up to 1 year after transplantation.

Methods: The study enrolled 269 Caucasian renal transplant recipients (165 males, 104 females, mean age 47.63 ± 12.96 years). Blood samples were collected for genetic analysis and the specificity was 91.9%.

Results: The study enrolled 269 Caucasian renal transplant recipients (165 males, 104 females, mean age 47.63 ± 12.96 years). Blood samples were collected for genetic analysis and the specificity was 91.9%.

Conclusions: Polymorphisms of IL-17 and CXCL9 genes, but not AIF1 gene, affect early kidney function after transplantation. These preliminary results indicate that there is a need of genome-wide association studies scoring on genomics implicated in the immune response after transplantation.

SA-PO997
Urinary K Cadherin Predicts Renal Allograft Dysfunction

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Background: To investigate whether urine and plasma Endothelial Cell Specific Molecule-1 (ESM-1) level could differentiate rejection from non-rejection in kidney transplantation (KTP) recipients, we compared ESM-1 levels according to allograft status.

Methods: We measured plasma and urine ESM-1 in 77 patients with underway KTP. The concentration of ESM-1 was analyzed by enzyme linked immunosorbent assay (ELISA). According to allograft status, Groups were divided stable, long-term good survival, immune tolerance, acute cellular rejection (ACR), acute antibody-mediated rejection (AMR) and chronic AMR.

Results: Plasma ESM-1 was not significantly different between all groups according to allograft status (p>0.42). Whereas, urine ESM-1 was significantly different between groups according to allograft status (p<0.001). Urine ESM-1 was higher in both ACR and acute AMR as well as chronic AMR than stable status. Patients with acute AMR showed significant higher level of urine ESM-1 compared with patients with ACR (p<0.05). Area under the curve (AUC) for differentiating acute AMR from ACR was 0.744 (p<0.01).

Conclusions: Urine ESM-1 may reflect endothelial injury of allograft and it could be used to differentiate the patient with acute AMR from ACR.

SA-PO998
Noninvasive Diagnostic and Predictive Value in Renal Transplant Recipients by Measurement of Urine BCA-1

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Background: To investigate the relationship between early-stage renal acute rejection and the level of BCA-1 in urine, explore the diagnostic value and noninvasive monitoring in cases with acute rejection after transplantation by measurement of urine BCA-1.

Methods: 145 patients were enrolled between January 2006 and October 2009, including 49 with biopsy-proved acute rejection, 58 patients with stable renal function and no abnormal histological findings, 9 patients with biopsy-proven acute tubular necrosis (ATN) and 30 patients with acute cellular rejection (ACR). ROC curve was constructed to determine the discriminatory power of BCA-1 levels for diagnosis of acute rejection. The area under ROC curve was 0.881 (95% CI 0.811-0.951), at a cut point of 0.23 µg/mmol creatinine, the sensitivity was 81.6% and the specificity was 87.9% (P<0.001). Patients with acute humoral rejection had significantly higher urinary BCA-1 concentration than patients with acute cellular rejection (24.2±6.68, 95% CI 5.93-34.8µg/mmol creatinine vs 2.91±0.65, 95% CI 1.64-22.4µg/mmol creatinine, P=0.0002). ROC curve was constructed to determine the discriminatory power of BCA-1 levels for diagnosis of acute humoral rejection. The area under ROC curve was 0.867 (95% CI 0.725-1.005) at a cut point of 8.3 µg/mmol creatinine, the sensitivity was 75% and the specificity was 91.9%.

Conclusions: The monitoring of BCA-1 in urine may be a new and noninvasive approach for detection acute rejection as well as useful to discriminate the type of rejection.
SA-P0992
B Cell Attracting Chemokine 1 in Urine Is a Biomarker of Acute Humoral Rejection
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Background: Presently, there are no noninvasive approaches which can be directly applied to clinical diagnosis of acute rejection (AR) or distinguish type of rejection in renal transplant recipients. The aim of this study was to construct diagnostic models of biomarkers in urine and serum from patients with AR or acute humoral rejection (AHR) in renal transplant recipients.

Methods: Concentration of nine biomarkers in urine of 81 patients with AR and 167 patients with stable renal function (No-AR) was determined by ELISA technique. Firstly, by discriminant analysis, we screened a number of biomarkers to construct the diagnostic models for AR and AHR. Secondly, another 102 patients with No-AR and AR were analysed to test the accuracy of the diagnostic model.

Results: Four biomarkers were selected to set up the diagnostic model of AR or No-AR. Based on the model of AR, 84.3% patients were correctly diagnosed. Two biomarkers were selected to set up the complementary diagnostic model of AHR. Based on the two model of AR, 100% patients with No-AR and 96.3% patients with AR were correctly diagnosed. Only B cell attracting chemokine 1 (BCA-1) was selected for the diagnostic model for AHR or acute cellular rejection (ACR). Rejectation rate of 81.5% patients with AR were correctly classified. Another 102 patients tested the accuracy of the diagnostic models. Diagnostic accuracy of AR or No-AR and AHR or ACR were 100% and 95.4% respectively.

Conclusions: Urinary BCA-1 was a valuable biomarker for determining AHR. These diagnostic models might directly identify AR and types of AR.

Funding: Government Support - Non-U.S.

SA-P0993
18FDG-PET/CT Imaging in Suspected Acute Renal Allograft Rejection
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Background: The diagnosis procedure for kidney transplant recipients (KTR) with suspected acute rejection (AR) relies on needle biopsy. Still, noninvasive tests to predict nonrejection would be useful to save selected patients from undergoing inessential biopsy. AR is associated with a recruitment of activated leucocytes into the transplant, which are characterized by a high metabolic activity and an increased uptake of glucose analog 18 fluoro-deoxy-glucose (18FDG). Thus, 18FDG-PET/CT imaging may help discriminate nonrejection, thereby avoiding unnecessary transplant biopsy in KTR with suspected AR.

Methods: From January 2013 to February 2015, we prospectively performed 32 18FDG-PET/CT in 31 adult KTR with suspected AR who underwent a biopsy. Biopsies were categorized as “normal”, “borderline”, “AR” or “others” according to Banff classification. PET/CT imaging was performed within 201 ± 18 minutes after i.v. administration of 3.2 ± 0.2 MBq/kg of 18FDG, before any modification of immunosuppression.

Results: Biopsies were diagnosed as “normal”, “borderline”, “AR” or “others” in 8, 10, 8 and 6 (including 3 polyoma-BK nephropathies) cases. AR was antibody-mediated in 1 case, whereas Type I, II and III cellular AR were found in 5, 1 and 1 cases, respectively. Mean SUV ranged 1.5 ± 0.2, 1.6 ± 0.3, 2.9 ± 0.8, 2.2 ± 1.2 in each category. Mean SUV of biopsy-proven AR was significantly higher than “normal” cases (p<0.01). No difference was found between “normal” vs. “borderline”, or between ”AR” vs. “others” histopathology. Still, a positive correlation between mean SUV and acute composite (g+i+t+v+ptc) Banff was found between “normal” vs. “borderline”, or between “AR” vs. “others” histopathology. A significant difference (p<0.01) was found in 11/18 (61.1%) patients with AR vs. “normal” cases. No difference was found in the other parameters.

Conclusions: 18FDG-PET/CT imaging may help discriminate nonrejection, thereby avoiding unnecessary transplant biopsy in KTR with suspected AR. The diagnostic model might be able to test the accuracy of the diagnostic model.

Funding: Government Support - Non-U.S.

SA-P0994
High Remnant-Like Particle-Cholesterol Is a Risk Factor of Worsening Graft Function in Japanese Kidney Transplant Recipients

Background: Many factors cause dyslipidemia after kidney transplantation. Low density lipoprotein cholesterol (LDL-C) has been focused to reduce cardiovasucular disease (CVD). However, residual risk factors such as triglyceride (TG), remnants or small dense low density lipoprotein cholesterol (LDL-C) and omega-6 fatty acid (18:2n6) has been focused to reduce CVD. We investigated whether residual risk factors affect graft function of kidney transplant function.

Methods: This study is a retrospective cohort study at a single center. Three hundred and seventy seven kidney transplant recipients (male 223) in more than six months after transplantation were enrolled. TG, Remnant-like particle-cholesterol (RLP-C), non-high density lipoprotein cholesterol (HDL-C), LDL-C, ApoB, eGFR (estimated glomerular filtration rate), Urine protein /day (UP), Body Mass Index (BMI) and other parameters at baseline were measured and we studied the association of residual risk factors with kidney function. High RLP-C is a risk factor of worsening graft function in Japanese kidney transplant recipients.

Conclusions: High RLP-C is a risk factor of worsening graft function in Japanese kidney transplant recipients.

SA-P0995
The Modification of Erythrocyte Membrane Fatty Acid Contents According to Kidney Transplantation: Prospective Study
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Background: Modifications of erythrocyte membrane fatty acid (FA) contents may affect on cellular function or transmembrane receptors. The high erythrocyte membrane FA contents are related with acute cardiac syndrome. It is known that kidney transplant recipients have lower cardiovascular event than dialysis patients. Therefore, we prospectively evaluated whether erythrocyte membrane FA contents were modified after kidney transplantation (KTP).

Methods: We recruited 22 kidney transplanted recipients from September 2011 through May 2014. Blood samples were obtained just before KTP and at 6 months after KTP. The erythrocyte membrane FA contents were measured by gas chromatography.

Conclusions: The mean ages were 45.3 ±10.9 years. The erythrocyte membrane contents of omega-3 FA (10.1±3.9 vs. 5.5±3.63, p <0.001), omega-6 FA (26.6±6.2 vs. 20.7±7.7, p=0.008), arachidonic acid (11.6±4.1 vs. 7.7±4.7, p=0.001), docosapentanoic acid (1.4±0.7 vs. 0.7±0.5, p<0.001), docosahexaenoic acid (2.0±0.8 vs. 1.2±1.0, p=0.001), omega-3 index (70.3±2.5 vs. 4.1±2.7, p <0.001) were significantly higher but erythrocyte membrane contents of total saturated FAs (44.9±8.0 vs. 52.6±9.4, p=0.003), total monounsaturated FAs (17.2±1.6 vs. 19.9±2.2, p<0.001), total trans FAs (0.9±0.3 vs 1.1±0.2, p=0.011), oleic acid (15.7±1.5 vs. 18.0±1.9, p<0.001), and omega-6/omega-3 ratio (3.1±1.4 vs. 4.6±1.7, p=0.14) were significantly lower at 6 months after KTP.

Conclusions: FA contents of erythrocyte membranes including increased omega-3 FAs, decreased oleic acid and omega-6/omega-3 were significantly modified after KTP. These changes of erythrocyte membrane FA contents may effect on cellular function or transmembrane receptors. The high erythrocyte membrane oleic acid contents are related with acute cardiac syndrome.
**SA-PO996**

**Diffusion Impairment Measured by Functional MRI Correlates with Allograft Fibrosis After Kidney Transplantation in Patients with Delayed Graft Function**

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**Background:** Functional MRI parameters derived from diffusion weighted (DWI) and diffusion tensor imaging (DTI) correlate with renal fibrosis and cell infiltration in experimental studies. Aim of this study was to investigate these non-invasive techniques in patients with delayed graft function (DGF) and to correlate diffusion parameters with renal function and renal histology of allograft biopsies.

**Methods:** 33 patients with initial graft function between day 4 and 11 after kidney transplantation and 31 patients with DGF were examined on a 1.5 Tesla MRI. DTI and DWI sequences were acquired and apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were calculated. Kidney biopsies were available in 26 patients and analysed for acute rejection (Banff), amount of fibrosis, inflammatory infiltrates, and tubular injury as well as edema.

**Results:** ADC was significantly reduced in patients with DGF compared to patients with initial function. Similarly, FA, representing the degree of directed diffusion along anatomical structures such as tubules, collecting ducts and vessels, was impaired in DGF patients. ADC and FA positively correlated with renal function (r=0.573 and r=0.53, p<0.001) and negatively with the amount of renal fibrosis. Diffusion parameters in DGF patients did not discriminate between acute rejection and tubular injury. Histological evaluation of the allograft biopsies did not reveal any significant differences between DGF or initial function in the following parameters: leukocyte infiltration (CD4, CD8, CD15, CD20, CD68), CD31 positive peritubular capillaries or edema (interstitial tubular).

**Conclusions:** Functional MRI with diffusion techniques detects allograft dysfunction early after kidney transplantation correlating with allograft fibrosis. Biopsy is needed to verify rejection.

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

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**SA-PO997**

**Identification of Common Biological Mechanisms of Fibrosis in Transplanted and Native Kidneys with Chronic Diseases**

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**Background:** In both primary kidney diseases and in transplants fibrosis is caused by chronic progressive diseases. Hence, we hypothesised that fibrosis has fundamental common biological pathways in native and transplanted kidneys.

**Methods:** We studied the molecular associations with fibrosis in 703 kidney transplant indication biopsies (bx) 3 days to 35 years post-transplant. The number of bx with fibrosis increased with time post-transplant and most bx with ci>1 (74%) were attributable to time-dependent diseases (ABMR, GN, TG).

**Results:** By microarrays we compared bx with ci<1 to those with little or no fibrosis (ci<1) and determined the association strength of transcripts (p-value) for ci<1. First we focused on transcripts previously associated with fibrosis: immunoglobulin, mast cells and AKI-associated transcripts. Strongest associations with ci<1 were for immunoglobulin and mast cell transcripts, but not for AKI transcripts. Because time of bx post-transplant is highly correlated with ci, we repeated the comparison of ci<1 vs. ci<1 after correcting for time. This resulted in a massive reduction in association strength for the immunoglobulin transcripts, whereas AKI transcripts were now more strongly associated with fibrosis (from 10e-9 to 10e-18). Thus time correction emphasised the injury-repair response at expense of inflammation. We then analyzed the fibrosis associated transcripts in native kidneys (CKD). 73% of CKD transcripts overlapped with our transcripts.

**Conclusions:** Fibrosis in transplants and native CKD is characterized by the same inflammatory compartment, response to injury and loss of metabolism. Some of these processes might be related to the duration of chronic disease.

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**SA-PO998**

**DNA Double Strand Breaks Induced Collagen Type V1 Secretion of Glomerular Endothelial Cells in Renal Allografts**

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**Background:** The relationship between DNA injury and glomerular fibrosis in renal allografts remains unclear.

**Methods:** We examined renal allograft specimens from 35 patients in which DNA double-strand breaks and glomerular fibrosis were detected by phospho-histone H2A.X (γ-H2AX) expression and collagen (COL) types III, IV, and VI accumulation. We also examined the in vitro relationship between DNA damage and COL accumulation by mitomycin C (MMC)-induced DNA damage in human glomerular endothelial cells (HRGEc).

**Results:** The γ-H2AX and COL type V1, which mainly accumulated in the subendothelial and mesangial regions, were positively correlated with the duration of the post-renal transplant (RT) period (r=0.691, p<0.01; r=0.760 p<0.01, respectively). In multiple regression analysis, the duration of the post-RT period and cd in the Banff’07 classification were identified as significant predictors of COL type V1 accumulation (β value=0.699 p=0.001; 5.556, p=0.035, respectively) and γ-H2AX expression in the glomerular capillaries (β value 0.700 p=0.001; 2.031, p=0.011, respectively). In addition, the γ-H2AX-positive area was also identified as a predictor of glomerular accumulation of COL type V1 (β value=0.439, p=0.028). In the immunohistochemistry examination, γ-H2AX was detected in most cells after 24 hours’ MMC treatment, whereas no γ-H2AX expression had been detected before the MMC treatment. Although COL type V1 was detected around the nuclei of the HRGEc before the MMC treatment, it was not present there after the MMC treatment. COL type V1 was detected in the cytoplasm of the HRGEc, which was secreted into the supernatant after MMC stimulation with γ-H2AX expression. The number of γ-H2AX + COL type V1 (+) cells was inversely associated with the number of γ-H2AX (+) COL type V1 (+) cells (r=0.655, p=0.001) during 24 hours’ MMC treatment.

**Conclusions:** Our findings suggested that over the long term RT may induce DNA double-strand breaks and HRGEc-secreted COL type V1 accumulation in the glomerular capillaries, which might progress to intractable glomerular fibrosis.
SA-PO999

Imatinib Improves Interstitial Fibrosis in Deceased Donor Kidney Transplant: A Case Report

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Background: Imatinib (IM) is an oral inhibitor of tyrosine kinases. Early short term PDGF inhibition with IM has been shown to prevent intestinal fibrosis and tubular atrophy in pre-clinical kidney transplantation (KT). We assess the effect of long term IM therapy on renal allograft histology in a KT recipient who received IM for gastrointestinal stromal tumor (GIST).

Methods: Patient is a 47 year old female with ESRD due to hypertension, s/p living donor KT in 2007 which failed in 2010. She was then resumed on hemodialysis. A gastric mucosa was biopsied incidentally in 2012. Fine needle aspiration showed c-KIT positive spindle cells consistent with GIST. Patient received deceased donor KT in 7/2012 with Thymoglobulin induction. Maintenance immunosuppression included tacrolimus and mycophenolic acid. Patient was started on IM 100mg daily on day 19 post-KT because of GIST. Post-KT course was complicated by biopsy proven acute tubular necrosis, requiring dialysis in the first month post-KT. Serum creatinine (CR) improved to 1.6mg/dl by 3 months post-KT when she underwent partial gastrectomy. Pathology showed low grade GIST (low mitotic count and low Ki67 labeling index). Surveillance KT biopsy was performed at 6 months, 1 and 2 years post-KT. We compared the 6-month and the 2-year post-KT biopsies for the presence of renal cortical interstitial fibrosis using the Histolab software (Microvision Instruments, France). The core sections stained with Masson trichrome were scanned at high-resolution, and divided into individual images at 200X for quantitative analysis. The software program was then run to quantify fibrosis of the selected areas.

Results: The cortical fibrosis percentage was 20.17% for the 6-month biopsy and 14.35% for the 2-year biopsy. The corresponding serum CR was 1.52mg/dl and 1.71mg/dl, respectively. Though tacrolimus levels were maintained between 5 and 7ng/ml.

Conclusions: IM reduced renal cortical interstitial fibrosis in deceased donor KT. The role of long term IM in the prevention of interstitial fibrosis in renal allograft warrants further studies.

SA-PO1000

Factors Associated with Referral, Evaluation and Listing for Kidney Transplant: A Survey of Dialysis Patients

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Background: Kidney transplant (KT) is the treatment of choice for most patients with end stage renal disease (ESRD). Disparities in referral, evaluation, listing and transplantation have been documented. We studied factors associated with the likelihood of referral, evaluation and listing for KT.

Methods: We sent 1,283 dialysis units of. Since 2013 we invited participants who fulfilled inclusion criteria, we randomly selected and invited 1400 to complete the questionnaire. Independent variables were demographic factors, location, and mode of education about KT. In multivariate analysis, we calculated odds ratios (OR) and 95% confidence intervals (CI) for the probability of referral, evaluation and listing for KT.

Results: Of 673 participants, 401 had been referred, 361 had been evaluated and 201 were listed. Having received 3 or more modes of education about KT was associated with higher likelihood of referral (OR:5.03;CI:2.76-9.18), evaluation (OR:5.67;CI:3.23-9.46), and listing (OR:2.70;CI:1.43-4.18). Having attended a pre-ESRD class was associated with higher likelihood of referral (OR:2.20;CI:1.44-3.35) and listing (OR:1.83;CI:1.91-2.80). A transplant center within 10 miles was associated with higher likelihood of referral (OR:1.64;CI:1.09-2.56) and listing (OR:2.17; CI:1.32-3.57). Age > 60 was associated with lower likelihood of referral (OR:0.51;CI:0.33-0.79), evaluation (OR:0.46; CI:0.30-0.72) and listing (OR:0.28; CI:0.17-0.45).

Conclusions: Many factors influence the decision about KT; a process that begins with referral. Though difficult to change, proximity to a transplant center unsurprisingly improves chances for KT evaluation. Emphasis on educating patients > 60 may improve referral and evaluation. In this study, the quantity and diversity of educational modalities are the most important contributors to the referral, evaluation and subsequent listing.

Funding: NIDDK Support

SA-PO1001

Patient Navigation Program in Kidney Transplantation: A Randomized Study

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Background: We developed a patient navigation program in a kidney transplantation (KTx) clinic to improve KTx evaluation completion for patients deemed “high-risk” of not being placed on the KTx waiting list, based on known disparities in completion of KTx evaluation. We examined whether the addition of patient navigation to standard care was associated with a decrease in the number of days from a patient’s referral for KTx evaluation to KTx candidacy decision.

Methods: During evaluation scheduling at a single KTx center, patients answered questions from a risk assessment tool created using existing data; high-risk patients were randomized prior to KTx evaluation to either standard of care (control) or the additional assistance of a patient navigator (intervention). The patient navigator helped guide patients through the KTx process, serving as a point of contact and providing support and education from the time of referral for KTx evaluation through candidacy decision (patient approved for placement on waiting list or deemed “not a candidate”).

Results: From January 2013 to October 2014, 394 patients were enrolled in the study. Patient demographics were similar among intervention and control groups (80% Black, 88% female, 50% < age 55). A total of 311 (79%) accepted candidacy decision (79% of intervention and 79% of control patients) and were included in preliminary analyses. Intervention patients reached candidacy decision a median of 8 days faster than control patients (119 vs. 127 days). Shorter time to decision for intervention vs. control patients was observed in most examined subgroups, including blacks (9 days), patients who completed high school (10 days), Medicare patients (15 days), patients with BMI-35 (30 days), married (11 days) and single patients (7 days), and patients < age 55 (19 days).

Conclusions: Preliminary results support the efficacy of a patient navigation program in reducing time from patient KTx referral to candidacy decision in a KTx setting. The use of a similar program in other KTx centers may help patients who require additional assistance during the KTx process complete KTx evaluation more quickly.

Funding: Private Foundation Support

SA-PO1002

Knowledge of Treatment Options in Patients Evaluated for Kidney Transplantation: iChoose Kidney Randomized Trial

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Background: Although kidney transplantation (KTx) provides a significant survival advantage over long-term dialysis, many end stage renal disease (ESRD) patients are not educated about KTx options. We developed a clinical decision tool (iChoose Kidney) to provide individualized risk estimates of patient survival on dialysis vs. KTx to evaluate whether use of the decision tool during KTx evaluations improved patient knowledge of the survival benefit of KTx vs. dialysis and of living vs. deceased donor KTx.

Methods: In December 2014, we began enrolling patients from three large KTx centers across the U.S. in a trial, where patients are randomized to usual KTx evaluation (control) or an appointment during which the nephrologist uses iChoose Kidney with the patient (intervention). Pre- and post-nephrology consultation, we surveyed patients on whether they believed their chance of survival was higher, lower, or the same with 1) dialysis vs. KTx and 2) living vs. deceased donor KTx. Improvement in knowledge was defined as a change from incorrect to correct post-nephrology consultation. Health literacy was measured using the Newest Vital Sign and categorized into low/moderate vs. high (0-3 vs. 4-6 correct out of 6, respectively).

Results: To date, 214 patients are enrolled (target enrollment n=450). Among 106 intervention patients, 29% improved their knowledge of the survival benefit of dialysis vs. KTx, vs. 19% of 108 control patients (p=0.07). Among patients with low or moderate literacy, 35% of intervention patients improved vs. 13% of control patients (p=0.01); this difference was not observed among high literacy patients (26% improved in each group). For knowledge of the survival benefit of living vs. deceased donor KTx, 19% of intervention patients improved, vs. 11% of control patients (p=0.17).

Conclusions: Preliminary results show that the use of the iChoose Kidney decision tool in comparing survival estimates for dialysis vs. KTx may improve patient knowledge of treatment outcomes during KTx evaluation, and the tool may be especially effective among low/literacy populations.

Funding: Private Foundation Support

SA-PO1003

Hemodialysis Social Networks Facilitate the Completion of Transplant Testing and Successful Kidney Transplantation

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Background: Hemodialysis (HD) social networks may promote access to a kidney transplant (KT). We set out to observe the formation of HD social networks and their role in completing the steps of the transplantation process in a newly formed HD clinic.

Methods: Between 8/2012 - 2/2015, 46 patients admitted to a newly formed HD clinic were enrolled, 63% were new to HD. Patients spoke either English (78%) or Spanish (22%). All eligible patients were referred for transplant evaluation and testing. Progress on each step of KT was tracked. Patients were surveyed on admission and then quarterly using a previously validated questionnaire. Social interactions and seating were recorded, this data was merged with survey data and analyzed in SPSS 21.

Results: Two thirds of patients were observed to participate in social networks. There were no significant differences in geographic, education or socioeconomic variables between patients who participated in social networks “social” vs. those who didn’t “non-social”. More social patients wanted a KT, 100% vs. 73.3% (p=0.008). Social patients reported talking to other patients about their health or KT 64.5% vs. 6.7% (p < 0.001). Social patients completed more steps, 2 steps (range 0-6) steps completed vs. 0.3 steps on average for the “non-social” group (p=0.037). In a multivariate regression analysis, only participating in a social network was positively associated with completing more steps (β 1.44 p = 0.028), and vintage was negatively associated (β -0.973, p = 0.029).

Funding: None
Kidney Transplant Referral Among Incident Georgia Dialysis Patients with and without Systemic Lupus Erythematosus: The RaDIANT Community Study

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Background: Although providers often wait to start patients with systemic lupus erythematosus (SLE), shorter overall times to transplant are generally associated with more favorable transplant outcomes in SLE patients. We examined whether referral for evaluation—the first step in the often-years-long process of kidney transplantation—is delayed in dialysis patients with SLE, relative to other dialysis patients.

Methods: United States Renal Data System data on a cohort of 18,419 incident (1/1/05-9/30/12) adult (18-69 years) dialysis patients were linked to a patient referral, such as education and outreach activities targeting the patient, facility staff, and facility policy level. After the intervention, facility staff were asked to complete a 20-item questionnaire on the helpfulness (Likert scale) of each intervention activity and the likelihood (percent) of their facility continuing the activity.

Results: A total of 86 staff (51.2% social workers) at the 67 intervention facilities completed the survey. The median number of the 12 intervention activities completed by dialysis facilities was 9 (range, 0-11). Most facilities reported discussing the benefits of KT at a staff orientation (86.6%), attending monthly webinars (80.7%), and developing a referral improvement plan (76.3%) to be helpful or very helpful. The median number of prescribed intervention activities the facilities reported they would continue was 2, with the distribution of educational brochures (41.9%), a staff orientation focused on KT (41.9%), and patient and family education session (34.9%) among the most commonly cited.

Conclusions: Dialysis facility staff perceived that RaDIANT intervention activities were feasible to implement, with staff education potentially being the most helpful and sustainable component. Sustainability may be limited to intervention components that were at least as expensive and time intensive to implement. Additional ongoing support from ESRD Networks may be necessary to sustain increased KT referrals observed in the RaDIANT Community Study.

Funding: Other NIH Support - The RaDIANT Community Study is funded in part by NIMHD Award R24MD008077

SA-PO1007

Psychosocial Differences Between Living and Deceased Donor Renal Transplant Recipients Anna Bertram, Selma Pabst, Martina De zwaa, Tanja Zimmermann, Mario Schiffer. 1Clinic for Psychosomatics and Psychotherapy, Hannover Medical School, Hannover, Germany; 2Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.

Background: The specific impact of living donor (LD) as compared to deceased donor (DD) kidney transplants on psychosocial functioning has received surprisingly little attention. The present study aimed to assess whether LD and DD recipients differ in socio-demographic variables, time since transplantation, emotional variables, knowledge about immunosuppressant (IS) intake, and self-reported adherence to IS.

Methods: A questionnaire study was performed among 72 LD and 169 DD recipients who attended the kidney transplant outpatient clinic of Hannover Medical School for a follow-up visit at least 1 year after transplantation. Emotional responses were assessed using the Hospital Anxiety and Depression Scale (HADS) and the Transplant Effect Questionnaire (TEQ). Knowledge about IS (test consisting of 8 multiple choice questions, and IS adherence was measured by self-report (BAASIS), physicians’ estimates, IS trough level variability, and allograft rejection.

Results: Overall, LD recipients were younger and had a shorter follow-up since transplantation. Our results indicate that LD and DD transplantation may lead to different emotional responses with more feelings of guilt towards the donor and perceived responsibility to do well and with a generally higher anxiety level in LD recipients. LD recipients apparently had more knowledge about IS medication. However, they did not report more adherence to IS. No differences between LD and DD recipients were found for gender, educational level, depression, perceived social support, and allograft rejection.

Conclusions: Feelings of guilt and anxiety may be an important focus for interventions to improve emotional adjustment to transplantation, especially in LD recipients.

Funding: Other NIH Support - The RaDIANT Community Study is funded in part by NIMHD Award R24MD008077

SA-PO1006

Feasibility and Sustainability of the RaDIANT Community Study Among Georgia Dialysis Facilities Jennifer C. Gandee, Leighann Sauls, Teri Browne, Laura Plantinga, Laura J. McPherson, Eric M. Gibney, Laura L. Mulloy, Stephen O. Pastan, Rachel E. Patzer. Emory Univ; 1Southeastern Kidney Council, Univ of South Carolina; 2Piedmont Hospital, Georgia Regents Univ.

Background: The Southeastern Kidney Transplant Coalition developed the randomized, dialysis facility-level Reducing Disparities In Access tokidney Transplantation (RaDIANT) Community Study to address racial disparities and low rates of kidney transplantation (KTxs) in Georgia. We aimed to evaluate the feasibility and sustainability of the RaDIANT intervention activities.

Methods: The 67 dialysis facilities that completed a 12-month intervention as part of the RaDIANT study consisted of 12 recommended activities intended to increase KTxs referral, such as education and outreach activities targeting the patient, facility staff, and facility policy level. After the intervention, facility staff were asked to complete a 20-item questionnaire on the helpfulness (Likert scale) of each intervention activity and the likelihood (percent) of their facility continuing the activity.

Results: A total of 86 staff (51.2% social workers) at the 67 intervention facilities completed the survey. The median number of the 12 intervention activities completed by dialysis facilities was 9 (range, 0-11). Most facilities reported discussing the benefits of KTxs at a staff orientation (86.6%), attending monthly webinars (80.7%), and developing a referral improvement plan (76.3%) to be helpful or very helpful. The median number of prescribed intervention activities the facilities reported they would continue was 2, with the distribution of educational brochures (41.9%), a staff orientation focused on KTxs (41.9%), and patient and family education session (34.9%) among the most commonly cited.

Conclusions: Dialysis facility staff perceived that RaDIANT intervention activities were feasible to implement, with staff education potentially being the most helpful and sustainable component. Sustainability may be limited to intervention components that were at least as expensive and time intensive to implement. Additional ongoing support from ESRD Networks may be necessary to sustain increased KTxs referrals observed in the RaDIANT Community Study.

Funding: Other NIH Support - The RaDIANT Community Study is funded in part by NIMHD Award R24MD008077

SA-PO1005

Association of Kidney Transplantation Referral with Other Indicators of Quality Care Among Incident Georgia Dialysis Patients: The RaDIANT Community Study Lauren Plantinga, Stephen O. Pastan, Jenna Krisher, Eric M. Gibney, Laura L. Mulloy, Rachel E. Patzer. Emory Univ, Atlanta, GA; Southeastern Kidney Council, Inc., Raleigh, NC; Piedmont Transplant Inst, Atlanta, GA; Georgia Regents Univ, Augusta, GA.

Background: Dialysis facility referral of patients for kidney transplant is a potential indicator of quality care. We examined whether referral within a year of dialysis start (1-year referral) was associated with other quality indicators among incident Georgia dialysis patients.

Methods: We examined a cohort of 14,120 incident (7/1/05-9/30/11; follow-up through 9/30/12) adult (18-69 years) dialysis patients using United States Renal Data System data linked to concurrent referral data from all three adult Georgia kidney transplant centers. Multilevel, multivariable logistic regression was used to examine the association of 1-year referral with dichotomous quality indicators [pre-ESRD nephrology care, dialysis modality, permanent vascular access in place at dialysis start (HD patients only), pre-ESRD erythropoietin use, and transplant information at dialysis start], with adjustment for demographic and clinical variables and accounting for variation across clinics.

Results: Overall, 1-year referral was 24.8% and was higher among patients with other indicators of quality care: 26.0% vs. 23.8%, with vs. without pre-ESRD care (P=0.005); 27.8% vs. 24.6%, PD vs. HD (P=0.03); 28.3% vs. 22.9%, with vs. without a permanent vascular access in place at HD start (P=0.001); and 27.2% vs. 16.5%, informed vs. not informed of transplant options at dialysis start (P=0.001). With adjustment, pre-ESRD care [OR=1.34 (95% CI, 1.22-1.47)] and permanent vascular access in place [OR=1.44 (95% CI, 1.41-1.70)], and transplant information at dialysis start [OR=1.63 (95% CI, 1.45-1.85)] remained associated with higher 1-year referral.

Conclusions: These findings suggest that patients who receive quality care in multiple domains are more likely to be referred for kidney transplantation within a year of starting dialysis, independent of demographic and clinical characteristics. Interventions to increase transplant access should be targeted to patients whose care fails to meet other quality indicators.

Funding: Other NIH Support - NIMHD
SA-PO1010

The Difficult Road for Native Americans in Kidney Transplantation: Decreased Access and Reduced Long-Term Survival

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Background: Native Americans (NAs) have disproportionately high rates of end-stage renal disease, yet wait-listed NAs have lower rates of kidney transplantation than other racial/ethnic groups and worse long-term post-transplant survival outcomes than whites. This study evaluates these disparities across multiple medical and socioeconomic dimensions.

Methods: Using data from the Organ Procurement and Transplantation Network (OPTN), we evaluated wait list removal reasons and post-transplant survival rates from 3/1/95 to 12/31/12. We use a logistic regression model, controlling for patient, donor, match characteristics, and center and year fixed effects, along with a Blinder-Oaxaca decomposition of the results.

Results: Among registered patients removed from the wait list, NAs were less likely to receive a transplant (odds ratio, 0.71 [95% CI, 0.64-0.80]) and more likely to die on the wait list (1.88 [0.89-3.94]), compared to whites. NAs are less likely than whites to survive at least two years (odds ratio, 0.80 [95% CI, 0.70-0.92]) and at least three years (0.81 [0.71-0.94]), but these disparities become statistically insignificant with risk adjustment.

Conclusions: NAs experience higher rates of adverse wait list removal reasons than other racial/ethnic groups. Among NAs who do receive transplants, short term survival outcomes are similar to those of whites, but longer term survival outcomes are lower. The decomposition of our results indicates that the disparity in three-year post-transplant survival between NA and whites is driven primarily by the prevalence of lower quality donors among NA donors. Further investigation is required to identify source characteristics of survival disparities among NA. NAs also tend to receive transplants at centers associated with worse outcomes and would benefit disproportionately from receiving transplants at better centers.

Funding: Private Foundation Support

SA-PO1011

Estimated GFR for Living Kidney Donor Evaluation

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Background: All living kidney donor candidates undergo an evaluation of GFR. Guidelines recommend measured GFR (mGFR) rather than estimated GFR (eGFR), but measurement methods are difficult, time consuming and costly. We questioned whether eGFR using creatinine (eGFRcre) with or without sequential cystatin C (eGFRcre-cys) is sufficiently accurate to identify donor candidates with high probability that mGFR is above or below thresholds for clinical decision making.

Methods: We combined the pre-test probabilities for mGFR thresholds <60, <70, <80 and <90 mL/min/1.73 m² in varying age, sex and race groups estimated from the National Health and Nutrition Examination Survey (NHANES) with test performance of eGFR (categorical likelihood ratios [LRs] determined from the Chronic Kidney Disease Epidemiology Collaboration) to compute post-test probabilities of meeting a given mGFR threshold.

Results: Using NHANES pre-test probabilities, we found that in some circumstances, eGFRcre and eGFRcre-cys provides high accuracy (post-test probability≥95%) in candidate donors. Using data from the Scientific Registry of Transplant Recipients, we determined that 54% and 82% of recent donors had pre-donation eGFRhigh enough to ensure ≥95% probability that mGFRwas ≥90 and ≥80 mL/min/1.73 m² respectively, suggesting a large fraction of donor candidates might not require mGFR.

Conclusions: Implementation strategies could include eGFR as a first test and possibly eGFRcre-cys as confirmatory test. If post-test probabilities are of sufficient magnitude, eGFR could be used to accept or reject donors without measurement of GFR. We will provide a web-based application.

SA-PO1012

Change of Physical Activities in Male and Female Recipients in 12 Months After Living Kidney Donor Transplantation

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Background: Since renal dysfunction and immunosuppressive drugs cause muscle degeneration, physical activities decrease in CKD, dialysis patients and transplant recipients. In addition, elderly kidney transplant recipients are increasing in Japan, so improving physical activities and increasing muscle strength and volumes are important to prevent fractures and fall accident.

Methods: Consecutive 58 patients (male 33) older than 40 years were enrolled in this study from 2012. Immunosuppression basically contains steroid, cyclosporine or tacrolimus, and mycophenolatemofetil or everolimus. Hypertension, hyperlipidemia, and osteoporosis were treated as needed. Parameters of physical activities such as hand grip, SMI (skeletal muscle index) and Body fat mass using by DEXA (dual-energy x ray absorptiometry).

Results: Each year we are still growing the number of KT. The age of our recipients is diminishing and age of donors is increasing. Months before KT are also increasing lately reflecting the great number of ESRD patients. Recipient age, HLA mismatching, induction therapy use and generic drugs can explain the 13.2% of patients with Cr above 1.5 mg/dl.

Conclusions: Each year we are still growing the number of KT. The age of our recipients is diminishing and age of donors is increasing. Months before KT are also increasing lately reflecting the great number of ESRD patients. Recipient age, HLA mismatching, induction therapy use and generic drugs can explain the 13.2% of patients with Cr above 1.5 mg/dl.

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Underline represents presenting author.

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absorptiometry), and Body mass index (BMI) were measured and compared at prior, 6, and 12 months after kidney transplantation. Recipients were encouraged to do daily exercise for 30 to 60 minutes every day.

**Results:** Mean age (years) were 52.3±10.0 in male, and 53.6±10.4 in female. In male patients, any parameter did not change after transplantation in male patients. In female patients, SMI improved in 12 months (p<0.005), and Hand grip also tended to increase with statistically difference.

![Figure 1](image)

**Conclusions:** Disturbances of bone and mineral metabolism after transplantation are prevalent and are strongly correlated with the kidney function and transplantation duration.

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**SA-PO1015**

**Risk of Adverse Maternal and Fetal Outcomes During Pregnancy in Living Kidney Donors**

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**Background:** A frequently asked question by potential kidney donors is risk of nephrectomy on maternal and fetal outcomes in pregnancy. Studies regarding the risks of living kidney donation and pregnancy outcomes are conflicting. The purpose of this study was to determine the risk of adverse maternal and fetal outcomes in donors vs. non-donors.

**Methods:** Using data from an integrated health care delivery system in Utah from 2000 through 2014, a total of 72 women were living kidney donors that became pregnant after kidney donation. Using a pool of 74,105 women who were not donors, we selected 1223 to use for matches for the living kidney donors. These women were matched 1:3 by age and race. Adverse pregnancy outcomes were defined as preterm delivery, delivery via cesarean section, preeclampsia/eclampsia, length of stay in the hospital and low birth weight (<2,500 g). Logistic regression analysis was used to examine the association between donation and adverse outcomes.

**Results:** Of the living kidney donors, the mean (SD) age and mean (SD) gestational age at delivery was 31.0 ±3.6 and 19.5 ±2.4 months, respectively. The mean (SD) length of stay in the hospital was 2.7 ±0.7 days. Six cases (8%) had a history of chronic hypertension. Living kidney donors did not have a higher risk of preterm delivery (OR 1.82, 95% CI 0.87–3.77), preeclampsia/eclampsia (OR 1.11, 95% CI 0.47–2.65), delivery via cesarean section (OR 1.51, 95% CI 0.85–2.66), length of stay = 3 days (OR 1.29, 95% CI 0.63–2.64) or low birth weight (OR 1.94, 95% CI 0.87–4.35) compared to non-donors.

**Conclusions:** Living kidney donation is not associated with a higher risk of adverse outcomes in pregnancy.

**Funding:** NIDDK Support

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**SA-PO1016**

**The Quality of Life of Parents of Pediatric Kidney Transplantation**

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**Background:** The purpose of the study is to investigate how the Quality of life (QOL) of parents whose child had received kidney transplantation (KT) would change by delivering questionnaires four times; before, one month after, three months after and one year after KT.

**Methods:** The QOL of thirty-one parents (30 mothers and 1 father) with a mean age of 38.5 years old whose child received KT at Toho University Omoni Medical Center from May 2012 to March 2015 was measured using WHO Quality of Life (WHOQOL), Visual Analogue Scale (VAS), and General Health Questionnaire (GHQ). The mean age of the recipients was 5.8 years old (18 boys, 13 girls). Congenital anomalies of the kidney and urinary tract were the most frequent primary diseases (54.8%). Among them, twenty-two children received dialysis before KT, and nine received preemptive KT.

**Results:** Based on the results, the average WHOQOL scores show the QOL of parents decreased one month after KT (3.15) with a statistical difference compared with before KT (p=0.042), but increased at three months (3.40) (p=0.0073), and maintained until one year (3.41). The average QOL of the parents of a child with frequent infection was statistically lower than those without any infection (p=0.448) at three months after KT and one year after KT (p=0.046). The average QOL scores of nineteen donor parents had a statistically higher QOL before KT then reversed at one month after KT, but became higher again at three months after KT.

**Conclusions:** The QOL of the parents would decreased one month after KT when infection or other problems often occurred, but increased after three month when the condition of recipients stabilized and maintained until one year after KT, which became as high as before KT.

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**SA-PO1013**

**Search for New Data to Predict Kidney Transplant Outcomes in the Organ Procurement and Transplantation Network Database**

Mohamed A. Sheta,1 Bertram L. Kasiske,2 Charles E. Alexander,3 Joseph Kim.4 SA-PO1014

**Background:** The Organ Procurement and Transplantation Network (OPTN) collects data used to monitor transplant program outcomes for quality assurance and regulatory oversight. It is imperative that the variables in the OPTN database used by the Scientific Registry of Transplant Recipients to determine expected outcomes after kidney transplant be reliable, complete, and up-to-date.

**Methods:** We conducted a systematic review to identify risk factors not included in current OPTN data that predict graft failure or mortality after kidney transplant. We searched for studies with publication date between Jan 1 2000-May 1 2015; at least 1000 subjects in one or more risk prediction models; multivariate analysis used to select variables predicting patient or graft survival; inclusion in the multivariate model of at least one risk factor collected before or at the time of transplant that is not already collected by OPTN, and English language. For duplicate publications we selected the most recent. For publications with overlapping but distinct cohorts, we selected the one with the largest cohort. We arbitrarily limited the search to studies including 1000 participants in at least one risk-prediction model. Although a small single-center study may convincingly show that a newly described risk factor predicts outcomes at that center, there are likely major barriers to measuring and collecting this risk factor uniformly at every program in the US.

**Results:** We identified 33 studies that met inclusion criteria; 6 (18%) were single-center, 4 (12%) were multicenter, and 23 (70%) were registry studies. Promising new variables included: myocardial infarction, coronary artery revascularization, atrial fibrillation, congestive heart failure, valvular heart disease, cerebral vascular accident, congestive heart failure, aortic aneurysm repair, ischemic leg amputation, or revascularization, tobacco abuse, alcohol and illicit drug dependence, ZIP code, and socioeconomic status.

**Conclusions:** This review provides evidence for the new OPTN Ad Hoc Data Advisory Committee to update the OPTN database.

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**SA-PO1014**

**Prevalence of Mineral and Bone Disorders Among Living Kidney Transplant Recipients**


**Background:** Mineral and bone disorders (MBD), frequent complications of chronic kidney disease (CKD), occur frequently in kidney transplant recipients. Still, is known about its prevalence and clinical correlates in transplanted patients.

**Methods:** We conducted a cross-sectional analysis of 504 stable living kidney allograft recipients. Detailed medical history, demographic data and routine laboratory investigations, including s. creatinine, s. corrected Calcium, s. Phosphorus, serum iPTH and s. Alkaline Phosphatase (ALP) were collected. Estimated GFR was calculated using the abbreviated MDRD formula. Patients were stratified into three groups based on duration of kidney transplantation. Group I: 6 months to 1 year, group II: from 1 to 5 years and group III: more than 5 years. Correlations were done between bone minerals and all laboratory results. We also analyzed the possible relation between various immunosuppressant drugs and bone minerals, serum iPTH and serum ALP.

**Results:** The mean age was 32±8 years in group I, 45±3.7 years in group II, and 40±5 years in group III, with no significant difference between the three groups (p=0.005). There was no significant difference between the studied groups as regards of laboratory parameters (p=0.05). 115 patients had iPTH levels > 170 ng/dl, while 365 patients (72.4%) had iPTH levels >70 ng/dl. Only 24 patients had hypercalcemia, and 34 patients had hyperphosphatemia. We also found that 68 patients had hypophosphatemia. Serum iPTH and s. Alkaline Phosphatase levels were higher in group III (156±66 ng/dl; 135±54 IU respectively) when compared to group I (98±3.4 ng/dl; 120±3.3 IU) and group II (138±35 ng/dl;122±60 IU) (p<0.001). In group I, iPTH levels were negatively correlated with s.cGFR (r value = −0.37, p<0.05). Both serum ALP and iPTH levels showed significant negative correlation with s.cGFR in groups II and III (p<0.05). In all groups, bone minerals, iPTH and serum Alkaline Phosphatase levels had no statistically significant relation with the immunosuppressant agent used (p>0.05).

**Conclusions:** Disturbances of bone and mineral metabolism after transplantation are prevalent and are strongly correlated with the kidney function and transplantation duration.

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

867A
SA-PO1017

Disparities in Access to Renal Transplant in Puerto Rican Children

Nilda deJesus-Gonzalez,1 Sonia M. Caraballo,1 Eduardo J. Santiago-Rodriguez,2,3 Marta P. Suarez-Rivera,1 Melvin A. Bonilla-Felix.1 1Medical School, Pediatric Nephrology Div, Univ of Puerto Rico; 2Univ Central del Caribe; 3Puerto Rico Clinical and Translational Research Consortium.

Background: Disparities in access to renal transplant have been reported in racial minorities living in US. No data is available from children with ESRD living in Puerto Rico (PR). Although PR is the largest Hispanic group in a single pediatric dialysis unit in US. We describe the pediatric population with ESRD in PR from 2003–2013, the renal transplant rates and possible barriers to receiving a graft.

Methods: Retrospective chart review of patients diagnosed with ESRD in PR from 2003–2013. Incidence, prevalence rates, means/standard deviations (SD), medians/interquartile range (IQR), frequencies and percentages were calculated and compared to national rates.

Results: From 2003–2013 99 patients, male: 52%, age:13.5yrs (8-16yrs), were diagnosed with ESRD. Congenital anomalies were the primary cause in 40%, and FGSG in 24% . Incidence of ESRD ranged from 3-14 subjects per million population/year, with prevalence per dialysis modality from 7-18 subjects per million population/year. 38% were transplanted in PR (Median age: 14yrs, IQR: 9-16); 23% from living donors. 14.1% received a transplant in the first year (National rate: 38%); 63% of these non-transplanted children had Medicare coverage. None of 9 infants diagnosed with ESRD were transplanted during infancy. 46% of the children who were not transplanted stayed at our unit for a median time of 2 yrs (IQR: 1-3). The rest was transferred to a dialysis unit outside PR (15%) or to an adult facility without being transplanted (39%). 67% of these non-transplanted children were covered by Medicare. The mortality rate during the first year of diagnosis was 3% (National rate: 4%).

Conclusions: Children with ESRD in PR face striking disparities in access to renal transplant. Lack of pediatric transplant surgeons, geographical isolation and minimal living donation are potential barriers. Medicare coverage does not appear to be a factor, as it was similar between transplanted and non-transplanted. Interventions to reduce these inequities are needed.

Funding: Other NIH Support - Supported by grant 2U54MD007587 (RCMI Clinical and Translational Research Consortium, University of Puerto Rico Medical Sciences Campus) from the National Institute on Minority Health and Health Disparities (NIMHD), a component of the National Institutes of Health (NIH).

SA-PO1018

The Case against Declining Donors with Impaired Fasting Glucose

Robert N. Foley, Naim S. Issa, Danielle M. Berglund, Arthur J. Matus, Hassan N. Ibrahim. Univ of Minnesota, Mpls, MN.

Background: The definition of diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have changed over time. IFG was defined in 1997 by fasting glucose 110-125 mg/dL and in 2003 the definition changed to fasting glucose 100-125 mg/dL. With the introduction of this new definition, many potential donors with fasting glucose 110-125 mg/dL and in 2003 the definition changed to fasting glucose 100-125 mg/dL. With the introduction of this new definition, many potential donors with fasting glucose 110-125 mg/dL and in 2003 the definition changed to fasting glucose 100-125 mg/dL. With the introduction of this new definition, many potential donors with fasting glucose 110-125 mg/dL.

Methods: We assessed the risk of death, new onset diabetes, hypertension, proteinuria and reduced GFR (<45 ml/min/1.73m2 or eGFR <30ml/min/1.73m2 as compared to those with FBG <100 mg/dL. In contrast, those with FBG between 110-125 mg/dL were more likely to become diabetic and hypertensive but not proteinuric or reduced GFR. Those with FBG ≥126 mg/dL were more likely to die, develop DM and HTN but not suffer any adverse renal consequences.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fasting Blood Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100-109</td>
</tr>
<tr>
<td>Death</td>
<td>1.08 (0.8-1.47)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.19 (0.83-1.69)</td>
</tr>
<tr>
<td>HTN</td>
<td>1.2 (0.99-1.47)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0.68 (0.44-1.06)</td>
</tr>
<tr>
<td>eGFR &lt;45 ml/min</td>
<td>0.78 (0.43-1.43)</td>
</tr>
<tr>
<td>eGFR &lt;30 ml/min</td>
<td>0.96 (0.73-1.25)</td>
</tr>
</tbody>
</table>

* p-value <0.05 compared to FBG <100 mg/dL.

Conclusions: Excluding potential donors with a fasting glucose (100-109 mg/dL) should be revisited as these donors do well in the long-term.

Funding: Other NIH Support - N (SP01 DK103803)

SA-PO1019

Psychosocial Distress and Adherence in Adolescents Post-Kidney Transplant

Jessica L. Stahl,1 Angela P. Presson,2 Chong Zhang,2 Raoul D. Nelson,1 Matthew M. Grinsell.1 1Pediatrics, Univ of Utah, Salt Lake City, UT; 2Study Design and Biostatistics Center, Univ of Utah, Salt Lake City, UT.

Background: Adolescents who are post-kidney transplant have comorbidities in medical and psychosocial arenas and high risk of non-adherence and graft loss. Limited data exists to describe the relationship between mental health and adherence in this population. Descriptive statistics were used to assess the relationship of adherence to psychiatric diagnosis, psychosocial distress, gender, and time from transplant, as well as differences in parent-child reporting.

Results: Overall, 52% reported a psychiatric diagnosis, which is significant compared to 13% in the general adolescent population (p<0.001), with 38% evidencing elevated levels of psychosocial distress on self-report and 25% elevated per parent report. 68% of adolescents reported a different distress level than estimated by their parent. The psychiatric diagnosis rate was 64% in the non-adherent group and 36% in adherent adolescents. Only 40% of the adherent group reported elevated distress versus 57% of the non-adherent group. There was a gender bias toward male non-adherence in this group with 100% of the non-adherent population being male. The mean time from transplant of non-adherent groups was 6.1 years versus 3.9 years in the adherent group. These differences were not statistically significant except as above.

Conclusions: Our population’s rate of psychiatric diagnosis was significantly elevated compared to community norms and also correlated with elevated psychosocial distress and non-adherence. Disagreement in parent and adolescent reporting was common regardless of adherence status. Our sample did demonstrate gender differences in non-adherent behavior as well. Interpretation of these results, as well as statistical significance is limited by the small sample size.

Funding: Other NIH Support - This investigation was supported by the University of Utah Study Design and Biostatistics Center, with funding in part from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant R01AT000105 (formerly U1RRO25764).
The aim of this study was to investigate the influence of body composition, and body composition affect to kidney function and other prognosis of donors in our country. Sarcopenia is the independent risk factor of hypertension. It is unclear whether obesity baseline kidney graft biopsy findings and clinical course 1 year-after donation.

Four groups; (A) Obesity negative + Sarcopenia negative (ONSN) (B) Obesity positive + Sarcopenia negative (OPSN) (C) Obesity negative + Sarcopenia positive (ONSP) (D) Obesity positive + Sarcopenia positive (OPSP). We evaluated kidney function at donation, baseline kidney graft biopsy findings and clinical course 1-year after donation.

Results: Seven patients were OPSN (11.7%), 22 patients ONSP (36.7%), and 4 patients OPSP (6.7%). Visceral fat area >100 m^2 (which is defined as central obesity in Japanese criteria) and skeletal muscle index (SMI) from the appearance of muscle on cross-sectional CT images (L3 SMI, Under 38.5 cm^2/m^2 for women and 52.4 cm^2/m^2 for men are defined as a sarcopenia)(1). We divided donors into four groups; (A) Obesity negative + Sarcopenia negative (ONSN) (B) Obesity positive + Sarcopenia negative (OPSN) (C) Obesity negative + Sarcopenia positive (ONSP) (D) Obesity positive + Sarcopenia positive (OPSP). We evaluated kidney function at donation, baseline kidney graft biopsy findings and clinical course 1 year-after donation.

Conclusions: This is a retrospective single center study of 60 living kidney transplant donors from 2009 to 2014. Donors are stratified according to Body Mass Index (BMI)25kg/m^2 is defined as an obesity in Japanese criteria) and skeletal muscle index (SMI) from the appearance of muscle on cross-sectional CT images (L3 SMI, Under 38.5 cm^2/m^2 for women and 52.4 cm^2/m^2 for men are defined as a sarcopenia)(1).

SA-PO1012


Background: Currently obesity is a risk for chronic kidney disease. It is also suggested that sarcopenia is the independent risk factor of hypertension. It is unclear whether obesity and body composition affect to kidney function and other prognosis of donors in our country. The aim of this study was to investigate the influence of body composition, the findings of graft biopsy and 1-year after clinical outcome.

Methods: This is a retrospective single center study of 60 living kidney transplant donors from 2009 to 2014. Donors are stratified according to Body Mass Index (BMI)25kg/m^2 is defined as an obesity in Japanese criteria) and skeletal muscle index (SMI) from the appearance of muscle on cross-sectional CT images (L3 SMI, Under 38.5 cm^2/m^2 for women and 52.4 cm^2/m^2 for men are defined as a sarcopenia)(1). We divided donors into four groups; (A) Obesity negative + Sarcopenia negative (ONSN) (B) Obesity positive + Sarcopenia negative (OPSN) (C) Obesity negative + Sarcopenia positive (ONSP) (D) Obesity positive + Sarcopenia positive (OPSP). We evaluated kidney function at donation, baseline kidney graft biopsy findings and clinical course 1 year-after donation.

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SA-PO1013

Assessing Adherence Barriers in Pediatric Kidney Transplant Recipients - Charles D. Varnell,1 Kristin Loselle,1 Alina Lh Pai,2 Avani Modi,2 David K. Hooper.1 Div of Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Center for Treatment Adherence and Self-Management, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Nonadherence in pediatric kidney transplant recipients (KTRs) is associated with poor outcomes and poses a significant financial cost to society. Patient and family reported barriers to taking medications predict nonadherence, rejection, graft failure, and death. Despite their clinical importance and amenability to intervention, barriers to medication adherence are not routinely assessed in pediatric settings.

Methods: From Jan 2015 - May 2015, barriers to immunosuppressant adherence in KTRs were assessed using a standardized checklist of 14 common barriers. For KTRs≤10 y.o. the caregiver completed the assessment. For KTRs>10 y.o. both the patient and caregiver, if present, completed the assessment. Assessments were completed during routine outpatient clinic appointments.

Results: 36 pediatric KTRs [M(SD)age=13.1(4.3)years;56.7%male] and 50 primary caregivers completed a barriers assessment. At least one barrier was reported by 47% of KTRs compared to 42% of caregivers. For KTRs the most frequent barriers were forgetting(22%), hating the taste(13.9%) and running out of medicine(8.3%). For caregivers, the most frequently endorsed barriers were forgetting(20%), side effects(6.0%) and patient refuses to take their medication(6.0%). There was excellent concordance(96.2%) in dyads where both KTR and caregiver reported barriers. Assessing for barriers to adherence was easy to perform in practice and required<60 seconds.

Conclusions: Nearly half of all patients report at least one barrier to taking their immunosuppression, and there is generally consistent agreement between patient and caregiver perception of barriers. Standardizing the approach to assessing barriers to immunosuppression adherence in the clinical setting can quickly produce information that might be missed by the provider. Future research should evaluate the effectiveness of interventions delivered as part of routine medical care to overcome identified barriers and prevent known complications associated with nonadherence.
SA-PO1024
A Longitudinal Follow-Up of Hispanic Living Kidney Donors
Clarence E. Foster III,1 Pinky J. Patel,1 Hirohito Ichii,1 Madeleine V. Pahl,2 Elani Streja,3 Jonathan R. Lakey,1 Kamyar Kalantar,1 John C. Allen,2 Terence Kee Yi Shern,1 Tazeen H. Jafar,2 Sarah Stith,2 Abhijit Zadeh.
Universities of California, Irvine, Orange, CA; University of California, Irvine, Orange, CA.

Background: This is a long-term follow-up of living kidney donors (LKD) in an ethnically diverse patient population. Hispanics are known to have an increased risk of developing chronic kidney disease, associated with hypertension and obesity. The hypothesis is Hispanic living kidney donors or uninsured living kidney donors would have poorer long-term outcomes secondary to lack of access to health care and secondary to the higher risk factors for developing chronic kidney disease.

Methods: The objectives were to measure obesity, hypertension, diabetes, mean CrCl post-donation and compare to the pre-donation CrCl. LKD were contacted & invited to participate & had a questionnaire about their general health & history and physical. Analysis included a CBC, serum chemistry, a 24-hour urine collection to measure creatinine, protein and albumin. A Patient Data Visit Sheet, RAND 35 Health Questionnaire. The IRB approved this study.

Results:

Demographics

<table>
<thead>
<tr>
<th>Hispanic (23)</th>
<th>Non-Hispanic (19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36 +/- 12 (18 to 55)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>57</td>
</tr>
<tr>
<td>U.S. Citizen (%)</td>
<td>55</td>
</tr>
<tr>
<td>Health Insurance (%)</td>
<td>57</td>
</tr>
<tr>
<td>Years Post-Donation</td>
<td>3.8 (1.1 to 13.8)</td>
</tr>
<tr>
<td>Pre-Donation BMI</td>
<td>25.6</td>
</tr>
<tr>
<td>Pre-Donation GFR, ml/min, mean</td>
<td>122</td>
</tr>
</tbody>
</table>

Pre- and post-donation systolic and diastolic blood pressures were similar between Hispanics and non-Hispanic LKD. Non-Hispanic LKD had a greater decrease in systolic blood pressure post-donation -4.5 mmHg vs. 6.3 mmHg (p=0.0378). The decrease in CrCl post-donation was the same in Hispanic and Non-Hispanic LKD, 33 ml/min vs. 35 ml/min. None of the LKD in the study had significant proteinuria or microalbuminuria.

Conclusions: Post living donor kidney donation in our ethnically diverse patient groups are not at a higher risk for developing obesity, HTN, or CKD. Overall, our LKD feel they have a good overall quality of life including both physical and emotional realms.

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals

SA-PO1025
Predictors of Low Estimated Glomerular Filtration Rate After Living Kidney Donation in a Southeast Asian Population from Singapore
Bo-Yu Tan,1 John C. Allen,2 Terence Kee Yi Shern,3 Tazeen H. Jafar.1 Dept of Renal Medicine, Singapore General Hospital, Singapore; 2Duke-NUS Graduate Medical School, Singapore.

Background: We aim to investigate patterns of change in kidney function and factors and associated with low estimated glomerular filtration rate (eGFR) following living kidney donation in Southeast Asian.

Methods: We retrospectively studied living kidney donors with nephrectomy performed at Singapore General Hospital between 1976 and 2012. Quantile regression analysis was performed on pre- to post-nephrectomy percent change in CKD-EPI eGFR levels. Donors were grouped according to elapsed time from donation as short-term (>6 months to <5 years after donation), medium-term (5 to <10 years after donation), and long-term (³10 years after donation), and compared on pre-nephrectomy demographic and clinical characteristics.

Results: 174 donors, predominantly female (63.8%) and of Chinese ethnicity (73%), of average age 40.6 years, were recruited. Median (range) follow-up was 7.8 (0.1–33.8) years during which 30 donors (17%) developed low eGFR, defined as <60 ml/min/1.73m2. A 5.1% (1% to 9.7%) of donors recovered to a level that is at least 75% of pre-nephrectomy eGFR levels, and 9.8% exhibited 100% recovery to pre-nephrectomy eGFR levels at 19.2 years, on average. High pre-nephrectomy eGFR was predictive of low post-donation eGFR. A pre-nephrectomy eGFR cutpoint for prognosticating low post-donation eGFR was obtained using ROC analysis.

Conclusions: In general, kidney function is well preserved following kidney donation in Southeast Asian donors. Pre-nephrectomy eGFR is a good predictor of post-donation eGFR, especially in the short-term.

SA-PO1026
Post-Kidney Transplant Follow-Up in Native American: An Opportunity for Improvement
Fidel Barrantes,1 Sarah Stith,2 B. Presbytery Transplant Center, Renal Medicine Associates, Albuquerque, NM; 2Economics, Univ of New Mexico, Albuquerque, NM.

Background: Native Americans have been shown to face decreased access to waitlisting and transplantation. We explore the possibility that Native Americans might face decreased access to high quality post-transplant care, especially in the long-run, due to a decreased general access to healthcare, as is faced by many socioeconomically disadvantaged minority populations.

Methods: Using data from the OPTN, we evaluated the quantity and type of post-transplant care received by Native Americans. We compare Native American populations with other ethnic groups from October 1, 1987 to December 31, 2012 using multivariate regression analysis, controlling for time-invariant factors affecting all patients in a given year (year fixed effects) and time-varying factors associated with a specific transplant center (center fixed effects). (Standard errors are clustered at the center level to account for heterogeneous and spatial correlation among patients in a given center).

Results: Statistically significant regression results (p<0.05) indicate that Native Americans are less likely to receive transplant program-based aftercare than other racial/ethnic groups (Black, White, Hispanic and Asian/Pacific Islander), opting instead to see other types of specialists. They also see two percentage points more likely to be lost to follow-up (mean=0.15), one percentage point less likely to participate in an immunosuppression-related research study (mean=0.03), and receive 0.3 fewer follow-up visits (mean=2.2) than whites. They face the lowest number of follow-up visits, the lowest probability of participating in a research study, and the highest probability of being lost to follow-up. They also are 13% points less likely to work post-transplant (mean=0.35) than whites.

Conclusions: The results indicate that Native Americans have reduced access to high quality post-transplant care. Further research will explore how much of the disparity in post-transplant care is related to the high correlation between being Native American and poor and between being Native American and living in a rural area, especially on tribal lands.

Funding: Private Foundation Support

SA-PO1027
Medication Adherence Barrier Burden Predicts Subsequent Taking Adherence in Adolescents: A Social Media-Based Cross-Sectional Study
B. Presbytery Transplant Center, Renal Medicine Associates, Albuquerque, NM; 2Economics, Univ of New Mexico, Albuquerque, NM

Background: Longitudinal studies of objectively-measured medication adherence among high-risk adolescent kidney transplant recipients are lacking.

Methods: We aimed to determine whether the burden of perceived barriers to medication adherence predicted taking adherence (proportion of prescribed doses taken) during the subsequent 3 mo., as monitored with a multidose electronic pillbox. We evaluated the 126 participants of TAKE-IT with electronic adherence data available for the 3-mo. run-in period during which no intervention was applied. Participants (11-24 y; < 3 mo. post-transplant) were followed in 8 transplant centers (Canada and USA). Adherence barriers were assessed at baseline using the Adolescent Medication Barriers Scale (AMBS). A higher score indicates greater burden barrier (possible range 17-85). We used linear regression to estimate the association between baseline AMBS scores (total score and ingestion, disease adaptation, and cognitive/orGANization subscores) and taking adherence. Models also included sex, age, race, and time since transplant.

Results: 66% were male and 67% were white. Median age at baseline was 15.8 (IQR 13.2-17.1) y. Median time since transplant was 3.1 (0.7-7.5) y. Mean SD taking adherence for the interval was 87.0% ±28.9. Higher barrier burden (median score 38 (IQR 30-44)) was significantly associated with poorer adherence: a 5 unit higher total AMBS score was associated with 1.5% (95% CI 0.04, 3.0) lower taking adherence. Males had 7.5% (0.8, 14.3) lower taking adherence than females. The only subscale score significantly associated with taking adherence was disease adaptation: a 5 unit higher subscore was associated with 3.3% (0.4, 6.2) lower taking adherence.

Conclusions: While the absolute impact of barrier burden on adherence is small, higher burden of perceived barriers is a significant predictor of poorer adherence. Future analyses of the TAKE-IT data will determine the impact of an intervention targeting individual barriers on objectively-measured adherence.

Funding: NIDDK Support

SA-PO1028
Pre-Procurement Iodinated Contrast Exposure Is Associated with Early and Late Kidney Transplant Outcomes
Fidel Barrantes,1 Sarah Stith,2 Abhijit S. Naik,3 Isaac E. Hall,3 Mark A. Perazella.7 7Renal Medicine Associates, Albuquerque, NM; 7Economics, Univ of New Mexico, Albuquerque, NM; 7Internal Medicine, Univ of Michigan, Ann Arbor, MI; 7Internal Medicine, Yale Univ, New Haven, CT.

Background: Among high-risk adolescent kidney transplant recipients are lacking. We aim to investigate patterns of change in kidney function and factors and associated with low estimated glomerular filtration rate (eGFR) following living kidney donation in Southeast Asian.

Methods: We retrospectively studied living kidney donors with nephrectomy performed at Singapore General Hospital between 1976 and 2012. Quantile regression analysis was performed on pre- to post-nephrectomy percent change in CKD-EPI eGFR levels. Donors were grouped according to elapsed time from donation as short-term (>6 months to <5 years after donation), medium-term (5 to <10 years after donation), and long-term (³10 years after donation), and compared on pre-nephrectomy demographic and clinical characteristics.

Results: 174 donors, predominantly female (63.8%) and of Chinese ethnicity (73%), of average age 40.6 years, were recruited. Median (range) follow-up was 7.8 (0.1–33.8) years during which 30 donors (17%) developed low eGFR, defined as <60 ml/min/1.73m2. A 5.1% (1% to 9.7%) of donors recovered to a level that is at least 75% of pre-nephrectomy eGFR levels, and 9.8% exhibited 100% recovery to pre-nephrectomy eGFR levels at 19.2 years, on average. High pre-nephrectomy eGFR was predictive of low post-donation eGFR. A pre-nephrectomy eGFR cutpoint for prognosticating low post-donation eGFR was obtained using ROC analysis.

Conclusions: In general, kidney function is well preserved following kidney donation in Southeast Asian donors. Pre-nephrectomy eGFR is a good predictor of post-donation eGFR, especially in the short-term.

Funding: NIDDK Support
Effect SA-PO1030

View in a Prospective Cohort Study

Further research into the effects of deceased-donor management strategies is warranted to
organ procurement and subsequent adverse early as well as later kidney transplant outcomes.

Post-transplant patient survival. At three years recipients from donors with contrast exposure
in serum creatinine in the first week of transplant (mean=0.56). These patients also face
coronary angiograms. From this group, 14,628 kidneys were transplanted. Statistically
factors associated with a specific transplant center (center fixed effects with standard errors
during the week (OR=1.20, p<0.001).

1.82±0.57 vs 1.84 ±0.56, p=0.018). Fri-Sat DDK were more likely to be shared without
only were Fri-Sat DDK were more likely to be discarded (18.6 vs 16.4%, p<0.001), these
39.1±17.6, p<0.001) and of lower quality (KDRI 1.33±0.49 v 1.31±0.49, p<0.001). Not
attributed to the donation. The recommendations are to pursue the development of
the donation (96%).

recovered, three still feel physical pain, .4 have not recovered their PCS pre-donation
indicators. Three quarters of the donors underwent laparoscopy, associated with less
older. On average a 75 year-old donor has the PCS SF36 level of 35 year-old men in the
reflects the high commitment of donors.

Euroqol) and recovery were sent home. Medical data were from CRISTAL register. 384
of donors has been less studied and understood.

Underline represents presenting author.

SA-PO1029

One Year Recovery After Kidney Donation: The Medical and Donor Point of View in a Prospective Cohort Study Briançon Serge, 1 Lucie Germain, 1 Michele Kessler, 1 Marie-Alice Macher, 2 Marc Soudant, 2 Michele Kessler, 1 Marie-Alice Macher, 2 Marc Soudant, 1 Marie Thuong. 2

Conclusions: This large database analysis provided statistical power to detect an association between donor exposure to indinated contrast from coronary angiograms before organ procurement and subsequent adverse early as well as later kidney transplant outcomes. Further research into the effects of deceased-donor management strategies is warranted to expand the organ pool while decreasing adverse transplant outcomes.

Funding: Private Foundation Support

SA-PO1032

Deceased Donor Procurement in the U.S.: Measurement of Surgical Damage Inflicted Upon the Procured Organ Tim E. Taber, 1 Nikole Neidlinger, 2 Muhammad Ahmad Mujtaba, 1 Elling E. Eidbo, 1 Anil S. Paramesh. 1

Background: Deceased organ donation provides healthy allografts for the majority of organ transplants done in this country. While there are many factors involved in determining suitability of allografts for transplantation, one of the most important is careful
determination of the organ non-transplantable. For 12 consecutive months starting in January of
2014, 36 of 58 OPOs prospectively submitted quality data regarding organ damage seen
on the weekends adversely impacts organ procurement, acceptance and transplantation.

Background: Studies of adherence to timing of medication dosing in high-risk
adolescent kidney transplant recipients are lacking.

Methods: We aimed to determine whether the burden of perceived barriers to
medication adherence predicted timing adherence (proportion of doses taken £1 h. before
to £2 h. after the prescribed dosing time) during the subsequent 3 mo., as monitored with
a multidose electronic pillbox. We evaluated the 126 participants of TAKE-IT who had
electronic adherence data available for the 3-mo. run-in-period (no intervention). Participants
(11-24 y.; ≥ 3 mo. post-transplant) were followed in 8 centers (Canada and USA). Adherence
barriers were assessed at baseline using the Adolescent Medication Barriers Scale (AMBS).
A higher score indicates greater barrier burden (possible range 17-85). We used linear
regression to estimate the association between baseline AMBS scores (total score and
ingestion, disease adaptation, and cognitive/organization subscores) and timing adherence.
Models also included sex, age, race, and time since transplant.

Results: 60% were male and 67% were white. Median age at baseline was 15.8 (IQR
17.4, 17.6). Median time since transplantation was 1.1 (0.7-7.5) y. Higher burden of perceived
timing adherence for the interval was 82.6%±32.8. Higher barrier burden (median score 38 (IQR 30-44)) was
significantly associated with poorer timing adherence: A unit higher total AMBS score was
associated with 2.0% (95% CI 0.4, 3.6) lower timing adherence. A unit higher score was
associated with 4.3% (1.2, 7.5) lower timing adherence for the disease adaptation sub-scale,
and with 5.9% (0.2, 11.6) lower timing adherence for the cognitive/organization sub-scale.
Males had 10% (2.9, 17.6) lower timing adherence than females.

Conclusions: Higher burden of perceived barriers was a significant predictor of poorer
timing adherence in this longitudinal study. Future analysis of the TAKE-IT data will
determine the impact of an intervention targeting individual barriers on timing adherence.

Funding: NIDDK Support

SA-PO1030


Background: The experience alters neither the initial impetus nor the meaning
attributed to the donation. The recommendations are to pursue the development of
laparoscopy in informing organ management completely, to better prepare the donor to the
surgical procedure, its risks and aftermath, including professional ones in younger, to
maximize the opportunity for organ transplantation.

Results: Of 93,811 donors listed in study period, 8.5 % (8012) were exposed to
coronary angiograms. From this group, 14,628 kidneys were transplanted. Statistically
significant regression results (p<0.01) indicate that patients receiving organs from donors who
were exposed to coronary angiograms are 2% points more likely to receive dialysis within the
first week after transplant (mean=0.24) and are less likely to experience a ≥25% decline in
serum creatinine in the first week of transplant (mean=0.56). These patients also face
a 61 day shorter average graft survival time and a 1% point lower probability of 6-month
post-transplant patient survival. At three years recipients from donors with contrast exposure
have 2% decrease in survival rate (p=0.005).

Conclusions: This large database analysis provided statistical power to detect an association between donor exposure to indinated contrast from coronary angiograms before organ procurement and subsequent adverse early as well as later kidney transplant outcomes. Further research into the effects of deceased-donor management strategies is warranted to expand the organ pool while decreasing adverse transplant outcomes.

Funding: Private Foundation Support

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

871A
**SA-PO1035**

Deceased Directed Kidney Donations: A Three-Year Experience at a Single OPO

**Background:** The UAGA allows for deceased directed organ donations. Our OPO has incorporated the practice of offering the option of directed donations during every donation discussion in response to routine donor family requests. However, facilitating directed donations for donor families remains a controversial topic. Opponents suggest that directing gifts is not only inequitable, but that it may encourage malfeasance in the form of organ solicitation via media or social media. In an effort to standardize the language and timing of the directed donation discussions, we retrospectively reviewed our practice and examined our results in detail. For the three-year period, 176 of our 1,056 authorized donors had a potential directed donation. Of these, 80% were directed to patients on the kidney waiting list. However, only 16% of the attempted directed kidney donations resulted in a transplant. The data illuminate that incompleteness/mismatch of potential directed kidney recipients is the most common reason that directed kidneys are not transplanted, despite the fact that directed donations are allocated ahead of highly sensitized patients, mandatory shares, and significant requestors.

**Conclusions:** Facilitating directed donations will continue as part of our routine practice. Each year approximately one in six of our donor families identified potential recipients, but transplants from these requests remained consistently less than 2% of our annual total. Future studies are planned to evaluate recipient outcomes, assess donor family satisfaction with a recipient known to them, as well as to examine our practice in detail in an effort to standardize the language and timing of the directed donation discussions.

**SA-PO1034**

**Jeevandan: Deceased Donor Transplantation Programme from a Developing Country**

**Background:** In developing country like India the prevalence of end stage organ disease is increasing. Though transplantation has been in practice in India, its been grossly inadequate in terms of actual numbers of organs and organs. The only solution for the shortage of organs is deceased donor transplantation.

**Methods:** In India the Human Organs Transplantation Act, was enacted in 1994 with the objective of promoting and regulating the transplantation of human organs like kidney, liver and heart - both live as well as cadaver there was no significant increase in cadaver transplantation over the past two decades for various reasons. India follows “opt in” system and brain death declaration is not mandatory. Andhra Pradesh and Telangana are the two most populous states in India, situated on the country’s southern coast. It is India’s fourth largest state by area and fifth largest by population. Government of Andhra Pradesh, considering the shortage of organs and burden of end stage organ failure in the state, has come up with a Government Order called “Jeevandan” to streamline the procedure for facilitating and regulating the cadaver and organ transplantations on an end-to-end basis.

**Results:** There were 129 deceased donations in 2 years. Male were 93 and female 36: male to female ratio being 1: 2.58. The mean age was 41 years (range 8 to 79). Most common Blood group was O in 51 (39.5%) donors followed by B in 39 (30.23%), A positive in 22 (18.07%), AB in 10 (7.75%) donors. Total 593 organs included. Donor organs were retrieved from 129 deceased donors; 233 kidneys, 126 livers, 7 hearts, 118 heart valves, 103 corneas , 5 lungs and 1 Pancreas. Total deceased donor renal transplantations done during this period were 24.67%. Out of 129 donors, 6.8 % kidneys and 3% livers were not utilized. Mean age of renal recipients was 44.07 years (range 13 to 72). There were 26.8% females and 73.2% males, female to male ratio being 1: 2.73. Among deceased donor renal transplant recipients, O blood group was most common, seen in 36.79% followed by B in 32.38%, A in 22.64% and AB in 8.17% patients.

**Conclusions:** Deceased donor transplantation is the solution for organ shortage and increasing demand of organ requirement.

| Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only | Underline represents presenting author. | 872A |
primary failure modes. Evaluation of all transplant-related outcomes at specific follow-up
intervals will allow practitioners to assess the success of kidney transplantation and overall
recipient health and focus clinical outcome improvement efforts.

SA-PO1037
Clinical Outcome of Elderly Living Kidney Donors: A Single-Center Study in Japan
Jumpei Hasagawa, Kohei Unagami, Masayoshi Okumi, Kazuya Kwon, Hideki Ishida, Kazunari Tanabe. Urology, Tokyo Women's Medical Univ, Tokyo, Japan.

Background: Previous studies and current guidelines have suggested that elderly
persons can be living kidney donors; however, reports on elderly donors >70 years old are
limited. In order to clarify the donor safety and feasibility, we investigate the clinical outcomes of living kidney donors >70 years old after nephrectomy.

Methods: We conducted a case-series study of living kidney donations involving 48 donors aged >70 years at the time of transplantation. The kidney donations occurred between 2001 and 2014 at Tokyo Women’s Medical University in Tokyo, Japan. The primary outcomes were survival or end-stage renal disease (ESRD)-free rate and all crude event-free rates, including death, hypertension, infection, ESRD, or vascular failure rate. The secondary outcome was serum creatinine level at the end of the follow-up period.

Results: The 48 cases were followed up for a median of 4 years. The survival rate among the donors was 100% until the fifth year, and only two donors died during follow-up. The ESRD-free rate was 100% during the follow-up period. The overall event-free rate was 100% at 1 year, 85.7% at 3 years, and 75.0% at 5 years. The mean serum creatinine level was 1.18 ± 0.24 mg/dL at the time of hospital discharge and did not increase (1.18 mg/dL) at the end of follow-up.

Conclusions: Living kidney donation from elderly donors >70 years old appears to be a safe and acceptable option for patients requiring renal-replacement therapy.

SA-PO1038
Immunosuppressive Medication Adherence following Kidney Transplantation in the Military Healthcare System
Dustin J. Little, Matthew Ward, Robert Nee, Christina M. Yuan, Rahul M. Jindal. Walter Reed National Military Medical Center, Bethesda, MD; Uniformed Services Univ of the Health Sciences, Bethesda, MD.

Background: Limitations on the amount and duration of Medicare coverage of immunosuppressive medications (ISM) may contribute to ISM non-adherence and allograft failure. ISM adherence has not been reported in US patients who receive these medications at no cost. We therefore designed a prospective cohort to investigate the incidence of ISM non-adherence in Military Healthcare System (MHS) beneficiaries, who receive lifelong ISM coverage as well as prevention, identification, and treatment of depression should be prioritized for future study in order to improve outcomes following renal transplantation.

Funding: Other U.S. Government Support

SA-PO1039
Clinical Impact of Kidney Donor Follow-Up by Nephrologists
Hee Jin Kwon, Jin Hae Kim, Jeen Eun Park, Subin Hwang, Jung Eun Lee, Woosong Huh, Yoon-Goo Kim, Dae Joong Kim, Ha Young Oh, Hye Ryoun Jung. Nephrology Div, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea.

Background: Compensatory and adaptive mechanisms in the remnant kidney occur immediately after nephrectomy. The adaptability in early postoperative period may affect the renal function of the remaining kidney. Since the introduction of extended criteria living donor program, the numbers of marginal donors with risk of new morbidities are increasing. The aim of this study was to evaluate the clinical impact of kidney donor follow-up by nephrologists at a donor clinic (DC).

Methods: Our study included 427 living kidney donors from January 2010 to December 2014 in Samsung medical center. Nephrologist-run donor clinic was established in January 2013. The study period was divided into pre-DC and post-DC. Primary outcomes were incidence of CKD and renal functional adaptability (%MARD = post/pre eGFR X100) at 6 months after donation. Secondary outcomes were changes in compliance and incidence of co-morbidities; hyperuricemia and microalbuminuria.

Results: A total of 215 and 172 donors were included in pre-DC and post-DC, respectively. Before donation, age, sex, proportion of hyperuricemia and microalbuminuria were similar. Preoperative eGFR in pre-DC was significantly higher than post-DC (p<0.001). After donation, poor renal adaptation (post-donation eGFR at 6 months < 60% of preoperative eGFR) was less frequent in the post-DC period compared to the pre-DC period (p=0.026). CKD development tended to be higher in pre-DC period. Donors in the post-DC period had shorter mean outpatient clinic visit intervals (p<0.001), more visits within 6 months after donation (p=0.001), earlier detection of de-novo hyperuricemia (p<0.001)

Conclusions: After establishment of kidney donor clinic operated by nephrologists, donors tended to show better renal adaptability and earlier diagnosis and treatment of hyperuricemia. In conclusion, donor clinic may be a good strategy for improving renal outcome and detecting potential risk factors of CKD in donors.

SA-PO1040
Predicting Kidney Allograft Half-Life Using a Podometric Approach

Background: Increasing donor age is a powerful predictor of worse renal allograft outcome. Podocyte depletion is part of the normal aging process (Hodgin, JASN, 2015). Recently we showed that kidney hypertrophy that occurs at time of transition from a 2 kidney to 1 kidney state (transplantation), leads to a 20% reduction in podocyte density and a 6-fold increased rate of podocyte detachment associated with transplant glomerulopathy and allograft failure (Yang, JASN, 2014). To test the hypothesis that podocyte depletion could impact allograft half-life we used a model combining age specific podocyte nuclear density decrease and rate of podocyte attrition after transplantation for comparison with actual allograft outcome data.

Methods: Podocyte density was estimated from immediate post perfusion biopsies from living and deceased donors or from non-diseased nephrectomy specimens. Projected allograft life was predicted based on modeling age-specific podocyte density and the observed attrition of podocytes. Observed data were drawn from the OPTN/UNOS STAR files as of Sep 2014, using all transplants performed between Oct 1987-June 2013. A “conditional” Kaplan Meier analysis using the “period” method was used to calculate observed half-lives at different donor ages.

Results: The podometric projected average half-life for a 40 year old donor is 15.1 years, similar to the observed average allograft half-life (15.1 years). The projected effect of increasing donor age on allograft half-life from podometric measurements is similar to the observed effect of donor age on allograft half-life at all calculated donor ages (p=NS).

Conclusions: Quantitative podometric modeling predicts both shorter-than-expected average renal allograft survival and the donor age effect, compatible with the concept that hypertrophic processes at transplantation significantly impact half-life.

Funding: Other NIH Support - RW acknowledges the support of the National Institutes of Health (grants DK R01 46073 and the University of Michigan O’Brien Kidney Core Center P30 DK081943). F.A. was supported by NIH grant 5T32DK7378-34., Other U.S. Government Support, Private Foundation Support

SA-PO1041
Abstract Withdrawn
SA-PO1042
Prediction of Patient Survival After Kidney Transplantation (Tx): Construction, Validation and Evaluation of Decision Models Using Data Mining Approaches
Irina Scheffner,1 Kaixun Hua,2 Dan Simovici,2 Tanja Abeling,1 Hermann G. Haller,1 Wilfried Gwinnner.1 1Hanover Medical School, Germany; 2Univ of Massachusetts.

Background: Understanding the risk factors that predispose to death is important to deliver the most appropriate therapy to Tx patients (pts). Aim of this study is to build reliable tools for the prediction in order to identify the relevant risk factors for death using different data mining approaches.

Methods: We analyzed 761 pts transplanted between 2000 and 2007 (follow-up of up to 10 years). Data included biopsy results, clinical & laboratory factors. After conventional statistical feature selection, 28 variables we build Naïve Bayesian (NB), C5.0, RPART and Random Forest (RF) models.

Results: Compared to C5.0 and RPART, NB and RF resulted in models with a higher sensitivity to predict death and a high specificity. Using different partitions for training and test set, NB models had a sensitivity of 62-65% and a specificity of 89-91% to predict death. With RF, sensitivity was 64% and specificity 96%. Because of the imbalance of the outcome groups (13% deceased pts) modeling was repeated with balanced datasets obtained by oversampling. With the balanced data, sensitivity was 82% and specificity 79% with NB. With RF, sensitivity was 83% and specificity of 68%. These models were externally validated with two separate datasets showing sensitivities of 64 and 59% and specificities of 86% and 78% for the NB models and sensitivities of 84 and 61% and specificities of 60 and 65% for the RF models. Highly important variables were recipient age, pre-Tx diabetes mellitus, peripheral arterial and coronary heart disease, cold ischemia time, graft function within the first 6 weeks and annual GFR loss, and post-Tx systolic and diastolic blood pressure, urinary tract infections, and hyperparathyroidism. Modestly important variables included donor age, time on dialysis, HLA DR mismatches, delayed graft function; the predictive value of these models is very low. The models performed well for death prediction in our dataset and can be used to identify pts on risk. Moreover, with the identified (modifiable) risk factors pts can be assigned to different treatment strata to offer each patient the optimal therapy.

Funding: Government Support - Non-U.S.

SA-PO1043
The Decline of Dialysis in Northern Ireland Kathryn E. Larmour. Regional Nephrology Unit, Belfast City Hospital.

Background: The first session of haemodialysis in Northern Ireland (NI) was in 1959 for acute kidney injury. There has been an inexorably rise in the prevalent dialysis population in the province since then, with expansion of dialysis facilities to accommodate ever increasing numbers. However, in addition to inferior outcomes compared to transplantation, there are considerable costs and potential costs associated with chronic haemodialysis provision. This study considered the impact of an expansion in the living donor (LD) transplant programme on dialysis in NI and the financial implications.

Methods: The prevalence dialysis population from 1999-2011 inclusive data were retrieved retrospectively from collected data. The number of LD transplants in NI patients is prospectively recorded. The economic impact of the changes evident in our centre were studied. DN was classified as 1) donor related if present on biopsy <2 yrs from transplant and could be attributed to the donor, 2) recurrent if >2 yrs with history of pre-transplant DN, or 3) de novo if post-transplant biopsy may confer increase risk of allograft dysfunction.

Results: Underline represents presenting author.

Conclusions: Despite careful screening of transplant kidney donors, donor related DN may be missed on pre-surgical biopsy or not effectively reported and leads to renal dysfunction in the early post-transplant period. Donor related DN is a significant contributor to early allograft loss compared to recurrent or de novo DN and predicts poor long term graft survival.

SA-PO1045
Maternal and Fetal Outcomes in Living Kidney Donors in Korea Kyung Don Yoo, Hajeong Lee, Joo Yoon Park, Eunjin Bae, Jung Pyo Lee, Dong Ki Kim, Kwon Wook Joo, Youn Su Kim. Seoul National Univ Coll of Medicine.

Background: Maternal and Fetal Outcomes in Living Kidney Donors in Korea.

Methods: We tried to contact all of 417 female kidney donors. The thirty five donors who had no experience of pregnancy, and finally we could have got 253 questionnaires of kidney donors. Donors were compared in the three groups according to pregnancy pre-post kidney donation group and non-donor control group. The proportion of predonation pregnancies was 82% (370cases, Mean age 38.8 years), and postdonation pregnancies were 14% (56cases, Mean age 27.2 years). In the majority of postdonation pregnancy cases were detected in recent years from 2007 to 2014 (72.3%). There were no differences of fetal outcomes such as incidence of prematurity, low-birth weight and fetal death between the two groups. Gestational hypertension were no differences between the postdonation group and non-donor control group (5.4% vs. 5.8%). Donors with pregnancy after donation were more likely to have undergone Cesarean section (40.4%) than those with pregnancy before donation (21.9%).

Conclusions: This study revealed that maternal and fetal outcomes had little difference between the kidney donors and normal control. Further research using matched controls should be warranted.

SA-PO1046
Self-Monitoring Renal Function After Transplantation: A Clinical Trial on Safety and Usability Céline Lianne VanLint,1 Sandra Van dijk,2 Wenxin Wang,2 Mark Neerincx,3 Ton Rovekamp,3 Ton J. Rabelink,1 Paul J. Van der Net,1 Leiden, Netherlands; 2Faculty of Computer Science, Delft Technical Univ, Delft, Netherlands; 3Dept of Technology in Healthcare, Prevention and Health, TNO, Leiden, Netherlands.

Background: Kidney transplantation requires intensive monitoring which is burdensome for both patient and healthcare. With the availability of an innovative creatinine device, patients are enabled to monitor renal function at home. To investigate safety and usability of self-monitoring during the first year after transplantation an RCT was conducted.

Methods: The intervention group used a Statusensor® Xpress™ to measure creatinine at home during the first year after transplantation. Measurements were registered in a web-based system using a traffic light analogy to support interpretation of creatinine trends. Differences between groups regarding GFR were assessed at baseline (discharge) and at 1 year. Creatinine trends measured at home were compared to clinically relevant increases (>10%) measured in the hospital laboratory. A subsample of intervention patients were interviewed on self-monitoring experiences.

Results: In total 119 patients were included (intervention n=64; control n=55). GFR did not differ between groups at baseline, nor at 1 year (72.8 and 71.1 ml/min at 1 year for intervention and control group, respectively). For 34 out of 65 laboratory-based creatinine increases, sufficient home-based creatinine measurements were available for trend comparison. In 76% a similar trend was observed. Self-monitoring enhanced early detection of rejection in 3 out of 5 cases, none were missed. Satisfaction was high: 71% of the observed patients (n=26) would have liked to extend self-monitoring creatinine monitoring beyond 1 year.

Conclusions: The study revealed that maternal and fetal outcomes had little difference between the kidney donors and normal control. Further research using matched controls should be warranted.
Comparison of Heart Rate Variability in Kidney Transplantation and End-Stage Renal Disease Patients on Dialysis

**Background:** Heart rate variability (HRV) is a method for evaluation of autonomic nervous system activity by expressing the balance of sympathetic and parasympathetic tones. Some studies of HRV in patients with end-stage renal disease (ESRD) have been performed. However, few have examined kidney transplantation (KT) patients. Therefore, we investigated autonomic nervous system activity by means of HRV in patients with KT due to ESRD.

**Methods:** We compared the pattern of cardiac sympathetic and parasympathetic activity by time- and frequency-domain analyses of HRV with 24-h Holter monitoring of 23 KT and 56 dialysis patients. Patients underwent KT between January, 2008 and June, 2011.

**Results:** The mean ages of KT and dialysis patients were 54.2 ± 12.3 and 53.7 ± 12.6 years, respectively. The KT group showed increased time- and frequency-domain HRV (including HRV index), very low frequency (VLF), and standard deviation of normal R-R intervals for all 5-min segments of the entire recording (SDNNi), low frequency (LF), LP in normalized units (LFnorm), and LF to high-frequency power ratio, compared with the dialysis group.

**Conclusions:** Autonomic tone in patients with KT is higher than that in patients with ESRD on dialysis.

**Funding:** Private Foundation Support

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**SA-PO1049**

**Pregnancy in the Renal Transplant Recipient: Pregnancy Viability and Effects on Graft Function**

**Background:** Fertility in women is recovered few months after kidney transplantation. However, pregnancy viability and maternal complications remain unclear.

**Methods:** We studied data from patients from a kidney transplant center in Brazil from 2001 to 2012. In this retrospective study, we identified all pregnant kidney transplant recipients and collected clinical and laboratory data before pregnancy, every quarter and 12 months after delivery. Each pregnancy was considered a single event.

**Results:** We included 36 subjects and 53 events were found. The average age was 28.15 years. Pregnancy occurred 4.4±3 years after transplantation. Maintenance immunosuppression before pregnancy was prednisone, tacrolimus and azathioprine in 74% of the cases. The frequency of chronic hypertension was 38%, and 8% had preexisting proteinuria greater than 0.5g. 8 (15%) unintended termination of pregnancy (UTP) were observed in the first quarter and 4 (8%) occurred in the second quarter. Delivery was induced by medical conditions in 41% of cases. 9 (22%) premature births and 7 (17%) very premature births were observed. Two (5%) stillbirths and two (5%) neonatal deaths occurred. Maternal complications were proteinuria de novo (60%), urinary tract infection (23%), preeclampsia (9%) and high blood pressure (9%). During the follow-up period, two (6%) acute rejection and one (2%) graft loss occurred. Average baseline creatinine was compared with third quarter and 12 months follow-up creatinine and significant increase (1.17 vs. 1.46 vs. 1.59mg/dL, p<0.001) was found.

**Conclusions:** Although the sample is limited, the number of UTP was higher than the general population, with high rates of maternal complications. Besides, diagnosis of preeclampsia may be challenging because of the high frequency of hypertension and preexisting proteinuria. The sustained increase in creatinine suggests higher risk of long-term graft loss. Further research regarding the issue of pregnancy and kidney transplantation is required, in order to improve maternal safety and preserve graft function.

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

**SA-PO1050**

**Outcomes of Twin, Triplet and Quadruplet Pregnancies in Kidney Transplant Recipients**

**Background:** Pregnancy with multiple gestations. Given the increase in multiple gestations with the use of assisted reproductive techniques and the greater risks to the resulting fetuses, heightened surveillance in the transplant recipient population is warranted.

**Funding:** Pharmaceutical Company Support - Astellas Pharma, US, Inc., Pfizer, Inc., and Bristol-Myers Squibb Co.
SA-PO1051
Kidney Transplantation for End-Stage Kidney Disease After Hematopoietic Stem Cell Transplantation Akihiro Tsuchimoto, 1 Kosuke Masutani, 1 Kei Kurihara, 2 Hidetsuya Kitada, 1 Takehiro Nishiki, 1 Morihito Oto, 3 Masayoshi Okumi, 1 Tomokazu Shimizu, 1 Hideki Ishida, 1 Kazunari Tanabe, 2 Kazuhiko Tsuruya, 1 Takanari Kitazono. 1 Medicine and Clinical Science, Kyushu University, Fukuoka, Japan; Surgery and Oncology, Kyushu University, Fukuoka, Japan; 2 Surgery, Tomishiro Central Hospital, Okinawa, Japan; 3 Urology, Tokyo Women’s Medical University, Tokyo, Japan.

Background: Hematopoietic stem cell transplantation (HSCT) is associated with various kidney diseases. The safety of kidney transplantation (KT) for end-stage kidney disease (ESKD) after HSCT has not been established. In this retrospective multicenter study, we investigated the immunological background, immunosuppressive regimens, and outcome in the KT patients after HSCT.

Methods: We report our experience with 5 KT patients following HSCT: 4 patients received bone marrow transplantation and 1 received umbilical cord blood transplantation. Median age at the time of HSCT was 29 years old (ranged 13-54 years old), and ESKD developed after 119 months (67-307 months). The median duration of pre-transplant dialysis therapy was 18 months (7-69 months). In one patient, bone marrow and kidney were from the same donor.

Results: Median observational period was 18 (5-60) months. All patients were treated antibody-induction with basiliximab followed by triple immunosuppression consists of tacrolimus, mycophenolate mofetil and methylprednisolone. In one patient with positive complement dependent cytotoxicity cross match, we added rituximab, splenectomy and tacrolimus, mycophenolate mofetil and methylprednisolone. After KT, only one patient experienced severe diastolic hypertension (OR=4.833, P=0.048), but high mortality caused by infections, whereas we temporary gave immunosuppressive drugs. After KT, only one patient experienced severe diastolic hypertension (OR=4.833, P=0.048), but high mortality caused by infections, whereas we temporary gave immunosuppressive drugs. After KT, only one patient experienced severe diastolic hypertension (OR=4.833, P=0.048), but high mortality caused by infections, whereas we temporary gave immunosuppressive drugs. After KT, only one patient experienced severe diastolic hypertension (OR=4.833, P=0.048), but high mortality caused by infections, whereas we temporary gave immunosuppressive drugs.

Conclusions: Previous studies of KT patients after HSCT suggested low incidence of rejection and stable graft function, but high mortality caused by infections, whereas temporary gave immunosuppressive drugs. Although limited by small sample size and low event rate, our analysis suggests that pre-OLT CKD3 may have an effect on development of ESRD post-OLT. These effects if generalizable in larger cohorts are important for organ allocation.

SA-PO1052
The Risk Factors of Chronic Kidney Disease Occurrence in Patients Received Liver Transplantation Li Yuehong. Nephrology, Tsinghua Changgung Hospital, Medical Center, Tsinghua Univ, Beijing, China.

Background: Analysis the risk factors of chronic kidney disease (CKD) occurrence in patients with liver transplantation.

Methods: 190 patients received liver transplantation followed up during 2001 to 2013 were analyzed retrospectively. 40 patients developed CKD. The observation items included patients’ gender, age, primary diseases, surgical approach, postoperative complications, laboratory examinations (hemoglobin, albumin, creatinine, glomerular filtration rate), intraoperative blood loss and blood transfusion volume, postoperative complications and average serum calcium concentration (from liver transplantation to the onset of CKD). Clinical data of CKD occurrence group were compared with the non-CKD group. Chi square test, t test, and logistic regression analysis were used.

Results: The incidence of CKD in patients with liver transplantation was 21.1%. Renal pathology included IgA nephropathy, hepatitis B virus associated nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerular sclerosis and cryoglobulinemia associated renal injury. 85.7% patients had tubulointerstitial damage. Univariate analysis showed that preoperative renal function, hemoglobin, intraoperative blood loss and transfusion volume, postoperative acute kidney injury, average calcium concentration in serum from liver transplantation to the onset of CKD.

Conclusions: Although limited by small sample size and low event rate, our analysis suggests that pre-OLT CKD3 may have an effect on development of ESRD post-OLT. These effects if generalizable in larger cohorts are important for organ allocation.

SA-PO1054
Pre-Transplant CKD, but Not AKI, Impacts Survival in Liver Transplant Recipients Yorg Al Aziz, Girish N. Nadkarni, Vinay Nair, Thomas Schiano, Madhav C. Menon. Medicine, Icahn School of Medicine, New York, NY.

Background: Chronic kidney disease (CKD) stage and duration of RRT pre-liver transplant (OLT) have been associated with increased risk of progression to ESRD in OLT recipients. Currently, allocation of dual organ transplantation (liver/kidney) is limited to CKD stage 4 and/or RRT > 4 weeks. The data regarding the associations of less severe pre-OLT AKI (RRT=4 weeks) and, of CKD stage 3, with ESRD post-OLT is unclear. We examined the renal outcomes of OLT recipients at our center.

Methods: We reviewed charts of OLT recipients at Mount Sinai for clinical, demographic, laboratory and outcome data from the medical record. We utilized multivariable logistic regression for analysis.

Results: We had data on 115 OLT recipients from 2008-14 (mean age 57.7 years, 66% male). 55/115(47%) patients developed AKI pre-transplant, most often from HRS (47%). Pre-existing CKD-3 was present in 26/115 patients. Pre-OLT AKI developed in 23/26 CKD-3 patients. RRT was required in 8/26 CKD-3 patients. Mean eGFR at 1- and 2-year follow-up in the CKD-3 group compared to non-CKD group were 37.4 ± 16.6 vs. 33.3 ± 23.1(p=0.01) and 59.8 ± 20.8 vs. 62.7 ± 22.9(p=0.01) respectively. At a mean follow up of 1.4 years post OLT, proportion of patients developing ESRD was higher in CKD vs. non-CKD group (23.1% vs. 2.3%,p<0.01). Although, AKI was a significant predictor of ESRD (adjusting for age, sex, race, diabetes), its effect was attenuated after adjusting for CKD. CKD3 was the strongest predictor of ESRD (OR 8.34; 95% CI 1.55 7.9=0.02) (figure 1). Overall, patient survival at a mean of 2.4 years of follow-up was lower in CKD3 vs. non-CKD groups (76.9%vs. 91%=0.08).

Conclusions: Pre-OLT CKD, but not AKI, impacts survival in liver transplant recipients. Therapy to prevent AKI should be considered to improve patient survival.
C3 Alone Is Not a Prognostic Indicator of Patient or Graft Survival in Post-Transplant Glomerulonephritis

**Background:** The prognostic implications of glomerular C3 in the post-transplant setting are not well characterized.

**Methods:** We examined the presence and graft outcomes in 71 kidney transplant recipients diagnosed with glomerulonephritis (GN). Biopsies were studied by immunofluorescence (IF) for glomerular C3 staining and divided into two categories, C3-positive or C3-negative. Primary outcomes were graft and patient survival at 3, 12, and 36 months and at last follow-up. Serum creatinine (Cr) at last follow-up was a secondary outcome.

**Results:** Thirty-three (46%) patients were C3-positive and 38 (54%) were C3-negative. Mean follow-up was 103 months for positive C3 and 117 months for negative C3 groups. There were no significant differences among groups by age, gender, type of donor, or prevalence of hypertension, diabetes, and hepatitis B or C. A total of 57% of C3-positive patients had a functioning graft at 36 months post-transplant, compared to 75.1% of C3-negative (p=0.16). A total of 88.2% of C3-positive patients were alive at 36 months post-transplant, compared to 85.7% of C3-negative (p=0.9). The mean serum Cr for C3-positive patients at 36 months was 1.59 mg/dl compared to 1.71 mg/dl for C3-negative (p=0.15). There were no significant differences in graft and patient survival between two groups.

**Conclusions:** There was no significant difference in patient or graft survival, or in serum Cr between patients with GN and C3-positive IF compared to patients with C3-negative IF.

Pretransplant Hepatitis B Viral Infection Increased Risk of Death After Kidney Transplantation: A Multicenter Cohort Study in Korea

**Background:** Outcomes in kidney transplant recipients (KTRs) with hepatitis B virus (HBV) have not been well evaluated. Here, we aimed to investigate the recent posttransplant clinical outcomes of KTRs with HBV infection compared with those with hepatitis C virus (HCV) or seronegative patients.

**Methods:** Among 3885 kidney recipients from April 1999 to December 2011, 3490 patients were enrolled whose viral hepatitis serology data was available. Numbers of patients with HBV and hepatitis C virus (HCV) were 166 (4.8%) and 55 (1.6%), respectively. We analyzed the overall mortality and graft failure (GF) among patients who had taken KT.

**Results:** Patients with HBV showed poorer patient survival (P=0.030, adjusted HR=2.296, 95% CI 1.084-4.884) than KTRs without HBV. However, HCV did not affect patient survival (P=0.763). Patients with chronic hepatitis C showed increased incidence of GF (P<0.015, adjusted HR=2.306, 95% CI 1.178-4.606). However, the GF of patients with chronic hepatitis B (CHB) was not different (P=0.066). Among causes of mortality of KTRs with HBV, hepatic failure was predominant (44.4%). The KTRs with HCV had increased incidence of acute rejection (log-rank P=0.005; crude HR=2.147, 95% CI 1.344-3.432, P<0.001). Among KTRs with HBV, mortality was significantly correlated with higher grade of inflammation in pretransplant liver biopsy (P=0.007) and lower rate of prophylactic antiviral treatment (P=0.019).

**Conclusions:** The KTRs with CHB could show poor survival due to posttransplantation hepatic complications. Serious chronic liver disease and antiviral management of KTRs with CHB patients will be needed, even if liver function is within normal range.

Does Hepatitis B Virus Impact the Outcomes in Kidney Transplant Recipients? Analysis by Phases of Infection

**Background:** In kidney transplant recipients (KTRs) with hepatitis B virus (HBV) infection, immunosuppression may increase the risk for the progression of liver disease. HBV may contribute to allograft disease and anti-HBV therapy can have nephrotoxic potential.

**Methods:** Using OPTN/UNOS database, we selected adult KTRs from 2001 - 2011 who received peri-operative operative antibody induction followed by calcineurine inhibitor/mycophenolate mofetil maintenance along with without steroid. The cohort was divided into 4 groups based on the presence/absence of hepatitis B surface antigen (HBsAg) and core antibody (HBcAb) at the time of transplantation: HBsAg+/HBcAb- (acute infection); HBsAg+ /HBcAb- (developing immune response); HBsAg+/HBcAb+ (resolving infection) and HBsAg-/HBcAb- (HBV naive). Graft and patient survivals were compared among the groups in the table by using multivariate Cox model. Donor, recipient and transplant related confounders including lamivudine therapy were adjusted in the model.

**Results:** Adjusted graft and patient survival comparisons are shown in the table.

Incidence of Hepatitis B Viral Reactivation After Kidney Transplantation with Rituximab Administration

**Background:** The efficacy of antiviral prophylaxis for rituximab (RIT)-associated hepatitis B virus (HBV) reactivation in patients with malignant lymphoma has been reported. However, the effect of single-dose RIT on HBV reactivation in kidney transplant patients with hepatitis B surface antigen-negative (HBsAg−) and hepatitis B core antigen antibody-positive (HBcAb+) results is unclear, and there is no evidence for the necessity of prophylaxis in those patients.

**Methods:** From 2001 through 2014, 1021 patients underwent kidney transplantation (KTx) at Kyushu University and Tokyo Women’s Medical University, of whom 76 (7.4%) had HBsAg−/HBcAb+. Those patients showed hepatitis C virus (HCV)-RNA-negative, hepatitis B surface antibody-positive (HBsAb+) and HBV-DNA-negative. A RIT dose of 200mg/body was administered to 49 patients, and 45 patients did not receive prophylaxis. We monitored HBV-DNA and alanine transaminase levels 1-3 months after KTx. HBV reactivation was defined as an elevation of serum HBV-DNA level to >2.1 log copies/ml.

**Results:** HBV reactivation was found in 1 of 45 patients (2.2%) without prophylaxis. In the patient with HBV reactivation, serum HBV-DNA was detected at 6 weeks after KTx, and the maximum and maximum HBV-DNA levels were 2.1 and 2.6 log copies/ml, respectively. Although the patient was not treated with antiviral therapy, the HBV-DNA disappeared at 8 months after KTx. HBV reactivation was not found in the patients without RIT, and all 4 patients who received both RIT and prophylaxis. Four (8.9%) of the 45 patients developed acute rejection, and 1 patient (2.2%) died of sepsis during the observation period.

**Conclusions:** The incidence of RIT-associated HBV reactivation in the HBsAg−/HBcAb+ patients without prophylaxis was less than 5%, suggesting that low-dose RIT might be associated with low incidence of HBV reactivation. However, sequential monitoring of HBV-DNA is necessary to prevent severe de novo hepatitis.
Direct Acting Antiviral Agents for HCV-Infected Patients Transplanted with a Kidney from a HCV Positive Donor

**Methods:**
- **HCV RNA** (±) pts on the waiting list were consented to receive a kidney from a HCV (+) donor. Acceptance of a HCV (+) kidney significantly shortened wait time. Response to DAAs appears similar to that being reported for pts with cirrhosis with a mean age of 49.4 yrs. No pts were HIV or HBV co-infected. All pts were treatment naïve, genotype 1 and non-cirrhotic. Median wait time was 30 days after consenting to accept a HCV (+) kidney. Viral clearance rates are shown in figure 1.

**Results:**
- Ten pts have started DAAs therapy (5 others pending): 6 blacks and 4 hispanics with a mean age of 49.4 yrs. No pts were HIV or HBV co-infected. All pts were treatment naïve, genotype 1 and non-cirrhotic. Median wait time was 30 days after consenting to accept a HCV (+) kidney. Viral clearance rates are shown in figure 1.

**Conclusions:**
- Treatment of HCV with pegylated interferon during dialysis results in significant improvement of patients and graft survival following transplantation as compared to untreated patients. There is also trend of decrease in serious infection in treated patients. Sepsis and liver failure are two most common cause of mortality in untreated patients.

**SA-PO1065**

Impact of Treatment of HCV Infection on Renal Transplant Outcome

**Methods:**
- Adult patients on dialysis with HCV infection treated with pegylated interferon and subject to renal transplant (RT) formed the study group. Untreated patients subjected to RT during same period served as controls. Primary end points were patient’s and graft survival and secondary end points were serious infections and NODAT. Factors which affect the outcome like age, gender, diabetes as basic disease, diabetes vintage, HBV co-infection, HCV genotype, viral load, liver biopsy grade and stage, induction and baseline immunosuppression were considered for analysis.

**Results:**
- At the time of study, 2010 RT were done in department of which 133 had HCV infection. 30 were treated with 68% SVR and 103 were untreated. In untreated group, there were more males (92% Vs 77%), less dialysis number (137 Vs 211), less HBV co-infection (0.9% Vs 10%), less use of Tacrolimus (13.6% Vs 30%). There was no difference in terms of age, diabetes, HCV genotype, viral load, liver biopsy grade and stage, use of induction, Mycophenolate mofetyl and duration of follow-up in the groups. With mean follow-ups of 59 ± 22 months (range 12- 105), there was no statistically significant difference in terms of acute rejection (23% vs 15%), NODAT (10% vs 16.7%) and overall serious infections (23% vs. 15%) between two groups. However, there were 11 deaths in untreated group (8 sepsis related, 3 liver failure and 1 coronary artery disease) while only one death related to sepsis in treated group. Patients survival (97% vs 89%) and graft survival (97% vs 84%) was significantly better (p=0.05) in treated group as compared to untreated group.

**Conclusions:**
- High dose steroid therapy in BK viremia has been tried for the management of confusing cases of BK nephropathy (±mixed cellular rejection). However, the eventual fate of renal allograft after steroid therapy in the long term is still unknown. Therefore we investigated the graft survival and the change of BK viral load after steroid therapy in patients with BK viremia.

**Methods:**
- The study population comprised 144 kidney transplant recipients with BK viremia (serum BK viral load>1x10^4 copies/mL) consecutively detected at least twice, followed by steroid pulse treatment between July 2004 and March 2013. Patients were divided into two groups based on the amount of steroid: low dose (steroid 0-2g) or high dose (steroid>2g).

**Results:**
- A total of 123 patients belonged to low dose group and 21 patients were in high dose group. There were no differences in baseline characteristics, including age, gender, and the rates of biopsy-proven BK nephropathy and acute rejection. Serum BK viral loads at the time of steroid pulse therapy were 5.3±1.10 log copies/mL in low dose group and 6.00±0.98 in high dose group (p=0.054). They were changed into 5.25±1.05 and 6.14±1.45 in each group one month after steroid treatment (p=0.03) and 4.92±1.25 and 5.86±1.74 at two months (p=0.133), respectively. From three months to one year, serum BK viral loads were not different from each group. Kaplan Meier analyses demonstrated that the incidences of further 50% decline in renal function assessed by estimated GFR and graft failure were significantly higher in the high dose group (p=0.004 and p=0.04, respectively). In multivariate regression analysis, high dose steroid treatment (p=0.002, HR 9.61, 95% CI 2.25-40.99) and log serum BK viral load at two months after high dose steroid administration (p=0.027, HR 1.72, 95% CI 1.06-2.78) were important risk factors of further 50% decline in renal function.

**Conclusions:**
- In kidney transplant recipients with BK viremia, high dose steroid therapy induced BK viral activation and subsequently resulted in poor long term graft function and early graft failure.
SA-PO1063

Donor Seroreactivity Strongly Correlates with Recipient BKV-Viremia and Nephropathy

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Background: Incidence and severity of reactivating latent infections in kidney transplant (KTx) recipients are difficult to predict. In case of BK polyomavirus (BKV)-induced nephropathy, donor origin of infection is likely. Since BKV-seroreactivity reflects BKV-reactivity, we hypothesized that donor BKV-seroreactivity correlates with infectivity and predicts BKV infection of recipients.

Methods: In a retrospective cohort of 407 living donor-recipient pairs transplanted between 2003 and 2013 at LUMC, pre-KTx sera from donors and recipients were tested for presence and intensity of BKV IgG-seroresponses. Measured seroresponses were compared with recipient BKV-loads (viremia) determined post-KTxs and compared with other potential risk factors for BKV-infection.

Results: Within one year after KTx, BKV-viremia was observed in 27% of patients. Baseline BKV-serore prevalence among donors (96%) and recipients (95%) was high and not correlated with viremia. However, a strong association was observed between the strength of donor BKV-seroreactivity and occurrence of both viremia and PVAN (p=0.001). Baseline recipient BKV-seroreactivity as such was not associated. The hazard ratio of viremia was almost 10-fold higher in recipients of high compared to low seroreactive donors. In multivariate analysis, donor seroreactivity was the strongest baseline factor associated with viremia and nephropathy post-KTxs (p<0.001), outcompeting other described risk factors.

Conclusions: The strong association between donor BKV-seroreactivity and recipient BKV-infection points directly to the donated kidney as the source of BKV-induced disease and possibly reflects the BKV allograft load. Our findings warrant further research into the usefulness of BKV-serological testing prior to transplantation.

Funding: Private Foundation Support

SA-PO1064

The Role of BK Viral Subtypes in BK Viral Infection After Renal Transplantation

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Background: Risk factors for developing BK virus (BKV) infection after renal transplantation are unresolved, including the role of BKV subtypes.

Methods: We report on 146 patients with viral replication in urine tested by quantitative PCR (Cepheid-Affigene Kit) before transplantation (29 donors and 11 recipients, spontaneous replication in urine) and after transplantation (106 infected recipients, routine recipient BKV testing). Genotyping of BKV DNA subtypes was performed. Patients were grouped as: 1) BKV-negative (n=40, group 3).

Results: Twelve patients met inclusion criteria: mean age of 60.5, 3.1 years, 8 African Americans, 6 Black non-Hispanic, 2 without race data. There were 6 liver- kidney, 4 kidney, and 2 pancreas-kidney transplant recipients. All but 1 patient received tacrolimus as their CNI. Ten of 12 patients (83.3%) achieved SVR12. Mean tacrolimus levels increased significantly by 1.5 μg/mL between week 0 and 4 (p=0.014). Five (41.7%) required a mean tacrolimus dose decrease of 2 mg during treatment. Nine (75%) required a mean dose increase of 2 mg between EOT and SVR12. The ARI scores decreased from 0.64 to 0.17 between baseline and 12 weeks of treatment, but this is not statistically significant (p=0.216). Both serum creatinine and urine protein/creatinine ratio remained stable pre- and post-treatment (p=0.260 and 0.375, respectively).

Conclusions: SVR12 was achieved in 83.3% of KTRs treated with SMV + SOF. Renal allograft function was stable during and after HCV therapy. Treatment with SMV + SOF increased CNI levels during treatment.

SA-PO1065

Inflammation and Reconstitution Injury in Resolving Polyomavirus Nephropathy: Good or Bad? Insights from a Protocol Biopsy Based Prospective Study

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Background: Polyomavirus nephropathy (PVN) has been extensively studied at time of disease onset and in index biopsies. In contrast, little is known about acute and chronic changes occurring during PVN resolution under low dose maintenance immunosuppression. Aim: Enhance understanding of resolving PVN.

Methods: From 1/2009-9/2014 423 adult renal transplants with an 8.5% incidence of PVN (n=37) were prospectively followed at UNC. PVC patients were monitored with the urinary PV-Haufen test and protocol biopsies collected in 9/37 patients when the test turned from positive to negative as marker for PVN resolution. Histology in index PVN (n=9), and 11 post-transplant biopsies (n=9) was compared; clinical, treatment and long-term outcome data were obtained from electronic medical records.

Results: Serum creatinine and Banff scores at time of index PVN biopsy and follow-up protocol biopsy in Table 1.

SA-PO1066

Effectiveness of Simeprevir and Sofosbuvir in the Treatment of Hepatitis C Virus in Genotype 1 Post-Kidney Transplant Recipients

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Background: The 2014 American Association for the Study of Liver Diseases (AASLD) guidelines recommended the use of simeprevir (SMV) + sofosbuvir (SOF) for the treatment of liver transplant recipients with genotype (GT) 1 hepatitis C virus (HCV). There is a paucity of data on the treatment of other solid organ recipients. We conducted a retrospective, single-center analysis of kidney transplant recipients (KTRs) who received HCV treatment.

Methods: All KTRs who received HCV treatment with 12 weeks of SMV + SOF between January and November 2014 were evaluated. The primary endpoint was the sustained virologic response at 12 weeks after the end of treatment (SVR12). Secondary endpoints included HCV PCR levels, serum creatinine, urine protein/creatinine ratio, trough calcineurin inhibitor (CNI) levels and dose changes, and AST to platelet ratio index (APRI) at week 4, end of treatment (EOT), and 12 weeks post-treatment.

Results: Twelve patients met inclusion criteria: mean age of 60.5, 5.1 years, 8 African American, 6 Black non-Hispanic, 2 without race data. There were 6 liver-kidney, 4 kidney, and 2 pancreas-kidney transplant recipients. All but 1 patient received tacrolimus as their CNI. Ten of 12 patients (83.3%) achieved SVR12. Mean tacrolimus levels increased significantly by 1.5 μg/mL between week 0 and 4 (p=0.014). Five (41.7%) required a mean tacrolimus dose decrease of 2 mg during treatment. Nine (75%) required a mean dose increase of 2 mg between EOT and SVR12. The ARI scores decreased from 0.64 to 0.17 between baseline and 12 weeks of treatment, but this is not statistically significant (p=0.216). Both serum creatinine and urine protein/creatinine ratio remained stable pre- and post-treatment (p=0.260 and 0.375, respectively).

Conclusions: SVR12 was achieved in 83.3% of KTRs treated with SMV + SOF. Renal allograft function was stable during and after HCV therapy. Treatment with SMV + SOF increased CNI levels during treatment. CNI dose adjustment is needed to maintain therapeutic levels after SMV + SOF therapy.

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

Underline represents presenting author.

879A
Differences were observed in patients with early-onset (85%, P=0.139) or combined cases. Graft survival at 4 years was inferior in patients with late-onset CMV DNAemia occurred in 18%, 25%, and 13% of the patients being asymptomatic in majority (91%) of early+late-onset DNAemia groups, respectively.

2) early-onset (<3 months) DNAemia, late-onset (³3 months) DNAemia, and 4) combined prophylaxis for 3 months was given to 132 (high-dose valacyclovir, n=87; valganciclovir year post-transplant for CMV viremia (WHO standardization) and CMI (QuantiFERON® - Nice, France, Metropolitan; 2Laboratory of Immunology, Univ Medical School and Teaching Hospital, Pilsen, Czech Republic; 3Laboratory of Virology, Univ Hospital, Pilsen, Czech Republic; Hematooncology, Biomedical Center, Charles Univ Medical School and Teaching Hospital, Pilsen, Czech Republic.

Background: Although occurring very often the role of cytomegalovirus (CMV) DNAemia in patients managed by preemptive therapy or by universal antiviral prophylaxis is not established. The aim of the study was to determine the impact of different types of CMV DNAemia during 4 years after transplantion. Methods: A total of 180 consecutive renal transplant recipients at risk for CMV (donor and/or recipient CMV seropositive) were included and followed prospectively. Universal prophylaxis for 3 months was given to 132 (high-dose valacyclovir, n=87; valganciclovir n=45) patients, 48 patients were managed by preemptive therapy. Based on CMV DNAemia status during the first year after transplant patients were stratified to 1) no DNAemia, 2) early-onset (<3 months) DNAemia, late-onset (3 months) DNAemia, and 4) combined early+late-onset DNAemia groups, respectively. Results: Early-onset, late-onset, and combined early+late-onset CMV DNAemia occurred in 18%, 25%, and 13% of the patients being asymptomatic in majority (91%) of cases. Graft survival at 4 years was inferior in patients with late-onset CMV DNAemia compared to patients without CMV DNAemia (73% vs. 94%, P=0.002) while no significant differences were observed in patients with early-onset (85%, P=0.139) or combined early+late-onset CMV DNAemia (96%, P=0.682). Patient survival was comparable in all groups. Most severe to severe interstitial fibrosis and tubular atrophy assessed by protocol biopsy at 36 months was not increased in early-onset (15%, P=0.05), late-onset (21%, P=0.180), and combined (29%, P=0.069) CMV DNAemia compared to no CMV DNAemia group (36%). Likewise, renal function was not different at 36 months. Conclusions: Late-onset CMV DNAemia is a risk factor for graft loss after renal transplantation.

Funding: Government Support - Non-U.S.

SA-PO1069

Assessment of Cytomegalovirus-Specific Cell-Mediated Immunity for the Prediction of Cytomegalovirus Spontaneous Clearance in High-Risk Kidney Transplant Recipients with Cytomegalovirus Viremia Marie Lochouarn,1 Sylvia Benzaken,2 Laetitia Albano,1 Elisabeth Cassuto,1 Ahmed Jeribi,1 Anne Caramella,1 Valérie Giordanoen,1 Ghislaine Bernard,1 Vincent L.M. Esnault,1 Barbara Szeitz-Polksi,1,2 Nephrology and Kidney Transplantation Dept, Univ Hospital, Nice, France, Metropolitan;1 Laboratory of Immunology, Univ Hospital, Nice, France, Metropolitan;1 Laboratory of Virology, Univ Hospital, Nice, France, Metropolitan.

Background: Cytomegalovirus (CMV) is the most common virus pathogen in kidney transplant recipients (KTR) and CMV disease impacts patient and graft survival. CMV-specific CD8 T cell-mediated immunity (CMI) kinetics may help to assess the risk of CMV disease and to adapt preventive treatment strategies. Methods: High-risk KTR with CMV seropositive donor/seronegative recipient (D+R−) were longitudinally monitored after CMV prophylaxis discontinuation and during the first year post-transplant for CMV viremia (WHO standardization) and CMI (QuantiFERON®-CMV). We analyzed the ability of the CMI-test to predict subsequent spontaneous viral clearance in case of asymptomatic viremia after prophylaxis discontinuation or CMV disease recurrence after curative treatment.

Results: We enrolled 12 consecutive (D+/R−) KTR. Eleven patients developed viremia during follow-up. Spontaneous viral clearance occurred in 7 of 11 (63.6%) patients and 4 of 11 (36.4%) developed CMV disease. At viremia onset, 6 of 11 (54.5%) patients had a positive CMI-test. In those patients, the incidence of subsequent spontaneous viral clearance was 6 of 6 (100%) compared with only 1 of 5 (20%) among patients displaying a nonreactive CMI (p = 0.02). This latter patient revealed a positive CMI-test one month later. In the 4 patients who developed CMV disease, persistence of a nonreactive CMI after treatment in one patient was associated with disease recurrence, while patients whose CMI-test became positive under treatment showed no recurrence.

Conclusions: We show for the first time that D+/R− KTR with asymptomatic viremia attested by WHO standardized CMV viral load monitoring after prophylaxis discontinuation may benefit from QuantiFERON®-CMV to predict spontaneous viral clearance or CMV disease.

Funding: Pharmaceutical Company Support - Cellestis GmbH, a QIAGEN company, Darmstadt, Germany provided equipment entity (QuantiFERON®-CMV blood collection tubes)

SA-PO1070

Prevalence of Double Stranded DNA (dsDNA) Viral Infections Among Kidney Transplant Recipients Essays Mozaffari,1 Jay Lin,2 Melissa Lingolr-Smith,1 Chimerix Inc., Mendham, NJ;1 Novosys Health, Green Brook, NJ.

Background: Management of immunosuppression following solid organ transplant is a delicate balance between preventing graft rejection and minimizing the risk of infection. Antimicrobial prophylaxis can decrease the risk of infection, while increased immunosuppression can increase these same risks. Our objective was to estimate the occurrence of opportunistic infections, specifically dsDNA viral infections, in kidney transplant recipients.

Methods: Patients who received a kidney transplant between January 2009 and September 2013 were identified from the Premier Hospital database using ICD-9-CM codes. The first transplant procedure was defined as the index event. The frequencies of opportunistic infections, documented by diagnostic codes, were evaluated during the first 12 months after kidney transplant.

Results: Of patients who received kidney transplant (n=5,402; mean age: 50.8 years) 61% were male. Most patients received transplant in urban (98%), large (≥600 beds: 61%), teaching hospitals (84%). During the 12 month post kidney transplant, 33% (1,800 patients) had a diagnostic code for 1 opportunistic infection, and among these 25% (n=448) had at least one dsDNA viral infection. Among the 448 dsDNA viral infections, 81% (n=365) were cytomegalovirus (CMV), 8% (n=36) BK virus, and 16% (n=70) other dsDNA viral infections (HSV, VZV, HHV, HPV, EBV).

Conclusions: Opportunistic infections frequently result from the immunosuppression required following kidney transplantation. In our study, one-third of the kidney transplant recipients had a discharge diagnosis for at least one opportunistic infection. One of four opportunistic infections were classified as dsDNA viral infections, with the majority caused by human herpesviruses including CMV despite the common use of anti-CMV agents. Our study also highlights the rate of BKV-related complications, which represent an unmet need given the absence of therapeutic options for this dsDNA virus and the known association with BK-associated nephropathy.

Funding: Pharmaceutical Company Support - Chimerix Inc.

SA-PO1071

Antibiotics, Gut Microbial Diversity, and Infectious Complications in Kidney Transplant Recipients Anjali Masand,1 John R. Lee,2 Thangamami Muthukumar,1 Darshana Dadhania,1 Lilan Ling,3 Eric Pamer,1 Manikkam Suthanthiran.1 Medicine, Weill Cornell Medical College, NY, NY;2 Medicine, Memorial Sloan Kettering Cancer Center, NY, NY.

Background: Emerging data suggests that antibiotic usage can decrease gut microbial diversity and predispose patients to future bacterial complications.

Methods: We profiled serial fecal specimens by 16s rRNA deep sequencing in 26 kidney transplant recipients. Microbial diversity was assessed using the Shannon diversity index in subjects exposed to antibiotics in the 1st post-transplant month and in subjects not exposed. Based on a higher number of infections in antibiotic-exposed subjects, we conducted a retrospective study of 301 consecutive kidney transplant recipients and stratified antibiotic usage in the 1st month of transplantation and development of bacterial complications in post-transplant months 2-12.

Results: Subjects exposed to antibiotics during the 1st month of transplant had decreased gut microbial diversity and an increased number of infections in the 1st year of transplant.

Funding: Government Support - Non-U.S.
Hepatitis C infection (HCV) in kidney transplant (KTx) recipients has been shown to be an independent risk factor for decreased patient and allograft survival. Historically treatment of HCV has been interferon-alpha based, which is associated with acute rejection in KTx patients. With the development of new, oral, interferon-free directly acting antiviral (DAA) medications, treatment of HCV in renal transplant recipients is possible, but limited data exists on its safety and efficacy.

Methods: We performed a retrospective review of all KTx patients at our center with HCV on initiation of DAA. Analysis of the 9 studies (8 complete articles and 1 abstract; 1,735 patients) showed a RR of 0.58 (95% CI: 0.31-1.07) for incidence of CMV infection upon initial screening. Analysis of the 9 studies (8 complete articles and 1 abstract; 1,735 patients) showed a RR of 0.58 (95% CI: 0.31-1.07) for incidence of CMV infection in patients receiving alemtuzumab versus ATG. Other reported adverse effects in both induction groups (infections, post-transplant lymphoproliferative disorder (PTLD) and/or malignancy, decrease in estimated glomerular filtration rate , and post-transplant diabetes mellitus) were similar in both groups.

Conclusions: This study suggests that for induction therapy in kidney transplantation, the incidence of CMV infection associated with alemtuzumab is not significantly different than that associated with ATG.

SA-PO1074
Occurrence and Determinants of Antibiotic Resistance in Bacteruria After Kidney Transplantation

Background: Asymptomatic bacteriuria is often treated after kidney transplantation, which can result in the development of antibiotic resistance. Our aim was to assess the antibiotic resistance profile of gram-negative bacteria in our kidney transplant population, and to determine the factors associated with antibiotic resistance.

Methods: We performed a single center, retrospective cohort study in patients who received a kidney allograft at our center between January 1st, 2008 and June 1st, 2013. Through chart review, information on all bacteriuric episodes involving gram negative bacilli was collected during follow-up, which ended on June 1st, 2014. Bacteriuria was defined as growth exceeding 10^4 CFU/ml. Multivariable logistic regression using a generalized estimating equation (GEE) procedure was performed to identify the factors associated with resistance to antibiotics.

Results: Amongst the 318 patients studied, 629 bacteriuric episodes involving gram negative bacilli occurred in 143 patients. Resistance to TMP-SMX occurred in 336 episodes (53%), resistance to ciprofloxacin in 142 episodes (23%) and extended beta-lactamase production occurred in 30 episodes (5%). An increased risk of resistance to ciprofloxacin and/or extended spectrum beta-lactamase production was statistically associated with the number of previously treated bacteriuric episodes (2-4 previous treatments (odds ratio (OR):2.29, 95% confidence interval (CI):1.16-4.52), and ≥5 previous treatments (OR:3.05, 95%CI(1.28-7.26)), diabetes (OR:2.57, 95%CI:1.01-6.55), caucasian race (OR:0.38, 95%CI:0.16-0.91) and a longer time elapsed between bacteriuria and transplantation (OR:0.32, 95%CI:0.15-0.66, for episodes supervening >1 year post transplant versus ≤ 1 year).

Conclusions: Elevated resistance rates to TMP-SMX and ciprofloxacin were observed in our kidney transplant population, which can reduce the usefulness of prophylaxis with TMP-SMX and argue against treating asymptomatic bacteriuria, given the association we observed between the number of previous treatment of bacteriuric episodes and resistance to ciprofloxacin/ESBL production.

Funding: Government Support - Non-U.S.

SA-PO1075
Carbenapenem-Sparing Antibiotic Regimens for the Treatment of Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae Infections: A Comparative Study
Tiffany Ebony Biss, Gregory Malat, PharmD, Akshay Sharna, Dong Heun Lee, Alden Michael Doyle, Pharmacy, Hahnemann Univ Hospital, Philadelphia, PA; Surgery, Drexel Univ, College of Medicine, Philadelphia, PA; Infectious Diseases and HIV Medicine, Drexel Univ, College of Medicine, Philadelphia, PA.

Background: Extended spectrum beta-lactamase producing Enterobacteriaceae (ESBL-P) has been recognized as a significant cause of mortality in solid organ transplant recipients. Carbenapenem are the considered the drug of choice for the treatment of ESBL-P infections. However, antibiotic selective pressure associated with carbenapenem use may
Glomerular Diseases following Prednisolone Free Transplant with Low Dose Rituximab and ATG Induction and Protocol Biopsies
Vivek Pathak, Nephrology, Kovai Medical Center and Hospital, Coimbatore, Tamil-Nadu, India.

Background: The purpose of this study is to document the incidence of post transplant glomerulonephritis in a steroid free protocol and other recurrent renal diseases leading to graft loss.

Methods: 883 patients, who underwent renal transplantation at our institute in nine years and eight months since July 2005 till March 2015 were studied. Thymoglobulin was used for the induction of a dose of 1.5mg/kgm 3 doses rituximab 200 mg was given before transplant to those patients who were considered to be at high risk for rejection. Maintenance immunosuppression was Tacrolimus and Mycophenolate mofetil. Prednisolone was rapidly discontinued by fifth post operative day. All patients underwent protocol biopsies at 3 months, 1 year and 5 years and indicated biopsies whenever required. The total number of biopsies was 2928. Discussion Our results show only 1% graft loss due to cumulative recurrent Glomerulonephritis at nearly 10 years. Our figures could be low due to Thymoglobulin induction therapy. We could prevent graft loss due to recurrent FSGS by achieving complete or partial remission by using Rituximab in 15/19(79%) patients.

SA-PO1079
Pre-Transplant Rituximab in Recurrent Focal Segmental Glomerulosclerosis
John Manllo, 1 Dany Matar, 1 Sami Alasfar, 1 Jochen Reiser, 2 Nada Alachkar. 1 Johns Hopkins Univ; 2 Rush Univ.

Background: Focal segmental glomerulosclerosis (FSGS) recurs in 30-40% of patients after kidney transplant (Tx). Rituximab was suggested to have cross-reactivity with podocyte sphenogomelin-phosphodiesterase-ase-like-3b (SMPLD-3b), which was found to contribute to resistance, further stressing hospital epidemiology. Our study sought to compare the effectiveness of carbapenem sparing regimens to carbapenem-containing regimens on clinical outcomes in transplant patients with ESBL-PE infections.

Methods: We conducted a retrospective analysis of 1513 renal transplants between January 1980 and December 2013, included in our database, medical records and biopsy register, collecting all patients who presented recurrence of PGN. We excluded from the study patients with secondary GN and those without biopsy study. Renal biopsy was indicated according the following criteria: impairment of renal function, proteinuria $\geq$1g/day and/or microhematuria. The analysis statistic was SPSS version 18.

Results: 414 of 1513 RT (27%) had chronic GN as underlying disease. 317 patients (260 man;57 woman) were primary GN (21%). The most frequent primary GN was IgA nephropathy (IgAGN) n=122(38,4 %); Membranoproliferative GN (MPGN), n=90(28 %); Focal segmental GN(FSGS), n= 58(15,1 %); membranous GN(MGN), n= 33(10,4 %) and rapidly progressive GN (RPGN), n=14(4,4%). Forty(12,6%) patients with primary GN recurred. IgA GN (5%), FSGS (20%), MPGN (17%), MNGN (12%) and GRNP (12%). Three MPGN patients recurred in the second RT. The mean time of recurrence was: 48.18, 33.2, 18 and 33.2 months respectively Patients with graft loss due to GN recurrence were: IgAGN (n=10;75%), MPGN (n=14;93%), FSGS(n=10,75%), MNGN(n=3,70%). No significant difference was observed between GN types(p=0.15) and graft survival. In the Kaplan Meier analysis and COX test, recurrence primary GN had low survival at 10 years (p: 0.002). No significant differences was observed at 20 years (p: 0.15).

Conclusions: Clinical Recurrence of primary GN is an important cause of graft loss. GN with most recurrence was GSF and graft lost was MPGN. We didn’t observe differences in graft survival between type of primary glomerular disease. Graft survival was higher in the group without recurrence at 10 years and no differences at 20 years.

SA-PO1082
Kaplan-Meier Analysis of Allograft Loss Due to Recurrence of Glomerulonephritis, Rejection.Death(with a Functioning Allograft) and Other Causes.
to be reduced in post perfusion biopsies of kidney Tx recipients who later on developed recurrent (rFSGS). However, the use of rituximab to prevent rFSGS remains controversial. In this study, we assessed the efficacy of pre-Tx rituximab in preventing or delaying the recurrence of FSGS.

Methods: We enrolled 56 adult patients, 50 with biopsy proven FSGS and 6 with a pre-Tx course highly suggestive of FSGS. Patients underwent kidney transplant between 2008-2014. We compared FSGS recurrence and allograft survival between recipients who received rituximab and those who did not.

Results: Mean time of follow-up was 28.6 months. 24 patients received rituximab (tx 11), 35 patients developed rFSGS (17 (48%) of them received rituximab). Of the 21 who did not develop recurrence, 7 patients (33%) received rituximab. This difference was not statistically different (p=0.26). The time from Tx to rFSGS in the patients who received rituximab was 9.3 ±3.4 vs 8.7 ±3.7 months in patients who did not receive rituximab (p=0.7). The mean and standard deviation (SD) of eGFR at the most recent follow-up in the patients with rFSGS who received rituximab was 42.2 ±28 versus 39.2 ±21 mL/min/1.73m² in those who did not receive it, respectively (p=0.74). There was no difference in allograft survival in the two groups.

Conclusions: Our data showed that pre-transplant rituximab did not decrease the incidence or delay the development of recurrent FSGS, and did not improve allograft survival.

SA-PO1080

Role of Plasmapheresis in Post-Transplant Focal Segmental Glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) commonly recurs after kidney transplant (Tx). This is attributed to the presence of a circulating permeability factor that may be removed or diminished by plasmapheresis (PP). In this study, we assessed the efficacy of PP in prevention and treatment of post-Tx (rFSGS).

Methods: We prospectively enrolled 56 Tx-patients with biopsy proven FSGS (50) or de novo FSGS with a pre-Tx course suggestive of FSGS (6); patients were transplanted between 2008-2014. We compared between the preventive and non-preventive PP groups.

Results: Mean time of follow-up was 28 months. Differences between the 2 groups are as following:

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Preventive PP (n=25)</th>
<th>No PP (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>15 (60)</td>
<td>13 (43)</td>
<td>0.2</td>
</tr>
<tr>
<td>White (%)</td>
<td>17 (68)</td>
<td>14 (47)</td>
<td>0.23</td>
</tr>
<tr>
<td>Time from FSGS diagnosis to renal replacement initiation,(SD)</td>
<td>6.1 (8.6)</td>
<td>10.9 (11.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior Tx (n)</td>
<td>11 (44)</td>
<td>8 (27)</td>
<td>0.21</td>
</tr>
<tr>
<td>Living donor (n)</td>
<td>21 (84)</td>
<td>12 (40)</td>
<td>0.008</td>
</tr>
<tr>
<td>Induction with ATG (n)</td>
<td>25 (100)</td>
<td>26 (87)</td>
<td>0.23</td>
</tr>
<tr>
<td>rFSGS (n)</td>
<td>19 (76)</td>
<td>16 (53)</td>
<td>0.12</td>
</tr>
<tr>
<td>Time to rFSGS, month (SD)</td>
<td>7.7 (3.7)</td>
<td>10.5 (3.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean of most recent UPC, g/SD</td>
<td>2.7 (0.5)</td>
<td>2.0 (1.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

rFSGS developed in 35 patients (62%); of whom preventive PP was performed in 19. Out of the 21 cases that did not develop rFSGS, 7 received PP (P=0.1). Patients who received preventive PP had a shorter time from FSGS diagnosis to ESRD compared to those who did not (6.1±8.6 yr vs 10.1±9.1 yr (p 0.047)). 33 out of the 35 patients (95%) with rFSGS received therapeutic PP, and 24 also received anti-CD20 therapy. Only 5 (15%) did not respond; 2 lost their grafts. Of the 28 who responded, 14 (50%) subsequently relapsed. 71% of the relapses responded to a second course of PP; only 4 lost their grafts. Kaplan-Meier allograft survival in both groups is shown in figure 1.

Conclusions: Preventive PP does not reduce the incidence or delay the development of rFSGS. However, PP remains an effective therapy for post-transplant FSGS.

SA-PO1081

Post-Transplant Thrombotic Microangiopathy: A Single Center Experience

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Background: Thrombotic microangiopathy (TMA) occurs in 1-15% of kidney transplant allografts and predicts poor outcomes.

Methods: We reviewed 35 cases of TMA in the kidney allograft diagnosed at our institution between 2011-2015.

Results: The mean age was 39.1±14 years with 18 (51%) women. Three (9%) patients were recipients of simultaneous pancreas-kidney transplant. Among the recipients of kidney transplant alone, 21 (66%) received deceased donor grafts. The cause of end stage renal disease was unknown (37%), chronic glomerulonephritis (31%), obstructive uropathy (11%), diabetes (9%), hemolytic uremic syndrome (3%) or others (9%).

Induction with thymoglobulin or basiliximab was performed in 24 (63%) patients. Maintenance immunosuppression was prednisone (PRED), tacrolimus (TAC), and azathioprine in 15 (43%), PRED, TAC and mycophenolate sodium in 12 (37%) and PRED, TAC and everolimus in 3 (9%) patients. Patients were diagnosed with TMA at a median of 71 days (range: 5-1645) from transplant, wherein 37% patients developed TMA within 1 month of transplantation and 31% after 1 year. Mean serum creatinine was 4.5±3.3 mg/dL and 13 (41%) patients needed renal replacement therapy after TMA diagnosis. TMA was renal-limited in 22 (66%) patients. Concomitant acute rejection was present in 12 (34%) cases and cellular rejection was the most common (92%) type of rejection related to TMA. Cytomegalovirus infection occurred in 5 (14%) and other infections were present in 19 (54%) patients. Following diagnosis of TMA, calcineurin inhibitor (CNI) withdrawal was the first step in the management of 22 (63%) patients and 8 (23%) also received fresh frozen plasma (FFP) and/or plasmapheresis. The mean follow-up was 375 days (range: 2-4840); 22 (62%) patients had improvement or stabilization of renal function and 11 (31%) had allograft failure.

Conclusions: High clinical suspicion is essential for early diagnosis of TMA after kidney transplant. Withdrawal of CNI and treatment of concomitant rejections and infections contribute to renal function maintenance.

Funding: Private Foundation Support

SA-PO1082

Outcome After Eculizumab Therapy to Prevent Recurrence of Atypical Hemolytic Uremic Syndrome: Experience in Eleven Renal Transplant Recipients

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease with a high recurrence rate after kidney transplantation. aHUS is associated with histological lesions of thrombotic microangiopathy (TMA) that mainly leads to graft loss. The successful use of Eculizumab (Ecu) to prevent or to treat post-transplantation aHUS recurrence has been scarcely reported. In this study, we describe 11 patients who received a renal transplantation for aHUS and who were treated by Ecu after renal transplantation.

Methods: Eleven renal transplant recipients, with aHUS on their native kidney, received Ecu at our center between 2010 and 2015. Nine patients received prophylactic
Ecu at day 0. Two were treated at time of recurrence (day 6 and 25). We reviewed clinical, genetic, histological and data, and posttransplant course. Mean follow-up was 21.6±11 months.

Results: Five patients had at least one previous transplantation that failed secondary to recurrent aHUS. A genetic mutation was identified in ten patients (H factor (4); 1 factor (2), C3 (1), C4d (2), CFHR1 deletion and anti-H-factor antibody (1)). There was no graft loss and mean serum creatinine was 135± 60mmol/l at last follow-up. No patient experienced biological TMA recurrence under treatment. We found transient histological lesions in the 2 patients with later Ecu intervention. Three antibody mediated rejection (AMR) recurrences were noted during treatment including one associated with TMA lesions.

Conclusions: These data confirm that Ecu is highly effective to prevent post-transplantation aHUS recurrence, without graft loss and with a good renal function. However, Ecu doesn’t prevent AMR. The best treatment duration remains to be defined.

SA-PO1083

Recurrent of Scleroderma Renal Crisis After Renal Transplant Is Associated with Decreased Rates of Graft Survival and Earlier Graft Failure
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Background: The recurrence of Scleroderma Renal Crisis (SRC) after renal transplant has been previously described though its effects on outcomes and allograft survival are uncertain. Prior estimates suggest a recurrence rate of 20-50% (Pham et al, American Journal of Transplantation 2005, 5:2565-2569). Such rates of recurrence if leading to graft failure will have important implications. This study was conducted to better define the probability of recurrence and understand its impact on allograft and patient survival.

Methods: We identified cases of renal transplant recurrence for patients with SRC and all cases of disease recurrence in the UNOS database from 1987 to 2014. We analyzed the impact of recurrence on graft survival and compared this to outcomes of patients with other renal diseases: SLE, FSGS, and HUS.

Results: 11 patients were identified as having SRC as their primary diagnosis. Of those, 5.28% (26) had documented disease recurrence, which was similar to those with SLE (2.59%), FSGS (7.38%), and HUS (8.71%). Graft failure for any reason excluding death occurred in 80.8% (21) of patients with recurrence, compared to 24.5% (114) of those without recurrence (p = 0.00). Recurrent disease accounted for 11.9% (16) of graft failures in SRC, compared to 6.10% in patients with SLE as the cause of ESRD, 16.4% with FSGS, and 20.9% with HUS. The 5 year graft survival rates were similar: 68.7%, 63.2%, 67.8%, and 57.1% for SRC, SLE, FSGS, and HUS, respectively. SRC recurrence was associated with earlier graft loss; graft failure occurred an average of 628 days sooner than the recurrence group compared to non-recurrence, 1072 days versus 1700 (p = 0.021). Age, gender, and ethnicity were not associated with an increased risk of recurrence.

Conclusions: Identification of disease recurrence after renal transplantation holds prognostic significance. Both the rate and timing of kidney transplant failure is made more severe by recurrence. Post-transplant recurrence rates for SRC appear to be similar to those observed with SLE, FSGS, and HUS. Monitoring for recurrence of disease in these patients should be part of routine measures to reduce risk of allograft failure.

SA-PO1084

Clinical Characteristics of Recurrent IgA Nephropathy within the First Year After Renal Transplantation: Single Center Study
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Background: There are a few studies showing that the long-term allograft survival of patients with IgA nephropathy (IgAN) is lower than that of non-IgAN, indicating that the cause of lower graft survival is recurrence of IgAN. There have been no large, prospective studies defining the risk factors contributing to the development of recurrent IgAN, and preventive therapy for recurrent IgAN is unknown.

Methods: Retrospective data was collected from 2008 to 2013 on 61 consecutive biopsy-proven IgAN patients who underwent renal transplantation (RTx) in a single center, excluding one case of medication nonadherence. Protocol biopsies were performed at one week, six months and one year after RTx. Recurrent IgAN (rIgAN) is defined as positive for IgA in mesangial area and previously negative for IgA in immunofluorescence study.

Results: Of 61 patients, 7 had rIgAN within the first year after renal transplantation. There were no significant differences between rIgAN group and NOT rIgAN group in recipient age (mean±SD) (39±11.18, 41±12.33) years, sex (63%:19, 31%:23), donor age (55±9.5, 56±9.8) years, diabetes mellitus (2, 8) cases, PEKT (5, 23) cases, living-related donor kidney (5, 53) cases, immunosuppressants, time before transplant (11, 11), cases, ABO incompatible (18, 18) cases, HLA matching, HLA alleles in recipient including HLA-B35, DR4, DR3, HLA-B8, DR5, DR3, serum IgA concentration (263±0.66, 254±1.05)mg/dl, and urinary protein (0.57±1.29, 0.07±0.13)g/day. Duration of dialysis before transplantation (months) was significantly shorter in rIgAN group (11±2.03 vs 34.8±5.94, p=0.0383, Fisher’s exact test). Urine occult blood was also significantly higher in rIgAN group (p=0.008841, Mann-Whitney U test).

Conclusions: Both PEKT was not risk factor for recurrence of IgAN in this study, short-duration dialysis before transplantation could be novel risk factor for recurrence of IgAN. Further analysis is needed to determine risk factors for rIgAN and to establish preventive therapy for rIgAN for better graft survival.
Results: 16 suspicious masses were detected (12.5%). Of these only 9 had evidence of an aggressive disease (ACD) (four or more cysts) pre-transplant. The remainder had normal pre-transplant scans showing only small contracted kidneys or less than the required number of cysts to make a diagnosis of acquired cystic disease. We are following 14 of these patients with scans every 6-12 months to detect growth in newly discovered, less than 1 cm solid lesions. We have found 2 patients in which frank renal cell cancers were discovered. We have now adopted an annual screening process for all post-transplant patients at their one-year post-transplant visit.

Conclusions: Routine screening of native kidneys post-transplant appears critical to detect renal cell carcinoma at a stage early enough to achieve a cure by nephrectomy.

SA-PO1088

Non-Melanoma Skin Cancer Mortality in Kidney Transplant Recipients

Michael Thomas Burke,1 Annie-Claire Nadeau-Fredette,1 Carmel M. Hawley,1 Elaine M. Pascoe,2 Stephen P. MacDonald,2 Sunil V. Badve,1 David W. Johnson,1 Underline represents presenting author.

Background: Non-melanoma skin cancer (NMSC) frequently occurs in kidney transplant recipients (KTRs). However, the frequency of, and risk factors for NMSC mortality in KTRs are poorly characterised.

Methods: To determine the proportion and predictors of fatal NMSC in KTRs. This cohort study included all KTRs transplanted in Australia and New Zealand between 1980 and 2013, using Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry data. A multivariable competing-risk survival analysis was used to calculate risk factors for fatal NMSC in KTRs.

Results: During the study, 21875 transplant episodes occurred in 19344 patients. Of the 6780 patients who subsequently died, 231 (3.4%) died from NMSC. Of these, 172 (74%) were male, 226 (98%) were Caucasian, 219 (95%) were first graft recipients and 213 (92%) died with a functioning graft. Amongst first graft KTRs who died from NMSC, the mean age at transplantation was 48.8 +/- 13.7 years and the mean age at death was 61.8 +/- 11.1 years. Male sex (HR 2.0, 95% CI, 1.48 -2.74); Caucasian ethnicity (HR 5.31, 95% CI, 2.15-13.11) and pre-transplant skin cancer (HR 3.79, 95% CI, 2.38-6.04) were associated with NMSC mortality. Age at transplantation and multiple kidney transplants had time-dependent associations for NMSC mortality with the 5-year post-transplant HR 1.08 per year (95% CI, 1.06-1.1) and 2.90 (95% CI, 1.39-6.05); and the 15-year post-transplant HR 1.03 per year (95% CI, 1.02-1.04) and 1.29 (95% CI, 0.66-2.35) respectively.

Conclusion: NMSC is an important contributor to mortality in KTRs. Risk factors for mortality from NMSC include male sex, Caucasian ethnicity, pre-transplant skin cancer, multiple kidney transplants and older age at transplantation.

SA-PO1089

NFAT-Regulated Gene Expression in Patients Developing Non-Melanoma Skin Cancer

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Background: After transplantation the risk of non-melanoma skin cancer (NMSC) is significantly increased. Immunosuppression with calcineurin-inhibitors (CNIs) is associated with the development of NMSC. Association to the individual immunosuppressive loads of CNIs assessed by residual NFAT-regulated gene expression was investigated in renal allograft recipients.

Methods: Renal allograft recipients from the Department of Nephrology, University Hospital Heidelberg, Germany, were included. All patients had a regular annual skin examination. Residual expression of NFAT-regulated genes (IL-2, IFNγ, GM-CSF) in PMA/ionomycin-stimulated peripheral blood was measured by quantitative real-time PCR at predose and 2h after Ciclosporin A (CsA) intake.

Results: 258 renal allograft recipients were enrolled (160 male, age 51+14y). Of these patients 75 allograft recipients developed NMSCs after renal transplantation (29.1%). The following NMSCs were histologically confirmed: 36 basal cell carcinoma, 34 squamous cell carcinoma, 33 actinic keratosis, 27 Bowen disease, 8 kerato-acanthoma. As risk factors to develop NMSC were identified: age 60 years, skin type ( Fitzpatrick 1 and 2), and load of immunosuppression. NFAT-regulated gene expression was significantly lower in patients who developed NMSCs compared to patients without NMSCs (8.3±6.5 vs. 12.7±12.8%, p<0.001). Squamous cell carcinoma and actinic keratosis were significantly associated with a high inhibition of IL-2 and IFNγ. Patients with basal cell carcinoma and Bowen disease showed a general low expression of NFAT-regulated gene expression. However, in patients with kerato-acanthoma no significant inhibition of NFAT-regulated gene expression could be detected.

Conclusions: The immunosuppressive load contributed to the risk of NMSC. NFAT-regulated gene expression was significantly inhibited in patients developing NMSCs. Monitoring of NFAT-regulated gene expression in CNI treated transplant recipients provides an individual profile of response to CNIs and is a useful tool for an individual immunosuppression with respect to safety and toxicity.
Role of Toll-Like Receptors in Aristolochic Acid Nephrotoxicity
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Background: Studies demonstrated that aristolochic acid (AA) is toxic to renal tubular epithelium and carcinogenic to renal epithelium. Although the exact extent of AA nephropathy (AAN) is unknown, case series have been reported in throughout the world and it has been implicated in the etiology of Balkan endemic nephritis (BEN) suggesting that this is a global health problem. The precise mechanisms of AA nephrotoxicity are not known. We investigated the role of Toll-like receptors (TLRs) in the pathophysiology of AAN using human renal proximal tubule epithelial cells (RPTECs).

Methods: Confluent RPTECs were exposed to AA (50 µM – 480 µM) for 24 – 48 hr and cytotoxicity was measured using lactate dehydrogenase (LDH) assay. RNA and protein were isolated from AA-exposed and unexposed RPTECs. Real-time RT-PCR was performed for various gene primers to evaluate the role of innate immunity in AAN development.

Results: At 240 µM after 48 hr exposure, AA induced significant Cytotoxicity in RPTECs as measured by LDH release in the culture medium and significant cell injury was observed morphologically. AA significantly increased mRNA expression of acute kidney injury (AKI) biomarker neutrophil gelatinase-associated lipocalin (NGAL), but at the same time significantly decreased the expression of another AKI biomarker kidney injury molecule 1 (KIM-1). AA also significantly upregulated the expression of prominent AKI-related TLRs (TLR2, TLR4 and TLR6) and their adaptor molecules (MyD88 and TICAM-1) followed by the activation of pro-inflammatory cytokines (IL-6 and TNF-α) and the tumor suppressor protein and a biomarker for apoptosis, p53, in the down-stream signaling pathways of TLRs. AA also significantly upregulated expression of multi drug resistant family gene MDR1 in RPTECs. Conclusion: AA is toxic to RPTECs and restricts cell growth. NGAL but not KIM-1 could be a diagnostic biomarker for AAN. AKI prominent TLR2 and TLR4 could be potential candidates for therapeutic target in developing new strategies for AAN and BEN treatment.

A Case of Severe Symptomatic Iatrogenic Hypermagnesemia
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Background: Hypermagnesemia is an uncommon but a potentially life threatening condition. Symptoms may develop in patients with acute kidney injury (AKI) or chronic kidney disease with the administration of pharmacologic dose of magnesium (Mg), and with use of oral laxatives or magnesium containing enzymes.

Methods: A 30-year-old African American man with baseline Cr of 1, admitted for management of multiple fractures, subdural hemorrhage and traumatic brain injury sustained in a motor vehicle accident, suddenly became hypotensive and developed AKI. UOP declined from 2-3 ml/day on admission to 700 ml over the next 24 hours. He became areflexic and developed ARDS, with increasing FiO2 requirements. Repeat laboratory data showed Cr 3.9, hemoglobin 6.9 and Mg 9.5 mg/dL. Review of his chart revealed he had received a total of 8.75g of magnesium citrate through enemas on the previous day. Aggressive resuscitation was started, including IV calcium, but he continued to require multiple pressors.

Results: Underline represents presenting author.

Conclusions: We found histological evidence of ilium injury following both ischemia and bilateral nephrectomy. MDA and apoptosis, which was quantified by histone-associated DNA fragmentation enzyme-linked immunosorbent assay, were increased after 6 and 24 hr of renal ischemia or nephrectomy.

Serum from Rats with Acute Kidney Injury Contains Reactive Oxygen Species Generating Activity That Causes Oxidative Stress in Vitro
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Background: The uremic state that is induced by acute kidney ischemia or renal failure activates oxidative stress and promotes apoptosis, and tissue damage in gut. Whether the AKI induced-gut injury by itself is sufficient to provoke systemic inflammatory response needs further investigation.

Funding: Government Support - Non-U.S.

Properdin Deficiency Enhances Renal Ischemia Reperfusion Injury in Mice
Zinh Dhevaa Zawmi, 1, 3 Nigel J. Brunskill, 1 Hans-Wilhelm Schwebele, 1 Cordula M. Stover, 1 Bin Yang, 1, 5, 6, 7, 8, 9 Infection, Immunity and Inflammation, Univ of Leicester; 7 Renal Group, Univ Hospitals of Leicester; 3College of Medicine, Univ of KwaZulu, 9 Basic Medical Research Centre, Medical school of Nantong Univ, China; 8Nephrology, Affiliated Hospital of Nantong Univ, China.

Background: Properdin is the only positive regulator of the alternative pathway of complement activation via stabilizing C3bBb convertase. Properdin has been detected on proximal tubular epithelial cells associating with proteomic renal damage. Previous studies showed that mice with combined deficiencies of properdin (Pf), DAF and CD59, the negative regulators of complement activation, had less renal ischemia reperfusion injury (IRI), 24 hours.

Methods: Pf mice (n=9) and their wildtype (WT) littermates (n=7) were used to assess the role of properdin in renal IRI. Ischaemia was induced by bilateral clamping of the renal pedicle for 30 minutes followed by 72-hour reperfusion using normal (n=2) and sham-operated mice (n=4 or 5) as controls.

Results: Renal IRI was successfully induced in the WT and Pf mice with more prominent injury in Pf mice as evidenced in renal function. Serum creatinine was significantly increased after IRI compared with the sham groups, which was further increased bilaterally nephrectomy for 24h. Ilium and blood were collected. The damage of gut mucosa was assessed by histological staining. Malondialdehyde(MDA) and apoptosis of the ilium were measured to determine the underlying mechanism of the AKI-induced gut injury.

Results: We found histological evidence of ilium injury following both ischemia and bilateral nephrectomy. MDA, an index of lipid peroxidation, increased in both the renal ischemia and nephrectomy groups, suggesting activation of oxidative stress. Ilium apoptosis, which was quantified by histone-associated DNA fragmentation enzyme-linked immunosorbent assay, were increased after 6 and 24 hr of renal ischemia or nephrectomy.
in P-ko in relation to WT mice (1.78±0.29 vs. 1.19±0.18, P=0.046) post IRI. Similarly, blood urea nitrogen in IRI mice was higher than the sham animals, with significant increase in P-ko in comparison with WT mice.

This difference was supported by histological examination, in which P-ko mice showed a worse score of tubulointerstitial damage than WT (2.67±0.26 vs. 1.94±0.22, P=0.025) post IRI.

Conclusions: This study shows, for the first time, that properdin deficiency alone causes IRI injury shown by worsened renal function and histology. The underlying mechanisms for these unexpected phenotype are under present investigation.

Funding: Government Support - Non-U.S.

PUB006

Neurogenic Function of Neurons with Renal Afferents Is Altered by Lipopolysaccharides -LPS Kristina Rodionova,1 Martin Ziemer,1 Tilmann Ditting,1 Stefan Karl,1 Sonja Heinlein,1 Peter Linz,1 Peter Reeh,1 Kerstin U. Amann,2 Roland Veelken.1 1Dept of Medicine 4 - Nephrology and Hypertension, Universitaetsklinikum Erlangen-Nuernberg, Erlangen, Bavaria, Germany; 2Dept of Nephropathology, Universitaetsklinikum Erlangen-Nuernberg, Erlangen, Bavaria, Germany.

Background: Renal afferent nerves (RNs) exert complex neurogenic sympathomodulatory and paracrine effects. Recently, we could demonstrate that lipopolysaccharide (LPS) sensitized TRPV1 receptors and increased the release of CGRP from afferent axons in kidney. Hence, we wanted to test the hypothesis that LPS alters firing patterns and acid induced inward currents in cultured neuron sample.

Methods: Dorsal root ganglion neurons (Thr1-1.2) of rats were incubated with LPS (E.coli O127:B8,20mg/ml) 12h before patch clamp recordings. Inward currents were assessed during stimulation of TRPV1 and ASICs with protons (pH 6.5 and 5.0). Current clamp mode was performed at physiological conditions and after 12h of LPS-incubation.

Results: Firing patterns and currents induced by acidic superfusion were studied in 246 neurons. Renal neurons (RNs) exhibited in 59% tonic firing pattern under control conditions. The number of neurons with tonic response was significantly reduced by exposure to LPS (59%vs.42%; p<0.05) under control conditions. 70.8% of RNs exhibited both sustained (i.e. sustained AP firing or phasic, i.e.<5 APs in response to current injections).

Conclusions: 1. Efficiently produce controlled releasing Curcumin-loaded nanoparticles by amphilic mPEG-PCL block copolymers. Drug loading content(DLS) and encapsulation efficiency(EE) were more than other peports. Data indicated that incorporated Cur could be slow released from the core-shellstructured polymericnanoparticles. 2. Curcumin can ameliorate ischemia-reperfusionrenal injury in vitro. 3. The protective effects of Cur-NP against ischemia-reperfusion renal injurywere involved in the suppression of oxidative stress reaction.

Funding: Other NIH Support - Germany, Bavaria, Erlangen

PUB007

Protective Effect of Nitric Oxide in Aristolochic Acid-Induced Toxic Acute Kidney Injury Ines Jadot,1 Anne-Emilie Declives,2 Vanessa Colombo,1 Blanche Martin,1 Isabelle Habsch,1 Eric De Prez,2 Joelle L. Nortier,2 Nathalie Caron.1 1 Molecular Physiological Research Unit - URPHYM, Faculty of Medicine, Univ of Namur, Namur, Belgium; 2Laboratory of Experimental Nephrology, Faculty of Medicine, Un Libre de Bruxelles, Bruxelles, Belgium.

Background: Aristolochic Acid (AA) nephropathy is a pertinent example of tubulo-interstitial (TI) nephritis characterized by an early phase of acute kidney injury (AKI) leading to progressive fibrosis and chronic kidney disease (CKD). Nitric oxide (NO) has been shown to play a critical role in the AKI-to-CKD transition. Here, the AAN model was used to determine the role of NO in this process, focusing on the acute phase.

Methods: C57BL/6J male mice were randomly selected to daily i.p. injection of control solution or AA (3.5mg/kg) for 4 days and L-Arginine (L-Arg; substrate for NO synthesis) was supplemented in drinking water (5%) until mice were euthanized, 5 days after the beginning of AA injections.

Results: At day 5, AA-treated mice displayed polyuria, increased plasma creatinine levels, and tubulointerstitial (TI) nephritis. In addition, histological analyses revealed severe proximal tubular cell necrosis, renal inflammation and increased oxidative stress in AA-treated mice. These changes were associated with a significant reduction of NO bioavailability, as attested by urinary NOx and cGMP levels. L-Arg supplementation in AA-treated mice significantly improved kidney function, as reported by a significant reduction in urine volume, plasma creatinine level and proteinuria. Moreover, L-Arg treatment resulted in a significant reduction of tubular cell necrosis, renal inflammation and oxidative stress. These were concomitant to normalized NO levels.

Conclusions: Our findings demonstrated that sustaining NO bioavailability due to L-Arg supplementation improve the renal outcome of AA-induced AKI phase. Further investigations are ongoing to determine whether increasing NO bioavailability can also prevent chronic injuries in the AAN model.

Funding: Veterans Administration Support, Private Foundation Support

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

Underline represents presenting author.

887A

PUB008

The Study of Curcumin-Loaded Nanoparticles against Renal Ischemia-Reperfusion Injury Function and Mechanism Yong Xu, Lili Zhong. Dept of Nephrology, Huaian Second Hospital, Huaian, Jiang Su, China.

Background: To study the effects of curcumin-loaded nanoparticles against ischemia-reperfusion renal injury, and to investigate its mechanism.

Methods: Synthesize controlled releasing curcumin-loaded nanoparticles by amphilic mPEG-PCL block copolymers and cultured renal tubular epithelial cell (cell line HK-2) in vitro. HK-2 cells were divided into four groups: Control group; Ischemia reperfusion injurygroup(IRI group); Curcumin group(Cur group); Curcumin nanoparticle group(CurNP group). In each group, HK-2 cells viability was assessed by dimethyl-thiazol-diphenyl tetrazolium bromide (MTT) test. Apoptotic Cells were measured by Flow Cytometry. HeLaF2-DA was used to detect intracellular generation of ROS. BCA were used to detect SOD activation and the Concentration of MDA. Protein levels of procaspase-3 were analyzed by Western Blot.

Results: Successfully constructed curcumin-loaded nanoparticles by amphilicmPEG-PCL block copolymers.

Conclusions: 1. Curcumin-loaded nanoparticles by amphilicmPEG-PCL block copolymers.

Funding: Government Support - Non-U.S.
**PUB010**

**Protective Effect of NDH2 Oxidase 4 Inhibition in Contrast Induced Nephropathy**

Se-Hee Yoon, Won Min Hwang, Sung-Ro Yun, Sukyung Lee, Hee-Yeon Jung, Ji-Young Choi, Sun-Hee Park, Chan-Duck Kim, Yong-Lim Kim.

**Background:** The objective of this study was to investigate the protective effect of NDH2 oxidase 4 (Nox4) inhibition in contrast induced nephropathy.

**Methods:** HK-2 cells were incubated with iohexol (nonionic low-osmolar radiocontrast agent) at a concentration of 75 mg/mL, 150mg/mL for 2 h. Cells were pre-exposed to GKT137831, a selective Nox1&; inhibitor (Genkyo克斯, Switzerland), for 30 min before exposure to iohexol. Cell viability was measured at 0, 3, and 22 h after removal of iohexol by ATPBio assay. Apoptosis was investigated by caspase 3/7 activity assay. Nox4 protein expression level and mitochondrial ROS production was assessed by DHE assay. NDH2 oxidase activity was measured by lucigenin-enhanced chemiluminescence method, and Nox3 expression by western blot and real time PCR.

**Results:** Nox4 protein expression significantly increased at 30 min after iohexol exposure. GKT137831 pre-exposure showed significantly less cytotoxicity compared to 3 h after removal of iohexol. Caspase 3/7 activity was significantly lower in GKT137831 pre-exposed cells than only iohexol exposed cells at 22 h after removal of iohexol. ROS generation was higher with only iohexol exposed cells compared to GKT137831 pre-exposed cells.

**Conclusions:** A selective Nox4 inhibitor induced fewer cytotoxic effects on cultured HK-2 cells than iohexol along with a lower induction of Nox4-dependent ROS generation. This enzyme may represent a potential therapeutic target to prevent iodinated radiocontrast medium related oxidative stress.

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**PUB011**

**Autophagy Increased in the Early Stage of Rat Acute Kidney Injury Model**

Junyi Liu, Xing Mao, Yiwen Shen, Huijuan Wu, Aimin Xue.

**Background:** Acute kidney injury (AKI) is a major kidney disease without effective therapies, and is thus associated with a high mortality. The pathogenesis of AKI is very complex and still unclear. Recently, researches have shown the induction of autophagy in proximal tubular cells and kidneys during AKI. In the present study, we investigated the role of autophagy in the pathogenesis of rat renal ischemia-reperfusion (IR) model which causes AKI.

**Methods:** All male Sprague-Dawley rats were subjected to clamping of bilateral renal artery only for 25 min except sham group, and then they were randomly divided into four groups depended on different reperfusion time point, including 3h, 6h, 12h and 24h. The Sham group underwent surgical procedures without ischemia as the control.

**Results:** The level of blood urea nitrogen (BUN) and serum creatinine were increased from 3h after IR. By H&E staining, protein casts were found at 3h after IR, which kept increasing at 6h and 12h after IR. At 24h after IR, we found some necrotic proximal tubules. Immunohistochemistry showed the protein level of Beclin-1 and Vps34 and the ratio of LC3 II/I increasing at 6h and 12h after IR. At 24h after IR, we found some necrotic proximal tubules. Immunohistochemistry staining clearly showed an increased positive staining of Vps34 and LC3 at 3h after IR compared to the control.

**Conclusions:** Taken together, our results demonstrate the occurrence of autophagy in the very early stage of rats AKI model.

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

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**PUB012**

**The Previous Cardio Exercise (Exe) Normalizes Renal Function of Wistar Rats Subjected to Acute Kidney Injury by Ischemia, and Reperfusion**

Wesley Vicente Ling, Waldemar S. Almeida, Nestor Schor.

**Background:** The acute kidney injury (AKI) is characterized by acute reduction of renal function and has a high mortality rate in hospitalized patients and in severe cases may progress to chronic kidney disease (CKD). The AKI by ischemia and reperfusion (IR) causes tubular damage mainly in the proximal convoluted tubule, reducing mitochondrial activity in renal cell and increasing the reactive oxygen species (ROS). It is known that aerobic Exe lowers blood pressure (BP), slows the heart rate (HR), improves muscle aerobic capacity, increases both the number and size of muscle mitochondria, however little is known about the effects of the previous Exe in AKI. We suspect that aerobic Exe may be protective against the effects of IR.

**Methods:** We used male Wistar rats with 10 weeks of life and they were separated into two groups Sham clamp (SC) and trained control clamp (TC), moreover the TC were subjected to a prior physical training protocol for four weeks. After completed 14 weeks each group, ischemia renal injury was carry out in the two groups, the rats were given rest in 8 hours after that they were placed in metabolic cages for 24 hours. We evaluate renal function (serum creatinina and proteinuria) and renal morphological study by light microscopy and mitochondrial (number and size) by electron microscopy. Finally, we will evaluate apoptosis through caspases 3 activity.

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**PUB013**

**Angiogenin Mediates a Non-Cell Autonomous Response to Endoplasmic Reticulum Stress in the Kidney**

Nicolas Pallé, Dany Anglicheau, Eric Thervet, Iadh Mami.

**Results:** We found that 100 ng of angiogenin (ANG) when applied to the kidney cortex was sufficient to induce a marked transient increase in Nox4 protein expression at 30 min after iohexol removal. Caspase 3/7 activity was significantly lower in GKT137831 pre-exposed cells than only iohexol exposed cells at 22 h after removal of iohexol. ROS generation was higher with only iohexol exposed cells compared to GKT137831 pre-exposed cells.

**Conclusions:** A selective Nox4 inhibitor induced fewer cytotoxic effects on cultured HK-2 cells than iohexol along with a lower induction of Nox4-dependent ROS generation. This enzyme may represent a potential therapeutic target to prevent iodinated radiocontrast medium related oxidative stress.

**Funding:** NIH/NIH.

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**PUB014**

**Sustained Infiltration of Th17 Cells Is Associated with Pulmonary Fibrosis in Rats with Salt Induced CKD Secondary to Renal Ischemia**

Purvi Mehrotra, Jason Andrieu Collett, David P. Basile.

**Background:** Acute kidney injury (AKI) is associated with high mortality rates and is a leading cause of prolonged hospitalizations. The high risk of death is due in part to distant organ damage (e.g., lungs, heart, brain). It is well established that experimental AKI induced by renal ischemia and reperfusion (IR) increases an increase in pulmonary infiltrated immune cells like T cells as early as 24 hours post surgery, which may alter endothelial barrier function in the lung. However, the long-term effect of kidney injury induced pulmonary inflammation on lung function and structure is not known. We hypothesize that T cells infiltrate into the lung post kidney injury with potential effect on pulmonary structure.

**Methods:** SD rats were subjected to a model of AKI-to-CKD in which rats are allowed to recover from unilateral IR (40 min ischemia) for 5 weeks on standard salt diet (0.4% NaCl) and then subjected to contralateral UNX and 4% NaCl diet for 4 additional weeks. Rats consistent with eEPCs infiltration of CD4+ T cells were detected as early as 24 hours post surgery in the BAL fluid, and these were shown to be predominantly Th17 cells. These cells persisted in the lungs even after 5 weeks of post surgery after resolution of kidney injury (2.5X10^6±0.3), when compared to sham (0.53X10^6±0.03). Exposure of rats to high salt diet to hasten CKD further increased the number of Th17 cells in the lungs (4.1X10^6±0.23, p<0.05). There was a corresponding increase in pulmonary fibrosis in post-AKI rats on high salt relative to sham-controls.

**Conclusions:** Taken together, these data suggest that AKI leading to CKD is associated with pulmonary fibrosis, an activity that may be due in part to the infiltration of Th17 cells into the lung and influenced by dietary salt.

**Funding:** NIDDK Support.
The Role of Endosialin in Renal Ischemia-Reperfusion Injury
Chia-Hsiun Liu, Shui-Liong Lin. 1,2

Background: Endosialin is a glycoprotein found on hematopoietic cells and is involved in adhesion and migration to inflamed tissues. In vivo experiments have shown that endosialin-deficient mice had a reduced renal ischemia-reperfusion injury (IRI). However, the role of endosialin in acute kidney injury remains unclear.

Methods: We examined the protective effect of endosialin-deficiency on renal IRI by administering an endosialin-deficient mice model. The glomerular filtration rate (GFR) and blood urea nitrogen (BUN) were measured in wild type (WT) and endosialin-deficient (Endo−/−) mice subjected to 30 minutes of left renal artery clamping (IRI) followed by 4 hours of reperfusion (R). The kidneys were harvested for histological examination and mRNA expression analysis.

Results: The GFR and BUN of Endo−/− mice were significantly higher than those of WT mice, indicating a protective effect of endosialin-deficiency against renal IRI. The histological examination showed less interstitial edema and tubular damage in Endo−/− mice compared to WT mice. The expression of pro-inflammatory cytokines and chemokines was also lower in Endo−/− mice, indicating a reduced inflammatory response.

Conclusions: Endosialin-deficiency can protect against renal IRI by reducing inflammation and preserving renal function. Further studies are needed to elucidate the molecular mechanisms underlying this protective effect.

Funding: Government Support - Non-U.S.

PUB019

The Mechanism of β2-Adrenergic Receptor / Protein Kinase A Signal Transduction Pathway in Restoration of Acute Kidney Injury by Endothelial Progenitor Cells
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Background: Endothelial progenitor cells (EPCs) can improve renal microenvironment, stimulate endogenous repair and angiogenesis, and promote AKI recovery. However, the molecular mechanism is not well elucidated.

Methods: We investigated the role of β2-adrenergic receptor (β2-AR) and its downstream factors (protein kinase A, protein kinase C) in the restoration of AKI by EPCs. The model of ischemia-reperfusion acute kidney injury (I-R AKI) was used in vivo, while sham operation was performed in control group. Renal tissue was harvested at 7 days after IRI. Histological examination and mRNA expression analysis were performed.

Results: The expression of β2-AR and its downstream factors (PKA, PKC) was measured. The levels of β2-AR and PKA were significantly higher in I-R AKI group than in control group (p<0.05). The protein levels of PKB and PKC were not significantly different between groups. Western blotting showed that the expression of β2-AR and PKA was significantly higher in I-R AKI group than in control group (p<0.05).

Conclusions: The model of I-R AKI occurred, the mRNA levels of specific proteins on surface of EPCs increased significantly, which suggested that I-R AKI might induce EPCs homing to kidney. At the same time, the mRNA levels of β2-AR and PKA were significantly up-regulated, which suggested that β2-AR/PKA pathway may play a role in the restoration of AKI by EPCs.

Funding: Government Support - Non-U.S.
PUB020

Alpha Lipoic Acid and Dexamethasone Counteract Contrast Media-Induced Proximal Tubule Cell Dysfunction
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1Dept of Nephrology, Ondokuz Mayis Univ Medical Faculty, Samsun, Turkey; 2Dept of Medical Biochemistry, Ondokuz Mayis Univ Medical Faculty, Samsun, Turkey.

Background: Contrast medium induced nephropathy (CIN) is one of the most common cause of hospital-acquired acute renal failure. But its pathogenesis is unclear. In this study, we observed the effect of lipoic acid, low osmolar contrast medium, on tubular cells in HK-2 cell line.

Methods: We observed the effect of iopromide, low osmolar contrast medium, on tubular cells in HK-2 cell line. First, we examined the effects of different doses of iopromide (10, 20, 40 and 80 mg/ml iodine) on proliferation of HK-2 cells by the real time cell analyser (RTCA). According to the results of RTCA we examined whether the non-toxic doses of iopromide (10 and 20 mg/ml iodine) is causing of the EMT by scratch assay for 20 h. We also observed whether alpha lipoic acid (0.5 mM) and dexamethasone (5 µg/ml) is preventing to EMT in this assay.

Results: We observed whether alpha lipoic acid (0.5 mM) and dexamethasone (5 µg/ml) is preventing to EMT in this assay. Although cytotoxic effect was observed for iopromide (10 and 20 mg/ml iodine) is causing of the cell migration which an indicator show any effects for HK-2 cells. In scratch assay, we observed that the non-toxic doses of iopromide (10 and 20 mg/ml iodine) is causing of the cell migration which an indicator of EMT and alpha lipoic acid and dexamethasone prevent the cell migration.

Conclusions: In conclusions, the EMT caused by contrast medium is prevented or reduced by dexamethasone and lipoic acid in HK-2 cells. This result suggest that dexamethasone and lipoic acid may be a potential treatment to prevent the development of CIN in individuals with high-risk.

PUB021

Contribution of Proliferating Endothelial Cells for Endothelial Repair After Site Specific Endothelial Injury of the Mouse Kidney
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Background: Our previous studies have shown that renal endothelial cell regeneration occurs exclusively via local mechanism. To further dissect the relevance of local mechanisms for endothelial repair, we now investigated the contribution of local endothelial cell proliferation in the kidney in our model of site specific endothelial injury (ECI).

Methods: Selective ECI was induced in 9 out of 15 mice by renal arterial perfusion with Concanavalin A (ConA)anti-ConA, while 6 mice served as sham operated controls. Edu (15µg/g), a marker of proliferation, was injected starting 24hours after ECI every 12hours intraperitoneally. Kidneys were harvested on day 7 and Edu⁺ cells were analyzed using flow cytometry and histology. Endothelial cells were stained using CD31, CD105, CD44 and CD46 and hematopoietic cells were detected as CD45⁺. Inflammatory cells (macrophages, dendritic cells and neutrophils) were analyzed via GR1, CD11c, CD11b and F4/80 positivity. By histology, proliferating EC were detected as anti-ERG/Edu double positive cells.

Results: Significantly more Edu⁺ cells could be detected after ECI on day 7 (sh: 1.2%±0.7; ECI: 7.6%±4.8). Most of those Edu⁺ cells were positive for CD45 (65%±8) and 3% (sh) to 7% (ECI) were positive for EC surface markers. In diseased kidneys more endothelial cells were found (sh: 5.5%±0.7; ECI: 7.3%±0.5; p<0.01). A larger amount of Edu⁺ EC was found in injured kidney (sh: 1.5%±0.8 0160 cells; d7: 5%±1.5 O630 cells p<0.01). Histological analysis supported these findings. Gliomeruli of ECI kidneys had more ERG/Edu⁺ cells (Ø 8: 0.23±0.16; Ø 7: 1.22±0.6; p<0.01). Inflammatory cells in injured kidneys were slightly increased. Many macrophages (21%±13), neutrophils (38%±17) and dendritic cells (19%±13) were Edu⁺. The 21days was the most worst for mitochondria under EM. For the TUNEL, a lot of DNA strand breaks were detected by TUNEL in 21days. For the Edu and TUNEL, the 21days was the most worst for mitochondria under EM.

Conclusions: Enhanced endothelial proliferation was detected following ECI. Therefore EC proliferation reflects an relevant repair mechanism following site specific ECI. The further investigation of EC repair will have to dissect the contribution of the proliferative response by adult local EC from other contributors such as local progenitor cells.

PUB022

Injury of Proximal Tubular Cells in Neonate Rats with Hypoxic-Ischemia Brain Damage
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Background: Proximal tubular cells play a critical role in renal injury. To investigate the consequence of mitochondria in renal proximal tubular cells after hypoxic-ischemia brain damage (HIBD) in rats and the apoptosis in it.

Methods: Neonatal (7 days old) Sprague Dawley rats were randomly divided into 2 groups: sham group and operation group (n=5 per group). The Rice method was used for establishment of HIBD model, proximal tubular cells Mitochondria pathology and histology were examined under electron microscope at 1 day, 7days, 14days and 21days after the hypoxic-ischemic treatment, and apoptosis was analyzed by TUNEL.

Results: After the HIBD, the mitochondria of proximal tubular cells were showed damage under EM, some membrane and ridges were broken, the mitochondria bodies were swelling, and partial cristae fragmentation were observed from the 1day till 21days after. And the 21days was the most worst for mitochondria under EM. For the TUNEL, after HIBD, it showed significant increased for 1day, 7days, 14days and 21days groups comparing with sham group, (p<0.05).

Conclusions: After the hypoxic and ischemic brain injury of neonate rats, the mitochondria were damaged in proximal tubular cells, even in 21days after HIBD. And the apoptosis maybe one of the causes of this damage.

Funding: Government Support - Non-U.S.

PUB023

Ex-Vivo Normothermic Perfusion (EVNP) to Repair Monoethylene Glycol Toxicity in Human Kidneys
Ivonne Palma,1 Sasha Karaan Narayan,1 Ivania Palma,1 Rajendra Ramsamojo,1 Junichiro Sageshima,1 Jakub Woloszyn,1 Nam Tran,2 Chandrashankar Santhanakrishnan,3 Richard V. Perez.1 1Surgery, Univ of California-Davis, Sacramento, CA; 2Pathology and Laboratory Medicine, Univ of California-Davis, Sacramento, CA.

Background: Monoethylene glycol (MeG), a component of radiator fluids, results in crystal-induced acute kidney injury, hypocalcemia and often death, if ingested. Utilization of kidneys from deceased donors with MeG poisoning may not be suitable for transplant. EVNP may be utilized to potentially assess/repair high-risk kidneys in this setting.

Methods: A pair of transplantable human kidneys from a brain dead 38 year old female suicide victim from MeG poisoning were discarded due extensive intratubular crystal deposition. The kidneys were placed on 3 hours of EVNP with leukocyte depleted packed red blood cells at 37°C. Oxygenation via a hollow fiber membrane oxygenator supplemented with parenteral nutrition/insulin. One kidney was given Furosamide (10 mg) at the beginning to induce diuresis and assess acute kidney injury. Hemodynamic pump parameters and urine output were monitored. Blood and urine samples were collected at the start and every 30 minutes and analyzed for pH, electrolytes, creatinine, and lactate. Wedge biopsies were collected pre & post perfusion & stained with alizarin red to measure calcium oxalate tubular deposition.

Results: Blood flow and resistance improved over time in both kidneys. EVNP reduced crystal deposition compared to baseline wedge biopsies. Kidney treated with furosamide showed slightly better hemodynamic profile and fewer crystals after EVNP.

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Underline represents presenting author.

890A
transfusion in the perioperative period of cardiac surgery has been associated with acute kidney injury. Our purpose was to analyze the influence of transfusion of red blood cell in the incidence of acute kidney injury after cardiac surgery.

Methods: We performed a prospective cohort study carried out in a tertiary hospital specialized in Cardiology. Adult patients who had undergone elective myocardial revascularization surgery, valvular and aortic surgery and who had agreed to participate in the study were included. The primary endpoint was acute kidney injury defined by KDIGO criterion. Secondary outcomes was serious clinical complications defined according to the guidelines of the Society of Thoracic Surgeons.

Results: According to KDIGO criterion, the incidence of AKI was 46.5%. The mean age was 60±12 years old in the AKI group and 58 ± 12 in the no AKI group (p=0.145), and mostly male (56%). The surgical risk assessed by EuroSCORE was greater in the AKI Group 5 (1-25) when compared to the no AKI group 4 (2-10), (p=0.047). There were no differences between the groups for the secondary outcomes. The use of red blood cells in the perioperative period (OR=3.166, p=0.001) and the presence of prior chronic kidney disease (CKD) (OR=2.027, p=0.036) was associated with AKI postoperatively.

Conclusions: EVNP may have the potential to repair MeG acutely injured kidneys rendering them suitable for transplantation. Ex vivo administration of furomeside may be a useful tool to assess injured deceased donor kidneys being considered for transplantation.
showed acute thrombotic microangiopathy, acute tubular injury, and moderate interstitial fibrosis. The presentation suggested the diagnosis of aHUS. Eculizumab, an anti-C5 antibody, was initiated at 900 mg weekly for four weeks followed by 1200 mg every two weeks. Eculizumab therapy resulted in resolution of hemolysis. Dialysis was continued thrice weekly. Eculizumab was continued every two weeks, and LDH and platelet counts remained stable. Two weeks after initial presentation, urine output improved, lower eGFR, and interdialytic weight gains were negligible. Pre-dialysis serum creatinine was 3.9 mg/dL, and a urine collection showed creatinine clearance of 30 ml/minute. She has remained off dialysis for twenty weeks, and latest serum creatinine is 3.4 mg/dL. Screening for complement and paroxysmal nocturnal hemoglobinuria was negative.

Conclusions: Experience with eculizumab is ongoing. Most patients with aHUS have a rapid hematologic response. If they need dialysis, then recovery of renal function is usually prompt; late recovery is rare. We hypothesize that sustained control of complement activation has led to vascular improvement and all but renal remodeling and regeneration, even months later. Patients are at risk for relapse if they stop treatment. This case points out that the presumed genetic defect may require lifelong treatment, and that late recovery of renal function is possible with complement inhibition and supportive care.

PUB029
The Effectiveness of Theophylline in Preventing Cisplatin Related Nephrotoxicity in Patients with Cancer
Jamil Khavjoo,1 Derya Karademir,1 Fatma Dogrul,1 Cvet Yazić,2 Aydin Unal,1 Murat H. Sipahioglu,1 Oktay Oynak,1 Bulent Tokgoz,1 Nephrology, Erciyes Univ Medical School, Kayseri, Turkey; 2Biochemistry, Erciyes Univ Medical School, Kayseri, Turkey.

Background: Cisplatin is a potent antineoplastic agent used in treatment of many solid tumors. The major limiting side effect of cisplatin is nephrotoxicity. Theophylline is a competitive inhibitor of adenosine which has antiinflammatory and antiapoptotic activity. In this study, early detection of acute kidney injury with biomarkers such as neutrophil gelatinase associated lipocalin (NGAL) and cystatin C and investigation of the potential nephron-protective effects of theophylline were aimed.

Methods: Sixty patients who are planned administration of cisplatin for the first time were included in the study. Patients were divided into two groups as group I (n=30) (standard treatment arm) and group II (n=30) (theophylline arm). Glomerular filtration rate (GFR), NGAL, cystatin C were measured at 3rd day in all of the patients. Also, these parameters were repeated measured at the administration of cisplatin, at 2nd hour, 5th and 20th days.

Results: In both groups after the administration of cisplatin, glomerular filtration rate (GFR) showed a significant decrease within time (p<0.001). In creatinine, in spite of the decline in GFR, no significant difference was observed between groups and within time. After 2 hours of cisplatin administration, in spite of the decline in GFR, a significant decline was detected in serum cystatin C (p<0.001). Urine NGAL was significantly high after 2 hours of cisplatin administration (p<0.001). No significant difference was observed between groups. However, when the time*group effects were considered together, higher NGAL was detected in the group not receiving theophylline (p=0.025). After 5 days of cisplatin administration, urine protein levels were significantly higher in both groups (p<0.001).

Conclusions: Results showed that urine NGAL level is a superior biomarker compared to creatinine and cystatin C in the detection of early acute kidney injury. Theophylline was found not to bring a complete protection for the kidneys, but less nephrotoxicity was developed when compared to the group not receiving theophylline.

PUB030
IgA Nephropathy Presenting as RPGN After G-CSF Administration: An Interesting Case
Talal A. Khan,1 Ahmad Hassan,2 Agba Seyed Shabbir Ali,2 Hafiz Armaghan Saeed,2 Abdul Mateen Nagaria,2 Azka Arsl,1 Freeman Heath System; 3Rawalpindi Medical College.

Background: IgA nephropathy is the most common form of primary glomerulonephritis & a major cause of ESRD in the world, its pathogenesis involves lymphocyte infiltration within renal interstitium as well as glomerulus. Selectins are adhesion molecules that play very important role in leukocytes to endothelial cell attraction. G-CSF is commonly used to induce neutrophil production. It induces E-selectin expression on endothelial cells & E selectin ligand on leukocytes. We present an interesting case of IgA nephropathy presenting as RPGN after G-CSF administration.

Methods: 66-year-old male with past medical history significant for T-cell leukemia on cyclophosphamide(CY) who presented with epistaxis was found to have acute C1q, albumin, fibrinogen, & kappa and lambda light chains. There were mesangial granular deposits with IgA (3+), C3 (1+), lambda (1+); kappa was negative. The remaining stains showed no significant deposits. Patient underwent induction with CYC and pulse steroids, days 1-2, with prednisone 60 mg/ day. Renal biopsy was scheduled but patient refused and was discharged. During hospitalization in patients with CKD, hypotension, or planned surgical procedures.

Results: Among the 184 patients included, 92 patients developed AKI (age 66±13 yrs; male 52%, male 58%). Patients with AKI had a higher baseline serum creatinine (1.1±0.4 vs. 1.0±0.3, p<0.001), lower eGFR (54.10 vs. 56.7mL/min/1.73m2, p<0.03), and were more likely to have a diagnosis of CKD (40% vs.14%, p<0.001), an ICU stay (44% vs. 17%, p<0.001), a surgical procedure (34% vs. 14%, p<0.001), hypotension (24% vs. 2%, p<0.001), and concomitant loop diuretic therapy (52% vs. 36%, p<0.03). The AKI group had a longer length of stay (14±11 vs. 8±3 days, p<0.001) and a higher rate of all cause hospital mortality (8% vs. 1%, p<0.03). Factors associated with a significant increase in risk of AKI in the multivariable analysis were CKD (OR=4.3, 95% CI 1.6-9.3, p<0.001), hypotension (OR=14.2, 95% CI 3.1-65.0, p<0.001), and surgical procedures (OR=7.9, 95% CI 1.6-42.9, p=0.001).

Conclusions: Conclusion of ACEIs/ARBs during hospitalization may increase the risk of AKI in select patients. Temporary discontinuation of ACEIs/ARBs may be warranted during hospitalization in patients with CKD, hypotension, or planned surgical procedures.
Sequences of Neprilysin: Associated Lipocalin: A Novel Biomarker for Prediction of AKI Development in Critically Ill Patients

Background: Acute kidney injury (AKI) is a frequent complication in critically ill patients and is associated with high morbidity and mortality; therefore, its prophylaxis, diagnosis and intervention positively impact patient evolution. Neprilysin-associated lipocalin (NGAL) is thought to be a novel biomarker of AKI of several etiologies and is increased in both serum and urine before the increase of serum creatinine.

Methods: A prospective cohort study was conducted on 100 critically ill patients in ICU. Patients were stratified into 2 groups based on AKI development. Group I which included 50 patients who did not develop AKI, and group II which included 50 patients who developed AKI. AKI was defined based on acute kidney injury network (AKIN) classification. The Sequential Organ Failure Assessment (SOFA) scores were also calculated for all patients. Detailed medical history, demographic data and routine laboratory investigations were done. Serum NGAL was measured upon admission to ICU and upon AKI development.

Results: 60 males and 40 females were included in the study with mean age 37.52 years. As regards risks of AKI development, 9% of patients had sepsis, 15% were dehydrated, 11% had contrast exposure, 12% had rhabdomyolysis, 29% had shock and 24% had history of NSAID intake recently. On admission, there were no significant differences between the patients as regards s.creatinine, hemoglobin level and other laboratory parameters (p>0.05). Serum levels of NGAL were significantly higher in group II, before AKI development, with mean value 958.5 ng/ml, when compared with group I, mean value 272.17 ng/ml (p<0.01). Serum NGAL levels were significantly higher in group II after AKI development when compared with the levels before AKI development in the same group (1660.35 ng/ml) (p<0.01). There was no significant correlation between NGAL levels and AKIN classification stages.

Conclusions: In the absence of diagnostic increases in serum creatinine, NGAL detects patients with likely subclinical AKI who have an increased risk of adverse outcomes. Reassessment of AKI classification and stages should be considered.

Does Previous CKD Affect Renal Recovery After Acute Kidney Injury?

Maria Isabel Acosta-Ochoa, Josefina Martin, Alicia Mendiluce. Nephrology, Hospital Clinico Univ, Valladolid, Spain.

Background: AKI definition includes a sharp increase of serum creatinine (Scr), essentially reversible. There is a lack of consensus of a standard definition of Renal Recovery (RR). The exact course of the repair process is subject of thorough investigation. Few studies have engaged in comparing rates of RR in patients with previous impaired vs. normal renal function.

Methods: Retrospective cohorts study, 12-months period. We defined RR as discharge Scr with maximum increment £25% over basal value, and non recovery as >25% HD persistence, and death. We studied 2 groups: AKI and Acute on Chronic Kidney Disease (AoCKD). We tested epidemiological features, Charlson Index (ChaI), and KDIGO stages. We plotted a Kapplan-Meier survival curve 24 months post-discharge.

Kaplan-Meier Curves for 2 Years Survival

Results: 270 patients, AKI=125, AoCKD=145, clinical features and KDIGO stages: see table 1.

<table>
<thead>
<tr>
<th>Features</th>
<th>AKI (N=125)</th>
<th>AoCKD (N=145)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>77 (62)</td>
<td>98 (68)</td>
<td>0.50</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>66.9 ± 15</td>
<td>75.4 ± 11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT (%)</td>
<td>96 (77)</td>
<td>131 (90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>44 (35)</td>
<td>70 (48)</td>
<td>0.003</td>
</tr>
<tr>
<td>CHI (SD)</td>
<td>3.8 ± 2.5</td>
<td>4.4 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>KDIGO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage1 (%)</td>
<td>43 (34)</td>
<td>47 (32)</td>
<td>0.19</td>
</tr>
<tr>
<td>Stage2 (%)</td>
<td>17 (14)</td>
<td>16 (11)</td>
<td>0.52</td>
</tr>
<tr>
<td>Stage3 (%)</td>
<td>65 (52)</td>
<td>82 (57)</td>
<td>0.45</td>
</tr>
<tr>
<td>Results</td>
<td>44 (35)</td>
<td>51 (35)</td>
<td>0.99</td>
</tr>
<tr>
<td>HD Dependence (%)</td>
<td>1 (1)</td>
<td>7 (5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>21 (17)</td>
<td>38 (26)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

When meta-analysis was limited only to RCTs, the pooled RR of CIAKI in patients receiving nebulol was 0.69 (95% CI, 0.38-1.15, I²=0).

Conclusions: Despite no statistical significance, there was a trend toward reduced CIAKI risk in patients receiving nebulol. This finding suggests the need for further studies on the use of nebulol in addition to standard IV crystalloid hydration in the prevention of CIAKI.

The Effect of Nebivolol on Contrast-Induced Acute Kidney Injury: A Meta-Analysis

Nephrology, Ain Shams Univ, Cairo, Egypt.

Background: Nebivolol provides protective effect on contrast-induced acute kidney injury (CI-AKI) in animal models. However, the reports on the efficacy of nebulol for the prevention of CI-AKI in human remain unclear. The objective of this meta-analysis was to assess the effect of nebulol for the prevention of CI-AKI.

Methods: Comprehensive literature searches were performed using MEDLINE, EMBASE, and Cochrane Database from inception through February 2015. Studies that reported relative risks, odd ratios or hazard ratios comparing the risk of CI-AKI in patients who received nebulol versus those who did not included. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

Results: Four studies (2 RCT and 2 cohort studies) with 543 patients were included in our analysis to assess the risk of CI-AKI and the use of nebulol. Of 543 patients with contrast exposures, 30 patients (5.32%) had CI-AKI. Patients in the nebulol group had an overall lower incidence of CI-AKI (14.35%) compared to the control group (17.43%). The pooled RR of CIAKI in patients receiving nebulol was 0.66 (95% CI, 0.38-1.15, I²=0).

Conclusions: Despite no statistical significance, there was a trend toward reduced CIAKI risk in patients receiving nebulol. This finding suggests the need for further studies on the use of nebulol in addition to standard IV crystalloid hydration in the prevention of CIAKI.

Patients with Cardiovascular Diseases Are Susceptible to Acute Kidney Injury After Non-Carcid Surgery Under Preoperative Use of Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers

Hiro Masunaga, Takeshi Hamaoka, Masaru Matsui, Katsumi Morimoto, Ken-ichi Samejima, Yasuhiro Akai, Yoshihiko Saito. Nara Medical Univ, Nara, Japan; Osaka Univ, Osaka, Japan.

Background: It is unknown in which subgroups of patients the preoperative use of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) is a predictor for acute kidney injury (AKI) after non-cardiac surgery.

Methods: This is a retrospective cohort study on patients who underwent non-cardiac surgery from 2007 to 2009. After exclusion of urological surgery, missing creatinine clearance, and preoperative dialysis, the data for 2,725 patients were available. The exposure of interest was preoperative use of ACE-I/ARB. Primary outcome was postoperative AKI (AKIN criteria). The odds ratio (OR) of postoperative AKI among ACE-I/ARB users compared to non-users was analyzed using multivariable logistic regression models, adjusted for the logit of propensity score for ACE-I/ARB use. P<0.1 was considered statistically significant for interaction.

Results: Mean(SD) age was 61(16) and estimated glomerular filtration rate was 81(24) ml/min/1.73m². There were 574(21%) patients with previous impaired renal function. 36(1.3%) of postoperative AKI in ACE-I/ARB users and 97(2,265 (4.3%) in non-users. The addjusted OR of AKI were shown.
Whole Ischemia-Reperfusion Injury: The Effect of Whole-Body Cooling on Renal Function

Background: Hypothermia is able to reduce the risk of renal failure after renal ischemia-reperfusion injury in animals. In humans, Cardiac Arrest (CA) as a whole-body ischemia-reperfusion syndrome causes warm renal ischemia-reperfusion injury, similar to animal models of ischemic acute kidney injury (AKI). Induced hypothermia (IH) is a treatment potentially efficacious for post-ischemic injury. It is unclear what effect could have on renal function. The aim of the study was to investigate the development of AKI during the IH.

Methods: Between Jan 2013-Mar 2015, we performed a prospective observational study of 36 comatose pts resuscitated from CA and treated with IH performed with 2 different surface cooling devices: 1) Arctic Sun Temperature Management System (Medivance, Loviutville, CO); 2) Blanket. Temperature rate and trend, and the development of AKI during induction (0-6hrs), maintenance (24hrs), rewarming (48hrs) and normothermia (72hrs) was assessed with RIFLE and KDIGO criteria.

Results: Pts were enrolled and followed for the development of AKI during intensive care unit stay. In the induction and maintenance phase, the rate and temperature was similar; conversely, the rewarming phase was shorter with a target temperature higher in Blanket than in ArcticSun group (458 mins vs 61 min; 37.2°C vs 36.3°C). The trend and the rate of temperature, but also the development of AKI is shown in figure 1.

Conclusions: IH could be associated with development of AKI in the rewarming phase (rate 0.25 to 0.5 °C). The optimal rewarming rate is unknown. Randomized controlled trials are needed to determine the real effect of temperature on kidney, the optimal rewarming strategy and applications of this treatment for kidney in other settings.

Funding: NIDDK Support

PUB038

Decongestion-Associated Worsening Renal Function Does Not Increase Mortality of Patients with Acute Heart Failure

Background: A significant subset of patients admitted for acute decompensated heart failure (ADHF) develop worsening renal function (WRF). While there is consistent data regarding the negative impact of baseline renal dysfunction on the outcomes of these patients, the evidence on the prognostic implication of WRF during admission for decongestion is less well-understood. The aim of this study is to provide a reappraisal of the effect of decongestion on the prognostic value of WRF in patients admitted for ADHF.

Methods: Articles cited in PubMed database from 1995 to 2015 using key words "congestion," "heart failure," "worsening renal function," and "hemococoncentration" were searched. Those studies evaluating the relationship between decongestion, renal function, and ADHF in patients treated with diuretic-based conventional therapies were selected. Ultrafiltration trials were excluded. Relevant data including change in renal function, diuretic dose, change in weight, and mortality were extracted and compared.

Results: A total of 12,843 patients from 19 trials (9 retrospective and 4 prospective) with data pertaining to decongestion in ADHF patients were included in this study. The mean age of the patients was 67.1 years with follow up periods ranging from 60 days to 5.3 years. Eleven studies reported development of WRF following decongestion. The incidence of WRF was reported to be 10 to 50.1% with weight reduction ranging from 2 to 5.4 kg. Twelve studies did not observe any negative impact for WRF on the mortality of patients with ADHF unless associated with markers of persistent congestion such as lack of hemococoncentration.

Conclusions: Decongestion is associated with markers of fluid removal and WRF in the setting of ADHF. Currently available data suggest that decongestion-associated WRF does not result in increased mortality whereas persistent congestion is likely to be the driving factor for adverse outcomes in these patients. Randomized controlled trials are needed to confirm these findings as they could portend significant therapeutic implications in cardiological syndrome.

PUB039

A 13-Year Mayo Clinic Retrospective Study of the Syndrome of Rapid Onset End Stage Renal Disease (SERO-ESRD) in an Incident Hemodialysis Cohort

Background: We first described the syndrome of rapid onset end stage renal disease (SERO-ESRD) in 2010 - acute yet irreversible ESRD after AKI. However, its overall impact on ESRD outcomes in the general US ESRD population remains speculative.

Methods: A retrospective examination of SERO-ESRD among the incident Mayo Clinic ESRD population, 2001-2013 was completed in November 2014.

Results: 149 of 1461 (10%) incident ESRD patients had SERO-ESRD – M:F = 76:73, mean age 62 years (19-95), 139 (93%) native kidneys, 10 (7%) kidney transplant recipients (RTRs). Ninety-nine percent of SERO-ESRD patients’ initial vascular access was a dialysis catheter. Kidney biopsy - the commonest pathologic diagnoses were acute tubular necrosis (ATN) in 3 (25%) KTRs and in 7 (21%) native kidneys. Cardiac arrest was the leading cause of death in SERO-ESRD.

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

Underline represents presenting author.

894A
Conclusions: Among 1461 incident ESRD patients seen at Mayo Clinic Dialysis Services, Rochester, 2001–2013, 149 (10%) had SORO-ESRD. There was no gender age disparity between SORO-ESRD patients and the general ESRD cohort. Ninety-nine percent (99%) SORO-ESRD patients’ initial vascular access was a dialysis catheter. ATN was the leading pathologic diagnoses for AKI among KTRs and in native kidneys. Cardiac arrest was the leading cause of death in SORO-ESRD, similar to the general ESRD population. We conclude that SORO-ESRD contributes significantly to incident ESRD here in the USA both among KTRs and in native kidneys. Furthermore, it negatively impacts on the success of AVF-First Programs. Efforts to mitigate AKI in CKD patients must be given more attention and priority by practicing nephrologists in particular, and by physicians in general.

PUB040
Saline-Induced, Diuretics-Responsive Acute Renal Failure (ARF): Evidence that Anasarca Is Nephrotoxic and Diuresis Is Therapeutic
Grant Melzer, Kai Lau, Maria Isabel Acosta-Ochoa, Josephine Martin, Alicia Mendiluce, Nephrology, Hospital Clinico Univ, Valladolid, Spain.

Background: Recent studies showed the association of fluid overload in ARDS & surgical patients and increased ventilator dependency, ICU & hospital stays, short-term mortalities, & incidence of ARF. But a cause-and-effect relationship was unproven in cross-sectional observations. In grossly edematous in-patients with unexplained ARF, we tested the hypothesis that anasarca caused the renal failure & diuresis induced recovery.

Methods: Entry criteria were fully evaluable patients, ³3 kg weight or ³3 L fluid gain, ≥50% acute loss of estimated creatinine clearance (CrCl) or ≥ 2 x rise in serum creatinine (Scre) without identifiable causes. All data were reviewed, recorded, tabulated & statistically analyzed, notably vital signs, weight, intake, output & lab. 36 qualified patients were diuresed by IV furosemide at rates keeping normotension off anti-hypertensives. Serial volume markers & renal responses were noted. Palliative care & hepatorenal syndrome were excluded.

Results: Fluid overload was due to heart failure (40%), liver failure (22%), CKD (16%), proteinuria (9%) & iatrogenic factors (10%). During 42 ARF episodes, mean weight was up 12.5 kg in 13.7d. Scre rose (4.41 vs. 1.27mg%) & CrCl fell (25 vs. 76 ml/min). Decrements in CrCl correlated with edema weight gain (p=0.02). Over 11.9, d 15.2 kg of fluid were diuresed. Renal function greatly improved in 33 patients & unchanged in 3 despite >4 kg diuresis. As an entire group, Scre fell to 1.45 mg% & CrCl rose to 67 ml/min. Increments of CrCl also correlated with diuresis volume (p=0.04). At a diuretic rate of 1.5 kg/d, no adverse events occurred.

Conclusions: 1. Our data support the hypothesis for the entity of Saline-Induced, Diuretics-Responsive Acute Renal Failure. 2. Likely mediated by reduced cardiac output, venous congestion, renal interstitial edema &/or abdominal hypertension, it is analogous to congestive kidney failure. 3. Preventable & treatable, it could cause or aggravate ARF from other etiologies. 4. Diuresis in cohorts at rates & monitored as ours should be safe & efficacious.

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

PUB041
Is RIFLE Classification a Good Shot for Staging Acute on Chronic Kidney Disease? Maria Isabel Acosta-Ochoa, Josephine Martin, Alicia Mendiluce, Nephrology, Hospital Clinico Univ, Valladolid, Spain.

Background: 8-16% of worlds population may have CKD, which is a risk factor and prompter of AKI. We tested the performance of RIFLE and KDIGO classifications in staging severity and predicting outcomes in Acute on CKD (AoCKD) individuals. KDIGO with a 0,3mg/dL Scre increase includes patients in stage 1 category, and includes automatically in stage 3 patients with peak SCr ≥4.0 mg/dL.

Methods: Retrospective cohort study. Patients were divided in 2 groups: AKI and AcoCKD. We collected clinical data, and classified AKI severity contrasting distribution strata between groups by RIFLE and KDIGO criteria. And tested the ability of both classifications for predicting need for HD and in hospital mortality with a AUC ROC analysis.

Results: 270 patients were included, AKI=125, AcoCKD=145. Clinical features and RIFLE and KDIGO stages are listed in table 1.

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>AKI (N=125)</th>
<th>AcoCKD (N=145)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>77 (62)</td>
<td>98 (68)</td>
<td>0.30</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>66.9 ± 15</td>
<td>75.4 ± 11.9</td>
<td>&lt;0.001</td>
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<tr>
<td>HT (%)</td>
<td>96 (77)</td>
<td>131 (90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>44 (35)</td>
<td>70 (48)</td>
<td>0.003</td>
</tr>
<tr>
<td>Chl (SD)</td>
<td>3.8 ± 2.5</td>
<td>4.4 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RIFLE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No AKI (%)</td>
<td>21 (17)</td>
<td>23 (16)</td>
<td>0.83</td>
</tr>
<tr>
<td>Risk (%)</td>
<td>22 (17)</td>
<td>35 (24)</td>
<td>0.18</td>
</tr>
<tr>
<td>Injury (%)</td>
<td>17 (14)</td>
<td>44 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Failure (%)</td>
<td>65 (52)</td>
<td>43 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>KDIGO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage1 (%)</td>
<td>43 (34)</td>
<td>47 (32)</td>
<td>0.19</td>
</tr>
<tr>
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<td>17 (14)</td>
<td>16 (11)</td>
<td>0.52</td>
</tr>
<tr>
<td>Stage3 (%)</td>
<td>65 (52)</td>
<td>82 (57)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Conclusions: The KDIGO staging criteria we obtain more homogeneous distribution strata. With the ROC analysis neither classification performs better in predicting adverse outcomes. We found no practical advantage when using neither classification. In the noAKI (by RIFLE) stratum no adverse event was present, so by including a 0,3mg/dL Scre increase augments sensitivity, but may not be specificity.

PUB042
Incidence of Acute Kidney Injury, Risk Factors for Acute Kidney Injury and Absence of Renal Recovery in Patients on Aminoglycosides Francois Paquette,1 Amelie Bernier-Jean,1 Veronique Brunette,1 Vincent Pichette,2 Helene Ammann,3 Stephan Troyanov,3 Josee Bouchard.3 Hospital du Sacre-Coeur de Montreal, Canada; Hôpital Maisonneuve-Rosemont, Canada.

Background: The KDIGO guidelines recommended to avoid aminoglycosides (AG) in patients at risk or with acute kidney injury (AKI). We determined the frequency of administration, incidence of AKI, and risk factors for AKI and absence of renal recovery in patients receiving AG over the last decade.

Methods: We performed a retrospective cohort study on AG administration in two university-affiliated centers, and then performed a nested case-control study, pairing AG-AKI cases to 2 controls for age and gender. AKI was defined by a 50% increase in creatinine after ≥5 days of AG up until 7 days after cessation of AG, and renal recovery, by a decrease in creatinine to within 50% of baseline creatinine over 3 weeks after cessation of AG.

Results: Between 2001 and 2015, the frequency of AG administration and drug dosing progressively decreased. Out of 562 patients, sixty-five developed AKI attributed to AG (12%). In the case-control study (n=195), age was 71 (IQR 58-81) and 46% were male. The duration of AG administration was 10.0 (IQR 7.0-15.0) days, excluding days after AKI diagnosis in AKI patients. Maximal AKI stage was 1 for 55.3%, 2 for 29.2% and 3 for 15.4% of patients. Independent risk factors associated with AKI were concomitant vancomycin administration, high trough levels, heart failure, and site of infection (endocarditis and febrile neutropenia vs. other). Only fifty-one percent (50.8%; 33/65) of patients recovered their kidney function. These patients had an AKI duration of 7.0 (IQR 4.0-11.5) days. Heart failure was associated with a lower likelihood of renal recovery, while cancer patients more likely recovered their kidney function.

Conclusions: Over the last decade, the frequency of AG administration and dosing have progressively decreased but the incidence of AKI remained unchanged. In our cohort, vancomycin administration, high trough levels, heart failure, and site of infection were independent risk factors associated with AKI. Almost half of patients did not recover their kidney function, which was more often seen in patients with heart failure.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PUB043

Prairie Continuous Renal Replacement Therapy (CRRT) Study – Outcomes of CRRT in a Single Canadian Tertiary Centre

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Background: Patients with stage III Acute Kidney Injury (AKI) requiring Renal Replacement Therapy (RRT) have the highest short-term and long-term mortality of any group with AKI. Our study aimed to prospectively follow patients with stage III AKI on Continuous Renal Replacement Therapy (CRRT) during their hospitalization in our tertiary care centre from April 2013 to September 2014.

Methods: We prospectively gathered the following: date and time of hospital admission, transfer to ICU, and starting CRRT, creatinine at admission and at CRRT initiation, weight on admission and at CRRT initiation. Duration of oliguria and anuria, exposures (sepsis,critical illness, circulatory shock, trauma, cardiac surgery, major non cardiac surgery, nephrotoxic medications, and radio contrast agents) and susceptibilities (dehydration, >65 years of age, female, pre existing CKD), APACHE score II, Inotrope support, FiO2, ECMO. Survival on CRRT, in ICU and hospital survival and renal recovery was documented.

Results: Of the 2634 patients (2201/2634) 83.6% had no AKI, and (269/2634) 10.2% had stage III AKI of whom 106/269 (40%) were started on CRRT. 8/106 died in ICU and 17/106 died within 24 hours of initiating CRRT. This raises a clinical concern of the benefit vs futility of initiating therapy. 5/106 patients recovered within 24 hours.

Stage III AKI needing CRRT was associated with 62% mortality in hospital. 17/106 died within 24 hours of initiating therapy. 5/106 patients recovered within 24 hours.

Conclusions: Of the 2634 patients (2201/2634) 83.6% had no AKI, and (269/2634) 10.2% had stage III AKI of whom 106/269 (40%) were started on CRRT. 8/106 died in ICU and 17/106 died within 24 hours of initiating CRRT. This raises a clinical concern of the benefit vs futility of initiating CRRT in specific settings.

PUB044

Urinary Liver Fatty Acid Binding Protein Predicts Acute Kidney Injury Associated with Abdominal Aortic Repair

Daisuke Ichikawa,1 Atsuko Ikemori,1 Takeshi Sugaya,1 Kenjiro Kimura,1 Yugo Shibagaki.3 Nephrology and Hypertension, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan; 2Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: Acute kidney injury (AKI) is common problem after cardiovascular surgery. AKI is usually diagnosed on the basis serum creatinine (SCr) and urinary output. However, SCr is of low sensitivity in patients with poor renal function. Because urinary liver-type fatty acid binding protein (L-FABP) reflects renal tubular injury, we evaluated whether periparative changes in urinary L-FABP can predict AKI.

Methods: Subjects were 68 patients who underwent EVAR and 32 patients who underwent open repair. We obtained urine samples before surgery, immediately after surgery, and on POD 1, 2, and 3 for measurement of urinary L-FABP and urinary albumin in the EVAR patients. We obtained urine samples before surgery, after anesthesia induction, before aortic cross-clamping (AXC), 1 and 2 hours after AXC, at the end of surgery, and on POD 1, 2, and 3 for measurement of urinary L-FABP and urinary albumin in the open repair patients. We obtained serum samples before surgery, immediately after surgery, and on POD 1, 2, and 3 for measurement of SCr.

Results: AKI developed in 5 (7.4%) EVAR patients and in 9 (28.1%) open repair patients with EVAR, urinary L-FABP was increased 4 hour after the procedure (P = 0.002) and it decreased but remained elevated for 3 POD (P = 0.003). With AKI, SCr increased significantly to its maximum by 2 hour after AXC (P = 0.008) and then decreased gradually over the 3 PODs (P = 0.038). The increase in urinary L-FABP was greater with open repair than with EVAR. ROC analysis showed urinary L-FABP to be more sensitive than SCr, and it decreased but remained elevated for 3 PODs.

Conclusions: Urinary L-FABP appears to be a sensitive biomarker of AKI in patients undergoing abdominal aortic surgery, especially those treated by EVAR.

PUB045

Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a Biomarker for Acute Kidney Injury in Patients with Chronic Kidney Disease

Ha yeon Kim,1 Eun Hui Bae,2 Soo Wan Kim,3 Seong Kwon Ma.1 Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.

Background: The aim of this study was to evaluate plasma NGAL levels as a predictor of early AKI in patients with with/without chronic kidney disease (CKD) and to assess whether plasma NGAL level could represent a useful marker of recovery in patients undergoing emergent renal replacement therapy (CRRT).

Methods: This was a single center retrospective observational study included 343 patients with AKI or CKD. The patients were classified into 3 groups: AKI (N=69), AKI on CKD (N=162), CKD (N=112). The cut-off values of NGAL was 200 ng/ml and those of cystatin-C was 1.0 mg/L. Study II: The retrospective observational study included 404 patients treated with CRRT. The patients were divided into 2 groups: renal recovery (N=120) vs. renal non-recovery (N=284) and survivor (N=193) vs. non-survivor (N=211).

Results: The prevalence of abnormal NGAL values was 69.0% in AKI group, 94.5% in AKI group and 91.8% in CKD group, the value of NGAL was positively correlated with aGFR (r = 0.41, p < 0.001), and cystatin C (r = 0.45, p < 0.02). The mean values of follow-up NGAL were 475.9 ± 435.9 ng/ml in AKI group, 773.2 ± 370.6 ng/ml in AKI group, 709.4 ± 401.6 ng/ml in CKD group (p < 0.001). In AKI group, the difference of NGAL (baseline NGAL – follow-up NGAL) was the highest (110.8 ± 322.0 ng/ml in AKI group, 35.7 ± 205.2 ng/ml in AKI group, 14.1 ± 203.1 ng/ml in CKD group, p < 0.001). In comparisons between renal recovery group and non-recovery group and survivors and non-survivors in CRRT patients, both baseline NGAL and follow-up NGAL were not different, but the difference of NGAL (baseline NGAL – follow-up NGAL) was increased significantly in a renal recovery and survivors group (96.8 ± 82.9 ng/ml in renal recovery group vs. 33.8 ± 53.7 ng/ml in renal non-recovery group, 129.8 ± 182.4 ng/ml in survivor group vs. 98.5 ± 162.6 in non-survivor group, p < 0.001, respectively).

Conclusions: The value of serum NGAL per se has a limitation on diagnosis of AKI in patients with underlying CKD. In patients treated with CRRT, hourly urine output and follow up of serum NGAL value may predict renal recovery and survival.

PUB046

C3 Glomerulopathy: A Pediatric Case

Luis A. Ortiz,1 Daniel Kleven,2 Harika Gorri,1 Ped. Nephrology, Georgia Regents Univ, Augusta, GA; 2Pathology, Georgia Regents Univ, Augusta, GA; 3MG, Georgia Regents Univ, Augusta, GA.

Background: C3 glomerulopathy (C3G) is characterized by C3 deposit in the glomeruli with minimal Ig deposition. C3G is described as an unregulated activation of the alternative complement pathway due to a genetic mutations in Factor H or, or acquired factors such as C3 nephritic factor, an IgG autoantibody stabilizing C3 convertase. The pattern of the injury varies from mesangio-proliferative, membranoproliferative, to endocapillary proliferative glomerulonephritis. EM finding is subendothelial and subepithelial hump shaped deposits, characteristic of acute post-infectious glomerulonephritis (PIGN). We present a pediatric case that meet the initial criteria for PIGN, but was diagnosed as C3G according the pathology.

Methods: 15 y/o AA M with Thin Basement D, HTN, asthma presented with 1 hx of sore throat, gross hematuria, facial swelling, no distal edema. Initial criteria and high Cr. PE revealed periorbital edema, no pharyngeal erythema, lung clear, abdomen with no ascites. On admission, Hb 11.6 g, Cr 3.26mg, albumin 2.5 gr, UA:50-120 BRC, UOP: 0.37 ml/hr. Despite treatment with methylprednisolone, albumin and furosemide, his Cr. increased to 15 y/o AA M with Thin Basement D., HTN, asthma presented with one Hx of sore throat, gross hematuria, facial swelling, no distal edema. Initial criteria and high Cr. PE revealed periorbital edema, no pharyngeal erythema, lung clear, abdomen with no ascites. On admission, Hb 11.6 g, Cr 3.26mg, albumin 2.5 gr, UA:50-120 BRC, UOP: 0.37 ml/hr. Despite treatment with methylprednisolone, albumin and furosemide, his Cr. increased to 15 y/o AA M with Thin Basement D., HTN, asthma presented with one Hx of sore throat, gross hematuria, facial swelling, no distal edema. Initial criteria and high Cr. PE revealed periorbital edema, no pharyngeal erythema, lung clear, abdomen with no ascites. On admission, Hb 11.6 g, Cr 3.26mg, albumin 2.5 gr, UA:50-120 BRC, UOP: 0.37 ml/hr. Despite treatment with methylprednisolone, albumin and furosemide, his Cr. increased to...
Conclusions: SRC is a serious kidney and life threatening complication of SSC. Delay in blood pressure control increases risk of ESRD in SRC patients.

PUB048

Acute Kidney Injury Risk Assessment at the Hospital Front Door: What Is the Best Measure of Risk? Aled O. Phillips,1 Dafydd Phillips,1 Mohamed Hassan,2 John Gee,2 Vikas Lodhi,3 Hermann Bolusani,1 Gareth Roberts,1 1Nephrology, Cardiff Univ School of Medicine, Cardiff, Wales, United Kingdom; 2Dept of Clinical Biochemistry, Univ of South Wales, Wales, United Kingdom; 3Dept of Medicine, Royal Gwent Hospital, Newport, Wales, United Kingdom. Background: We examined the prevalence of AKI risk factors in the emergency medical unit, generated a modified risk assessment tool and tested its ability to predict AKI. Methods: 1196 patients admitted to medical admissions units were assessed for patient associated AKI risk factors. Subsequently, 898 patients were assessed for a limited number of fixed risk factors with the addition of hypotension and sepsis. This was correlated to AKI episodes. Results: In the first cohort the prevalence of AKI risk factors was 2.1 ± 1.0 per patient, with a positive relationship between age and the number of risk factors and a higher number of risk factors in patients ≥65yrs. In the second cohort 12.3% presented with or developed AKI. Patients with AKI were older and had a higher number of AKI risk factors. In the AKI cohort 72% of the patients had ≥2 AKI risk factors compared to 43% of the cohort with no AKI. When age ≥65 yrs was added as an independent risk factor risk 84% of those with AKI had ≥2 AKI risk factors compared with 55% of those with no AKI. ROC analysis suggest that use of common patient associated known AKI risk factors performs no better than age alone as a predictor of AKI. Conclusions: Detailed assessment of well established patient associated AKI risk factors may not facilitate clinicians to apportion risk. This suggests that additional work is required to develop a more sensitive validated AKI predictive tool which would be useful in this clinical setting.

PUB049

Acute Kidney Injury, Requiring Renal Replacement Therapy – Incidence, Causes and Outcomes: One Center Experience Elena Zakharyova, Nephrology, City Clinical Hospital n.a. s.P. Botkin, Moscow, Russian Federation. Background: Acute Kidney Injury (AKI) is complex condition, associated with high mortality and morbidity. We aimed to evaluate AKI incidence, causes, risk factors and outcomes in patients, managed in nephrology unit of general hospital and urgently requiring Renal Replacement Therapy (RRT). Methods: Using electronic database for 2010-2014 (4531 admissions, 2257 patients), we searched 604 cases which met KDIGO AKI definition, and selected patients, required RRT. Results: Study group included 115 patients (19% of all AKI cases), 51 (44%) male, 64 (56%) female, median age 61 [22; 89] years. In 102 (89%) cases AKI was community acquired. Median serum creatinine prior to start of RRT was 981 [242; 2665] µmol/l, 37 (32%) patients had known CKD. Causes and susceptibilities for AKI are shown in table.

<table>
<thead>
<tr>
<th>Cause/exposure</th>
<th>n of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased kidney perfusion</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Intestinal nephritis</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Sepsis</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Critical illness</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Circulatory shock</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nephrotic drugs</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Radiocontrast agents</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Poisoning</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hantavirus infection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Cast-nephropathy</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>

Conclusions: In our cohort incidence of AKI was 27%, proportion of patients requiring RRT constituted 19% of AKI cases. Vast majority had community acquired AKI, 1/3 developed AKI on the top of pre-existing CKD, 16% were elder than 75 years. Main trigger for RRT requiring AKI in 29% of cases was initially considered as decreased kidney perfusion, with volume-unresponsiveness due to severe underlying conditions, such as CKD, chronic heart and liver diseases, multiple myeloma, cancer, diabetes and amyloidosis. Other most frequent causes of AKI were sepsi, rhabdomyolysis, vasculitis, and interstitial nephritis. Mortality rate was 10%, ESRD developed in 23% of cases.

PUB050

Renal Manifestations in Paroxysmal Nocturnal Haemoglobinuria Rama R.,1 Dakshinamurty K.V.,2 Krishna Parasad A.3 1Nephrology, Sri Venkateswara Inst of Medical Sciences, Tirupati, AP, India; 2Nephrology, Mahatma Sri Ramachandra Centenary Memorial Hospital, Hyderabad, Telengana, India; 3General Medicine, NIMS, Hyderabad, India. Background: Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired chronic disorder characterized by a triad of clinical features- haemolytic anaemia, purpura, and thrombosis. Not many reports of renal involvement in PNH are available in literature. Methods: We present a case series of PNH with renal involvement. We present the data of PNH patients attended to departments of General Medicine and Nephrology at a government run tertiary care institute in South India. The diagnosis of PNH in these patients during initial phase, between 1998 and 2004 was based on sucrose lysis and Ham’s test. After 2004, the diagnosis was based on flow cytometry to detect CD59 (MIRL), a glycoprotein, and CD55 (DAF) in regulation of complement action. The patient data was collected from 1998 to 2014. Results: There were 13 patients of paroxysmal nocturnal haemoglobinuria in this period. The mean age was 37 years and the range was 16 to 68 years. There were 7 females. Acute renal failure was noted in 5 patients. Dialysis was performed in three of them. The mean serum creatinine and urea at the initiation of dialysis was 5.4 ± 0.6 mg/dl and 64.1 ± 6.1 mg/dl respectively. The median number of haemodialysis sessions done was four. Renal biopsy was done in four patients. The indication for the biopsy was acute renal failure of more than four weeks. The median number of glomeruli was 9. The tubules showed prominent brown granular pigment within the epithelial cells. It was confirmed as hemosiderin with the Perl’s Prussian blue reaction. A few deposits of hemosiderin were also seen within the tubular lumina. The pathological diagnosis in these four patients was acute tubular necrosis secondary to hemosiderin deposition. In three patients the urinalysis and serum chemistry was suggestive of Fanconi syndrome. Conclusions: In our patients, three renal manifestations of PNH were identified. They were acute renal failure, renal vessel thrombosis and Fanconi syndrome. Chronic renal failure was not identified.
Filling the Gaps in Acute Kidney Injury Epidemiology: A Multicenter Prospective Study in Amazon

Matthew L. Howse.

Background: In some areas of developing countries, infectious tropical diseases or animal venoms may be important causes of Acute Kidney Injury (AKI). Epidemiological studies of AKI in these areas are scarce and expensive population-based studies are even scarcer.

Methods: Prospective data on all adult patients admitted in all intensive care units (ICU) in the Western Amazon region (600 square kilometers and 100,000 inhabitants) were collected for 6 months in 2014. Patients with chronic kidney disease stage 5, kidney transplant or ICU stay < 48 hours were excluded. AKI was diagnosed by KDIGO and mortality was assessed 30 days after ICU discharge. Data are presented as mean±SD or percentage.

Results: 367 patients aged 57.8 ± 19.2 years and with 39% white were evaluated. Main reasons for ICU admission were postoperative (34%), hemodynamic instability (22%) and respiratory failure (13%), with only 1% with tropical diseases. AKI incidence was 38%, but was lower in postoperative patients (28% vs 47% in non-postoperative, p = 0.005). Mortality was higher in AKI patients (53% vs 30% in non-AKI, p < 0.001). Postoperative patients who developed AKI had similar mortality to those non-operative (46% vs 56%, p = 0.302).

Conclusions: AKI has a high incidence in ICU patients of the Western Amazon area. The causes of ICU admission did not differ from those seen in developed countries. The few number of patients with the typical tropical diseases of Amazon may be due to poor access to health care. The peculiar social geographical region characteristics, with rivers that are not navigable most of the year, long rain period that difficult access to larger cities and the lack of health services in diverse areas, may be associated to the present findings.

Funding: Government Support - Non-U.S.

Uncovering Complement Mediated Thrombotic Microangiopathy: Use of a Real Time Genetic Assay in the Diagnosis of Atypical Hemolytic Uremic Syndrome

Araujo Lopes de Melo,1,2 Tarcisio Andrade Souza,2 Natalia Mendes,1 Luis Yu,2 Emmanuel A. Burdnham,3 Dirce M T Zanetta.1

Background: Improved diagnostic tests and greater understanding of pathophysiology of thrombotic microangiopathy (TMA) have led to more rapid differentiation of various types of TMA. While ability to rapidly diagnose TTP (ADAMTS13 activity <5%) has improved, atypical HUS (aHUS) remains diagnosis of exclusion due to poor sensitivity, high cost, and long turnaround time (TAT) of aHUS genetic assays. We describe a patient (pt) with hypothyroidism and renal insufficiency diagnosed with aHUS, using appropriate clinical algorithms for TMA, including “real-time” aHUS genetic assay (TAT 2-5 days).

Methods: 59 y.o. female with 1-2 week (wk) history of fatigue, anemia, thrombocytopenia, renal insufficiency, and recent diagnosis of hypothyroidism with changes in CBC and creatinine (Cr) over 3 wks: hemoglobin (hgb) 13.9 to 7.1 g/dl, platelet count (pt ct) 241 to 68 X 10^9/L, and Cr 0.71 to 1.41 mg/dl (baseline Cr 0.56, BMI 19.5). Pt’s history with hypothyroidism and renal insufficiency were consistent with aHUS, using appropriate clinical algorithms for TMA, including “real-time” aHUS genetic assay (TAT 2-5 days).

Results: Pt received 11 plasma exchange (PE) treatments (txs) (hospital day [HD] 3-21). By day 4 of PE (HD 7), pt hgb 197 X 10^9/L; despite 11 PE txs, LDH remained elevated (866-2123) and Cr rose to 2.72 (3.8-4.9X higher than baseline). aHUS genetic panel (sent HD 10, results on HD 17) revealed: positive variant in CFI gene (predicted to be significant, but not previously described) and heterozygous mutations for 3 CFH polymorphisms. Pt clinically diagnosed with aHUS, received meningococcal vaccine (HD 20), and cirilloxacin (2 wk course). Induction eculizumab started and PE stopped (HD 21). After 2 months of eculizumab, pt’s Cr normalized.

Conclusions: With development of improved genetic testing (ie, increased sensitivity and speed), aHUS genetic assays may represent “real-time” diagnostic tools enabling more rapid assessment of selected TMA cases leading to more targeted treatment.

Intravenous Contrast Material Administration Increases Mortality in Patients with Acute Kidney Injury Requiring Renal Replacement Therapy

Katsuhito Igarashi, Atsuki Ohashi, Yoshiho Iida, Makiko Kubayashi, Hitomi Tanaka, Seiji Inoshita. Internal Medicine, Tokyo Metropolitan Bokutoh Hospital, Japan.

Background: Contrast material exposure is well known to induce acute kidney injury (AKI); however, it is yet unclear whether contrast material administration is related to the prognosis of AKI. We hypothesized that intravenous contrast material administration might be a poor contrast prophyaxis which was given in 2.93 mL/kg. Contrast material was administered in 50.6 % of the patients. Each the exposure group and non-exposure group included 86 and 153 patients, respectively. The 28-day mortalities of each group were 55.8 % and 36.9 % respectively. The hazard ratio in the exposure group was 2.966 [95% confidence interval (CI) 1.573-4.517] (p = 0.000) by univariate analysis. After adjustment by hypertension, sepsis, ischemia, and diuretics usage, which were the significant different confounders of the two groups, the hazard ratio was 1.987 [95% CI. 1.093-3.610] (p = 0.024).

Conclusions: Our results demonstrated that intravenous contrast material administration is an independent risk factor for mortality in patients with AKI requiring RRT.
PUB056

Dabigatran Induced Acute Kidney Injury and Management with Hemodialysis

Daren W. Grabs,1,2 Syed S. Haqiqi.1,2 1Dept of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, NY; 2Dept of Medicine, Div of Nephrology and Hypertension, Albany Medical College, Albany, NY.

Background: A 55-year-old man with a history of A Fib, cirrhosis, portal HTN, esophageal varices arrives in the ED, transferred from an outside hospital following initial presentation with multiple episodes of hematoma and melena. Medication regimen recently changed with a switch from warfarin to dabigatran 8 months prior to admission in order to avoid frequent INR checks.

Methods: On admission, initial blood work was obtained and revealed: Hg 6.3 g/dL, INR 6.9, Scr 15.6 mg/dL, and BUN 189 mg/dL. Patient was admitted to the intensive care unit for management of acute blood loss and AKI. On physical exam shows a pulse of 95 bpm and BP of 111/75 mmHg and mild hepatosplenomegaly, the physical exam was unremarkable. Dabigatran was discontinued and patient was transfused with packed red blood cells and fresh frozen plasma and administered vitamin K. Hemodialysis was initiated and continued throughout the hospital course. Kidney biopsy was performed and was consistent with ATN, chronic tubulointerstitial nephritis, and IgA Nephropathy (HAAS class I).

Results: Serum dabigatran concentration (conc) drawn on admission was 860 ng/mL. Following the initial emergent hemodialysis (HD) procedure, subsequent dabigatran conc. were determined during the second HD procedure. Predialysis and postdialysis dabigatran conc. were 130 ng/mL and 30 ng/mL, respectively. Pharmacokinetic parameters were calculated and shown in the table.

<table>
<thead>
<tr>
<th>Group</th>
<th>K0 (L/hr)</th>
<th>t1/2 (hr)</th>
<th>Cl(H) (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.489</td>
<td>1.4</td>
<td>571</td>
</tr>
</tbody>
</table>

k = elimination rate constant; t1/2 = half-life; D = dialytic

Over the hospital course, patient required regular HD. Hg stabilized following transfusion and vitamin K. Patient was stable on discharge with a serum creatinine of 5.9 mg/dL and remained on dialysis.

Conclusions: Dabigatran induced AKI is rare. The mechanism of the insult in this case was unclear but acute blood loss leading to prolonged ischemic insult was largely contributive. Hemodialysis was successful in removing the offending agent with resolution of bleeding but patient remains dialysis dependent.

PUB057

Relation Between BNP And NGAL, with Bioelectrical Cardiothoracic Impedance Hemodynamics Parameters in Patients with Cardiorenal or Renocardiac Syndrome


Background: Evaluate the application of cardiothoracic bioelectrical impedance (CTBIA) in the classification of patients with cardiological or renocardiac syndrome.

Methods: We use a cohort with 18 patients (mean age years 72 SD 2.6, males 77 %) with cardiological or renocardiac syndrome. We evaluate hemodynamic parameters (cardiac output –CO, cardiac output index –COI, left ventricular work index –LVWI, and systemic vascular resistance index –SVRI) with BNP (pg/ml, limits 0-100) and NGAL (ng/ml, limits 0-4.9).

Results: Mean levels of BNP were 545.71 (SD 128.8) and mean levels of NGAL were 500.11 (SD 96.25). Only vascular resistance index was associated with NGAL (r=0.461, p=0.054). Not found associations with BNP. However we classify patients in four groups: Group 1 (BNP high, NGAL normal) (n=7), Group 2 (BNP high, NGAL high) (n=1), Group 3 (BNP normal, NGAL high) (n=7) and Group 4 (BNP normal, NGAL normal) (n=3).

The associations indicate that in Group 1 are patients with cardiac dysfunction (cardiological) and higher BNP (BNP-NGAL), with lower cardiac output and higher vascular resistance, and in group 3 are patients with renal dysfunction (renocardiac) and higher NGAL (BNP-NGAL), with higher cardiac output and lower vascular resistance.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Cr]k, mg/dL</td>
<td>42.70</td>
<td>17.67</td>
<td>11.35</td>
<td>35.23</td>
<td>8.10</td>
<td>6.86</td>
</tr>
<tr>
<td>[Cr]k, ng/ml</td>
<td>34.70</td>
<td>5.58</td>
<td>8.97</td>
<td>8.11</td>
<td>7.77</td>
<td>5.16</td>
</tr>
<tr>
<td>[Cr], to [Cr], hours</td>
<td>3.6</td>
<td>14.7</td>
<td>2.9</td>
<td>12.3</td>
<td>3.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Cvr, mL/min</td>
<td>45</td>
<td>56</td>
<td>59</td>
<td>88</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>Predicted [Cr], mg/dL</td>
<td>1.97</td>
<td>1.24</td>
<td>0.99</td>
<td>2.99</td>
<td>0.24</td>
<td>1.48</td>
</tr>
<tr>
<td>Measured [Cr], mg/dL</td>
<td>1.60</td>
<td>1.52</td>
<td>0.87</td>
<td>2.17</td>
<td>0.87</td>
<td>1.41</td>
</tr>
</tbody>
</table>

*Patient 2 died while [Cr] was decreasing

A modeling of the decline in [Cr] of patient 3 is presented in figure

PUB058

Recovery of Renal Function After Removal of Functional Causes of Advanced Renal Failure

Maria-Elvira Roumelioti1, Faraz Khan Luni, Sandeep Vetterth, Darlene Melinda Vigel,1 Kavitha Ganta,1,3 Deepak K. Malhotra,2 Antonios Tzamaloukas.1,3 1Univ of New Mexico; 2Univ of Toledo; 3Raymond G. Murphy VA Medical Center.

Background: It is important to predict whether renal function recovers completely, early in the course of functional azotemia. We hypothesized that the level of renal function can be predicted from the early change in serum creatinine concentration ([Cr]) during treatment of functional azotemia.

Methods: Taking into account the changes in the body pool of Cr at diagnosis and Cr production during treatment, we calculated the Cr clearance ([Cr]k) between the [Cr] levels in the blood sample obtained at presentation ([Cr]k) and in the first blood sample after the initiation of non-dialytic treatment ([Cr]k) in 6 pts, 5 men with urinary retention and a woman with prerenal azotemia. The calculated Ck values was used to predict [Cr] levels corresponding to times of subsequent [Cr] measurements. We compared the predicted [Cr] levels to the corresponding measured ones.

Results: The table shows [Cr]k and [Cr]k levels, calculated Ck values, predicted and measured [Cr] levels at steady state after correction of the azotemia ([Cr]k). Predicted and measured [Cr]k values were close.

Conclusions: Computation of early Ck after removal of the cause of functional azotemia may provide estimates of post-treatment [Cr] levels reasonably close to the measured levels. More observations are needed.

Funding: Veterans Administration Support

PUB059

Relation of Cardiothoracic Bioelectrical Impedance Hemodynamics and Volemic Parameters with Acute Kidney Injury Prognosis


Background: Evaluate the relation of hemodynamics and volemic parameters with AKI. We evaluate hemodynamic parameters (cardiac output –CO, cardiac output index –COI, left ventricular work index –LVWI, and systemic vascular resistance index –SVRI) and thoracic volemic parameters (Thoracic fluid volumen -TFV-, Thoracic fluid volumen index –ISI), analytical parameters (creatinine –Cr, prealbumin –PRALB, albumin –ALB) and chronic health index (Karnofsky –K).

Methods: We use a cohort of 21 patients (mean age years 69 SD 2.8, 76.2% males) with AKI. We evaluate hemodynamic parameters (cardiac output –CO, cardiac output index –COI, left ventricular work index –LVWI, and systemic vascular resistance index –SVRI) and thoracic volemic parameters (Thoracic fluid volumen -TFV-, Thoracic fluid volumen index –ISI) with clinical index prognosis (severity individual index –SI), analytical parameters (c-reactive protein –CRP, prealbumin –PRALB, albumin –ALB) and chronic health index (Karnofsky –K).

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>mean/ sd</th>
<th>BNP pg/ml</th>
<th>NGAL ng/ml</th>
<th>CO l/min</th>
<th>COI l/min</th>
<th>LVWI Kg/m2</th>
<th>SVRI dyns cm–5 m2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1068 ±18.9</td>
<td>252 ±36</td>
<td>4.3 ±0.47</td>
<td>2.56 ±0.23</td>
<td>2.53 ±0.25</td>
<td>2338 ±245.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>15.6 ±20.0</td>
<td>1300</td>
<td>2.9</td>
<td>2.6</td>
<td>1842</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>189.45 ±24</td>
<td>706 ±141</td>
<td>6.3 ±0.20</td>
<td>3.05 ±0.20</td>
<td>3.26 ±0.36</td>
<td>2082 ±206.83</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>158.49 ±27</td>
<td>177 ±65</td>
<td>3.03 ±0.20</td>
<td>1.53 ±0.08</td>
<td>1.75 ±0.12</td>
<td>4322 ±394.5</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: The use of CTBIA is useful to evaluate and classify patients with cardiological or renocardiac syndrome. There are association between vascular resistance and renal tubular necrosis.
Results: Patients with lower vascular resistance and higher cardiac work have worse prognosis, associated with inflammatory state and thoracic hypervolemia, oliguria and higher renal replacement therapy requirements. But patients with higher thoracic volumes have higher risk of respiratory failure.

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>CO/min</th>
<th>COI min/m2</th>
<th>TFV/kOhm</th>
<th>TFVI/kOhm/m2</th>
<th>SVRI dyn s/cm-5 m2</th>
<th>SV ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISI r p</td>
<td>0.556</td>
<td>0.009</td>
<td>0.085</td>
<td>-0.483</td>
<td>0.082</td>
<td>0.087</td>
</tr>
<tr>
<td>CRP p</td>
<td>ns</td>
<td>ns</td>
<td>-0.392</td>
<td>-0.480</td>
<td>-0.038</td>
<td>ns</td>
</tr>
<tr>
<td>Hypo p</td>
<td>0.019</td>
<td>0.009</td>
<td>0.233</td>
<td>0.016</td>
<td>2992/1920</td>
<td>0.056</td>
</tr>
<tr>
<td>Vent. R p</td>
<td>YES/NO</td>
<td>33.5/5.0</td>
<td>0.064</td>
<td>18.3/25.8</td>
<td>0.181</td>
<td>0.064</td>
</tr>
<tr>
<td>RRT. p</td>
<td>YES/NO</td>
<td>0.022</td>
<td>2.4/3.2</td>
<td>0.016</td>
<td>2845/2177</td>
<td>0.066</td>
</tr>
</tbody>
</table>


Conclusions: CTHBA can be used to evaluate prognosis and therapy of higher risk AKI. Patients with vasopressive state (with inflammatory origin and higher multiorgan failure risk) or thoracic hypervolemia (with higher respiratory failure and intubation risk).

PUB060

Abruptio Placenta as a Complement Amplifying Condition for Atypical Hemolytic Uremic Syndrome

Sved S. Haagc, Amro Elshoury, Daniel Sedhom, Arif Asif, Albany Medical College, Albany, NY.

Background: Endothelial injury resulting in microvascular thrombosis is the underlying pathology leading to target organ injury in aHUS. The syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic injury to multiple organs including the kidney. Complement amplifying conditions often lead to the activation of complement cascade involved in the pathogenesis of aHUS. In this report, we present 33-year-old Hispanic women with abruptio placenta at 33 weeks of gestation and fetal death who underwent cesarean section. Post procedure, patient developed microangiopathic hemolytic anemia (6.7 mg/dl), thrombocytopenia (39,000/μL) and renal failure necessitating initiation of hemodialysis. Fibrinogen (267 g/dL), PT, PTT were normal while LDH was markedly elevated at 2670 IU/L haptoglobin was severely reduced at 5.8 mg/dL. Marked schistocytosis was observed on peripheral smear. ADAMTS 13 was ordered and plasma exchange was initiated. Five sessions failed to show any improvement and ADAMTS 13 activity returned at 56%. Plasma therapy was not applicable when plasma serum creatinine (sCR) is rapidly changing. Chen et al (JASN 2013) has recently proposed KeGFR formula to calculate GFR from fluctuating sCR values. The aim of this study was to compare KeGFR values with eGFR using the Modification of Diet in Renal Disease (MDRD).

Methods: We analyzed data from a cohort of 735 ICU patients screened in a prospective observational study on the incidence of aHUS from June 06 to Dec 08 at an academic center. Demographic data, comorbidities, clinical course, and laboratory parameters were recorded from ICU admission. We estimated KeGFR and eGFR for each patient during the first 48 hrs of ICU stay. We defined KeGFR = (SSPcr × CrCL/ Mean Pcr) × (0.742 if African American). We compared estimated GFR assessed by kinetic modeling with that of the Modification of Diet in Renal Disease (MDRD) equation.

Results: We analyzed data from a cohort of 735 ICU patients screened in a prospective observational study on the incidence of aHUS from June 06 to Dec 08 at an academic center. Demographic data, comorbidities, clinical course, and laboratory parameters were recorded from ICU admission. We estimated KeGFR and eGFR for each patient during the first 48 hrs of ICU stay. We defined KeGFR = (SSPcr × CrCL/ Mean Pcr) × (0.742 if African American). We compared estimated GFR assessed by kinetic formula with MDRD GFR equation.

Conclusions: Our study highlights the overestimation of renal function by MDRD equation in critically ill patients with acute kidney injury (AKI). KeGFR may be more accurate in tracking renal function changes in AKI. Further studies are needed to confirm these findings.

PUB062

Comparison of Estimated Glomerular Filtration Rate (eGFR) and Kinetic eGFR (KeGFR) in Critically Ill Intensive Care Unit (ICU) Patients

Rakesh Malhotra, Ettiene Maccio, Josse Bouchard, Ravindra L. Mehta, Albany Medical College, Albany, NY.

Background: Estimation of kidney function in critically ill patients is important for appropriate drug dosing and therapeutic strategies. However, current GFR equations are not applicable when plasma serum creatinine (sCR) is rapidly changing. Chen et al (JASN 2013) has recently proposed KeGFR formula to calculate GFR from fluctuating sCR values. The aim of this study was to compare KeGFR values with eGFR using the Modification of Diet in Renal Disease (MDRD).

Methods: We analyzed data from a cohort of 735 ICU patients screened in a prospective observational study on the incidence of aHUS from June 06 to Dec 08 at an academic center. Demographic data, comorbidities, clinical course, and laboratory parameters were recorded from ICU admission. We estimated KeGFR and eGFR for each patient during the first 48 hrs of ICU stay. We defined KeGFR = (SSPcr × CrCL/ Mean Pcr) × (0.742 if African American). We compared estimated GFR assessed by kinetic formula with MDRD GFR equation.

Results: We analyzed data from a cohort of 735 ICU patients screened in a prospective observational study on the incidence of aHUS from June 06 to Dec 08 at an academic center. Demographic data, comorbidities, clinical course, and laboratory parameters were recorded from ICU admission. We estimated KeGFR and eGFR for each patient during the first 48 hrs of ICU stay. We defined KeGFR = (SSPcr × CrCL/ Mean Pcr) × (0.742 if African American). We compared estimated GFR assessed by kinetic formula with MDRD GFR equation.

Conclusions: Our study highlights the overestimation of renal function by MDRD equation in critically ill patients with acute kidney injury (AKI). KeGFR may be more accurate in tracking renal function changes in AKI. Further studies are needed to confirm these findings.
Contrast Induced Nephropathy Among Hospitalized South Africans – Impact of Serum Albumin

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Background: Despite ranking 3rd as cause of hospital acquired acute kidney injury in hospitalized patients, contrast induced nephropathy (CIN) causes significant morbidity, mortality, and high hospitalization costs. In sub-Saharan Africa, information on rates of CIN is lacking. This study investigated the rates of CIN and influence of serum albumin on CIN.

Methods: This is an on-going prospective case controlled study conducted at Charlotte Maxeke Johannesburg Academic Hospital, in South Africa. In-patients undergoing contrast media exposure and consented to this study were consecutively recruited to the study. Ethical approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. CIN was defined as serum Creatinine $>$250µmol/L or $>$4.4µmol/L from baseline over a 48-72 hours post exposure to contrast media. CIN clearance was calculated using the CKD-EPI. The following were exclusion criteria: age below 18years, evidence of AKI (clinical or laboratory), ESRD and prior contrast media administration.

Results: Among 285 recruited hospitalized patients, a rate of CIN was 16.9%. Serum albumin below 35g/dl positively predicted development of CIN (RR 2.3, 95% CI 1.4-4.6; p=0.020). The mean albumin was 28.4±4.6 SD and 41±2.39 SD in the CIN and non CIN groups respectively. An eGFR $<$60ml/min was associated with a 6 fold risk of developing CIN with 4±4.6 SD and 41±4.6 SD in the CIN and non CIN groups respectively. An eGFR $<$60ml/min was associated with a 6 fold risk of developing CIN (P=0.00001).

Conclusions: Rates of CIN is significantly high in developing countries and the presence of hypalbuminemia, a traditional bio-marker is significantly associated with development of CIN.

Rosuvastatin Has a Protective Effect against Hypertonicity-Induced Cell Damage

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Background: Contrast-induced nephropathy (CIN) is one of the causes of acute kidney injury. Some studies raised a concern that statins have protective effect against CIN. Hypertonic stress in renal tubular cell is a possible factor inducing cell damage in CIN. Reactive oxygen species (ROS) can induce apoptosis. We studied the effect of rosuvastatin on hypertonicity induced cell damage in MDCK cells.

Methods: Hypertonic medium was made by addition of NaCl. Rosuvastatin was added 24 hours before the hypertonic exposure. Cell damage was assessed by LDH activity in culture medium. Apoptosis was evaluated by caspase-3 activity. Content of cellular glutathione (GSH), an important antioxidant, was measured.

Results: Hypertonicity more than 600 mOsm showed significant cytotoxic effect in MDCK cells. LDH activity in culture medium of 620, 640 and 660mOsm cells increased in osmolality dependent manner (Figure). Low concentration (0.1 and 1.0 µM) of rosuvastatin had a protective effect against the hypertonicity-induced cell damage. On the other hand, 10 µM rosuvastatin that had no significant cytotoxic effect in 300mOsm condition, stimulated hypertonicity induced cell damage.

Conclusions: Low osmolality condition is a possible factor inducing cell damage in CIN. Rosuvastatin has a protective effect on hypertonicity-induced cell damage in MDCK cells.

Funding: Government Support - Non-U.S.

Anticoagulation-Free Continuous Renal Replacement Therapy: A Single Center Observation


Background: Renal failure in the ICU setting is associated with 40-60% mortality. Continuous renal replacement therapy (CRRT) is used for volume and electrolyte management in critical care units. To avoid clotting of hemofillets, patients are routinely started on anticoagulation. In literature, anticoagulation has been associated with complications of increased risk of bleeding and metabolic or electrolyte disturbances based on type of anticoagulation used. We aimed to investigate the length of cartridge use and the association of anticoagulation.

Methods: We conducted a retrospective review of 20 ICU patients who were started on CRRT over a course of 6 months for acute renal failure. We looked at the number of cartridges used per day. Prescription for CRRT was dialysate flow rate of 25-35 ml/kg/h and blood flow rate of 250 ml/h. No anticoagulation was ordered initially due to bleeding risks in this cohort. All patients were ordered 100 ml of normal saline flushes every 4 hours.

Results: Of the 20 patients, the hemofilter cartridge lasted >24 hours. 30% of the patients required more than 1 filter per day, of which only 1 patient was started on a heparin drip for anticoagulation due to multiple filter changes. We used predilution replacement fluid to reduce the blood viscosity and hemoconcentration for the patients requiring > 2 filter changes per day. Decreased requirement of filter change was noted after these changes were made. Among the patients with increased filter clotting, 33% had femoral non-tunneled dialysis catheters and 50 % had internal jugular tunneled dialysis catheters. Longer duration of dialysis was associated with increased cartridge use per pearson correlation 0.818 (p=0.000). No documentation was made in the nursing notes to distinguish between vascular access problems versus filter clotting.

Conclusions: Recurrent filter clotting leads to interruption of RRT. Frequent filter changes is not cost effective. However anticoagulation in critical care settings poses multiple potential problems. There was an association between percutameters and increased cartridge use.

Transcription Factor SRF Promotes Renal Fibrosis in IgA Nephropathy

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Background: The role of transcription factors SRF, which regulate C4G element contained genes, in IgA nephropathy is unknown.

Methods: We carried out expression of SRF in human IgA nephropathy tissues from 10 IgA nephropathy patients with renal biopsies diagnostic of IgA nephropathy. Western blotting and qRT-PCR were used to measure SRF expression in IgA nephropathy kidney tissues.

Results: We found significant up-regulation of SRF expression in IgA nephropathy tissues in comparison to normal kidney tissues.

Conclusions: This result indicates that SRF is a potential therapeutic target in IgA nephropathy.
Conclusions: In summary, high expression of SRF associates with increased fibrosis and decreased survival in IgA nephropathy, and perhaps by enhancing TGF-β-mediated downregulation of snail and E-cadherin in HC-RBC.

PUB068
Increased Erythroid Reactive Oxygen Species Production Induced by Indoxyl Sulfate Precedes Red Blood Cell Death
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Background: The uremic toxin indoxyl sulfate (IS) triggers erytosis, an event characterized by phosphorylidyserine (PS) exposure on red blood cell (RBC). The aim of the present study was to evaluate whether increase in RBC reactive oxygen species (ROS) induced by IS precedes PS exposure.

Methods: RBC from healthy controls (HC) were incubated for 4, 12 or 24h with IS (free concentration 4.5 mg/L) in the presence or absence of free radicals scavenger N-acetylcysteine (NAC 0.5 mM). Flow cytometry was employed to assess erytosis (annexin-V binding) and ROS (DCFH-DA).

Results: Incubation of HC-RBC with IS over 4h did not trigger significant erytosis compared to control cells incubated without IS (4.5±1.2% vs 3.6±1.0%, p=0.67). However, 12h and 24h incubation with IS increased levels of erytosis in a time-dependent manner (10.4±3.4% and 16.6±6.1%, respectively). This IS-induced PS exposure on HC-RBC was inhibited in the presence of NAC (6.0±1.3% and 6.5±1.4%, respectively). On the other hand, ROS production by HC-RBC was increased even after only 4h of incubation with IS in a time-dependent manner (14±4.2%, 22±1.5±3 and 34±4.15% for 4h, 12h and 24h respectively) when compared to control cells (6.6±2.3%, 4.2±0.5% and 5.2±1.8%, respectively). ROS production was inhibited in the presence of NAC (6.6±3.4%, 6.3±2% and 13±4.10.5%) demonstrating the ability of an antioxidant to reverse the oxidative stress induced by IS.

Conclusions: Taken together our results suggest that IS in a high free concentration, which is in accordance with reported free toxin concentration in patients, induces ROS production in HC-RBC that precedes PS exposure. Thus, imbalance of RBC redox status induced by IS appears to be an important mechanism of elevated erytosis observed in CKD that consequently may contribute to renal anemia.

PUB069
Impact of Constitutive C-MIP Expression on Mouse T-Cell Proteome
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Background: The protein c-mip is overexpressed in lymphocytes and podocytes of MCNS patients. In order to dissect its role in INS pathogenesis, we generated a transgenic mouse expressing c-mip in peripheral mature T-cells. We aimed to evaluate the impact of c-mip expression on T-cell proteome in basal and stimulating conditions.

Methods: T-cells from transgenic (Tg) and control (Wt) mice (n=3) were purified by negative immunoselection, and subjected to anti-CD3 and anti-CD28 stimulation, to mimic T-cell activation by antigen presenting cells. At 0 and 60 min post-activation, total proteins were collected and proteins from Tg and Wt were labeled with iTRAQ and mixed in a 2:1 ratio for mass spectrometry analyses.

Results: The expression levels of 2660 proteins were compared in the four conditions. As a result, 46 proteins were found differentially expressed between Tg and Wt mice as a function of stimulation (p<0.05).

Conclusions: Our results indicate that increased c-mip expression can affect T-cell proteome in basal and stimulating conditions, which could be a valuable tool for investigating T-cell regulation mechanisms.

PUB070
An Investigation into the Prognosis of Nephrotic Syndrome and Regulatory T Cells in Elderly People
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Background: Peripheral blood flow cytometry analysis of nephrotic syndrome (NS) in children has been performed, and among T cells, regulatory T cells (Tregs) are involved in NS. Therefore, there are reports about Tregs and ANCA-associated glomerulonephritis, and the nephritic inhibitory effect of Tregs has become clear. As there has been no investigation focusing only on NS in elderly people, we conducted the analysis in this study.

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

902A
Effects of 1,25-Dihydroxy Vitamin D₃ on Treg Cells, Interleukin-17, RORγt in Rats with IgA Nephropathy  

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Background: To investigate the relationship between Treg cells, RORγt, IL-17 and rats with IgA nephropathy; to explore the intervention effect of 1,25(OH)₂D₃ on Treg cells, RORγt, IL-17 expression in rats with IgA nephropathy.

Methods: We chose Wister 52 rats, with which 8 rats were chosen in control group (group E) in random, while other 44 rats were established the IgA nephropathy group. After treatment with 1,25(OH)₂D₃, the level of Foxp3 increased significantly.

Conclusions: Treg cells, IL-17 and RORγt may participate in the occurrence/development of IgAN; 1,25(OH)₂D₃ may play a role in immune regulation by regulating the expression of Treg cells, IL-17 and RORγt directly or indirectly.

Funding: Government Support - Non-U.S.

MGRS, Complement and C3 Glomerulopathy  

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Background: Monoclonal gammapathy of renal significance (MGRS) implies a causal relationship between clonal B cell proliferation and renal failure. By definition, these patients do not meet criteria for overt multiple myeloma/B-cell proliferation, however the significance of this disorder is not of undetermined significance. Rather, it is associated with high morbidity secondary to renal compromise induced by circulating monoclonal immunoglobulins (MIg). Recently, a subset of MGRS with dominant glomerular C3 deposition or MGRS-C3 glomerulopathy (C3G) has been reported.

Methods: Factor H (FH) autoantibodies, free light chains against FH and factor B (FB) autoantibodies were detected by ELISA. C3 nephritic factors were detected using ELISA and hemolytic-based assays.

Results: Six patients developed MGRS-C3G triggered by four different mechanisms of action. The first mechanism of action, identified in three patients, was an IgG form of MIg to FH. These FH autoantibodies compromised function of FH, the only fluid-phase negative regulator of the alternative pathway (AP) of complement. The second mechanism, identified in one patient, was a free light chain (FLC) form of MGRS against FH. The FLCs acted as min autoantibodies against the N-terminus of FH and impaired cofactor activity. The third mechanism, also identified in one patient, was an IgG form of MIg to FB as FB autoantibodies, resulting in increased activity of C3 convertase (C3bBb). The final mechanism, identified in one patient, was an IgG form of MIg, as a C3 nephritic factor that bound to and stabilized C3bBb.

Conclusions: These findings highlight the variability in autoantibodies associated with MGRS-C3G, thus mandating a comprehensive and detailed analysis of the alternative pathway in these patients. Acknowledgment: We gratefully acknowledge both the clinicians across North America who allow us to study their patients, and the patients, whose participation enhances our understanding of rare complex renal diseases.

Funding: Private Foundation Support

Elucidation of Tubulo-Interstitial Injury in Chronic Kidney Ischemia by Use of Novel Renal Artery Coiling Model  

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Background: Recent studies emphasize an essential role for tubulointerstitial hypoperfusion in the progression of chronic kidney disease (CKD) as a common pathway to end stage renal disease (ESRD). However, the mechanism of renal injury needs further to be elucidated.

Methods: Most previous animal models which aimed to simulate renal ischemia have been ischemic-reperfusion injury model, which shows major characteristics of acute kidney injury. To elucidate the progression of kidney dysfunction with chronic ischemia, we developed novel renal ischemia model by setting a coil around a left renal artery of right hemi-nephrectomy rats and reducing the kidney bloodstream by 80.5% . The coil was made of the titanium and the inside diameter is from 0.17 to 0.28 mm.

Results: After transient decline in renal function until post-operative day 14, slowly progressive renal functional decline and elevation of N-acetyl-

Toll Like Receptor 2, 4 and 9 Expression Is Enhanced in Kidneys of Patients with Anti Neutrophil Cytoplasmic Antibody Associated Vasculitis (AAV)  

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Background: Toll like receptors (TLRs) may be the possible link between infection and autoimmunity. This study investigates the distribution of TLR2, 4 and 9 in human kidney biopsies from patients with AAV (40), lupus (8) and controls (with non proliferative glomerular lesions, minimal change and thin membrane disease, 10).

Methods: Biopsies were examined by confocal microscopy with immunofluorescent staining in serial sections for the cellular distribution of TLR2, 4 and 9. Mean fluorescent intensity (MFI) was measured by imaging software (Image J) and was correlated with histopathological parameters.

Results: TLR2, 4 and 9 in the AAV group, (for both MPO and PR3 patients) had significantly stronger staining than controls in glomeruli (1.5 ± 13.3AU; 0.25 ± 12.0AU, 0.7 ± 32.6AU, all P<0.05, respectively) and the interstitium (7.4 ± 63.0AU; 0.41 ± 53.8AU; 1.6 ± 59.6 AU, all P<0.05, respectively). The lupus patients also had higher remarkable changes from control kidneys and there are no findings of tissue injury and infiltration of inflammatory cells. However, the progression of tubulointerstitial fibrosis and the increase in the markers for apoptosis and oxidative stress were significant from post-operative day 28 to 84. Real-time quantitative PCR analysis in ischemic kidney revealed the progressive changes of the hypoxia-responsive gene expressions such as pyruvate kinase and hypoxia inducible factor.

Conclusions: These data suggest that the novel chronic renal ischemia model by coiling renal artery is an appropriate animal model for CKD, which shows a slowly progressive tubulointerstitial injury.

Funding: Government Support - Non-U.S.

Dialysis Induces Morphological Changes and Erythropoiesis in Erythrocytes  

Grazia Maria Virzi, Sabrina Milan Manani, Anna Clementi, Alessandra Brocca, Massimo de Cal, Claudio Ronco. IRRIV and Dept Nephrology Vicenza.

Background: Suicidal death of erythrocytes (erytosis) is characterized by cell shrinkage, membrane blebbing, activation of proteases, and phosphatidylserine (PS) externalization. Exposed PS is recognized by macrophages that engulf and degrade affected cells. Erytosis is a physiological mechanism under complex regulation. During their daily life, erythrocytes (RBCs) are exposed to several stressors, such as oxidative stress, osmotic shock, energy depletion. Erytosis is observed in a wide range of clinical conditions, such as CKD, malignancy, diabetes and sepsis. The aim of this study was analysed cell volume and PS abundance at the RBC surface in peritoneal dialysis (PD) and hemodialysis (HD).

Methods: 40 PD patients, 30 HD patients and 17 healthy subjects (CTR) were included in the study. All measurements were made in isolated RBCs. RBC volume and morphology was estimated from forward scatter, PS exposure at the cell surface was estimated from FITC-AnnexinV binding using flow cytometric analyses.

Results: We observed that PD and HD patients are indeed rather dramatically deranged in their morphology. Furthermore, the PS externalization on the RBC surface was significantly higher in these groups than in CTR (PD patients: 2.6%; IQR 1.6-3.7, HD patients: 2.2%; IQR 1.2-4.1 versus CTR: 0.8%; IQR 0.7-1.3; p<0.000001). We did not find significant differences in PS exposure between the PD and HD patients (p=0.47).

Conclusions: In conclusion, the percentage of erytosis has indeed been shown to be significantly higher in patients on dialysis than CTR. Our data suggest that dialysis may induce morphological changes in erythrocytes and may lead to a significant increase in erytosis, hence differences in its level were observed between PD and HD. Additional efforts will be required to define major erytosis-inducing components in uremic, PD and patients.

Funding: Private Foundation Support
expression of TLR2 (4.8 AU), 4 (12.6 AU) and 7 (7.3 AU, P<0.05) compared with controls, but this difference was not significant compared to the AA V group for all TLRs (P<0.05). Cellular infiltrates contained intense staining for TLR2, 4 and 9 on macrophages and neutrophils in both glomeruli and interstitium. TLR2 and TLR4 staining was prominent on both endothelial cells and podocytes, although TLR9 was particularly evident on podocytes. In AA V glomerular TLR4 expression correlated with the % of normal glomeruli (r=0.48, P<0.05) suggesting TLR4 prominence occurs in early glomerular lesions. Glomerular TLR2 and 9 were present concurrently in more severely affected glomeruli (r=0.71, P=0.0001). TLR2, 4 and 9 were prominent in all crescentic glomeruli of AA V and lupus patients.

Conclusions: This study demonstrates that TLR expression is most prominent in AA V. Significant expression of TLRs was evident on leukocytes and intrinsic glomerular cells. TLR4 is prominent in early glomerular lesions, while TLR2 and 9 correlate with severe glomerular lesions.

Funding: Government Support - Non-U.S.

PUB080
An Oxalate-Induced Mouse Model of CKD That Displays Common CKD Features

PUB080
Cyclosporine A Reduces Renal Injury Through Protecting Glomerular Charge Barrier in Passive Heymann Nephritis

PUB079
Increased Cellular Microchimerism in Women with Systemic Lupus Erythematosus

PUB078
Podocyte CD40 Expression in Patients with Post-Transplant FSGS

Results: Mc was detected more often in SLE patients than in controls (54.4% vs 13.6%, P<0.05). Mc was mostly fetal in origin in almost all cases. The median total number of fetal chimeric cells was significantly higher in patients than in controls (5.10^4 versus 2.510^4, P=0.048). In 50% of SLE patients with Mc, Mc originated from multiple relatives whereas in controls Mc was derived from only one relative. We found no relationship between Mc and clinical or laboratory parameters.

Conclusions: SLE patients had Mc in peripheral blood more often than controls, and at higher levels. We showed that Mc was mostly fetal in origin and, in SLE patients, could be derived from multiple relatives. Our findings substantiate the role for Mc in autoimmune diseases such as SLE.

Funding: Private Foundation Support

PUB080
An Oxalate-Induced Mouse Model of CKD That Displays Common CKD Features

Juan D. Diaz de Pool, 2 Mathilde M.M. Almekinders, 1 Hans J. Baelde, 1 Jan A. Rutger Maas, 1 Ingeborg M. Bajema.

Private Foundation Support

Government Support

U.S.

Podocyte CD40 Expression in Patients with Post-Transplant FSGS

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Background: antibodies against CD40 were recently reported to predict post-transplant recurrent FSGS (rFSGS) with 78% accuracy (Delville et al. Sci Transl Med 2014). Using immunohistochemistry, the authors reported strong focal podocyte CD40 expression in glomerular lesions of two patients with rFSGS. We sought to validate this novel finding of podocyte CD40 expression as a potential marker of rFSGS.

Methods: We used formalin-fixed, paraffin embedded kidney tissue from five patients with rFSGS. Two samples were obtained from nephrectomy specimens, and three were needle biopsy specimens. All patients had nephrotic range proteinuria at the time of tissue sampling. A human tonsil was used as a positive control. For immunohistochemistry, four mm slides were cut and deparaffinized. After endogenous peroxidase block, antigen retrieval was performed by boiling in a microwave with EDTA buffer (pH 9.0). Slides were incubated with primary antibody mouse anti CD40 (clone 11E6, Abcam ab50849) diluted in PBS with 1% BSA overnight at 4°C. Detection was done with Brightvision biotin-free goat anti mouse/mouse poly HRP (Immunologic) and DAB as substrate.

Results: specificity and adequacy of the staining was confirmed by strong CD40 expression in tonsillar germinal centers (Figure, panel A). In kidney samples from patients with rFSGS, CD40 staining was found in areas of interstitial cellular infiltration, and some tubular epithelial cells (Figure, panel B). However, no glomerular CD40 was detected in any of the rFSGS samples.

Conclusions: we could not confirm glomerular CD40 staining in rFSGS with immunohistochemistry. The role of CD40 antibodies in rFSGS pathogenesis needs further study and validation.

Funding: Private Foundation Support

PUB079
Increased Cellular Microchimerism in Women with Systemic Lupus Erythematosus

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Background: Microchimerism (Mc) has been suggested to play a role in the development of systemic lupus erythematosus (SLE). We previously showed that Mc occurs twice as often in kidney biopsies of patients with lupus nephritis as in controls. Recently, it was demonstrated that the amount of Mc in lupus nephritis is associated with renal function deterioration (Tu et al. Am J Nephrol 2015). In this study, we examined the frequency, amount and origin of chimeric cells in SLE patients and controls, by using insertion-deletion polymorphisms and null alleles for the detection of Mc.

Methods: We included 11 SLE patients and 22 controls, as well as their children and mothers. A quantitative PCR for insertion-deletion polymorphisms and null alleles was used to detect Mc in peripheral blood mononuclear cells and granulocytes. The relationship between the presence of Mc and disease onset, disease activity and accumulated damage since disease onset was investigated.

Results: Mc was detected more often in SLE patients than in controls (54.4% vs 13.6%, P<0.05). Mc was mostly fetal in origin in almost all cases. The median total number of fetal chimeric cells was significantly higher in patients than in controls (5.10^4 versus 2.510^4, P=0.048). In 50% of SLE patients with Mc, Mc originated from multiple relatives whereas in controls Mc was derived from only one relative. We found no relationship between Mc and clinical or laboratory parameters.

Conclusions: SLE patients had Mc in peripheral blood more often than controls, and at higher levels. We showed that Mc was mostly fetal in origin and, in SLE patients, could be derived from multiple relatives. Our findings substantiate the role for Mc in autoimmune diseases such as SLE.

Funding: Government Support - Non-U.S.
Absence of Caspase-1 Attenuates Adrenalin-Induced Nephropathy

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Background: Recent studies have demonstrated a pathogenic role of caspase-1 in mediating proteinuria-associated renal injury. As a chronic proteinuric renal disease model, adrenalin-induced nephropathy (ANN) is characterized by podocyte injury followed by glomerulosclerosis (GS), tubulointerstitial inflammation and fibrosis, but the mechanisms underlying it remain poorly understood. Based on the evidence that oxidative stress stimulates inflammatory activation which subsequently contributes to renal injury, we hypothesized that abolishing caspase-1 expression in the kidney may be protective.

Methods: Male caspase-1 knockout (KO) and wildtype (WT) mice on the BALB/c background were injected with ADR (10.5 mg/kg) or saline at 8-10 weeks of age. Twenty-four-hour urine was collected and the mice were sacrificed 14 days post the injection. Creatinine, triglyceride, total cholesterol (TC), albumin and cell mitosis were determined.

Results: ADR triggered overexpression of caspase-1 and IL-1β in kidney tissue of WT mice, but not in that of KO mice. ADR induced albuminuria and GS, which was accompanied with decreased kidney weight/body weight ratio (Kw/Bw), and increased Cr and TCH levels in both KO and WT mice. Compared with WT animals, KO mice showed significantly lower ACR, reduced GS scores, increased Kw/Bw, and attenuated Cr levels (P<0.05 each). Meanwhile, elevated expression of TNF-α and INF-γ, augmented iNOS, and decreased PPAR-α, SDHA, and SOD2 levels were observed in ADR-treated kidneys, and all these changes were shown to be significantly ameliorated in KO mice. In addition, positive correlation between Cr and TCH was recognized in both KO and WT ADR-treated mice.

Conclusions: Cytokine-mediated inflammatory cascade, hyperlipidemia, and impaired mitochondrial function are all responsible for ADR-induced kidney injury. Caspase-1 may be a potential therapeutic target in proteinuric renal disease. 

Funding: NIDDK Support, Other NIH Support - ASN-Nephone Foundation

Glucomer H1-O1 Expression Control by Hemin: Role of Hemoxpin

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Background: Hemoxpin (HPX) maintains low free heme levels in serum thus mitigating heme-associated cell injury. HO-1 induction also minimizes injury by degrading heme to CO and bile pigments. In hemolytic disorders, heme scavenging by HPX is hypothesized to be sufficient. In contrast, in hemolytic disorders (HPX+/−) or HPX-deficient (HPX−/−) mice, exposure to high heme (200, 400 µM) markedly reduced HO-1. This reduction was attenuated in incubations with varying dilutions of HPX medium, and increased by 2-fold in incubations with 10% HPX+ serum. The effect of heme was added at concentrations encountered in hemolytic disorders (100-400 µM). HO-1 protein levels were assessed by western blot.

Results: HO-1 protein was reduced by 70% in hemoxy 1 and increased by 2-fold in 10% HPX+ glomeruli. HO-1 protein levels were different between 10% HPX+ serum vs serum-free media. In incubations with varying dilutions of HPX serum (1.25, 2.5, 5, 10, 100, 1000 µM) HO-1 levels in WT glomeruli progressively increased and were 2.5-fold higher with 10% HPX serum compared to 100% HPX serum. Co-incubation with 10% HPX serum and heme (200, 400 µM) markedly reduced HO-1. This reduction was attenuated in incubations with higher dilutions (2.5%) of HPX serum or with 10% HPX+ serum. The effect of heme on HO-1 levels in glomeruli incubated with HPX serum was recapitulated in GECs

Conclusions: Heme-mediated HO-1 induction in glomeruli is limited by HO-1 expression levels attained. This may serve to limit level of HO activity thereby preventing heme to CO and bile pigments. In hemolytic disorders, heme scavenging by HPX is hypothesized to be sufficient. In contrast, in hemolytic disorders (HPX+/−) or HPX-deficient (HPX−/−) mice, exposure to high heme (200, 400 µM) markedly decreased compared to Wt. In contrast, HO-1 expression and cell adhesion were all responsible for ADR-induced kidney injury. Caspase-1 may be a potential therapeutic target in proteinuric renal disease.

Funding: NIDDK Support, Other NIH Support - ASN-Nephone Foundation

Glocomer H1-O1 Over Expression: Protective Effects in Secondary but Not Primary GEC Injury

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Background: In contrast to tubular epithelial cells, induction of the cytoprotective enzyme, Heme Oxygenase (HO-1), in response to injury in epithelial glomerular cells (GEC) is limited or absent and this may increase their vulnerability to injury. We, therefore, expected that abolishing HO-1 expression in GEC, the protectant against primary injury, induced by puromycin aminonucleoside (PAN) or secondary injury resulting from anti-GBM Ab induced glomerulonephritis (GN).

Methods: HO-1 over expression in GEC of Sprague-Dawley (SD) rats was achieved by overexpressing aFLAG-human(h)HO-1 sequence under the control of a murine nephrin promoter using transposon-mediated gene-trap insertion mutagenesis based on a Sleeping Beauty(SB) transposon system (SB rats). GEC-targeted over expression was validated by FLAG immunolocalization and/or western blot. PAN-mediated GEC injury was induced in SD rats by a single intraperitoneal injection. GN was induced by a single intravenous injection of a rabbit anti-rat GBM Ab. At defined points following PAN or anti-GBM Ab injection, albuminuria (Ualb/Ucreat) was assessed and glomeruli were isolated to determine changes in HO-1 and nephrin expression (GEC integrity marker).

Results: In glomeruli from SB rats HO-1 levels (protein) increased compared to Wild type (Wt). Administration of either PAN or anti-GBM Ab to Wt rats increased gloomerular HO-1. In SB rats receiving PAN, HO-1 markedly decreased compared to Wt. In contrast, HO-1 protein levels were increased by 4-fold following an injection of Exogenous nephropathy (NPX) ex vivo in glomeruli from SB rats treated with PAN. In contrast, nephrin was preserved in glomeruli from SB rats treated with anti-GBM Ab. Ualb/Ucreat was significantly higher in WT compared to SB rats treated with anti GBM Ab. In contrast, there was no difference in Ualb/Ucreat between Wt and SB rats receiving PAN.

Conclusions: Augmentation of HO-1 expression in primary GEC injury is impaired. This could be yet another mechanism contributing to GEC vulnerability in primary podocytopathies.

Funding: Government Support - Non-U.S.

Comparative Evaluation of Cellular Injury Models Based on Conditionally Immortalized and Primary Podocytes

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Background: Podocyte injury is a hallmark of proteinuric chronic kidney disease. The two podocytopathies to study the cellular level of renal reorganization, oxidative stress, de-differentiation & detachment. The purpose of this study was to compare commonly used conditionally immortalized podocytes with primary podocytes, by measuring podocyte markers and responses to injury.

Methods: Primary human podocytes were isolated and cultured from a healthy human donor kidney and compared to 1) a subclone (C5) of conditionally immortalized human podocytes (selected based on podocyte specific gene expression) and 2) conditionally immortalized mouse podocytes. Cellular phenotypes and gene expression were measured using high content screening (HCS), qPCR and western blots. For assessment of diabet onic stress the stressor used was streptozotocin and a-smooth muscle actin and 2) cytoketal and cell cycle phenotypes. C5 cells were also evaluated by comparing gene expression profiles in response to TGF-b treatment. C5 podocytes were judged to be similar to primary human podocytes based on these analyses. Current cellular models of podocyte protection often use the stressors puromycin aminonucleoside and TGF-b. We demonstrate cytoprotection by multiple reference compounds with these insults. We have also increased the disease relevance of stressors by showing that serum isolated from diabetic db/db mice differentially elicits podocyte injury across multiple parameters.

Conclusions: Our results validate the use of conditionally immortalized C5 podocytes by benchmarking against primary human podocytes. We have also enhanced the pathologic relevance of models of podocyte injury by incorporating key disease-relevant stressors and readouts.

Funding: Pharmaceutical Company Support - AbbVie

Hypoxia Stimulates the Expression of Tissue Factor in Human Podocytes in Culture

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Background: Hypoxia contributes to tubulointerstitial injury, however, the effect on podocytes and its underlying mechanisms are less well understood. Tissue factor (TF) is the initiator of extrinsic coagulation pathways and is also related to various biologic effects such as migration, proliferation, and apoptosis. We demonstrate the expressions of TF and tissue factor pathway inhibitor (TFPI) in the hypoxic conditions. We further tested the roles of known transcription factors of TF such as, nuclear-factor-kB (NF-kB) and early growth response gene-1 (Egr-1), as well as hypoxia-inducible factor-1 (HIF-1a) which regulates numerous changes in hypoxia.

Methods: Conditionally immortalized human podocytes were grown at 33°C and differentiated at 37°C. The cells were treated in normoxic or hypoxic conditions. mRNA expressions of TF and TFPI were analyzed by quantitative RT-PCR, and protein levels of TF and TFPI were assayed by western blot and found that TFPI was upregulated by HIF-1a. The expression of TF and HIF-1a were demonstrated by immunofluorescent staining. We used siRNA for the temporal knockdown of HIF-1a and Egr-1, and pyrrolidine dithiocarbamate (PDTC) for the inhibition of NF-kB.

Results: Hypoxia increased mRNA expression of TF (6h: 2.3±0.05 fold, p<0.001, 24h: 5.6±2.9 fold, p<0.001 ) compared with Normoxia. The protein levels of TF in the cell lysate were increased and TFPI in the supernatant were decreased. The TF staining was enhanced in

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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the cytoplasm of podocyte. As expected, HIF-1α was strongly stained in the nuclei of podocytes exposed to hypoxia for 6h. The expression of TF was not affected by HIF-1α siRNA, and neither Egr-1 siRNA. Whereas, PDTC reduced the induction of TF by hypoxia.

Conclusions: Hypoxia upregulated the expression of TF in human podocyte NF-κB dependently, and HIF-1α and Egr-1 independently. These changes may be related to the podocyte disorders and lead to proteinuria in the hypoxic condition.

PUB087

Integrity of the Mature APOL1 Protein Is Indispensable for Its Toxicity Xianan Lan,1 Hongxiu Wen,2 Aswathi Mallhotra,1 Karl Leon Skorecki,2 Pravin C. Singhal.1 1Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; 2Medicine, Rambam Health Care Campus, Haifa, Israel.

Background: Several clinical reports have demonstrated that the development of higher rates of non-diabetic glomerulosclerosis (GS) amongst African Americans can be attributed to two coding sequence variants (G1 and G2) in the APOL1 gene. Recent studies indicate that the gene products of these APOL1 risk variants have augmented toxicity in kidney cells. The APOL1 protein is composed of several functional domains, including signal peptide (SP), pore forming domain (PFD), membrane address domain (MAD), and SRA-interacting domain. However, it is not clear, which domain contributes to APOL1 induced cellular toxicity. In case, specific domain is contributing to APOL1-induced cellular toxicity, it will suggest us to design therapeutic strategy to target the specific domain.

Methods: To investigate the relative contribution of each domain to cell injury, we constructed serial of expression vectors to delete each domain, we transfected these vectors into the human embryonic kidney cell line 293T, and then compared the cytotoxicity. In addition, we conducted studies in which APOL1 wild type (G0) was co-transfected in combination with G1 or G2 to see whether G0 could counteract the toxicity of the risk variants.

Results: The results showed that deleting the SP did not abrogate the toxicity of APOL1, though deletion of 26 amino acid residues at the N-terminal partially decreased the toxicity. Deleting PFD or MAD or SRA-interacting domain abolished toxicity, while, overexpressing each domain alone could not cause toxicity to the host cells. Deletion of the G2 sites while retaining G1 sites in the risk state resulted in persistent toxicity. Either deletion or exchanging the BH3 domain in the PFD led to complete loss of the toxicity in this experimental platform. Adding G0 to either G1 or G2 did not attenuate the toxicity of the either moiety.

Conclusions: These findings indicate that the integrity of the mature APOL1 protein is critical for its toxicity.

Funding: NIDDK Support

PUB088

Human Podocyte Depletion: The Effects of Ageing and Hypertension Victor G. Puelle's,1 Luisa A. Cullen-McEwen,1 Jinhua Li,1 Peter G. Kerr,2 Wendy E. Hoy,2 John F. Bertram.1 1Dept of Anatomy and Developmental Biology, Monash Univ, Melbourne, Victoria, Australia; 2Dept of Nephrology, Monash Medical Centre, Melbourne, Victoria, Australia; 1Centre for Chronic Kidney Disease, The Univ of Queensland, Brisbane, Queensland, Australia.

Background: Podocyte depletion plays a major role in the development and progression of glomerulosclerosis. Many kidney diseases are more common in older age, and usually coexist with the presence of hypertension. We hypothesize that podocyte depletion develops with aging and is exacerbated by the presence of hypertension.

Methods: Kidneys from 21 adult Caucasian American males without overt renal disease were collected at autopsy in Mississippi, USA. Subjects were categorized based only on age as young adults, middle-aged adults and older adults. Subjects were also categorized based on age and hypertension as young normotensives, older normotensives, and older hypertensives. Demographic data were collected from available medical records. Design-based stereology was used to estimate individual glomerular volume (IGV), podocyte number and podocyte density. Data are presented as mean±SD.

Results: Glomeruli from young adults (22.0±2.7 years; n=6) were smaller (1.72±0.50 x10³/mm²) and contained 457±97 podocytes and 278±66 podocytes per 10³/m² of glomerular tissue. Glomeruli from older adults (60.0±8.6 years; n=7) were larger (2.94±1.41 x10³/mm²; P<0.001), contained fewer podocytes (390±105; P<0.05) and had lower podocyte density (156±65 podocytes per 10³/mm²; P<0.001). Among normotensives, older age was associated with a 15% increase in IGV (P=0.28), a 12% decrease in podocyte number (P=0.06) and a 17% decrease in podocyte density (P=0.03). Glomeruli from hypertensives and normotensives contained similar numbers of podocytes, but hypertensives had larger glomeruli (P=0.0001) and a markedly lower podocyte density (P<0.001).

Conclusions: These findings demonstrate that both aging and hypertension are independent and additive contributors to podocyte depletion in this cohort of white American men without overt kidney disease.

PUB089

Alport Nephropathy Progression Involves Altered Glomerular Mechanical Properties and Activation of the Unfolded Protein Response Addie Embry,1 Liping Liu,1 Leslie A. Bruggeman,2 Paul A. Janney,3 R. Tyler Miller.1 1Medicine, UTSW, Dallas, TX; 2Medicine, CRWRU, Cleveland, OH.

Background: Tissue and cell mechanics are important factors in the development and maintenance of tissues but are not well defined in renal disease. We determined the biophysical properties of glomeruli over the course of disease in the Col4a3−/− (Alport) mouse.

Methods: Glomerular EMod was measured with microindentation, gene transcript levels with qRT-PCR and immunofluorescence, and kidney structure with histology.

Results: Col4a3−/− kidneys have normal histology, no proteinuria, and a normal glomerular EMod (~2200Pa) through 2.0 mo of age. At approximately 4.0 mo, early interstitial and glomerular fibrosis and proteinuria appear, and the glomerular EMod decreases (~1400Pa). Glomerular softening is characterized of injured glomeruli, is associated with injured podocytes, and could lead to capillary injury even with normal hemodynamics. By 6 mo, the glomeruli regain their original EMod (~ 2200 Pa) but with increased proteinuria and more severe glomerular and interstitial fibrosis. By 7-8 mo, the glomerular EMod increases (~ 2,600 Pa) with further increases in proteinuria and glomerular and interstitial fibrosis. At 2 mo, glomerular transcripts for matrix and fibrinotic factors (CTGF, α-SMA, filamin, lysyl oxidase) are increased and remain so, demonstrating early responses of cells to alter their mechanical environment. Transcripts associated with UPR activation (BiP, CHOP, grp94) are elevated, suggesting that loss of the Col4a3 chain leads to activation of the UPR. Tunicamycin-treated glomeruli demonstrated a markedly reduced EMod (~1100Pa), suggesting that UPR activation causes glomerular injury.

Conclusions: Biophysical abnormalities occur early in the course of this Alport model, suggest that the reduced EMod of glomeruli (increased deformability) may lead to mechanical injury of capillaries even with normal hemodynamic force, that cells of glomeruli respond by producing proteins that will reduce deformability, and that glomerular or podocyte injury may be attributable to activation of the UPR.

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

PUB090

A New Assay to Study Podocyte (De)Differentiation Frances Kindt, Karlhans Endlich, Nicole Endlich. Anatomy and Cell Biology, Univ Medicine Greifswald, Greifswald, Germany.

Background: Podocytes play an essential role in the formation and maintenance of the glomerular filtration barrier. Glomerular disease is associated with podocyte damage, frequently resulting in podocyte dedifferentiation. The loss of podocyte differentiation is poorly understood. Moreover, there are no drugs available that could halt or even reverse podocyte dedifferentiation. Since podocytes of isolated glomeruli have long been known to spontaneously lose their highly differentiated state over time, we established an assay to follow dedifferentiation of living podocyte in isolated glomeruli over time.

Methods: Using magnetic separation with dynabeads, glomeruli were isolated from transgenic mice that express cyan fluorescence protein (CFP) under control of a nephrin promoter fragment (Cui et al., "in press"-“font-family: ‘Times New Roman’; font-size: 10pt;”>). Isolated glomeruli were transferred to 35-mm tissue culture dishes with a medium containing 10% FBS, and fed with low calcium. After 72 hours, isolated glomeruli showed intact immunostaining for nephrin, and expressed high levels of CFP fluorescence as a measure of differentiation, we recorded z-stacks of several glomeruli with confocal laser scanning microscopy on each day. Mean total fluorescence intensity (CFP fluorescence) was calculated from a stack of images taken at different times.

Results: Isolated glomeruli dedifferentiated over time, as indicated by free Bowman’s capsule, exhibited diminished cell damage as assessed by propidium iodide, showed intact immunostaining for nephrin, and possessed intact interdigitating foot processes as judged by scanning electron microscopy. Isolated glomeruli were cultured for up to 9 d in RPMI containing 10% FBS. To quantify CFP fluorescence as a measure of differentiation, we recorded z-stacks of several glomeruli with confocal laser scanning microscopy on each day. Mean total fluorescence intensity per glomerulus (CFP) was calculated from z-stacks after background correction. CFP remained stable for 5 d. Thereafter, CFP gradually decreased to 10% of the initial value on day 9. Dedifferentiation of podocytes could be accelerated by treatment of isolated glomeruli with doxorubicin, strongly decreasing CFP within the first 3 days.

Conclusions: In summary, we established a new assay to study podocyte (de)differentiation. This assay may help to understand the molecular mechanisms of the loss of podocyte differentiation, and may allow to screen for compounds that stabilize podocyte differentiation.

Funding: Government Support - Non-U.S.

PUB091

Methods to Selectively Remove Murine Endothelial Glycocalyx In Vivo Using Glycosaminoglycan Digesting Enzymes without Causing Non-Target Effects Karen L. Onions, Anjila Onifade, Chris R. Neal, Monica Gamez, Gavin Iain Welsh, Andy Salmon, Simon C. Satchell, Rebecca R. Foster. Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.

Background: The endothelial glycocalyx (e-GLX) is an important component of the glomerular filtration barrier (GFB), damage to which increases vascular permeability and microalbuminuria. Jeunsson and Haraldsson previously used glycosaminoglycan (GAG) digesting enzymes to study the role of the e-GLX in glomerular permeability. However, e-GLX removal was not directly quantified. The aim of this research was to confirm removal of systemic e-GLX and identify any non-targeted effects in the glomerular or coroanary microcirculation.

Methods: Mice were injected L.V with chondroitinase (Ch) and hyaluronidase (Hy) at a high (Ch: 87 mg/kg, Hy: 15 mg/kg) or low (Ch: 0.87 mg/kg, Hy: 15 mg/kg) dose. Mice
were whole body (cardiac) perfusion fixed with gluteraldehyde containing Alcian blue to stain the e-GLX. Transmission electron microscopy (TEM) was used to image the ultrastructure of the heart and glomerular microcirculation, which was quantified using an image analysis program which is augmented in response to salt deprivation.

**Results:** In summary, we developed a novel and sensitive method to monitor changes in GP using two-photon microscopy, which can be used for rodents and bigger animals.

**Conclusions:** In summary, we identified how e-GLX contributes to glomerular albumin permeability in different pathological scenarios and may highlight new therapeutic targets. This work was supported by the British Heart Foundation (FS/13/09/2957).

**PUB094**

**A Novel Method to Measure Glomerular Permeability**

**Jin Wei, Shaohui Wang, Lei Wang, Gensheng Zhang, Jie Zhang, Byeon Cho, Kay-Pong D. Yip, Ruisheng Liu.**

**Molecular Pharmacology & Physiology, Univ of South Florida, Tampa, FL.**

**Background:** Glomerular capillaries are relatively impermeable to proteins, but in certain kidney diseases, such as diabetic nephropathy, the glomerular permeability (GP) is increased and some of the lower molecular weight (LMW) proteins, especially albumin, are filtered through the glomerular barrier into the Bowman’s space. Increased GP is a hallmark for many kidney diseases. Proteinuria is often implicated for impaired GP. However, since LMW proteins can be reabsorbed by proximal tubules, proteinuria is detected only when the GP is significantly increased. Recently, real-time quantification of GP can be visualized by two-photon microscopy, but it can only be applied to superficial nephrons, where laser can penetrate, in Munich-Wistar rats. We developed a novel method to monitor GP in C57/BL6 mice by using florescent lysine-fixable dextran conjugates without these limitations.

**Methods:** 100µl Tomato Lectin 594 (endothelial cell marker) plus 50µl 40 KD lysine-fixable dextran 488 (fluid phase marker) were injected intravenously. The kidneys were removed 1 min later and put into liquid nitrogen immediately for 10 minutes followed by fixation with 10% Formalin on ice overnight. Then 10µm thick sections were prepared using a vibratome and the florescent images were collected with two-photon microscopy. The ratio of florescent intensity in Bowman’s space over that of in glomerular capillary lumen was used as an index of GP.

**Results:** In WT mice, the GP is extremely low with a ratio of 0.16±0.08%, N=6 (figure1). In contrast, in diabetic mice induced by alloxan for 8 weeks, the GP is significantly increased with a ratio of 5.9±1.3%, N=6 (figure2).

**Conclusions:** In summary, our data are consistent with highly dynamic cellular remodeling of the renal interstitium, vasculature, glomerulus, and the proximal tubule by single progenitor cells. These results also suggest the presence of a complex nephron repair program which is augmented in response to salt deprivation.

**Funding:** NIDDK Support

**PUB095**

**Vasopressin Regulates the Uptake of Extracellular Vesicles by Kidney Collecting Duct Cells**

**Wilna Oo Oo Thuzaw, 1  Jonathan Street, 1  Andrea Caporali, 1  David J. Webb, 1  Chris Gregory, 1  Matthew A. Bailey, 1  James W. Dear. 1  Centre for Cardiovascular Science, Univ of Edinburgh, United Kingdom; 2 National Inst of Diabetes and Digestive and Kidney Diseases, National Insts of Health; 3 MRC/Univ of Edinburgh Centre for Inflammation Research, Univ of Edinburgh, United Kingdom.**

**Background:** Urine contains extracellular vesicles (ECVs) originating from the circulation and all cells lining the urinary tract. ECVs are a route of inter-cellular communication along the nephron able to transfer protein and RNA. It is not known whether this is a regulated process analogous to other cell-to-cell signalling systems.

**Methods:** Kidney cortical collecting duct cells (CCDs) were stimulated with desmopressin, a vasopressin analogue, and uptake of fluorescently-loaded or microRNA-loaded ECVs was measured. In mice, fluorescently-loaded ECVs were intravenously injected before and after administration of the V2 antagonist, tolvaptan, and urinary ECV excretion was measured. By combining antibodies to nephron segment-specific proteins with nanoparticle tracking analysis we measured human urinary ECV excretion in central diabetes insipidus (DI) and after radiocontrast exposure (n=37).

**Results:** Desmopressin stimulated ECV uptake into CCDs via V2 receptor stimulation. Intra-cellular uptake of ECVs was confirmed by microRNA specific mRNA down-regulation. Mechanistically, ECV uptake in response to desmopressin required cyclic AMP production, was mediated by clathrin-dependent endocytosis and was selective for ECVs from kidney tubular cells. In mice, basally, 2.5% of injected ECV’s were recovered in urine; tolvaptan treatment resulted in a 5-fold increase. In DI, desmopressin reduced the excretion of ECVs derived from upstream glomerular and proximal tubule cells. In patients exposed to radiocontrast, urinary ECVs from the glomerulus were positively correlated with the tubular injury markers KIM-1 and NGAL.

**Conclusions:** Tubular ECV uptake is a specific, hormonally regulated process that is reduced with injury. Physiologically, ECV’s are a mechanism of inter-cellular communication; therapeutically, ECVs represent a novel vehicle by which RNA therapy could be targeted for the treatment of kidney disease.

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

Underline represents presenting author.
**PUB096**

**Systemic Hypertension and Pro-Inflammatory Cytokines**

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**Background:** Cytokines produced by renal tubular epithelial cells are critical factors in inflammatory processes of renal ischemia-reperfusion injury. Increased levels of cytokines have been reported after resuscitation from cardiac arrest. Pro-inflammatory cytokines, such as IL-1β, IL-6 and IL-18, produced in the kidney during ischemia-reperfusion injury, are able to contribute to the renal damage. The purpose of this investigation was to define the proinflammatory cytokines response after resuscitation and during extended observation following therapeutic hypothermia phases.

**Methods:** We performed a prospective observational study in 36 post-cardiac arrest patients treated with Induced Hypothermia (IH) with two different cooling device: 1)Artic Sun; 2)Blanket. On Admission time and at 12, 24, and 72 hours after the start of treatment, blood and urine samples were collected. Plasma cytokines were measured by ELISA.

**Results:** During IH, we observed a decrease of IL-6, IL-1β and IL-18u levels in both groups, and an increase of inflammatory during rewarming phase. The results are showed in table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>IL-1β</th>
<th>IL-6</th>
<th>IL-18u</th>
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<tbody>
<tr>
<td>Arctic Sun (26 pts)</td>
<td>18 (12-20)</td>
<td>102 (40-121)</td>
<td>412 (163-978)</td>
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<tr>
<td>Blanket (10 pts)</td>
<td>17 (13-18)</td>
<td>100 (40-121)</td>
<td>412 (163-978)</td>
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<tr>
<td>p value</td>
<td>0.227</td>
<td>0.136</td>
<td>0.749</td>
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**Conclusions:** Optimal rewarming rate is unknown. Adverse effects from suboptimal rewarming could diminish a protective effect from hypothermia. These biomarkers may serve as indicator of an individual patient’s place in the injury-repair continuum. Further investigations are needed.

**PUB097**

**Impact of Different I.V. Iron Preparations on Monocyte Function and Differentiation**

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**Background:** Treatment of iron deficiency with intravenous (i.v.) iron is a first-line strategy to improve anaemia and quality of life in patients with chronic kidney disease (CKD). However, in vitro and in vivo experiments demonstrated that certain i.v. iron preparations have immunological side-effects. In the present study we now investigated substance-specific impacts of different i.v. iron preparations on monocyte function and differentiation.

**Methods:** We in vitro stimulated monocytes with different concentrations (0.133 mg/ml, 0.266 mg/ml, 0.533 mg/ml) of iron sucrose (IS), sodium ferric gluconate (SFG), ferric carboxymaltose (FCM), and iron isomaltoside 1000 (IIM) and assessed monocytic adhesion and transmigration capacity. Monocyte differentiation into M1 and M2 macrophages and transmigration capacity were significantly reduced in IS and SFG stimulated monocyte derived cells. Finally, we performed ultra-deep miRNA sequencing and immunoprecipitation showed that phosphorylated CD16-CD7-nephrin interacted with wild type c-Abl indicated that the colocalization of nephrin and c-Abl showed in table.

<table>
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<tr>
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**Conclusions:** Optimal rewarming rate is unknown. Adverse effects from suboptimal rewarming could diminish a protective effect from hypothermia. These biomarkers may serve as indicator of an individual patient’s place in the injury-repair continuum. Further investigations are needed.

**PUB098**

**The Involvement of p38 MAPK in Neutrophil Bacterial Dysfunction of Hemodialysis Patients**

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**Background:** Mortality from infection has been reported to be higher in hemodialysis (HD) patients than that in healthy subjects. However, the precise mechanism causing it remains to be investigated. Neutrophils play crucial roles in host defenses against bacterial infection. Therefore, we investigated the impact of neutrophil inflammatory signal on bactericidal function in HD patients.

**Methods:** Four HD patients and six healthy subjects were recruited for this study. None of HD patients had diabetes, cardiovascular disease and cancer. Neutrophils were isolated from peripheral blood by density gradient centrifugation. The purity was tested by flow cytometry after lactofemin staining. Microarray analysis was performed to assess global gene expression in leukocytes. Neutrophil bactericidal function was evaluated by the growth rate of Staphylococcus aureus (S.aureus) after co-culture of it with neutrophils obtained from HD patients or healthy subjects. Reactive oxygen species (ROS) production and myeloperoxidase (MPO) activity were analyzed by florescence intensity.

**Results:** Microarray analysis showed the impairment of p38 mitogen activated protein kinase (MAPK) signal in neutrophils from HD patients. The growth rate of S.aureus was higher in HD patients than that in healthy subjects (490.1±147.1%, 144.5±40.4%, respectively; p=0.01) suggesting that neutrophil anti-bacterial killing function was dysregulated in HD patients. The levels of ROS from neutrophils after co-culture with S.aureus were lower in HD patients than those in healthy subjects (14±6±8.3, 32±4.1±5.4, respectively; p=0.01). On the other hand, there was no difference of MPO activity between both groups. To confirm the importance of p38 MAPK, we examined the effect of the selective pharmacological p38 MAPK inhibitor SB202190 on neutrophil bactericidal function. The treatment with SB202190 suppressed anti-bacterial killing function as well as ROS production in neutrophils.

**Conclusions:** Impaired of p38MAPK signaling pathway might contribute to the suppression of neutrophil bactericidal function in HD patients through the dysregulation of ROS production.
Nrf2 and NF-xb mRNA Expression in Chronic Kidney Disease: A Focus on Non-Dialysis Patients

Denise Mafra,1 Viviane Oliveira Leal,2 Juliana Saldanha,1 Milena Barzca Stockler-Pinto,3 Ludmila Fmf Cardo,4 Felipe Rizzetto Santos,2 Alex Sandro Duarte Albuquerque,4 Maurilio Leite.4 *Graduate Program in Medical Sciences, Federal Univ Fluminense, Rio de Janeiro, Brazil; 2Pedro Ernesto Univ Hospital, State Univ of Rio de Janeiro (UERJ), Rio de Janeiro, Brazil; 3Graduate Program in Cardiovascular Sciences, Federal Univ Fluminense, Rio de Janeiro, Brazil; 4Div of Nephrology, Federal Univ of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil.

Background: Nuclear factor erythroid 2-related factor 2 (Nrf2), a regulator of genes encoding antioxidant and detoxifying enzymes appear to be downregulated in chronic kidney disease patients undergoing hemodialysis (HD). However, data regarding the expression of Nrf2 in non-dialysis patients are scanty. Thus, the aim of this study was to evaluate Nrf2 and nuclear factor kappa-B (NF-xb) mRNA expression in non-dialysis patients, comparing with data from HD patients.

Methods: 20 non-dialysis patients, 20 HD patients and 11 healthy subjects were enrolled. The peripheral blood mononuclear cells were isolated and processed for the evaluation of NF-xb and Nrf2 expression by quantitative real-time polymerase chain reaction.

Results: Nrf2 mRNA was significantly higher in non-dialysis when compared to HD patients but similar to healthy individuals. Inversely, NF-xb mRNA was lower in non-dialysis when compared to HD patients and also similar to healthy individuals i.e.

**Figure 1.** Nrf2 and NF-xb mRNA expression in healthy individuals, non-dialysis and HD patients.

Nrf2 mRNA was positively correlated with NF-xb mRNA in non-dialysis patients and healthy individuals. By contrast, Nrf2 mRNA was inversely correlated with NF-xb mRNA in HD patients.

Conclusions: Non-dialysis patients may conserve regular homeostatic balance between Nrf2 and NF-xb expressions, being comparable to healthy individuals. As renal disease progresses to more advanced stages, an impaired Nrf2/NF-xb balance can be observed, as in HD patients.

Funding: Government Support - Non-U.S.

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Chinese Herbal Medicine for IgA Nephropathy, ShenPing Decoction, Blocks Platelet-Derived Growth Factor Signaling Pathway Activated by IgA1-Containing Immune Complexes in Human Mesangial Cells

Xiaowan Zhang,1 Xi Chen,2 Zhiqiang Huang,2 Stacy D. Hall,2 Lin Wang,2 Yueyi Deng,2 Bruce A. Julian,2 Yiping Chen,1 Jane Mei. Nephrology: The First Affiliated Hospital of China Medical Univ, Shenyang, China.

Background: IgA nephropathy (IgAN) is characterized by mesangial immunodeposits containing galactose-deficient IgA1 (Gal-IgA1) usually associated with mesangial proliferation and matrix expansion. There is no disease-specific therapy of IgAN, although a herbal medicinal preparation, ShenPing decoction (SP), has been used in China for decades to effectively treat IgAN. Mesangial cell proliferation in IgAN is likely induced by Gal-IgA1-containing immune complexes (CIC) and this process may involve activation of platelet-derived growth factor (PDGF) signaling pathway. We have shown previously that SP blocks the activation of PDGF pathway induced by PDGF. In this study, we investigated the effect of CIC on PDGF signaling pathway in human mesangial cells (HMC) and assessed the effects of SP on this pathway.

Methods: CIC were isolated from sera of IgAN patients using size-exclusion chromatography. Primary HMCs were incubated with PDGF or CIC for 15 min or 24 h with or without SP. Cellular proliferation was measured by Syto60. PDGF signaling was evaluated by SDS-PAGE and Western blotting.

Results: 24-h incubation with CIC increased MC proliferation and SP inhibited this effect. Stimulation of HMC with CIC increased phosphorylation of PDGFR and ERK1/2 after 15 min and 24 h. PDGF degradation was not observed in CIC-treated group, which is different from PDGF. SP inhibited CIC- and PDGF-induced phosphorylation and degradation of PDGFR.

Conclusions: CIC induced cellular proliferation of HMC and activation of PDGF pathway by the different times group; Fluorofenidone control group; High glucose and LPS for different concentrations and different times group; Fluorofenidone intervene group.

Funding: NIDDK Support, Private Foundation Support

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Effects of Fluorofenidone on the Expression of Thioredoxin-Inter-Acting Protein and Thioredoxin of Human Peritoneal Mesothelial Cell in High Glucose and Lipopolysaccharide

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Background: Peritoneal dialysis is one of an important alternative therapies for end-stage kidney disease, But the occurrence of peritoneal dialysis correlation peritonitis has brought high cost and resistance for the development of peritoneal dialysis. Significance of oxidative stress in peritoneal dialysis related peritonitis has been paid more and more attention. In cells that did not receive stimulation, Txnip combined with thioredoxin, when the elevated ROS concentration inside the cell, the formation of the compounds are separated. After dissociation Tx play its functions to remove ROS, whereas Txinap participation NLRP3 activation. Objective: To observe the effects of Fluorofenidone on the Expression of Thioredoxin, Trx of HPMCs in High Glucose and Lipopolysaccharide.

Methods: The expression of CIC and Trx mRNA was measured by real-time PCR, The level of IL-6, TGF-b1 and IP-10 were measured by ELISA, Experimental groups: Control group; High glucose and LPS for different concentrations and different times group; Fluorofenidone intervene group.

Results: Compared with the normal control, high glucose and LPS can significantly increase the expression of Txnip, Trx, IL-6 and TGF-b1 in a concentration and time dependent manner, all have statistically significant (P<0.05). Compared with 2.5% glucose and 10mg/L LPS group, Fluorofenidone can reduce the expression of Txnip, IL-6 and TGF-b1, increase the expression of Trx, all have statistically significant (P<0.05).

Conclusions: High glucose and LPS up-regulate the expression of Txnip, Trx, in the protein and gene levels, and increase the expression of LIF-g and TGF-b1. Fluorofenidone could reduce the increase of Trx, IL-6 and TGF-b1, and increase the expression of Trx in HPMCs that have been pre-treated with high glucose and LPS. Fluorofenidone have the effect of anti-oxidant and anti-fibrosis.

Funding: None

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Effects of Resveratrol on NRF2 Expression in Raw 264.7 Macrophages Cells and Non-Dialyzed CKD Patients

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Background: Oxidative stress and inflammation are common in CKD. Bioactive compounds as resveratrol may modulate the NRF2 expression, a transcription factor that could up-regulate cellular antioxidant systems. The aim of this study was observe NRF2 expression in macrophages cells and in non-dialyzed CKD patients treated with resveratrol.

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

Underline represents presenting author.
Methods: Mouse RAW 264.7 macrophages cells were treated with 50µM of resveratrol in DMSO 1% (+/v). Nucleus and cytoplasm were separated. Western Blot (WB) was performed to quantify Nrf2. qRT-PCR was performed to evaluate Nrf2 expression. 7 non-dialyzed CKD patients (5 women; 64.0±6.5 years) were analyzed. Cellular bioenergetics were assessed with a Seahorse XF-96 extracellular flux analyzer. Intracellular ROS were produced and cell viability was reduced. Mitochondrial respiration and the cellular bioenergetic reserve capacity were decreased following glyoxylate oxidation. The expression of AGT or GR reduced the antioxidant response of glycolate metabolism to glyoxylate and oxalate. Limited mitochondrial dysfunction might be a therapeutic approach in treating PH patients.

Results: Cells treated with resveratrol showed a significant activation of Nrf2 with an increase in the ratio nucleus/cytoplasm compared to control cells i.e. p<0.02. The same was observed in qRT-PCR (p=0.02). In patients, we observed a trend to increase Nrf2 expression with resveratrol supplementation (p=0.06).

Conclusions: We concluded that both cells and patients treated with resveratrol increased Nrf2 expression. So, we suppose that supplementation with resveratrol can lead to an increase in oxidative stress and inflammatory status among CKD patients.

PUB105 Mitochondrial Implications of Glycolate Metabolism in Primary Hyperoxaluria Sonia Farque, Tanecia Mitchell, John Knight, Ross P. Holmes.

Urology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: The primary hyperoxalurias (PH) are rare but severe inherited diseases characterized by an increased endogenous production of oxalate and calcium oxalate kidney stones in patients. Deficiency in alanine glyoxylate aminotransferase (AGT, deficient in PH1) or glyoxylate reductase (GR, deficient in PH2) have repercussions on the metabolism of the oxalate precursors glyoxylate and glycolate. Excessive amounts of glycolate are characteristic of PH1, through glyoxylate to glycolate cycling in the presence of glycolate oxidase (GO) and GR. Perturbations in glycolate metabolism may affect mitochondrial function in PH patients. The objective of this study is to assess how over-expression of these enzymes regulates glycolate and glyoxylate generation and mitochondrial function.

Methods: An established transformed CHO cells model was used in which cells express GO ± AGT or GR. Cells were incubated with glycolate or glyoxylate and the extracellular concentrations of oxalate and glycolate, and the induction of oxidative stress were analyzed. Cellular bioenergetics were assessed with a Seahorse XF-96 extracellular flux analyzer.

Results: The metabolism of glycolate by GO generated glyoxylate, oxalate and H2O2. Intracellular ROS were produced and cell viability was reduced. Mitochondrial respiration and the cellular bioenergetic reserve capacity were decreased following glyoxylate oxidation. The expression of AGT or GR reduced the antioxidant effects of glycolate metabolism to glyoxylate and oxalate.

Conclusions: The disruption of normal glycolate metabolism by GO, AGT and GR in a cell model of PH1 causes the production of stress related metabolites and mitochondrial dysfunction. Limiting mitochondrial dysfunction might be a therapeutic approach in treating PH patients.

Funding: Private Foundation Support

PUB106 Effect of Fasudil on Response Oxidative Stress in High Glucose and Lipopolysaccharide Induced Human Peritoneal Mesothelial Cells Ye Hu, Jianfei Ma.

Nephrology, The First Affiliated Hospital of ChinaMedical Univ, Shenyang, Liaoning Province, China.

Background: Peritoneal fibrosis is a common cause of chronic peritoneal dialysis patients withdrawn from peritoneal dialysis. Research shows that there are oxidative stress exists in peritoneal dialysis patients. Rho/Rho kinase signaling pathway is involved in the regulation of multiple biological process, including inflammation, oxidative stress and fibrosis. The transcription factor Nrf2 related factor is a central regulator of cellular antioxidant responses. Rho kinase inhibitor fasudil is a Rock inhibitor which currently used in clinic and experiment, it can regulate cell proliferation, migration, adhesion and movement at the cellular level. It also can regulate a variety of factors in inflammation, thrombogenesis is, oxidation stress and fibrosis at the molecular level.

Methods: By using the method of Real Time PCR to detect the expression of RhoA, Rock1, Nrf2 and HO-1 mRNA, Western Blot to detect the expression of RhoA, Rock1, Nrf2 and HO-1 protein; chemistry fluorescence test to detect the expression of ROS protein; chemical colorometry to detect the expression of GSH-PX protein; ELISA to detect the expression of TGF-b1 protein in the human peritoneal mesothelial cell. Experimental groups: Control group; High glucose and LPS for different concentrations group; Fasudil intervene group.

Results: Compared with the normal control, high glucose and LPS can significantly increase the expression of RhoA, Rock-1, ROS and TGF-b1, reduce the expression of Nrf2, HO-1 and GSH-PX in a concentration dependent manner, all have statistically significant (P<0.05). Compared with 2.5% glucose and 10mg/L LPS group, fasudil can reduce the expression of RhoA, Rock-1, ROS and TGF-b1, increase the expression of Nrf2, HO-1 and GSH-PX, all have statistically significant (P<0.05).

Conclusions: High glucose and LPS up-regulate the expression of RhoA and Rock1 but reduce Nrf2 in the protein and gene levels, and increase the expression of ROS and TGF-b1 but reduce the expression of HO-1 and GSH-PX. Fasudil could reverse the increase of RhoA and Rock-1 and the reduction of Nrf2 in HPMCs that have been pre-treated with high glucose and LPS, play the role of anti-oxidant and anti-fibrosis.

PUB107 Glucose Induces Mitochondrial Reactive Oxygen Species Through Carbonyl Stress and Respiratory Chain in Rat Peritoneal Mesothelial Cells Satoshi Shimada,1 Takefumi Mori,2 Yusuke Ohsaki,2 Ikuo Oba,1 Shinichi Sato,1 Kenji Koizumi,1 Sadayoshi Ito.1 1Nephrology, Endocrinology and Vascular Medicine, Graduate School for Medicine, Tohoku Univ, Sendai, Miyagi, Japan; 2Div of Integrative Renal Replacement Therapy, Graduate School of Medicine, Tohoku Univ.

Background: Glucose and its degradation products (GPDs) play a major role in the peritoneal injury and affect peritoneal dialysis vintage. Peritoneal mesothelial cell dysfunction has been demonstrated to involve in peritoneal injury by glucose and GPDs. GPs induced carbonyl stress has been demonstrated to induce mitochondrial dysfunction in several cell types. The present study was designed to determine the role of GPs and respiratory chain in glucose induced mitochondrial ROS in peritoneal mesothelial cells. To this end, primary rat peritoneal mesothelial (RPMC) and immortalized (RDCM) renal cells were isolated from Wistar rats. Real-time mitochondrial superoxide was monitored using a specific fluorescent indicator Mito SOX red under fluorescence microscope equipped with temperature controlled chamber. RPMC was stimulated with 90 mmol/L of glucose and compared to those of control. In separate experiments, RPMC was pre-incubated with a mitochondrial specific superoxide dismutase mimetic mitoTEMPO, respiratory chain inhibitor rotenone or carbonyl stress inhibitor pyridoxamine to determine the mechanism of glucose induced mitochondrial ROS production.

Results: 90 mmol/L glucose significantly increased mitochondrial superoxide production within 200 seconds in primary cultured RPMC (0.21±0.07 AU, n=8, P<0.05 vs vehicle). These responses were abolished when RPMC was pre-incubated with mitoTEMPO (-0.04±0.15 AU, n=5, P=0.34 vs vehicle), rotenone (0.00±0.06 AU, n=6, P=0.42 vs vehicle) or pyridoxamine (-0.34±0.34 AU, n=5, P=0.26 vs vehicle), indicating that mitochondrial superoxide production through respiratory chain and GDP.

Conclusions: The results in the present study indicate that glucose and GDP present in the PD effluent is responsible for oxidative stress in the peritoneal mesothelial cells by stimulation of mitochondrial ROS production, which could play a role in peritoneal function and injury during PD.


Background: Renal Cell Carcinoma (RCC) is a leading cause of renal cancer worldwide. The cause of RCC remains unknown, with many chemicals implicated in its development. We have developed an in vitro model of RCC using the carcinogen, potassium bromate, to investigate potential prevention and possible treatment options of RCC. Chemoprevention is the use of different chemicals, natural or synthetic, to halt, block or reverse the process of carcinogenesis. It is one of the novel approaches that is being used to control cancer and it is a good alternative to the conventional therapies that are associated with a long list of side effects and limitations. These agents have antioxidant, anti-inflammatory, antiangiogenic effects and induce phase II enzymes, apoptosis, cell cycle arrest, and differentiation. They antagonize hormones and growth factor-induced tumor proliferation. The aim of this study was to examine the functional and mechanistic effects of chemopreventative agents on chemically induced RCC using human (RPTEC/TERT1) renal cells and cancerous (AChN) renal cell line.

Methods: Morphological changes, viability and cytotoxicity assays were used to assess the toxicity of both the chemopreventatives and the carcinogen when RPTEC/TERT1 cells were exposed to them individually and in combinations. Oxidative stress was also assessed.oxidative stress...
assessed by measuring the intracellular concentration of H2O2. Oxidative stress-induced DNA damage was estimated qualitatively by measuring 8-OHdG concentrations. Western blot analysis was used to detect the changes in particular oxidative stress-induced proteins.

Results: The carcinogenic effects induced by potassium bromate were reduced by the co-administration with all of the chemopreventive agents used. Oxidative stress markers, H2O2 and DNA adduct formation, were reduced.

Conclusions: The results suggest that these chemopreventive agents show significant potential against KBrO3-induced carcinogenicity. Further analysis is being carried out to understand the functional mechanisms of this chemoprevention on the cells, in particular on the genetic and epigenetic mechanisms involved.

Funding: Government Support - Non-U.S.

PUB109

The Podocyte as a Target for the Actions of Levamisole in Nephrotic Syndrome

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Background: Levamisole is an antihelminthic agent that has also been shown to be effective as a second line treatment for steroid-dependent or frequently-relapsing nephrotic syndrome (SD/FRNS) in children. Levamisole is able to decrease steroid dosages and reduce the relapse frequency and severity. We have recently reported the effectiveness of levamisole in a small cohort of adult patients and provided evidence which suggests that levamisole’s mode of action in SSNS is attributable to its direct effects on podocytes.

Methods: To further clarify its therapeutic effectiveness and identify the therapeutic targets of this drug, we have employed RNA-sequencing technology to profile transcriptomic changes of human podocytes in response to levamisole.

Results: We have identified a number of genes which are differentially expressed in podocytes in response to levamisole. These include genes linked to the cellular interferon response pathways and a number which overlap with those regulated by dexamethasone in podocytes. These have been validated in vitro and are now being studied in animal models of nephrotic syndrome.

Conclusions: Together, our molecular evidence strongly supports the promising use of levamisole in treating nephrotic syndrome.

PUB110

The PRIMAVERA Study: A Prospective, Randomized, Multicenter Trial Assessing the Effect of Continuous Erythropoiesis Receptor Activator (C.E.R.A.) on Renal Function in Non-Anemic Patients with Chronic Kidney Disease (CKD)

Daniel Fliess, 1 Frank Delmanno, 1 Michael Koch, 1 Jochen Seufert, 1 Oliver Witzke, 1 Affonso Weggenshaar, 1 Ingeborg A. Hauser. 1 Saarland Univ Medical Center, Homburg/Saar, Germany; 2 Center of Nephrology, Mettmann, Germany; 3 Univ Hospital of Freiburg, Freiburg, Germany; 4 Univ Hospital Essen, Essen, Germany; 5 Roche Pharma AG, Grenzach-Wyhlen, Germany; 6 Frankfurt Univ Medical Center, Frankfurt, Germany.

Background: Erythropoiesis stimulating agents (ESAs) are the mainstream of renal anemia management. ESAs may provide a beneficial non-hematopoietic effect on deterioration of kidney function in CKD, but such an effect has not been examined in a prospective controlled trial. PRIMAVERA is the first randomized study to assess whether low-dose ESA therapy can slow CKD progression in patients with near-normal hemoglobin levels (11–14g/dL) (NCT01194154).

Methods: PRIMAVERA was a single-blind, 2-year, multicenter trial which enrolled patients with type 2 diabetes or recipients of a kidney transplant, all with CKD stage 3, urinary albumin to creatinine ratio <3000mg/g or total urine protein <3000mg/24h. Patients were randomized in a 1:1 ratio to placebo or once-monthly low-dose C.E.R.A. (30-75 mg). We designed a 4 arm parallel group randomized double blind trial comparing lanthanum carbonate (1000mg tid), nicotinamide (750mg bid), neither, or both. Supported by the NIDDK CKD Pilot Clinical Trials U01, 200 participants with eGFR 20-45 ml/min/1.73 m² recruited from 7 centers across the US will be randomized: 1:1:1:1 and treated for 12 months. Main exclusions include phosphate > 2.8mg/dL, liver disease, and thrombocytopenia. The dual primary efficacy endpoints are change in phosphate and FGF23. Secondary endpoints are change in L.V mass and renal fibrosis by MRI. Enrollment began in March 2015.

Results: To date, 45 persons were screened, 33 were eligible, 26 entered run-in, and 18 were randomized. Baseline characteristics of randomized participants are shown in the table. Updated data will be available at presentation.

Randomized Patients (n) 18
Age/SD 65±14
Male, n(%) 12 (67%)
Black, n(%) 5 (28%)
Diabetes, n(%) 7 (44%)
eGFR/SD 30±9
Urinary ACR mg/g, median (IQR) 505 (48, 905)
Serum Phosphates/SD 3.9±0.6
Serum Calcium/SD 9.5±0.4
Inact PTH, median (IQR) 104 (71, 135)

Conclusions: Simultaneous blockade of NaPi2b and intestinal phosphate binding using nicotinamide and binders provides a new strategy for phosphate and FGF23 lowering in CKD, but efficacy, safety, and tolerability are uncertain. The COMBINE trial will inform us about combined therapy compared to either therapy alone, and to dual placebo in CKD 3b-4.

Funding: NIDDK Support

PUB111

A New Approach to Phosphate and FGF23 Lowering: Design of the COMBINE Trial

Joachim H. L. 1 Tamara Isakova, 2 Stuart M. Sprague, 2 Kalani L. Raphael, 1 Jennifer J. Gassman, 1 Linda F. Fried, 1 Dominic S. Raj, 6 Alfred K. Cheung, 2 Andrew N. Hoofnagle, 7 John W. Kusek, 7 Michael F. Flessner, 7 Geoffrey A. Block, 6 Myles S. Wolf, 7 The pilot clinical trials in Ckd study group. 1 UCSD, 2 Northwestern, 3 U of Utah, 4 U of Pittsburgh, 5 Cleveland Clinic, 6 George Washington U; 7 NIDDK; 8 Denver Nephrology; 9 Northshore; 10 U Washington.

Background: Elevated serum phosphate and FGF23 are associated with CVD, CKD progression, and mortality in CKD. Phosphate binders inconsistently reduce phosphate and FGF23 levels. Nicotinamide (vitamin B3) decreases active phosphate transport by down regulating Nalp2b in the gut. Whether nicotinamide alone or in combination with binders can safely and tolerably lower phosphate and FGF23 levels in CKD is unknown.

Methods: We designed a 4 arm parallel group randomized double blind trial comparing lanthanum carbonate (1000mg tid), nicotinamide (750mg bid), neither, or both. Supported by the NIDDK CKD Pilot Clinical Trials U01, 200 participants with eGFR 20-45 ml/min/1.73 m² recruited from 7 centers across the US will be randomized: 1:1:1:1 and treated for 12 months. Main exclusions include phosphate > 2.8mg/dL, liver disease, and thrombocytopenia. The dual primary efficacy endpoints are change in phosphate and FGF23. Secondary endpoints are change in L.V mass and renal fibrosis by MRI. Enrollment began in March 2015.

Results: To date, 45 persons were screened, 33 were eligible, 26 entered run-in, and 18 were randomized. Baseline characteristics of randomized participants are shown in the table. Updated data will be available at presentation.

Costly Option

Achromatoplasia

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Background: Hepatitis C virus (HCV) infection is a serious issue in hemodialyzed patients (HD pts) and treatment is complex and rapidly evolving with the advent of newer direct-acting antivirals.

Methods: We evaluated SOF given with RBV in an 86 years old male HD pt, 90 kg, on HD since 7 years for a diabetes-related ESRD and infected by a nosocomial transmission of HCV genotype 2 overseas. SOF was given at a dose of 400 mg three times a week after dialysis session and RBV given 200 mg daily during 12 weeks. Plasma HCV RNA values were measured with the COBAS Taqman HCV Test, Roche diagnostics. Safety, efficacy and pharmacokinetics issues were studied as well as standard laboratory tests. Sustained virologic response(SVR) is evaluated six months after treatment.

Results: HCV infection was associated with cirrhosis with Fibroscan staging score of 10.3 KPa. HCV viral load at diagnosis was 7.52 log. The viral decline was < 1.18 log only 3 months after HD session and RBV given 200 mg daily during 12 weeks. Plasma HCV RNA values were measured with the COBAS Taqman HCV Test, Roche diagnostics. Safety, efficacy and pharmacokinetics issues were studied as well as standard laboratory tests. Sustained virologic response(SVR) is evaluated six months after treatment.

Conclusions: The PRIMAVERA study provides the first prospective examination of a potential effect for low-dose ESA therapy in ameliorating kidney function decline in CKD patients. Analysis of the study data is planned shortly.

Funding: Pharmaceutical Company Support - Roche Pharma AG
The rationale and design of TREV1 TR02: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Treatment for Uremic Pruritus in Hemodialysis Patients

Vandana S. Mathur, Michael J. Germain, Roberta Duncan, Thomas Sciascia, Mathur Consulting, Woodside, CA; Western New England Renal & Transplant Associates, PC, Hamden, MA; Trevi Therapeutics, New Haven, CT.

Background: Uremic pruritus (UP) is common in hemodialysis patients, but there are no FDA-approved treatments or "regulatory roadmap" for the development of new drugs. Nevertheless, the significant quality of life (QOL) burden of chronic itching underscores need for treatments. The striking bilateral, non-dermatomal distribution of itching and perception of non-pruritogenic skin stimuli as itch suggest that UP is centrally mediated, like neuropathic pain. Reduction in endogenous κ/µ opioid ligand ratio is hypothesized to be a mechanism. Our goal was to evaluate nalbuphine ER tablet (NAL), a κ-agonist and μ-antagonist as a treatment for UP.

Methods: The study was powered for an α = 0.05, β = 0.9 for a group difference of 1.5 (SD = 3.5) in worst itching numerical rating scale (NRS, 0-10); N = 120/arm (NAL 120 mg BID, NAL 60 mg BID, and placebo BID). Patients with NRS ≥ 4.5 (moderate to severe pruritus) were enrolled at ~45 US and 6 EU sites.

Results:

Conclusions: The trial design overcame the challenges. Unblinded results will be presented.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

The Rationale and Design of Trevi TR02 Extension: A Multi-Center Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl Extended Release Tablets in Uremic Pruritus Patients on Hemodialysis

Thomas Sciascia, Howard Hatt, Annale Havi, Roberta Duncan, Vandana S. Mathur, Trevi Therapeutics, Inc., New Haven, CT; Edenridge Associates LLC, Wilmington, DE; Havi Consulting, Ridgefield, CT; Mathur Consulting, Woodside, CA.

Background: Nalbuphine HCl is a μ agonist/kappa agonist being investigated for the treatment of pruritus in hemodialysis patients (UP). The safety and long-term benefits of Nalbuphine ER in the treatment of uremic pruritus is being investigated in this ongoing open-label extension study.

Methods: TR02ext is a 26-week multicenter open-label extension study of a double-blind placebo controlled study in which UP patients with a baseline NRS ≥4.5 were treated with Nalbuphine ER or placebo for 8 weeks followed by a 2-week washout period. At the end of study, patients that opt to roll over into the extension study, and have an NRS ≥ 2 enrolled in a 26-week Treatment Period (TP), while patients with an NRS ≤2 entered a 13-week Observation Period (OP). If a patient’s itch worsened (NRS > 2) within the OP, they entered the TP for the remainder of the study.

All patients on treatment were titrated between 30 mg QD-120 mg BID over a 3-4 week period based on reported tolerability and efficacy and then maintained their dose until end of study. Patients whose itch intensity failed to improve during the TP were discontinued from treatment.

Conclusions: Approximately 70% of the eligible patients who completed the blinded controlled study, enrolled in the extension study. Final study data will be presented once the trial is complete.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

Assessing Treatment Safety and Efficacy of a New Patient-Centered Hemodialysis System

Luis Alvarez, Geoffrey A. Block, May L. Yau, Glenn Matthew Chtontow, Palo Alto Medical Foundation, Palol, CA; Denver Nephropathy, Denver, CO; Outset Medical, San Jose, CA; Stanford School of Medicine, Stanford, CA.

Background: Many studies designed and conducted for the evaluation of new technologies utilized in hemodialysis have been small, observational studies. These studies may have underestimated the rate of clinical symptoms yielding biased safety results.

Methods: We designed a prospective, multicenter, open-label, non-randomized, cross-over study where patients serve as their own control. The study was designed with novel approaches to ensuring accuracy of clinical symptom reporting both in the home and clinic setting. Up to 50 patients will be enrolled in the study for 19 weeks and will use the TeleH® Hemodialysis System for treatments 4 times/week.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

Interim Analysis of Comprehensive CKD Education Modality Choice Outcomes

Andrea K. Eason, Damitra Rotaru, Fahd Syed, Manisha Singh, Ashutosh M. Shukla, Sudhir V. Shah, Univ of Arkansas for Medical Sciences; University of Florida.

Background: Preliminary data from a study comparing telemedicine vs conventional CKD education is presented here. The primary aim is to test if patients are able to make a modality choice by the end of the third visit.

Methods: Patients are enrolled in three groups as shown in the pilot study design.

Conclusions: During each study phase, patients will record inter- and intra-dialytic symptoms for each treatment via questionnaire. Research staff will review all responses weekly to determine if an adverse event (AE) has occurred. In addition, research staff will conduct weekly visits to the dialysis clinic and to home to educate patients on AEs and to collect questionnaires. Patients will also be assessed to determine if a standardized weekly Kt/V of 2.1 has been achieved.

Results: Study enrollment is expected to begin in 2015 with results expected in 2016.

Conclusions: By utilizing patients to collect AE data both in-center and at home, we should more accurately capture AE rates due to the uniformity of the reporting mechanism. In terms of the clinical efficacy endpoint of the study, modelled clearance data suggests the majority of patients will achieve the weekly standard Kt/V target. Actual clearance data will be forthcoming at the completion of the trial.

Funding: Pharmaceutical Company Support - Trevi Therapeutics
Determination of Oxidative Stress and Inflammation Index in Patients with Different Dialysis Modalities and Analysis of Related Factors

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Background: This study through the determination of serum AOPPs, GSH-PX, PTX-3, IL-6 level in ESRD patients with different treatment groups, to explore the changes and influence factors of oxidative stress and inflammation in dialysis patients.

Methods: 70 cases of ESRD patients divided into three groups: 26 cases of PD patients, 26 cases of hemodialysis patients, 18 cases of CKD5 patients. Select 14 normal persons as control group. Age, gender and other data of the four groups were matched. Get Serum of each group of subjects, using ELISA for determination of serum AOPPs, GSH-PX, PTX-3, IL-6 content in each group.

Results: 1. The concentration of AOPPs: PD Group (25.04 ± 12.18) ng/mL, MHD group (18.46 ± 10.47) ng/mL, CKD5 group (17.96 ± 8.13) ng/mL, healthy group (15.73 ± 6.68) ng/mL. PD group was statistically significant different with other groups (p < 0.05). 2. The concentration of GSH-PX: PD group (188.54 ± 112.04) U/mL, MHD group (157.12 ± 82.47) U/mL, CKD5 group (133.59 ± 65.59) U/mL, healthy group (176.03 ± 93.25) U/mL. There was no significant difference between the groups. 3. The concentration of PTX-3: PD Group (9.55 ± 5.13) ng/mL, MHD group (7.54 ± 4.79) ng/mL, CKD5 group (6.69 ± 3.12) ng/mL. The PD group was statistically significant different with other groups (p < 0.05). 4. The concentration of IL-6: PD group (123.69 ± 84.46) ng/L, MHD group (81.17 ± 72.48) ng/L, CKD5 group (64.92 ± 36.92) ng/L, healthy control group (59.08 ± 19.27) ng/L. The PD group was statistically significant different with other groups (p < 0.05). Through Correlation analysis in PD group (p < 0.05): AOPPs was positively correlated with PTX-3 (R = 0.956, P = 0.000), AOPPs was positively correlated with IL-6 (R = 0.934, P = 0.000), PTX-3 and IL-6 levels were positively correlated (R = 0.939, P = 0.000).

Conclusions: Determination of serum AOPPs, GSH-PX, PTX-3, IL-6 content in Experience group is significantly increased compared with the control group. The PD patients compared with patients in other treatment groups have more severe oxidative stress and microinflammation state. Oxidative stress is closely related to the state of inflammation in PD patients.

Impact of Type of Referral and Dialysis Start on Clinical Outcomes and Final Renal Replacement Therapy in a Multicenter Integrated Care Setting

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Background: Early referral, choice of RRT modality and planned start increase patient survival, however international reports show disparities between desirable patterns and practice. Objectives: To analyze the effects of Integrated Care and education on dialysis start patterns vs. planned and RRT modality choice.

Methods: Retrospective analysis of 547 incident patients starting dialysis in 23 HD/PD clinics from PL, HU and RO during 2012. Scheduled initiation of dialysis with a permanent vascular or peritoneal access was considered as planned start.

Results: Population: 30% DM, mean age 64 years, 84% with previous medical care of renal disease, 49% late referral, 58% unplanned start, 92% on HD as modality. 37% of those with unplanned start had previous Nephrology follow-up. Patients (n=332) with GFR <30 ml/min were followed up mainly by “general nephrologists” (68%) and 29% in structured practice. Both RRT modality information (80% of all information expected) and general education (56%) and patient-specific education (87%) were more frequent (p < 0.001) in planned start. Half of patients were involved in therapy choice whereas informed and dialysis start consents were signed by 57% and 77%. The median time from information to dialysis start was 2 months. Unplanned start (p<0.05) correlated with nephropathy of uncertain origin, worse clinical status, shorter time from information to RRT start and less PD. Patient non-compliance (36%) and unexpected GFR loss (19%) contributed to unplanned start. “Optimal care” defined as combination of Nephrology follow-up (> 3 months), modality information and planned start occurred in 22% of the patients.

Conclusions: Despite the high rate of late referral, information and education were widely provided. Unplanned start was frequent and may underlie the low frequency of PD choice. Measures such as implementation of structured predialysis units may facilitate better and timely referral and improve well-being and planning of RRT start as well as increased PD use.

ATHENA: A Natural History Study to Observe Disease Progression, Standard of Care, and Investigate Biomarkers in Alport Syndrome Patients

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Background: Alport syndrome (AS) is a rare genetic disorder caused by mutations in genes coding for type IV collagen (COL4A3), COL4A4, and COL4A5 proteins leading to hematuria, renal failure, hearing loss and eye involvement in affected patients. Patients with COL4A5 mutations develop end stage renal disease (ESRD). While there are currently no approved therapies for AS, ACE-inhibitors have been shown to delay the onset of ESRD. A better understanding of the decline of kidney function in AS is necessary to design clinical trials to enable the development of new therapeutics.

Methods: Regulus’ Natural History of Disease Study, ATHENA, is an international multi-center observational study designed to characterize the progression of renal dysfunction in up to 120 subjects that have been clinically or genetically diagnosed with AS with a measured GFR (mGFR) between 30-75cc/min/1.73m². Genetic mutation analysis is performed at enrollment. mGFR (iohexol), 24 hour urine protein excretion and serum creatinine levels are measured every 3-6 months. Serum and urine biomarkers of renal stress (microRNAs, ADMA, TGFβ, CTGF and NGAL) will also be collected.

Results: 48 subjects with clinically or genetically diagnosed Alport syndrome have been enrolled to date. The population has an age range of 20 to 67 years of age and 29% are male. Average baseline mGFR was 54.8 cc/min/1.73m². Ethnicity is reported at 91% Caucasian, 2% Hispanic or Latino, 2% African American and 5% Asian.

Conclusions: Data gathered from the ATHENA study will investigate links between genetic mutations, biomarkers of renal stress and disease progression in AS patients. The correlative data collected from the ATHENA study will provide clinically important basis for the design of the Phase 2 clinical proof of concept study to determine efficacy of RG-012 (an anti-miR targeting microRNA-21) on the decline in renal function and time to end-stage renal disease in Alport syndrome patients.

Health-Related Quality of Life in Dialysis Patients: Effect of Type D Personality

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Background: Measurement of HRQoL is a useful tool to describe the burden of illness and impact of treatment. These informations could be crucial to develop a personal care. Type D (distressed) personality is defined as a tendency to experience both negative affectivity (NA) and social inhibition (SI). The prevalence of this personality and his effect on HRQoL in dialysis patients are assessed.

Methods: Participants were from outpatient clinic. DS 14 was used. A score of 110 on both NA and SI subscales indicates that the person has a type D personality. HRQoL was measured using the Dutch version of the Kidney Disease Quality of Life. Six components of the KDQOL were the primary end points (general health perceptions, burden of kidney disease, effect on daily life, cognitive function, pain, emotional welfare).

Results: 147 patients with mean age of 71.2 (±1.7). Mean time on dialysis 37 months. The prevalence of type D personality was 30% HRQoL in patients with type D personality was lower compared with non type D. It was statistically significant in all components except for emotional welfare.
Early Stages of Chronic Kidney Disease
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PUB121
Sleep Disorder and mRNA Expression Profile of Sleep-Related Gene in Peripheral Blood Cells in Patients with CKD

Conclusions: Type D personality may be an important determinant of individual differences in HRQoL and should be an important consideration in a personal care of dialysis patients.

<table>
<thead>
<tr>
<th>NA</th>
<th>r</th>
<th>p-value</th>
<th>SI</th>
<th>r</th>
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<tr>
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<tr>
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<td>&lt;0.001</td>
<td>-0.27</td>
<td>0.001</td>
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<tr>
<td>Effect on daily life</td>
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<tr>
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<tr>
<td>Pain</td>
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<td>&lt;0.001</td>
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<tr>
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<td>0.07</td>
<td>-0.03</td>
<td>0.7</td>
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</table>

Conclusions: These data raise the possibility that sleep related gene expression on PBC in CKD/HD patients may be associated with sleep disorder.

PUB122
Potential Link Between Iron, Inflammation and FGF23 in Patients with Early Stages of Chronic Kidney Disease

Results: There were no statistically significant associations between FGF23 and TSAT, ferritin and hsCRP. We revealed significantly higher concentrations of FGF23 in patients with type 2 diabetes (mean logFGF23: 4.0 ± 0.5 vs 3.8 ± 0.5, P<0.03) and with heart failure (mean logFGF23: 4.0 ± 0.6 vs 3.8 ± 0.5, P<0.04) in comparison to those without these diagnoses.

Conclusions: Kidney function, inflammation and iron status were the parameters affecting FGF23 in the early stages of CKD. Our data are paving the way for further studies on the role of FGF23 in cardiorenal anaemia-iron deficiency syndrome, in particular in the early stages of CKD.

PUB123
Echocardiography and Cardiovascular Risk: What’s the Relationship in the Renal Transplant Recipient?

Results: Among 107 patients (57,9% males, 50,4±13,9 years old), 7-years risk for MACE was >10% in 30,9% of patients and 7-years risk for death >10% in 56,1%. Left ventricular hypertrophy (LVH) was found in 55,1%, diastolic dysfunction in 39,3%, dilated LA in 41,2%, moderate to severe mitral regurgitation in 31,7%, and mean Ejection Fraction was 68,36±6,87%. Univariate analysis showed with statistical significance an increased risk of MACE in patients with LVH, diastolic dysfunction, dilated LA, moderate to severe mitral regurgitation. Multivariate analysis showed statistically significant on increased risk of death in patients with LVH, diastolic dysfunction, dilated LA, moderate to severe mitral regurgitation. Multivariate analysis identified an independent association between the risk of MACE >10% and valvular calcifications [OR 3.499 (1.115-10.982, P=0.032)] and high PASP [OR 7.954 (2.421-26.238, P<0.001)]. Risk for death >10% in multivariate analysis had an independent association with diastolic dysfunction [OR 3.989 (1.261-12.115, P=0.016)] and with high PASP [OR 4.319 (1.201-15.535, P=0.025)].

Conclusions: Echocardiographic abnormalities identify RTR at increased risk of MACE and death. Valvular calcifications and high PASP are significant predictors of MACE whereas diastolic dysfunction and high PASP are significant predictors of death.
PUB124

Hemodynamic Determinants of Glomerular Filtration Rate in Pulmonary Hypertension: A Prospective Cohort Analysis. Laurent Birker,¹ Cecile Payet,³ Florence Senn,¹ Turquier Segolen,² Antoine Duclos,¹,4 Vincent Cottin,²,4 Laurent Juillard,¹,4 ¹Nephrology, Hospices Civils de Lyon, Lyon, France; ²Pneumology, Hospices Civils de Lyon, Lyon, France; ³Medical Research and Statistics Dept, Hospices Civils de Lyon, Lyon, France; ⁴Univ of Lyon, Lyon, France.

Background: Up to date, renal dysfunction incidence and determinants remain unevaluated in pulmonary hypertension (PHT). We aim to assess hemodynamic and demographic factors associated with a decrease in glomerular filtration rate (GFR) in the context of PHT.

Methods: The regional center competence for PHT of Lyon (France) prospectively compiles demographic, hemodynamic and biological variables among newly diagnosed patients. We retrospectively analyzed data for patients with pulmonary arterial hypertension (PAH, group 1 of PHT classification) after exclusion of the following causes of PHT: thromboembolic, lung diseases and/or hypoxia and left heart disease. Hemodynamic variables from the right heart catheterization and estimated GFR (eGFR, CKD-EPI formula) were assessed at PAH diagnosis time.

Results: 209 patients (mean age 59.1±17.1, 63.2% women) were included from October 1998 to July 2012. 40.2% presented with systemic arterial hypertension (HT) and 12.9% with diabetes. Mean eGFR was 83.9±27.1 ml/min/1.73m² (eGFR inferior to 60 ml/min/1.73m² in 18.5% of cases). Mean values of mPAP, right atrial pressure (RAP) and cardiac index (CI) were 45±12.6 mmHg, 7.8±5.3 mmHg and 2.6±0.9 L/min/1.73m².

In multivariate analysis, age, male gender, HT, anorectic-related PAH and a CI inferior to 2.5 L/min/1.73m² were associated with a significant decrease in eGFR of 1.0 ml/min/1.73m²/year, (95% confidence interval, 0.8 to 1.2), 11.8 ml/min/1.73m² (5.8 to 17.8), 6.6 ml/min/1.73m² (0.1 to 13.2), 13.4 ml/min/1.73m² (2.3 to 24.5) and 10.1 ml/min/1.73m² (4.4 to 15.9). RAP were not statistically related to eGFR levels.

Conclusions: Renal dysfunction is frequent from diagnosis among PAH patients. A low CI is associated with a significant decrease in eGFR, whereas RAP seem unrelated. Equally, male gender, HT and anorectic-related PAH are correlated with a significant decrease in eGFR. These results should incite renal prevention in PAH patients presenting these risk factors.

PUB125

Kidney Function and Cause-Specific Mortality in Drug-Treated Older Cardiac Patients: A 10-Year Follow-Up Study. Ellen K. Hoogeveen,¹ Johanna M. Geleijnse,² Daan Kromhout,² Theo Stijnen,³ Erik Giltay,² ¹Nephrology, LUMC, Leiden, Netherlands; ²Human Nutrition, WU, Wageningen, Netherlands; ³Medical Statistics and Bioinformatics, LUMC, Leiden, Netherlands; ⁴Psychiatry, LUMC, Leiden, Netherlands.

Background: Chronic kidney disease (CKD) is highly prevalent among older (>60y) cardiac patients. The relation between CKD and cause-specific mortality among older cardiac patients who are treated with state-of-the-art pharmacotherapy is unclear.

Methods: From 2002-2006, 60-80 years old Dutch post-myocardial infarction patients were enrolled in the Alpha Omega Trial and followed until death or January 2012. We estimated Glomerular Filtration Rate (eGFR) with serum cystatin C (cysC) and creatinine using the CKD-EPI equations. Kidney function was available in 4,561 (94.3%) participants and analyzed in relation to major causes of death using Cox models and four-knot restricted cubic splines.

Results: At baseline mean age was 69y, 79% were men, 21% had diabetes, 90% used antihypertensive drugs, 85% used statins. Patients were divided into four categories of eGFR:<90 (33%; reference), 60-89 (47%), 30-59 (18%), and <30 (2%) ml/min/1.73m². Median follow-up was 6.4y. During follow-up, 973 (19%) patients died, of which 370 (42%) from cardiovascular causes, 309 (35%) from cancer, and 194 (22%) from other causes.

The hazard ratios (95%-CI) for any death according to eGFR (Q5: ≥90 (33%; reference), 60-89 (47%), 30-59 (18%), and <30 (2%) ml/min/1.73m²) were: 1 (reference), 1.4 (1.1-1.7), 2.9 (2.3-3.6) and 4.4 (3.0-6.4). For cardiovascular mortality the corresponding figures were 1.6, 3.6 and 6.0, for cancer 1.2, 2.1 and 1.6, and for other causes 1.4, 3.1 and 6.7. Similar, but weaker, results were obtained with creatinine-based eGFR.

Conclusions: We found a strong inverse graded relation between kidney function and mortality in drug-treated older cardiac patients, in particular due to cardiovascular and non-cardiovascular-non-cancer causes.

Funding: Other NIH Support - Dutch Kidney Foundation (P41) US National Institute of Health (NIH) Netherlands Heart Foundation

PUB126

The Association Between Serum Uric Acid and Incidence of Non-Fatal Stroke in a Community-Based Population: A Longitudinal Survey of a Nationwide Cohort in Japan. Keita Kamei,¹ Kazunobu Ichikawa,¹ Tsunuo Konto,¹ Shouichi Fujimoto,² Kunitoshi Ibeki,² Toshiki Moriyama,² Kunihito Yamagata,³ Kazuhiko Tsuruya,² Kenjiro Kimura,² Ichiei Narita,² Masahide Kondo,² Koichi Asahi,² Tuyoshi Watanabe. ¹Dept of Cardiology, Pulmonology, and Nephrology, Yamagata Univ School of Medicine, Yamagata, Japan; ²Steering Committee of Research on Design of the Comprehensive Health Care System for Chronic Kidney Disease (CKD) Based on the Individual Risk Assessment by Specific Health Checkup, Japan.

Background: Hyperuricemia is a risk for adverse renal outcomes in chronic kidney disease. This study investigated the effect of uric acid on incidence of non-fatal stroke in a community-based population.


Results: During the follow-up period 2,081 non-fatal stroke occurred (1.3%). The incidence of non-fatal stroke showed a significant J-shaped association with the increase in serum uric acid levels (P for trend <0.001, lowest [1.2%] in the 3rd quintile of uric acid [Q3: males 5.7–6.2 mg/dL, females 4.4–4.8 mg/dL] and highest [1.6%] in the 5th quintile [Q5: males ≥7.1 mg/dL, females ≥5.5 mg/dL]). After adjusting for possible confounders, the odds ratio for incident stroke was significantly higher in Q5, compared with Q3 (OR 1.21, 95%CI 1.05–1.39, P = 0.007). The odds ratio of hyperuricemia (serum uric acid ≥7 mg/dL) for incident stroke was significantly increased in total subjects (OR 1.22, 95%CI 1.05–1.39, P = 0.003).

Conclusions: This study showed that serum uric acid level is significantly associated with incident non-fatal stroke and that hyperuricemia might be an independent risk for non-fatal stroke in the general population.

Funding: Government Support - Non-U.S.

PUB127

The Association Between Serum Calcium and Mortality in a Community-Based Population: The Takahata Study. Sayumi Watanabe, Keita Kamei, Kazunobu Ichikawa, Tsunuo Konto, Isao Kubota. Dept of Cardiology, Pulmonology, and Nephrology, Yamagata Univ School of Medicine, Yamagata, Japan.

Background: The low intake of calcium is a risk for cardiovascular events. This study investigated the association between serum calcium and mortality in a community-based population.

Methods: This study included 1,314 participants (aged 40–87, males 45%) at local health checkup in Takahata, Japan. We divided them into 3 groups according to the tertiles of serum calcium at baseline and compared the mortality during 8-year follow-up period. Serum calcium was corrected for serum albumin.

Results: At baseline serum calcium level was 9.8 ± 0.4 mg/dL (mean ± SD). In the multivariate linear regression analysis serum calcium was positively associated with serum sodium, potassium, phosphorus, albumin, uric acid and total cholesterol, and was negatively associated with serum chloride and HDL-cholesterol, and urinary beta2-microglobulin. During the follow-up period 62 deaths, including 14 cardiovascular deaths occurred. In Kaplan-Meier analysis all-cause mortality was significantly increased along with the decrease in serum calcium (Log-rank P = 0.03). In Cox proportional hazard analysis adjusted for confounders including age, gender, smoking and drinking habits, comorbidities and other serum electrolytes, the association of serum calcium was of borderline significance with all-cause mortality (HR 2.09, 95%CI 1.94–4.75). P = 0.07, low tertile [5.6 mg/dL vs. high tertile [≥ 10.0 mg/dL]] and was significant with cardiovascular mortality (HR 6.33, 95%CI [1.13–43.7]). P = 0.04, low tertile vs. high tertile). In addition, there was a significant interaction between serum calcium and sodium on all-cause mortality (P = 0.03) and the association of serum calcium with the mortality was significant in the subjects with low serum sodium (< 150 mEq/L), but not high sodium.

Conclusions: This study showed that serum calcium was significantly associated with various environmental factors and low serum calcium was an independent predictor for the mortality in the general Japanese population.

Funding: Government Support - Non-U.S.
Coronary Artery Calcification in Predialysis Diabetic and Nondiabetic CKD Patients

Sonozi Mizuri, Yoshiko Nishizawa, Kazuomi Yamashita, Michael J. Choi, Jung-hwa Kim, Ono Kyoko, Mariko Asai, Masahiro Iishine, Shigehiro Doi, Takao Masaki, Kenichiro Shiogemoto, Satoru Harada,

Methods: We examined Agatston coronary artery calcium score (CACS), BMD of T8 vertebra using MDCT, age, sex, presence of diabetes, hypertension, smoking history, statin administration, BMI, eGFR, uric acid, blood glucose, serum iron, calcium, phosphate, and triglyceride in 128 predialysis CKD patients, 82 nondiabetics, and 46 diabetics. Factors related to CACS were assessed by multivariate regression and logistic regression analyses using all of the above independent variables.

Results: Coronary artery calcification was present in 106 (82.8%) patients. Significant associations between CACS: 400H and age, diabetes, and statin administration were observed, and odds ratios were 1.1, 3.4, and 3.7, respectively, in all subjects (P < 0.05). Log CACS showed a significant association with age, diabetes, statin administration, serum phosphate, and triglyceride in all subjects (P < 0.05). Mean age and eGFR were 70.14 vs. 70.9 years (ns) and 37±20 vs. 30±19 ml/min/1.73m2 (P < 0.05), in nondiabetics and diabetics, respectively. Serum phosphate levels were not significantly different in the both groups. CACS (H) was 239±411 in nondiabetics and 942±1258 in diabetics (P < 0.001). Significant associations were observed between Log CACS and age (P = 0.0001, P = 0.042), statin administration (P = 0.01, P = 0.031), and serum phosphate (P = 0.05, P = 0.020) in nondiabetics, and between Log CACS and blood urea (P = 0.01, P = 0.55), serum iron (P = 0.01, P = 0.41), age (P = 0.01, P = 0.41), BMI (P = 0.05, P = 0.029) and smoking history (P = 0.05, P = 0.029) in diabetics. BMD showed no association with CACS.

Conclusions: Hyperphosphatemia is a risk factor for coronary artery calcification in nondiabetic but not diabetic CKD patients, and an association between CACS and BMD of T8 vertebra was not observed.

Funding: Private Foundation Support

Prevalence of Hematuria and Associations with All-Cause and Cardiovascular Mortality in China

Jinwei Wang, Fang Wang, Luxia Zhang, Ming Hui Zhao. Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China.

Background: Hematuria is one of the indicators of kidney damage. We aimed to estimate the prevalence of hematuria in China and evaluate its association with mortality and cardiovascular adverse outcome.

Methods: A nationally representative sample of 47,204 Chinese adults was obtained during the survey conducted between January 2009, and December 2012. Each participant’s survival status was identified through Dec 31, 2013. Causes of death in ICD code 100-199 were classified as cardiovascular disease. Hematuria was defined as ≥3 red cells per high-power field in microscopic examination. Subjects with pyuria and women undergoing menstruation were excluded from the analysis. The associations between hematuria and all-cause and cardiovascular mortality were studied by using the Cox regression model.

Results: The mean age of the participants at baseline was 49.6±15.2 years, and 42.7% of the participants were male. Altogether, 2126 (4.5%) of the population was detected with hematuria. The all-cause and cardiovascular mortality for participants with hematuria were 3.8 and 2.6 per 1000 person-years, while those for participants without hematuria were 3.4 and 1.3 per 1000 person-years. Hematuria was found to be significantly associated with increased risk of both cardiovascular mortality with the multivariable adjusted hazard ratio of 1.7 (95% confidence interval: 1.1-2.7), compared with those without hematuria. However, no significant associations were found between hematuria and all-cause mortality.

Funding: National Science Foundation, National Science Foundation of China.
Conclusions: Mortality, especially due to cardiovascular diseases, was greater among the Chinese patients with hematura. These results suggest the possible effect of hematura on cardiovascular mortality.

Funding: Government Support - Non-U.S.

PUB133
Glomerular Filtration Rate Is a Predictor of Subclinical Left Ventricular Diastolic Dysfunction in Patients with Rheumatoid Arthritis

Suad Hannawi, Khalfi Nacem, Issa Al Salmi, Medicine, MOH, United Arab Emirates; Medicine, MOH, United Arab Emirates; Medicine, The Royal Hospital, Oman.

Background: Rheumatoid arthritis (RA) is a systemic disease effecting primarily joints. Subclinical cardiovascular disease (CVD) is a leading cause of morbidity & mortality in RA & chronic kidney disease (CKD) at early stages. Left ventricular diastolic dysfunction (LVDD) is a principal pathophysiological mechanism & essential diagnostic indexes of HF with preserved ejection fraction (HFpEF).

Methods: Renal parameters correlated with echocardiographic findings in patients with RA& eGFR as estimated (MDRD equation). Doppler echocardiography was performed by pulse wave Doppler with sample volume at tip of mitral valve in apical 4-chambers view. Peak early (E) & late (A) diastolic velocities were measured as indicator of LVED pressure. Peak early (E)/late (A) diastolic velocities were measured as indicator of LVED pressure. Assessment of peak early (E′) & late (A′) diastolic mitral annular velocity was performed by pulsed wave tissue Doppler imaging (TDI) of lateral wall in apical 4-chamber view & diagnose LVDD (E/E′>8).

Results: Interim analysis: 29(3.26%) with RA diagnosed (ACR 1988), age 44+12y, CKD GFR 130+36 ml/min. Univariate regression showed a negative linear relationship of GFR & age (p<0.001, CI 2.77 -1.13, age) (RA onset p<0.001, CI 2.32-0.63, age) (RA diagnosis p=0.002, CI 0.25-0.55, -0.66) SBP p<0.032, CI 1.51-0.07, ER p=(0.005, CI 1.19-0.21, ferritin level p=0.008, CI 0.45-0.08, EE p<0.05, CI 20.76, 4.26). Multiple regression maintained a negative relationship between GFR & each of age (p<0.004, CI 2.59-0.4, EE p<0.04, CI 0.15, 0.01) &R2 was 0.54.

Conclusions: RA patient have subclinical CKD and cardiac dysfunction & eGFR independently & negatively correlated to LVDD with moderate correlation (0.54). E/E′ increased with decreasing GFR & higher than in patients GFR<90. LVDD influenced by increase LV preload due CKD progression & it’s a pre-clinical predictor of future HF & mortality. However, milder form of LVDD may stabilize or improve & subset of patients may, over time, be at risk for functional deterioration. Inflammation as a major pathological key in RA may be underlying cause for increased subclinical kidney & VD.

PUB134
The Association Between Creatinine versus Cystatin-C-Based eGFR and Cardiovascular Risk Factors in Children with Chronic Kidney Disease

Sheena Sharma,1 Ji Young Kim,3 Susan L. Furth,1 Nephrology, Children's Hospital of Philadelphia, Philadelphia, PA; 2Biosstistics Core, Clinical and Translational Research Center, Children's Hospital of Philadelphia, Philadelphia, PA.

Background: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular events (e.g. stroke, myocardial infarction) in adults. Children with mild-moderate CKD have a high prevalence of cardiovascular risk factors (CRF). Higher levels of cystatin-C demonstrate a stronger predictive value for cardiovascular events compared with creatinine-based eGFR in adults. However, whether similar associations exist in children and young adults has yet to be determined. We hypothesize that cystatin-C-based eGFR will demonstrate a stronger association with CRF compared with creatinine-based eGFR in children and young adults.

Methods: We used cross-sectional data of 93 subjects aged 8-25 years with CKD and 120 healthy controls. eGFR was calculated using age-appropriate creatinine and cystatin-C based formulas. The CRF included were anemia (hemoglobin <2 standard deviations below the mean), hypertriglyceridemia (>130mg/dL) and proteinuria (urine protein/creatinine >0.2mg/dL or urine albumin/creatinine >30mcg/g). Multiple regression analysis assessed the association between creatinine and cystatin-based eGFR and each risk factor after adjusting for age, gender and race.

Results: These results suggest that creatinine and cystatin-based eGFR have similar associations with CRF.

Funding: Other U.S. Government Support

PUB135
The Influence of Selected Demographics and Clinical Factors on Left Ventricular Function Presented by Echocardiographic Study in Patients Treated with Peritoneal Dialysis

Maria Wanic-Kossowska, Krzysztof Pawlacz, Krzysztof Schwerner, Krzysztof Hoppe. Dept of Nephrology, Transplantology and Internal Medicine, Poznan Univ of Medical Sciences, Poznan, Poland.

Background: The purpose of the study was to perform a cross-sectional analysis between the selected demographics including age, sex, BMI as well as peritoneal dialysis treatment volume, volume of residual diuretics, presence of arterial hypertension, anemia, inflammatory states, malnutrition, mass of the left ventricle, problems with the contractile function of the left ventricle as well as decreased relaxation of the left ventricle in the group of patients treated with peritoneal dialysis with regard to survival prognosis.

Methods: The study was conducted on 105 patients (40 men, 56 women) treated with peritoneal dialysis with the average time of 36.1±23.7 months. The control group consisted of 30 healthy volunteers (20 women, 10 men, mean age 55.0±23.8 years). Based on general known vascular and cardiac risk factors the patients were divided into subgroups: elderly patients (<65 years of age), male, patients treated on peritoneal dialysis over 3 years, daily diuretes <500 ml, Kt/V<2.1, arterial hypertension, anemia, inflammatory states, malnutrition.

Results: Analyzing the frequency of vascular and cardiac risk factors resulting in inadequate echocardiogram results showed the inflammatory states were the most common reason for increased left ventricular mass, diastolic dysfunction of the left ventricle as well as decreased ejection fraction. In the model of logistical regression taking into account age, sex, dialysis vintage, concentration of CRP, ejection fraction of the left ventricle, left ventricle mass, and factoring E/A from the echocardiogram study only advanced age of the patient treated on peritoneal dialysis decreased survival rate.

Conclusions: Chronic low-grade inflammation and advanced age seem to be two most common negative prognostic factors decreasing life expectancy. Further research is necessary to verify the intricate relationships between demographic factors and prognosis in the group of patients undergoing peritoneal dialysis.

Ankle Brachial Index and Exertional Leg Pain Among Hemodialysis Patients without a Clinical Diagnosis of Peripheral Arterial Disease

Pranay S. Garinella,1 Lucia Kwak,2 Kunihiro Matsushita,2 Esther D. Kim,3 Michelle M. Estrella,3 Stephen M. Sozio,3 Lucy A. Mooni,3 Rulan S. Parcek,4 Bernard G. Jaac.2 Tufts Medical Center; Johns Hopkins Univ; Univ of Toronto.

Background: Exertional leg pain is considered pathognomonic for diagnosing peripheral artery disease (PAD). However, patients on dialysis may have multiple comorbidities causing or masking leg pain, potentially precluding its use to diagnose PAD. Furthermore, the utility of the ankle-brachial index (ABI) to diagnose PAD in this population is questionable due to the presence of arterial calcification. In this context, there are no data on the association of leg symptoms with ABI in dialysis patients despite having an extremely high burden of PAD.

Methods: We evaluated the cross-sectional association of exertional leg symptoms with the spectrum of ABI in 247 incident hemodialysis patients without clinical diagnosis of PAD enrolled in the Predictors of Arrhythmia and Cardiovascular Events (PACE) study. The presence of exertional leg pain was based on questionnaire and ABI was categorized as low (<0.90), borderline (0.90–1.00), normal (1.00–1.39) and high (>1.4). We used logistic regression analysis to report odds of exertional leg pain.

Results: Mean age was 54 years, 76% were black and 51% had diabetes. The prevalence of exertional leg pain was lowest in the normal ABI category and increased towards both ends of the spectrum. Compared to normal ABI, low ABI was associated with 2.8 fold higher odds of exertional leg pain, although it did not reach significance. After adjusting for age, gender and race this association was attenuated to 2.5 fold odds. Borderline and high ABI were also similarly associated with exertional leg pain.
Conclusions: Low ABI tended to be associated with higher risk of execlional leg pain. A low ABI value may be useful to identify ischemic etiology of leg pain even among dialysis patients with high prevalence of leg symptoms due to various conditions.

Funding: NIDDK Support

PUB137

Chronic Kidney Disease Is Highly Prevalent at Emergency Department and Associated with Cardiovascular Comorbidity
Jolanta Malyszko, Anna Swietochowska.
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Background: Different stages of CKD affects more than 10% of the population, while in high-risk patients, the incidence of 30-50% is reported. The aim of this work was to evaluate the prevalence of CKD in patients admitted to the non-surgical emergency department in one year, the impact of CKD risk factors, rate of hospitalization and mortality.

Methods: From 10500 patients admitted to ED, the group of patients with serum creatinine measured, i.e. 3835 (40%) patients over 18 years was selected, including 2095 (55%) patients over 70 years. Age, gender, medical history of hypertension, heart failure, ischemic heart disease, acute coronary symptoms (ACS), diabetes, inflammation, current medications, physical examination, laboratory results: creatinine, C-reactive protein (CRP), leukocyte count, hemoglobin, the alcohol level in serum, urinalysis were analyzed.

Results: 1797 patients were hospitalized (57%) mainly for cardiovascular reasons, remaining were discharged home. 561 (15%) were admitted to the ED more than once. Abnormal serum creatinine was found in 27%, while 19% have CKD stage 3 and 5% stage 4. Active urine sediment was present in 20% of studied patients. Patients and physicians were unaware of this finding. A small percentage of patients were under nephrology care. Accumulation of risk factors such as gender, age, hypertension, diabetes, results in an increased prevalence of CKD. Prevalence of hypertension in the population of patients with CKD is high (59% vs 29% in non-CKD, p<0.001), similarly to prevalence of CAD (24%), DM (15%) and CHF (16%). In CKD, 30% of patients have anemia. In-hospital mortality was 6%. Analysis of mortality of patients admitted to the emergency department and then hospitalized showed that the majority of patients were over 70, with CKD 64%, CHF (75%), DM (35%), ACS (25%) and anemia (56%). Deaths were mainly from cardiovascular causes.

Conclusions: Prevalence of CKD is high in patients admitted to ED, and associated with mainly cardiovascular disease. Education is of utmost importance to diagnose and treat CKD in a timely manner and decreased cardiovascular morbidity and mortality in this population.

Funding: Government Support - Non-U.S.

PUB138

Predictors of In-Hospital Mortality of CKD4-6 Patients with Takotsubo Cardiomyopathy
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Background: the pathophysiology of Takotsubo cardiomyopathy (TTC) remains poorly understood and little is known about the factors predicting mortality in these patients among those with chronic kidney disease. We aimed to study the epidemiology of TTC and predictors of mortality in these patients.

Methods: All patients with CKD 4 to CKD 6 (ICD9 585.4-585.6) diagnosed with TTC (ICD9 429.83), in the Nationwide Inpatient Sample database between 2007 and 2012, were compared to CKD4-CKD6 patients without TTC. Capturing only cases undergoing left heart catheterization (ICD9 procedure code 32.22) and excluding those receiving stent (ICD9 procedure code 90.66; 36.01 - 07.00.45.00.48) as a main treatment. Both groups were matched, using propensity matching score for chronic conditions including diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, obesity, alcohol use, smoking, heart failure and ventricular arrhythmias. Non-cardiovascular conditions were also used to match individual cases. Multivariable logistic regression analysis was performed.

Results: 143 cases of TTC were diagnosed from 2007-2012 patients having CKD4-6. Were 138 cases were matched (n to 1) and posteriorly analyzed. Among to control groups, CKD 4-6 patients with TTC was more commonly diagnosed in Women (86.23% vs 13.77 p=1.0). Alcohol, older, smoking and anxiety, were significantly more prevalent in TTC group. In-hospital mortality rate was not different among both groups even after multivariable regression analysis. Contrary to epidemiologic studies in the general population, Age, Race Stress, anxiety, smoker, Obesity and HTN did not predict mortality with TTC.

Conclusions: In CKD4-6 patients, TTC does not carry higher mortality outcome compared to the general CKD4-6 patients. Older CKD4-6 females, with anxiety disorder and smokers are at higher risk to develop TTC.

PUB139

The Importance of Evaluating Coronary Artery Disease by Multi-Director Row Computed Tomography in Advanced CKD
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Background: There is a growing body of evidence that CKD contributes to the severity of coronary artery disease (CAD). Although Multi-director row computed tomography (MDCT) provides valuable information about CAD, its use for patients with CKD is difficult due to the risk of contrast induced nephropathy (CIN). To our knowledge, there have been no studies to explore the association of CAD and advanced CKD. The objectives of this study are to assess the severity of CAD in advanced CKD patients by MDCT and clarify the association between CAD and renal function.

Methods: We retrospectively collected the data from 168 advanced CKD patients, stage 3b to 5, who underwent MDCT angiography at St Luke’s international hospital between 2011 and 2014. We assessed CAD by coronary artery calcification score (CASC), coronary plaque characteristics and number of vessel disease. Risk factors for CAD were sought using univariate and multivariable logistic regression.

Results: Among the 168 patients (56 females, age 60.0±17.0), 108 patients were CKD stage 3b, 42 patients were stage 4, and 18 patients were stage 5. No patient developed CIN by MDCT. On univariate analysis, patients with CASC>=100 were older (p=0.003), male sex (p=0.011), diabetic (p=0.045), and more likely to be a smoker (p=0.014). Multivariable logistic regression analysis identified age (hazard ratio = 1.08, P<0.01), male sex (hazard ratio = 2.97, P=0.013), and CKD stage (hazard ratio = 2.58, P=0.041) as independent risk factors for CASC>=100.

Conclusions: Coronary artery calcification is worsened significantly with decreasing renal function in advanced CKD. Given the high morbidity and mortality of cardiovascular disease in CKD, our study underscores the importance of evaluating CAD in advanced CKD.

PUB140

Cardiovascular Biomarkers and Coronary Calcification in CKD Patients
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Background: Cardiovascular calcification and mortality are highly prevalent in patients with CKD. Biomarkers can help to an early diagnose, like Osteoprotegerin (OPG) a glycoprotein from TNF family that has been associated with cardiovascular (CV) disease. FGF-23, a phosphaturic protein has been linked to vascular calcification, ventricular remodeling and mortality. Coronary artery calcification (CACC) measured by Agatston score (AS) by CT is associated to CV disease in CKD patients. We hypothesized that OPG and FGF-23 are abnormally elevated in CKD and are associated CACC measured with AS.

Methods: An observational study including 138 CKD 3-5patients, and 20 control subjects were included. Serum FGF-23 and OPG levels were measured by ELISA and CAC was determined by multi-detector computed tomography (AS). Biochemical regular labs (sCr, Ca, P and PTHi) were measured.

Results: Compared with control subjects, CKD patients exhibited significantly augmented serum FGF-23 (16.2 vs 304 ng/mL; p<0.001) and OPG levels (157.0 vs 711.7; p<0.05; LR=b2.48; p<0.001), and increased proportionally to CKD stage. FGF-23 and OPG were correlated to PTHi and P (p<0.001) and OPG correlated with renal function (sCr) in non-dialysis patients (p<0.05). CKD 5 patients showed significantly augmented serum FGF-23 (1380.7) compared with CKD 3 (144.3; p<0.05) or CKD 4 (527.7; p<0.05). FGF-23 and OPG were associated with AS (r=0.2-0.4; p=0.05 and r=0.37; p<0.001, respectively). Among CKD patients, high CACC (AS>800) compared to low CACC (AS<150) showed higher FGF-23 (374.9 vs 156.1; p<0.05) and OPG levels (2121.2 vs 1305.2; p<0.001).

Conclusions: CKD is related to high coronary artery calcification levels. FGF-23 and OPG are higher in CKD patients and are significantly associated to coronary artery calcification. Further investigations are needed to determine if they could promptly assess increased cardiovascular risk in CKD patients.

PUB141

Rate of Kidney Function Decline and Risk of Hospitalizations
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Background: Risk of hospitalizations is increased in patients with chronic kidney disease (CKD). We sought to examine the association between rate of kidney function decline and risk of hospitalization in a cohort of patients with early CKD.

Methods: We built a cohort of 241,274 United States veterans with an estimated glomerular filtration rate (eGFR) between 60 and 45 mL/min on October 1, 1999 and who had at least 1 additional eGFR measurement between October 2003 and September 2004. Patients were followed longitudinally from October 2004 until September 2013. We built
survival models to examine the association between rate of kidney function decline and risk of hospitalization, and readmission. We built linear regression models to estimate the survival models to examine the association between rate of kidney function decline and risk of hospitalization, and readmission. We built linear regression models to estimate the length of hospital stay.

**Results:** Over a median follow-up of 9 years (IQR 5.42 - 9.00), compared to patients who experienced mild eGFR decline, patients with moderate and severe eGFR decline exhibited an increased risk of hospitalizations HR=1.10 (CI:1.07-1.12), and HR=1.29 (CI:1.26-1.32) respectively. The number of hospitalizations modified the association between rate of decline and risk of hospitalizations in that the risk was increasingly more pronounced with increased number of hospitalizations (p value for interaction <0.0001). Compared to patients with mild decline in kidney function, patients with moderate and severe kidney function decline had increased risk of future readmission, HR=1.16 (CI:1.10-1.21), and HR=1.47 (CI:1.39-1.55) respectively. Among patients with severe kidney function decline, the risk of readmission was increasingly stronger with increased number of readmissions (p value for interaction < 0.0001). Compared to patients with mild decline in kidney function, patients with moderate and severe decline experienced an additional length of stay of 0.91 (CI: 0.58-1.25) and 2.82 (CI: 2.43-3.20) day/year; respectively.

**Conclusions:** Our findings suggest that rate of kidney function decline is associated with future risk of increased health care utilization.

**Funding:** Veterans Administration Support

**PUB142**

**Racial Influences on the Association of Albumin and Hemoglobin in Chronic Kidney Disease**

**Authors:** Divya Shankararanyanan, Avaneesh Jakkoju, Goutham Gudavalli, Ziad Maurice Ashkar. Dept of Internal Medicine, Louisiana State Univ, Lafayette, LA.

**Background:** In CKD, anemia is associated with reduced kidney function, female gender, diabetes, older age, African-American race (AA), iron deficiency, low albumin, renin-angiotensin blockade, and chronic inflammation. There is a paucity of studies evaluating relationship of albumin and hemoglobin(Hb) in CKD among racial groups.

**Methods:** Retrospective cross section design of 196 patients with CKD stages 2-5, in a community clinic over a 7 months period. Averages of hemoglobin, albumin, body mass index (bmi), and glomerular filtration rate (GFR) were obtained for each individual patient. Patients on dialysis and on erythropoiesis-stimulating agents were excluded. Multi-linear regression analysis (MLR) was then done between serum albumin and hemoglobin adjusting for age, sex, diabetic status, GFR, bmi and Ace inhibitors/angiotensin receptors blockers intake (ACEi) among African-Americans (AA) and Caucasians (W).

**Results:** 51% were AA. 49% were diabetics. Mean Hb was 11.7 in AA compared to 12.3 in Caucasians. Mean serum albumin was also lower (3.5 AA versus 3.8 in W). Bmi and GFR were higher in AA (36.4 and 42.8 in AA vs 32.3 and 39.9 in W respectively). Using MLR, there was a statistically significant positive association between GFR(coefficient=0.02, p<0.001), albumin (coefficient=0.77, p=0.002), and hemoglobin. AA race was negatively related to hemoglobin(coefficient= -0.68, p=0.02). When MLR was done separately among racial groups, there was a persistent positive relationship between albumin and hemoglobin among AA (coef=0.95, p<0.001). In Caucasians however there was no association between albumin and hemoglobin (p=0.181).

**Conclusions:** In CKD2-5, using multilinear regression analysis, there was a positive association between serum albumin and hemoglobin. This relationship occurs only in AA and disappears among Caucasians. It is of interest that in our sample AA had higher baseline bmi and GFR and lower serum albumin and hemoglobin. More needs to be done to understand the interplay between bmi, albumin and markers of inflammation and nutrition among African Americans with chronic kidney disease and their relationships to hemoglobin levels.

**Funding:** Pharmaceutical Company Support - Extramural grant: Roche Products Limited UK

**PUB143**

**Mircera Use in Chronic Kidney Disease Patients with Symptomatic Renal Anemia: The Real Life Setting**

**Authors:** Sai Krishna Derasingham, Suzanne H. Forbes, Muhammad M. Yaqoob. Renal and Transplantation Medicine, Baris Health NHS Trust on behalf of the Mircera Audit Consortium, London, United Kingdom.

**Background:** Randomized controlled trials have confirmed non inferiority of Mircera in the management of renal anemia when compared to other erythropoietin stimulating agents (ESAs). Many of these trials had strict exclusion criteria which perhaps confounded any benefit that may be seen in an unselected cohort of patients. This multicenter audit assessed the outcomes of Mircera use in the real life setting.

**Methods:** A prospective audit was conducted by 6 UK Renal Centers between 2009 and 2011. Demographic data, as well as haematological and biochemical parameters were longitudinally collected from 1000 adult patients requiring ESAs, over a 1 year period. A cohort of 500 patients were switched from previous ESAs to Mircera and 500 patients were excluded. Achievement of target hemoglobin (Hb) as per the National Institute of Clinical Excellence (NICE) guidelines was ascertained as the primary objective. Hb variability was reviewed as a secondary objective.

**Results:** Demographic data confirmed both cohorts were comparable. Only 11% of Mircera treated patients had their Hb maintained within range (10-12g/dl) over the entire 1 year versus 4% in the non-Mircera group (p=0.05). (If an Hb recording was out of range the patient was classified as ‘not maintained’). Parameters such as B12, folate and iron were similar in both cohorts. Hb was less variable in the Mircera group.

**Conclusions:** The results of this audit confirm that Mircera use in the correction of anemia associated with CKD is equally efficacious as other ESA therapies in this real life setting. Over a year period, Hb variability was noted to be reduced in the Mircera treated cohort suggesting a role for its use in patients with fluctuating Hb levels.

**Funding:** Veterans Administration Support

**PUB144**

**Latent Profiles of Patient Reported Outcomes in Nephrotic Syndrome Patients**

**Authors:** Jonathan P. Troost,1 Debbie S. Gipson,1 Bryce B. Reeve,2 Patrick H. Nachman,3 Rashed A. Ghaedegisini,3 Ichuan Wang,3 Frank Medorsitzki,4 Susan F. Massengill,5 John D. Mahan,6 Howard Trachtman,7 David T. Seleowski.1 1Univ of MI; 2Univ of NC; 3Duke Univ Medical Center; 4George Washington Univ; 5New York Univ; 6Levine Children’s Hospital; 7The Ohio State Univ.

**Background:** Nephrotic syndrome (NS) can significantly impair the quality of life in children and adults. The purpose of this study was to demonstrate the feasibility and utility in using a latent profile analysis (LPA), a type of cluster analysis, to identify subgroups of patients based on their patient reported outcomes using the Patient Reported Outcomes Measurement Information System® (PROMIS®) measures as well as identifying significant predictors of these subgroups.

**Methods:** Prospective data were collected on 121 children with NS from the PROMIS-II study. Data from 55 children and 254 adults with biopsy confirmed NS from the NEPTUNE cohort were used as validation. LPA was used to identify patterns and subgroups of patients based on PROMIS domain scores. Classification was assessed using entropy statistics. Generalized multinomial logit models were used to identify predictors of profile membership as well as transitions between profiles over time.

**Results:** We identified three patient reported outcome profiles (figure1) in the PROMIS-II cohort with strong indicators of membership classification (entropy>0.86).

**Conclusions:** The models derived from the PROMIS-II cohort were also present in NEPTUNE. Reaching complete proteinuria remission, reduction in symptom number, increase in serum albumin and shorter disease duration were significant predictors of better quality of life over time.

**Funding:** NIDDK Support

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

Underline represents presenting author.

919A
Sex Hormone Status in Women with Chronic Kidney Disease. A Survey of Nephrologists. Sharranya Rashmi, Ellen Wells Seely, Matthew T. James, Jayna M. Holroyd-Leduc, Stephen B. Wilton, Sofia B. Ahmed, Medicine, Cumming School of Medicine; 2 Brisbane and Women’s Hospital; 3 Community of Health Sciences, Univ of Calgary; 4 Libin Cardiovascular Inst of Alberta.

Background: Chronic kidney disease (CKD) in women is often accompanied by menstrual and fertility disorders due to kidney-mediated endocrine disturbances. Whether this issue is recognized by nephrologists and discussed by them with their patients is unknown.

Methods: We electronically surveyed 111 nephrologists in Canada, identified via Canadian Society of Nephrology membership (39% response rate), regarding their impression of sex hormone loss and menstrual and fertility disturbances and the role of postmenopausal hormone therapy (HT) in women with CKD. Responses were stratified by kidney transplant nephrologist status.

Results: Fourteen percent of respondents were transplant nephrologists. There were no differences in age or sex between transplant and non-transplant nephrologists. Ninety-three percent of respondents agreed that kidney function has an important impact on regulation of sex hormones. However, only 35% reported discussing fertility, and even fewer (14%) reported discussing menstrual irregularities with their patients. Only 40% of respondents advised their patients to address these concerns with their family physician or an endocrinologist or gynecologist. Most of the of nephrologists responded that they do not know if there is a role for hormone replacement therapy in patients with CKD (48%), 23% of nephrologists disagreed with the statement. Nephrologists did not know whether the potential benefits of postmenopausal hormone therapy outweighed the risks in CKD (51%) or if the formulation (44%), route of administration (46%), and time of HRT initiation (50%) play a role in the actions of postmenopausal hormone therapy.

Conclusions: While nephrologists recognize the impact of CKD on sex hormone status in women, few address fertility and menstrual disorders with their patients. Our survey highlights the need for future studies to investigate the impact of CKD on sex hormone status and how to manage the disturbances of sex hormones in people with CKD.

Funding: Private Foundation Support

PUB146
Clinical and Pathological Analysis of Elderly Hospitalized Patients with Chronic Kidney Disease Fu-You Liu, Yinghong Liu. Inst of Nephrology, the Second Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: To investigate the primary disease and to examine the pathological patterns of renal in elderly patients with CKD.

Methods: Medical histories, laboratory test results and renal biopsy data were collected and retrospectively analyzed from 967 elderly patients with CKD.

Results: (1) The average age of 967 cases of elderly patients was 68.27 ± 6.41 years old. The leading cause of CKD was primary glomerular diseases (37.33%), followed by diabetes nephropathy (23.27%) and hypertension nephropathy (19.75%). (2) The left kidney was larger than the right kidney and males were larger than the females (P < 0.05). There was a positive correlation between eGFR and the left kidney width, depth, and the right kidney width, depth. (3) In 75 patients who underwent renal biopsy, the most common renal histopathology in primary glomerular disease was membranous nephropathy (MN) (48%), in patients with MN, 88.00% presented as nephrotic syndrome. (4) The prevalence of hypertension was 80.66%, eGFR was negatively correlated with systolic blood pressure levels. (5) The anemia rate of elderly patients with CKD was 77.97%, and eGFR and hemoglobin levels were positively correlated. (6) There was a positive correlation between eGFR and HDL-C, LDL-C, total cholesterol and triglyceride respectively. (7) Calcium-phosphate metabolism were mainly hypocalcemia (27.92%) and hyperphosphatemia (34.91%) eGFR was negatively related to the level of blood phosphorus and intact parathyroid hormone (iPTH), and positively related to blood calcium levels.

Conclusions: (1) This study shows that primary glomerular disease is still the leading cause of elderly patients aged 60 and above with CKD, followed by diabetes nephropathy and hypertensive nephropathy. (2) In elderly patients receiving renal biopsy, the most common renal histopathology pattern was MN in primary glomerular disease. (3) It indicated that high systolic blood pressure, renal atrophy, anemia, low HDL-C, hyperphosphatemia and secondary hyperparathyroidism may be associated with deterioration of renal function level.

Funding: Government Support - Non-U.S.

PUB147
Measurement of Breath Ammonia for Detection of Patients with Chronic Kidney Disease. Sebastian Beve, Evelina Mohorko, Krista Kolari, Polonca Breglez, Andrej Holobar, Daniela Kniepseis, Matej Podbrdar, Nina Hojs, Masa Knehtl, Robert Eckart, Radovan Hojs. 1 Univ Clinical Centre Maribor, Slovenia; 2 Faculty of Chemistry and Chemical Engineering Maribor, Slovenia; 3 ECHO d.o.o., Slovenes Kongice, Slovenia; 4 Medical Univ Graz, Austria; 5 Univ Clinical Centre Ljubljana, Slovenia.

Background: In a healthy individual, ammonia is converted to urea in the liver through urea and citric acid cycles. Urea is then transported through the blood stream and excreted into the urine by the kidneys. In patients with chronic kidney disease (CKD) an equilibrium concentration of ammonia and urea becomes imbalanced, concentrations exceeding physiological values and breath ammonia can be used for detecting increased ammonia wastes in the body. In our pilot study, breath ammonia was used to measure and analyze breath ammonia in healthy volunteers and CKD patients.

Methods: Six CKD patients and eight healthy volunteers were enrolled. The mean age of CKD patients was 47.2 years, mean age of healthy volunteers 61.3 years. One controlled breath sample was given to each participant immediately after the sample was collected breath gas analyzer (BA-NH3, Echo, d.o.o.). This was used for measuring breath ammonia in our participants. BA-NH3 detects breath ammonia in parts per million (ppm) and measures the electric current in milliamperes (mA). BA-NH3 was validated with reference gas current measurements prepared with a precise accredited gas mixing device (M4-1 S-2, Echo, d.o.o.) using calibrated mass flow controllers controlled with computer software.

Results: Mean serum creatinine in CKD patients was 455.17 ± 294.12 µmol/L and 62.13 ± 7.5 µmol/L in healthy volunteers. BA-NH3 detected more ppm of ammonia in breath of CKD patients (mean ± std: 2.2 ± 1.9; range: 1.26-6.33) compared to healthy volunteers (mean ± std: 0.49 ± 0.08; range: 0.38-0.64 ppm) (p = 0.003) and measured higher electric current from breath samples of CKD patients (mean ± std: 4.33 ± 0.25; range: 4.10-4.67 mA) compared to healthy volunteers (mean ± std: 4.01 ± 0.01; range: 4.00-4.03 mA) (p = 0.003).

Conclusions: Results of our pilot study show that breath monitoring of ammonia can be an useful simple, fast and noninvasive tool for detection of kidney impairment.

Funding: Other NIH Support - The WHIS Kidney Aging Study is funded by grant 1 R01 AG034853-01A2 (PI, Shiplak), which was administered by the Northern California Institute for Research and Education, and with resources of the Veterans Affairs Medical Center, San Francisco, California. Data in this manuscript were collected by the Women’s Health Initiative HIV Study (WHIS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). WHIS (Principal Investigators): UAB-MS WHIS (Michael Saag, Mirjam-Colette Kempf, and Deborah Konkle-Parker), U01-AI-103401; Atlanta WHIS (Ghavriwer Gorofukun and Gina Wingood), U01-AI-103400; Denver WHIS (Kathy Anastos), U01-AI-035004; Brooklyn WHIS (Howard Minkoff and Deborah Gustafson), U01-AI-031834; Chicago WHIS (Mardine Cohen), U01-AI-034993; Metropolitan Washington WHIS (Mary Young), U01-AI-034994; Miami WHIS (Margaret Fisch and Anne Thaler), U01-AI-034851; San Diego WHIS (Bonnie Adinolfi, U01-AI-103397; UNC WHIS (Carolina Women’s Initiative), U01-AI-034992; Bronx WHIS (Kathie DeMers), U01-AI-034988; WHIS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub), U01-AI-042590; Southern California WHIS (Alexandra Levine and Marek Nowicki), U01-HD-032632 (WHIS – HIV IV).

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PUB419

Minimizing Erythropoietin Stimulating Agents Requirement by Comprehensive Clinical Care
Rachita Singh Dhull, Rossana Baracco, Melissa J. Gregory, Tej K. Mattoo. Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI.

Background: Anemia is a common problem in children with chronic kidney disease (CKD). The objective of the study was to evaluate prevalence of anemia, use of iron supplement and erythropoietin stimulating agents (ESA) in children with CKD stage 2-4, and compare the same with previous pediatric studies.

Methods: This is a retrospective chart review of children with CKD stage 2-4 (defined per KDOQI), aged between 1-18 years followed at Children’s Hospital of Michigan (CHM) in 2013. Data on transferrin saturation, hemoglobin level, use of iron supplements and ESA was collected.

Results: Total number of patients were 62. The mean age was 10.12 ± 5.52 years and 27.4% were female. The main causes of CKD were renal dysplasia (20%), obstructive uropathy (18%), reflux nephropathy (14.5%), cystic dysplasia (13%), glomerular pathology (11.2%) and others (23.3%). In our cohort, 27% patients had anemia compared to 44% in CKiD study and 43.5% in study by Wong et al. Also, only 6.5% of CKD patients were on ESA, compared to 18% in CKiD study and 19.5% in study by Wong et al. Results are elaborated in the table below.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient(s)% with anemia*</th>
<th>Patient(s)% with anemia*</th>
<th>Transferin saturation &gt;=20%</th>
<th>On iron supplement on ESA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>21/39</td>
<td>17/37</td>
<td>75(5.8%)</td>
<td>6(62.5%)</td>
</tr>
<tr>
<td>3</td>
<td>37/217</td>
<td>27/37</td>
<td>24(64.8%)</td>
<td>21(56.7%)</td>
</tr>
<tr>
<td>4</td>
<td>73/82</td>
<td>50/12</td>
<td>80(66.7%)</td>
<td>97(95.7%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>343/338</td>
<td>247/362</td>
<td>83(43.3%)</td>
<td>89(63%)</td>
</tr>
</tbody>
</table>

Notes:
*Anemia as defined by hemoglobin (Hb) level < 12 g/dl or on medical management for anemia.

Conclusions: Our CKD patients had a lower prevalence of anemia and lower use of ESA compared to other pediatric studies. We maintain adequate iron stores by using iron supplements even in children with normal hemoglobins. The administration of supplemental iron prior to the development of anemia in children with CKD decreases the need for ESA.

PUB510

Validation of Urinary Biomarkers for the Diagnosis of Urothelial Carcinoma in Patients with Chronic Kidney Disease
Chin-Ching Huang,1 Che-yi Chou,1 Chao-Jun Cheng,2 and Meng-Ju Liao,1 National Taiwan University Hospital, Taipei, Taiwan.

Background: Many urine biomarkers for diagnosis of urothelial carcinoma(UC) have been published. CKD patients are prone to have UC. Most of the studies are tested in healthy controls and UC patients. Whether these biomarkers are specific to diagnose UC in CKD patients have not been studied before. AIMS: To investigate whether these urinary biomarkers are specific to diagnose UC in CKD patients.

Methods: This is a multicenter prospective case-control study, carried out at 7 tertiary medical centers in Taiwan (Taiwan UC Consortium). Subjects were healthy adults (healthy controls), patients with CKD but without UC (disease controls) and patients with ongoing UC.Urine was collected from each patient and frozen immediately after collection. We measured 9 urinary UC biomarkers: BLCA-1.HAI-1.HtrA1, NMP22, CYFRA21-1, TSCSTD2, PUB150, BTA and Midkine. Mann-Whitney Rank Sum Test was used for statistical analyses.

Results: A total of 47 UC cases, 288 CKD patients and 20 healthy controls were recruited. We selected 47 CKD control patients who were age, sex and CKD-staging best matched with 47 UC patients. Among the 9 biomarkers tested, six biomarkers, e.g. NMP22, CYFRA21-1, TSCSTD2, PUB150, BTA and Midkine showed significant increase of urinary concentrations in UC patients when compared to healthy controls. Nevertheless, only Midkine and CYFRA 21-1 had significantly increased concentrations in UC patients when compared to CKD controls. The other 4 UC biomarkers did not show significant higher concentrations in UC patients than CKD controls.

PUB515

Predictors for 30-Day Hospital Readmission in a Nephrology Ward
Carolina Melo,1 Victoria A. Wong,2 Asia Roy,2 Rachel R. Mehta,3 Michelle L. Ong,2 Jaceson J. Young,2 S. Joselynne Costanza,4 and Michele S. Clarke.1 Austin Health, Melbourne; 2Univ of Melbourne, Melbourne; 3St. Vincent’s Hospital, Melbourne; 4Sal Aqua Diagnostics, New York.

Background: Rehospitalization, particularly 30-day hospital readmission is a growing concern in health care services. In this study we searched for predictors of 30-day readmissions (including emergency department visits) and 12-months hospitalization rate in patients admitted to a nephrology ward.

Methods: A group of 144 patients admitted to our nephrology ward from 2012 to 2013 were randomly selected. Their medical records regarding demographic and clinical-laboratorial data were collected. The statistical analysis was performed using univariate and multivariate logistic regression, and poisson regression.

Results: Median age was 66yos (IQ 56-81), with 63% of male patients. The majority of the patients had an emergent admission (63%) and regular hospital follow-up (55%). The median length of hospital stay was 7 days. The readmission rate was 23% and the median length until readmission was 13 days. The prevalence of chronic kidney disease was 89%, with 30% of these patients undergoing chronic intermittent hemodialysis and 11% peritoneal dialysis. The median Charlson Comorbidity Index (CCI) was 7 points (IQ 4-11). In the univariate analysis we found a significant association between diabetes mellitus (OR =2.45, p <0.05), lower (<3.5 g/dL vs ≥ 3.5 g/dL) albumin level (OR=8.73, p =0.006), higher (>8 vs ≤ 8) CCI score (OR=2.94, p =0.02) and 30-day hospital readmission. In the binary logistic regression only albumin level kept its significant association (OR=7.9, p=0.01), with diabetes mellitus maintaining a tendency for significance (OR=2.97- p=0.09). The rate of rehospitalizations at the first year adjusted for gender was 2.6 vs 6.4 rehospitalizations/100 patients-month in the lower and higher CCI score groups, respectively (p=0.01). The rate of emergency department episodes adjusted for gender was 29 versus 75 episodes/100 patient-month in the lower and higher CCI score groups, respectively (p=0.001).

Conclusions: The Charlson Comorbidity Index and albumin level may be valuable predictors of hospital readmission risk in patients from a nephrology ward.

PUB512

Urinary Protein Fragment Excretion in Diabetic Patients with Chronic Kidney Disease
Michele V. Clarke,1 Elif Ekinci,1,2 Nicholas J. Radcliffe,1,2 Richard J. Mac slaac,3 George Jerums,1 Wayne Comper.1 Austin Health, Melbourne; 2Univ of Melbourne, Melbourne; 3St. Vincent’s Hospital, Melbourne; 4Sal Aqua Diagnostics, New York.

Background: Albuminuria is an established marker for the development of diabetic nephropathy. Normal renal handling of albumin involves endocytosis by proximal tubule cells through a lyososomal pathway. This returns small albumin fragments, undetectable by standard clinical assays, to the tubular lumen. Albuminuria has been shown in patients with type 1 diabetes to be associated with an impaired degradation pathway, and urinary peptides have been shown to be reduced in patients with macroproteinuria. However, urine peptide excretion studies have not controlled for changes in estimated glomerular filtration rate (eGFR) in patients with diabetes.

Methods: Patients with diabetes and eGFR <60ml/min were stratified into normo- (<20mg/min, n=9), micro- (20-200mg/min, n=12) or macroalbuminuric (>200mg/min, n=9) groups. 24 hr urines were passed through a 10kDa protein filter, and the <10kDa and >10kDa fractions were assayed separately using the BCA protein assay to detect peptide bonds.

Results: Macroalbuminuric patients had a reduced proportion of peptide fragment excretion (<10kDa compared to micro- and normalalbuminuric patients (81.1% vs 89.0%, p=0.08 and 86.8%, p=0.001 respectively), however there was no difference between micro- and normalalbuminuric groups (Figure 1). Mean fragment concentrations were lower in micro- and macro- groups compared to normalalbuminuric patients, (338g/ml and 348g/ml vs 4396g/ml) but did not reach statistical significance.
In patients with diabetes and reduced renal function, we have demonstrated a reduction in peptide fragment proportional excretion in macroalbuminuric patients. These findings are consistent with the hypothesis that albuminuria is linked to defects in the renal tubule resorption and fragmentation pathways.

**Conclusions:** In patients with diabetes and reduced renal function, we have demonstrated a reduction in peptide fragment proportional excretion in macroalbuminuric patients. These findings are consistent with the hypothesis that albuminuria is linked to defects in the renal tubule resorption and fragmentation pathways.

**PUB155**

**Clinical and Pathological Features of Idiopathic Membranous Nephropathy in Young Adults**

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**Background:** Membranous nephropathy (MN) is a common pathological type in elderly nephrotic syndrome (NS) patients. Few researches focus on the young idiopathic MN population.

**Methods:** 583 patients hospitalized between Jan 2009 and Dec 2014 in our department, with biopsy-proved MN eliminating secondary causes, are enrolled. All patients were divided into 3 groups: 150 patients (25.1%) in young adult group (44 yrs), 202 (34.7%) in middle-aged group (45-59 yrs) and 231 (39.6%) in elderly group (60 yrs). We collected and compared their clinical and pathological data as well as therapy strategies.

**Results:** 310 male and 273 female enrolled. The young adult group had a lower rate of NS (P<0.02), higher serum albumin (P<0.01), estimated-GFR (P<0.01) and hemoglobin level (P<0.01), and lower fast blood glucose level (P<0.01).

**Table 1. Clinical features in three groups**

<table>
<thead>
<tr>
<th></th>
<th>young adults (n=450)</th>
<th>middle-aged group (n=202)</th>
<th>elderly group (n=231)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>proteinuria (mg/dL)</td>
<td>4.7±3.8</td>
<td>4.6±3.9</td>
<td>5.1±3.4</td>
<td>0.271</td>
</tr>
<tr>
<td>albuminuria (%)</td>
<td>23.8±7.8</td>
<td>23.9±6.9</td>
<td>21.2±6.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>nephrotic syndrome</td>
<td>73</td>
<td>105</td>
<td>143</td>
<td>0.022</td>
</tr>
<tr>
<td>fast blood glucose (mmol/L)</td>
<td>4.5±0.9</td>
<td>4.8±0.9</td>
<td>4.9±1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>serum creatinine (μmol/L)</td>
<td>64.2±175</td>
<td>71.0±24.8</td>
<td>85.2±40.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>eGFR(ml/min/1.73m²)</td>
<td>124.6±31.2</td>
<td>102.2±29.3</td>
<td>83.8±25.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>hemoglobin (g/L)</td>
<td>135.4±18.1</td>
<td>132.8±18.1</td>
<td>123.2±17.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

There’s no significant difference in the disease staging or immunofluorescences staining. However, the young adult patients had fewer mesangial, interstitial, tubular and arteriolar lesions, and fewer inflammatory cells infiltration as well (P<0.01). For the therapy, the number of ACE/ARB regimen applied in the three groups was 72/95/75, while corticoid associated with immunosuppressive agents regime was 66/92/140 (P<0.01).

**Conclusions:** About a quarter of all IMN patients are young adults. They had fewer cardiovascular risk factors, higher serum albumin level and better renal function. Their pathological lesions were milder. ACE/ARB regimen is more widely applied in young adults patients.

**PUB156**

**Effect of Glycemic Control on Estimated Glomerular Filtration Rate by Cystatin C**

MasaHiro Horio,1 Enyu ImaI,2 Yoshinari Yassuda,3 Tsuyoshi Watanabe,4 Hitoshi Yokoyamaa,5 Seichi Matsu,6 1Osaka Univ Graduate School of Medicine, Osaka, Japan; 2Nakayamaderia Imai Clinic, Takarazuka, Japan; 3Nagoya Univ Graduate School of Medicine, Nagoya, Japan; 4Fukushima Medical Univ, Fukushima, Japan; 5Kanazawa Medical Univ School of Medicine, Kanazawa, Japan; 6Okayama Univ Graduate School of Medicine, Okayama, Japan.

**Background:** Cystatin C has been proposed as an alternative marker for estimating glomerular filtration rate (GFR). But, some factors other than GFR affect the accuracy of estimated GFR (eGFR). Some studies raised a concern that poor glycemic control may cause inaccuracy of estimation of GFR. We studied the effect of glycemic control on eGFR based on serum cystatin C (cGFR).eGFR.

**Methods:** eGFR was measured by inulin clearance (Cin). Estimated GFRs were calculated by CKD-EPI equation (CKD-EPI) and Japanese GFR equation (J-Eq) based on standardized cystatin C. Glycemic control was evaluated by serum glycated albumin (GA). Three hundred and forty five Subjects with normal GA (12.4±6.3%) and 126 subjects with high GA (>16.3%) were included. Effects of age, gender, BMI, GA and serum albumin on eGFR/Cin ratio was analyzed by multiple regression analysis.

**Results:** Cin, eGFRcys(J-Eq) and eGFRcys (CKD-EPI) in normal GA were 57.9±34.0, 56.1±31.7 and 57.9±33.9 ml/min/1.73m², respectively. Cin, eGFRcys(J-Eq) and eGFRcys (CKD-EPI) in high GA were 36.2±28.9, 36.7±27.5 and 36.7±28.5 ml/min/1.73m², respectively. There was no significant difference among Cin, eGFRcys(J-Eq) and eGFRcys (CKD-EPI) in both subjects. Slopes (95% CI) of the regression lines with zero intercepts in subjects...
with high GA were 0.989 (0.944-1.033) in J-Eq and 0.966 (0.922-1.009) in CKD-EPI. The slopes were not significantly different from 1.0, suggesting that eGFReqs performed well in subjects with high GA. Multiple regression analysis showed that age, gender, BMI, GA and serum albumin were not significant factors affecting both eGFReqs(CKD-EPI) /Ctin and eGFReqs(Eq)/Cin.

Conclusions: Estimated GFR based on cystatin C performed well in subjects with high GA.

Funding: Government Support - Non-U.S.

PUB157
Renal Hyperfiltration and Outcome in HIV-Infected Subjects
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Background: Although highly active antiretroviral therapy (HAART) improves life expectancy of HIV-infected subjects, it is also associated with numerous comorbidities. Evidence suggests that renal hyperfiltration (RFH) is associated with various lifestyles, clinical conditions and portends poor prognosis in the general population. We sought at determining prevalence of RFH and its associations with traditional and HIV-related risk factors as well as all-cause mortality in a large cohort of HIV-infected subjects.

Methods: Retrospective study of 3875 HIV-infected patients attending at the “Modena Metabolic Clinic”. The Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) was used to estimate glomerular filtration rate (eGFR). Linear regression was used to model eGFR against age and sex. RFH was defined as eGFR with residuals above the 95th percentile. Anova, Chi-square, logistic regression and survival analyses were used to identify factors and the risks associated with RFH.

Results: Overall, we investigated middle-age (44.5±7.5 years) men and women (male 65.1%) with preserved renal function (eGFR 94.5±17.1 ml/min/1.73 m²). RFH was inversely associated with age (Odds Ratio 0.93), hemoglobin (OR 0.8), WBCs (OR 0.93) and positively associated with HIV-infection (OR 1.07). Of interest, no association with HAART was noted. Over mean follow-up of 7 years, 75 persons died. RFH was associated with all-cause mortality independently of potential confounders (Hazard ratio: 4.17, 95%CI: 1.81 - 9.6; p<0.001).

Conclusions: RFH is influenced by HIV infection duration independently of established factors and is related with the risk of all-cause of death. Future efforts are needed to clarify what are the mechanisms that link RFH with poor prognosis and if RFH modulation improves survival in HIV-infected subjects.

PUB158
Bioelectrical Impedance Analysis as a Screening Tool for Chronic Kidney Disease
Anita Saxena, Amit Gupta. Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, UP, India.

Background: Chronic Kidney Disease (CKD) has a latent period during which the disease is present but asymptomatic. With increasing incidence of hypertension and diabetes, incidence and prevalence of CKD is on increase. Bioelectric impedance analysis (BIA) is a noninvasive method for estimation of body composition in clinical setting but it has not been used for CKD screening. Purpose: To evaluate applicability of BIA as a screening tool for presence of kidney disease in general population with creatinine clearance and glomerular filtration rate (GFR).

Methods: A pilot cross-sectional CKD screening study on randomly selected 52 subjects from general population. Maltron BIOSCAN analyzer 915/916 was validated with Hume etal’s equation for estimation of total body water. BIA derived GFR was validated with 99mTc-DTPA nuclear scan derived GFR, a study done on voluntary healthy kidney donors.

Results: There was no significant difference between total body water estimated with BIA and Hume etal’s equation and BIA derived GFR and DTPA nuclear scan GFR. Mean serum creatinine for males was 0.94 ± 0.14 mg/dl and 0.91 ± 0.84 mg/dl for females. BIA derived creatinine clearance was 97.39%: 28.98 in males and 107.60%: 34.03 in females. GFR was 74.1±25.98 ml/min/1.73 m² in males and 65.17±21.14 ml/min/1.73 m² in females. Based on GFR subjects were classified into CKD. Out of 52 subjects 8 were in CKD stage 1 (15.5%), 23 (44.2%) were in CKD stage 2, 18 (34.6%) were in CKD stage 3, 1 (1.9%) patients were in CKD stage 4 and CKD stage 5 respectively. Incidentally, 15.5% were diabetic, and 65.8% were hypertensive. Mean blood pressure was 133.90±80.82/76.7±27.79 mmHg in males and 132.10±16.20/83.46: 7.85 mmHg in females. Based on American Heart Association classification for hypertension, 19 (36%) patients had normal blood pressure, 8 (15.3%) were in prehypertension stage, 20 (37.7%) patients were in hypertension stage 1, 6 (11.5%) were in hypertension stage 2 and 2 had crisis hypertension.

Conclusions: Population-based CKD screening programs can identify people with renal injury for early intervention. BIA can be used for screening CKD in general population. It can also be a routine test as 99m-Tc-DTPA scan for estimation of GFR.
Evaluation of Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI), Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (CG) Equations to Assess Glomerular Filtration Rate (GFR) in Kidney Cancer Patients

**Background:** Equations used to estimate GFR were not validated in kidney cancer patients. The aim of this study was to assess the performance of CKD-EPI, abbreviated (a) MDRD and CG equation in these patients.

**Methods:** Prospective evaluation of 124 outpatients with kidney cancer admitted to treatment at São Paulo State Cancer Institute between September 2012 and February 2015. Estimated (e) GFR was calculated using CG, aMDRD and CKD-EPI equations and compared to "true" GFR via radiotopic (r) clearance. The bias was given as the mean difference between the eGFR and rGFR values and the precision as the SD of the differences. Accuracy was described as the number of eGFR studies within 10 and 30% of the rGFR values.

**Results:** Patients were 59.0 ± 10.3 years old, 50.2% were women, rGFR (mL/min/1.73 m²) was 78.7 ± 24.6 and eGFRs (mL/min/1.73 m²) using the CKD-EPI, aMDRD and CG (mL/min) equations were respectively 80.7 ± 22.1, 83.4 ± 25.3 and 87.8 ± 26.5. Equations bias is detailed on table 1.

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean Bias (mL/min)</th>
<th>Mean (SD)</th>
<th>rGFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aMDRD</td>
<td>2.0</td>
<td>4.7</td>
<td>91.1</td>
</tr>
<tr>
<td>CG</td>
<td>21.5</td>
<td>21.5</td>
<td>24.1</td>
</tr>
<tr>
<td>SD</td>
<td>0.306</td>
<td>0.017</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

The accuracy of eGFR equations within 10% of rGFR were 31.4%, 27.4% and 19.4% with CKD-EPI, aMDRD and CG, respectively. Within 30% of eGFR, the accuracy of eGFR equations were 75.8%, 78.2% and 68.5% with CKD-EPI, aMDRD and CG, respectively.

**Conclusions:** CKD-EPI equation showed smaller bias and satisfactory accuracy when compared with the GFR assessed by "true" GFR in this group of kidney cancer patients.

Impacts of Chronic Kidney Disease on Other Non-Communicable Chronic Diseases – The Burden in the Health System of China

**Background:** The spread of non-communicable diseases (NCDs) presents a global crisis, and accumulating evidence based on individual disease reveals that major NCDs including heart disease and stroke have a worse prognosis in the presence of chronic kidney disease (CKD). However, there is neither large-scale study quantitatively evaluating the burden of CKD on various NCDs, nor studying the burden of CKD with other NCDs, especially among low- and middle-income countries like China.

**Methods:** A national in-patient database involving 19.5 million patient-records was used. Diagnoses of CKD and other major NCDs, including hypertension, coronary heart disease, stroke, chronic obstructive pulmonary diseases, and cancer, were extracted from International Classification of Diseases-10 codes of the discharge diagnoses. The effect of CKD on costs, length-of-stay, and hospital mortality were analyzed for each NCD. Then the effect of CKD on those outcomes was compared with other major NCDs.

**Results:** For each NCD, the presence of CKD was associated with increased length-of-stay and in-hospital mortality. And the costs were also increased by 0.1-20.3%, except for coronary heart disease and diabetes. Among those NCDs, CKD was associated with the highest length-of-stay, and with in-hospital mortality only lower than that of cancer.

**Conclusions:** Using database with large sample size and broad geographic coverage in China, we found that the presence of CKD was associated with substantial increased healthcare resources utilization and increased risk of in-hospital mortality.

Funding: Government Support - Non-U.S.
comparatively analyzed adjusted for age, sex, race and center. The asking questions revealed comfort asking questions was independently associated with higher confidence / empowerment, β = 0.23 (95% CI: 0.04, 0.45), p < 0.02. Our 10-item confidence / empowerment measure showed excellent internal reliability (Cronbach alpha = 0.89).

Discussion: Patients in a multi-disciplinary CKD clinic reported being comfortable asking their doctor questions and rated confidence and empowerment as high. Comfort asking the doctor questions was positively associated with patient confidence and empowerment in care. More work is needed to compare patient-centric quality measures across care models and assess changes over time.

PUB166
Factors Affect Use of Healthcare Services Among Different Ethnicities
Enchi K. Chang,1 Li-Li Hsiao,2 Harvard College, Cambridge, MA; 2Renal, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background: Use of healthcare services by medically underserved minority populations varies by ethnicity and cultural factors. Healthcare providers may address ethnicity-specific barriers to healthcare service usage to decrease disparities in healthcare use. Through free community health screenings provided by the Kidney Disease Screening and Awareness Program (KDSAP), we seek to elucidate ethnicity-specific differences and sociocultural barriers to healthcare service use.

Methods: A questionnaire available in English, Chinese, and Spanish was administered to KDSAP participants in Massachusetts, New Jersey, and Toronto from 2012 to 2014. Participants were asked to provide their ethnicity, health insurance, primary care physician, and difficulties and alternatives to receiving care.

Results: Of 3730, 30% were African-American, Hispanic, and 50 Caucasian participants were surveyed. Participants lacking health insurance comprised 29.1% of Asian and 45.1% of Hispanic participants, compared with 17.3% of African-American and 8% of Caucasian participants. 25% of Asian and Hispanic participants reported language barriers with their healthcare provider compared with 6% of African-American and Caucasian respondents. 50% of Asian and Hispanic participants were prevented from seeking care due to lack of insurance, and as an alternative, 51% of Asian participants would ignore the problem. African American participants without insurance primarily reported seeking emergency care (51%), and Hispanic participants reported seeking free clinics (40.5%) as an alternative to emergency care (37.8%).

Conclusions: Culture and ethnicity-specific barriers to receiving care affect use of healthcare resources for medically underserved populations. Asian and Hispanic populations experience greater difficulty accessing healthcare services and are less likely to have health insurance compared to African-American and Caucasian populations, suggestive of linguistic and sociocultural barriers to healthcare for immigrant populations. Healthcare services targeting medically underserved communities must address ethnicity-specific sociocultural differences to reduce healthcare disparities between ethnic populations.

Funding: Private Foundation Support.

PUB167
Trends in Access to Care in Adults with Kidney Disease, United States 2002-2011
Mukoso N. Ozieh,1 Kinfe Gebreegziabher Bishu,2 Rebekah J. Walker,2 Leonard Egede,2 Nephrology, MUSC, 2‘Center for Health Disparities Research, Internal Medicine, MUSC, Charleston, SC.

Background: Access to healthcare is essential in order to attain health equity in the US. Studies on access to healthcare in kidney disease (KD) are scant and there are no studies on national trends in access to healthcare in people with KD. This study aims to evaluate trends in access to healthcare, prescription medication and factors associated with access to healthcare in people with KD.

Methods: Data on 4,399 adults with KD aged ≥18 from the Medical Expenditure Panel Survey were analyzed. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157-acute/ unspecified renal failure; 158-chronic renal failure; 160- acute or chronic renal failure and 161 - other diseases of kidney and ureters. Access to healthcare was defined as having a usual provider, ability to get necessary medical care and no delay in getting medical care. Assess to prescription medications was defined as ability to get necessary prescription and no delay in getting prescription. We used unadjusted and adjusted logistic regression to examine factors associated with access to care overtime. Covariates included demographics and comorbidities.

Results: Of the 4,399 adults with KD, 81% and 97% reported having access to medical care and prescription medications respectively. Access to medical care was stable while access to prescription improved over time in people with KD. Factors associated with increased access to medical care were age ≥65, higher income, high income, region, sociability-hypertension while marital status, being uninsured, regional community and comorbidity- joint pain were associated with decreased access to medical care. Factors associated with increased access to prescription were Hispanic race, age ≥65 and 4+ college degree while being uninsured, regional region and comorbidities – diabetes and joint pain were associated with decreased access to prescription medication.

Conclusions: Access to medical care has remained stable and access to prescription medication in people with KD has improved over time. Further studies on access to healthcare in people with KD compared to the overall US population are needed.

PUB168
Patient-Centered Care in United States Adults with Kidney Disease
Mukoso N. Ozieh,1 Kinfe Gebreegziabher Bishu,2 Rebekah J. Walker,2 Leonard Egede,2 Nephrology, MUSC, 2‘Center for Health Disparities Research, Internal Medicine, MUSC, Charleston, SC.

Background: Patient-centered care is a quality of personal, professional, and organizational relationships. There is no studies on factors associated with patient-centered care in patients with kidney disease (KD). This study examines trends in and factors associated with patient-centered care (PCC) in people with KD.

Methods: Data on 3,868 adults with KD aged ≥18 from the Medical Expenditure Panel Survey (MEPS) Household Component were analyzed. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157 - acute and unspecified renal failure; 158 - chronic renal failure; 160 - acute or chronic renal failure and 161 - other diseases of kidney and ureters. Patient-centered care was ascertained if the usual care provider asked about prescription medications and treatments other doctors may give them; showed respect for mental, traditional, and alternative treatments that the patient is happy with; asked the person to help make decisions between a choice of treatments; presented and explained all options to the person; and spoke the persons language or provided translator services if person is uncomfortable speaking in English. We used unadjusted and adjusted poison regression to examine the association of patient-centered care overtime. Covariates included demographics and comorbidities.

Results: Of the 3,868 adults with KD, 3%, 7%, 22%, 63% and 4% reported a positive response to 1, 2, 3, 4, and 5 out 5 questions on patient-centered care respectively. Patient-centered care was significantly reported in 2010/2011. Hispanic race was significantly associated with increased while residence in the west was associated with decreased patient-centered care. Compared to 2002/2003, year 2004/2005 and 2010/2011 were significantly associated with increased patient-centered care in the poison regression analysis.

Conclusions: Patient-centered care in people with kidney disease has improved in recent years. Prospective studies examining the impact of patient-centered care on kidney disease outcomes especially end stage renal disease is imperative.

PUB169
Hypertension and Correlating Factors in a Minority-Rich Population
Andrew A. Lin,1 Jennie Kuo,2 Li-Li Hsiao,2 Harvard College, Cambridge, MA; 2Renal, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background: Analysis of demographic variations in hypertension (HTN) in minority-specific populations presents a major opportunity for understanding the factors that influence chronic kidney disease (CKD). This study analyzes the influence of various factors in BP control in a minority-rich population.

Methods: Data from 417 participants from minority populations in the Boston area (38.4% Black; 17.6% White; 5.0% other race) was sampled via Kidney Disease Screening and Awareness Program screenings from 2012-2014. Participants were assessed via questionnaire for awareness of their BP, healthcare, insurance, and an assessment of their own health as well as their race, gender, age, and education. Participants then had their systolic (SBP) & diastolic (DBP) blood pressure measured, which was in turn classified according to American Heart Association guidelines & analyzed via T-tests & one-way ANOVA.

Results: Of the 417 participants, 28.8% had normal BP, 47.2% were pre-HTN (130 ≤ SBP < 140 or DBP < 90), 18.5% had stage 1 HTN (140-160/90-100), & 5.5% had stage 2 HTN (>160/100). Participants aware of their HTN had higher SBP (p=0.001) & DBP (p=0.007) than those who self-reported HTN. Men had significantly higher SBP & DBP than women (p=0.002, p=0.003, respectively), & individuals with little/no education had higher SBP than those with college (p=0.005) or post-graduate degrees (p=0.001). Younger age groups (below 30 years: mean BP 125/76) had significantly lower BP than older age groups (60-69+: years: mean BP 136/81); p<0.0001 & p<0.037 for SBP & DBP. Notably, no significant differences in SBP among ethnicities emerged.

Conclusions: Our results revealed that awareness of HTN status, gender, education level & age influence BP variations in minority communities. Services tailored to these factors may help reduce HTN prevalence in minority communities. Services tailored to these factors may help reduce HTN prevalence in minority communities.

Funding: Private Foundation Support.

PUB170
Veterans Affairs (VA) eKidneyClinic: A Freely-Available Online Tool to Help Close the Chronic Kidney Disease (CKD) Patient Education Gap
Devasinna Choudhury,1 R. Brooks Robey,2 Rosemary M. Pries,3 Dorian R. Schatell,1 Susan T. Crowley.4 VA eKidneyClinic (http://ckd.vacloud.us). This freely-available, Veteran-centered, virtual health literacy, and varied, fragmented presentation of patient education materials (PEMs) compound the gap in understanding CKD.

Methods: To address these deficiencies, VA developed a comprehensive web tutorial, VA eKidneyClinic (http://ckd.vacloud.us). This freely-available, Veteran-centered, virtual...
Leveraging Predictive Modeling to Improve the Participant Identification Process for Transition to Dialysis Support Programs

**Background:** Evidence demonstrates that renal care management is beneficial to patients suffering from late-stage chronic kidney disease (CKD) and end-stage renal disease (ESRD), especially around the time of transition to dialysis. Integrated care management solutions provide assessment, education, and care coordination. Engagement in these programs improves health outcomes, including compliance with dialysis schedules and vascular access, and also reduces costs.

**Methods:** Traditionally, patients are identified for renal care management programs via a qualified estimated glomerular filtration rate (eGFR) lab value of $<20\text{mL/min/1.73}\text{m}^2$. However, since eGFR is not always available, there may be a gap in identifying people who could benefit from this type of support. A predictive model (PM) was developed to identify candidates for a transition to dialysis program. The PM identifies individuals with CKD over the prior 12 months and determines their likelihood of starting dialysis within the subsequent 12 months. It is based on claims, demographics, and lab and consumer data.

**Results:** 630 CKD patients with DM attending CKD clinic at our trust were identified. 195/630 (31%) of patients had diabetic nephropathy. 54.6% (100/195) had progressive CKD, but only 57% (37/100) of these patients attended a diabetic clinic. Conversely, 45.4% did not have progressive CKD, potentially representing a group of patients who could be safely monitored by general physicians. Patients with progressive diabetic nephropathy were more proteinuric than those with stable CKD (161 vs.46mg/mmol, p=0.004) but did not significantly differ in terms of age, weight, glycemic control or BP. 9.2% (58/630) were lost to follow-up from nephrology services, 31% (18/58) of this subset of patients continued to attend the diabetic clinics and 69% (40/58) were lost to follow-up from both diabetic and renal services.

**Conclusions:** Not all patients with diabetic nephropathy develop progressive CKD. Identifying patients (e.g. low-level proteinuria) who could be safely monitored by general physicians may relieve pressure on CKD clinic and reduce hospital visits for patients. However, many patients with progressive CKD were not being monitored in a diabetic clinic, potentially missing out on specialist interventions. Development of a joint diabetic-renal clinic could streamline care and improve management for these patients.

**Funding:** Clinical Revenue Support

<table>
<thead>
<tr>
<th>Year</th>
<th>CKD cases</th>
<th>Controls</th>
<th>% change in eGFR</th>
<th>% change in eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>53.166</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2008</td>
<td>50.224</td>
<td>2007-2008</td>
<td>1.72%</td>
<td>2007-2008</td>
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<tr>
<td>2009</td>
<td>47.449</td>
<td>2008-2009</td>
<td>5.43%</td>
<td>2008-2009</td>
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<tr>
<td>2010</td>
<td>47.651</td>
<td>2009-2010</td>
<td>-0.32%</td>
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<td>2011</td>
<td>42.846</td>
<td>2010-2011</td>
<td>10.0%</td>
<td>2010-2011</td>
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<tr>
<td></td>
<td>Net change in eGFR</td>
<td>2006-2011</td>
<td>19.41%</td>
<td>2006-2011</td>
</tr>
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</table>

Table 1. Adjusted rate of decline in GFR across time

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

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926A
There is a positive correlation between IL6 and all oxidative stress markers and an inversely correlation with eGFR (all, p<0.05). We divided CKD patients in CDK1-2 (n=10) and CKD3-5 (n=15): a significant higher level of oxidative stress was observed in CKD3-5 (p<0.008).

Conclusions: CKD is characterized by ROS and RNS disequilibrium and inflammation that promote additional damage to the kidney and to distal tissues with development and progression of concomitant diseases. This pilot study demonstrates the significantly heightened presence of dual oxidative stress pathway induction in CKD patients that increase with the progression of CKD: each stage of CKD could be characterized by differing levels of ROS/RNS disequilibrium. Our findings indicate that oxidative stress is a potential therapeutic target, as it promotes inflammation by ROS/RNS-linked pathogenesis. Future research should focus on interventions that aim to reduce oxidative stress and inflammation in patients with various stages of CKD and slow the progression of CKD during its early stages.

**PUB175**

Comparative Biomarker Analysis Reveals Serum and Urine sTNFR1 Correlates with eGFR and Albuminuria in Man

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**Background:** It has been demonstrated that soluble tumor necrosis factor receptors (sTNFR1 & sTNFR2) are elevated in serum of patient cohorts with various renal disease etiologies with a strong association to early renal decline with or without proteinuria. The current study was designed to gain further insight into the relationship of renal function to sTNFR1 and sTNFR2. Serum and urine samples from a recently completed clinical study in high risk subjects undergoing non-cardiac surgery. A subset of baseline serum and urine samples from patients with and without CKD (mean age of 70, 64% male, mean eGFR of 58 ml/min/1.73 m², and mean total urinary protein concentration 70 g/l) were evaluated to assess sTNFR1 and other select BMs reflective of progression of DN, CV risk, inflammation, fibrosis or renal injury.

**Methods:** Samples were selected based on medical history (DM, DN, other CKD, or no renal disease) and stratified for analysis based on eGFR values. All samples examined were from baseline/pre-dose collections prior to drug administration or surgery and analyzed in blinded manner.

**Results:** In serum, several BMs correlated with eGFR with sTNFR1 (P <0.0001) and uromodulin (P =0.0004) being significant but moderate for FGF-23 (P<0.01), and ADMA (P<0.01). In urine, results revealed that several BMs correlated with eGFR with a strong significance for sTNFR1 (P<0.0001) as well as complement C9 (P=0.011) and IC3b (P=0.013). Significant correlations were also observed for qualified biomarkers such as NGAL (P=0.01), albumin (P<0.001), and cystatin C (P=0.05). sTNFR1 in urine also strongly correlated with albuminuria (P=0.0002) and UACR (P<0.0001).

**Conclusions:** Our studies demonstrate that sTNFR1 correlates with renal functional decline across a wide eGFR range (22 to 116 ml/min/1.73 m²) regardless of renal disease, which was assessed in both serum and urine. Limitations of this preliminary study are small sample size and use of static eGFR values. Additional correlation analyses in longitudinal cohorts can shed further light into the relationships of sTNFR1 and other BMs to CKD.

**Funding:** Pharmaceutical Company Support -Abbvie

**PUB176**

The Association of Plasma Uric Acid with Renal Vascular Lesions and Intertstitial Fibrosis in Biopsy-Confirmed Kidney Disease

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**Background:** Elevations in plasma uric acid (PUA) have been hypothesized to play a pathogenic role in the development of chronic kidney disease (CKD) through multiple mechanisms, including mitochondrial dysfunction, oxidative stress, endothelial dysfunction, vascular smooth muscle proliferation, and intra-renal inflammation.

**Methods:** We measured PUA in plasma samples obtained from 272 patients on the day of native kidney biopsy at three tertiary care hospitals in Boston, MA. We compared PUA against measures of kidney function and pathology, including estimated glomerular filtration rate (eGFR) and adjudicated semi-quantitative measures of kidney pathology using Spearman correlation coefficients. Arterial and arteriolar sclerosis/hyalinosis were classified as none (0), mild (1), moderate (2), or severe (4). Fibrosis was classified as 0% (1), 1-10% (2), 11-25% (3), 26-50% (4), and > 50% (5) of cortical volume.

**Results:** The primary indications for kidney biopsy were proteinuria in 61%, hematuria in 33%, abnormal eGFR in 35%, and nephrotic syndrome in 14% (sum exceeds 100% due to multiple indications). Mean age was 51.2 ± 16.0 yrs, 53% were women, 18% were black, and median eGFR was 50 (IQR 30–80) ml/min/1.73 m². Median PUA was 6.3 (IQR 5.1-7.5) mg/dl, and was inversely correlated with eGFR (r=-0.43) and positively correlated with arterial sclerosis (r=0.21), arteriolar hyalinosis (r=0.23), and interstitial fibrosis (r=0.28) (p<0.05 for all). The association between PUA and fibrosis was observed and no longer statistically significant after adjustment for eGFR. Findings were generally consistent in subgroup analyses of those with diabetes, glomerulonephritis, vascular disease, and tubulointerstitial disease.

**Conclusions:** We found no independent associations between PUA and semi-quantified measures of kidney pathology. The cross-sectional associations of PUA with renal vascular lesions and interstitial fibrosis appear to be confounded by eGFR.

**Funding:** NIDDK Support

**PUB177**

Association of Plasma Sphingomyelins and Ceramides with Chronic Kidney Disease and Glomerular Filtration Rate

Maria Lourdes Gonzalez Suarez, 1 Vesa D. Garovic, 1 Norman James Haughey, 2 Veera Venkatat Ratnam Bandaru, 2 Susan Resnik, 2 Luigi Ferrariu, 2 Michelle M. Mielke. 3

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**Background:** Sphingolipids are a class of bioactive lipids linked to insulin resistance and diabetes. Ceramides have been implicated in acute renal failure and diabetic nephropathy. We cross-sectionally examined the associations of plasma ceramides and sphingomyelins (SM) with glomerular filtration rate (GFR) and Chronic Kidney Disease (CKD).

**Methods:** Baltimore Longitudinal Study of Aging participants (N=486) with plasma ceramides, SM and GFR were included (median age 63, 58% men); 23 had CKD defined as GFR <60 ml/min. Ceramides and SM were quantitatively measured using a HPLC-coupled electrospray ionization tandem mass spectrometer. Logistic regression was used to determine the association between the log transformed sphingolipids and odds of CKD, adjusting for age, sex, and race. Among participants without CKD, linear regression was used to examine the association between the sphingolipids and GFR adjusting for age, sex, race, BMI, and hypertension.

**Results:** Higher levels of all SM were associated with increased odds of CKD: each log unit increase in SM C18:1 was associated with six-fold increased odds of CKD (OR=6.92, p=0.002). Among individuals without CKD, higher SM were also associated with lower GFR. This association was most pronounced among the 290 individuals without diabetes or pre-diabetes: each log unit increase in SM C18:1 was associated with lower GFR (b=-8.40, p=0.002).

**Conclusions:** These results suggest that elevated plasma SM are associated with CKD. Likewise, among those without CKD, elevated SM are associated with lower GFR. The cross-sectional study design limits specific conclusions on the mechanisms and temporality of these associations but suggests that further research is warranted.

**Funding:** Other NIH Support - U01 AG37526 (National Institutes of Health/National Institute on Aging)

**PUB178**

Clinical and Pathologic Predictors of Progression to End Stage Renal Disease following Renal Biopsy

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1Div of Nephrology, MGH, Boston, MA; 2Dept of Pathology, MGH, Boston, MA.

**Background:** The value of renal biopsy in prognosis of chronic kidney disease remains unclear. Irreversible, chronic changes such as interstitial fibrosis and glomerulosclerosis are thought to provide prognostic information. We sought to define the relative prognostic value of biopsy pathology and clinical factors for predicting progression to end stage renal disease (ESRD).

**Methods:** Retrospective, single center review of renal biopsies performed between 2004-2014 in four kidney diseases. Cox regression was used to evaluate nine pathologic findings on light microscopy and 21 clinical variables as potential predictors of progression to ESRD.

**Results:** 231 cases were reviewed (34% IgA nephropathy, 29% focal segmental glomerulosclerosis, 19% tubulointerstitial disease, 18% diabetic nephropathy). 83/231 (36%) subjects progressed to ESRD within 5 years follow-up. Median estimated glomerular filtration rate (eGFR) at time of biopsy was 32 [IQR: 18, 54] ml/min. Median percent interstitial fibrosis was 20% [IQR: 10%, 40%]. In multivariable Cox regression adjusting for pathologic diagnosis and eGFR at the time of biopsy, independent predictors of progression to ESRD by 5 years of biopsy were: interstitial fibrosis > 20% (HR 1.94 [95% CI 1.09, 3.44]; p=0.02), presence of endocapillary inflammation (HR 2.35 [2.12, 4.53]; p<0.01), and presence of arteriosclerosis (HR 2.50 [1.01, 5.05]; p=0.05), history of liver disease (HR 1.55 [0.95, 2.53]; p=0.08) and congestive heart failure (HR 1.85 [0.99, 3.49]; p=0.06).

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Severe AKI was induced in male adult CD-1 mice, while blood urea and creatinine levels were statistically different between two groups. The rats were killed to get kidney tissues for pathological examination.

Results: The concentration of IS by High performance liquid chromatography-fluorescence detection (HPLC-FLU) and urea and creatinine by automatic biochemical analyzer, while the rats were killed to get kidney tissues for pathological examination.

Conclusions: Mutagenic lactobacilli can not only reduce serum concentration of IS, but also lowering the expression of TGF-β1 < 0.05). And also Blood urea and creatinine levels were statistically different between two groups. 

Funding: NIDDK Support, Other NIH Support - NIA

PUB180

Lower Dietary Intake of Magnesium Is Associated with Faster Decline in Kidney Function: The Healthy Aging in Neighborhoods of Diversity Across the Life Span Study

Background: Lower dietary magnesium intake has been associated with higher prevalence of chronic kidney disease (CKD). We hypothesized lower dietary magnesium intake would be associated with more rapid decline in kidney function.

Methods: Participants with estimated glomerular filtration rate (eGFR) ≥ 60mL/min/1.73 m² at baseline (2004-2008) of the population-based, Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study were followed for a median of 4.7 years. Baseline dietary magnesium intake was calculated from two 24-hour dietary recalls. eGFR was calculated from serum creatinine using the CKD-EPI equation. We defined rapid decline as eGFR decline ³3% per year. The association between dietary magnesium intake and eGFR decline was evaluated using Cox regression.

Results: Among 1,326 participants, those with lower dietary magnesium intake (tertile 1 vs. 3) were significantly younger (mean age of 46 vs. 49 years), more likely to be African-American (67% vs. 48%) and male (45% vs. 31%); had lower mean body mass index (BMI, 29 vs. 30 kg/m²), higher mean baseline eGFR (99 vs. 94 mL/min/1.73 m³) and lower prevalent diabetes (10% vs. 18%); p<0.05 for all. In the overall study population, eGFR was stable without any decline (mean change: 0.1 mL/min/1.73 m³) while 189 participants experienced an eGFR decline ³3% per year. Lower dietary magnesium intake was associated with higher risk of eGFR decline ³3% per year (tertile 1 vs. 3, hazard ratio 1.9, 95% confidence interval: 1.1, 3.3) adjusted for socio-demographics, baseline eGFR, prevalent diabetes and hypertension status, BMI, serum magnesium, total energy intake, and dietary intake of calcium, potassium, and phosophorus.

Conclusions: Among persons with preserved eGFR, we detected a significant association between lower dietary Mg intake and increased risk of rapid kidney function decline independent of traditional CKD risk factors. These results highlight the importance of magnesium intake in the overall diet for the preservation of kidney function.

Funding: NIDDK Support, Other NIH Support - NIA

PUB181

Renin-Angiotensin System: A Possible Mechanism for AKI-CKD Continuum

Background: Based on many clinical observations and studies, acute kidney injury (AKI) was now regarded as an important risk factor causing chronic kidney disease (CKD). Not only does CKD lead to end-stage renal disease (ESRD), but also increases the risk of cardiovascular disease or even death. Clinical studies often disclose that the higher the AKI severity of a patient is, the more likely her/his kidneys progress into CKD. To this end, the mechanism underlying the progression of kidneys into CKD after AKI remains illusive. Since the higher severity of the AKI leads to more reduction of nephron numbers, we propose that activation of renin-angiotensin system (RAS) may be involved in the progression to CKD after recovery from AKI.

Methods: Severe AKI was induced in male adult CD-1 mice by right uni-nephrectomy (Nx) followed by ischemia-reperfusion injury of left kidney 2 weeks later. Drinking water was replaced with a type 1 angiotensin II receptor blocker losartan or direct vasodilator hydralazine administered to mice from 4 weeks after surgery. Mice with Nx only were served as the control.

Results: Compared to Nx group, AKI mice showed acute rise of plasma creatinine levels on day 2 after Nx+1RI surgery, which decreased to baseline on day 7. Moreover, elevated systolic blood pressure and increased urinary ACR were noted since 4 weeks after Nx+1RI surgery. During the 4-month experimental period, progressive increase of urinary ACR and plasma levels of creatinine were noted. On the contrary, systolic blood pressure, urinary ACR and plasma creatinine level were normalized in mice administered with losartan since 4 weeks after Nx+1RI surgery. However the increase of urinary ACR and plasma creatinine level were not prevented in mice administered with hydralazine despite similar normalization in blood pressure.

Conclusions: These data suggest that RAS activation may underlie the mechanism for development of CKD in mice after recovery from AKI. Future studies are needed to explore the effect of RAS blockade in prevention of CKD and its pressure in patients recovered from AKI.

Funding: Government Support - Non-U.S.

PUB182

The Renal Effects of Neprilysin Inhibition in Heart Failure and Hypertension

Background: Neprilysin inhibitors (NEPi) represent an emerging therapeutic option for treatment of hypertension (HTN) and heart failure (HF) through enhancement of natriuresis. While these agents have shown promising results with regards to lowering blood pressure (BP) and HF events, their impact on the kidney remains largely unknown.

The aim of this study is to evaluate the currently available evidence on the effect of NEPi use on kidney-related parameters in patients with HTN or HF.

Methods: A search of articles cited in PubMed database from 1995 to 2015 using key words “neprilysin”, “heart failure” and “hypertension” found 237 articles. Animal studies were excluded. Those studies containing kidney-related parameters such as serum creatinine, glomerular filtration rate (GFR), or ACR were selected. Relevant data including changes in renal function, blood pressure and mortality were extracted and compared.

Results: A total of 42,487 patients from 12 randomized controlled trials with data pertaining to NEPi use were included (8 in HTN and 4 in HF). Seven studies used NEPi combined with ACE-inhibitors andARB, and 1 with endothelin converting enzyme inhibitors. The follow up periods ranged between 7 days and 27 months. All studies in HTN (including 27,401 patients) reported significantly better BP lowering effect for NEPi compared to control group, while 94% of the patients in the HF studies presented with improvement in left ventricular remodeling. Although most studies did not reach endpoint, all HF studies (including 15,086 patients) showed less frequent renal impairment (expressed as increase in plasma creatinine and ACR) in NEPi group compared to placebo group (12%).

Conclusions: Current evidence suggests that in patients with HF, NEPi can lower HF-related events and mortality while potentiating favorable impact on renal function. In patients with HTN, although NEPi have been shown to reduce BP, there is no conclusive evidence of their role in improvement of renal function in this setting.
The Differences of Renal Protective Effect by Hyperuricemia Treatment Using Febuxostat in Various CKD Subgroups
Akinori Yamaguchi, Makoto Harada, Yousuke Yamada, Koji Hashimoto, Makoto Higuchi, Yuji Kamiyo. Dept. of Nephrology, Shintei Univ, Mutsuno, Nagano, Japan.

Background: We often experience the CKD cases exhibiting the attenuation of eGFR decline by hyperuricemia treatment using febuxostat. However, renal protective effect by the hyperuricemia treatment has not yet been established. We hypothesize that the therapeutic response of febuxostat treatment might differ among various subgroups of CKD patients.

Methods: To investigate the difference of the therapeutic response in CKD patients, 272 outpatients with hyperuricemia who were treated by febuxostat from May 2011 to March 2015 were enrolled. Patients undergoing hemodialysis and/or peritoneal dialysis treatment, and patients lacking essential clinical data were excluded. Finally, 178 patients were analyzed. Correlation coefficient between the average of serum uric acid level and the eGFR variation during 6 months after the treatment were statistically investigated in various clinical subgroups.

Results: In all patients, significant correlation between the average of serum uric acid levels and the eGFR variation was detected (Brockman’s correlation coefficient r=-0.163, p=0.019). This significant correlation was also detected in each patient groups as follows: male patients (n=121, r=-0.211, p=0.020), non-elderly (below 70 years old) patients (n=107, r=-0.261, p=0.007), patients whose systolic blood pressure were below 130 mmHg (n=72, r=-0.238, p=0.044), patients without dyslipidemia (n=133, r=-0.316, p=0.005) and non-diabetic-nephropathy patients (n=133, r=0.184, p=0.034). However, the significant correlation was not detected in each opposite subgroups.

Conclusions: The current study suggest that therapeutic response of febuxostat treatment might be well in each CKD subgroups, including male, non-elderly, non-hypertension, non-dyslipidemia and non-diabetic-nephropathy. It is possible that various risk factors of atherosclerosis conceal the beneficial renal protective effects of hyperuricemia treatment using febuxostat.

Urinary RBP as an Independent Predictor of “Hard Composite Outcome” in Albuminuric Diabetic Nephropathy
Gesime Fernandes Tavares, Roberto Zatz, Silvia M. Titan. Renal Div. Dep. Clinical Medicine, Faculty of Medicine, Univ. of Sao Paulo, Sao Paulo, Brazil.

Background: The current search for new biomarkers in CKD is intense, with particular emphasis on hard end-points, such as ESRD, creatinine duplication and cardiovascular and overall mortality. In this analysis, we sought to evaluate which baseline clinical and laboratory variables were related to ESRD/mortality in 56 patients with albuminuric diabetic nephropathy after mean follow-up time of 5 years.

Methods: Baseline clinical and laboratory data of 56 participants of a clinical trial were evaluated as predictors of major outcomes (primary outcome: PO: ESRD, creatinine duplication or mortality). Mann-Whitney and chi-square tests were used for univariate analyses. Several univariate and multivariate COX regression models were built on the risk of PO. Kaplan-Meier curve and LOG rank test were also performed.

Results: PO occurred in 39 participants after a mean follow-up time of 5 years (70%). In univariate analyses, sex, creatinine clearance, 24h proteinuria, uRBP, urinary VEGF and serum TGF-beta were related to the event group. In univariate COX regression models, sex, proteinuria, creatinine clearance, VLDL, cholesterol, ferritin, PTH, RBP and uMCP-1, uVEGF and uTGF-beta were significantly associated to the risk of PO. However, after adjustments for creatinine clearance and proteinuria, only uRBP and uMCP-1, uTGF-beta and uVEGF remained significantly associated to PO. In a stepwise model, only creatinine clearance (HR 0.98, 95%CI 0.97 - 1.00, P=0.06) and uRBP (HR 1.13, 95%CI 1.07 - 1.20, P=0.0001) were left as independent predictors of PO in this population. KM curve for uRBP is shown in figure 1.

Conclusions: Urinary RBP is an independent predictor of PO in albuminuric diabetic nephropathy. Its role as a risk biomarker should be further explored in larger studies of CKD patients.

Association Between Urinary RBP and Renal and Cardiovascular Risk Factors in a Population with CKD: The Progredir Study
Maria Alice Muniz Domingos,1 Alessandra C. Goulart,2 Paulo Lotufo,2 Isabel M. Bensoner,2 Silvia M. Titan.1 Renal Div. Dep. Clinical Medicine, Faculty of Medicine, Univ. of Sao Paulo, Sao Paulo, Brazil,2 Clinical Research Center, Univ Hospital, Sao Paulo Univ, Sao Paulo, Brazil.

Background: Urinary RBP (uRBP) has been related to the risk of ESRD in glomerulonephritis and renal transplant. However, its role in CKD is not well established.

Methods: Baseline clinical and laboratory data on 454 participants of the Progredir Study was analysed. uRBP was measured by an immunoenzymatic assay with monoclonal antibody. Descriptive data is presented according to tertiles of uRBP, and correlation coefficients were calculated. Several univariate and multivariate linear regression models were built. Lastly, binary regression models were built on the risk of presenting more advanced CKD (class IV-V versus class II-III).

Results: In the descriptive data, the tertiles of uRBP were significantly related to sex, diabetes, renal function, SBP, glcated hemoglobin, HDL, proteinuria, WHR, phosphorys, acidosis, albumin, pulse-wave velocity (PWV), left atrium diameter (LAD), systolic and diastolic left ventricular diameters and ejection fraction. These results were confirmed by correlation. In the univariate regression models, diabetes, SBP, WHR, renal function, proteinuria, phosphorus, albumin, lipids, glycated hemoglobin, PWV and echography variables remained related to uRBP. However, after adjustments, only renal function, proteinuria, SBP, bicarbonate and LAD remained associated to uRBP.

Table: Stepwise multivariate linear regression models on log of urinary RBP.

Conclusions: Urinary RBP is independently related to cardiovascular risk factors in the CKD population. Its role as a biomarker of hard clinical end-points should be further explored.

Treatment of Subclinical Hypothyroidism and the Progression of Chronic Kidney Disease
Padmavathi Mali,1 Sudheer Muduganti.2 Internal Medicine, Marshfield Clinic, Marshfield, WI.1 Nephrology, Univ of Wisconsin Hospitals and Clinics, Madison, WI.

Background: Evidence suggests that treatment of subclinical hypothyroidism may slow the progression of chronic kidney disease (CKD) and delay or prevent development of end stage renal disease (ESRD). The goal of this study was to provide additional evidence regarding the same.

Methods: Patients with subclinical hypothyroidism and CKD stages 3 or 4 were identified by retrospective chart review over a period of 6 years. Subjects were grouped based on L-thyroxine treatment. Subjects treated with L-thyroxine before first elevated thyroid stimulating hormone (TSH) were excluded. Index date was defined as the date of first L-thyroxine for treated patients. Index dates for untreated patients were assigned by random sampling of dates for treated TSH and serum creatinine values were captured from the electronic medical record. Change in eGFR (glomerular filtration rate) over time in treated and untreated patients was assessed using a linear random coefficients model in the subset with two or more eGFR results spanning a period of at least 6 months, both before and after the index date.

Results: A total of 258 patients meeting inclusion criteria were identified; 181 were treated with L-thyroxine and 77 were not. Treatment initiation began after the first elevated TSH in the study period for 110/181 subjects. Upon analysis, before the index date, eGFR showed a significantly decreasing trend (p<0.001) that was not significantly different

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between treated and untreated patients (p = 0.593). After the index date, the rate of gFR changes showed a similar trend (p = 0.017) for a gradual increase, but again this was not significantly different between groups (p = 0.522).

Conclusions: The similar results in the two groups, regardless of L.

### PUB87

**Effect of Hyperuricemia on the Blood Pressure-Dependent Proteinuria in Non-Nephrotic Chronic Kidney Disease**

Kentaro Kojiiura, 1,2 Ryo Yamamot, 2

**Background:** Patients with chronic kidney disease (CKD) are suggested to be highly susceptible for hypertensive renal damage due to disrupted autoregulation system in different arteriole. We reported that hyperuricemia was associated with renal arteriolar hyalinosis in the CKD patients. However, effect of hyperuricemia on a relationship between blood pressure (BP) and proteinuria is unknown in CKD patients.

**Methods:** A total of 288 consecutive patients who underwent renal biopsy at our department between 2003 and 2007 were considered for the study. We excluded patients receiving renin angiotensin inhibitor and nephrotic CKD patients defined as serum albumin equal or more than 3 g/dL, leaving us with 117 patients (57 men and 60 women) for analysis. Arteriolar hyalinosis were assessed by semi quantitative grading for arterioles. We compared the relationship between systolic BP and log-transformed urine protein (g/gCr) in the patients with or without hyperuricemia.

**Results:** The mean ± standard deviation values for age, BP, estimated glomerular filtration rate (eGFR), and uric acid were as follows: 63 ± 18 years, 126 ± 20/75 ± 12 mmHg, and 84 ± 37 ml/min/1.73 m², respectively. In the patients with hyperuricemia (n=63), systolic BP was significantly correlated with log-transformed urine protein (r=0.45, p=0.004). In contrast, there was no significant correlation between them in the patients without hyperuricemia (r=0.07, p=0.60). In the multiple regression model (R²=0.25, p=0.01), systolic BP was significantly correlated with log-transformed urine protein β(0.33, p=0.02) independent of age, sex and classical risk factors in the patients with hyperuricemia. However, its statistical significance was disappeared after additional adjustment with urinary hyalinosis.

**Conclusions:** These results suggested that hyperuricemia might potentiate the susceptibility for hypertensive glomerular damage via disrupted autoregulation in non-nephrotic CKD patients.

### PUB88

**HCV Independently Affects Kidney Function Among HIV Co-Infected Individuals**

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**Background:** Predictors of chronic kidney disease (CKD) include increasing age, hypertension and diabetes. Hepatitis C (HCV) infection has also been associated with increased risk for CKD. We sought to determine the relative contribution of HCV vs other co-morbidities on kidney dysfunction among individuals with HIV.

**Methods:** We analysed data from HIV-positive patients enrolled in the DC HIV Clinical Cohort study at Georgetown University Hospital (2011-2014). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. Analyses were conducted stratified by HCV status. Chi square, Cochran–Mantel–Haenszel and Breslow Day Test statistics were performed to determine factors associated with normal kidney function (eGFR > 90 ml/min/1.73 m²), compared with participants with decreased kidney function, stage 2 and 3 (≥30 eGFR <89) using SAS v9.4.

**Results:** Among 771 participants, median age was 48, 73.4% male, 50.3% black, median CD4+ T cell count 546.5 cells/μL, and HIV RNA <20 copies/μL 93 (12.1%) had HCV co-infection. There was significantly higher prevalence of stage 2-3 kidney dysfunction with HIV/HCV co-infection than HIV mono-infection (35% vs. 19%, p=0.0016; OR, (95% CI) 2.1 (1.3-3.6)). Prevalence of hypertension, diabetes, hyperlipidemia and chronic Hepatitis B was similar between HIV and HIV/HCV co-infected groups. Presence of these co-morbidities was not a confounder in the increased risk for CKD with HIV/HCV (Mantel-Haenszel chi-square OR, (95% CI) 2.1 (1.3-3.6) for hypertension, 2.18 (1.3-3.6) diabetes and 2.2 (1.3-3.6) hyperlipidemia (Breslow Day test p values<0.05 for each co-morbidity).

**Conclusions:** We identified a strong association between HIV/HCV co-infection and reduced kidney function independent of co-morbidities usually associated with kidney dysfunction in this group with well controlled HIV. Further investigation is needed to study the mechanisms by which HCV affects kidney function.

**Funding:** Other NIH Support - Division of AIDS. NIAID

### PUB89

**Vitamin D Deficiency Is a Cause and a Result of Renal Dysfunction in Rheumatoid Arthritis**

Suad Ma Hanaww, Issa AL Salmi.

**Background:** Asymptomatic kidney dysfunction is common in RA. Low vitamin D levels increase susceptibility to development of RAA disease activity. Sequential hydroxylations occurs in liver & kidney to form active 1,25-VD & patients with kidney failure are often resistant to VD & suffer from 2

**Methods:** A total of 475 patient (25-VD level & GFR calculated by MDRD at Rheumatology clinic visit. Univariate linear regression analysis carried out to determine the relationship between 25-VD and eGFR, other renal parameters & RA inflammatory markers.

**Results:** In univariate analysis of 52 RA(475M) with mean age 46±13 years(46±12, M±SD), 25-VD level is 40±29 mmol/l(INR:50-80) & GFR is 134±49 ml/min/1.73 m². Univariate linear regression showed a negative relationship between 25-VD level & eGFR (p=0.041,CI 0.23, 0.01), micro-albuminuria(p=0.046, CI 0.63, 0.01), CRP (p=0.01,CI 1.16, 0.16), neutrophil count (p=0.03,CI 1.67, 0.11). A positive linear relationship between GFR & weight (p=0.03,CI 0.06, 0.14), HSA(p=0.02, CI 0.11, 0.19) & BMI(p=0.009,CI 0.65 4.05), Ca(p=0.003, CI 7.24, 13.12 mmol/l).

**Conclusions:** Negative relationship between eGFR&25-VD, indicating a higher 25-VD as failure to convert to active form as GFR decreases. Extra-reformation of active VD requires a lower level of 25-VD>78 mmol/L & is necessary for maximal extra-renal production of 1,25VD. 1,25-VD is one of the most potent regulators of cellular growth & very effective modulator of the immune system. RA patients are present in most cells & tissues including body including activated T and B lymphocytes. Surveillance for VD deficiency, should be part of follow up as it may be linked to underlyng kidney dysfunction in RA. On the other hand, reduced VD might worsen RA & hence, increase the possibility of renal deterioration. VD supplementation may be needed early in management for prevention of kidney dysfunction & to reduce RA severity.

### PUB90

**Associations Between the Progression of Chronic Kidney Disease and Patient Demographics**

Daniele Xu, 1 Mark Stuart, 1 Barbara Cannon, 2 Chad Sowers, 1 John W. Larkin, 1 Sophia Rosen, 1 Carly R. Van Zandt, 1 Len A. Usvyat, 1 Yoongeun Oh, 1 Terry Ketchersid, 2 Dugan Maddux, 2 Franklin W. Maddux, 2 Unit of California, Santa Barbara; 2 Fresenius Medical Care North America; 3 Acumen Physician Solutions; 4 Frenova Renal Research.

**Background:** It is not well known if demographic factors are related to the progression of chronic kidney disease (CKD). We aimed to investigate whether age, sex, race, marital status and geography are associated with significant changes in kidney function determined by linear slopes of mean annual glomerular filtration rate (GFR).

**Methods:** We analyzed data from 90,240 CKD patients (Pts), who had significant declines in GFR, in the Fresenius Medical Care CKD Data Registry. Annual average decline in GFR was estimated on a per pt basis using linear regression with time as the predictor and GFR as the outcome variable. Univariate linear models were fitted for age groups (15-30, 31-40, 41-50, 51-60, 60-65, 65-75, 76-80, 80+ years), sex (female vs. male), race (African American, Caucasian, or other), marital status (married, unmarried) and geography (10 divisions of zip codes); a multiple linear regression model was utilized to investigate associations in mean annual GFR slope and demographics.

**Results:** In this analysis identifies significant associations between mean annual GFR slope and Pt demographics. CKD Pts age 15-30 years old were found to decline faster in GFR versus older Pts in all other age groups (p<0.001). Males were observed to decline slower in GFR versus females (p<0.001). Pts with a race of “other” were seen to decline slower in GFR versus Pts of African American or Caucasian race (p<0.001). The geographical location of Pts by zip code was observed to be associated with differences in GFR slope (p<0.001). The marital status of Pts was not found to be related to differences in slopes of GFR (p=0.218).

**Conclusions:** This study identifies that during the progression of CKD, younger Pts tend to have faster declines in GFR, as compared to older Pts; males have slower declines in GFR, as compared to females; Pts with a race of “other” have slower declines in GFR, as compared to Pts of African American or Caucasian race; and declines in GFR are related to Pt geography.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

### PUB91

**Correlation of Increased Th17 to Treg Cell Ratio with Endoplasmic Reticulum Stress in Chronic Kidney Disease**

On Tan.

**Background:** The study aimed to investigate the relationship between the regulatory immune network and endoplasmic reticulum stress (ERS) in patients with different stages of chronic kidney disease (CKD).

**Methods:** A total of 91 patients diagnosed with CKD were divided into different groups according to the stage of disease. Routine blood and biochemical tests were performed in parallel in healthy controls (n = 20). The frequencies of T helper type 17 (Th17) and regulatory T (Treg) cells in the overall T cell population was measured by flow cytometric analysis. Levels of Th17 cell (IL-17) and Treg cell (IL-10) cytokines and the ERS markers

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CHOP and GRP78 were measured by ELISA in serum samples collected from controls and patients. Correlations between each parameter and serum creatinine, an indicator of renal function, were analyzed by Spearman’s rank correlation and regression test.

**Results:** CKD stage showed a positive correlation with serum creatinine level, and increased levels of CHOP and GRP78 increased with advancing CKD stage. These correlations were most pronounced in patients in the CKD5 group, who also had the poorest response to hemodialysis and peritoneal dialysis treatment, compared with CKD5 patients in the non-dialysis group. Correlation analysis showed that serum levels of CHOP and GRP78 were independently and positively correlated with the ratio of TH17/Treg cells.

**Conclusions:** We have found that an increased TH17/Treg cell ratio and increased serum levels of ERS markers correlate with the progression of CKD. Our results indicate that the interplay between the immune network and management of ERS is closely associated with the pathogenesis of CKD. Although hemodialysis and peritoneal dialysis treatment manage chronic kidney conditions and prevent further deterioration of renal function, they have limited effects on improving the immune disorder and relieving ERS.

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

**PUB192**

**Metabolic Phenotyping in Thin Basement Membrane Nephropathy**


**Background:** Thin basement membrane nephropathy (TBMN) is the commonest cause of familial microscopic hematuria in children and adults, usually associated with benign clinical presentations and normal renal function. In a Greek-Cypriot cohort of TBMN patients, 35% of patients were shown to develop ESRD by age 70-years while ~50% of patients over 50-years developed CKD of variable degree. 40% of TBMN patients inherit heterozygous mutations in the COL4A3/A4 genes. What predisposes these TBMN patients to an adverse outcome and chronic kidney function decline during aging is presently unclear. Using Metabolic phenotyping techniques (NMR and mass spectrometry) our study should provide new biological insights in the development of extreme conditions in adult TBMN patients.

**Methods:** Spot urine samples from 81 patients with the same founder mutation, COL4A3-G1334E. Patients were classed; Severe (S) (n= 55): proteinuria >500 mg/day and CKD, irrespective of age. Mild (M) (n=26): normal kidney function with no proteinuria, regardless of age. It is expected that some will progress to CKD on follow-up. Samples were analysed by 600 MHz 1H NMR spectroscopy (detecting predominantly small molecules >1μM) and UPLC-MS (detecting water-soluble molecules >0.05 μM). Multivariate analysis (MVA) was used to elucidate class differences.

**Results:** MVA of M vs S samples revealed significant metabolic differences between the groups. From the UPLC-MS 15 MS features discriminate M and S. Among the discriminating metabolites discovered using NMR: citrate, glycine and creatinine were negatively correlated with M. Metabolite identification is ongoing, as well as application of additional metabolic profiling technologies.

**Conclusions:** Urine metabolic profiling may prove useful to classify renal disorders such as in the M and S cases of TBMN by their specific renal metabolite signatures and lead to the discovery of novel molecular disease biomarker profile patterns.

**Funding:** Other NIH Support - Financial support: EXPL-DTP-FTO/1792/2013; PDB/BD/10592/2014 (CGD)

**PUB193**

**Uric Acid and Its Association with Glomerular Filtration Decline Rate in an Incident Pre-Dialysis Population**

Pedro Viestra, Miguel Goncalves, Gil Silva. Nefrologia, Hospital Central do Panchal, Panchal, RAM, Portugal.

**Background:** Hyperuricemia is highly prevalent and there is cumulative evidence based on experimental models of its likely detrimental role in multiple pathologies, namely hypertension, vascular and renal diseases. Given hyperuricemia’s high occurrence on chronic kidney disease patients, we have tried to assess the association between uric acid basal levels (UABL) in an incident pre-dialysis population with renal function decline rate.

**Methods:** We have randomly selected incident patients with chronic kidney disease stages IV-V, referred to low clearance nephrology assessment from 2010 to 2014. We kept follow up until dialysis initiation, death or lost of follow up. Results: Sixty-six patients were selected with mean UABL of 8.15 (±2.10) mg/dl and a mean glomerular filtration rate of ~40ml/min/1.73m²/year. Of notice that by each unit increase in UABL an added variation of ~1.41 ml/min/1.73m²/year on glomerular filtration decline rate was observed (CI 95%, p=0.039). Adopting a linear mixed model analysis on UABL impact on glomerular filtration decline rate, despite adjustment for multiple demographic confounders and comorbidities, statistical significance (p<0.006) was conserved.

**Conclusions:** High UABL were associated, with statistical significance, to enhanced deterioration of kidney function.

**PUB194**

**Soluble α-Klotho in HIV-Infected Patients and Kidney Dysfunction**

Clara Dias, Sara Maia, Fernando G. Pereira, Pedro Pereira Campos, Ana Luisa Papoila, Alberto Ortiz, Sofia Pereira, Karina Soto.

**Background:** Chronic kidney disease is common among HIV-infected patients. Klotho is a new endocrine protein that exerts modulation of kidney solute transport and nephroprotection in AKI and CKD. We aim to explore whether levels of serum soluble α-Klotho are related with CKD progression in HIV-population.

**Methods:** As a part of an ongoing prospective study of HIV-infected patients, a cross-sectional analysis was performed. Glomerular filtration rate (eGFR) was estimated by CKD-EPI equation being Early Kidney Disease (EKD) when <90 ml/min/1.73m². Fractional excretion of phosphate (FePi) was also assessed and serum soluble α-Klotho was quantified by ELISA.

**Results:** A total of 169 HIV patients were included, 66% men, 75% non-Black, 55yo (48-62). Median values Klotho: 957 pg/mL (717-1213) and FePi: 21% (14-25). Klotho/FePi ratio was negatively correlated with eGFR when <75 ml/min/1.73m² (Spearman r=0.213, p=0.024), while the correlation was positive if eGFR>75 (Spearman r=0.410, p=0.002).

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No direct relation between Klotho and eGFR was found, while FePi was only related with eGFR<75 (Spearman r=0.396, p=0.002).

**Conclusions:** In HIV-infected patients, the association between Klotho and CKD progression has only significance when normalized by FePi levels. This association differed in opposite directions between patients with EKD and with normal kidney function, or in very early CKD stages. Of note, Klotho/FePi ratio seems to be better biomarker of EKD than Klotho itself.

**Funding:** Other NIH Support - Financial support: EXP:DTP-FTO/1792/2013; PDB/BD/10592/2014 (CGD)

**PUB195**

**Association of hsCRP and Kidney Damage Indicators in 5667 Adults Receiving Physical Examination**

Hao Zhang, Juan Mao, Bin Yi, Guo Xu, Wei Li. The Third Xiangya Hospital of Central South Univ.

**Background:** Chronic kidney disease and cardiovascular disease share many risk factors. Injury to the vascular endothelium, measured by elevated levels of serum high-sensitivity C-reactive protein (hsCRP), may play a role in kidney disease. We therefore examined the association of hsCRP with kidney damage indicators (ACR, eGFR) among 5667 participants receiving physical examination in the Third Xiangya Hospital.

**Methods:** We conducted a cross-sectional analysis of 5667 adults who received healthy physical examination in 2014. Spearman correlation analysis, multiple linear regression and multivariable logistic regression analysis were used to assess the correlation between hsCRP and uACR, eGFR. ROC curves was drawing to explore the statistically significant intercept point of hsCRP in predicting the occurrence of albuminuria and declining in eGFR. Multivariable logistic regression analysis was used to calculate the ORs for albuminuria, declining in eGFR according to the quartiles of hsCRP levels and other risk factors.

**Results:** Spearman correlation analysis showed that uACR was positively correlated with serum hsCRP (r=0.233, p=0.01). While hsCRP showed negative correlation with hsCRP (r=-0.135, p<0.01). Multiple linear regression analysis showed that hsCRP was independently correlated with uACR (B=0.205, p=0.156, P<0.01). While hsCRP didn’t enter the multivariate linear regression model of eGFR. Multivariable logistic regression analysis showed that male, central obesity, hypertension, diabetes and high hsCRP levels were independent risk factors for albuminuria. Based on the ROC curve, the 0.85mg/L of hsCRP was the best numerical value to predict the risk of albuminuria. Multivariable logistic regression analysis showed that the risk of albuminuria significantly increased in male, central obesity, hypertension, or diabetes combined with high hsCRP levels.
Conclusions: HoCRP was correlated with kidney damage indicators, and HoCRP was an independent risk factor of albuminuria. The 0.85μg/L of CRP was the best numerical value to predict the risk of albuminuria. Male, central obesity, hypertension, diabetes accompanying high serum CRP levels are more likely to have albuminuria.

PUB196
Serum Non-Protein Bound Homocysteine Levels Are Related with Chronic Kidney Disease Progression in HIV-Infected Patients Clara Dias, 1 Nelson Casimiro, 1 Nuno Coelho, 1 Ana R. Lemos, 1 Pedro Pereira Campos, 2 Ana Luisa Papolla, 3 Sara Maia, 1 Karina Soto, 1 Soﬁa Pereira. 1 Centro de Estudos de Doenças Crônicas, NOVA Medical School/Faculdade de Ciências Médicas (NMS/FCM), Univ Nova de Lisboa; 2Centro de Estatística e Aplicações da Univ de Lisboa (CEAUL); NOVA Medical School/Faculdade de Ciências Médicas, Univ Nova de Lisboa; 3Nephrology, Hospital Fernando Fonseca, Lisbon, Portugal.

Background: Homocysteine (Hcys) is present in serum in two major forms: disulﬁde protein-bound (PB) (70-80%, mostly albumin) and non-protein-bound (NPB) (20-30% combined thiol dimers + 1 % thiol free). Only the NPB-fraction of Hcys is able to enter into the cell and accumulates in both kidney failure and HIV-infected patients, hyperhomocysteinemia is a common feature. The present study was aimed to explore the relationship of Hcys NPB-fraction and chronic kidney disease (CKD) progression in HIV-infected patients.

Methods: As a part of an on-going prospective study of HIV+ population, a cross-sectional analysis was performed in a cohort of HIV-infected patients under combined antiretroviral therapy. Serum NPB-fraction of Hcys was quantiﬁed by HPLC with ﬂuorescence detection. Glomerular ﬁltration rate (eGFR) was estimated by CKD-EPI equation. The fractional excretion of phosphate (FePi) was also assessed.

Results: A total of 141 HIV-infected patients were included, 65% men, 73% non-Black, 52% non-smokers, 44% current smokers, 41% with previous smoking, 57% with antiretroviral therapy and 84% with CD4 cell counts over 200. Median values of eGFR and FePi were 85 ml/min/1.73m² in Renal Function infected patients.

Conclusion: These data add strength to the hypothesis that an active diabetic foot ulcer may contribute to a decline in renal function, particularly when associated with an episode of AKI. This decline may also be under-estimated due to loss of muscle mass and subsequent over-estimation of eGFR in the post hospitalisation period. These results support additional prospective epidemiological and mechanistic studies to further explore the relationship between diabetic foot ulcers, AKI and CKD progression.

PUB198
Gender – An Additional Cardiovascular and Chronic Kidney Disease Risk Factor in an Apparently Healthy Population Attilio Di Benedetto, 1 Annalisa Cioltola, 2 Fabrizio Cerino, 3 Annamaria Colao, 2 Daniele Marcelli, 1 Bernard J. Canaud, 3 NephroCare Italy, Naples, Italy; 3Medicina Clinica e Chirurgia, Univ Federico II, Naples, Italy; 4Fresenius Medical Care, Bad Homburg, Germany.

Background: Cardiovascular disease (CVD) is on the rise, presenting signiﬁcant social and economic burden. Early detection of CVD and chronic kidney disease (CKD) risk factors may prevent related complications. We report results of a CVD and CKD risk factor screening program in an apparently healthy population.

Methods: Participants and spectators of the “Prevention Races” held in 2013/2014 in Naples/Salerno (Italy) were screened for CVD and CKD risk factors by different specialists, including nephrologists. Parameters assessed were: systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height, waist circumference, BMI, and body composition. Lean (LTI) and Fat (FTI) tissue indexes and overhydration were evaluated by Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany) using multi-frequency bioimpedance spectroscopy at 50 different frequencies.

Results: 701 subjects (38.5% m; 61.5% f) were evaluated. Mean age was 54.54 ± 15.6 (m) and 50.06 ± 15.2 (f). 3.7% m and 6.8% f had dyslipidemia; 5.9% m and 3.0% f were diabetics; 18.6% m and 11.4% f were hypertensive; 2.2% m and 0.7% f had heart disease; 0% m and 3.5% f had hypothyroidism; 1.5% m and 1.2% f had CKD. Gender differences were significant in SBP, DBP, overhydration, FTI, LTI and BMI (Table).

Conclusions: In a large sample of apparently healthy persons, males had more CVD and CKD risk factors than females, such as SBP, overhydration, and FTI. In association with other CVD risk factors, these increase morbidity and mortality. Evaluation of body composition is important in the general population for identiﬁcation of CVD and CKD risk.

PUB199
Potential Effect of Treatment of Metabolic Acidosis on Reducing the Risk of End Stage Renal Disease in Chronic Kidney Disease Solomon Daleman, Candace D. Grant, Vladimir Liberman, Alejandro Pepen Romero, Shayan Shirazian, Nobuyuki (Bill) Miyawaki, Joseph Mattana. Medicine, Winthrop-Univ Hospital, Mineola, NY.

Background: There is increasing evidence that low serum bicarbonate levels impact adversely on the progression of chronic kidney disease (CKD) to end stage renal disease (ESRD). It is plausible that treatment could result in a signiﬁcant reduction in ESRD incidence though the potential impact in a CKD population and number needed to treat (NNT) are incompletely understood. We carried out the present study to estimate the potential impact of treatment of metabolic acidosis on the incidence of ESRD in a population of CKD patients.

Methods: We evaluated a cross section of 623 Stage 3 and 4 CKD patients at our institution. Their risk of developing ESRD at 2 and 5 years was estimated using the method of Targarini et al (JAMA 2011;305:1553-1559) which incorporates age, gender, eGFR, uric acid to creatinine ratio, calcium, phosphorus, albumin, and bicarbonate. ESRD risk was then recalculated after assuming correction of all serum bicarbonate levels to 28 mEq/L.

Results: The population had a mean serum bicarbonate level of 24.3 mEq/L, with 79.5% having levels below 28 mEq/L. When ESRD risk was calculated following correction of low serum bicarbonate levels to 28 mEq/L, 16 fewer patients were predicted to develop ESRD at 2 years and 27 fewer at 5 years (relative risk reductions of 0.31 and 0.23 respectively). This effect was greatest for patients with CKD stage 4, accounting for 13 fewer ESRD patients predicted at 2 years and 20 fewer at 5 years. For the population as a whole, the NNT to prevent one case of progression from CKD to ESRD was 40 and 23 at 2 and 5 years respectively, while for those with CKD stage 4 the NNT was only 16 and 11.

Conclusions: Our findings suggest that in a population of CKD patients correction of metabolic acidosis could potentially result in a substantial reduction in the number who reach ESRD given the large numbers of patients with low serum bicarbonate levels. Prospective studies are needed to determine whether sodium bicarbonate therapy in populations of CKD patients could prevent many cases of ESRD.

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Underline represents presenting author.

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The Impact of Vascular Disease on Risk of Development of End Stage Renal Disease in Patients with Chronic Kidney Disease

Vladimir Liberman, Sairah Sharif, Candace D. Grant, Alejandro Pepen Romero, Shanza Mujeeb, Nobuyuki (Bill) Miyawaki, Shayan Shirazian, Joseph Mattana. Medicine, Winthrop-Univ Hospital, Mineola, NY.

Background: Patients with chronic kidney disease (CKD) are not only at higher risk for development of end stage renal disease (ESRD) but also suffer disproportionately from vascular disease (VD), with associated high cardiovascular mortality. VD can plausibly impact progression of CKD and increase the risk of ESRD. However, VD also shortens survival, and may therefore reduce the risk of ESRD by increasing the competing risk of death. In the present study we evaluated the relationship between VD and the risk of development of ESRD in patients with CKD.

Methods: We carried out a retrospective cross sectional study of 623 CKD patients and recorded demographic, clinical and laboratory variables. We divided them in two groups based on presence or absence of VD and stratified them into different age groups. We estimated the risk of ESRD progression using the method of Tangri et al (JAMA 2011;305:1553-1559) and compared the risk levels between each group.

Results: Out of 623 patients with CKD 285 had VD (coronary artery disease and/or peripheral vascular disease) documented in the record. Patients with VD were significantly older than patients with no VD (76 vs 70 years), had lower serum albumin (4.0 vs 4.1 g/dL) and lower eGFR (33.8 vs 36.4 ml/min/1.73 m²). We found that older patients with VD had significantly higher risk of developing ESRD. For the 70 to 79 year age group the 2 year risk was 2.45 vs 1.50 (p=0.029) and 5 year risk was 6.80 vs 4.31 (p=0.03) in patients with and without VD. For patients ≥80 years the 2 year risk of developing ESRD was 2.18 vs 1.35 (p=0.029) and 5 year risk of developing ESRD was 6.80 vs 4.31 (p=0.03).

Conclusions: Our findings suggest that older patients with VD may be at increased risk for the development of ESRD despite the higher competing risk of death. This may be partly due to shared pathophysiological mechanisms between atherosclerosis and CKD progression. If validated in an ongoing prospective study this finding would suggest that VD should be considered a risk factor predisposing to an increased risk of developing ESRD.

Management of Renal Artery Stenosis Post-ASTRAL and CORAL: Outcome of Patients with Radiologically Confirmed Atherosclerotic Renal Artery Stenosis Treated Conservatively

Moheen Mohammed Ahmed, Nicholas John Railton, Abdelgalil Abdelrahman Ali, Anthony Chan. Renal Medicine, Mid Essex NHS Trust, Chelmsford, United Kingdom; Radiology, Mid Essex NHS Trust, Chelmsford, United Kingdom.

Background: Following the publications of ASTRAL and CORAL trials, the use of percutaneous renal artery angioplasty and stenting (PRAS) in the treatment of atherosclerotic renal artery stenosis (ARAS) has fallen dramatically. We report the outcomes of patients with radiologically confirmed diagnosis of ARAS who did not undergo PRAS and were managed medically.

Methods: Retrospective review of all patients undergoing CT/MRI angiography for suspected ARAS from 2008-2014 in Broomfield Hospital, Essex. Patients with more than >50% stenosis in a renal artery who were medically managed and did not undergo PRAS were included in analysis. They were followed for blood pressure control, renal events and mortality.

Results: 29 patients were identified, all Caucasians with a median age of 78 (49-85 years) of which 59% were males. None underwent PRAS. They were followed up from diagnosis till December 2014 or date of death with a mean period of 51 months. Systolic BP at end of study was <140 mmHg in 48%, 140-200 in 48% and >200 in 4% of patients. 69% were on 3 or more antihypertensives with 34% on renin angiotensin system blockade. 20 patients were CKD 3 and 8 with CKD 4 at baseline, with 3 patients progressing from stage 3 to 4 and 1 to stage 5 CKD, requiring dialysis.

Conclusions: From this study of patients with ARAS not indicated for PRAS, only a small number progressed to higher grades of CKD. Blood pressure control appeared adequate in a significant proportion of patients. This is in keeping with the findings from ASTRAL/CORAL trials and may be of significant benefit in terms of cost and reducing patient morbidity.
Factors Influencing Initiation and Choice of Immunosuppressive Therapy in Primary FSGS

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6  Dip of Nephrology, Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; 7  Dept of Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 8  Dip of Nephrology and Hypertension, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 9  Dip of Nephrology, McGill Univ Health Center, Montreal, QC, Canada.

Background: The treatment of patients with primary focal segmental glomerulosclerosis (FSGS) may include immunosuppressive therapy in patients not responding to conservative treatment or considered at high risk of progression to renal failure. We sought to determine the patient and disease characteristics associated with choice of therapy early in disease course.

Methods: Inception cohort of biopsy-proven patients with primary FSGS diagnosed between 1980 and 2012. Factors influencing choice of therapy were identified using multiple logistic regression; we report odds ratios (OR) with 95% confidence interval (CI).

Results: 458 patients met inclusion criteria; 183 had FSGS not requiring immunosuppressives; 173 treated with glucocorticoids [GC] alone; 90 with calcineurin inhibitors [CNIs] ± GC; 12 with other immunomodulatory agents.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No immunosuppression</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=183</td>
<td></td>
<td>N=275</td>
</tr>
<tr>
<td>Median age (yr)</td>
<td>48 (32-63)</td>
<td>36 (18-55)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>48.1</td>
<td>49.1</td>
</tr>
<tr>
<td>Black race (%)</td>
<td>45.1</td>
<td>45.9</td>
</tr>
<tr>
<td>Median eGFR (mL/min/1.73m²)</td>
<td>43.8 (27.2-69.9)</td>
<td>62.8 (41.7-85.7)</td>
</tr>
<tr>
<td>Median proteinuria (g/d)</td>
<td>3.8 (2.4-6.6)</td>
<td>6.0 (3.5-12.0)</td>
</tr>
</tbody>
</table>

Conclusions: Presence of tip lesion, preserved renal function at baseline and more severe hypoalbuminemia are associated with immunosuppressive therapy in primary FSGS, but only tip variant appears to influence choice of GC alone over CNIs.

Uric Acid Is Independent Risk Factor for Progression of Renal Dysfunction in IgA Nephropathy Female Patients

Yasuyuki Nagasawa, 1  Ryoho Yamamoto, 2  Maki Shizawa, 2  Sayuri Kawada, 2  Katsuyuki Nagatoya, 1  Aritoshi Kida, 1  Tatsuya Shoji, 1  Yukiko Hasume, 1  Terumasa Hayashi, 1  Takahiro Kuragano, 1  Atsushi Yamatani, 2  Yoshitaka Isaka, 2  Takeshi Nakanishi. 2  Dept of Internal Medicine, Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; 3  Dept of Nephrology and Geriatric Medicine, Osaka Univ, Suita, Osaka, Japan; 4  Dept of Internal Medicine, Osaka Rousai Hospital, Sakai, Osaka, Japan; 5  Dept of Nephrology, Osaka General Hospital, Osaka, Japan.

Background: IgA nephropathy is one of common primary glomerulonephritis. Hyperuricemia could be caused by reduced renal function. Therefore, it was difficult to distinguish hyperuricemia from the factors which promote renal dysfunction. Recently, several reports indicated that hyperuricemia might be independent risk factor for renal worsening, but there was little information about the effect of hyperuricemia itself upon progression of kidney diseases, especially in IgA nephropathy patients. Aim is to reveal effect of uric acid upon renal prognosis in IgA nephropathy patients.

Methods: This study is retrospective cohort study. Subjects were 923 IgA nephropathy patients who had not been treated uric acid lowering drugs, from 1001 IgA nephropathy patients who were diagnosed by renal biopsy, and over 15 years old in Osaka University Hospital, Osaka general medical center, Osaka Rosaki Hospital. Outcome was 1.5 times of serum creatinine. Exposure is uric acid at renal biopsy. Explanatory variables included sex, age, BMI, blood pressure, baseline eGFR, proteinuria, smoking status.

Results: Mean age was 34[23-46] years, proteinuria was 0.40[0.18-0.89] g/day. Uric acid was 6.5±1.3mg/dl in male patients, and 4.8±1.3mg/dl in female patients. Multivariate Poisson regression analysis revealed that uric acid was significant risk for progression of renal disease [Hazard Ratio 1.30[1.01-1.65] UA per 1mg/dl] in female patients along with proteinuria(g/day) [HR 1.27[1.08-1.47],p<0.001], Creatinine (mg/dl) [HR 2.73[1.34-3.74]]. In male patients, uric acid was not independent risk factor.

Conclusions: Hyperuricemia is independent risk for progression of kidney disease in female IgA nephropathy patients.

Kidney Inst, Gilbert, AZ.

Background: Long-term treatment with H.P. Acthar® Gel (repository corticotropin injection, Questa Pharmaceuticals, Inc., Hayward, CA), an FDA-approved treatment for remission of proteinuria associated with nephrotic syndrome, was examined in a patient with biopsy-confirmed idiopathic membranous glomerulopathy (mM).

Methods: A retrospective clinical record review examined Acthar Gel treatment over 2 years and 8 months in a patient with mM who received prescription-based treatment in a clinical practice. Outcomes included proteinuria level (mg/g), serum creatinine (SCr), serum albumin and treatment-related side effects. Complete remission was defined as proteinuria <500 mg/g. Partial remission was defined as ≥50% reduction in proteinuria from baseline and proteinuria 500-3500 mg/g.

Results: The 54-year-old Vietnamese patient with mM was treated over 7 years. At diagnosis, the patient’s proteinuria was 8000 mg/g, SCr 0.7 mg/dL, and serum albumin 2.1 g/dL. Initial treatment included prednisone, cyclosporine, mycophenolate mofetil, tacrolimus, and rituximab over 4.5 years. The patient showed partial complete remissions followed by relapse. At Acthar Gel initiation, proteinuria was 3400 mg/g, SCr 0.6 mg/dL, and serum albumin 4.2 g/dL. The patient did not tolerate 80 U twice weekly but did tolerate 40 U twice weekly. At 4 months, she showed complete remission (proteinuria <150 mg/g). Dose reduction to 20 U twice weekly resulted in relapse 7 months later (proteinuria 2300 mg/g). Dose increase to 40 U twice weekly led to complete remission 4 months after that. Loss of insurance and cessation of Acthar Gel for 4 months led to relapse (proteinuria 7700 mg/g). Acthar Gel was re-started at 32 U twice weekly followed by 24 U twice weekly. Partial remission occurred 4 months later (proteinuria 2100 mg/g) with greater improvement at 10 months (proteinuria 500 mg/g). The patient has maintained partial remission (proteinuria 970 g/g) 4 months post-therapy. Side effects over the course of Acthar Gel therapy included fatigue, myalgia, hyperglycemia, and weight gain.

Conclusions: Long-term treatment with H.P. Acthar® Gel may help meet an important treatment need in patients with treatment-resistant and frequently-relapsing mM. Funding: Pharmaceutical Company Support - Funding for editorial support provided by Mallinckrodt Pharmaceuticals.

Outcome of Steroid Dependent (SDNS) and Frequent Relapsing Nephrotic Syndrome (FRNS) in Children

Isabel Roberts, Shefali Vyas. Children's Kidney Center, Saint Barnabas Medical Center, Livingston, NJ.

Background: Management of SDNS and FRNS in children can be frustrating. With the goal of minimizing steroid toxicity while achieving a sustained remission multiple regimens have been used with variable results. We reviewed our cases of SDNS/FRNS who had kidney biopsy (BX) during the past 12 yrs. Methods: Charts of children with BX due to SDNS or FRNS (after failure of MMF) were reviewed. Congenital and secondary causes of NS were excluded. Demographics, medications, side effects and response to therapy were studied. IV cytoscan (CYP) was considered in non-FSGS cases with suspected non-adherence (800 mg/m2/dose monthly
x 3). Others received tacrolimus (TAC) (0.1mg/kg BID; trough up to 6 ng/ml). Rituximab (70mg/m² x 2 doses IV) was given if child became TAC dependent or resistant. Response to therapy was classified as: complete remission (CR), partial remission (PR), infrequent relapse (IR)(<2/yr), failure (F).

Results: 32 children had kidney biopsy (Bx) for primary SDND/FRNS. 14 females; 14 CH, 6 AA, 2 other race. Age at presentation: 2-14 yrs (median= 3 yrs). Bx: 15 MCNS (4 diagnosed later with FSGS), 9 IgMN, 5 FSGS, 3 C1QN, 1 idiopathic immune mediated GN. All children had normal GFR at the time of the bx.

MCNS (4 diagnosed later with FSGS); 9 IgMN, 5 FSGS, 3 C1QN, 1 idiopathic immune mediated GN. All children had normal GFR at the time of the bx.

Follow-up time as CYP had a failure rate 60% (p<0.01), including 4 cases with MCNS. However, those children who had CR were significantly higher for TAC (87.5%) and rituxan (100%) (4 had initial diagnosis MCNS but later bx had FSGS); 7 received rituxamab: all had CR (5 IR). The rates of CR were significantly higher for TAC (87.5%) and rituxan (100%)

24 children received TAC; 21 CR (13 became TAC dependent with IR), 2 PR, 1 IR, 15 received CYP: 6 CR, 9 F, 3 IR (2 before diagnosis MCNS but later bx had FSGS); 7 received rituxamab: all had CR (5 IR). The rates of CR were significantly higher for TAC (87.5%) and rituxan (100%) as CYP had a failure rate 60% (p<0.01), including 4 cases with MCNS. However, those who had CR from CYP didn’t have further relapses. Rate of IR among those who initially had CR was similar between rituximab and TAC. Follow-up time: 2-12 yrs (median= 4 yrs), including 6 discharged due to stable CR and 3 ESRD (all with FSGS).

Side effects: 4 AKI with TAC (reversible), 2 respiratory distress/allergy in rituximab group (IV D/C).

Late TAC resistance was seen in 3 patients.

Conclusions: Children with SDND/FRNS despite failure to respond to MMF had an excellent outcome. Some reported sequential use of tacrolimus and rituximab after failure of CYP with a rate of CR:IR=88% with minimal side effects.

PUB208

Granulomatosis with Polyangitis (GPA) versus Sarcoaidosis

Sruhti Jinna,
Samir S. Zarouk.

Methods: His BUN was 18 mg/dl, and creatinine 1.33 mg/dl. Urinalysis showed 3+ blood, 2+ protein, over 100 RBCs, 10 WBCs. Serology for Hepatitis B and C, HIV, EBV and CMV were negative. Antinuclear antibody, anti-neutrophil cytoplasmatic antibody, anti dsDNA antibody, smith antibody, RNP antibody, myeloperoxidase antibody, proteinase 3 autoantibody, anti SSA antibody, anti SSB antibody, and complement levels were negative. An angiotensin converting enzyme (ACE) level was 81 U/L (8-52). A chest Computed Tomography scan showed mediastinal, hilar lymphadenopathy, and multiple pulmonary nodules.

Results: Suspicion for relapsing GPA prompted renal biopsy. It showed 3 out of 13 glomeruli with pauci-immune crescentic glomerulonephritis. There were extensive non-caseating granulomas in the interstitium and associated tubular atrophy. No microorganisms were noted on AFB and PAS stained sections. Nalas septum biopsy showed non-necrotizing granulomatous inflammation. Medialastinal lymph node biopsy showed necrotizing granulomatous lymphadenitis. These 3 biopsy sites were consistent with sarcoidosis.

Conclusions: This case highlights the difficulty in differentiating between ANCA negative GPA versus sarcoidosis as both can cause granulomatous lesions. Glomerular involvement in sarcoidosis can show membranous glomerulonephritis, FSGS and rarely a crescentic glomerulonephritis. In our opinion, a TAC level combined with extensive presence of non-caseating granulomas in the nasal septum, mediastinal nodes and renal interstitium are more characteristic of sarcoidosis. He responded well to steroids and his weight loss in the last two months.

PUB209

Epidemiology of Glomerulonephritis in Southern Arizona

Benjamin Kweisi Sarsah, Irfan K. Moinuddin, Bijn Thajudeen, Amy Nicole Sussman, Pradeep V. Kadambi.

Nephrology, Univ of Arizona, Tucson, AZ.

Methods: Renal biopsy specimens from adult patients above the age of 18 years with glomerular renal disease were included. Renal transplant biopsies showing glomerulonephritis and biopsies showing co-existing diabetic nephropathies were excluded. Histological diagnoses were grouped into one of the following 8 categories: minimal change disease, FSGS, membranous nephropathy,membrane-proliferative glomerulonephritis, pauci-immune glomerulonephritis, IgA nephropathy, lupus nephritis and others. Demographic parameters were systematically collected from the medical records archive.

Results: The most common histopathological diagnosis was FSGS followed by membranous nephropathy and IgA nephropathy. There were male predominance in all histological variants except IgA nephropathy, lupus nephritis and pauci-immune glomerulonephritis. The race distribution was uneven, and all histovariantal diagnoses except minimal change disease and lupus nephritis were more commonly seen in whites. In separate analysis of the histological pattern in Hispanics, lupus nephritis was found to be the most common pathology followed by FSGS. In American Indian population the most common pathology was IgA nephropathy followed by FSGS. Bar diagram represents frequency of each glomerular disease

PUB210

Use of Rituximab to Induce Remission in Frequently Relapsing Pediatric Nephrotic Patients

Jason Peter Thomas, Teri L. Crumb, Alejandro Quiroga.

Pediatrics, Helen DeVos Children’s Hospital, Grand Rapids, MI; Pediatric Nephrology, Helen DeVos Children’s Hospital, Grand Rapids, MI.

Background: Rituximab has been shown to be effective in patients with frequent relapsing nephrotic syndrome (NS) with a reported 82% response rate. We evaluated the clinical response of pediatric nephrotic patients for induction of remission following one dose of rituximab.

Methods: This is an IRB approved, prospective clinical research trial. Informed consent was obtained from each family. Four pediatric patients with NS were enrolled prior to their clinically indicated rituximab infusion. Urine Protein/Creatinine ratio and albumin blood levels were collected.

Results: Urine Protein/Creatinine ratios obtained post infusion of rituximab decreased between 37-93% from pre infusion levels. 50% of patients identified had resolved edema noted on physical exam post infusion.

Conclusions: Rituximab may be an effective agent for inducing remission for pediatric patients with frequently relapsing nephrotic syndrome. 50% of patients had clinical response on physical exam post infusion and 100% of our patients had a decrease in the amount of protein excreted in their urine. The use of rituximab for the induction of remission is a novel and innovative treatment option for children with frequently relapsing nephrotic syndrome, warranting further investigation.

Funding: Private Foundation Support

PUB211

Lupus Nephritis: An Exploration of Management Style

Abhishek NANDAN.

Huzefa J. Syed, Christen Vagts, Jason M. Kidd.

Internal Medicine, Virginia Commonwealth Univ Medical Center, Richmond, VA.

Background: We aim to evaluate the differences and rationale behind the diagnostic and therapeutic approaches to proliferative lupus nephritis (LN) among nephrologists and rheumatologists.

Methods: A de-identified, multiple-choice survey was distributed to nephrologists and rheumatologists. The survey consisted of a demographic questionnaire and two case vignettes exploring the decision of when to biopsy, management of ISN Class III LN, and management of refractory ISN Class IV LN.

Results: There were 38 respondents to our survey: 12 rheumatologists and 26 nephrologists. Work setting: 81% academic, 19% non-academic. Management of abnormal UA findings in an asymptomatic lupus patient: 33% of rheumatologists versus 76% of nephrologists chose to biopsy. Induction regimen of ISN Class III LN: 79% of all providers chose MMF and 21% chose IV cyclophosphamide.

Choice of Induction Regimen in ISN Class III LN per Specialty

<table>
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<tr>
<th>Management Style</th>
<th>Predicted Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrology</td>
<td>18</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
</tr>
</tbody>
</table>
Maintenance regimen of ISN Class III LN: all surveyed rheumatologists chose MMF as a sole maintenance agent compared to 32% of nephrologists who elected the addition of low-dose corticosteroids to MMF. Choice of an adjunctive agent in refractory ISN Class IV LN: 68% of providers chose rituximab, 14% chose tacrolimus, 5% chose CTLA-4 Ig, and 14% elected not to add any agents listed.

Conclusions: The results of this survey suggest a significant difference among rheumatologists and nephrologists on the decision to perform initial kidney biopsy and maintenance long-term treatment with glucocorticoids.

Rationale for Induction Regimen Confirmation in ISN Class III LN

<table>
<thead>
<tr>
<th>Rationale</th>
<th>Both best efficacy and side effect profile only</th>
<th>Best side effect profile only</th>
<th>Best efficacy only</th>
<th>Both side effect profile only</th>
<th>Reason not listed</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Monthly IV cyclophosphamide</th>
<th>Mycophenolate mofetil</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ISN Class III LN- Induction Regimen</th>
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<tbody>
<tr>
<td>PUB212</td>
</tr>
</tbody>
</table>

**Background:** The clinical impact of the immune complexes in pauciimmune GN is not well studied. The purpose of this study was to evaluate the long-term prognosis after achieving a complete or partial remission among patients with iMN presenting with heavy proteinuria.

**Methods:** In this study, 25 patients with iMN with heavy proteinuria defined as ≥ 6 g/d were evaluated for the effect of a partial remission (50% reduction in baseline proteinuria to ≤ 3 g/d and ≤ 25% increase in baseline creatinine) and complete remission (proteinuria ≤ 0.5 g/d and serum creatinine ≤ 123 µmol/l) on renal outcomes compared with patients who did not attain a remission. Worse renal outcome was defined as doubling of the baseline serum creatinine value or development of end stage renal disease.

**Results:** Complete remission was attained in 7 (28%) patients, a partial remission in 12 (48%) patients, and no remission in 6 (24%) patients. The worse renal outcome was not observed in all patients who achieved complete remission, but it was seen in 16.7% of the partial remission group and in 66.7% of the no remission group. (P value 0.14).

**Conclusions:** Achieving a complete or partial remission compared to no remission in patients with iMN is associated with a significantly better renal outcome.

**PUB214**

**Eosinophilic Pneumonia with Renal Involvement** Geddie Goldet,1 Rachel Hung,1 Michael Sheaff,2 1 Basildon and Thurrock Univ Hosp; 2 Pathology, Barts and the London School of Medicine.

**Background:** Eosinophilic pneumonia is a rare condition and a well-established cause of pulmonary symptoms. It is often associated with eosinophilic pneumonia or eosinophilic granulomatosis with polyangiitis (EGPA). The clinical presentation can be varied, ranging from asymptomatic disease to severe respiratory failure. The diagnosis of eosinophilic pneumonia is often challenging due to the variable presentation and the need for a multidisciplinary approach toward renal and lung disease.

**Results:** In this case series, we report the outcomes of 7 patients with eosinophilic pneumonia and renal involvement, including 4 patients with interstitial nephritis and 3 patients with Goodpasture syndrome.

**Conclusions:** Eosinophilic pneumonia with renal involvement is a rare but important disease that requires a multidisciplinary approach to achieve better outcomes for patients.
Comparison of Short- and Long-Term IgA Nephropathy Clinical Remission Rates Between Tonsillectomy plus Consecutive and Intermittent Steroid Pulse Therapies


Div. of Nephrology, Iwate Prefectural Central Hospital, Morioka, Iwate, Japan.

Background: Tonsillectomy (Tx) plus steroid pulse therapy (TSP) is widely performed across Japan for clinical remission (CR) of IgA nephropathy (IgAN) but treatment protocol lacks a consensus. We used both TSP (methylprednisolone 0.5 g/day iv for 3 days)* thrice/3 consecutive weeks (TSP-C) and intermittent pulse (⋆) thrice/4 high-power field.

Results: Before treatments, there were no significant clinical [TSP-C (n = 57) vs. TPS-I (n = 33): age, 31.0 ± 11.2 v. 34.0 ± 11.9 years; male/female, 17:40 v. 17:21; eGFR, 82.2 ± 29.9 vs. 77.4 ± 28.7 mL/min; blood pressure, 121 ± 17/72 ± 12 vs. 120 ± 17/76 ± 13 mmHg; urinary protein, 0.41 (0.18, 1.19) v. 0.79 (0.20, 1.08) g/L; and positive occult blood, 91.2 ± 90.9%] and histological grade stratification differences between the groups. At TPS-I cessation, short-term CR rates were equivalent between the groups (TSP-C vs. TPS-I: 1 year, 78.9 (n = 19) vs. 80.0% (n = 10); 3 years, 73.6 (n = 19) vs. 66.7% (n = 6)]. CR continuation between the groups [TSP-C vs. TPS-I: 1 year, 64.1 (n = 39) vs. 59.1% (n = 22); 2 years, 74.2 (n = 25) vs. 80.1% (n = 10); 3 years, 76.6 (n = 19) vs. 66.7% (n = 6)] and histological grade stratification differences between the groups. At oPSL electrophoresis should be routinely performed in the patients with renal failure.

Conclusions: Multiple myeloma patients diagnosed by nephrologist did not show the diagnosis, but had not been treated accordingly.

A Case Series on the Treatment of Nephrotic Syndrome with Natural Adrenocorticotropic Hormone Gel in an Office Setting

Marco A. Bonilla, Xavier F. Panida, Mario A. Henriquez.
Nephrology, Bronx Nephrology-Hypertension, Bronx, NY.

Background: ACTH is a promising treatment for the nephrotic syndrome, associated with significant improvement in proteinuria and relatively few adverse effects. We present our experience using natural ACTH gel for nephrotic syndrome in patients with diverse diagnosis.

Methods: Retrospective case series of 7 Adults patients with nephrotic syndrome, treated with ACTH gel. Data was gathered by chart review, from the clinic EMR and paper based records. ACTH was given in the form of ACTHAR gel 80 USP units/ml SC twice a week for 6 months. Complete remission defined as stable or improved renal function with final proteinuria ≤500 mg/day; partial remission as stable or improved renal function with ≤50% reduction in proteinuria and final proteinuria 500 to 3500 mg/day. Failure to meet this criteria was classified as treatment failure.

Results: Table 1. Outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Diagnosis</th>
<th>Previous immunosuppression</th>
<th>eGFR (ml/min/1.73 m²)</th>
<th>Proteinuria pre-ACTH (mg/g)</th>
<th>Proteinuria post-ACTH (mg/g)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>M</td>
<td>Hispanic</td>
<td>IgA nephropathy</td>
<td>None</td>
<td>20</td>
<td>10312</td>
<td>871</td>
<td>Failure</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>M</td>
<td>Hispanic</td>
<td>MGN</td>
<td>Prednisone, MMF</td>
<td>104</td>
<td>1001</td>
<td>290</td>
<td>Failure</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>F</td>
<td>Black</td>
<td>MGN</td>
<td>Prednisone</td>
<td>20</td>
<td>10104</td>
<td>295.4</td>
<td>Complete</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>M</td>
<td>Hispanic</td>
<td>IgA nephropathy</td>
<td>None</td>
<td>48</td>
<td>2540</td>
<td>623</td>
<td>Partial</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>M</td>
<td>Hispanic</td>
<td>FSGS</td>
<td>Prednisone, MMF</td>
<td>48</td>
<td>1796</td>
<td>1157</td>
<td>Failure</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>F</td>
<td>Hispanic</td>
<td>IgA nephropathy</td>
<td>None</td>
<td>94</td>
<td>4000</td>
<td>161</td>
<td>Complete</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>F</td>
<td>Hispanic</td>
<td>MGN</td>
<td>MMF</td>
<td>36</td>
<td>17578</td>
<td>386</td>
<td>Complete</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.
Very few studies have reported on the prognosis of anti-GBM antibody-positive GN. Anti-GBM disease (GBM) is a renal vasculitis characterized by the formation of immune complexes in the glomerular basement membrane (GBM). Anti-GBM antibodies are directed against the alpha 3 chain of type IV collagen, a major component of the GBM. The hallmark of anti-GBM disease is rapidly progressive renal failure, which is often accompanied by proteinuria and hematuria. The prognosis of anti-GBM disease is influenced by several factors, including the type of GBM, the level of proteinuria, and the presence of hypertension. The presence of hypertension is associated with a worse prognosis, as it can lead to further damage to the kidneys. The disease is often treated with immunosuppressive agents, such as steroids, to reduce inflammation and the formation of immune complexes. However, the prognosis of anti-GBM disease remains guarded, and the outcomes for patients with this condition continue to be monitored closely.
The Clinical Predictors for Outcome of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis Patients with Renal Involvement

Guisen Li, Li Wang. Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: Primary anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are chronic multisystem autoimmune diseases and result in dysfunctions of multisystem. Renal involvement is the most common manifestation and is closely associated with the outcome of patients with vasculitis. We investigated the clinical determinants of the early mortality of patients with vasculitis-related renal injury followed up 2 years in a single west Chinese center to study the factors associated with patient outcome.

Methods: A total of 123 consecutive patients with AAV-related renal injury diagnosed in our center were recruited. Clinical and laboratory data were collected retrospectively. All the patients were followed up for 2 years after diagnosis. The predictive values of variables associated with mortality were analyzed.

Results: During 2 years follow up duration, 54 (43.9%) died, of whom 41 diedwithin the first year after diagnosis. Compared with surviving patients, the deceased patients had higher BVAS scores and higher incidence of pulmonary hemorrhage. They also had higher serum creatinine and ESR, lower hemoglobin and complement C3, more patients accepting renal replacement therapy than surviving patients during hospitalization. Higher BVAS scores and serum creatinine>400μmol/L were the predictors of death in patient with AAV-related renal injury independently.

Conclusions: The incidence of early mortality in patients with AAV-related renal injury was higher. Prudent monitoring and therapy should be given to patients with active vasculitis and serious renal dysfunction to reduce adverse events.

Significance of Resistive Index in Renal Arterial Ultrasonography as a Clinical Parameter for Tubulo-Interstitial Nephropathy

Kazuyuki Takayagami,1 Taisuke Shimizu,1 Hiroaki Hara,1 Nobuyuki Onizawa,1 Koki Ogawa,1 Yuka Tanaka,1 Kunihiko Yasuda,1 Tomonari Ogawa,1 Akihiko Matsuda,2 Hajime Hasegawa.1 1Nephrology and Hypertension, Saitama Medical Univ; Saitama, Japan; 2Ishikawa Kinenkai Kawasaki Ekimae Clinic, Kawasaki, Saitama, Japan.

Background: Renal arterial ultrasonography (RA-US) has been principally applied to evaluate the stenosis of the renal artery and the indication of catheter intervention by the measurement of peak systolic velocity (PSV). Resistive index (RI) is calculated as PSV/EDV (PSV: where EDV indicates end-diastolic velocity, and is reported to be related to the renal function. In this study, we aimed to investigate the possible clinical benefit of RI for the assessment of tubulo-interstitial nephropathy (TIN).

Methods: We studied 51 patients (51.6±2.3 years old) who underwent RA-US and sufficient laboratory tests for the analysis in the past 10 years in our hospital. PSV and RI were measured at both main renal arteries (RA-measurement) and intra-renal arteries roughly corresponding to the inter-lobar arteries (IRA-measurement). NAG index (urine excretion ratio of N-acetylglucosaminidase (NAG) to creatinine) was used as a conventional clinical parameter for the assessment of TIN.

Results: Stratified analysis by median value of RI (0.69) showed significant difference in eGFR in the RA-measurement (43.4±4.7 vs 60.3±4.2), but not in the IAR-measurement. In contrast, the analysis showed significant difference in NAG index in the IRA-measurement (median: 11.6 vs 5.4), but not in RA-measurement. When the patients showing NAG index ≥ 15, indicating advanced renal insufficiency, would be excluded from the analysis, NAG index significantly correlated with RI of IRA-measurement (R=0.50, p<0.05), but not RA-measurement. In addition, ROC analysis revealed that the cut-off value of RI to NAG index was 0.65.

Conclusions: In addition to the previous report showing the relevance of RI to the histological severity, the present study demonstrated the correlation of RI with the conventional parameter of TIN, NAG index. Particularly, for the assessment of TIN, RI value measured at intra-renal artery would be more beneficial.

Recovery of Renal Function with Eculizumab in a Girl with Dense Deposit Disease and Normal Soluble C5b-9 Levels

Martin Könighoff,1 Arjan Diepstra,2 Marc Maj Seelen,3 Coen A. Stegeman,1 Valentina Gracchi.1 1Pediatrics, UMCG, Groningen, Netherlands; 2Pathology, UMCG, Groningen, Netherlands; 3Nephrology, UMCG, Netherlands.

Background: Dense Deposit Disease (DDD) is a rare glomerulopathy characterized by electron-dense deposits in the glomerular basement membrane (GBM) and glomerular complement deposition. 50% of patients progress to ESRD and have recurrences after kidney transplantation. Dysregulation of the alternative complement pathway plays a key role in the pathogenesis. Increased soluble C5b-9 in blood is considered to predict response to eculizumab, an anti-C5 monoclonal antibody.

Methods: We report the case of a previously healthy 15-year-old girl who presented with acute kidney injury, hypertension, nephrotic syndrome (10.8 gr protein /24 hours) and microscopic hematuria.

Results: Biochemical (C3 &4, sC5b-9, factors H & I, C3 nephritic factor and anti-FH) and genetic workup of the complement system (CFI, CFB, C3 and MCP) showed normal results, except for a slightly increased C3d and a risk allele in the CFH gene. Renal biopsy showed cellular crescents and electron-dense deposits in the GBM. Glomerular C3 and C5b-9 immunofluorescence staining was positive. Despite escalating therapy, including methylprednisolone pulses followed by oral prednisolone, cyclophosphamide and plasma exchange (PE), the renal function further deteriorated and hemodialysis was started. Eculizumab was administered. This led to a rapid improvement of renal function (discontinuation of dialysis and increase of endogenous creatinine clearance from 11 to 53 ml/min/1.73m²). Three months later the girl is in a good clinical condition but proteinuria is still in the nephrotic range (3.6 gr/24 hours). Treatment with eculizumab is ongoing. Up to now no side effects have been observed.

Conclusions: Response to eculizumab in DDD cannot be predicted merely on the basis of levels of sC5b-9 in blood.
Manifestations of IgAN vary widely. The mainstay of therapy consists of supportive measures, which the majority of our cohort received. Immunosuppressive regimens are reserved for a select group, and in our cohort both mycophenolate and steroid based regimens yielded a reduction in proteinuria.

**Conclusions**: Manifestations of IgAN vary widely. The mainstay of therapy consists of supportive measures, which the majority of our cohort received. Immunosuppressive regimens are reserved for a select group, and in our cohort both mycophenolate and steroid based regimens yielded a reduction in proteinuria.

**Effect of Rituximab on Immunoglobulin Levels and Infection Risk in ANCA Associated Vasculitis**

*Shivani Shah,*1 *M-Hafizur Rahman,*2 *Duvuru Geetha.*1

1Div of Nephrology, Dept of Medicine, Johns Hopkins Hospital, Baltimore, MD; 2Bloomberg School of Public Health, Johns Hopkins Univ, Baltimore, MD.

**Background**: Rituximab (RTX), a B cell depleting anti-CD20 monoclonal antibody, is approved for treatment of ANCA associated vasculitis (AAV). Low immunoglobulin (Ig) levels are a consequence of RTX treatment. The association between the degree of Ig deficiency and infection risk is unclear in AAV patients.

**Methods**: AAV patients treated with RTX in a single center with available serum Ig measurements were included. The rates and types of infection after RTX administration were correlated with Ig level using correlation matrix and logistic regression analysis.

**Results**: Our cohort of 27 patients had a median age of 68 years, eight males, 15 GPA patients, and 17 with a new diagnosis of AAV. Twenty five received four doses of RTX 375 mg/m² weekly and two received RTX 1000 mg biweekly for two doses. Nine received concomitant cyclophosphamide. Twenty three patients had low serum IgG levels (<751 mg/dL) greater than one month following RTX treatment. Ten out of these 23 developed infections over the median follow up time of 338 days. Pneumonia was the most common infection. The odds of having an infection with IgG level ≤500 mg/dL is 3.6 times higher than with IgG level between 501-750 mg/dL, though p = 0.26. There is a significant association between infection and IgM level ≤20 mg/dL (p = 0.047).

**Conclusions**: Severely low Ig levels due to RTX therapy may increase the risk of infection in AAV patients, and these patients may benefit from IVIG therapy. Further investigation is warranted given our study is limited by small sample size, concomitant cyclophosphamide use, and variable timing of Ig measurement.

**Lipoprotein Glomerulopathy**

*Hostensia M. Beng,* Basema I. Dibas,* Hsiao Ling Lai,* Guillermo Hidalgo.*Pediatrics, ECU, Greenville, NC.

**Background**: Lipoprotein glomerulopathy has been associated with mutations in the Apolipoprotein E (APOE) gene. The average age of reported cases is 32 years and the youngest patient described to date is 4 yrs old. Here we present the first case of a 3 years old AA male with right hemihypertrophy, malignant hypertension, severe proteinuria & lipoprotein glomerulopathy, with a heterozygous mutation on APOE gene.

**Methods**: A 3 year old African American male presented to pediatrician complaining of hemihypertrophy, short stature, polydipsia & hypertension. Physical examination remarkable for right leg soft tissue hemihypertrophy. Echocardiogram revealed left ventricular hypertrophy likely secondary to chronic hypertension. Hypertension and proteinuria persisted despite adequate treatment. Renal US showed persistent echogenic kidneys. Kidney biopsy showed Lipid vacuolization of podocytes, endothelial cells, tubular epithelial cells, and glomerular capillary lumens. Labs & imaging studies AFP and abdominal US have been normal with exception of proteinuria and increased lipid profile. Patient currently on a trial treatment with fibrin acid and dietary modification.

**Results**: eGFR is stable at 60 ml/min/1.73 m², proteinuria has improved from a ratio of 2.1 to 0.8 mg/mg and lipid profile has significantly improved.

**Conclusions**: APOE is an important LDL in transporting cholesterol to the liver for processing. Four main alleles of the APOE gene located on chromosome 19 have been described and different alleles have been associated with various medical conditions. Mutations of the LDL bind domain of the APOE gene coexist and may be associated with certain kidney diseases. Renal biopsy shows lipid deposits and thrombi which results in glomerular damage and glomerular sclerosis. No effective preventative or curative treatments have been identified for apolipoprotein glomerulopathy. In our patient a trial of fibrates to lower cholesterol, Gemfibrozil and effective management of hypertension has resulted in some improvement but it is uncertain if these medication can effectively lower lipid and prevent long term progression of kidney disease. More research to find more effective treatment and management strategies of this disease in children.

**Proliferative Lupus Nephritis (LN) – 60 Month Evolution of an Argentinian Cohort**

*Gabriel Pedro Alvarez,*1 *Marcelo Alejandro De Rosa,*2 *Luis Alberto Togneda.*1 Hospital San Martin, La Plata, Buenos Aires; 2Univ of Buenos Aires, Argentina.

**Background**: Remission of proteinuria predicts good evolution in many glomerular diseases; we describe the behavior of the proteinuria, renal function and flare up in a group of patients with proliferative LN in a 60 month period.

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

**Underline represents presenting author.**
Methods: Data from 55 patients were obtained. Proteinuria and Creatinine were shown to be significant at 0 (time of the biopsy), 6 and 60 months; renal biopsies were classified using ISN-RPS criteria among patients with and without vasculitic lesions, only tubular atrophy was predictive of future decline in renal function (p=0.007). In this cohort, 21% reached ESRD within a mean follow up of 7 yrs which highlights the aggressive nature of this disease process.

Results: Significant differences (p=0.05) was between concentrations of cytokines EGF, G-CSF, GM-CSF, GRO, IFN, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-12(p70), IL-13, IL-15, IL-17, IL-1Ra, IL-1a, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IFN-α2, TNF-α, TNF-β, VEGF, scCD40L, RIL-2RA) using MILLIPLEX®-MAP Human Cytokine/Chemokine-Magnetic-Bead-Panel-Premixed 39 Plex.

Conclusions: Significant differences in plasma samples of these molecules may be considered.

Funding: Other NIH Support - Banco de la Republica de Colombia

PUB234
Clinical Outcomes of IgA Nephropathy with Necrotizing and Crescentic Lesions in Inner City Hospital


Nephrology, John H Stroger Jr. Hospital of Cook County, Chicago, IL.

Abstract: IgA nephropathy is the most common cause of glomerular disease worldwide. Segmental necrosis and crescents are seen only in small subset of patients and literature regarding their clinical outcomes is sparse.

Methods: Retrospective analysis of cases with primary IgA nephropathy from Stroger Renal biopsy database from January 2005 to May 2015 was performed. Demographic and clinical information was obtained from medical charts. Study was approved by IRB.

Results: Of 66 cases of IgA nephropathy, 10 (15%) had lesions with segmental necrosis and/or crescents. These patients responded well to cyclophosphamide based therapy with improvement in creatinine and proteinuria after a mean follow up of 4.6 years. However, patients without vasculitic lesions had a progressive decline in renal function despite immunosuppressive therapy. This group had longer follow up period (median 7.1 yrs) and 21% required dialysis.

Conclusions: Segmental necrosis and crescents in IgA nephropathy are not rare but not well understood. This study provides new insights into the natural history of this disease.

PUB233
Plasma Cytokines and Chemokines Profile in Patients with Systemic Lupus Erythematosus: Its Potential Use as Biomarkers of Kidney Damage

Gustavo Aroca Martinez,1,2 Lisandro Pacheco,1 Elkin Navarro Navarro;1 Yirys Diaz,1 Henry J. Gonzalez torres,1,2 Gloria Garavito,1 Eduardo Egea bermejo,3 Eduardo J. Navarro,3 Liseth Almendrals,4 Antonio De Jesus Iglesias-Garrama.5

1:Medicine, Univ Simon Bolivar;2:Banarrquilla, Atlantico, Colombia;3:Nephrology, Clinica de la Costa, Barranquilla, Atlantico, Colombia; 4:Medicine, Univ del Norte, Barranquilla, Atlantico, Colombia; 5:Medicine, Univ Nacional de Colombia, Bogotá DC, Cundinamarca, Colombia.

Background: Systemic lupus erythematosus is an autoimmune disease in which the innate and adaptive response plays a significant role, mainly mediated by cytokines. Lupus nephritis-LN is the most severe complication associated with SLE. Objective: To identify differential expression of cytokines profiles and circulating chemokines in plasma of SLE patients with different degrees of Caribbean region.

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

Underline represents presenting author.

941A
Acute Tubulo-Interstitial Nephritis (ATIN): Predicting Long Term Outcomes
Victoria C. Robins,1 Aravind Cherukuri,2 Padmini Prasad,1 Richard J. Baker.1, 2SUH; 3Pittsburgh.

Background: ATIN is a relatively common potentially reversible cause of acute kidney injury. It has become clear over the last 2 decades that the disease is not always reversible, particularly in the elderly. We present a large contemporary single centre retrospective series concentrating on factors that predict poor outcomes.

Methods: 62 cases retrospectively diagnosed histologically via pathology records as primarily ATIN were included. An experienced histopathologist, blinded to outcomes, graded biopsies according to the presence, absence and degree of 8 different parameters: Interstitial inflammation, tubular atrophy, eosinophilia, plasma cell infiltration, chronic vascular lesions, hyalinosis, granulomas + oedema. Patients were classified as a poor outcome if eGFR (variable MDRD) after 12 months was less than 30 ml/min/1.73m² or they died.

Results: 62 patients with biopsy proven ATIN were identified. 15 had a poor outcome. Baseline demographics are presented in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Good (eGFR&gt;30)</th>
<th>Poor (eGFR&lt;30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>47</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>66.2±16.8</td>
<td>56.6±19</td>
<td>Not significant(-)</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>19/28</td>
<td>6/9</td>
<td></td>
</tr>
<tr>
<td>Creatinine-diagnosis</td>
<td>366±245</td>
<td>545±334</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine-6 months</td>
<td>130±40</td>
<td>220±90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCR-diagnosis</td>
<td>103±72</td>
<td>126±90</td>
<td></td>
</tr>
<tr>
<td>Treatment: prednisolone</td>
<td>87%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Serum eosinophil count</td>
<td>0.4±1.0</td>
<td>0.4±0.5</td>
<td></td>
</tr>
<tr>
<td>Biopsy degree of interstitial Inflammation</td>
<td>2.1±0.8</td>
<td>2.1±0.7</td>
<td></td>
</tr>
<tr>
<td>tubular atrophy</td>
<td>1.2±0.4</td>
<td>1.3±0.6</td>
<td></td>
</tr>
<tr>
<td>eosinophilia</td>
<td>0.9±0.8</td>
<td>1.3±1.0</td>
<td></td>
</tr>
<tr>
<td>plasma cell infiltration</td>
<td>2.0±0.9</td>
<td>2.0±0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>chronic vascular lesions</td>
<td>1.3±0.5</td>
<td>1.6±0.5</td>
<td></td>
</tr>
<tr>
<td>hyalinosis</td>
<td>0.6±0.7</td>
<td>0.6±0.7</td>
<td></td>
</tr>
<tr>
<td>granulomas</td>
<td>0.3±0.6</td>
<td>0.9±1.1</td>
<td>0.03</td>
</tr>
<tr>
<td>oedema</td>
<td>0.3±0.5</td>
<td>0.5±0.8</td>
<td></td>
</tr>
</tbody>
</table>

Aetiology was difficult to definitely ascertain but consisted of drug induced, infectious, sarcoid or sjogrens. Parameters significantly associated with poor outcomes include higher creatinine at presentation & 6 months, presence of granulomas and chronic vascular lesions on biopsy at diagnosis. The effect of steroid treatment was difficult to assess since most patients were treated at the outset.

Conclusions: ATIN usually carries a good prognosis but some patients experience poor outcomes. Poor renal function at diagnosis and the presence of granulomas and chronic vascular lesions are predictive of poorer outcomes.

Cotreatment of Olmesartan and Caterpillar Fungus Attenuate Albuminuria in Patients with Glomerulonephritis
Hua Zhou, Ye Zhang, Ya Li, Hairong Tang, Congcong Jiao, Lining Wang. Nephrology Dept, 1st Hospital of China Medical Univ, Shenyang, China.

Background: Angiotensin II receptor blockers (ARBs) were demonstrated to reduce proteinuria since a decade ago. However, proteinuria still remains as the top of clinical symptoms in glomerulonephritis (GN). We aim to investigate the effect of cotreatment with olmesartan (Olm), an ARB and caterpillar fungus capsule (CF) on proteinuria in patients with GN.

Methods: 491 patients with GN were retrospectively studied. GN was diagnosed by their medical records, including the date of diagnosis and the approximate date of the first symptoms in 194 patients. We have also analyzed data related to ANCA subtype in each patient. The cotreatment with CF showed an increased statistical p value.

Results: Of the 209 patients, 160 (76.7%) were MPO-positive, 28 (13.3%) were PR3 positive and 21 (10%) were ANCA negative. Regarding the onset of symptoms, we found a greater number of cases in the months of January, February and March, compared with the rest of the year. This data correlates positively with the higher incidence of the symptoms in Barcelona between 2009 and 2013.
Considering the date of diagnosis we found a greater number of cases in two periods of the year; the months of May, June and July, and the months of October, November and December.

Conclusions: In our population, predominantly ANCA-PMO-positive related vasculitis, we found a higher incidence of the disease in the winter months, being diagnosed more frequently in May, June and July or October, November and December. One potential environmental factor, influenza disease, may explain this finding.

PUB239
Mycophenolate Mofetil for the Treatment of Idiopathic Nephrotic Syndrome: A Meta-Analysis of Randomized Controlled Trials Bin Zhu, Yongjun Wang. Nephrology, Hangzhou Hospital of Traditional Chinese Medicine (Guangxing Hospital) Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China.

Background: This meta-analysis was performed to investigate the efficacy and safety of mycophenolate mofetil (MMF) in treating idiopathic nephrotic syndrome.

Methods: We searched MEDLINE, EMBASE, the Cochrane Library database, the Database for Chinese Technical Periodicals, Wanfang, Chinese National Knowledge Infrastructure and the Chinese Database of Biology and Medicine for randomized controlled trials compared MMF with the other immunosuppressive agents for the treatment of idiopathic nephrotic syndrome. Weighted mean difference (WMD) and summary estimates of relative risk (RR) reductions with 95% CIs were calculated.

Results: We identified 36 trials that included 2007 patients, mainly on membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS) and refractory nephrotic syndrome without clearly pathological diagnosis (RNS). Overall, MMF therapy significantly reduced proteinuria (WMD=-462.31mg/d, CI: -219.69 to -704.92 P<0.001), increased the likelihood of complete remission (RR: 1.15, CI: 1.09 to 1.22, P<0.001) compared with the other immunosuppressors. The subgroup analyses shown that MMF was superior to other immunosuppressors, particularly than cyclophosphamide.

Conclusions: MMF seems superior to the other immunosuppressive regimens for the treatment of idiopathic nephrotic syndrome with mild adverse effects, particularly in MN, FSGS and RNS. High-quality large-sample trials are still required to reliably define the balance of efficacy and safety.

PUB240
A Retrospective Analysis of Acute Kidney Injury in Adult-Onset Minimal Change Disease Yosuke Nakagawa, Takuya Isegawa, Masahiro Koizumi, Masafumi Fukagawa. Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.

Background: Minimal change disease (MCD) is a major cause of primary nephrotic syndrome in adults, accounting for 10 to 25 percent of cases. In terms of treatment, steroid therapy is very effective, however in some cases an acute onset of moderate to severe decline in kidney function is seen, occasionally requiring transient dialysis. To the best of our knowledge, the risk factor for acute kidney injury (AKI) and clinical course of cases with AKI had not been fully elucidated.

Methods: This study is a single-center, retrospective observational study. The clinical records of adult (older than 18 years old) who had biopsy-proven MCD and who were followed at Tokai University Hospital from 2000 to 2015 were retrospectively analyzed. The diagnosis of AKI was based on KDIGO criteria, namely, serum creatinine changes ≥ 1.5 times baseline within 7 days and a 0.3 mg/dl increase in serum creatinine within 48 hours.

Results: 57 patients were enrolled, and AKI occurred in 24 patients at presentation or subsequently, among whom five patients underwent hemodialysis. Patients with AKI showed lower level of serum albumin and higher rates of use of diuretics, renin-aldosterone system (RAS) inhibitors, and NSAIDs. Logistic-regression analysis showed that use of these drugs before presentation at our institution could predict the development of AKI (odds ratio, 2.8, 95% CI, 2.2 to 3.2). Furthermore, use of these drugs could determine the time to remission (Hazard ratio, 2.4, 95% CI, 1.8 to 3.0), as well as the initial serum creatinine. All cases were initially treated with steroid, and there was no difference in the time to remission between oral and parenteral administration of steroid.

Conclusions: There is a high incidence of AKI in adult-onset MCD. The use of several drugs such as diuretics could influence the onset of AKI and clinical course of MCD.

PUB241
Expression of HLA-G Molecule in Crescentic Glomerulonephritis and Its Clinical Significance Guixue Li, Li Wang. Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chongdu, Sichuan, China.

Background: In recent years, human leukocyte antigen-G (HLA-G) was found to be an important immune-regulatory molecular. Our purpose of this study is to assay the concentrations of serum soluble HLA-G (sHLA-G) in patients with CGN and to analyze its clinical significance.

Methods: 48 patients with CGN from 2009 to 2014 were involved in this study. The clinical data were collected, include demographic characteristics, laboratory parameters, pathological examinations, prognostic information and immunosuppressive therapy. Analyze if oliguria or anuria, serum creatinine levels, the crescent formation ratio and therapy would affect the prognosis of patients.22 patients with CGN, 15 patients with MCD, and 30 healthy adults in control group were enrolled with serum levels of HLA-G measured by ELISA. The relationship between the clinical or pathological features and sHLA-G was studied and the value of the HLA-G in crescentic glomerulonephritis was analyzed.

Results: 3-years kidney survival rate was only 38% with one case of death. Cox regression analysis showed higher serum creatinine was associated with the patients with a poor prognosis (HR=4.04,95%CI:1.548-10.544, P=0.004). Serum level of HLA-G in CGN was significantly higher than in healthy control(2198.81 ± 1294.77pg/ml vs 1311.86 ± 448.84pg/ml, P=0.048), while higher than in MCD, (2198.81 ± 1294.77 pg/ml vs. 1181.33 ± 320.10 pg/ml, P=0.023). Kaplan Meier survival analysis showed elevated levels of HLA-G was associated with poorer patients.

Conclusions: High serum creatinine level(>5mg/dl) at admission is an independent risk factor for the development to be ESRD. sHLA-G was significantly elevated in the serum of patients with CGN, and the level of sHLA-G had relationship with the prognosis of the patients with CGN. sHLA-G may be used as a new biomarker in CGN with clinical value in the early diagnosis and prognosis.

PUB242
A Treatment of Nutcracker Syndrome Leads to a Resolution of Unexplained Proteinuria Badamkhand Baatarkhuu, Raymond Raut, Winston Y. Shih, Panupong Lisawat. Nephrology and Hypertension, WCHN Danbury Hospital, Danbury, CT.

Background: The nutcracker syndrome is rare and can be a cause of unexplained proteinuria. We report a case of nutcracker syndrome related proteinuria and resolution of the proteinuria is observed after the entrapment was surgically corrected.

Methods: This is a 22-year-old male with a history of unexplained proteinuria since he was 17 years old. He has moved to a new location and presented to our clinic with proteinuria. The patient’s initial work up at an outside hospital revealed 1.4g proteinuria per 24 hours. A left kidney biopsy showed mesangial hypercellularity and preserved foot processes. The patient at that time was treated with prednisone, cyclosporine and lisinopril. His proteinuria decreased to 196 mg per 24 hours. Due to intolerance, lisinopril was stopped and urine protein subsequently rose. At the time of evaluation, the patient’s 24 hour urine protein was 700 mg and the autoimmune and infectious work up was negative. Upon reviewing the medical record from 2 years ago, he had inferior venacavagram as a part of varicocele treatment. It showed compression of the left renal vein between the aorta and superior mesenteric artery. Nutcracker syndrome was suspected. Subsequently, he was referred to vascular surgery, and underwent an open reconstructive surgery. Postoperatively the patient remained off lisinopril and repeated 24 hour urine protein was down to 20mg.

Conclusions: Nutcracker syndrome can cause significant proteinuria. Although it is rare, an early recognition could lead to a definitive treatment, help avoid unnecessary medications and invasive procedure such as a kidney biopsy.
A 14 year old girl underwent a cadaveric renal transplant due to end-stage renal disease from obstructive uropathy and developed Parvovirus B19 viremia and graft dysfunction. Renal biopsy showed de novo immune complex glomerulonephritis with Parvovirus B19 DNA detected in renal tissue by PCR. We herein review of B19-associated glomerular diseases.

Methods: A search of the English-language medical literature was conducted. PubMed, Medline, and Google scholar were used. Adult and pediatric cases were included. Sources included case reports and series, including prior reviews. Articles were evaluated for design, sample size, the definition of primary MN, pathology, and clinical outcomes. We report the incidence of Parvovirus B19-DNA in renal tissue from patients with combined MN and FSGS, the percentage of patients with combined lesions showed higher stages of MN, no cellular variant on FSGS classification and more common (100%) tubulointerstitial injury than both primary MN and primary FSGS patients. The patients with combined lesions, 80% had circulating anti-PLA2R antibody and 68.4% had IgG4 predominant deposition in glomeruli, which were comparable to primary MN. No circulating antibody or IgG4 deposition was detected in primary FSGS patients. The patients with combined lesions had significantly lower urinary subPAR concentration, compared to the primary FSGS patients (315.6±302.0 vs. 691.3±1223.5pg/ up, P<0.01), but similar to primary MN patients (275.7±253.4pg/ml in MN).

Conclusions: We conclude that patients with combined MN and FSGS may share the same underlying pathogenesis with primary MN. The FSGS lesion might be secondary to primary MN.

Funding: Government Support - Non-U.S.

Glanzmanns Thrombasthenia: A Coagulation Antithrombin Disorder Causing Glomerular Injury

Methods: A case of a 53 year old female whose known past medical history included only hypertension who presented to the outpatient clinic with arthralgias, pancytopenia, alopecia, proteinuria and skin rash to this point had included an elevated ESR of 115, negative ANA, neg HIV, Hep B, and Hep C serology. She was then lost to followup until presenting to the hospital with anisocoria and acute kidney injury. Her further workup confirmed a negative ANA but also revealed positive Anti-SSa, and anti-SSb. Her platelet count during this time was decreased to 43 and 46 respectively. She had a renal biopsy performed revealing focal proliferative and membranous lupus nephritis, Class III-V. The patient was started on mycophenolate, plaquenil, and prednisone.

Conclusions: Once a byproduct of a technically variable laboratory test, the entity of ANA-negative Lupus has been decreasing.

Methods: We report a case of a 35 year old female whose known past medical history included only hypertension who presented to the outpatient clinic with arthralgias, pancytopenia, alopecia, proteinuria and skin rash to this point had included an elevated ESR of 115, negative ANA, neg HIV, Hep B, and Hep C serology. She was then lost to followup until presenting to the hospital with anisocoria and acute kidney injury. Her further workup confirmed a negative ANA but also revealed positive Anti-SSa, and anti-SSb. Her platelet count during this time was decreased to 43 and 46 respectively. She had a renal biopsy performed revealing focal proliferative and membranous lupus nephritis, Class III-V. The patient was started on mycophenolate, plaquenil, and prednisone.

Conclusions: Once a byproduct of a technically variable laboratory test, the entity of ANA-negative Lupus has been decreasing in its frequency. The adoption of the human epithelial substrate has brought standardization to this assay and also increased its sensitivity. The incidence of ANA negative Lupus has been decreasing.

Methods: We report a case of a 53 year old female whose known past medical history included only hypertension who presented to the outpatient clinic with arthralgias, pancytopenia, alopecia, proteinuria and skin rash to this point had included an elevated ESR of 115, negative ANA, neg HIV, Hep B, and Hep C serology. She was then lost to followup until presenting to the hospital with anisocoria and acute kidney injury. Her further workup confirmed a negative ANA but also revealed positive Anti-SSa, and anti-SSb. Her platelet count during this time was decreased to 43 and 46 respectively. She had a renal biopsy performed revealing focal proliferative and membranous lupus nephritis, Class III-V. The patient was started on mycophenolate, plaquenil, and prednisone.

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Acute Renal Failure in Thrombotic Microangiopathy and C3 Glomerulopathy? Tiziana Stellato, 1 Paolo Fabbrini, 1 Sonia Sirtori, 2 Andrea Stefl, 1, 2 Dept of Nephrology, San Gerardo Hospital, Monza, Italy; 1 Univ of Milano Bicocca, Milan, Italy.

Background: Thrombotic microangiopathy is a rare disease characterized by arteriolar and capillary thrombosis with endothelial damage. Clinical manifestations include renal involvement, such as focal segmental glomerulosclerosis and proteinuria and hypertension.

Methods: We report a case of a 75 years old man without past medical history that referred to us with oliguric acute renal failure diagnosis-diplopia. Laboratory work up revealed creatinine of 7.5 mg/dl, prolonged activated partial thromboplastin time (APTT) in order to 2.2 Ratio, normal serum creatinine (56 mg/dl) with normal proteinuria, VES augmented, positive low titer anti-cardiolipine and anti-beta2 glicoprotein1 antibodies, positive LAC screening. Urinalysis showed microhematuria and proteinuria 2.5 g/24 h, ANA, ANCA, antinuclear are negative. A renal biopsy was performed and showed mesangial proliferative glomerulonephritis associated to thrombotic microangiopathy with subendothelial and mesangial C3 deposits. Considering the clinical history, the laboristic tests and the biopsy result, suggestive of antiphospholipid syndrome (APS), we start treatment with plasma-exchange (total 4 sessions) with plasma sostitution and corticosteroids (500 mg IV methylprednisolone for 3 days, followed by 0.5 mg/Kg/die oral prednisone). So with plasma-exchange (total 4 sessions) with plasma sostitution and corticosteroids (500 mg IV methylprednisolone for 3 days, followed by 0.5 mg/Kg/die oral prednisone). So with plasma-exchange (total 4 sessions) with plasma sostitution and corticosteroids (500 mg IV methylprednisolone for 3 days, followed by 0.5 mg/Kg/die oral prednisone).

Conclusions: Our case represents an unusual finding of RBC casts in myoglobinuric ATN. We purpose then recovered with residual CKD.

Acute Renal Failure is a reversible kidney damage that can revert with a specific diagnosis and treatment. Kidney biopsy was always gold standard and a combination of clinical data and renal databases.

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

Underlines represents presenting author.

945A
Idiopathic Cryoglobulinemic Crescentic Glomerulonephritis – A Rare and Atypical Case
Pedram Joseph Kohan, 1 Akshatha Rao, 2 Sandeep Aggarwal. 1 Internal Medicine, Drexel College of Medicine/Hahnemann Univ Hospital, Philadelphia, PA; 2 Nephrology, Drexel College of Medicine/Hahnemann Univ Hospital, Philadelphia, PA.

Background: Cryoglobulinemic glomerulonephritis is an exotic entity, manifesting in middle-aged females. We report an atypical case of cryoglobulinemic crescentic glomerulonephritis in an 18-year-old African American Male without an identifiable viral, autoimmune or lymphoproliferative etiology.

Methods: Our case is an 18 y/o AAM with no significant PMH who presented for an incidental herniating and proteinuria. Patient did not complain of edema, recent illness, joint pains, rash, night sweats or weight loss. No history of IVDA, BP was 114/72, without significant physical exam findings. Urine microscopy: cellular casts and dysmorphic RBCs. Serum creatinine was 1.27 mg/dL.

Results: The primary outcome was reached in 24 patients, 16 with IgA and 8 with IgA+IgG (p=0.82). The incidence of renal replacement therapy, death, OR doubling of serum creatinine (SCr). The change in estimated GFR (eGFR) was also assessed. Covariates were age, sex, race, SCr and proteinuria at biopsy, length of follow-up, treatment, Oxford score, and presence of crescents.

Conclusions: This cohort was 64% male, 69% Caucasian and 14% Asian. IgA+IgG deposits were seen in 25 of the patients. There was no difference between IgA and IgA+IgG with respect to any of the covariates or between initial and follow-up proteinuria. There was a tendency for more endocapillary hypercellularity to be seen in IgA+IgG biopsies (p=0.08). The primary outcome was reached in 24 patients, 16 with IgA and 8 with IgA+IgG (p=0.82). Using multivariate modeling the change in eGFR over time was not different between IgA and IgA+IgG.

Conclusions: In this cohort of IgAN patients the presence of IgG co-deposits in the mesangium did not affect clinical outcomes.

PUB265
Renal Biopsy

Clinical Significance of Glomerular IgG Deposits in IgA Nephropathy
Anthony Alvardo, 1 Nicole K. Andeen, 1 Sergey V. Brodsky, 2 Alice Hinton, 3 Tibor Nadasy, 4 Charles E. Alpers, 2 Christopher D. Blosser, 5 Behzad Najafian, 2 Brad H. Rovin. 1 Faculty of Medicine, Nephrology Div, The Ohio State Univ, Columbus, OH; 2 Pathology Dept, Univ of Washington, Seattle, WA; 3 Pathology Dept, The Ohio State Univ, Columbus, OH; 4 Div of Biostatistics, College of Public Health, The Ohio State Univ, Columbus, OH; 5 Faculty of Medicine, Nephrology Div, Univ of Washington, Seattle, WA.

Background: IgAN is characterized by IgA dominant or IgA+, 1 Isao Kurihara, 1 Sayuri Suzuki, 1 Shintaro, 1 Akshatha Rao, 2 Sandeep Aggarwal. 2

Methods: We experienced a case of ChRCC with adrenal pheochromocytoma in a 69-year-old Japanese female. We noticed that iodine-123 MIBG scintigraphy showed uptake in ChRCC in addition to RCC. It is not cytotoxic, uptake is not observed in other cases of clear cell carcinoma. As a candidate transporter that mediate iodine-123 uptake in ChRCC, we determined the expression of pendrin, a Cl-/HCO3- exchanger expressed in the kidney cortex. The pendrin messenger RNA (mRNA) expressions, and protein expressions were analyzed in 4 cases of ChRCC and 3 cases of clear cell carcinoma.

Conclusions: The protein expression of pendrin, the candidate transporter, which related to iodine-123 uptake, was highly detected in ChRCC compared with clear cell carcinoma. Moreover, the mRNA expression was also exclusively increased in ChRCC.

Conclusions: The uniqueness of this case is underscored by a variety of factors: clinical presentation, laboratory, serologies, and pathology. Laboratory and serologic studies in cryoglobulinemia generally follow a characteristic pattern, detection of circulating cryoglobulins, low levels of complement, viral, autoimmune or lymphoproliferative etiology - yet a limited number of cases have presented with normal serological results, similar to the case presented here.

PUB268
Development of a Clinicopathologic Kidney Biopsy Database Using Billing and Diagnosis Codes: A Descriptive Study
Nosayaba Enok, 1 Anju A. Oommen, 1 Jason Cobb, 1 Jose E. Navarrete, 1 Demilade Adesinewo, 1 Oluwatobiloba A. Osikoye, 2 Helen B. Fevrier, 3 Frederic F. Rahhari-Oskou, 4 Alton Brad Farris, 1 Laura Plantinga, 1 Titilayo O. Ibiro, 1 Dept of Nephrology, Emory Univ School of Medicine, Atlanta, GA; 2 Morehouse School of Medicine, Atlanta, GA; 3 Lee Univ, Cleveland, TN; 4 Dept of Epidemiology, Rollins School of Public Health, Emory Univ, Atlanta, GA; 5 Dept of Pathology and Laboratory Medicine, Emory Univ School of Medicine, Atlanta, GA.

Background: A growing kidney disease population coupled with expanded use of electronic medical records (EMR) presents a unique opportunity for regional translational clinical research. We developed a comprehensive registry of all native renal biopsies at a major hospital in Southeastern US and described the pattern of glomerular diseases.

Methods: We identified all native percutaneous renal biopsies (n=2,245) performed at OhioHealth (18) between 2000 and 2011 using CPT and ICD-9 billing codes (50200 and 55 23). Transplant biopsies (V42.0) and cytopathology were excluded. Renal pathology reports were reviewed by at least two independent clinical nephrologists. Clinical, laboratory and demographic data were extracted and validated by independent chart review. A clinicopathologic diagnosis was subsequently entered. Descriptive and bivariate statistics were used to analyze patient characteristics at biopsy.

Results: Patients in the registry had a mean age of 44.2 years; approximately half were male and majority were African American (40%). Overall, lupus nephritis (n=278, 12.4%) was the most prevalent renal clinicopathologic diagnosis. Among primary glomerular diseases, FSGS (136, 9.2%) was the most prevalent, followed by IgA nephropathy (123, 8.3%), membranous glomerulonephritis (GN) (69, 4.6%), membranoproliferative GN (24, 1.6%) and minimal change disease (27, 1.8%). Diabetic nephropathy was the second most common secondary GN (97, 6.5%) followed by ANCA-associated vasculitis (31, 2.1%). Other diagnoses were all less than 2%.

Conclusions: We successfully established a kidney biopsy registry at our center, which will be instrumental to studying outcomes in this rare group of diseases, the most prevalent of which were lupus nephritis and FSGS.
Is There Clinical Significance of IgM and Complement Staining in Idiopathic Focal Segmental Glomerulosclerosis?  

Lilian M. Pereira, 1 Alicia Imada, 1 Alexander J.M. Darding, 1 Rudolphe De Sevaux, 1 Ron T. Connor, 1 2 3 4

1Nephrology, Barts & The London NHS Trust, London, United Kingdom; 2Pathology, Barts & The London NHS Trust, London, United Kingdom.

**Background:** Experimental evidence suggests that focal segmental glomerulosclerosis with complement deposits is associated with poor outcome. Whether this is transferrable or relevant in human disease is unclear.

**Methods:** We performed a proof-of-concept observational study on all patients with a diagnosis of idiopathic focal segmental glomerulosclerosis (fSGS) native renal biopsies from January 2004 to December 2014. A total of 40 renal biopsies were identified. Clinical outcome data were obtained to seek an association with complement deposits (CD) and outcomes. Immunosuppression administered was according to the local trust policy which included prednisolone and cyclophosphamide or calcineurin inhibitor.

**Results:** See Table 1

<table>
<thead>
<tr>
<th>No CD (n= 21)</th>
<th>CD (n= 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43 (35-50)</td>
<td>39 (30.5-54.5)</td>
</tr>
<tr>
<td>Sex Male</td>
<td>11 (52)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Race Black/Asian/White</td>
<td>6 / 9 / 6</td>
<td>8 / 5 / 6</td>
</tr>
<tr>
<td>Type of lesion : Flip/Collapsing/NOS</td>
<td>2 / 2 / 17</td>
<td>3 / 0 / 16</td>
</tr>
<tr>
<td>IgM</td>
<td>0 (0)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>12 (57)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Baseline urine protein creatinine ratio (UPCR)</td>
<td>540 (330-1000)</td>
<td>1000 (560-1200)</td>
</tr>
<tr>
<td>Baseline albumin</td>
<td>29 (24-38)</td>
<td>26 (21-36)</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>49 (25-71)</td>
<td>60 (48-81)</td>
</tr>
<tr>
<td>Change in UPCR</td>
<td>-370 [−700 -(-140)]</td>
<td>-430 [−790 -(-260)]</td>
</tr>
<tr>
<td>Change in serum albumin</td>
<td>8.5 (2.3-13)</td>
<td>4 (0-17)</td>
</tr>
<tr>
<td>Change in eGFR</td>
<td>4.5 (5.5-21)</td>
<td>4 (-15-11)</td>
</tr>
</tbody>
</table>

CD was present in approximately 50% of the biopsies, but there was no significant association between CD and baseline clinical or demographic characteristics, furthermore, there are no association between CD and markers of disease progression (change in proteinuria, serum albumin or GFR between baseline and 1 year follow up). IgM staining was strongly co-associated with CD.

**Conclusions:** Our results indicate that, unlike animal models of fSGS, IgM and complement deposition does not alter outcomes. However, these findings will need to be confirmed in a larger study.

**PUB258**

A Case of Intra-Ocular Lucentis (Ranibizumab) Induced Minimal Change Disease  
Ashwin Reddy Ganta, Dept. of Nephrology, Archbold Memorial Hospital, Thomasville, GA.

**Background:** Intravitreal monoclonal antibodies like Lucentis (Ranizibumab) , Eylea and Avastin are being increasingly used for the treatment of Wet Age-related Macular Degeneration (wAMD) and Diabetic Macular Edema (DME) of the eye. Though the systemic toxicity of these VEGF inhibitors is well known, not much is known about the renal toxicity profile of these agents when administered intravitreally.

**Methods:** A 78 y/o WM presented with worsening shortness of breath and anasarca. His Scr was 1.5 (0.9-2.0) mg/dl and platelet count was 12 (57) x 10^9/L. Given his h/o cancer with almost 3 gms of proteinuria, MCD (Minimal Change Disease) was high in the differential. Serology for HIV, SPEP, Hep C, SIEP, ANA and ANCA was negative. Given his h/o cancer with almost 3 gms of proteinuria, MCD (Minimal Change Disease) was high in the differential. Serology for HIV, SPEP, Hep C, SIEP, ANA and ANCA was negative. His PMH was significant for Afib, h/o Lung Cancer s/p RLL resection 8 years ago and he was receiving Lucentis intravitreal shots for his AMD and had just had his 5th monthly dose a few days ago. His urine showed 3+ protein with some RBCs and we were consulted for worsening renal function with a Scr of 2.4 mg/dl, up from a baseline of 1.0 mg/dl. Given his h/o cancer with almost 3 gms of proteinuria, MCD (Minimal Change Disease) was high in the differential. Serology for HIV, SPEP, Hep C, SIEP, ANA and ANCA was negative. His Scr continued to worsen and reached a peak of 4.6 and he had to undergo Diabetic kidney disease. Renal Biopsy performed showed 9 g/gm with no evidence of IC, double medullary bluing or MCD pattern confirmed on EM. He was started on high dose steroids and discharged with a diagnosis of MCD 2/2 Lucentis. He was taken off HD after he started showing signs of renal recovery in a few weeks and he was gradually tapered of Steroids over the next 4 months. His proteinuria has completely subsided and his Scr is back to his baseline.

**Conclusions:** Systemic use VEGF inhibitors and their renal toxicity is well documented. Now, they are currently being used to treat wAMD and DME. However, there is some evidence that intravitreal use may result in systemic absorption, with the potential for AKI. We report the first case to our knowledge of a patient who developed severe AKI needing HD with MCD pattern of injury after 5 intravitreal injections of ranibizumab that was successfully treated with cessation of Lucentis and Steroids. Because of the increasing use of these agents, ophthalmologists and nephrologists should be aware of the associated risks.
Methods: Multiplex ligation-dependent probe amplification (MLPA) kits have been developed for genetic analysis using proprietary MLPA technology. We obtained informed consent from nine patients (mean age, 45 years) and collected 8 mL of blood from each patient for analysis of genetic mutations in PKD1 and PKD2 genes using the MLPA method.

Results: In case 1 (a 39-year-old man), we found deletions in exons 3 and 39 of the PKD1 gene. The kidney was extracted due to enlargement and cyst infection. Dialysis was initiated when the patient was 39 years of age. The kidney capacity was 5013 mL. In case 2 (a 32-year-old woman), we found a deletion in exon 3 of the PKD1 gene. Renal function was maintained, and the serum creatinine level was 0.7 mg/dL. She has hope of the delivery. Tolvaptan does not have the safety about the dosage to a pregnant woman. Tolvaptan was administered after delivery.

Case 1

Case 2

No mutations were identified in the other subjects.

Conclusions: Genetic screening of the PKD1 and PKD2 genes using the MLPA method may decrease cost and labor. Indeed, the MLPA method was especially useful in cases exhibiting juvenile onset and rapid kidney enlargement.

The administration of tolvaptan significantly reduced body weight, eGFR, TBW, ICW and ECW in whole body and TBW in limbs. However, TBW in trunk were sustained (Table).

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>day2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>64.0±12.5</td>
<td>62.1±11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>53.9±27.2</td>
<td>51.4±24.8</td>
<td>0.013</td>
</tr>
<tr>
<td>TBW whole (kg)</td>
<td>38.2±8.1</td>
<td>36.0±7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECW whole (kg)</td>
<td>14.0±2.9</td>
<td>13.9±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICW whole (kg)</td>
<td>23.3±5.2</td>
<td>22.2±4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TBW trunk (kg)</td>
<td>16.8±3.7</td>
<td>16.5±3.5</td>
<td>0.75</td>
</tr>
<tr>
<td>ICW trunk (kg)</td>
<td>10.3±2.4</td>
<td>10.2±2.2</td>
<td>0.58</td>
</tr>
<tr>
<td>TBW limbs (kg)</td>
<td>16.9±4.3</td>
<td>15.7±4.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HtTKV at baseline correlated with rate of ICW in trunk and TBW in whole at baseline (r=0.39, P=0.049). There were no significant correlation between eGFR decrease and rate of change in body weight (r=0.02, P=0.46). Rate of TBW in limbs and TBW in whole at baseline correlated with rate of change in eGFR (r=0.45, P=0.028). These results suggest that cyst fluid might be measured as ICW by InBody720®. TBW in limbs can predict eGFR decline.

Conclusions: Measuring body water balance by InBody720® could be useful as predictors of HtTKV and eGFR decline in short term after administration of tolvaptan in ADPKD patients.

On admission biochemical tests;urea 132 mg/dl,creatinine 4.7 mg/dl,potassium 4.7 mmol/L, pH 7.32,HCO3 18.4.Urinary output was satisfactory,no uremic symptoms were present.Renal ultrasonography revealed bilateral renal cysts with normal size and parenchymal thickness.Histopathology of the Shagreen patch revealed dense collagen bundles in the dermis.Due to the skin lesions and renal cysts the patient was diagnosed as TS.Other manifestations of TS were not present.Renal biopsy was suggested but she did not accept the procedure.

Conclusions: As stated in diagnostic criterias,physical examination has a strong impact on diagnosis of TS.Hypomelanotic macules (~3),Shagreen patch,forehead plaque,non traumatic periumbilical fibromas,adenoma sebaceum,facial angiofibromas should remind the physicians TS.Kidneys are involved in almost 50-80% of the adult patients.Most frequent renal lesions in TS are angiomyolipomas.Bilateral and multiple characteristics of angiomyolipomas are pathognomonic.They may progress to end stage renal disease.However in some rare cases frank renal lesions may be absent.With a detailed inspection it is possible to recognize these specific dermatological signs,marking the Tuberous sclerosis diagnosis and taking these patients under nephrological follow up.

Use of Antidepressant Medications During the HALT-PKD Randomized Trials Vicente E. Torres,1 Kaleab Z. Abebe,2 Theodore I. Steinman,1 Charity G. Moore,3 Ronald D. Perrone,4 Arlene B. Chapman,5 Robert W. Schrier,6 Alan S.L. Yu,7 William E. Braun,8 Kyongtae Ty Bae,9 Peter C. Harris,10 Charity G. Moore,11 Michael F. Flesner,12 The HALT PKD Investigators,13-15 Mayo;16 U. Pittsburgh;17 BIDMC;18 Tufts U.;19 U. Chicago;20 U. Colorado;21 KS U. Med. Ctr.;22 Cleveland Clinic;23 NIH;24 Multi-Ctr.

Background: Depressive disorders are highly prevalent in a general population and are associated with poor outcomes. The use of antidepressants (ADs) has been associated with inappropriate release of vasopressin and hyponatremia. Since vasopressin exposure for less £30% and exposure for >30% of the time:

Table: Use of ADs During the HALT-PKD Randomized Trials

<table>
<thead>
<tr>
<th>Gender</th>
<th>No ADs</th>
<th>≤30% ADs</th>
<th>&gt;30% ADs</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26.4</td>
<td>61.5</td>
<td>12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>21.2</td>
<td>63.0</td>
<td>15.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: Measuring body water balance by InBody720® could be useful as predictors of HtTKV and eGFR decline in short term after administration of tolvaptan in ADPKD patients.

Conclusion: Tolvaptan does not have the safety about the dosage to a pregnant woman. Tolvaptan was administered after delivery.
five topics/outcomes (surgical management of cysts, patient education about end-stage kidney disease, psychosocial impact of diagnosis, need for dialysis, knowledge). Many more topics (33) and outcomes (44) were identified as priorities by health professionals than consumers. Six themes reflected reasons for consumer choices: clarifying ambiguities, resolving debilitating pain, concern for family, preparedness for the future, taking control, and significance of impact.

Conclusions: Although there was considerable concordance between the priority topics and outcomes of health professionals and consumers for guidelines of ADPKD, there was also important discordance with consumers focused on fewer but particularly on lifestyle, psychosocial support, pain management, and quality of life and renal outcomes.

Funding: Government Support - Non-U.S.

PUB268

Urinary AQP2 Is One of the Candidates for a Surrogate Marker in the Treatment of ADPKD Patients by Tolvaptan

Kenichi Akitaiguchi, Toshihiko Mochizuki, Miki Nishida, Masayo Sato, Hiroshi Katoita, Hidekazu Sugira, Ken Tsuchiyi, Kosaku Nitta. Medicine IV, Tokyo Women’s Medical Univ, Shinjyuku, Tokyo, Japan.

Background: Tolvaptan, arginine vasopressin (AVP)/V2 receptor antagonist is accepted for autosomal dominant polycystic kidney disease (ADPKD) patients in Japan since 2014. TEMPO study showed tolvaptan from 60 to 120 mg per day slowed renal cyst expansion and renal function decline. Tolvaptan dose is decided by preliminary study (TEMP01), which showed the maximum dose that meet both urinary osmolality (Uosm) under 300 mOsm/kg and patient’s tolerance. So that adequate dose for individual patient has not been suggested. Moreover, tolvaptan cause polyuria, thirsty, polydipsia due to aquaresis. Thus, it is necessary to find surrogate markers for determine the maximum effects and minimum side effects for long-term administration.

Methods: Seventeen ADPKD patients initiated tolvaptan of 60 mg were investigated. Physical data, plasma osmolality (Posm), Uosm, AVP, urine cyclic AMP (UCAMP), and urine AQP2 (UAQP2) were assessed. UCAMP was measured by radioimmunossay (Yamasa corp.), and UAQP2 was measured by a sandwich enzyme-linked immunosorbent assay method (Otsuka Pharmaceutical Co. Ltd.).

Results: After initiation of tolvaptan, average urinary volume was 862±1 m/L/day and daily weight loss was -1.42 kg/day on day 1. One month after, AVP increased from 3±3 to 7.3±11.2 pg/mL (p < 0.001). Uosm decreased from 367±349 to 243±436 mOsm/kg (p < 0.001). Posm and UCAMP were not statistically associated. UAQP2 decreased from 0.029±0.068 to 0.012±0.028 pmol/MgCr (p < 0.001). In our preliminary data (n=5), the serum copeptin, a precursor of vasopressin, was shown to be no consistent level.

Conclusions: It has been reported that 3% of total production of AQP2 excreted into the urine, it reflected directly the intracellural action of AVP. Thus, UAQP2 is likely to be one of surrogate markers of tolvaptan effect, moreover it could provide additional information of determination of individual dosage and monitoring for long-term usage.

Funding: Private Foundation Support

PUB269

Abnormalities in the Radius of Patients with Autosomal Dominant Polycystic Kidney Disease Measured by High-Resolution Peripheral Quantitative Computerized-Tomography Imaging

Danielle Diarra, Janina M. Patsch, Claudia Schuemel-Weidemann, Michael Weber, Arastoo Nia, Gere Sunder-Plassmann. 1Dept of Medicine III, Medical Univ of Vienna, Austria; 2Dept of Radiology, Medical Univ of Vienna, Austria; 3Dept of Medicine II, St. Vincent Hospital, Medical Univ of Vienna, Austria.

Background: ADPKD is a multi-organ disorder and the most common of all cystic kidney diseases. Mutation of the PKD1 or -2 gene causes epir- and endothelial cell proliferation, which lead to the dysfunction of various organs. Animal studies show that primary cilia are present in osteoblasts of mice and point mutation of the osteoblastic KIF7 gene induces osteopenia.

Methods: In this pilot-study, we examined the bone structure in 6 ADPKD patients in comparison to 6 matched patients with glomerular disease (GD), both in CKD stages I-II, by HR-pQCT of the radius and the tibia. The aim of the study was to identify microarchitectural target parameters for a subsequent larger study in patients with ADPKD.

Results: Demographic data see Table 1.

Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GD Patients (controls)</th>
<th>ADPKD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27±6.4</td>
<td>26±7.6</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.83±0.17</td>
<td>0.83±0.19</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>109±18</td>
<td>108±23</td>
</tr>
</tbody>
</table>

We found reduced cortical and trabecular microstructural parameters by HR-pQCT, mainly affecting the radius. The outer trabecular density, the cortical thickness and the total density of the radius showed the biggest differences between the two groups, see Figure 1.

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

Underline represents presenting author.

949A
The total density of the radius was the best parameter to distinguish between the bone structure of ADPKD in comparison to GD patients (AUC = 0.861).

Conclusions: We provide evidence of microstructural bone deterioration in the radius in patients with ADPKD. We thus hypothesize that ADPKD is associated with microstructure bone changes in men.

PUB270

An Accurate Formula for a Quick Estimate of Total Liver Volume in Polycystic Liver Disease Patients

Background: Polycystic liver disease (PLD) appears in two disorders; autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (ADPLD). The primary aim of treatment of PLD is reduction of total liver volume (TLV) as patients often suffer from hepatomegaly. The gold standard to assess TLV is CT volumetry which involves manual delineating of the liver outline. Unfortunately this is a time-consuming method (45–60 minutes per CT scan) and requires a certain level of expertise. An easily accessible and fast method to estimate TLV in routine clinical practice is needed. Therefore we aimed to develop an accurate formula for quick estimation of TLV.

Methods: We collected a cohort of PLD patients in whom CT scans were available. Manual delineation of TLV served as gold standard. PLD patients were distributed in 2 cohorts, a development cohort (N=80) and a replication cohort (N=50). We measured anterio-posterior (AP), transverse (T) and cranial (CC) distance (in meters) of the liver on CT. TLVs were logarithmically transformed as data were not normally distributed. R² was measured as it indicates the goodness of fit of the prediction model. The prediction model was tested in a replication cohort.

Results: Median liver volumes in the development and replication cohort were 4749 mL and 4810 mL respectively. All three diameters significantly correlated with TLV (p<0.0001). Linear regression analysis resulted in the following formula: Logarithm of TLV = 5.240 + T*0.680 + CC*2.522 + AP*0.041. Our model predicted TLV accurately in the development cohort (R²=0.898). The correlation in the development cohort was R²=0.848 and validation in the replication cohort resulted in a correlation of 0.937.

Conclusions: Our model accurately and quickly (<2 minutes) predicts TLV in PLD patients based on three liver dimensions.

PUB271

Clinical Significance of Urine NAG and L-FABP Excretion for the Assessment of ADPKD-Progression

Background: Polycystic Kidney Disease: Genetics and Disease Progression in HALT-PKD

Results: We provide evidence of microstructural bone deterioration in the radius in patients with ADPKD. We thus hypothesize that ADPKD is associated with microstructure bone changes in men.

Conclusions: We provide evidence of microstructural bone deterioration in the radius in patients with ADPKD. We thus hypothesize that ADPKD is associated with microstructure bone changes in men.

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

Underline represents presenting author.
**Results:** We identified 56 unique patient visits in the previous six months. Mean age was 44.6 (16.1-14.9) years. 29 (52%) were women. 28 patients had documentation of dietary discussions; 26 received water intake recommendations; and 8 received exercise advice. Only 5 patients received counseling on all 3 parameters.

### Table: Number of patients receiving counseling on X of 3 (Diet, Water intake, Exercise)

<table>
<thead>
<tr>
<th></th>
<th>Diet</th>
<th>Water</th>
<th>Exercise</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 of 3</td>
<td>21</td>
<td>13</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>1 of 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 of 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 of 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions: Prevalence of lifestyle counseling was moderate as ascertained by chart review of our electronic medical record. Discussion of exercise recommendations was low. Nephrologists could consider focusing more attention on offering lifestyle counseling to individuals with ADPKD.

**Funding:** Clinical Research Support

**PUB274**

**Lipid Alterations in Murine Models of Polycystic Kidney Disease**  
**Christine Podrin,1 2 Isaline Rowe,2 Marco Chiaravalli,2 Alessandra Boletta,2\*  
\*Univ Vita-Salute San Raffaele, Milan, Italy; 2Dibit San Raffaele Scientific Inst, Milan, Italy.

### Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic disorder characterized by massive bilateral renal cyst formation. ADPKD results from mutation in the PKD1 or PKD2 genes, encoding Polycystin-1 (PC-1) and 2 (PC-2) proteins respectively. Previous studies have suggested that the mTORC1 cascade might play an important role in PKD. Further, mTORC1 regulates the activity of SREBP which regulate the expression of genes required for the synthesis of fatty acids and cholesterol. However, the regulation of fat synthesis in ADPKD remains poorly understood. In this study, we seek to understand the relationship between fatty acid regulation and defective PKD1 function.

### Methods: We analyzed newborn kidneys of Ksp-Cre/Pkd1flox/+ mice and detected an increased expression of SREBP1 and its target genes including fatty acid synthase (FAS) and steroyl-CoA desaturase (SCD) when compared to control, non-cystic kidneys (Ksp-Cre/Pkd1flox/+ or Pkd1flox/flox).

### Results: As expected the increased expression of SREBP1 also correlated with increased transcript levels of SREBP2 concomitant with an increased transcript levels for sterol biosynthesis mevalonate kinase (MVK) and acetyl-CoA synthase (ACSL). Next, we performed a lipidomic profiling of Ksp-Cre/Pkd1flox/+ kidneys compared to controls Ksp-Cre/Pkd1flox/flox collected at P4 using shotgun lipidomics technology. The profiles confirmed the alteration of some lipid classes, particularly sphingolipids and sterol esters (cholesterol).

Of interest both have been implicated in regulating membranes trafficking and they may cross-talk to mTORC1 in response to altered nutrient/fatty acid signals. Notably, some of the lipid alterations that we observed appear to be gender-specific.

### Conclusions: We are currently characterizing this aspect further and trying to determine which lipid alterations might be dependent and/or independent of mTORC1 upregulation.

**Funding:** Private Foundation Support

**PUB275**

**Reactive Hyperaemic Index in Early Disease Stages of Autosomal Dominant Polycystic Kidney Disease**  
**Adebowale Olavinka Adekoya,1 Andrew J. Streets,1 Albert C. Ong.1**  
1Academic Nephrology Unit, The Medical School, Univ of Sheffield, Sheffield, South Yorkshire, United Kingdom; 2MRC Centre for Developmental and Biomedical Genetics, Univ of Sheffield, Sheffield, South Yorkshire, United Kingdom.

### Background: ADPKD is the commonest inheritable cause of ESKD. Cardiovascular complications are the commonest cause of death in ADPKD. Endothelial dysfunction (ED) has been reported to precede CVE events. In our pilot study of sixty ADPKD patients in the late stages of disease (CKD 3 and above), ADMA and 8 isoprostane were found to be increased suggesting ED. The aim of this study is to investigate ED in the ADPKD patients in early stages of the disease (CKD 1 and 2) and to identify factors associated with its severity.

### Methods: This is a single centre cross sectional study of ADPKD patients in the early stages of disease. Individuals with HBP, DM, CKD 3 and above, ADMA and 8 isoprostane were found to be increased suggesting ED. The aim of this study is to investigate ED in the ADPKD patients in early stages of the disease (CKD 1 and 2) and to identify factors associated with its severity.

### Results: The mean age of the patients was 40.80 ± 14.18 years. M:F was 1:2.3. Prevalence of lifestyle counseling was moderate as ascertained by chart review of our electronic medical record. Discussion of exercise recommendations was low. Nephrologists could consider focusing more attention on offering lifestyle counseling to individuals with ADPKD.

### Conclusions: The Cysts volume is useful to predict prospectively the EPO requirement in ADPKD in stage 4-5 CKD.

**Funding:** Private Foundation Support

**PUB277**

**A Novel Method to Determine Glomerular Volume Distribution from Few Serial Sections on a Single Slide**  
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### Background: Estimating glomerular volumes is important in understanding pathogenesis of glomerular diseases. Some methods are convenient but give a single mean volume for the entire kidney and do not provide volume profiles. Methods for volume profiling are too laborious for routine use. We describe here a new method to obtain glomerular volume profiles from few serial sections. The method uses the formula, R^2 = r_1^2 + (r_1^2 - r_2^2)/2h^2, where R is the radius of a sphere and r_1, r_2 are the radii of two parallel circular planes cut across the sphere h distance apart.

### Methods: To validate our method we compared glomerular volumes between normal (n=5) and STZ diabetic rats (n=4) by measuring 100 random glomeruli from each group. Three (or four) serial sections each 5µm apart were obtained on the same slide. Sections were stained with H&E and glomerular diameter was measured at four points to arrive at a mean diameter and radius r. The same glomerulus was identified on the third (h=10 µM) (or fourth; h=15 µM) section to similarly determine r_1, R was calculated by the formula to obtain the glomerular volume (4/3 π R^3).

### Results: The mean glomerular volume (10^5 µM^3) of normal rats was 1.04 ± 0.06, a value very close to that determined by MRI recently (Heilmann et al 2012). The mean glomerular volume of diabetic rats was 1.48 ± 0.06, which was 45% higher (P<0.03) than normal, confirming glomerular hypertrophy. While the volume distribution in normal rats was Gaussian, the distribution of glomerular volumes in diabetic rats was skewed towards higher volumes (42% glomeruli >1.4 X 10^5 M^3 compared to 12% in normals), suggesting that not all glomeruli but only a population of glomeruli hypertrophied in diabetic rats.

### Conclusions: Precise glomerular volumes can be conveniently determined by our method using a few serial sections of the kidney, making it possible to obtain glomerular volume distribution from experimental as well as human kidney biopsies.

**Funding:** Private Foundation Support
Amniotic Fluid Stem Cells Transplantation in Fetal Kidney to Regenerate Nephrons Loss
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Background: Amniotic fluid stem cells (AFSC) harbour the potential to differentiate toward renal lineages and contribute to the development of primordial kidney structures. To investigate whether AFSC can improve prenatal renal compensatory growth, cells were transplanted in a model of subtotal nephrectomy (5/6NX) in the fetal sheep.

Methods: Using AFSC labelled with GFP were selected using c-kit. In absence of LIF, AFSC formed embryonic bodies which cultured in an optimized medium generated a renal epithelial progenitor population (oAFSCd), expressing Pax-2. 5/6NX was performed at 70 days of gestation in 10 fetal lambs; 5 were injected with oAFSCd in the kidney poles. Sham-operated did not receive oAFSCd (SHAM, n=8). At 134 days of gestation, fetuses were euthanized, kidneys removed and processed.

Results: Body weight did not differ significantly among the groups and no morphologic abnormalities were observed, in spite of a severe reduction in amniotic fluid in 5/6NX vs 5/6NX+oAFSCd. Compensatory renal growth of the remaining kidney was observed in all 5/6NX, but in spite of oAFScd injection, catch-up kidney growth was similar in both 5/6NX groups: SHAM: 2711±644.7 g vs 5/6NX+oAFSCd: 5341±1499.7 g. Glomeruli number/section was similar in all groups: SHAM: 27±64.2 vs 5/6NX+oAFSCd: 25.5±1.4 KW/BW. Glomeruli number/section was similar in all groups: SHAM:27±1;237;5/6NX:2155±694;5/6NX+oAFSCd:1962±199. In 5/6NX+oAFSCd, GFP cells were present in renal proximal tubules, and proximal tubule hypertrophy was observed.

Conclusions: Transplantation of oAFSCd predifferentiated toward renal epithelial progenitor cells during nephrogenesis increases proximal tubule mass but has no effect on the number of glomeruli in 5/6NX and do not restore fully kidney damage. Funding: Private Foundation Support

Low Birth Weight Impairs Renal Development and Function

Background: Low birth weight (LBW) results in a significant risk to the newborn, with many of these babies developing acute kidney failure and dying soon after birth due to underdeveloped vascular and renal systems. Surviving LBW neonates are also susceptible to a variety of health problems later in life during adulthood including hypertension, diabetes and chronic kidney disease with an associated 70% increased risk of end-stage kidney failure.

Methods: Using a maternal malnourished mouse model, we examined the causes of vascular and renal underdevelopment and impaired function in the LBW neonate. Parameters measured in the LBW offspring included nephron development, stem cell levels, apoptosis, gene expression, circulating cyto-/chemokines, renal blood flow and renal function.

Results: Within 24 hours after birth, LBW male offspring had 40% reduced weight, while only 49% of LBW neonates survived the first week after birth. Within the first week after birth, LBW neonates had an up to 40% reduction in renal blood flow and elevation of serum creatinine up to 3.0 mg/dl. Nephrogenesis was impaired in the LBW neonates with a 75% reduction in renal vesicle formation and a significant downregulation of Wnt9B (which induces differentiation of progenitor cells into tubular epithelium) at day E17.5, which ultimately resulted in a 30% reduction in glomeruli at the conclusion of nephrogenesis. During nephrogenesis, six2-positive nephron progenitor cells were reduced by up to 70% in the LBW embryonic kidney, which was accompanied by 6-fold increase in apoptosis. At birth, the LBW neonate had significantly elevated circulating levels of proinflammatory IL-1beta. Using explanted embryonic kidneys, we observed IL-1beta dramatically reduces six2+ cell populations and their ability to aggregate and form renal vesicles during kidney development.

Conclusions: LBW impacts vascular and renal function due to underdeveloped renal and vascular systems that result from enhanced IL-1-beta, increased apoptosis, altered Wnt9B expression, and reduced six2 nephron progenitor cells in the embryonic and neonate kidney. Funding: Private Foundation Support

Increasing Podocyte Number in Neonatal Kidney Reduced Renal Injury in Adulthood
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Background: Preterm birth increases the risk of hypertension and renal disease, which has been linked to decreased podocyte number. We previously found that paronycin injection in mice at birth impairs glomerular maturation, and has renal pathology phenotype which is similar to that observed in human preterm births. In the present study, we tested the hypothesis that increasing podocyte number during glomerular maturation can rescue glomerular loss and thus reduce renal injury in adulthood.

Methods: We targeted podocin-rTA with TRE-SV40RT with mouse to generate double-transgenic mice (RS), in which podocyte proliferation can be activated by doxycycline (Dox). rTA mice (R) served as controls. After a single paronycin injection, doxycycline was given at P1 until P8. At 12 weeks of age, mice underwent uninephrectomy (UNx) and were started on a high salt diet. At 14 weeks of age, angiotensin II (Ang II) was given by minipump for the next 8 weeks. All mice were sacrificed at week 22.

Results: At week 3, there were more WT1 positive glomerular cells in RS than R mice (RS 10.3±0.41 vs. R 8.1±0.58 X10^4mm^2, p<0.05), while glomeruli in superficial cortex were less mature (RS 2.1±0.05 vs. R 3.2±0.06, maturase scale 1-3; p<0.05). At week 6, glomerular number increased in RS (RS 9097±2442 vs. R: 6932±12447/ kidney, p<0.05). Glomerular volume and albuminuria did not differ between groups at week 3 and 6. At week 22, after UNx, high salt and Ang II, blood pressure, albuminuria and glomerular number were similar in RS and R. However, RS mice had lower KW/BW ratio (RS 0.97±0.143 vs. R 1.62±0.041, p<0.05) and less mesangial expansion (0-4 scale) (RS 0.72±0.10 vs. R 1.14±0.14, p<0.05).

Conclusions: We conclude that increasing podocyte number in developing kidney rescue paronycin-induced reductions of glomerular growth, which in turn reduces renal injury following a second hit in adulthood.
Results: Restricted deletion of Ebf1 from podocytes did not result in any observable developmental changes as assessed at the functional and histological levels. The glomerular number, and glomerular development were unchanged regardless of genotypic. The mice were followed for up to 6 months. During this time renal function did not decline in the mice with podocyte-specific deletion of Ebf1, and in fact baseline proteinuria was reduced in Podocin-cre−/−, Ebf1−/− animals compared to littermate controls. To examine if Ebf1-deficient podocytes harbored differential response to injury 3 months old mice animals were subjected to BSA-overload and exhibited reduced proteinuria.

Conclusions: Taken together these results suggest that Ebf1 regulates nephronepithelial development through other cell types than the podocyte. While Ebf1 does not control glomerular development through its actions in the podocyte, it appears to participate in proper damage response by podocytes as its removal appears to be protective.

Funding: NIDDK Support

PUB285

Possible Renoprotective Effects of Acetazolamide Administration in Obese Diabetic Mice with Nephropathy

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Background: Administration of carbonic anhydrase inhibitors (CAI) is thought to decrease glomerular filtration rate (GFR) by activation of the tubuloglomerular feedback (TGF) system. Acetazolamide (ACZ), a major CAI, has been shown to decrease urinary albumin excretion in the patients of type 1 diabetes with nephropathy. Previously, we showed that ACZ treatment in mice could ameliorate the onset of diabetic nephropathy due to the reduction of intraglomerular pressure by activating the TGF system.

Methods: In the current study, we treated obese diabetic mice (KK-Ay/Tacl) with ACZ for 14 weeks, and evaluated the long-term effects on urinary albumin excretion and glomerular hyperfiltration.

Results: The blood glucose levels were significantly higher in KK-Ay/Tacl mice compared to the control mice (BALB/cAe1) at 14 weeks. The blood glucose levels were significantly reduced in KK-Ay/Tacl mice treated with ACZ (547±37 vs 250±75 mg/dL). Interestingly, urinary glucose excretion levels in the ACZ group were not significantly different compared to the non-treated group. Creatinine clearance was higher in KK-Ay and ACZ group, while not changed by ACZ (0.73±0.07 vs 0.69±0.15ml/min) (Figure A). Urinary albumin excretion was reduced with ACZ treatment by 29% (Figure B). The plasma renin activity was not reduced by ACZ in this model.

Conclusions: These results suggest that the long-term oral treatment with ACZ may exert renoprotective effects in obese diabetic model with nephropathy, not due to activation of the TGF system but to better glycemic control.

Funding: Government Support - Non-U.S.

PUB286

Inhibition of miR-34a Reduces Podocyte Apoptosis by Targeting Bel-2 and Autophagy

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Background: Podocyte apoptosis is a key event in the pathogenesis of diabetic nephropathy. MiR-34a has been reported to be involved in cell proliferation and apoptosis, but its potential roles in podocytes under the diabetic condition remains unknown.

Methods: Type 2 diabetic nephropathy was established by uninephrectomy (Unx) in nine-week-old db/db mice. In cultured human podocytes, expression of miR-34a was reduced by transfection with anti-miR-34a and increased by transfection with anti-34a. Western blot was used to observe the expressions of TGFβ, Smad1 and Smad3. Autophagy was detected by immunofluorescence assay using the autophagy marker LC3-II.

Results: In the current study, we treated obese diabetic mice (KK-Ay/Tacl) with ACZ for 14 weeks, and evaluated the long-term effects on urinary albumin excretion and glomerular hyperfiltration.

Conclusions: These results suggest that the long-term oral treatment with ACZ may exert renoprotective effects in obese diabetic model with nephropathy, not due to activation of the TGF system but to better glycemic control.
Increased Iron Deposition Is Associated with Decreased α-Klotho and Vitamin D Receptor Expression in the Renal Proximal Tubules in Ob/Ob Mice

Arianne van Koppen,1 Roel Baobao Wang,2 Yasunori Iwata,1 To explore this possibility, we performed genome-wide transcriptional profiling in human umbilical vein endothelial cells (HUVEC), which were stimulated by high glucose (HG) with/without EPO treatment and detected the expression of inflammation associated genes.

Methods: To explore this possibility, we performed genome-wide transcriptome profiling in human umbilical vein endothelial cells (HUVEC), which were stimulated by high glucose (HG) with/without EPO treatment and detected the expression of inflammation associated genes.

Results: Hierarchical clustering and principal component analysis showed the different pattern of mRNA expression in HG stimulated HUVEC with/without EPO. While inflammatory cytokines/chemokines mRNA expression were increased, the HG stimulation in HUVEC, Th2 related cytokine receptors and intracellular signaling molecules showed the reduced mRNA expression levels. EPO treatment reduced inflammatory cytokines/chemokines mRNA expression and increased Th2 related cytokine mRNA expression levels. Real-time PCR analysis confirmed the increased expression of inflammatory related genes, those were decreased in HG stimulated HUVEC with EPO treatment. Moreover, EPO stimulation increased mRNA expression of EPO receptor and b-common receptor. EPO signaling affect neither cell proliferation nor cell death.

Conclusions: Taken together, EPO signaling might protect high glucose induced cell injury by the regulation of immune balance.

Ob control mice

Iron enhanced with DAB

Ob/mice

Klotho

VDR

Cyp27b1

Conclusions: In ob/ob BTBR mice, increased iron deposition in the renal PCT is associated with a decreased in klotho expression, vitamin D hormone synthesis and VDR signaling in the PCT. These changes together contribute to the progression of diabetic renal injury in these mutant mice, and future treatments.

Erythropoietin Protects Endothelial Cells from High Glucose Induced Injury

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Background: Diabetic nephropathy (DN) is a major complication in metabolic syndrome/diabetes patients. We have developed a metabolic syndrome mouse model characterized by non-alcoholic steatohepatitis and atherosclerosis upon high fat diet feeding. These animals show mild renal changes, but don’t progress to moderate DN. Therefore, we investigate whether inducing hypertension on top of metabolic syndrome leads to progression of DN.

Methods: Male LDLr−/− mice (8 wk old) received high fat (45%) + high salt (6%) diet for 6 wk. To induce hypertension, combinations of several pro-hypertensive components were used (eninemproprionate (UNX), angiotensin II (ANGII), DOCA and a vasorestrictor), for an additional 10 wk. At regular intervals, systolic blood pressure (SBP), 24h diuresis and albumin/creatinine ratio (UACR) were assessed. 17 wk after start diet, mice were terminated and renal injury was scored. We used age-matched chow fed animals as controls.

Results: Cholesterol and diuretics were significantly elevated in all groups vs chow from wk 5 onwards. ANGII induced a 20 mmHg increase in SBP at wk 13 vs. chow. At wk 8, UACR was significantly increased by ANGII in combination with HFD+HS (264±303 μg/mg) and UNX+HFD+HS (438±781 μg/mg) vs chow (62±24 μg/mg). At wk 13, ANGII further elevated UACR in HFD+HS (593±377 μg/mg) but decreased it in UNX+HFD+HS (187±230 μg/mg). Combining ANGII and UNX induced a strong increase in UACR (717±585 μg/mg) at wk 5 but also caused fatal thoracic bleedings. This group was terminated at wk 11. Renal injury score showed glomerular hypertrophy, mesangium expansion, nodular glomerulosclerosis, mild hyalination and micro-aneurysms.

Conclusions: We show that LDLr−/− mice on high fat diet + HFD+HS and ANGII induces hypertension and mild progressive DN, in addition to NASH and atherosclerosis in a single high glucose induced the aberrant immune balance remains to be explored. Therefore, we hypothesized that EPO modulated high glucose induced injury via the regulation of inflammatory and anti-inflammatory balance.

Methods: To explore this possibility, we performed genome-wide transcriptome profiling in human umbilical vein endothelial cells (HUVEC), which were stimulated by high glucose (HG) with/without EPO treatment and detected the expression of inflammation associated genes.

Results: Hierarchical clustering and principal component analysis showed the different pattern of mRNA expression in HG stimulated HUVEC with/without EPO. While inflammatory cytokines/chemokines mRNA expression were increased, the HG stimulation in HUVEC, Th2 related cytokine receptors and intracellular signaling molecules showed the reduced mRNA expression levels. EPO treatment reduced inflammatory cytokines/chemokines mRNA expression and increased Th2 related cytokine mRNA expression levels. Real-time PCR analysis confirmed the increased expression of inflammatory related genes, those were decreased in HG stimulated HUVEC with EPO treatment. Moreover, EPO stimulation increased mRNA expression of EPO receptor and b-common receptor. EPO signaling affect neither cell proliferation nor cell death.

Conclusions: Taken together, EPO signaling might protect high glucose induced cell injury by the regulation of immune balance.

Hypertension Results in Moderate Diabetic Nephropathy in a Mouse Model of Metabolic Syndrome

Reinout Smeets,1 Arnaud van Koppen,2 Pavel Goldschmeding,2 1MHR, TNO, Leiden, Netherlands; 2Pathology, UMCU, Utrecht, Netherlands.

Background: Diabetic nephropathy (DN) is a major complication in metabolic syndrome/diabetes patients. We have developed a metabolic syndrome mouse model characterized by non-alcoholic steatohepatitis and atherosclerosis upon high fat diet feeding. These animals show mild renal changes, but don’t progress to moderate DN. Therefore, we investigate whether inducing hypertension on top of metabolic syndrome leads to progression of DN.

Methods: Male LDLr−/− mice (8 wk old) received high fat (45%) + high salt (6%) diet for 6 wk. To induce hypertension, combinations of several pro-hypertensive components were used (eninemproprionate (UNX), angiotensin II (ANGII), DOCA and a vasorestrictor), for an additional 10 wk. At regular intervals, systolic blood pressure (SBP), 24h diuresis and albumin/creatinine ratio (UACR) were assessed. 17 wk after start diet, mice were terminated and renal injury was scored. We used age-matched chow fed animals as controls.

Results: Cholesterol and diuretics were significantly elevated in all groups vs chow from wk 5 onwards. ANGII induced a 20 mmHg increase in SBP at wk 13 vs. chow. At wk 8, UACR was significantly increased by ANGII in combination with HFD+HS (264±303 μg/mg) and UNX+HFD+HS (438±781 μg/mg) vs chow (62±24 μg/mg). At wk 13, ANGII further elevated UACR in HFD+HS (593±377 μg/mg) but decreased it in UNX+HFD+HS (187±230 μg/mg). Combining ANGII and UNX induced a strong increase in UACR (717±585 μg/mg) at wk 5 but also caused fatal thoracic bleedings. This group was terminated at wk 11. Renal injury score showed glomerular hypertrophy, mesangium expansion, nodular glomerulosclerosis, mild hyalination and micro-aneurysms.

Conclusions: We show that LDLr−/− mice on high fat diet + HFD+HS and ANGII induces hypertension and mild progressive DN, in addition to NASH and atherosclerosis in a single high glucose induced the aberrant immune balance remains to be explored. Therefore, we hypothesized that EPO modulated high glucose induced injury via the regulation of inflammatory and anti-inflammatory balance.
model providing broad coverage of metabolic syndrome complications. Administration of additional hypoglycemic drugs (DOC and NNA) further aggravated the model but also led to early fatal thoracic bleeds thus precluding further studies. Funding: Government Support - Non-U.S.

PUB291

Autophagy Activation in Proximal Tubular Epithelial Cells in Diabetic Nephropathy Acts as a Renoprotective Role Ying Xu, Lei Liu, Wei Xin, Xu Zhao, Liyong Chen, Qiang Wan. Renal Div, Shandong Provincial Hospital Affiliated to Shandong Univ, Jinan, Shandong, China; ‘Shandong Provincial Hospital Affiliated to Shandong Univ, Jinan, Shandong, China; ‘Shandong Provincial Qianfoshan Hospital Affiliated to Shandong Univ, Jinan, Shandong, China.

Background: Previous studies revealed that lipotoxicity participated in epithelial-to-mesenchymal transition (EMT) of proximal tubular epithelial cells (PTECs) under diabetic conditions. Based on evidences that autophagy and lipid metabolism are closely related, the aim of the present study was to investigate autophagy under diabetic conditions and its role in lipotoxicity and EMT.

Methods: HK-2 cells were cultured in normal (5.5 mmol/L glucose) and high glucose medium (30 mmol/L glucose). At 6h, 24h, 48h, and 96h, autophagy activity was evaluated by western blot of LC3II/I, Beclin1 and p62. Next, the inhibition of autophagy was achieved by chloroquine diphosphate (CQ), 3-methyladenine (3-MA), or Atg5 knockdown using siRNA transfection. Rapamycin, which is a mammalian target of rapamycin (mTOR) receptor specific inhibitor and a known autophagy activator, was used to induce autophagy in HK-2 cells. Lipid accumulation was detected by Oil-Red O staining; EMT was estimated by western blot of vimentin and E-cadherin.

Results: In high glucose cultured HK-2 cells, Beclin1 and LC3-II were elevated, while p62 was decreased. These results indicate that autophagy activity was elevated under diabetic conditions. Autophagy deficiency induced by autophagy inhibitors, CQ and 3-MA, or by Atg5 siRNA transfection exacerbated lipid accumulation and EMT. Treatment of rapamycin attenuated high glucose induced lipid accumulation and EMT. The Atg5 silence counteracted the protective effect of rapamycin.

Conclusions: In conclusion, these results demonstrate that autophagy activity in PTECs is elevated under diabetic conditions and the elevated autophagy activity acts as a renoprotective response.

Funding: Government Support - Non-U.S.

PUB292

Insulin Sensitivity Before and Six Months After Kidney Transplantation Morten Baas Jorgenesen, 1 Mads Hornum, 1 Gerrit van Hall, 2 Claus Bistrup, 1 Jesper Hansen, 3 Bo Feldt-Rasmussen, 1 Dept of Nephrology, Rigshospitalet, Denmark; 2Clinical Metabolomics Core Facility, Rigshospitalet, Denmark; 3Dept of Nephrology, Odense Univ Hospital, Denmark; 4Dept of Nephrology, Herlev Univ Hospital, Denmark.

Background: Severe uremia is a known cause of insulin resistance. We aimed to investigate the effect of kidney transplantation (Tx) on peripheral and central insulin sensitivity.

Methods: Nine non-diabetic patients awaiting living related kidney Tx were examined prior to Tx (Pre-Tx) with an oral glucose tolerance test (OGTT) and a 3h hyperinsulinaemic euglycaemic clamp. The clamp was repeated six months after Tx (Post-Tx). Nine age, gender and BMI matched individuals with normal kidney function were examined once under euglycaemic clamp. The clamp was repeated six months after Tx (Post-Tx). Nine age, gender and BMI matched individuals with normal kidney function were examined once under euglycaemic clamp.

Results: Two patients had pre-Tx prediabetes whereas all other had both normal fasting plasma glucose and normal glucose tolerance. The amount of glucose utilized during clamp was non-significantly lower in patients before Tx (Pre-Tx: 15.1 [11.2–19.0], Ctrl: 20.2 [13.4–27.0], P = 0.17) but significantly reduced after Tx (Post-Tx: 9.8 [6.7–12.9], P = 0.01). The suppression of EGP were comparable before Tx (Pre-Tx: 7.0 [5.4–8.5], Ctrl: 7.0 [3.1–12.7], P = 0.097) but was significantly improved after Tx (Post-Tx: 9.4 [7.8–11.1], P = 0.04). Gd were comparable both prior to and after Tx (Pre-Tx: 18.1 [13.6–22.5], Ctrl: 22.3 [15.1–29.5], Post-Tx: 17.1 [13.4–20.8], P = 0.22). The suppression of glycolate rate of appearance were comparable before Tx (Pre-Tx: 11.0 [9.1–14.1], Ctrl: 11.0 [6.6–21.1], P = 0.96) but significantly improved after Tx (Post-Tx: 2.0 [1.0–3.8], P = 0.04).

Conclusions: The reduced insulin sensitivity after kidney Tx is characterized by a central insulin resistance with impaired suppression of endogenous glucose production, impaired suppression of lipolysis and comparable peripheral insulin sensitivity.

Funding: Private Foundation Support

PUB293

Renal Functional and Morphological Changes Related to Obesity and Hyperglycemia in Göttingen Minipigs Rikke Lindgaard Thomsen, 1 Berit Østergaard Christoffersen, 1 Trine P. Ludvigsen, 2 Rikke Kaæ Kik, 2 Jonas Kildegård, 2 Lisa Timdan Fuchs, 1 Pall Leifisson, 1 Henrik D. Pedersen, 1 Lisbeth Hoier Olsen, 1 Dept of Veterinary Disease Biology, Univ of Copenhagen, Frederiksberg, Denmark; 2Nordov Nordisk A/S, Malsvau, Denmark.

Background: Obesity and diabetes, two major health problems worldwide, both lead to renal functional and morphological changes, with diabetic nephropathy being the leading cause of end-stage renal failure. A large animal model displaying human-like features of obesity-related and diabetic nephropathy would be very valuable to study pathogenesis and effects of new drug candidates on these syndromes. The aim of the present study was to evaluate renal function and morphology in diet-fed obese, atherosclerotic Göttingen minipigs with or without mild diabetes.

Methods: Male castrated Göttingen minipigs, aged 8 weeks at study start, were fed normal chow (n=6) or high-fat, high-cholesterol diet (n=6) for 43 weeks. Mild diabetes was induced in 11 pigs after 18 (n=6) and 25 (n=5) weeks of diet-feeding, using streptozotocin (125 mg/kg IV) preceded by nicotinamide (67 mg/kg IV). The study included two cohorts. Parameters of interest were: Body fat percentage (BF) estimated by dual-energy X-ray absorptiometry, inulin clearance (IC), kidney resistive index (RI), plasma fructosamine reflecting plasma glucose (FRA), plasma urea, plasma creatinine (PCr), plasma total cholesterol (TC), uric acid excretion (proteinuria (UPC) and albumin (UAC)) adjusted for creatinine. Glomerulus area and number of nuclei/glomerulus area were estimated post mortem. Influence of BF, TC and FRA on in vivo kidney function and post mortem kidney changes was evaluated using ANOVA with cohort as fixed covariable. Glomerulus BF was positively associated with urea (P=0.01), IC (P<0.05), Glomerulus area (P=0.001) and UPC (P=0.05), and negatively with PCr (P<0.001). FRA was positively associated with UACr (P<0.05) and number of nuclei/glomerulus area (P=0.05). RI was not associated with BF, TC or FRA.

Conclusions: In conclusion, functional and histological renal changes were found in diet-fed obese, atherosclerotic Göttingen minipigs with and without mild diabetes. The changes were associated with obesity and hyperglycemia.

Funding: Pharmaceutical Company Support - Novo Nordisk A/S

PUB294

Activation of Toll-Like Receptors Through Fetuin-A Leads to an Inflammatory Response in Podocytes and Exacerbates Palmitic Acid-Induced Cell Death Jana Orellana, 1 Kapil Dev Kampe, 1 Andreas Werner 3 Dept. of Biomedical Sciences, Aarhus University Hospital, Aarhus, Denmark; 2Novo Nordisk A/S, Maaloev, Denmark; Dept of Biomedicine, Univ Hospital Basel, Basel, Switzerland; 3Dept of Biomedicine, Univ Hospital Basel, Basel, Switzerland.

Background: Inflammation participates in the pathogenesis of type 2 diabetes and contributes to diabetic nephropathy (DN). There is growing evidence that chronic elevated free fatty acids (FFAs) contribute to this chronic inflammatory milieu. Studies in pancreatic β-cells suggest that the inflammatory response mediated by FFAs depends on toll-like receptor (TLR) 4 and IL-1 receptor (IL-1R). The signaling pathways of TLRs and IL-1R involve activation of the transcription factor nuclear factor-κB (NF-κB) which induces a wide range of cytokines/chemokines including monocyte-chemoattractant protein-1 (MCP-1), and IL-1. Here, we addressed whether fetuin-A together with FFAs leads to an inflammatory response in podocytes and whether this exacerbates palmitic acid-induced podocyte death.

Methods: Conditionally immortalized murine podocytes were used. Murine and bovine fetuin-A were used alone or in combination with palmitic acid complex to BSA. MCP-1 was measured by ELISA. Podocyte death was determined by flow cytometry (annexin V and propidium iodide staining).

Results: Palmitic acid alone did not, but fetuin-A induced MCP-1 in podocytes and this was further increased by palmitic acid. The MCP-1 release was prevented by CI095 (TLR4 blocker). Fetuin-A or LPS exacerbated palmitic acid-induced podocyte death, and CL095 as well as the IL-1 receptor antagonist anakinra or an anti IL-1β antibody attenuated cell death.

Conclusions: Fetuin-A alone and in combination with palmitic acid leads to an inflammatory response in podocytes and promotes palmitic acid-induced podocyte death. As inhibition of IL-1R as well as II-1β prevents these effects, both pathways are promising targets to attenuate the progression of DN.

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PUB295

IL-1β Mediates the High Glucose Induced Endothelial-to-Mesenchymal Transition in Human Aortic Endothelial Cells Dongelang Zhu, Rui-ning Tang, Kun Ling Ma, Bi-Cheng Liu. Zhong Da Hospital, Southeast Univ Medical School, Nanjing, Jiangsu.

Background: Studies have shown that endothelial-to-mesenchymal transition (EndMT) induced by high glucose (HG) contributes to cardiac fibrosis. Additionally, proinflammatory cytokine interleukin-1β (IL-1β) has been implicated as one of the dominant players in the development of fibrosis and diabetic heart. In vitro studies, retinal endothelial cells (ECs), human intestinal ECs and human dermal ECs have been reported to undergo EndMT by

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 955A
IL-1β stimulation. Interestingly, most IL-1β immunoreactivity was localized to endothelial cells and interstitial macrophages in an animal model of cardiac hypertrophy. However, the potential role of IL-1β in high glucose induced EndMT remains unknown. Here, we hypothesize that IL-1β might mediate the process.

Methods: Primary human aortic endothelial cells (HAECs) were divided into three groups: a normal glucose (NG) group, an endothelial phenotype, wherein increased microvascular proliferation and a rounded endothelial cell phenotype were observed in the cytoplasm. The expressions of FSP1 and a-SMA were significantly increased in the HG group, and these changes were inhibited by anti-interleukin1β antibody or IL-1β siRNA treatment.

Results: The treatment of HAECs in the HG group resulted in significant increases in the expressions of FSP1 and a-SMA and IL-1β in dose- and time-dependent manners. The incubation of HAECs with FGF-23 induced a fibroblast-like phenotype, wherein increased microvascular proliferation and a rounded endothelial cell phenotype were observed in the cytoplasm. The expressions of FSP1 and a-SMA were significantly increased in the HG group, and these changes were inhibited by anti-interleukin1β antibody or IL-1β siRNA treatment.

Conclusions: These findings suggest that IL-1β mediates the HG-induced EndMT, which was inhibited by anti-interleukin1β antibody or IL-1β siRNA treatment.

PUB296

Serum Bilirubin and Asparaginase Aminotransferase Concentrations Predict Loss of Renal Function in Type 2 Diabetes

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Background: Higher serum bilirubin concentration is reported to slow the progression of nephropathy in type 2 diabetes. We examined associations of serum bilirubin and asparaginase aminotransferase (AST) concentrations with renal function loss (RFL) in a post-hoc analysis of a clinical trial of renoprotection with losartan in Pima Indians with type 2 diabetes (ClinicalTrials.gov number, NCT00340678).

Methods: Serum bilirubin and AST were measured at baseline in 168 subjects who underwent annual measurement of GFR by the urinary clearance of inulinodulose. RFL was defined by ≥40% decline in GFR from baseline. Cox regression was used to compute hazard ratios (HRs) for the association of a 1 standard deviation (SD) increment in bilirubin and AST concentrations with RFL adjusted for age, sex, treatment group, HbA1c, GFR, and urinary albumin/creatinine ratio (ACR). The sum of standardized AST and bilirubin was standardized to create a liver index variable with mean=0, SD=1.

Results: Participants (73% female, mean age 42±11 years, bilirubin 0.6-0.2 mg/dL, HbA1c 9.3±2.2%, GFR 103±63 ml/min, and median AST 19 U/L (IQR=13-31.5 U/L), ACR 31 mg/g (IQR=12-77 mg/g)) were followed for a median of 7.0 years (IQR=4.5-9.9 years); 73 subjects (43%) developed RFL. After multivariable adjustment, serum bilirubin and AST were independent predictors of RFL (HR=1.52). The combination of these liver function tests provided the strongest prediction (HR=1.52).

Conclusions: Higher serum bilirubin and AST concentrations predict loss of renal function in Pima Indians with type 2 diabetes.

Funding: NIDDK Support

PUB297

Baseline Data from the Multinational Prospective Cohort Study in Patients with Type 2 Diabetes for Validation of Biomarkers (PROVAILD)

Gert J. Mayer,1 Susanne Eder,1 Laszlo Rosvall,2 Peter Voros,3 Hiddo Jan Lambers Heerspink,1 Dick de Zeeuw,1 Beata Czerwiec,1 Andrzej Wieczek,1 Diianne Z. Hill,1 Patrick B. Murr,1 George Heinz,1 Peter Rosling1, Internal Medicine IV, Medical Univ Innsbruck, Innsbruck, Austria; 2Inst of Pathophysiology, Semmelweis Univ, Budapest, Hungary; 3Egyetemist Szent Istvan es Szent Laszlo Korhaz, Budapest, Hungary; 4Dept Clinical Pharmacy and Pharmacology, Dept of Nephrology, Medical Center Groningen, Groningen, Netherlands; 5Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ Silesia, Katowice, Poland; 6Inst of Cardiovascular and Medical Sciences, Univ of Glasgow, Glasgow, United Kingdom; 7Section for Clinical Biometry, Medical Univ Vienna, Vienna, Austria; 8STENO Diabetes Center, Gentofte, Denmark.

Background: We recruited 4065 subjects at the primary healthcare level in Austria, Hungary, Netherlands, Poland and Scotland, who will be treated according to local practise and followed for 4 years to compare the incidence and progression of renal and cardiovascular disease between the countries. Additionally extensive biobanking is performed.

Methods: We will determine the cumulative incidence of progression of albuminuria, doubling of serum creatinine, and end stage renal disease as well as fatal and non-fatal cardiovascular events. Exclusion criteria are active malignancy and age <18 years.

Results: The mean age of the population was 62 years, mean duration of diabetes as 9.9 years. 9% of the patients had eGFR values <45 and 22% <60 ml/min/1.73m2. Baseline data from the “lowest” country “highest” country

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log AST (per SD)</td>
<td>1.34 (1.04-1.74), P=0.025</td>
<td>1.39 (1.07-1.80), P=0.015</td>
</tr>
<tr>
<td>Bilirubin (per SD)</td>
<td>1.30 (1.05-1.62), P=0.016</td>
<td>1.33 (1.05-1.67), P=0.017</td>
</tr>
<tr>
<td>Liver index (per SD)</td>
<td>1.43 (1.13-1.81), P&lt;0.003</td>
<td>1.52 (1.18-1.95), P&lt;0.001</td>
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</tbody>
</table>

Conclusions: Higher serum bilirubin and AST concentrations predict loss of renal function in Pima Indians with type 2 diabetes.

Funding: NIDDK Support

PUB298

FGF-23 and Magnesium Are Independent Risk Factors for an Increased Albumin-to-Creatinine Ratio in Type 2 Diabetes with Chronic Kidney Disease

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Background: Microalbuminuria is the earliest sign of glomerular involvement in diabetes mellitus. The multiple physiological mechanisms involved are complex and not completely understood. Recently, it appeared that fibroblast growth factor-23 (FGF-23) and magnesium play a role in the emergence and maintenance of albuminuria in type 2 diabetes. The aim of this study is to investigate the role of FGF-23 and magnesium in relation to the urine albumin-to-creatinine ratio in type 2 diabetes with chronic kidney disease (CKD) stages 2-4.

Methods: In a cross-sectional study we included all eligible type 2 diabetic patients with CKD stages 2-4, followed in our outpatient Diabetic Kidney clinic. We included 150 patients, f=53–57, with a mean age of 66.6±7 years (40-85) and a mean follow-up of 76 months. We used descriptive statistics, the Student’s t and the chi-square tests. We also divided our population according to the pulse pressure (G I <50 mmHg and G2 ≥ 50 mmHg), and compared these groups regarding the several biological and laboratory parameters analyzed. We employed a multiple regression model to identify risk factors of increased urine albumin-to-creatinine ratio. In this model we used the urine albumin-to-creatinine ratio as the dependent variable and as independent ones age, duration of type 2 diabetes, systolic blood pressure, HbA1c, eGFR, HOMA-IR, malonialdehyde, hs-CRP and 1,25(OH)D3 levels.

Results: The patients in G2 displayed a lower eGFR (p=0.001) and magnesium (p=0.004) levels, as well as higher levels of FGF-23 (p=0.043) compared to patients in G1. The magnesium and FGF-23 were found to play a role in the urine albumin-to-creatinine ratio (β=0.006, p=0.002), and the magnesium (β=−0.016, p=0.001) are independent risk factors for increasing the urine albumin-to-creatinine ratio.

Conclusions: The present study shows that a dysregulation of mineral metabolism, reflected by altered levels of magnesium and FGF-23, correlates with an increased urine albumin-to-creatinine ratio in type 2 diabetic patients with CKD stages 2-4.

Funding: Nephrology, Centro Hospitalar do Algarve, Faro, Portugal; 1Dept of Biomedical Sciences and Medicine, Univ of Algarve, Faro, Portugal.

PUB299

FGF-23 and Klotho Influence the Pulse Pressure in Diabetic Patients with Nephropathy

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Background: The last decade have shown that FGF23 and Klotho may have relevant independent actions on the renal and CV systems. They interfere with vascular functions and may play a role in vascular calcification, atherosclerosis and arteriosclerosis. Their interactive activities may also have direct and indirect effects on interdependent renal and CV pathophysiology. The aim of this study is to investigate the relationship between FGF-23 and Klotho with pulse pressure in type 2 diabetic with chronic kidney disease (CKD) stages 2-3.

Methods: In a cross-sectional study we included 107 type 2 diabetic patients (67 males, 62.6±11 years), a mean age of 66.6±7.9 years and CKD stage 2-3. We used descriptive statistics, the Student’s t and the chi-square tests. We also divided our population according to the pulse pressure (G 1<50 mmHg and G2 ≥ 50 mmHg), and compared these groups regarding the several biological and laboratory parameters analyzed. We employed a multiple regression model to identify risk factors of increased pulse pressure (PP). In this model we used as dependent variable the pulse pressure, and as independent ones age, metabolism and albuminuria-to-creatinine ratio, insulin resistance, oxidative stress and eGFR.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: We found that G2 patients showed higher age (p = 0.017), phosphorus (p < 0.001), iPTH (p = 0.001), urine albumin-to-creatinine ratio (p = 0.001), Homa-IR (p = 0.001), FGF-23 (p = 0.001) and OxLDL (p = 0.001) and lower levels of eGFR (p = 0.001), Klotho (p = 0.001) and 1.25(OH)2D3 (p = 0.001). In the multivariable linear regression model we found that FGF-23 (β=0.377, P=0.047) and the Klotho (β= - 0.567, P=0.023) are independent risk factors for increasing the pulse pressure.

Conclusions: In conclusion, in a population of type 2 diabetic with chronic kidney disease stages 2-3, the Klotho and FGF-23 levels are independently associated with PP. Further studies with more patients are warranted to confirm whether an increase in Klotho and a decrease in FGF-23 would reduce the PP and consequently the cardiovascual risk of our patients.

Funding: NIDDK Support

PUB300

Prediction of Renal Outcome in Type 2 Diabetic Dephropathy by Estimating GFR from a Combination of Serum Creatinine and Cystatin C

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Background: serum cystatin C is an alternative to serum creatinine for estimating glomerular filtration rate (GFR), however, the utility of estimated GFR from combination of serum creatinine and cystatin C as marker to predict long-term renal outcome is uncertain, particularly in the Type 2 diabetic nephropathy (DN).

Methods: A total of 501 patients (The National Clinical Research Center of Kidney Diseases, 2003-2011) were recruited in prospective cohort study. Follow-up was 5-year. Renal outcome was defined by eGFRcre-cys<15 ml/min per 1.73m² or renal replacement therapy.

Results: The distributions of standardized serum cystatin C with eGFRcre and eGFRcre-cys are shown in. Kaplan-Meier curves showed significantly increased renal endpoints with higher quartile of cystatin C (p < 0.001) and lower eGFRcre-cys (p < 0.001). The highest AUCs for eGFRcre-cys was predicting the renal endpoint compared with eGFRcre or eGFRcre-cys. The best cut-off value for predicting the renal endpoint was 29.28% decline in the 24-month, which value showed 79.6% sensitivity and 82.6% specificity. Cox regression models with restricted cubic splines were shows a change of -30% in eGFRcre-cys was a precision, and accuracy marker in the predicting the renal output and 30% decline of eGFRcre-cys over 2 years was strongly associated with the risk of ESRD, suggesting it could be used as an alternative endpoint in T2DN.

Funding: Government Support - Non-US.

PUB301

Prevalence and Prognostic Role of Uncontrolled Risk Factors in Diabetic CKD (DM-CKD) Treated in Nephrology Clinics

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Background: Knowledge of prognosis of DM-CKD mainly derives from RCTs and cohorts followed in the dialysis setting. Epidemiologic features are less defined in patients with overt disease managed in renal clinics.

Methods: We studied 763 DM-CKD patients derived from 3 prospective cohorts that in 2000-2010 enrolled 2,488 CKD patients stage III-V under stable care from 26 months in 40 different renal clinics. Endpoints were ESRD (chronic dialysis-transplant) and first major cardiovascular (CV) events (fatal and non fatal) assessed through 12/2014. Uncontrolled risk factors were defined as high blood pressure (BP=140/90 or >130/80 if proteinuria >0.150 g/24h), HbA1c >7.5%, hemoglobin <10.5 g/dL, serum phosphorus (P) >4.5 mg/dL, LDL-C >100 or 70 mg/dL according to ESC 2012 guidelines, proteinuria (Uprot) >0.5 g/24h.

Results: HbA1c was 6.9%, (95% CI 6.6-7.2), Uprot 0.5 g/24h (95% CI 0.4-1.4), P 3.9±0.8 mg/dL, Hb 12.3±1.7 g/dL and BP 142±19/78±11 mmHg. During follow-up (43 months, IQR 21-56), 171 ESRD and 170 CV events occurred (incidence rate 6.4 and 6.9/100 pts/y). Multivariable Cox analyses for ESRD and CV risks (HR, 95% CI) stratified by the Table in the text.

Conclusions: eGFRcre-cys was a precision, and accuracy marker in the predicting the renal outcome and 30% decline of eGFRcre-cys over 2 years was strongly associated with the risk of ESRD, suggesting it could be used as an alternative endpoint in T2DN.

Funding: Government Support - Non-US.
Prevalence of Proteinuria, Albuminuria and Associated Factors in Obese Patients Undergoing Bariatric Surgery


Background: Obesity is associated with proteinuria. But the exact prevalence of proteinuria or albuminuria with and without additional risk factors in obese patients is unclear.

Methods: Consecutive patients undergoing bariatric surgery were included in study. Participating patients had a urine sample for protein creatinine ratio and albumin creatinine ratio prior to their surgery. We defined a positive protein to creatinine ratio as greater than or equal 300 mg and a positive albumin to creatinine ratio as greater than or equal to 30 mg. Associated factors such as diabetes mellitus (DM), hypertension (HTN), body mass index (BMI), and ACE/ARB use were collected.

Results: One hundred forty-three patients were included. The mean age was 43 years (SD: 12). Twenty five percent of the patients had DM, 50% had HTN, and the mean BMI was 44.7 (SD: 9.8). The prevalence of proteinuria and albuminuria was 8.5% (95% CI 4.5-14.4%) and 21% (95% CI 14-30%) respectively. Sixty six percent of the patients with proteinuria had DM as did 43% of the patients with albuminuria. Eighty three percent of patients with proteinuria had either DM or HTN. Seventy eight percent of patients with albuminuria had either DM or HTN. One renal failure with neither DM nor diabetes mellitus (DM), hypertension (HTN), body mass index (BMI), and ACE/ARB use were collected.

Conclusions: The majority of patients with proteinuria and albuminuria had diabetes and/or hypertension and there was a much lower prevalence of proteinuria/albuminuria in patients without these risk factors. Patients who had proteinuria had a higher BMI than patients who did not have proteinuria, though for albuminuria the BMI did not differ.

Risk Factors for Renal and Cardiovascular Events in Type 2 Diabetic Patients with Biopsy-Proven Nephropathy in Japan

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Background: Standardized pathological classification is an essential tool in the evaluation of disease progression and/or efficacy of clinical management. In this nationwide, multicenter, retrospective study, we examined pathological findings as risk factors for renal and cardiovascular events in Japanese patients with type 2 diabetes. The observational period was 76.3 months and the observation period was 2264 person-year in total. Nine glomerular lesions, two interstitial lesions, and two vascular lesions were classified and evaluated as pathological predictors.

Methods: One hundred sixty nine composite renal events (dialysis and doubling of serum creatinine or death) in 13 centers in Japan. The median follow-up period was 76.3 months. We then identified 9902 patients with type 2 diabetes who met the diagnostic criteria of the Japan Diabetes Clinical Practice Guidelines of 2011. The aim was to determine if similar relationships exist in adolescents with T1D, analyzed on the basis of low GFR and lower renal blood flow in adults with type 1 diabetes (T1D). Our overall aim was to determine if similar relationships exist in adolescents with T1D, analyzed on the basis of lower GFR and lower renal blood flow in adults with type 1 diabetes (T1D). Our overall aim was to determine if similar relationships exist in adolescents with T1D, analyzed on the basis of lower GFR and lower renal blood flow in adults with type 1 diabetes (T1D).

Results: Sixty eight diabetic patients undergoing maintenance hemodialysis (6 men and 2 women; mean age, 64.4±11.9 years; mean dialysis period, 4.0±5.0 years; 2 insulin users, 6 nonusers) were instructed in CBGFM with BCC and followed for 3 months to assess changes in their predialysis blood glucose (BG), hemoglobin A1c (HbA1c), Hemoglobin HbA1c, triglycerides (TG), Potassium (K), Phosphorus (P), albumin (Alb), total cholesterol (T-Ch), high-density lipoprotein-Chol (HDL-Chol), low-density lipoprotein-Chol (LDL-Chol), protein catabolic rate (PCR), dry weight (DW), body mass index (BMI), and the Geriatric Nutritional Risk Index (GNNR).

Conclusions: The results demonstrated that the CBGFM with BCC is a useful method of dietary management for glycemic control that can be applied independently of, but concurrently with, the control of potassium and phosphorus intake in dietary therapy for diabetes patients.

The Clinical Effects of Renoprotection with DPP-4 Inhibitors

Koichi Kanzawazaki, Saeo Sato, Yoshimi Okada, Hiroaki Haru, Minoru Hatanou, Nobutada Onizawa, Takatsugu Iwashita, Tomonori Ogawa, Hajime Hasegawa. Nephrology and Hypertension, Saitama Medical Center, Saitama Medical University, Kagawa, Saijina, Japan.

Background: Recently, not only animal models of diabetic nephropathy, but also non-diabetic neprhopathy models, DPP-4 inhibitors could be used to develop renoprotective effects that improve albuminuria or tissue damage, through inhibition of oxidative stress, inflammation, and fibrosis. The aim of this study is to clarify the mechanisms of renoprotective effect by DPP-4 inhibitors in diabetic nephropathy models, DPP-4 inhibitors (DPP-4i) are reportedly associated with the change rate of UACR (p=0.03). MDA-LDL (34 mU/L (p<0.01), decreased from 7.49±0.18 to 5.97±0.12 (p=0.01)). DPP-4 inhibitors were investigated in 128 patients with type 2 diabetes (G1-3a, A1-2), either 1,5-anhydro-d-glucitol (1,5AG) was increased from 11.0±15.0 to 15.3±15.0 (p<0.01), carotid-femoral pulse wave velocity (Car-Fem PWV) were measured in 65 HC, 64 low-, 74 middle- and 50 high-tertile T1D participants from normo- to microalbuminuria and albuminuria groups with lower GFR and higher values for BP and arterial stiffness in T1D adolescents but not HC.

Conclusions: We proposed that the CBGFM with BCC is a useful method of dietary management for glycemic control that can be applied independently of, but concurrently with, the control of potassium and phosphorus intake in dietary therapy for diabetes patients.

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

Underline represents presenting author.

958A
Conclusions: In DMN, DPP-4i have oxidative stress relief and renoprotective effect, by the improvement of short-term blood sugar fluctuations, also by oxidative stress reduction which independently of the improving glycemic control.

PUB309
Fibrinogen: A Potential Predictive Factor for the Progress of Diabetic Kidney Disease
Wenbo Zhao, Hui-juan Li, Zhenda Zheng. The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong.

Background: To evaluate the potential of fibrinogen as a predictor of the progress of proteinuria in diabetic kidney disease.

Methods: For a Cross-Sectional Study, collecting 1121 type 2 diabetes patients without or with microalbuminuria or massive proteinuria were treated during January 2008 to January 2013. Proteinuria was negative in 755 cases, 285 cases with microalbuminuria, and 181 cases with massive proteinuria. We analyzed the correlation factors of the negative protein urinal group and the microalbuminuria group; the correlation factors of the microalbuminuria group and the massive proteinuria group. Fibrinogen levels were compared between three groups.

Results: Retinopathy, hypertension grading, SBP, Fibrinogen levels, serum albumin, serum creatinin were the related progress factors of Microalbuminuria; Diabetes course, retinopathy, waist to hip ratio, Fibrinogen levels, serum albumin levels, serum creatinin, C, serum creatinine were the related progress factors of the massive proteinuria; Except fibrinogen, other factors had been known relating to the progress of diabetic kidney disease. There were differences in the levels of three groups of fibrinogen (P < 0.05), which were 3.43 + 0.91 g/L, 4.15 + 1.31 g/L, 5.16 + 1.44 g/L.

Conclusions: Fibrinogen was a potential predictive factor for the development of diabetic kidney disease. The conclusion needs to be confirmed by further study.

PUB310
Interaction of HDLc, Iron, and Diabetes on Kidney Function
Baqiyyah, 1 Tina Costacou, 2 John M. Arthur. 3 Epidemiology, West Virginia Univ; 2Epidemiology, Univ of Pittsburgh; 3Univ of Arkansas for Medical Sciences.

Background: The effect of HDL cholesterol (HDLc) on kidney function has recently received attention, partly due to the finding of increased hemoglobin (hb) inside of the HDL protein in persons with high risk haplotgbin (hp) genotypes. Such hb w/in the HDL protein may lead to iron induced lipid peroxidation products. These lipid peroxidation products may lead to iron-induced kidney damage. We have recently shown an interaction between HDLc and iron w/ kidney function (eGFR) in persons with diabetes that after controlling for hb, higher serum iron levels were associated w/ reduced eGFR but only in those w/ HDLc levels above the median for the population. Because of the diabetes-specific association of increased hb inside the HDL protein in those w/ high risk hp genotypes, we hypothesize that this interaction between HDLc and iron w/ kidney function varies by diabetes status. To test this hypothesis, we examined the inter-relationship between HDLc, iron, and diabetes status w/ eGFR in approximately 55,000 individuals in West Virginia and Ohio.

Methods: Data on adults aged ≥20 years were obtained from the C8 Health Project. eGFR was estimated using the CKD-EPI formula. Linear regression analysis was used to test the relationship between HDLc, serum iron, and diabetes status, and their interactions, with eGFR.

Results: Mean age was 57.8 in those w/ diabetes and 45.1 in those w/out diabetes. In multivariable analyses controlling for age and sex, iron was positive related w/ eGFR in those w/ (p<0.03) and inversely in those w/out diabetes (<0.0001), while HDLc was positively associated w/ eGFR only in those w/out diabetes (p=0.97 in diabetes; p<0.001 in those w/o diabetes). As previously reported, an interaction existed between HDLc and iron in diabetes (p=0.04). However we report that this relationship was even stronger in those w/out diabetes (interaction p=0.0008). A significant 3-way interaction existed between HDLc, serum iron, and diabetes status w/ eGFR (p=0.008). Controlling for hb, the interaction between iron and HDLc disappeared in those w/ diabetes but remained robust in those w/out diabetes.

Conclusions: The divergent relationship between iron and HDL on the eGFR by diabetes status needs further investigation.

PUB311
Molecular-Selective Plasma Exchange in Acute Kidney Injury due to Multiple Myeloma
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Background: Benefit of plasma exchange in overall survival of patients with multiple myeloma (MM) remains to be determined, however, it is evident that lowering free light chain (FLC) reverses renal function in acute kidney injury (AKI) due to MM. High cut-off hemodialysis is recommended to remove FLC as an initial treatment for MM related AKI, which is different from traditional plasma exchange (PE) in preventing loss of large size molecules. As another option, we show the effect of molecular-selective plasma exchange to remove FLC, which enables target size removal without losing other size molecules.

Methods: A 49 year male with Bence-Jones type M protein was admitted with AKI; serum creatinine rose from 3.8 to 7.9mg/dL in 1 month. Past history included bone fracture and anemia. Serum FLC lambda was elevated to 29800 mg/dL. MM was confirmed by plasma cells in the bone marrow. The patient was treated with sequential molecular-selective plasma exchange (Evacure) and on-line HDF every other day combined with Bortezomib.

Results: PE was performed 6 times and removed 43.1% of FLC each on average without losing small and large size molecules.

Conclusions: Fibrinogen was a potential predictive factor for the development of diabetic kidney disease. The conclusion needs to be confirmed by further study.

PUB312
Preliminary Evaluation of a New CRRT Machine: Kibou™
Mauro Neri, Francesco Garzotto, Anna Lorenzin, Silvia Guggia, Alessandra Brendolani, Federico Nalesso, Monica Zanella, Claudio Ronco. IRRIV and San Bartolo Hospital, Vicenza, Italy.

Background: Kibou™ (Asahi Kasei Medical Co., Tokyo, Japan) is a new multifunctional automatic machine for Continuous Renal Replacement Therapy (CRRT) system (figure 1).

Methods: Based on the traditional experience of International Renal Research Institute of Vicenza (IRRIV), in vitro and in vivo test evaluations of Kibou and related disposables have
been conducted. 12 treatments were performed. Machine’s usability and accuracy has been evaluated by the staff through scores table. The measurement of fluid balance accuracy was even performed.

**Results:** Based on score given by the staff (engineers, nurses and physicians), the machine hardware results compact and well organized, with 3 well separated compartments (dialyzer replacement, blood and effluent) that facilitate the preparation phase. Automatic priming function allows short priming time. The interface is user friendly in all the modalities (SCUF, CVVH, CVVHD, CVVHDF, TPE, both for adults and pediatrics). The measured fluid balance error was always lower than 0.3%. On the contrary CVVHDF pre-infusion and pre-pump infusion are not performable. For pediatric treatment the continuity of the flow of blood pump need to be maintained and improved.

**Conclusions:** Kibou is a promising CRRT machine that can perform multiple continuous therapies with just one platform. In particular, we evaluated a highly accurate gravimetric fluid balance control system and a user friendly interface. Kibou is one of the first machines of the new frontier of CRRT devices: the fourth generation of CRRT machines.

### PUB313

**The Effect of MySleeve on Fluid Restriction Adherence in Hemodialysis Patients**

Prima Health Analytics, 1Prima Health Analytics; 2Dialysis Center of Lincoln; 3Medicine, Div of Nephrology, Maastricht Univ Medical Center, Maastricht, Netherlands.

**Background:** In hemodialysis patients, non-adherence to fluid restriction is associated with high interdialytic weight gain (IDWG) and adverse outcomes. Monitoring drinking behaviour and direct feedback to the patient can lead to better adherence. We developed the MySleeve, a device that can be wrapped around a drinking glass to monitor fluid intake throughout the day. The MySleeve will also provide a subtle vibration on the glass when the amount drunk exceeds target. The information about drinking behaviour can be found in the accompanying application on a mobile phone. In this study, we investigate the effect of direct feedback and information to the patient on fluid restriction adherence measured by the IDWG.

**Methods:** We will include prevalent, anuric hemodialysis patients from the Catharina Hospital Eindhoven, The Netherlands in a randomised controlled trial. Patients in the intervention group are provided a MySleeve device, a mobile phone and an activity tracker. BCM measurements are performed weekly and IDWG will be calculated before every dialysis session. The patients in the control group will continue with regular hemodialysis.

**Results:** We expect that by providing patients insight in fluid intake, there will be an increase in fluid restriction adherence and an increase in activity levels and better quality of sleep. Due to less IDWG, patients will experience less discomfort of fluid overload.

**Conclusions:** Introducing a MySleeve device to provide direct insight into drinking behavior will help the patients to adhere to their fluid restriction, leading to less IDWG and better quality of life measured by daily activity and better sleep.

**Funding:** Private Foundation Support

### PUB314

**A Time and Motion Study of Erythropoiesis Stimulating Agent Administration in United States Dialysis Centers**

Mark Stephens, 1Larry C. Emerson, 1Leslie A. Spry, 1John P. Caloyeras, 1Ernest R. Anderson, 1John Reitan, 1Akhtar Ashfaq, 1Prima Health Analytics; 2Dialysis Center of Lincoln; 3Amgen, Inc.; 4RJM Group.

**Background:** Previous research suggests that ESA administration in dialysis is a time-consuming task and switching to less frequently dosed ESAs may offer opportunities for more efficient and effective patient care. This study estimated the time required for activities involved in the ESA process at US dialysis centers using epoetin alfa (EPO) or darbepoetin alfa (DPO), and examined potential time savings of switching from EPO to DPO.

**Methods:** Time and motion study conducted from 10/2014 to 1/2015 to assess activities involved and staff time required to prepare, administer and document ESA doses. A sample of 11 dialysis centers using either 3 times-per-week (TIW) EPO or once-weekly (QW) DPO were selected in pairs (one EPO, one DPO), where possible, from the same organization or nephrology practice to help control for patient management protocols and staffing patterns. ESA-related tasks were timed by trained nurse observers. Time savings were calculated from switching from TIW EPO to QW DPO were estimated. Staff were interviewed about alternate patient-focused activities that could be accomplished if time were saved in the ESA process.

**Results:** 200 administrations were observed (81 DPO, 119 EPO). A mean of 2.3 (95% CI: 2.1-2.5) minutes per dose were required for ESA-related activities. RNs performed 95% of tasks; LPNs 5%. ESA process time did not vary significantly between EPO and DPO (p>0.83). Staff time savings would accrue due to fewer ESA administrations using QW DPO: 10-20 minutes per nurse/day. For an average facility, the total monthly nurse time would be reduced substantially in de novo conversion.

**Conclusions:** Switching from TIW EPO to QW DPO for anemia management in dialysis patients can result in time savings and opportunities to redirect nurse time towards activities aimed at improving patient care while still offering the ability to respond to changing clinical circumstances to effectively manage anemia.

**Funding:** Pharmaceutical Company Support - Amgen

### PUB315

**Observational Study on the Use of Darbepoetin Alfa in Hemodialysis Patients in Central Eastern Europe – ANREG Final Analysis**

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**Background:** This study observed anemia treatment patterns in HD patients (pts) treated with darbepoetin alfa (DA) in clinical practice in CEE.

**Methods:** Multicenter observational study in HD pts treated with DA. From 2007 to 2014, 14 cohorts were observed for 6 months (mo) each. Primary outcome: % pts maintaining an average Hb >at 11 (cohorts 1/2 enrolled prior to label change in 02/2008) or 10-12 g/dL (cohorts 3-12) during mo 4-6. Secondary: conversion versus de novo pts, Hb trends, ESA and iron use, adverse drug reactions (ADR).

**Results:** Of 2923 enrolled pts (n=1101 de novo; n=1822 converted from other ESAs), 2647 (91%) completed 6 mo of DA, 276 (9%) discontinued (155 [5%] due to death). At baseline (BL) 83% received iron.

**Conclusions:** Patients receiving DA achieved target Hb (HR:0.25, P=0.04), and patients with normal TSAT (20-30%) were significantly lower risk for adverse events (fatal: intracranial hemorrhage; myocardial infarction, death).

**Funding:** Pharmaceutical Company Support - Amgen

### PUB316

**Dysutilization of Iron for Erythropoiesis Is a Significant Predictor for Adverse Events and Survival in Maintenance Hemodialysis Patients**

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**Background:** Patient with high serum ferritin and low transferrin saturation (TSAT) levels could be considered as dysutilization of iron for erythropoiesis. Long-term safety and iron administration to these patients has not been well studied.

**Methods:** Study design was the observational multicenter study for period of 3 years. In 805 patients with maintenance hemodialysis (MHD), we evaluated Hb, ferritin, TSAT levels in each 3 months, and high sensitive C reactive protein (hsCRP) and b2microglobulin (MG) levels every 6 months. We defined dysutilization of iron for erythropoiesis as the patients with lower TSAT (<20%) and higher ferritin (100 mg/mL) levels. The association between dysutilization of iron for erythropoiesis and adverse event was investigated with the time dependent cox hazard model.

**Results:** Compared with low TSAT (≤20%) level, patient with normal TSAT (20-30%) was significantly lower risk for cerebrovascular and cardiovascular disease (CVVD) (HR:0.25, P=0.04), and patients with higher TSAT (>30%) were significantly lower risk for death (HR:0.12, P=0.01). In multivariate logistic regression analysis, male, younger patients, without diabetes, low hsCRP and low b2MG were selected as significant predictors of high TSAT, but iron administration or ferritin were not. Compared with low ferritin (<100 ng/mL) and high TSAT (>20%), patients with high ferritin (100ng/mL) and low TSAT (<20%)
Inflammatory and Metabolic Syndrome Biomarkers Analysis of Vascular Outcomes in End-Stage Renal Disease

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Background: The relevance of some biomarkers of inflammation and metabolic syndrome to vascular outcomes in end stage renal disease (ESRD) is not clear. To study these relationships, biochip array technology method was used to profile the complex plasma biomarkers in the setting of various comorbid outcomes such as Stroke or Transient Ischemic Attack (TIA), Acute Coronary Syndrome (ACS), Congestive Heart Failure (CHF), and Coronary Artery Disease (CAD).

Methods: Plasma samples were collected from 83 ESRD patients (mean age 65) prior to hemodialysis and were profiled using biochips for metabolic and inflammatory biomarker levels. Inflammatory cytokine and Metabolic Syndrome arrays were used to profile C peptide, ferritin, insulin, leptin, resistin, TNFα, PAI-1, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, EGF, IFNG, and MCP1. Retrospective review was performed to group patients based on history of Stroke or TIA, ACS, CHF, and CAD.

Results: Of the 83 ESRD patients, 25 (30.1%) were found to have history of Stroke/TIA, 14 (16.9%) were found to have history of ACS, 30 (36.1%) were found to have history of CHF, and 39 (47.0%) were found to have history of CAD. Stroke/TIA patients were found to have decreased plasma IFNG levels (p=0.042) and elevated plasma resistin, IL-1α, and leptin levels (p=0.008, 0.021, 0.026; respectively) when compared to patients without Stroke/TIA. ACS patients had elevated plasma IL6 levels (p=0.040) when compared to those without ACS. CHF patients had decreased plasma leptin levels (p=0.031) and elevated plasma IL1β levels (p=0.042) when compared to patients without CHF. CAD patients had elevated plasma IL1α levels (p=0.049) when compared to ESRD patients without CAD.

Conclusions: Profiling of multiple inflammatory and metabolic syndrome biomarkers may aid in the risk stratification of ESRD patients for cerebrovascular and cardiovascular disorders. These studies demonstrate that biomarker profiling of vascular comorbidity levels in ESRD may provide useful diagnostic and prognostic information in the management of ESRD patients.

Individualized Anemia Management in Pediatric Nephrology Patients

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Background: Anemia management in pediatric patients on dialysis poses a great challenge to the nephrologist. In this study, we tested the hypothesis that individualized approach anemia management, previously demonstrated successfully in adult patients, improves hemoglobin maintenance within target range in pediatric dialysis patients.

Methods: We performed prospective evaluation of Clinical Decision Support System “Smart Anemia Manager” (SAM) in pediatric dialysis patients at Riley Hospital for Children at Indiana University. SAM was implemented as a stand-alone software on a desktop computer used by the nurse anemia manager and connected to a database containing Hemoglobin (Hgb) and ESA dose data. The anemia manager was allowed to override dose recommendations from the system and each override was documented. The followup period was 10 months, including 4 month washout period. We compared the hemoglobin distribution within 9–12 g/dL range during 6 months immediately before SAM implementation and 6 months after the washout period. Only patients who received ESA and had at least 4 Hgb values within each period were included in the analysis.

Results: 13 patients satisfied the inclusion/exclusion criteria. The percentage of monthly Hgb within target range varied between 82% and 92% in 6 months prior to deployment of SAM and between 69% and 100% during 6 months after SAM deployment. Quarterly Hgb distribution varied between 86% to 87% prior to SAM deployment and 87% to 95% after. There was a significant decrease in low Hgb numerix after SAM deployment, but no change in high Hgb levels, compared to the period before SAM deployment.

Conclusions: Individualized anemia management in pediatric patients improves distribution of Hgb within the target range, compared to a standard population-based protocol approach.

Funding: NIDDK Support

Extracorporeal Ultrafiltration Therapy for Acute Decompensated Heart Failure

Neeraj Pourashkar, Ashkan Karimi, Amir Kazory. Medicine, Univ of Florida, Gainesville, FL.

Background: There has been a renewed interest in the use of ultrafiltration (UF) for management of patients with acute decompensated heart failure (ADHF). While a number of studies reported on the efficacy of this therapy and lack of any significant adverse impact, the more recent trials have challenged its safety. The aim of this study is to provide a reappraisal of the current evidence on the use of UF in ADHF.

Methods: Articles cited in PubMed database from 2000 to 2015 using key words “ultrafiltration” and “heart failure” were searched. Those randomized and non-randomized trials using recent portable devices dedicated for UF were selected. Case reports, and case series were excluded. Relevant data such as renal function, cardiac status, and weight change were extracted and compared.

Results: A total 940 patients from 15 trials (7 randomized and 8 non-randomized) that used dedicated UF devices were included. Eleven studies reported either no change or non-significant decrease in serum creatinine, while 4 found worsening renal function after UF therapy; these studies had included patients with more severe renal dysfunction at baseline. Concerning weight, a reduction of 2 to 9 Kg was reported that was similar to conventional therapies in 9 studies but was significantly lower with UF in 6 trials. Length of stay was evaluated in 5 studies, 2 of which showed a significant reduction. Three studies showed fewer re-hospitalizations in the UF group at 30 days, 90 days, and 1 year follow ups. None of the studies evaluated long-term outcomes of patients undergoing UF therapy.

Conclusions: Based on the currently available data, UF is efficient for management of volume overload in ADHF. However, these studies do not support any beneficial impact for this therapy on renal function, and suggest that it might be associated with suboptimal renal outcomes if used for patients with more severe renal dysfunction at baseline. Currently there is no data on the effect of UF on long-term outcomes of patients with ADHF. Whether this would translate into a lack of effect for UF on these outcomes needs to be elucidated by future studies.

Ultra-Sensitive Troponin I Predictive Value in Remote Ischemic Preconditioning in Hemodialysis: A Randomized Double Blinded Clinical Trial

Marcelo Bacci,1 Lívia Yadova Vasconcelos, Felipe R. Bruniera, Filipê Moreira Ferreira, Neif Murad, Antonio Carlos palandri Chagas, Fernando Luiz yffonso Fonseca. ABC Medical School, Brazil.

Background: Remote ischemic cardiopreconditioning(RIPC) is a procedure that generates a brief period of ischemia followed by reperfusion Areas submitted to RIPC in the experimental ischemia models have less occurrence of necrosis. RIPC role in protecting myocardial ischemia during hemodialysis is not established yet.The aim of the study was to evaluate RIPC as myocardial protection achieved by ultra sensitive I troponin in hemodialysis outpatients.

Methods: It is a double blind randomised trial with two groups: intervention,submitted to RIPC with external compression in the right arm with sphygmomanometer with 200mm/Hg of pressure with three-5 minute rounds alternating with deflation totalising 30 minutes and control group without RIPC.Intervention group received RIPC in three consecutive hemodialysis sessions.Blood samples were taken before and after each session. Randomization was made by a software stratified by sex and age.BUN for calculation of single pool Kt/V and ultra sensitive I troponin were measured to evaluate dialysis adequacy and myocardial injury.

Results: A total of 47 patients were randomized.About 60.8% were men and 54% diabetic.The mean single pool Kt/V was 1.51 in the intervention group and 1.49 in control.
Racial Differences in the Evolution of Subclinical Cardiovascular Disease from CKD to ESRD: The CRIC Study  
Nisha Bansal,1 Jason Roy,2 Hsiang-Yu Chen,2 Alan S. Go,3 Martin Keane,4 Rajat Deo,5 Elyse Foster,1 Sankar D. Navaneethan,6 Jiang He,7 Mahboob Rahman,1 Mirela A. Dobre,8 John W. Kusek,9 Michael J. Fischer,10 Emile Mohler,11 Chi-yuan Hsu,12 1 UW; 2 UPenn; 3 Temple; 4 UCSC; 5 Case Western; 6 Tulane; 7 UH; 8 NIDDK; 9 UIC.

Background: Studies have reported that black incident dialysis patients have better survival compared with white dialysis patients, even after accounting for adverse profile of comorbidities among blacks. We hypothesized that differences in subclinical cardiovascular disease (CVD) may explain this paradox.

Methods: We studied incident dialysis patients in the CRIC study who had a research echocardiogram performed before and after the initiation of dialysis. Left ventricular mass index (LVMi) and ejection fraction (LVEF) were measured at CKD (mean eGFR 24 ml/min/1.73 m2) and at dialysis initiation (median 7.9 months after initiation).

Results: Of 316 participants, 74% were black and 26% were white. After initiation of dialysis, there were 88 deaths. In multivariable models, black (vs. white) race was independently associated with a 38% (95% CI: 1%, 61%) lower risk of mortality. From CKD to incident dialysis, mean LVEF worsened in whites (51±10% to 47±11%; p-value for change <0.0001) and blacks (52±9% to 48±10%; p=0.0001). LVMi trended worse in whites (54±16 g/m2 vs 57±15 g/m2; p=0.1) and significantly improved in blacks (61±16 g/m2 vs 58±15 g/m2; p<0.004). Adjusting for LVMi, change in LVMi, LVEF and change in LVEF did not change the association between black race and lower risk of death.

Conclusions: In CRIC, black dialysis patients had better survival than whites. This association was not explained by differences in subclinical CVD at incident dialysis or by differences in the evolution of CVD from CKD to ESRD. Further studies are needed to understand mechanisms underlying the differential survival by race among dialysis patients.  
Funding: NIDDK Support.

PUB323

Whole Blood Viscosity at Low Shear Rate Is Associated with Cardiovascular Mortality in Patients with Hemodialysis  
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Background: The change of whole blood viscosity (WBV) may increase risk of major atherosclerotic events, including congestive heart failure, myocardial infarction, and stroke. However, there is few report about the relationship between WBV and mortality rate due to atherosclerotic vascular disease. The objective of the present study was to investigate correlation between values of WBV at shear rates of 1, and 5 S⁻¹ before and after hemodialysis in patients with end-stage renal disease (ESRD) and mortality, especially cardiovascular or cerebrovascular mortality.

Methods: Forty three patients with ESRD receiving maintenance hemodialysis had initially participated in this study. In a prospective observational study, we examined the effect of WBV in pre- or post-dialysis on cardiovascular or cerebrovascular mortality in dialysis patients for approximately 5.8 years.

Results: Twenty seven patients among total 43 patients died and 2 patients had received transplantation of kidney within period of this study.Cerebrovascular deaths occurred in 8 patients among 27 patients, and cerebrovascular deaths occurred in 5 patients among the 27 patients. The hazard ratios for overall survival in the patient with hemodialysis according to increase of predialylic diastolic WBV at low shear rate of 1 S⁻¹ in an univariate Cox proportional analysis were 1.585 (95% CI, P=0.382) in the group of moderate blood viscosity and 2.351 (95% CI, P=0.128) in the group of high blood viscosity. However, pre-DBV1 was not still statistically significant after adjustment for covariates. In addition, the HRs for overall survival according to increase of pre-DBV5 were 1.357 and 1.930 in each moderate and high blood viscosity group. In Kaplan-Meier’s survival analysis, when pre-DBV1 increased, cumulative mortality relatively showed rising tendency, but, unfortunately there was no statistical significance.

Conclusions: These results suggest that the diastolic low-shear WBV may impact on cardiovascular or cerebrovascular mortality in hemodialysis patients. New prospective and large-scaled studies to more exactly evaluate the correlation between WBV and mortality will be needed in the future.
Survival of Patients Over 75 Years Old in a Chronic Hemodialysis Program
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Background: The intensity of medical care for people over 75 years of age has increased over the past decade. In this surrounding context is increasing the number of individuals with this profile that has clinical indication starting renal replacement therapy. Published studies have shown that survival of patients after initiation of hemodialysis (HD) according to the presence of comorbidities. The aim of this study was to evaluate the survival of elderly patients with chronic kidney disease on regular HD.

Methods: From analysis of medical records was assessed the rate of survival of incident patients starting HD in the months of January to December 2000 to 2010. Demographic and clinical data were collected. It was made a comparison, based on these data, among the elderly (over 75 years old) and non-elderly groups who died.

Results: During the study period, 158 patients started HD program, 69% male and 46% over 75 years old. The average age of patients was 60 years, all patients were adults. The overall mortality rates at 6 and 12 months were, respectively, 7.5% and 17%. Considering only the elderly, mortality rates at 6 and 12 months were respectively 14 and 27%. The median survival of these patients was 33 months. Considering only patients younger than 75 years mortality rates at 6 and 12 months were, respectively, 2% and 8%. Comparing elderly patients with non-elderly, we observed that the first group had a higher proportion of diabetic and hypertensive patients and with a history of cardiovascular disease and cancer. Considering only the patients who died, there were no important significant differences in the presence and score of comorbidities, when the elderly was compared with the non-elderly.

Conclusions: Patients over 75 years in HD had a mortality rate two times higher than younger patients and the presence of comorbidities may be a contributing factor to the age to explain this data.

Prevalence of Abnormal Ankle – Brachial Index in Haemodialysis Patients in Mexico and its Association with Other Cardiovascular Risk Factors
Laura E. Izguerra Ochoa, Heriberto Reyes López. Nefrología, Regional General Hospital #46, Guadalajara, Jalisco, Mexico.

Background: Abnormal Ankle-Brachial index (ABI), defined as ≤ 0.9 or ≥ 1.3, is considered an independent predictor of mortality in hemodialysis patients, in other countries abnormal ABI is found between 35% and 80% of hemodialysis patients. In Mexico the prevalence of abnormal ABI has not been reported. The aim of the study was to determine the frequency of abnormal ABI and its association with other cardiovascular risk factors.

Methods: Prevalent hemodialysis patients over 16 years old were included; data were obtained from medical records and interviews. ABI was measured by oscillometry (Model HEM-705CPINT) and classified as a normal result between 0.91 - 1.3 (NABI), ≤ 0.9 (LABI) or ≥ 1.3 (HABI). NAVI was considered as the control group and the data were analyzed using descriptive and inferential statistics, using T Student and Chi2.

Results: Of the 119 patients analyzed abnormal ABI was present in 36 (30%); 26 (21.9%) with HABI. The mean age was 44.9 years, 68% were male, duration of dialysis of 7.1 years. In univariate analysis ABI was significantly associated with smoking history (p<0.003), smoking history (p<0.001), diabetes (p<0.04), lower creatinine (p<0.001) and albumin (p<0.001) and higher calcium (p<0.01); HABI was significantly associated with lower age (p<0.01), smoking history (p<0.05), lower systolic blood pressure (SBP) (p<0.02), higher levels of sodium (p<0.04) and calcium (p<0.01). No differences were found between normal ABI and history of hypertension, dyslipidemia, heart disease, stroke; there were no differences with the dose of calcium carbonate or calcitriol, the value of Kt / V, the type of vascular access and serum phosphorus.

Conclusions: Abnormal ABI was less prevalent than in other populations, among these HABI is the most common. LABI was associated with older age, DM, smoking history, high calcium and low creatinine and albumin (probably associated with poor nutritional status). HABI patients were younger, with smoking history, lower SBP, high serum sodium and calcium levels.

PUB329
A Lower Serum Uric Acid Is Associated Not Only with All-Cause Mortality but Also Cardiovascular Mortality Among Patients Receiving Hemodialysis in Japan
Naoki Sugano, 1 Yukio Maruyama, Keitaro Yokoyama, Koki Takane, Yasuhiro Takahashi, Chisa Kobayashi, Shinichiro Nishio, 1 Daikusei Takahashi, Satoshi Kidoguchi, Kosuke Honda, 1 Northiko Morisawa, Gorou Tokudome, Iwao Ohno, Tatsu Hoosyota, Takashi Yokoo, 1 Takashi Shigematsu, Kunitoshi Iseki, 1 Ikuto Masakane. 2 1Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; 2Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan.

Background: High level of serum uric acid is prevalent in chronic kidney disease (CKD), however it has a controversy whether high or low serum uric acid level appears to be a risk factor of cardiovascular event and mortality in the patients of receiving renal replacement therapy.

Methods: We collected the baseline data of 222,434 patients receiving HD thrice weekly (males: 63.0%, 66 ±12 years, median HD vintage of 60 months, females: 68 ±13 years, median HD vintage of 72 months) extracted from a nationwide dialysis registry at the end of 2011 in Japan. Then we evaluated the patient survival and development of complication using the registry at the end of 2012.

Results: During one-year follow-up, 18775 (8.4%) died of all causes including 8094 (3.6%) cardiovascular death. All-cause mortality and cardiovascular mortality were lower in the line with the increase of baseline uric acid. In a multivariable logistic regression analysis, patients of the highest quartile of uric acid had lower all-cause, and cardiovascular mortality compared with those of the lowest quartile (males: OR, 0.745; 95% CI, 0.673 to 0.8207, females: OR, 0.833; 95% CI, 0.726 to 0.9366, and males: OR, 0.720; 95% CI, 0.6266 to 0.8278, females: OR, 0.8375; 95% CI, 0.7029 to 1.0462, respectively).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: In this large observational cohort study, lower levels of serum uric acid were independently associated not only with all-cause mortality but also cardiovascular mortality among Japanese HD patients. Close monitoring of serum uric acid is thought to be necessary for the management of HD patients.

**PUB330**

*Post Stroke Disability Deterioration and Mortality of Hospital Onset Stroke in Patients with and without End-Stage Renal Disease*  Tomoko Usui,1 Norio Hanafusa,1 Hideo Yasunaga,2 Masaomi Nagakuni.1 1Dept of Hemodialysis and Apheresis, The Univ of Tokyo Hospital, Japan; 2Dept of Clinical Epidemiology and Health Economics, School of Public Health, the Univ of Tokyo, Japan.

**Background:** Increasing evidence suggests that end-stage renal disease is associated with higher risk and severity of cerebrovascular disease. However, the risk factors for post stroke disability and mortality is not clear. We examined the association between risk factors including diastolic treatment and disability deterioration and mortality during the hospital stay of hospital onset stroke.

**Methods:** The Japanese Diagnosis Procedure Combination database includes administrative claims and discharge abstract data of about 50% of all acute-care inpatients in Japan. Using this database, we extracted data of inpatients age ≥20 years old, hospital-onset stroke between July 2010 and March 2013. Disability level was divided into modified Rankin Scale (mRS) 0-1, 2-3, 4-5, and 6 (death). Deterioration of disability was defined as an increase in disability level. The odds ratio (OR) for in-hospital deterioration of disability and mortality was calculated using a logistic regression model.

**Results:** Out of 26,834 patients, 593 (2.2%) had diastolic therapy. The median length of stay was 39 and 33 days for patients with and without diastolic, respectively. During the hospital stay, there were 7,655 (28.5%) disability deterioration and 3,851 (14.4%) death. The patients with diastolic had higher disability deterioration (47.9%) and mortality rate (31.3%) compared to those without. After adjustment with age, gender, BMI, mRS, Activities of Daily Living, smoking habits, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, heart failure, peripheral arterial disease, cerebrovascular complications, antithrombotic, anticoagulant, and thrombolytic medications, multivariate-adjusted ORs of diastolic for disability deterioration was 2.88 (95%CI: 2.40-3.45), and in-hospital mortality was 3.57 (95%CI: 2.94-4.33).

**Conclusions:** Diastolic treatment was an independent risk factor for in-hospital disability deterioration and mortality of hospital onset stroke.

**PUB331**

*Role of Bioimpedance as Tool for Fluid Management in Hemodialysis Patients*  Maria Cecilia Recalde,1 Manuela Bello,1 Cecilia Arruabarrena,2 Alvaro Herou,1 Fabian Cano,1 Laura Sola,1,2 1Hemodialysis Unit, CASMU, Uruguay; 2Preventive Medicine, Univ of the Republic, Uruguay.

**Background:** Fluid management in hemodialysis patients is difficult, hypertension and fluid overload is frequent as well as hypotensive episodes leading to cerebral and cardiac injury and increased mortality risk. The objective of the study is to evaluate if bioimpedance could be a tool to optimize fluid management in hemodialysis patients.

**Methods:** Patients were included after giving informed consent when fulfilled inclusion and exclusion criteria. Were recorded age, gender, diabetes status, dialysis vintage, body mass index (BMI) estimated dry weight, and mean in previous month: systolic blood pressure and was prescribed more number of other antihypertensive drugs than control group. After matching, there were no differences in age, sex, dialysis modalities, comorbidities and number of other antihypertensive medications. Before PSM, patient survival was significantly better in the RAAS group using the Gehan-Wilcoxon test (P=0.001), however, this difference disappeared after matching (P=0.450). Cardiovascular event-free survival was not different between RAAS group and control group before and after PSM analysis.

**Conclusions:** RAAS blockade did not affect all-cause mortality and MACE-free survival in the Korean ESRD patients. Further researches such as randomized control study will be needed.

**PUB333**

*Effect of Renin Angiotensin Aldosterone System Blockade on Clinical Outcomes in Patients with End-Stage Renal Disease: A Prospective Cohort Study in Korea*  Kyung Don Yoo,1 Jung Pyo Lee,1 Jung Nam An,1 Yun Kyu Oh,1 Shin-Wook Kang,1 Chul Woo Yang,1 Yong-Lim Kim,1 Chun Soo Lim,1 Yon Su Kim.1 1Seoul National Univ College of Medicine; 2Yonsei Univ College of Medicine; 3The Catholic Univ of Korea College of Medicine; 4Kyungpook National Univ School of Medicine.

**Background:** Adequate blood pressure control plays a key role in the management of patients with end-stage renal disease (ESRD). Although renin angiotensin aldosterone system (RAAS) blockade is known as the best treatment option for chronic kidney disease with hypertension, there is debate in the ESRD patients maintaining dialysis.

**Methods:** A total of 5,223 patients in the Clinical Research Center for ESRD (CRC for ESRD) prospective observation cohort from Aug 2008 to Dec 2014 were enrolled in this study. We compare overall survival and major cardiovascular event (MACE)-free survival between RAAS group and control group for using 1:1 propensity score matching (PSM) analysis. We defined the RAAS group as using ACE inhibitor or angiotensin receptor blocker more than 3 months.

**Results:** Before matching, the RAAS group was younger; however, had more comorbidities such as diabetes and cardiovascular disease. The RAAS group had higher systolic blood pressure and prescribed more number of other antihypertensive drugs than control group. After matching, there were no differences in age, sex, dialysis modalities, comorbidities and number of other antihypertensive medications. Before PSM, patient survival was significantly better in the RAAS group using the Gehan-Wilcoxon test (P=0.001), however, this difference disappeared after matching (P=0.450). Cardiovascular event-free survival was not different between RAAS group and control group before and after PSM analysis.

**Conclusions:** RAAS blockade did not affect all-cause mortality and MACE-free survival in the Korean ESRD patients. Further researches such as randomized control study will be needed.

**PUB334**

*Hemodynamic Changes in Maintenance Hemodialysis Patients with Intradialytic Hypotension*  Meijun Meng, Hong Ye, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

**Background:** Intradialytic hypertension (IDH) is a common complication in patients undergoing maintenance hemodialysis (MHD) which leads to high mortality. This study is to explore the hemodynamic changes in MHD patients with IDH.

**Methods:** Thirty-seven patients were included in our study. IDH were defined as a decrease of systolic blood pressure (SBP)<20mmHg or the lowest SBP below 90 mmHg during dialysis. Twenty-three patients were diagnosed with IDH. Among them, 13 were...
asymptomatic while the other had the hypotensive symptoms, such as abdominal discomfort, sighing, nausea, vomiting, muscle cramps and restlessness. All of them underwent a noninvasive hemodynamic evaluations before, during and after dialysis.

Results: Compared to the patients without IDH, the dialysis age was longer and the prevalence of diabetes was higher in the patients with IDH. There were no difference in age, amount of ultrafiltration, pre-dialysis cardiac index (CI), systemic vascular resistance index (SVRI) and thoracic fluid capacity (TFC) between these two groups. During dialysis, CI decreased while SVRI increased generally especially in patients with IDH. At the end of dialysis, ΔCI was markedly higher in patients with IDH. However, there was no significant difference in the change of CI, SVRI and TFC ten minutes before and after hemodialysis between these two groups. Meanwhile, the hemodynamic changes were analyzed in IDH patients with or without symptoms. It was found that there were no difference of change values and absolute values of CI and SVRI in these subgroups.

Conclusions: It was found that CI decreased while SVRI increased during hemodialysis. In the mid and later period, the CI decreased much more in patients with IDH. It was suggested that CI might be an indicator of IDH.

Funding: Government Support - Non-U.S.

PUB335

Dual Relationships of Serum Leptin on Heart Rate Variability in Patients with Stage 5 Chronic Kidney Disease Ningning Wang, Yao Jiang, Jingjing Zhang, Changying Xing. Nephrology, First Affiliated Hospital of Nanjing Medical Univ; Nanjing, China.

Background: Leptin regulates nutrition, bone metabolism and cardiovascular function. Lower heart rate variability (HRV) in chronic kidney disease (CKD) predicts higher risk of cardiovascular disease (CVD). Relationships between leptin and HRV in CKD is obscure.

Methods: This study included cross-sectional observation and longitudinal follow-up on parathyroidectomy (PTX) patients.

Serum leptin/BMI is transformed using natural logarithm (ln [leptin/BMI]).

Results: In PTX/BMI showed no difference between stage 5 CKD and controls. However, quartile 2 of ln [leptin/BMI] level in CKD patients prone to have higher HRV indices

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<tr>
<th>Quartile</th>
<th>Mean 24-h HR (beats/min)</th>
<th>Mean SDNN (ms)</th>
<th>Mean rMSSD (ms)</th>
<th>ln VLF</th>
<th>ln HF</th>
<th>ln LF/HF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1 (≤ 34)</td>
<td>87.4±12.7</td>
<td>70.2±10.3</td>
<td>17.5±9.8</td>
<td>269.4</td>
<td>2.7±1.5</td>
<td>0.9±0.9</td>
<td>0.020</td>
</tr>
<tr>
<td>Quartile 2 (35-39)</td>
<td>79.4±11.6</td>
<td>72.3±33.9</td>
<td>21.4±9.7</td>
<td>64.5±32.9</td>
<td>2.5±2.1</td>
<td>2.5±2.1</td>
<td>0.483</td>
</tr>
<tr>
<td>Quartile 3 (40-46)</td>
<td>81.9±10.5</td>
<td>73.4±24.3</td>
<td>16.4±7.1</td>
<td>54.5±23.1</td>
<td>2.6±1.9</td>
<td>2.5±2.1</td>
<td>0.111</td>
</tr>
<tr>
<td>Quartile 4 (≥ 47)</td>
<td>81.1±9.2</td>
<td>71.1±22.3</td>
<td>20.0±10.5</td>
<td>62.9±19.1</td>
<td>2.4±2.4</td>
<td>2.6±1.9</td>
<td>0.212</td>
</tr>
</tbody>
</table>

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

PUB336

Association of Geriatric Nutritional Risk Index and Responsiveness to Erythropoiesis-Stimulating Agent in Mortality of Chronic Hemodialysis Patients Kosaku Nitta, Ken Tsuchiya. Dept of Medicine, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan.

Background: Responsiveness to erythropoiesis-stimulating agent (ESA) may be associated with mortality in hemodialysis (HD) patients. The aim of the present study was to assess the effects of geriatric nutritional risk index (GNI) and responsiveness to ESA in outcome in HD patients.

Methods: The ESA response index (ERI) was determined as the weekly weight-adjusted dose of ESA divided by hemoglobin concentration. Patients were divided into four groups by quartiles of ERI. Odds ratios were estimated using a Cox proportional model for the association between GNI and ERI and mortality, adjusting for potential confounders. Patients were divided into four groups by quartiles of ERI.

Results: Of the 298 subjects enrolled, 51 died with 31 cardiovascular deaths during the follow-up period of 34.6 ± 6.1 months. The ERI was inversely correlated with the GNI (r = 0.287; p < 0.0001). Age, gender, serum total cholesterol, phosphorus, total phosphorus, and albumin were independent predictors of ERI. Older age, female gender, serum total cholesterol, transferrin saturation and GNI were independent predictors for ESA hyporesponsiveness. Receiver operating confidence intervals for the cut off values of GNI and ERI for mortality were 94.9, 13.5, respectively. When subjects were stratified by ERI and GNI value into four groups, those who had low GNI and high ERI were associated with the highest risk of mortality among the four groups (log-rank p < 0.001).

Conclusions: High ERI and low GNI were associated with an increased risk of all-cause mortality.

PUB337

A Multidisciplinary Approach Is Required to Reduce Hospitalizations for Cardiovascular Disease in Maintenance Hemodialysis Patients David L. Epstein,1,2 Thomas Parker,1,2 Daniel Levine,1,2 Jeffrey I. Silberzweig,1,2 Medicine, The Rogosin Inst, New York, NY; Medicine, Weill Cornell Medical College, New York, NY.

Background: Patients receiving maintenance hemodialysis have hospital admissions rates significantly greater than patients with other chronic diseases.1,2 Approximately 40% of the hospital admissions are related to cardiovascular disease including both acute events and pulmonary edema.1 We sought to assess the contribution of fluid weight gains to hospital admissions.

Methods: We compared inter-dialytic weight gains as a percentage of target weight and changes in blood pressure for the approximately 1200 patients receiving maintenance hemodialysis in our seven dialysis clinics in New York City between January and April 2015. We compared these data to total and cardiovascular hospital admissions using t-tests.

Results: Greater relative weight gains were significantly associated with pre-treatment systolic blood pressure (2.7 mmHg increase in BP per 1% increase in weight; p < 0.0001) and hospitalizations for cardiovascular complications (p = 0.03). In contrast, neither greater relative weight gain nor pre-treatment systolic blood pressure was significantly associated with all-cause hospitalization (p > 0.5). The clinic with both the greatest relative weight gains and the highest rate of hospitalization for cardiovascular disease was without a full-time dietitian for the months of the study.

Conclusions: In our population of maintenance hemodialysis patients, we report a statistically significant association between relative weight gains, hypertension and hospitalization for cardiovascular disease. We suggest that this relationship may be related to the absence of a full-time dietitian leading to a lack of a true multidisciplinary team approach to fluid management in these patients. References: 1. U.S. Renal Data System: USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2012.

PUB338

Acute Effects of Cinacalcet on Arterial Stiffness and Ventricular Function in Hemodialysis Patients Mohsen Agharazii,1 Kosaku Nitta,2 Carolina Marin-Blanco,1 INTRODUCTION Chestnut P, Emery C, Leslie K, Billings J, Parent L, Timmons B, York E, Wu J, Chu C, Asano M, Families, Fondation, Children, M. CHU de Quebec Research Center, Dept of Medicine, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan. A Multidisciplinary Approach Is Required to Reduce Hospitalizations for Cardiovascular Disease in Maintenance Hemodialysis Patients...
m/s, p<0.139). In 14 subjects, who underwent echocardiography, there were no significant changes in cardiac output, stroke volume and ejection fraction. However, left ventricular end-systolic volume (52 ± 22 versus 57 ± 25 ml (p=0.20) and end-diastolic volumes (92 ± 35 versus 97 ± 17, p=0.08) were numerically higher under cinacalcet, but not statistically significant. There were no significant changes in the parameters of diastolic dysfunction.

Conclusions: In this short term study, there were no detectable effects of cinacalcet on aortic stiffness and diastolic dysfunction despite the expected reduction in serum calcium concentration. The numerically higher left ventricular volumes with cinacalcet, may need to be investigated. Clinical trials: NCT01250405.

Funding: Pharmaceutical Company Support - Amgen

PUB339

Kidney Transplantation and Cardiac Repolarization Descriptors

Dimitrios J. Poulikakos,1 Debashish Banerjee,2 Marek Malik,1 Renal, Salford Royal, United Kingdom; St. George’s Univ of London, United Kingdom; Imperial College, London, United Kingdom.

Background: Selected descriptors of cardiac repolarization derived from the computerized analysis of electrocardiogram (ECG) can predict cardiac risk in hemodialysis (HD) patients. Kidney transplantation improves cardiovascular survival. The aim of the study was to investigate the impact of kidney transplantation on these descriptors.

Methods: The study was conducted in two phases. In phase 1, Holter ECGs were obtained during HD sessions and repeated 5 times at 2-weeks intervals in stable HD patients. The repolarisation descriptors QRS-to-T angle (TCRT) and T wave morphology dispersion (TMD) were calculated in overlapping 10 second ECG segments and averaged over the first hour of recordings. In phase 2, continuous 1-hour ECG recordings were obtained in patients who received a kidney transplant minimum three months after transplantation and if they were stable with EGFR>30 ml/min/1.73m2. Average values of post transplant repolarisation descriptors were compared with average values over the first hour of HD using Wilcoxon test and t-test was used for baseline comparisons.

Results: In 80 HD patients in phase 1 both descriptors showed intrasubject stability and exhibited extreme values in subjects that suffered major arrhythmic events. During a period of 35.9±3 months 10 eligible transplanted subjects were recorded and although TMD and TCRT improved 7 months following kidney transplantation (see table) the difference did not reach statistical significance (p=0.05). However these subjects had better baseline TCRT and TMD values compared to the study population (TCRT 0.463 vs. 0.078 p < 0.05 and TMD 17.9 vs 32.4 p>0.05).

Conclusions: In transplant recipients with healthier baseline repolarisation profiles the improvement did not reach statistical significance in the early post transplant period. Larger studies with longer follow up are needed.

PUB340

Prognostic Significance of Cardiopulmonary Exercise Test and 6-Minute Walk Test in Chronic Dialysis Patients

William Dziubek,1 K. Bulinska,2 B. Ochman,1 Ukasz Rogowski,1 Mariusz Kuształ,2 Tomasz Golebiowski,2 D. Markowska,1 A. Zembron-Lacny,1 Marian Klinger,3 M. Wozniewski,3 Imperial College, London, United Kingdom; Univ School of Physical Education, Wroclaw, Poland; 3Non-Public Medical College of Wroclaw, College, Wroclaw, Poland; 4Nephrology and Transplantation Medicine, Wroclaw Medical Univ, Wroclaw, Poland; 5Physical Education, Univ of Zielona Gora, Zielona Gora, Poland.

Background: Dialysis patients (pts) are burdened by significant morbidity and the majority of deaths result from cardiovascular causes. Identifying patients with an increased risk of ominous prognosis is of essential clinical relevance. The aim of the study was to evaluate prognostic value of cardiopulmonary exercise test (spiroergometry) and 6-minute walk test (6MWT) in chronic dialysis pts.

Methods: In prospective study 90 pts receiving high-flux dialysis (12h/week) were examined by means 6MWT and spiroergometry (VO2max, VE, VO2CO2, METS). After 3 years of follow-up data were evaluated in term to assess prognostic value of physical performance tests. Patients were divided into 2 groups: survivors and non-survivors (died within 3 years).

Results: Mortality at 3 years was 22.2% (20 pts) – non-survivors. They showed significantly lower values in cardiopulmonary exercise test and achieved shorter distance in 6 MWT compared to survivors – table. In multivariable analyses controlling for age, and sex and low dided distance in 6 MWT was significantly correlated with all lower measures of spiroergometry (r=0.5-0.6). VO2max and 6 MWT were independently (from age) associated with death within 3 years.

Funding: Government Support - Non-U.S.

PUB341

Adaptive Servo-Ventilator Therapy Improves the Cardiac Dysfunction in Hemodialysis (HD) Patients with Sleep-Disordered Breathing

Fumiko Fukuuchi,1 Ken Tsuchiya,2 Kosaku Nitta.3 Nephrology, Komagome Kyuritsu Clinic, Bunkyo-ku, Tokyo, Japan; 2Medicine II, Tokyo Women’s Medical Univ, Shinjyuku-ku, Tokyo, Japan.

Background: Cardiac dysfunction is a very serious problem in HD patients. Sleep Disordered Breathing (SDB) is considered to cause cardiac dysfunction. Dialysis patients have a disordered respiratory center and a high prevalence of central apnea. Adaptive Servo-Ventilator (ASV) is automated modality used to treat heart failure patients with SDB, especially central apnea. The aim of this study is to explore the relationship between sleep apnea and cardiac dysfunction, and to evaluate the effects of ASV therapy in HD patients.

Methods: Sleep study was performed using a portable sleep test device (Sleeptester LS-300, Fukuda Denki Co., Ltd, Japan). We measured the variables of cardiac function by echocardiogram. The relation between apnea index and the echocardiogram indicates was evaluated. We also collected baseline information on demographics, lab tests, plasma BNP level, medications, and clinical conditions. ASV therapy was used in the patients diagnosed with severe SDB and/or central apnea. The cardiac function variables were evaluated in comparison to the previous year.

Results: The 27 dialysis patients (sixteen diabetics, eleven non-diabetics) were included in this study. Out of them, echocardiogram, SDB indications showed a connection. The obstructive apnea hypoxemia index was related to the left ventricular posterior wall thickness (LVPWT) (r=0.49, p=0.02). Seven patients received ASV therapy. There has been improvement of overall of their cardiac function with significant increase of ejection fraction (p=0.02) 1 year after ASV introduction.

Conclusions: In this study, we demonstrated the efficacy of ASV therapy in hemodialysis patients with SDB. Near future, ASV is possible to be one of attractive devices for HD patients, with aging, several complications, to improve their poor prognosis.

PUB342

Endovascular Renal Denervation: Effects on Dyslipidaemia and Vascular Inflammation in Dialysis Patients

Neil A. Hove,1 J. Christopher Baldi,1 David L. Jardine,1 John B. Scholllum,1 Gerard T. Wilkins,1 Luke C. Wilson,2 Robert J. Walker,1 Dunedin School of Medicine, Univ of Otago; 2Christchurch School of Medicine and Health Sciences, Univ of Otago.

Background: Endovascular renal denervation (RDN) reduces arterial and effluent sympathetic nerve activity. Its effects on vascular inflammation and cholesterol levels in dialysis patients are unknown. We hypothesized RDN would reduce sympathetic activity, resulting in improvement in biomarkers of vascular inflammation and dyslipidaemia.

Methods: Nine dialysis patients with uncontrolled office BP (>140/90mmHg despite two or more agents at maximal tolerated dosages) were recruited into this feasibility study. Office and ambulatory BP monitoring (ABPM) were performed at baseline, one and three months post RDN, along with supine muscle sympathetic nerve activity (MSNA) and venepuncture. Bilateral RDN was undertaken with an EnligHTN™ catheter.

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

Background: Hemodialysis practice varies based on health system, payer practice, patient choice and socioeconomic environment. We analyzed the practice pattern and characteristics of non survivors and survivors among twice weekly hemodialysis patients across 9 centers in India.

Methods: Retrospective study of patients on HD between July 1, 2013 to Dec 31, 2014. Inclusion criteria: > 30 days of HD & 1.8 - 2.3 HD sessions/week. Demographic data, the use of OAC, were included in the study. Thyroxine-3 (T3), free thyroxine-4 fT4, Thyroid Stimulating Hormone (TSH), and Thyroid Peroxidase Antibodies (TPO-Ab) were measured. Data was presented as non survivors vs survivors: Hospitalizations: 42.6% vs 25.8% (<0.01), DM: 65.2% vs 34.5% (<0.01), CAD: 17.5% vs 6.4% (<0.05), CV A: 1.8% vs 2.3%; HCV: 1.8% vs 10.9% (p<0.05), Office Systolic BP (mmHg) 90±17 vs 76±13, Office Diastolic BP (mmHg) 173±19 vs 173±23, Total Protein (g/L) 66±6.1 vs 68±8.2, CRP (mg/L) 27±28 vs 20±20, Albumin (g/L) 3.8±5.0 vs 3.9±6.3, Chol (mmol/L) 4.1±0.9 vs 4.1±1.0, HDL Chol (mmol/L) 1.2±0.3 vs 1.2±0.2, LDL Chol (mmol/L) 2.2±0.7 vs 2.4±0.9, Triglycerides (mmol/L) 1.4±0.8 vs 1.2±0.6. Conclusions: RDN in dialysis patients improves office systolic BP, impacts uraemic dyslipidaemia and possibly reduces vascular inflammation. Further controlled studies are warranted.

PUB343

Management of Subclinical Thyroid Dysfunction Can Reduce Cardiovascular Events in Patients with End-Stage Renal Disease on Hemodialysis Hong Joo Lee, Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Republic of Korea.

Background: Normal thyroid function influences basal metabolic rate and general body metabolism and thyroid dysfunction is often associated with dyslipidemia and increased cardiovascular risk in general population. It is known that about 25% of patients with end-stage renal disease (ESRD) on hemodialysis had subclinical thyroid dysfunction. We investigated that subclinical hypothyroid dysfunction associate with dyslipidemia and cardiovascular event in hemodialysis patients. Hence, we conducted our study to elucidate whether subclinical thyroid dysfunction treated or not in ESRD patients.

Methods: All hemodialysis patients in Red Cross Hospital within a period of one year were included in the study. Thyroxine-3 (T3), free thyroxine-4 fT4, Thyroid Stimulating Hormone (TSH) and lipid profiles in the serum were estimated and death from all causes and CV events served as outcome variables over a median follow-up period of 12 months. Participants were divided into groups based on the thyroid function. Statistical analysis was carried out by using SPSS.

Results: Among the 92 cases, 28.2% of the patients were having thyroid disorder. In which 21.2% were of hypothyroid, 13.7% were of subclinical hypothyroid, and 0.8% were of hyperthyroid, 11.6% were of subclinical hyperthyroid. We observed negative correlation between T3 & T4. Total cholesterol was raised in hypothyroidism in comparison to euthyroid ESRD patients. However, thyroid function didn’t have significant association with lipid profiles. Cardiovascular disease significantly often occurred in subclinical thyrotoxic patients than other groups.

Conclusions: Our results show that the blood thyroid hormone level isn’t affected by dyslipidemia but affected by occurrence of CVD. Therefore, the management of subclinical hypothyroidism in hemodialysis patients should be considered.

Non survivors were significantly older, had lower number of total sessions, lower albumin and Hb. But dialysis adequacy and UF were comparable. Short duration of follow up may limit the ability to study other factors influencing outcomes.

PUB344

New Anticoagulant Free Strategy for Non Valvular Atrial Fibrillation in Hemodialysis Patients Teresa Arcidiacono, Patrizio Mazzone, Marco Simonini, Donatella Spotti, Maria Teresa Sciarri Alibrandi, Rita Quartagno, Marco Melandri, Stefano Tenitori, Giorgio Slaviero. San Raffaele Scientific Inst, Italy.

Background: Vascular calcification in patients with CKD-5 is associated with increased cardiovascular morbidity and mortality. An excessive calcification of coronary arteries and of aortic valve has been reported during Warfarin treatment. In addition use of oral anticoagulation (OAC) seems to be an important risk factor for calciphylaxis. Atrial fibrillation (AF) is the most frequent reason for OAC use in CKD patients.

Methods: An alternative to OAC could be the percutaneous Left Atrial Appendage Closure (LAAC) closure. With this technique an implantable component is permanently fixed in the LAA to prevent thrombus embolization. Different studies demonstrated that this procedure is not inferior to systemic anticoagulation with OAC in prevention of thromboembolic risk. We reported our clinical experience with the use of this technique in haemodialysis patients with non valvar AF.

Results: In the last few months seven (7) haemodialysis patients were treated with percutaneous LAA closure. Bleeding and stroke risks were evaluated by HAS-BLED score and CHA2DS2-VASc score: HAS-BLED score was 4.5±0.58 (equal to 9%/±0.11 yearly risk of major bleeding); and CHA2DS2-VASc score was 4.1±0.81 (equal to 4.47%/±1.5 yearly risk of stroke). This procedure was well tolerated by each patient. OAC treatment was interrupted after the procedure and doubled antiplatelet therapy was introduced for a month. At this moment median of 9 months of follow-up was archived (IQR 3-12); no adverse events has been assessed.

Conclusions: To the best of our knowledge this is the first consecutive series of LAA closures in haemodialysis patients. This procedure represents a real clinical alternative to the use of coumarin derived drugs. Our experience leads the way to the possible routine use of this procedure in CKD-5 patients. As well as this procedure could be used in those patients with contraindications to OAC, even more this treatment should be used in haemodialysis population, in which the use of OAC should be avoided for both increased risk of life-threatening bleeding events and well known negative cardiovascular effects.

PUB345

Results: Similar to previous, office systolic BP reduced and the effect on ABPM was attenuated. MSNA did not change, a novel finding. Despite lack of change in MSNA, total cholesterol-HDL ratio increased along with a falling trend in CRP and rising trend in albumin, all novel findings.

Conclusions: MSNA may impact on arterial stiffness and cardiovascular disease. This study further adds to the evidence that office BP and ABPM are different, with ABPM being the better predictor of cardiovascular disease.
Effect of Altitude on All-Cause Mortality in End-Stage Kidney Disease Patients Ongoing Hemodialysis in Peru

Katia Bravo-Jaime,

Vicky Y. Sunicion,

Jose Ernesto Rojas,

Christian R. Mejia,

Sandra C. Schult.

Medicine, Univ of Rochester Medical Center, Rochester, NY; Medicine, Jackson Memorial Hospital, Miami, FL; Inst de Investigaciones de Altura, Univ Peruana Cayetano Heredia, Lima, Peru; Asociacion Medica de Investigacion y Servicios en Salud, Lima, Peru; Pediatrics, Inst Nacional de Salud del Niño, Lima, Peru.

Background: Worldwide, end-stage kidney disease (ESKD) prevalence has tremendously risen. Previous studies suggested that receiving hemodialysis (HD) at high altitude confers mortality benefits; however this effect has not been proved above 2000 m or in developing countries.

Methods: This historical cohort study analyzed medical records from six HD centers of the Peruvian Social Security System. Adult ESKD patients who started HD between 2000 and 2010 were included. Patients were classified into two strata (< 2000 m and > 2000 m). The outcome variable was death from any cause. Cox proportional hazards models were built and patients were censored by year and death from any cause. Stratification by year was included. Patients were classified into two strata (< 2000 and > 2000 m). The period prevalence for the patients undergoing renal dialysis was 52 patients per 100,000. The mortality rate for the same period of time was four patients per 100,000. The expenditure on these 380 patients in 2014 was 6.5 million dollars. However, to determine the size of the burden, we need a comprehensive study covering the whole country of Oman and we need to receive data from neighboring countries to compare with.

Conclusions: In Peru, patients receiving HD at high altitude do not experience mortality benefits. In fact, diabetics have higher mortality rates at > 2000 m (p = 0.003), independently of age.

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Follow up in years

p = 0.001

Results: 723 patients were enrolled, including 248 women (38.2%). The mean age was 52.8 ±16.9 years. 166 patients lived > 2000 m (22%). In first years after follow-up, survival rates were lower in the group > 2000 m, however after 8 years of follow-up this trend reversed. Age and gender were not significantly associated to mortality at altitude levels > 2000 m. Patients with diabetes had higher mortality rates at > 2000 m (p = 0.003), independently of age.

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Depression Is Associated with Frailty and Malnutrition but Not Comorbidity Load in Chinese Peritoneal Dialysis Patients Cheuk-Chun Szeto,1 Shin Man Choy.2 1Dept of Medicine & Therapeutics, The Chinese Univ of Hong Kong, Shatin, Hong Kong; 2Dept of Medicine & Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong.

Background: Depression is common amongst patients with chronic kidney disease and is associated with excessive mortality in dialysis patients. This study determines the prevalence and risk factors of depression in Chinese peritoneal dialysis (PD) patients.

Methods: We studied 178 prevalent PD patients (103 males). Depression was screened by the 15-item self-reported Geriatric Depression Scale (GDS). We also determined patients’ comorbidity load, dialysis adequacy, residual renal function, nutritional status, and degree of frailty.

Results: The mean age was 60.7 ± 11.7 years; vintage of dialysis 42.5 ± 44.1 months. Average GDS score was 4.9 ± 4.4. GDS score is closely associated with the frailty score (r = 0.692, p < 0.0001), malnutrition inflammation score (r = 0.406, p < 0.0001), and subjective global assessment score (r = -0.386, p < 0.0001). GDS score also has a modest but significant correlation with Charlson’s comorbidity index (r = 0.164, p = 0.028) and serum albumin level (r = -0.192, p = 0.019), but not with patient age, vintage of PD, dialysis adequacy, or residual renal function. When defined as a GDS score ≥8, 50 patients were introduced in multivariate analysis: HD/HDF*, vintage, age*, weight, CCI*, use of EA.

Results: Table 1 shows the association between depression and various parameters.

Table 1: Association between depression and various parameters

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<th>p-value</th>
</tr>
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<td>Age</td>
<td>1.03</td>
<td>1.01 – 1.06</td>
<td>0.003</td>
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<td>Charlson Comorbidity Index CCI</td>
<td>1.30</td>
<td>1.16 – 1.45</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Weight</td>
<td>0.98</td>
<td>0.97 – 0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Calcium concentration of dialysate</td>
<td>3.60</td>
<td>1.06 – 12.24</td>
<td>0.04</td>
</tr>
<tr>
<td>Vascular access</td>
<td>1.43</td>
<td>1.19 – 1.72</td>
<td>0.0002</td>
</tr>
<tr>
<td>Interdialytic weight gain</td>
<td>1.31</td>
<td>1.07 – 1.61</td>
<td>0.009</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.38</td>
<td>0.39 – 0.97</td>
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Conclusions: In an aged Western dialysis population, treatment with HDF did not improve all-cause mortality compared to high-flux HD. Mortality seems to be determined by comorbidity rather than by clinical practice patterns.

Trends in anemia management with Darbepoetin Alfa on Maintenance Hemodialysis Robert H. Yenchek,1 Anne C. Beaubrun,2 Jeffrey Petersen,3 David G. Dalpiaz,4 Alfred K. Cheung.1 1Univ of Utah, Salt Lake City, UT; 2Ameren, Inc., Thousand Oaks, CA.

Background: In the US, darbepoetin alfa (DA) is primarily used to treat anemia in patients receiving treatment in hospital-based dialysis centers. Epoetin alfa (EA) doses and hemoglobin (Hb) levels declined in response to recent regulatory and reimbursement events but little is known about trends in anemia management with DA in the US maintenance hemodialysis (HD) population receiving treatment in free-standing dialysis centers (FSDCs). We describe herein anemia management in FSDCs within the University of Utah (UU) Dialysis Program who switched from the use of EA to DA program-wide in 2005.

Methods: We included ~650 adults (age ≥18 yrs) with ≥1 months on HD between 2008-2013 in 18 FSDCs within the UU Dialysis Program. We summarized quarterly inpatient and HD and iron dose use, and dialysis transferrin saturation (TSAT) and ferritin levels.

Results: 70-78% of patients received DA over the study period. Mean Hb levels among patients who received DA fell from 12.2 g/dL in 2008 before leveling around 10.3 g/dL from Q4 2011 to 2013 (Figure). The mean monthly DA dose was 209 mcg in Q1 2008, reached a peak of 256 mcg in Q1 2010, and decreased to ~105 mcg in 2013. Iron dose use rose from 52% in 2008 to 67% of patients in 2013. Iron dose also rose from 129 mg in Q4 2008 to 194 mg in Q4 2010, but declined to 163 mg in Q4 2013. Mean serum TSAT levels remained relatively constant at ~30% between 2008-2013 but serum ferritin levels increased from 449 ng/mL in Q1 2008 to 770 ng/mL in Q4 2013.

Conclusions: Trends in anemia management parameters among patients on HD treated with DA within FSDCs in the UU Dialysis Program were consistent with national reports of patients treated with EA.
A Prospective Study of Routine Heparin-Free Hemodialysis (HFD) with Streamline® Bloodlines (SL) in a Large Tertiary Acute Care Inpatient Practice Sami Safari,1 Mary Ann Ryan,2 Amanda L. Severson,3 Scott Klarenbach,1 Anita Molzahn,1 Mark Haykowski,1 Anita Lloyd,1 Marcello Tonelli,2 1Univ of Alberta, Edmonton, AL, Canada; 2Univ of Calgary, Calgary, AB, Canada.

Background: Intradialytic exercise (IDE) is associated with improved dialysis adequacy and amelioration of dialysis-related symptoms. However, the uptake of IDE is limited by knowledge gaps on efficacy—what type of exercise to prescribe to optimize outcomes, and on feasibility. The results of this pilot will inform the design of a full-scale efficacy study evaluating two types of IDE (aerobic and resistance) and will also provide research users with practical information on IDE.

Methods: In this single center, randomized, factorial (2 x 2) study, chronic adult hemodialysis patients were randomized to one of four IDE groups: cycling, resistance, cycling and resistance, or stretching (an attention control). Exercise was semi-supervised by a kinesiologist. Outcomes focused on a priori feasibility criteria: recruitment, fidelity to the protocol, and participant and unit staff response to IDE. As a secondary outcome, we evaluated the main effect of cycling and weights each compared with control on quality of life and physical performance at baseline and 12-weeks. To better understand feasibility, we conducted interviews with users.

Results: We exceeded targeted accrual of 28 people over 12 weeks. Of 100 patients screened, 51 were enrolled (36 did not meet inclusion criteria, 33 declined participation); 16% dropped out after randomization. Fidelity to the intervention was high: of 1,039 training sessions offered, 87% were delivered. Participant response to the intervention was favorable: 92% of participants continued exercising after the trial. There were no crossovers and no reported contamination. Dialysis staff were not consistently available to assist with implementation, so staff were necessary to deliver IDE. Secondary outcomes were not statistically significant.

Conclusions: This pilot study demonstrated feasibility of high patient acceptability, and low risk of contamination. However, IDE will not be feasible in the long term unless dialysis staff assist with implementation. This will need to be addressed before executing a definitive trial.

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

Underline represents presenting author.

PUB355
Patterns of Oral Disease in Adults with Chronic Kidney Disease Treated with Long-Term Hemodialysis: A Multinational Ecological Study Giovanni F.M. Strippoli,1,2,3,4,5 On behalf of the ORAL-D Study Investigators;2 Diaverum Medical Scientific Office; 3Univ of Bari; 4Univ of Sydney.

Background: Oral disease is a potentially treatable risk factor for premature death and impaired quality of life. However, the oral disease burden and candidate preventative strategies are uncertain in the dialysis setting.

Methods: ORAL-D was a prospective study in 4726 adults treated with hemodialysis in Europe and Argentina recruited from a convenience sample of 80 dialysis clinics within a treatment network. Oral disease was assessed using standardized WHO methods. Participants self-reported oral health practices and symptoms. Socio-demographic and clinical factors associated with oral diseases were assessed within nation states.

Results: Of 4726 eligible adults from 80 dialysis units, 4205 (88.9%) participated. Overall, 20.6% were edentulous (95% CI, 19.4-21.8). Participants had on average 22 (21.7-22.2) decayed, missing or filled teeth while moderate to severe periodontitis affected 40.6% (38.9-42.3). Oral disease patterns varied markedly across countries. Participants in Spain, Poland, Italy and Hungary had the highest mean adjusted odds of edentulism (2.31, 1.90, 1.90, and 1.54) whilst those in Poland, Hungary, Spain and Argentina had highest odds of ‘14 decayed, missing, and filled teeth (23.2, 12.5, 8.14, 5.23). National levels of tobacco consumption (R²=0.79), diabetes (R²=0.49), and child poverty (R²=0.66), were associated with edentulism within countries.

Conclusions: Oral disease in adults on hemodialysis is very common, frequently severe, and highly variable among countries, with much of the variability unexplained by patient characteristics or oral practices. Given the substantial variation among countries and high burden of disease, strategies to improve oral health in hemodialysis patients will require national strategies.


PUB356
Low Serum Albumin Is a Risk Factor for In-Hospital Mortality Among Hemodialysis Patients Hospitalized with Infectious Diseases: A Multicenter Retrospective Cohort Study in Japan Shun Minatozumi,1,2 Hideaki Shimizu,1,2 Takaya Ozeki,1 Daisuke Uchida,2 Hiroko Kawarazaki,1 Hiroti Nishiwaki,2 Takahiro Imaizumi,2 Yoshito Fujita,2 Yugo Shibagaki,2 1Nephrology, Chubu Rosai Hospital, Nago-yama, Ichinomiya, Japan; 2TOMEI Nephrology Group for Clinical Research, Japan.

Background: Serum albumin is the known marker of nourishment and inflammation. Several studies in the past have shown the relationship between low serum albumin and long-term mortality among dialysis patients. However, there is insufficient data on the

Funding: Pharmaceutical Company Support - Medisystems, a NxStage Company
The relationship between serum albumin levels and short-term mortality among chronic dialysis patients who are hospitalized with infectious diseases. This multicenter retrospective cohort study in Japan evaluated if serum albumin levels at the occurrence of infection is a risk factor for in-hospital mortality among hemodialysis patients.

Methods: From June 2011 to July 2013, a total of 418 hemodialysis patients who took blood cultures were reviewed retrospectively in five tertiary dialysis units participating in "TOMEI Nephrology Group for Clinical Research" study. After exclusion of 232 patients diagnosed with non-infectious diseases, 186 patients diagnosed with infections were analyzed. Patients were divided into two groups according to the serum albumin level at hospitalization (median 3.5 g/dL), lower serum albumin (Serum albumin<3.5 g/dL), or not. Outcome measured was in-hospital mortality. For statistical analysis, cox proportional hazard model was used.

Results: Among 186 patients with infectious diseases, there were 117 patients (62.9%) in low albumin group, and 69 patients (37.1%) in normal albumin group. During hospitalization (median 19 days, interquartile range 10-37), 29 patients (15.5%) died, 25 of 117 (21.4%) in low albumin group, and 4 of 69 (5.8%) in normal albumin group. The cox proportional hazard model revealed that low serum albumin and bacteremia were associated with in-hospital mortality. The hazard ratio of in-hospital mortality among low albumin group was 4.203 (95% CI: 1.36-13.55).

Conclusions: Although low serum albumin is a known risk factor for long-term mortality, this study showed that low serum albumin strongly predicts short-term mortality among hemodialysis patients hospitalized with infectious diseases.

PUB357
Usefulness of High-Frequency Wave-Length Ultrasonography as a Diagnostic Tool for Carpal Tunnel Syndrome in Hemodialysis Patients Tadashi Yamazaki,2 Tokie Hayasaka,2 Tetsuo Saito,2 Shuichi Tsuruoka.1 1Nephrology, Nippon Medical School, Tokyo, Japan; 2Dialysis Unit, Moka Hospital, Moka, Tochigi, Japan.

Background: Carpal tunnel syndrome (CTS) is a common complication in dialysis-induced amyloidosis. In orthopedics, high-frequency wave-length ultrasonography (US) with improved resolution is recently used for diagnosing disorders of the upper extremities. We aimed to determine the value of US for diagnosing CTS in hemodialysis (HD) patients, through a cross-sectional analysis.

Methods: All maintenance HD patients (N ~ 150) at our hospital were recruited after providing written informed consent. Patients with apparent paralysis or pain in the upper extremities due to causes other than CTS were excluded. Longitudinal scan of the median nerve around the carpal tunnel area was performed with US (Toshiba Viamo TM, 12-MHz probe) during HD, and the compression rate (CR) of the nerve was calculated as (1 - shortest diameter/longest diameter of the nerve around the carpal tunnel area). The CTS symptoms were evaluated with the visual-analogue scale (VAS) of pain around the index finger area and the quick form of the Disabilities of the Arm, Shoulder and Hand (Quick-DASH) questionnaire. Pinch strength was also measured. Serum C-reactive protein (CRP) and b2-Mg concentrations, and medical histories related to CTS or dialysis-induced amyloidosis were extracted from the patients’ records.

Results: Total 250 wrists from 125 patients (Mean age = 65.6±10.6 years) were studied. The mean CR was 11.8±7.0 and the cut-off values of CR from ROC curve for history of carpal tunnel release was 25.7% (sensitivity 0.80, specificity 0.91). Multivariate analysis revealed that CR was significantly positively correlated with dialysis career, VAS and carpal tunnel release was 25.7% (sensitivity 0.80, specificity 0.91). Multivariate analysis of Korea; 2Dept of Internal Medicine, Wonkwang Univ College of Medicine School of Medicine, Ewha Womans Univ Mokdong Hospital, Seoul, Republic

Conclusions: CR significantly correlated with symptoms and factors associated with dialysis-induced CTS.

Funding: Government Support - Non-U.S.

PUB358
Technique Failure in Korean Incident Dialysis Patients: A National Population-Based Study Shina Lee1, Hyunwoo Kim2, Seung-Jung Kim1, Duk-Hee Kang1, Kyu Bok Choi1, Dong-Ryol Ryu1, 1Dept of Internal Medicine, School of Medicine, Ewha Womans Univ Mokdong Hospital, Seoul, Republic of Korea; 2Dept of Internal Medicine, Wonkwang Univ College of Medicine Sanhon Hospital, Gunpo, Republic of Korea.

Background: Technique failure is an important issue for dialysis patients. In this study, we aimed to analyze a detailed technique failure rate and to determine the predictors for technique failure in Korea.

Methods: We identified all patients who had started dialysis between January 1, 2005 and December 31, 2008 in Korea, using the Korean Health Insurance Review and Assessment Service database. A total of 32,357 eligible patients [24,743 hemodialysis (HD) patients and 7,614 peritoneal dialysis (PD) patients] were included, and the median follow-up was 26.7 months.

Results: The crude incidence rates of technique failure among HD patients and PD patients were 3.4 and 5.1 per 1000 patient-years, respectively. When comparing technique survival rate between HD and PD in both Kaplan-Meyer analysis and competing risks analysis, it was significantly higher in patients on PD than those on PD. The gap of technique failure incidence between HD and PD was exaggerated in Kaplan-Meier analysis compared to competing risks analysis. In multivariate analyses, diabetes mellitus and Medical aid as a crude reflection of low socioeconomic status were independent risk factors in both Cox proportional hazard model and Fine and Gray subdistribution model.

Conclusions: Technique failure in PD is higher than that in HD, and it is major concern in patients initiating dialysis in Korea. The results of our study offer a basis for risk stratification and customized care for technique failure.

PUB359
Frequency of Not Achieving Target Weight in Hemodialysis Patients and the Reasons Behind It Tine Malha,1 Frank Modersitzki,1 Lada Beara Lasic,2 1Internal Medicine, Div of Nephrology, New York School of Medicine, New York, NY; 2Internal Medicine, Div of Nephrology, New York Harbor VA Healthcare System, New York, NY.

Background: Volume overload and volume depletion have both been associated with morbidity and mortality in patients with end stage kidney disease (ESKD) on hemodialysis (HD). A recent study demonstrated an increased mortality risk when post HD weight is more than 2kg above or below the prescribed estimated dry weight (EDW) for >30% of HD sessions. Our aim was to determine the frequency of sessions with weight difference (WD)≥2kg, determine the prevalence of patients WD≥2kg for >30% of sessions and identify the possible reasons in our outpatient chronic HD population.

Methods: 32 outpatients on chronic HD at the New York Harbor VA Healthcare System in Manhattan were monitored for 2 months. Data for 631 sessions was obtained. Charts and HD nursing notes were reviewed every 2-4 weeks for: weight, prescribed EDW, ultrafiltration (UF) rate, intradialytic complications (hypotension with systolic BP<90, dizziness, cramping, administration of intravenous fluids). Sessions with a missing documented EDW or post HD weight were excluded. 502 sessions were used in the analysis.

Results: The mean WD for all sessions was 0.67±1.64 kg with a majority (83.7%) of HD sessions ending with post HD weight within 2kg of EDW which is consistent with the literature. 6 out of 31 (19.3%) patients had WD≥2kg for >30% of the evaluated sessions. The inability to achieve post HD weight within 2kg of EDW was most commonly (51.2%) associated with an elevated UF rate (defined as >875ml/hour). Possible reasons for not achieving EDW included cramps (4.9%) and hypotension (2.4%).

Conclusions: Failing to achieve EDW within 2kg range is most commonly associated with high UF rates, indicating high weight gains between treatments. Proposed strategies to continue aiming at achieving EDW while compensating for the constraints of elevated UF include: decreasing intradialytic weight gain, increasing treatment frequency or treatment time. Further studies identifying the best strategies to achieve this goal are needed.

PUB360
Comparative Effectiveness of Dialyzers: A Longitudinal Propensity Score-Matched Study Scott Sibbel,1 Abigail Hunt,1 Suzanne Laplante,2 Werner Beck,2 Mary Gellens,2 John Alan Laich,1 Steven M. Brunelli.1 1DaVita Clinical Research, Minneapolis, MN; 2Baxter Healthcare Corporation, Deerfield, IL.

Background: Differences in dialyzer design may affect systemic inflammation and extracorporeal blood sequestration and thereby impact anemia management and control. We evaluated the comparative effectiveness of commonly used dialyzers with respect to longitudinal hemoglobin (Hb) levels, and ESA and IV iron utilization.

Methods: Patients included in the analysis received hemodialysis between 01 Jan 2009 and 31 Dec 2013 and were new users of Revaclear, Optiflux 160, or Optiflux 180 dialyzers. Patients were followed for 1 year or until end of study or censoring for dialyzer switch, modality change, or loss to follow up. For each comparison, eligible patients were propensity score-matched 1:1 on a range of demographic, comorbidity history, and baseline laboratory parameters. Outcomes were assessed using linearized mixed models including fixed effects for dialyzer type, time, and their interaction term.

Results: Matched patient pairs (21,551 for Revaclear-Optiflux 160 comparison; 21,008 for Revaclear-Optiflux 180 comparison) were assessed. ESA doses evolved differently over time among Revaclear patients versus both Optiflux 160 and Optiflux 180 patients (p interaction=0.001 for both). Differences in ESA dose were significant from month 3 for Revaclear versus Optiflux 160 (range, 173-483 U/treatment) and at all time points for Revaclear versus Optiflux 180 (range, 120-392 U/treatment) and at all time points for Revaclear versus Optiflux 180 (range, 120-392 U/treatment). Hb levels were equivalent between Revaclear and Optiflux patients at all times. IV iron dosing was lower for Revaclear patients than Optiflux 160 and 180 patients (p=0.001 for each) but differences were small (≤1 g/dL iron/month).

Conclusions: Use of Revaclear versus Optiflux dialyzers was associated with lower ESA doses, modestly lower IV iron doses, and equivalent Hb concentrations.
PUB362

Fluid Overload Predicts Mortality Risk in Maintenance Hemodialysis Patients
Carlo Donadio, Valentina Vigo. Clinical and Experimental Medicine, Univ of Pisa, Pisa, Italy.

Background: Maintenance hemodialysis (MHD) patients have a high mortality rate, mainly due to cardiovascular disease and malnutrition. The aim of this study was to evaluate the efficacy of the analysis of body composition by bioimpedance (BIA) to predict the mortality risk in hemodialysis patients.

Methods: Observational longitudinal study lasting six years on 78 prevalent MHD patients (68% male, mean age 65 ± 14 years; dialysis vintage 7 ± 7 years). Every two years, starting from the baseline, we collected clinical, laboratory and BIA data, including vectorial analysis (BIVA) and hydration scale, that is the hydration as percentage of extracellular body mass. We compared the BIA data of patients dead during the study period (n = 45; 65%) with those of survivors (n = 24; 35%). The significance of the differences between the mean values of the two groups at the baseline was evaluated.

Results: Nine patients moved to another hemodialysis facility. The patients dead at different times during the six years had significantly higher values of BMI (28 ± 6 vs 24.8 ± 3.1 kg/m², p < 0.01) and fat mass index (11.2 ± 4.1 vs 8.4 ± 2.8 kg/m², p < 0.003) compared to the survivors, while there were no significant differences for body cell mass (BCM) index (7.1 ± 1.7 vs 7.9 ± 1.8 kg/m²) and serum albumin (4.1 ± 0.4 vs 4.1 ± 0.1 mg/dl). Furthermore, deceased patients had lower values of reactance (53.5 ± 11.7 vs 67.3 ± 13.7 Ohm, p < 0.000003), phase angle (5.1 ± 0.9 vs 5.9 ± 0.8 degrees, p = 0.000003) and the percentage of extracellular water was higher (50.6 ± 5.2 vs 46.1 ± 3.6%, p < 0.00003). Finally the BIVA analysis confirmed that the hydration was significantly higher in the deceased (73.3 ± 1.8 vs 71.2 ± 3.3%, p < 0.000006). In summary survivors had normal values of BMI and fat mass, a smaller reduction in BCM and less fluid overload than deceased patients.

Conclusions: The survival of HD patients is influenced by the nutritional status. In particular, fluid overload and decrease in muscle mass play a decisive role on survival. Fluid overload, low values of electrical resistance and phase angle predict mortality risk in MHD patients.

Funding: Government Support - Non-U.S.

PUB363

A Single Center 2-Year Experience with Haemodialysis Care in Nigeria
Bala Waziri,1 Isah Alhaji Umar.2 Dept of Medicine, IBB Specialist Hospital, Minna, Niger State, Nigeria; 2Dept of Medicine, IBB Specialist Hospital, Minna, Niger, Nigeria.

Background: In Nigeria, sustaining maintenance haemodialysis while awaiting renal transplantation is largely being hampered by high cost of care. Furthermore, the scarcity of dialysis units, lack of government funding or subsidy on haemodialysis have made survival very difficult for patients with End Stage Renal Disease in Nigeria. Thus the aim of this study was to share our experience with the challenges of providing maintenance haemodialysis in a developing country.

Methods: We retrospectively reviewed records of all the patients with ESRD who had haemodialysis at our dialysis facility over a period of 24 months. Data on their demographic characteristics, etiology of Chronic Kidney Disease, types of vascular access for dialysis, frequency of haemodialysis, history of blood transfusion and patient outcomes were collected.

Results: This study included 64 patients on maintenance haemodialysis. The mean age was 43.9±18.1 years, and there were 39 males (60.9%) and 25 females (39.1%). The underlying presumed etiology of Chronic Kidney Disease were hypertension (73.4%), diabetes mellitus (31.3%) chronic glomerulonephritis (1.6%) and (21.0%) was unknown. Their mean haemoglobin level at the time of commencing dialysis was 7.2±2.2 g/dL, with 17.5% receiving 3-4 pints of blood transfusion. The mean systolic and diastolic blood pressure were 169±37.6mmHg and 103.3±15.5mmHg respectively. A significant inverse correlation between haemoglobin level and serum creatinine was observed (r= -0.413, p<0.001). A predominant proportion of the patients (68/93.8%) were dialyzed via femoral access for dialysis, frequency of haemodialysis, history of blood transfusion and patient outcomes were collected.

Conclusions: The high mortality in this study, is likely due to a combination of inadequate dialysis with other predictors of cardiovascular events such as anaemia and uncontrolled hypertension as demonstrated in our results.

PUB364

Characteristics and Patient Survival in Nursing Home Residents on Maintenance Dialysis
Robert Nee,1 Lawrence Agodoa,2 Kevin C. Abbott.3 1Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 2NIDDK, National Insit of Health, Bethesda, MD.

Background: There is limited data on the growing nursing home (NH) population with end-stage renal disease (ESRD) in the United States. We evaluated the characteristics and predictors of mortality of NH patients on dialysis.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 782,161 patients initiated on maintenance dialysis from January 1, 2007 through December 31, 2013, followed until 31 May 2014. Covariates include age, gender, race, dialysis modality, body mass index, serum albumin, indicators

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Underline represents presenting author.

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of poor functional capacity and other co-morbid conditions from the Medical Evidence Form 2728. We conducted both Kaplan-Meier and Adjusted Cox regression analyses with death as the outcome variable.

Results: 56,194 (7.18%) were identified as nursing home residents upon initiation of dialysis. Among NH patients, 50.53% were female, 69.92% were white, and 99.49% were on hemodialysis and the mean age was 71.1 ± 12.1 years. The overall incidence rates of death of NH vs. non-NH patients were 51.8/100 and 17.6/100 patient-years, respectively (p<0.001). The unadjusted 1-year mortality was 50% in NH patients (vs. 20% in non-NH patients, p<0.001). Adjusted Cox analysis showed that NH patients were at significantly higher risk of death when compared to non-NH patients (adjusted hazard ratio [AHR] 1.37; 95% confidence interval 1.35-1.38). Within this NH cohort, age (AHR 1.02; 95% CI 1.02-1.03), inability to transfer (AHR 1.25; 95% CI 1.22-1.29), inability to ambulate (AHR 1.08; 95% CI 1.05-1.11), cancer (AHR 1.15; 95% CI 1.12-1.19) and other co-morbid conditions were significantly associated with death.

Conclusions: NH patients on dialysis have a high mortality rate, even when compared to the broader ESRD population. Further studies on modifiable risk factors of mortality in this particularly high-risk ESRD population are warranted. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, or the United States government.]

PUB365

Background: Protein-energy malnutrition (PEM) is prevalent in the hemodialysis (HD) population and is associated with a high morbidity-mortality burden. Metabolic acidosis and PEM are closely related. Protein intake, which constitutes an acid load, is an important factor of pH regulation in end-stage renal disease patients. Therefore, a higher bicarbonate serum level could be the result of insufficient protein intake and be a useful marker of malnutrition?

Methods: We conducted a retrospective study in our HD service using a computer database with measurements obtained simultaneously for all 342 patients. Correlation between pre-HD session bicarbonate, albumine, prealbumine and normalized protein catabolic rate (nPCR) was assessed by the use of Pearson’s and Spearman’s correlation test. Subgroup analysis were realised for patients with negative C-Reactive Protein (CRP < 5) and patients classified as clinically stable.

Results: We found a significant, negative and moderate, correlation between bicarbonate and nPCR, (spearman’s r = -0.27, p<0.001). Subgroup analysis showed similar results, (spearman’s r: -0.28; p<0.001) for 196 clinically stable patient and (spearman’s r: -0.24, p<0.05) for 144 patients with a negative CRP. There was no association between albumin (spearman’s r: -0.06, p=0.1511) or prealbumin (spearman’s r: -0.08, p=0.1511) and bicarbonate in any group.

Conclusions: A higher serum level of bicarbonate is associated with a lower nPCR, reflecting of poor protein intake, but not with a malnutrition state defined by albumin or prealbumin criteria. These patients are at risk to develop a clinically apparent malnutrition state after a prolonged period.

PUB366
Scope and Consistency of Outcomes Reported in Randomized Trials of Hemodialysis Gabrielle J. Williams, Allison Tong, Jonathan C. Craig. School of Public Health, Univ of Sydney, Sydney, NSW, Australia.

Background: Inconsistent outcome selection and reporting in clinical trials may limit their capacity to inform evidence-based decision making and the ability to combine findings in systematic reviews. Aim: We aimed to assess the scope and consistency of outcome selection and reporting in trials included in systematic reviews of interventions for patients on hemodialysis (HD).

Methods: The Cochrane Database of Systematic Reviews was searched from 1999 to January 2015 for published systematic reviews of interventions for patients on chronic HD. The description and frequency of outcomes reported within the source randomized controlled trials were assessed.

Results: The 18 systematic reviews included 282 trials that reported over 518 outcomes. There was considerable heterogeneity among the outcomes reported. Across all trials, 320 outcomes were measured, and the units and threshold changes that defined an outcome. For example, blood pressure was reported as pre-dialysis, post-dialysis, maximum, difference in pre and post dialysis, intermittent, resting, rise, and time to restore.

Conclusions: A wide array of outcomes are reported in trials of interventions in HD, with large heterogeneity in timing of measurements, units of measure, and threshold changes that define an outcome. This highlights the need for a well-defined set of standardized core outcomes to improve the comparability of trial findings in meta-analysis and to provide greater confidence around treatment decisions for patients undergoing HD.

Funding: Government Support - Non-U.S.

PUB367
Blood Pressure and Cognitive Decline in Hemodialysis Patients Sarah M. Duncan,1 Hocine Tighiouart,2 David A. Drew,3 Tammy Scott,2,1 Daniel E. Weiner,4 Mark J. Sarnak,5 1Tufts Medical Center, Boston, MA; 2Tufts Univ, Boston, MA.

Background: Cognitive impairment is common in hemodialysis (HD) patients; however, the relationship between measures of blood pressure (BP) and longitudinal decline in cognitive function is unknown in this population.

Methods: 314 participants in the Cognition and Dialysis Study underwent an annual comprehensive battery of cognitive tests. Using principal components analysis (PCA), we reduced individual test results to two domains representing memory and executive function. Adjusted joint mixed models accounting for death, transplant, and drop-out were used to explore the association of blood pressure (systolic [SBP], diastolic [DBP] and pulse pressure [PP]) with change in cognitive function over time.

Results: Mean (SD) age was 63 (16) years, 47% were women, 22% were African American, and 44% had cardiovascular disease (CVD). Mean (SD) SBP, DBP, and PP were 141 (21), 73 (12) and 68 (13) mmHg, respectively. Median follow-up time was 1.8 years (IQR 1.0-3.4). Mean slopes of PCA memory and executive were 0.03 (95% CI -0.01, 0.07) and -0.11 (95% CI -0.15, -0.06) per year, respectively. Lower DBP and higher PP were associated with decline in measures of both memory and executive function. There was no association between SBP and cognitive decline.

Changes in Slopes of Test Scores per Year (with 95% CI)*

<table>
<thead>
<tr>
<th>Test</th>
<th>Slope per 1 SD</th>
<th>Slope per 1 SD</th>
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<tbody>
<tr>
<td>SBP</td>
<td>-0.07 (0.06)</td>
<td>-0.05 (0.04)</td>
<td>-0.03 (0.02)</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.03 (0.02)</td>
<td>-0.05 (0.03)</td>
<td>-0.03 (0.01)</td>
</tr>
<tr>
<td>PP</td>
<td>-0.03 (0.01)</td>
<td>-0.03 (0.01)</td>
<td>-0.03 (0.01)</td>
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*Adjusted for baseline BP measure, age, sex, race, education, vascular access and CVD. Negative coefficients are associated with worse scores except on Trials Tests. Bold results are significant.

Conclusions: Lower DBP and higher PP are associated with faster rate of cognitive decline, in particular that related to executive function. Because impairment in executive function is a manifestation of vascular disease and lower DBP and higher PP are associated with CVD in HD patients, our results suggest that cognitive decline may be mediated by vascular disease in this population.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic Inc.

PUB368
High Ferritin Levels Achieved with Ferric Citrate as a Phosphate Binder Do Not Associate with Adverse Events Udavan Y. Bhatt,1 Kausik Umanath,2 Mohammed Sika,3 Mark Koury,3 Robert M. Nicastro,2 Barbara A. Greco,3 Dana G. Niewold,1 Wiktoria J. Chang,3 Emmanuel Stephen Z. Fadem,2 Molly McFadden,1 Julia Lewis,1 Jamie P. Dwyer,2 The Collaborative study group.4 1Ohio State; 2Henry Ford Hosp; 3Vanderbilt; 4CSC; 5Baystate Med Ctr; 6U of VT; 7Western Neph; 8U of Utah; 9Baylor College of Med.

Background: Ferric citrate (FC) as a phosphate binder increases Fe stores and reduces IV iron/ESA use while maintaining hemoglobin. This analysis compares effects of higher achieved ferritin levels in subjects on FC to those in subjects on sevelamer carbonate and/or calcium acetate (active control, AC).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Data were obtained from the 52-wk active control period of the FC pivotal trial. Subjects with a baseline ferritin 100ng/mL or TSAT:50% were excluded from the trial. We randomized 292 subjects to FC and 149 to AC. Any subjects who developed ferritin level ≥1500ng/mL at any time over 52ks were identified. CV, ID, and dialysis access related adverse events (AE) occurring at any time over the 52-wk period were tabulated. Results: 57 subjects (19.8%) in the FC group and 14 subjects (9.5%) in the AC group had at least a single ferritin≥1500ng/mL (p=0.021) during the 52 ks. CV events including MI, CHF, and arrhythmias, occurred in 12.3% of the FC group compared to 21.4% of the AC group. ID AEs occurred in 42.1% of FC and 50% of AC. Dialysis access related AE occurred in 15.7% of FC and 13.5% of AC. IV administration was statistically significant (p=0.003) for the FC group (2.95±3.7mg/wk) than the AC group (6.20±3.64mg/wk), consistent with the full cohort that saw a significant reduction in IV iron use. Cumulative ESA dosing was 1016±906 Units/wk FC and 1781±1756 Units/wk AC (p=0.256).

Conclusions: It was suggested that the adjustment of serum BNP by strictly managing the weight reduced pruritus in hemodialysis patients but it was difficult to improve long-term QOL.

Funding: Pharmaceutical Company Support - Novartis, Kowa, Tanabe-Mitsubishi, Kyowa-Kirin, Private Foundation Support

PUB371

The Mechanisms Study on Neointimal Hyperplasia of Autogenous Arteriovenous Fistula in Maintenance Hemodialysis Patients 
Nanmei Liu, Jimin Hospital of Shanghai.

Background: To evaluate the influence and the possible mechanism about neointimal hyperplasia of autogenous internal arteriovenous fistula in hypertensive nephropathy and diabetic nephropathy patients which was going maintenance hemodialysis and provide possible theory about how to prevent from intimal hyperplasia, extend the life of AVF in clinic.

Methods: Collecting cephalic vein when the hemodialysis patients had the surgery of AVF angioplasty and reconstruction. Vascular tissues were divided into chronic glomerulonephritis group, hypertensive nephropathy group and diabetic nephropathy group.

Immunochemistry was used to detect the expression of vascular smooth muscle actin (a-SMA). Selecting the control group and fistula vascular tissue which the useful life was 12-18 months, basic fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF-V), matrix metalloproteinase2 (MMP2) and matrix metalloproteinase9 (MMP9) were to detect expression change by immunochemical staining.

Results: Compared with chronic glomerulonephritis group, intima thickness of hypertensive nephropathy and diabetic nephropathy were significantly increased and the increase was more significant in diabetic nephropathy. Hyperplasia intima was eccentric hypertrophy and the hyperplasia intima showed obvious inflammatory cells infiltration and vascular degeneration. Immunochemical staining showed that compared with the group of chronic glomerulonephritis, hypertensive nephropathy and diabetic nephropathy groups’ a-SMA, bFGF, IGF-1 and MMP9 expression levels were significantly increased, expression of VEGF was significantly reduced, MMP2 was no significant change (P<0.05). Univariate regression analysis revealed that the expression levels of a-SMA was positively correlated with bFGF, IGF-1 and MMP9 negatively correlated with the VEGF. AVF intimal hyperplasia mainly dominated by the vascular smooth muscle cells (VSMC) proliferation. Hyperplasia intima showed evident inflammation. A possible hypothesis was that neointimal hyperplasia, shorten the life of fistula and diabetes promote intimal hyperplasia more significant. This study provides a theory and therapeutic targets for the prevention and treatment on intimal hyperplasia of AVF in dialysis patients.

Funding: Government Support - Non-U.S.

PUB372

Association of Nutritional Status with Depression and Sleep Disorders in Elderly Hemodialysis Patients 
Pavan V B., Enrue Turlut., 2 Nephrology, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey; 2Nephrology, Basant University Hospital, Ankara, Turkey.

Background: The relationship between depression, sleep quality, and malnutrition in an elderly population in maintenance hemodialysis is very complex and not yet fully understood. We aimed to determine the association between nutritional status and psychological factors such as depression and sleep disturbance in elderly dialysis patients.

Methods: Seventy three dialysis patients (41 female, 32 male; aged, 72±5.60 years) older than 65 years of age were enrolled in the study. Nutritional status was determined by Subjective Global assessment (SGA). Beck Depression Inventory (BDI) questionnaire was used to measure presence and degree of depression. Quality of sleep was measured using the Pittsburgh Sleep Quality Index (PSQI). Demographic and biochemical parameters and Charlson Comorbidity Index and frequency of infection in previous year period of all patients were recorded.

Results: In our elderly patients 15 (%20.5) had sleep disorder and 24 (%32.9) had mild to moderate depression and 11 (%15.1) had moderate to severe depression. When the well nourished group had higher albumin levels (4.28±4.56) vs 3.97±3.97 (p=0.009), lower CRP levels (7.51±4.23 vs 16.02±19.45), better quality of sleep (3.50±0.82 vs 5.56±1.73) and better depression scores (6.08±2.75 vs 16.28±4.56) than malnourished group. By multivariate analysis when factors affecting nutritional status were taken into consideration the nutritional status and depression scores were the present independent parameter.

Funding: Government Support - Non-U.S.

PUB369

Association Between Employment Status and KDQOL Scores in Dialysis Patients 
Duan Du,1 Deborah S. Evans,1 Elizabeth J. Jones,1 Caroline Hann,2 Rich Metu,2 Allen R. Nissenson,1 Deborah A. Benner.1 DaVita HealthCare Partners Inc, Denver, CO; 2Apx Health Innovations, Simi Valley, CA.

Background: Emunemployment negatively impacts dialysis patients’ quality of life (QOL).1 QOL can be quantified and low scores on the Kidney Disease Quality of Life (KDQOL) survey are associated with poor outcomes.2 Our study examines employment/unemployment status and KDQOL scores.

Methods: We collected employment status data on 122,166 adult patients at a large dialysis organization from Nov 2014-Apr 2015. Patients were grouped as either employed (received pay or in training), unemployed (including retirees and those on long- or short-term disability or Workers Compensation) or other (involved in work/activity but not paid). Data were matched with patients’ most recent KDQOL scores.

Results: The employed group (n=16,216) had the highest KDQOL scores in all categories compared to the unemployed (n=98,014) and other groups (n=7936) [Table]. A clinically meaningful difference (6.8) in Physical Component Score was found between categories, followed by the other (n=7936) and unemployed groups (n=98,014) [Table]. A reduction of pruritus in hemodialysis patients by adjustment of serum BNP.

Conclusions: More studies are needed to better understand the factors influencing KDQOL scores among dialysis patients. More studies are needed to better understand the factors influencing KDQOL scores among dialysis patients.
Conclusion: Depression and sleep disorders are important factors influencing the nutritional status and could be an independent risk factors for malnutrition in elderly patients receiving maintenance dialysis. Psychological assessment should be mandatory in the follow up of these patients to identify depression and sleep disturbance because many of them are reversible.

PUB373
Predialysis Hyponatremia and Mortality in Elderly Patients with Incident Maintenance Renal Replacement Seung Ho Ha, Sung Woo Lee, Shin-Young Ahn, Sejoong Kim, Ki Young Na, Dong-Wan Chae, Ho Jun Chin. Internal Medicine, Seoul National Univ Bundang Hospital, Republic of Korea.

Background: Predialysis hyponatremia recently have been reported to be associated with mortality in incident hemodialysis patients. However, little is known about whether predialysis hyponatremia is associated with unfavorable outcomes in elderly patients.

Methods: We retrospectively assessed mortality in 397 (mean age 73.0 year, male 226(171) patients aged ≥65 years with non-diabetic end-stage renal disease (ESRD) who initiated renal replacement therapy (RRT) at a tertiary university hospital between 2000 and 2010. 1 year survival, 2-year survival and multivariate mortality (ACM) was analyzed in relation to predialysis serum sodium (sNa). We divided subjects into 3 groups according to sNa: Group1, < sNa 125; Group 2, sNa 125-134; Group 3, sNa ≥ 135 mEq/L. Patients with sNa levels >145mEq/L were excluded.

Results: The median value of sNa was 137 mEq/L (interquartile range 133-140 mEq/L).

1. Chronic comorbidities included congestive heart failure (r = -0.215, P < 0.001) and liver cirrhosis (r = -0.174, P < 0.001), and lower estimated glomerular filtration rate (r = -0.150, P < 0.001) and albumin (r = -0.175, P < 0.001) and higher white blood cell count (r = -0.136, P = 0.006) were associated with lower sNa levels in elderly patients after full adjustment. One hundred and five (26.4%) patients had died at the 1-year follow up. Higher sNa level was associated with lower adjusted ACM in a continuous model (HR 0.433, 95% CI 0.261-0.718, P = 0.001). Group 1 had a higher mortality than normonatremia group in a categorical model (reference group: normonatremia, Group 1: hyponatremia, Group 2: hypernatremia). The associations of sNa and mortality difference was not observed between group 2-3 (reference group3). HR 1.511, P=0.161).

Conclusions: Predialysis hyponatremia was associated with increased 1-year mortality in elderly ESRD patients who initiated RRT. However, the higher mortality was only observed in elderly patients with severe hyponatremia (sNa < 125 mEq/L). These findings suggested that compared to adults <65 years, other comorbidities or factors rather than sNa may affect mortality in elderly.

PUB374
Observation of the Correlation Between the Uremic Toxins with Clinical Feature in Uremia Patients Mei Li,1, 2 Gong-Li Yin,1 Zhenda Zheng,1 Cai-Lian Cheng,1 Xun Liu,1 Cheng-Gang Shi.3 1VIP Healthcare Center, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China; 2Cardiovascular Dept, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China; 3Nephrology Dept, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China.

Background: To investigate the correlation between the uremic toxins with age, dialysis duration and the different blood purification techniques on removal uremic toxins with hemodialysis (HD) and hemodiafiltration (HDF).

Methods: 72 cases of maintenance hemodialysis patients were observed, age 28~80 years (mean age 64±13.6), duration 4~20 months (34.4±39.15). HD group (n = 50), HDF group (n = 22) (once 1~2 weeks). Before each conventional HD and HDF therapy, blood was sampled for small molecule water-soluble toxins BUN with automatic biochemical analyzer, Middle molecular and macromolecular toxins (MMS) with Ultraviolet spectrophotometry, pentosidine (PENT) with enzyme-linked immunosorbent assay methodfrom ALD Company, USA. Protein-bound toxins, indoxyl sulfate(IS) with high performance liquid chromatography method.

Results: For HD versus HD, there was no significant differences between BUN, MMS, pentosidine and IS. There was low positive correlation between MMS, PENT, IS and the age of the patients (r being 0.322, 0.263 respectively, P<0.05). MMS, PENT and IS were positively related with dialysis months (r being 0.406, 0.427, 0.742 respectively, P<0.05).

Conclusions: HD and HDF therapy may not good enough in clearing middle molecular toxins and protein-bound toxins, which results in their accumulation in patient’s body with the increase of dialysis course. It is recommended that better dialysis methods be adopted for patients who have received hemodialysis for a long time.

PUB375
Parathyroid Hormone Response in Chronic Hemodialysis Patients Converted from Intravenous Doxercalciferol to Oral Calcitriol Three Times a Week Anna Jeanette Jovanovich,1,2 Annegret Howe,2 Morgan E. Marceculi,3 Michel Chonchol.1 1Denver VA Medical Center; 2Freensien Medical Care; 3Univ of Colorado Denver.

Background: The purpose of this study was to characterize serum calcium, phosphorus and intact parathyroid hormone (iPTH) level response during the initial 24 weeks following conversion from intravenous doxercalciferol to oral calcitriol three times a week in a real world setting.

Methods: Data was collected by a retrospective chart audit of end stage renal disease patients on hemodialysis in an outpatient chronic dialysis unit. We identified 33 chronic hemodialysis patients that had a record of treatment with intravenous doxercalciferol (6 months to 3 years prior to conversion to oral calcitriol) and 19 patients (28~80years(59.75 ± 9.36)) with eGFR ≤ 5 and > 5ml/min upon initiation. The comparisons achieved statistical significance (p < 0.03 for all). 48% of patients were on calcinacel during each of the treatment periods. The median (IQR) change in iPTH increased slightly among those patients receiving oral calcitriol and sevelamer (3132 to 4797 pg/ml) while iPTH decreased among patients receiving oral calcitriol and other non-sevelamer binders (41029 to 155 pg/ml; P = 0.173).

Conclusions: This small retrospective study suggests that conversion from intravenous doxercalciferol to oral calcitriol using a conversion algorithm maintains iPTH within KDIGO recommended targets and does not appear to cause hypercalcemia or hyperphosphatemia. The clinical significance of other iPTH values among those treated with oral calcitriol and sevelamer needs further study.

Funding: NIDDK Support, Veterans Administration Support

PUB376
Pregnancy and Chronic Kidney Disease – A Case Study Morgan E. Lindsay, Syed S. Haqqie, Arif Asif. Albany Medical College.

Background: For women with underlying renal disease, pregnancy remains high risk. Case series have provided guidance on the interdisciplinary management of these patients. Herein, we report one institution’s management of five patients requiring dialysis in pregnancy. The present case series includes patients with chronic kidney disease secondary to lupus nephritis (n=2), cystinosis (n=1), malignant hypertension (n=1), and diabetic nephropathy (n=1). All five patients, one of whom was on dialysis prior to pregnancy and the rest were CKD 5 were placed on six-times weekly dialysis upon the presentation with pregnancy. Three of the patients, two with Lupus and one with Malignant HTN delivered infants with whom they were able to discharge home after NICU stays, two patients one with cystinosis and one with DM delivered infants who subsequently died in the NICU secondary to prematurity. All 5 patients post-delivery continued on maintenance hemodialysis. Although improving, maternal and fetal outcomes in those with chronic kidney disease remain variable. Our experience adds to the growing literature on dialysis for chronic kidney disease in pregnancy.

Methods: Restrospective study of patients at one institution.

Results: Out of five pregnancies three had successful outcome with intensive dialysis.

Conclusions: Pregnancy complications in dialysis patients and outcomes are generally poor. There are improved results with intensive dialysis and multidisciplinary approach to the management.

PUB377
When Shall the Advanced Chronic Kidney Disease Patients Start Dialysis? Lee Ying Yeol,3 San Yoon Paik, Hae Min Hong, Sung Min Lee, Hye-Eun Lee, Ji-Hye Lee, Ji-Young Lee, Ji-Hyun Jang, Ji-Won So, Ji-Sung Hahn, Joonkeun Shin, Jung-Kyung Kim, Soon-In Kang, Su Young Park, Seung Hoon Kim, Ji-Woo Jang. Jovanovich,1,3 Jovanovich,2 1Denver VA Medical Center; 2Fresenius Medical Care; 3Albany Medical College; 4Albany, NY.

Background: Recent guidelines suggest dialysis should be initiated when estimated glomerular filtration rate (eGFR) drops below 10-12ml/min. The aim of the present study was to analyse outcomes of those initiating dialysis at very low eGFRs.

Methods: A single center, prospective study of new ESRD patients who were initiated on dialysis between 2012–2014 and dialysis was performed for >90 days. The patients were categorized into 2 groups according to eGFR ≤ 5 and > 5ml/min upon initiation. The patients with incomplete data, and those who underwent transplantation were excluded.

Results: A total of 251 patients were included with mean age of 59.0 ± 11.9 years, mean eGFR of 5.4 ± 2.9ml/min; 57% were males and 51.4% were Chinese. Majority started on hemodialysis (81.7%) and 69.7% were unplanned. The survival rate till May, 31 2015 was 88.4%; 61% were initiated when eGFR ≤ 5 (mean 3.6±1.1 ml/min) and 39% with eGFR >5 (mean 8.3 ± 2.6 ml/min). Dialysis vintage was shorter in the group with eGFR ≤5 (18.2 ± 9.5 vs. 21.7 ± 11.1 months). The patients with eGFR < 5 had lower Charlson Comorbidity Index (4.0 ± 1.3 vs. 4.7 ± 1.2), and hemodialysis was preferred (90.9% vs. 67%). The death burden was significantly lower in the group with eGFR ≤5, including diabetes mellitus (72.1 vs. 88.7%), ischemic heart disease (23.4% vs. 37.1%) and peripheral arterial disease (4.5% vs. 12.4%). However, there were trends showing that these patients were younger, had higher serum albumin and shorter hospitalization for index admission. Underlying diabetes, ischemic heart disease, mortality selection and dialysis vintage remained significant after adjusted. Mean survival for both groups were comparable (36.3 months, 95% CI, 34.4-38.2 vs. 34.5 months, 95% CI 32.0-37.0). Among the patients who survived, 97.7% remained on their initial modality.

Conclusions: Our study suggests that the ESRD patients without significant morbidities may be able to delay dialysis initiation without significant short term adverse outcomes. Further studies are required.
The Incidence and Type of Cancer in Patients with End-Stage Renal Disease: A Prospective Cohort Study for End-Stage Renal Disease in Korea

Background: In patients with end-stage renal disease, urinary tract cancer is known to be related to the general population. However, the incidence and type of cancer is affected by variable factors such as age, gender, ethnic differences. Moreover, the causality of dialysis and cancer incidence in certain type of cancer is still needed to be clarified.

Methods: A total of 5,225 patients in the clinical research center for ESRD cohort were reviewed from Aug 2008 to Dec 2014. The primary outcome here is to compare the cancer incidence rate of ESRD patients with the general population. We obtained cancer incidence data from National Cancer Information Center Registry in healthy counterpart.

Results: A total of 2,200 incident and 3,035 prevalent dialysis patients was included the study. The mean follow-up duration was 22.5 months, and 116 (2.3%) patients were diagnosed with cancer during the observation periods. ESRD with cancer group was significantly older, longer dialysis duration and more comorbidity than control group. The incidence rate of cancer in prevalent dialysis patients was higher than that in incident dialysis patients (2.5% vs 1.3%, p=0.002). The proportion of primary organ was highest in digestive organ (33.6%) followed by urinary organ (25.3%) and others. The MSPSS (social support) is positively correlated with the incidence of cancer from dialysis initiation was 58.6 months in digestive cancer, 52.0 months in urinary tract cancer. The standardized incidence ratio (SIR) of overall cancer was 0.94 [95% CI: 0.72 –1.19]. Urinary tract cancer showed the highest SIR (4.7, 95% CI: 4.2– 8.19) and had the shortest duration (16.1%). Interestingly, the highest frequency (33.1%) of digestive organ cancer showed no difference in the incidence of cancer compared to the general population [SIR: 0.607, 95% CI: 0.36– 0.94].

Conclusions: Further research was needed to compare the organ-specific cancer incidence of ESRD patients with the general population. The screening test could be necessary for digestive and urinary tract cancer.

The Role of Social Support in Hemodialysis Patients

Background: A number of patients with End-Stage Renal Disease (ESRD) have significant impairment in social support. Social support is the major determinant of health-related quality of life in chronic renal failure. Social support is the major determinant of health-related quality of life in chronic renal failure. The aim of the current study was to identify the clinical and psychosocial factors including social support, the MSPSS (social support) of dialysis patients and to compare those to the general population.

Methods: The 101 participants on HD from the Daegu Catholic University Medical Center were assessed from September 2013 to September 2014. Patients on HD for acute kidney injury were excluded from this study. Multidimensional Scale of Perceived Social Support (MSPSS) was used for evaluating patients’ social support. Analysis was done to identify significant risk factors of social support of dialysis patients. Multivariate logistic regression with backward selection was performed.

Results: The mean score of MSPSS (social support) was 56.3 ± 9.1. In subgroup of social support, the MSPSS-family, MSPSS-friend, and MSPSS-medical team scores were 41.2 ± 11.3, 29.8 ± 9.1, and 16.4 ± 9.2, respectively. The variables showed the significant association with social support were quality of life (r=0.332, p=0.001), depression (r=-0.290, p=0.003), anxiety (r=-0.372, p=0.001), and serum creatinine (r=-0.270, p=0.007). Multiple regression showed that quality of life (95% CI: 0.615–0.799, p=0.037) and serum creatinine (95% CI: -1.543–0.319, p=0.003) were independent predictors of impaired social support.

Conclusions: This study explored the determinants of high susceptibility to the impaired social support in HD patients. We found that the impaired social support is associated with the quality of life and serum creatinine. Further study will be needed because of the possibility of different result depending on culture and ethnicity. As well as, we should consider the psychosocial interventions to improve the impaired social support.

Use of Portable Fundoscopic Photography to Screen for Diabetic Retinopathy in the Hemodialysis Unit

Background: Over 40% of dialysis patients have diabetes, yet only 25% get annual eye exams. Due to the frequency and duration of visits to dialysis centers, patients on dialysis likely have increased barriers to receiving eye exams and other recommended preventive care. This study evaluated the need for ophthalmic care, barriers to care, and prevalence of diabetic retinopathy (DR) in this population.

Methods: Prospective cohort study at two dialysis centers (1 urban, 1 suburban). A patient survey (measuring eye care utilization, barriers to eye care, and self-reported visual functioning) and eye screening (visual acuity test and non-mydriatic fundus photos) was conducted at baseline and every 3 months. Other variables were obtained from medical records and included demographics, duration of diabetes, co-morbidities, and insurance type. Descriptive analyses examined barriers to eye care and presence of DR. Cox regression data on satisfaction with eye screening were also obtained from both staff and patients.

Results: 58 patients (79.5% of diabetics at the two sites) were screened. Of the readable fundus photos, 50% had DR and only 10% had no ocular abnormalities. The majority (64%) had diabetic retinopathy and 8% had advanced DR. Only 11% of patients reported that getting an annual eye exam is a priority. The most commonly reported barriers to eye care were cost (89%) and transportation difficulty (82%). Qualitative data indicated that staff and patients were overall very satisfied with the program.

Conclusions: There is a significant under need for ophthalmic care among diabetics receiving dialysis. Since cost and transportation were reported as main barriers to eye exams, providing the screening at dialysis centers could improve adherence to eye care thereby improving ophthalmic and other health outcomes.

Recent Diabetic Beginning Is a Mortality Predictor for In-Patients

Background: Acute kidney failure occurs in 5% of hospital admitted patients. Dialysis need during patients stay in hospital is associated with higher mortality risk. The main objective was to evaluate patients profile in our dialysis center and the impact in the outcomes.

Methods: Prospective observational study. A check list was applied for every patient or who required intensive care or who died. The data was analyzed from 01/2010 to 10/2014. The main outcome was to evaluate the patients' profile in our dialysis center and the impact in the outcomes.

Results: The study shows about 64% of our participants believe that there is a paucity of information and awareness regarding organ donation in general population. The study was conducted to see the knowledge and beliefs towards organ donation programme in chronic kidney disease patients in western india.

Methods: The author conducted a cross sectional study among 85 CKD patients to evaluate the knowledge about and attitude towards organ donation at a large tertiary academic hospital in western india. The author used a questionnaire that included items on knowledge, attitude and demographics.

Results: Age of respondents participated in study ranged from 15 to 75 years. Around 2/3rd participants were males. About eighty-two percent belonged to hindu religion. All were aware of term organ donation and cadaveric organ donation. About 47% of people heard about organ donation through hospital or from doctor. The audiovisual media such as television (21%) followed by newspaper/magazines (14%) were the major source of information about organ donation. Strikingly, radio was not the source of information to any of the respondents. All respondents believed in medical colleges/government institutions should make awareness about organ donation. All respondents felt that the organs should go to the needy irrespective of the relationship. Almost 67% of patients were aware of term organ donation through hospital or from doctor. The aesthetic media such as television (21%) followed by newspaper/magazines (14%) were the major source of information about organ donation. All respondents believed in medical colleges/government institutions should make awareness about organ donation. All respondents felt that the organs should go to the needy irrespective of the relationship. About 64.70% believe that there is a danger that donated organs could be misused, abused or misappropriated. There seem to be paucity of information and awareness regarding organ donation among CKD patients.

Conclusions: The study shows about 64% of our participants believe that there is a paucity of information and awareness regarding organ donation among CKD patients. Mass media, religious and political leaders may be involved to maximize awareness about organ donation.
**Enhancing Patient Engagement in Future Clinical Trials – The Effects of Age and Ethnicity**

_Territa Santhakumaran, Kieran McCafferty. Renal, Royal London Hospital, London, United Kingdom._

**Background:** Increasing patient engagement from ethnic minority populations is crucial to the widespread applicability of research findings, but this represents a challenge in nephrology clinical research. Ethnicity, socio-cultural and language barriers along with a lack of understanding and awareness of clinical trials are potential factors that affect patient involvement in clinical trials.

**Methods:** We developed a patient survey in English, Urdu and Bengali to represent our ethnically diverse population in East London to explore the attitudes and understanding of clinical research. The surveys were offered to all patients attending the haemodialysis and renal outpatients department over a 2 week period.

**Results:** 151 forms were completed, 145 in English, 7 in Bengali and 1 in Urdu. 41% of respondents were from patients who attended transplant clinic and 31% from patients who attended for haemodialysis. Overall there was a strong message that patients wanted more trials in nephrology and felt that taking part in trials would help them take a more active role in their health. They also felt there was a lack of information on how to access research opportunities. Of those who completed the survey there was no significant ethnicity differences in their attitudes and understanding of clinical research, however transplant patients who identified themselves as White British were significantly more likely to take part in the survey (p<0.01). Patients who identified themselves as Black British were significantly less likely to take part in the survey (p<0.02). In the dialysis cohort, patients who identified themselves as White British were significantly more likely to take part in the survey (p<0.01). Whereas patients who identified themselves as Bangladeshis were significantly less likely to take part in the survey (p<0.01). Age did not appear to have an effect on patients' perception and understanding of clinical trials.

**Conclusions:** From our work it is clear that there is a patient led demand for greater engagement in translational research. However, challenges remain in engaging ethnic minority cohorts in clinical research.

_Funding: Other NIH Support - National Institute for Health Research_

**Deferred Educational App Personalization Increases Registration Completion**

_Daniel Schwartz,1 Chan Kruse.2 1Faculty of Medicine, Univ of British Columbia, Vancouver, BC, Canada; 2QxMD, Vancouver, BC, Canada._

**Background:** ‘Read by QxMD’ (http://qxd.md/read) is an app that curates the nephrology literature and personalizes reading recommendations based on a clinician’s or researcher’s interests. In order to provide highly accurate recommendations, the app must collect content preferences such as preferred journals and topics. In addition, it must collect email address and personal identifiers in order to complete registration and offer CME. When the registration process is too onerous, mobile app users may not complete registration. If the registration process fails to collect necessary user data, this may negatively impact the educational value of the app. We hypothesized that allowing users to delay providing personal information until after they set their preferences would increase registration completion.

**Methods:** We randomly assigned all users registering on the Android version of Read to two different registration processes. In version 1, “upfront personalization”, users are asked to provide personal identifiers prior to setting their preferences, while in version 2, “deferred personalization”, users set preferences first and after this has been completed are asked for personal identifiers. The Leamplum SDK was used to implement and automate the randomization of alternate registration pathways. The primary outcome was completion of registration.

**Results:** Between April 6, 2015 and June 1, 2015, a total of 5660 users who registered using the Android version of Read were randomized with 2834 users randomized to upfront personalization and 2836 to deferred personalization. Upfront personalization yielded a 47.4% (95% CI 46.0 to 48.8) registration completion rate versus 50.7% (95% CI 49.0 to 52.4) with deferred personalization (p < .05).

**Conclusions:** A strategy of deferred collection of personal identifiers yielded slightly higher completion rates. To maximize user registration when onboarding users to educational medical apps, consider deferring the collection of personal information until after user preferences have been provided. Further research is required to maximize app registration when data requested is extensive as in ‘Read’.

**Onconephrology Abstracts Trends in ASN Kidney Week 2012-2014**

_Jyotsana Thakkar, Rimda Wanchoo, Kenar D. Jhaveri. Nephrology, Hofstra NSLIJ School of Medicine._

**Background:** Onconephrology is an emerging new specialty of nephrology. The ASN created a forum dedicated to the field of Onconephrology in 2011 to improve collaborative care for cancer patients with kidney disease. One of the aims was to allow for collaborative research strategies in the field of onconephrology. However, the number of onconephrology related abstracts accepted to be presented at ASN Kidney Week (ASN-KW) 2012-2014 is not known.

**Methods:** We reviewed the abstracts presented in the ASN-KW over past 3 years from 2012-2014 which were related to Onconephrology. Search terms used to identify abstracts included cancer, myeloma, chemotherapy, tumor lysis, paraneoplastic syndrome and hypercalcemia. They were then categorized into: basic science, chemotherapy, myeloma, epidemiology, electrolyte disorders, AKI, tumor lysis, GN, paraneoplastic syndromes and obstructive uropathy. Abstracts were also categorized based on study design.

**Results:**

Figure above breaks down the total number(s) of abstract(s) Y axis) in the last 3 years presented at ASN-KW by category. There has been an increase in the number of onconephrology abstracts over last 3 years. A total of 175 abstracts were reviewed. In 2012, there were 50 onconephrology related abstracts, increased to 54 in 2013 and 71 in 2014. Abstracts related to basic science(16%), chemotherapy toxicities(16%), myeloma(16%) and epidemiology (16%) dominated most of the accepted abstracts. Of the clinical abstracts, > 50% were case reports, 41% were retrospective studies, 4.5% database studies and <1% RCT.

**Conclusions:** Over the last 3 years, we have seen a growing trend in the number of abstracts submitted in the ASN-KW related to the field of onconephrology. We suggest creating a separate section dedicated to onconephrology in the ASN meetings to allow for collaborative research and greater understanding of cancer related nephrology, leading to improved patient outcomes.

**Patients-Initiated Educational Research in a Digital Age**

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**Background:** The emergence of web-based technology in the digital age has become popular in the healthcare industry, particularly in the educational research field. A web-based technology can bridge the educational gap between researchers and patients.

**Methods:** We aimed to develop a user-friendly interface between a virtual community that is driven by patients and researchers and a preliminary knowledge-building activity. Wikiheart is a web research environment that creates a real-time community between researchers and patients without geographical restrictions.

**Results:** On patients have registered for free, the system allows these users to write their own articles or to edit other articles, which often leads to thought provoking medical research questions. Wikiheart also demonstrates a novel approach to population science that is based on huge databases with multiple cloud servers that reach the web research community. Nowadays Wikiheart has more than one million visitors, and serves as an educational web technology that provides its users with both a variety of learning methods, and several areas of research focus.

**Conclusions:** Wikiheart is an innovative web-based program for conducting educational research in the digital community. It is an excellent tool for researchers and patients to generate new hypotheses via the scientific method in an online environment.
DB-2 fell 2 to 7 days after folic acid injection, supporting tubules as a site of SLIT2 synthesis. In a separate experiment, mice were given folic acid, then recombinant human SLIT2 i.p. on days 2, 4, and 6. Kidney function measured directly as GFR or indirectly via BUN 14 days after injection was not significantly improved by SLIT2 treatment.

Conclusions: Folic acid induced injury increased expression of SLIT2 in proximal tubules, followed by detection of SLIT2 in the urine, which points to SLIT2 as a candidate urine biomarker for tubular injury. Amelioration of injury with systemic SLIT2 treatment was not observed, suggesting better utility as a marker than a mediator.

Funding: NIDDK Support

PUB390


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Background: Trefoil factor 3 (TFF3) is a small peptide involved in mucosal protection. TFF3 is widely expressed in multiple tissues including kidney. Previous studies have suggested that serum and urinary TFF3 significantly increases in patients with chronic kidney disease and that urinary TFF3 level decreases in rats with acute kidney injury. However, it is unclear whether serum or urinary TFF3 is associated with human renal tissue injury. The aim of this study is to elucidate the relationship between serum and urinary TFF3 levels and the degree of renal tubulointerstitial injury.

Methods: The total study population included 52 patients (tubulointerstitial nephritis: 31, minor glomerular abnormalities and thin basement membrane disease as controls; 21) who underwent renal biopsy. The serum and urinary TFF3 concentrations were determined by a specific ELISA. The degrees of tubulointerstitial cell infiltration and fibrosis were semiquantitatively graded in biopsy specimens and defined by the inflammation score and the fibrosis score, respectively. An immunohistochemical analysis was performed to reveal the localization of the TFF3 protein.

Results: The median serum and urinary TFF3 levels of the disease group were significantly higher than those of the controls (p=0.002 and p=0.008, respectively). A statistically significant positive correlation was observed between the urinary TFF3 level and the fibrosis score in the disease group. However, there was no correlation between the serum or urinary TFF3 level and the renal inflammation score in disease group. TFF3-positive cells were observed in the renal tubular epithelium.

Conclusions: The data indicate that serum and urinary TFF3 levels are significantly increased and, in particular, that urinary TFF3 could reflect renal tissue fibrosis in patients with tubulointerstitial nephritis. Further studies are required to elucidate the precise distribution of renal TFF3 protein and mRNA, and the mechanism underlying the contribution of TFF3 to renal fibrosis.

PUB391

Induction of Epithelial-to-Mesenchymal Transition and Fibrosis Signals via AKT and Peroxisome Activator-Receptor Pathway in Renal Tubular Cells Induced by a Plasticizer Di(2-ethylhexyl) Phthalate Shing-Hwa Liu, Li-Chen Huang, Bo-Lin Chen, Chih-Kang Chiang.

Dept of Toxicology, College of Medicine, National Taiwan Univ, Taipei, Taiwan; 1DIDT, NTUH, Taipei, Taiwan.

Background: Di(2-ethylhexyl)phthalate (DEHP) is a plasticizer and a probable genotoxic and reproductive carcinogen. More than 300 million tons of DEHP were used each year worldwide. Recent studies have suggested that DEHP has potential adverse effects on the liver, kidney, and reproductive system. It could also cause carcinogenicity and developmental toxicity. DEHP exposure might exacerbate kidney progression. Tubular epithelial-to-mesenchymal transition (EMT) is recognized to play pivotal role in the process of renal fibrosis. However, the mechanisms of nephrotoxicity induced by DEHP remain unclear. Here, we investigated whether DEHP could induce renal fibrosis via EMT process.

Methods: A rat renal proximal tubular cell model (NRK-52E cells) was used to evaluate EMT and fibrosis signaling. Cell morphology was observed by microscope. Cell viability evaluated by MTT assay. The molecular signals of EMT and fibrosis were analyzed by flow cytometry, confocal laser scanning microscopy, immunocytochemistry, and Western blotting.

Results: Treatment with DEHP (5-25 μM) for 72h caused the change in renal tubular cell morphology shifting to spindle-like shape. DEHP did not induce cell apoptosis, but significantly induced G2/M cell cycle arrest. Moreover, the expressions of vimentin, α-SMA, and CTGF, which are the markers of the mesenchymal phenotype, were significantly increased. The expressions of E-cadherin, a maker of epithelial cells, was significantly decreased by DEHP. DEHP could also inhibit the expression of peroxisome proliferator-activated receptor (PPARα) and γ. The phosphorylation of Akt and Smad 2/3 was also significantly increased by DEHP. Notably, treatment with MK2206 (an Akt inhibitor) significantly inhibited DEHP-induced phosphorylation of Akt and EMT. Further investigation revealed that MK2206 suppressed the expression of Akt downstream proteins (NF-κB and GSK3).

Conclusions: These findings suggest that DEHP is capable of inducing the EMT process through AKT and PPAR signaling pathway, which may lead to renal fibrosis.

Funding: Government Support - Non-U.S.
Optional
Discussion: The B Thalassemia is a hereditary disorder of hemoglobin synthesis in the B-globin gene that present clinically with microcytic hypochromic anemia, erythrocytosis ineffective, normal reticulocyte counts or slightly elevated and high levels of A2 hemoglobin. In the kidneys can cause tubular injury and GFR decline. Developing glomerulosclerosis and fibrosis. We can not rule out that CKD is secondary to B-thalassemia, a genetic study would be necessary. It is an uncommon diagnosis in Latin America, but should be considered in patients with CKD and microcytic hypochromic anemia refractory to conventional treatment.

**PUB397**

**Empirical Antifungals in Peritoneal Dialysis Patients with Bowel Obstruction: Time to Reconsider?** Ravinder Pal S. Bhatti, Elwaleed Elnagar, Dumitru Rotaru. Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR.

**Introduction:** Intestinal obstruction, even without perforation or ischemia, predisposes patients on peritoneal dialysis (PD) to peritonitis by gut commensals including fungi. Fungal peritonitis (FP), with (Secondary) or without (Primary) prior antibiotic use, is associated with increased mortality and technique failure. This raises the question of empirical antifungal use in PD patients with bowel obstruction. We present our experience with such a patient.

**Case Description:** A 74 year old male who had been on Continuous Cycling Peritoneal Dialysis for the past four years with his prescription being 5 exchanges of 2 liters of 1.5% and 2.5% dialysis with a last fill of 2 liters of icodextrin, presented with worsening abdominal pain. His dialysate was clear and had just 3 leucocytes. His CT abdomen showed small bowel obstruction (SBO) with conservative management pursued. Over the next few days, the SBO resolved and dialysate cell counts remained unremarkable. On day 5, he became hypotensive. Examination was notable for increased abdominal tenderness and a cloudy dialysate. Repeat dialysate studies were sent and intraperitoneal vancomycin and cephaloprim were started. Imaging suggested SBO. He responded appropriately to the antibiotics over 48 hours. His CT abdomen showed small bowel obstruction (SBO). With a high risk for both primary and secondary FP, these patient should be suspected in patients with HIV presenting with unexplained hematuria, and renal biopsy should be performed as soon as possible for early diagnosis and therapy. Current management recommendations are similar to those with idiopathic IgA, including ACE inhibitors or ARB for control of proteinuria (>1 g / day) or hypertension.

**Discussion:** Several reports have evaluated the predictive value of peripheral blood eosinophilia as a simple noninvasive diagnostic marker for ACR of transplanted kidneys and of acute cellular rejection. However, peripheral blood eosinophilia was not evaluated as a possible test predicting renal ACR. In a case report, Baradhin et al, described the etiology of AKI following treatment with armodafinil for narcolepsy. They indicated that both (AIN and ACR) has similar biopsy characteristics. However, our patient had no clinical features to suggest AIN, including no new medications. We conclude that leukocytosis and peripheral blood eosinophilia could represent signs of impending acute cellular rejection of transplanted kidneys.

**PUB399**

**A Case of IgA Nephropathy in an HIV-Positive Patient** Hermes Garcia-Sanchez, Vandana Niyyar, Thomas E. Rogers. Nephrology, Emory Univ, Atlanta, GA.

**Introduction:** IgA nephropathy has been described in patients infected with HIV. Though IgA levels are commonly elevated in HIV, these patients may also develop IgA antibodies against specific HIV antigens. Renal lesions may result from HIV antigen-specific immune complexes that are derived from the circulation and from in-situ complex formation.

**Case Description:** We present a case of a patient with HIV/AIDS, on highly active antiretroviral therapy (HAART), who was evaluated for microscopic hematuria and worsening renal function. The patient’s only complaint was early morning peri-orbital edema. On examination, BP was 103/72 mm Hg with a BMI 23 kg/m². Labs showed normal electrolytes, serum creatinine 1.7 mg/dL (baseline 0.7mg/dL), urine protein/creatinine ratio of 2.5 grams/dL. Other serologies were negative. HIV VL was undetectable, and CD4 count was 183. Renal US showed bilateral enlarged, echogenic kidneys. Renal biopsy revealed sclerosing glomerulopathy with IgA immune type deposits on immunofluorescence. The patient was initiated on an ACE inhibitor and a low salt and protein diet, with resolution of his proteinuria to 0.7 Grams/dL. His renal function stabilized, with a creatinine of 1.6 mg/dL.

**Discussion:** In conclusion, IgA glomerular disease arising in HIV positive patients has clinical and pathologic aspects similar to idiopathic IgA nephropathy. IgA nephropathy should be suspected in patients with HIV presenting with unexplained hematuria, and renal biopsy should be performed as soon as possible for early diagnosis and therapy. Current management recommendations are similar to those with idiopathic IgA, including ACE inhibitors or ARB for control of proteinuria (>1 g / day) or hypertension.

**PUB400**

**Calcium Channel Blocker Toxicity: Management Strategies and Considerations** Sreesh G. Iyengar, Mark I.C. Hong, Seyed-Ali Sadjadi. Nephrology, Loma Linda Univ, Loma Linda, CA.

**Introduction:** Calcium channel blocker overdose is rare but carries a high mortality due to cardiovascular complications. Generally the management is supportive with use of vasopressors, IV fluids, cardiac pacing, and insulin therapy. There are reports of CVVHDF, hemodialysis or hemofiltration alone and charcoal hemoperfusion for the treatment of CCB overdose. Effective management strategies are needed to improve outcomes.

**Case Description:** Here we describe a patient who presented to the ER after a suicide attempt with ingestion of Norvasc. On arrival to the ER he was awake but later he was intubated. The patient developed acute kidney injury and became anuric. Patient was started on CVVHDF that lasted 48 hours. Unfortunately after two days the patient continued to decompensate and expired.

**Discussion:** Amdioline is a CCB of the dihydropyridine group acting primarily on vessel walls whereas the non-dihydropyridines act more on cardiac muscle and pacer cells. In our case it was clear Norvasc selectively took its effect on the vasculature with profound hypotension with preserved systolic function and no arrhythmia. The case was complicated with ARDS related to diffuse pulmonary edema, a well known complication with CCB overdose. In our case renal failure was likely related to severe hypoperfusion leading to ischemia. There was development combined respiratory and metabolic acidosis. The metabolic acidosis was attributed to renal failure but it is possible that CCB induced inhibition of insulin secretion leading to ketoacidosis may also have contributed. In terms of management of CCB overdose, if recent ingestion then GI decontamination is reasonable with activated charcoal or whole bowel irrigation. The use of high dose insulin therapy has been tried and its role may include increasing ionized calcium levels, improvement of hyperglycemic acids, and improved myocardial function. Most case reports, though
few, have shown little benefit from hemofiltration or hemodialysis theoretically due to high protein binding, bioavailability, rapid metabolism, and low lipid solubility of the drug. One case report did show some promise when multiple therapies were used including IV lipid emulsion, CVVHDF and charcoal hemoperfusion.

**PUB401**

**A Rare Case of IgG1-Heavy Chain Deposition Disease Using Oral Prednisone and Therapeutic Plasmapheresis**

**Sachi Baldeosinh, Madhu Kandarpa. Internal Medicine, Kettering Medical Center.**

**Introduction:** Heavy chain deposition disease (HCDD) is rare, especially without light chain deposition and when causing non-amyloid tissue deposits. **Case Description:** A 75-year-old male with chronic kidney disease (CKD) stage 3 (baseline creatinine 2.3 mg/dL) and right single lung transplant for idiopathic pulmonary fibrosis in 2008 presented with extremity edema and decreased urine output. He has no history of diabetes or uncontrolled hypertension. Admission labs showed BUN 77 mg/dL, creatinine 4.37 mg/dL, and subtherapeutic tacrolimus levels at 3.9 mg/mL. Urine protein/creatinine ratio was 6.6. A 24-hr urine protein collection revealed 5822 mg/24hr. Serum protein electrophoresis showed hypalbuminemia, but no monoclonal proteins were identified. Urine protein electrophoresis was negative for Bence Jones proteins or monoclonal proteins. Urine protein concentration was 713 mg/dL, consisting of 57.8% albumin and 42.2% globulins. C3 and C4 complement levels were low at 46.5 mg/dL and 8.92 mg/dL respectively. Antinuclear antibodies (ANA), anti-streptolysin O (ASO), anti-neutrophil cytoplasmic antibodies (C-ANCA and P-ANCA), and cryoglobulins were negative. Renal ultrasound showed multiple renal cysts without hydropnephrosis. Renal biopsy revealed nodular sclerosing glomerulopathy and IgG1-heavy chain deposition disease. Immunohistochemical study showed negative foci for multiple myeloma. The patient was placed on oral prednisone and therapeutic plasmapheresis in an effort to prevent further renal damage and delay hemodialysis. The patient underwent eight plasmapheresis treatments, however still required hemodialysis for fluid overload.

**Discussion:** Histological and functional plasma cell proliferative disorder characterized by tissue deposits of heavy chain fragments which can lead to renal disease. In HCDD, deposits do not have a fibrillary structure and do not stain positive with Congo red such as with heavy-chain amyloidosis. The rarity of the disease and limited data on evidence-based guidelines for treatment make HCDD challenging to treat. We describe a rare case of IgG1 HCDD with no plasma cell dyscrasia. To our knowledge, no cases have been described using oral prednisone and therapeutic plasmapheresis to treat HCDD renal dysfunction.

**PUB402**

**Cocaine-Induced Vasculitis**

**David Aravapong. Nephrology, Univ of New Mexico, Albuquerque, NM.**

**Introduction:** An increasing number of cases of Cocaine-induced vasculitis are being found among cocaine users in the United States which is due to the use of Levamisole laced cocaine. It is estimated that about 70% of the cocaine used here in the US is contaminated with Levamisole. **Case Description:** We describe a 65 year old male, with a 20 year history of cocaine abuse, who presented with a 1 month history of a progressively worsening, non-painful rash on his trunk and extremities. He denied fever, weight loss and myalgias. He also denied history of otitis media and sinusitis. He reported increased cocaine use during this time. On physical examination he was found to have violaceous plaques with central necrosis on the trunk and extremities. These plaques showed 10% of glomerulitis and interstitial fibrosis and tubular atrophy involving approximately 70% of the specimen. **Treatment:** Mainly abstinence and supportive. •The clinical course of patients is difficult to assess due to the fact that few patients are able to abstain from cocaine use. Our patient was able to abstain from cocaine use for about 30 days and that almost resulted in complete resolution after 30 days of being cocaine-free (Fig. 5). •Although in the setting of worsening skin lesions and ongoing cocaine use, some patients have been treated with anticoagulation or thrombocytopenia, immunosuppression and corticosteroids with varying degrees of success, robust evidence lacking.

**Discussion:** With more than 2 million Americans using cocaine, occurrences of levamisole-induced vasculitis will increase Levamisole exposure should be included in the differential of patients with purpuric vasculitis, neutropenia and cocaine. 

**Funding:** Clinical Revenue Support

**PUB403**

**Morbidity Associated with Uremic Ascies Among Emergent Dialysis Patients**

**Shobana Sivan, Rajeev Raghavan. Nephrology, Baylor College of Medicine.**

**Introduction:** Patients with end-stage renal disease (ESRD) on emergent dialysis often develop complications of inadequate dialysis such as pleural effusion, ascites and pericardial effusion. Uremic ascies is characterized by exudative ascites with SAAG usually <1.1 and is diagnosed after excluding liver, cardiac, infectious and malignant causes. The incidence of uremic ascies in standard dialysis population was described as 0.7-20%. We believe that emergent dialysis patients with uremic ascites have higher morbidity and mortality.

**Case Description:** Total of 463 emergent dialysis patients, who were initiated on dialysis between July 2010 and April 2015 were analyzed. Among 36 patients with Ascites of unknown etiology, 12 patients were included in the study group of uremic ascites. A cohort of 36 patients without ascites was randomly selected for comparison. Two groups were compared based on demographics and morbidity indicators.

The mean age was 50 years with predominance of Hispanic male in both groups. The serum creatinine in the uremic ascites group and the cohort group was 2.6±0.4 and 3.29±0.2 respectively. The mean emergency center (EC) visits and hospital admissions in uremic ascites and cohort group were 79.6, 9 and 63.4, 5.2 respectively. Volume overload and abdomen pain were the major reasons for admissions in the study group. They underwent paracentesis and frequent dialysis during the hospital course.

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

**Underline represents presenting author.**

**981A**
An Unusual Case of Anticoagulant-Like Nephropathy in a Non-Anticoagulated Patient

Elyas Safar,1 Apurv Khanna.1

Introduction: Anticoagulant-related nephropathy is a well-known cause for Acute Kidney Injury (AKI), which was first described in Coumadin anti-coagulated patients, usually with excessive anticoagulation (INR >4). It was also reported to be associated with other Anticoagulants such as direct thrombin inhibitor Dabigatran. We report a case of Anticoagulant-related Like Nephropathy in a Non-anticoagulated patient.

Case Description: A 71-year-old male was admitted to the VA medical center for shortness of breath and hemoptysis. Past medical history was significant for Non Small cell Lung Cancer, cryoprecipitate liver cirrhosis and COPD. CT chest, showed no pulmonary emboli. He was treated with Vancomycin and Zosyn for Pneumonia. The patient reported gross hematuria initially, which resolved spontaneously. His admission creatinine was 1.1 mg/dl, (baseline 0.6 mg/dl), and went up to 2.4 mg/dl. The patient had another episode of gross hematuria and his creatinine went up to 3.5 mg/dl. The patient remained non-oliguric throughout the course of his AKI. Kidney biopsy showed Tubular epithelial cells injury with red cell casts, but no inflammatory changes and no Immune complexes by Immunofluorescence. The histopathologic pattern shown by the kidney biopsy was consistent with Anticoagulant-related nephropathy. However, the patient was not anticoagulated with Coumadin, Heparin, or any other Anticoagulants. His Pro-thrombin time (PT) was 13.1 seconds (normal 9-12 seconds) and INR 1.2. His PTT was 20.1 seconds (normal 25-34 seconds). He had a low platelets count between 55-100K/ mm3, due to liver cirrhosis.

The findings in this case, suggest a role for Thrombocytopenia in liver cirrhosis, in causing anticoagulant like intra-glomerular hemorrage, which may result in an AKI.

Discussion: Thrombocytopenia and likely Platelets dysfunction in Liver cirrhosis can cause intra-glomerular Hemorrhage and results in Anticoagulant-like Nephropathy, even in the absence of excess coagulopathy as evidenced by a normal PTT & near normal INR. To our knowledge, there has not been a reported case of Anticoagulant-like Nephropathy in Non-Anticoagulated patients.

Smoking Related Idiopathic Nodular Glomerulosclerosis with Crescents

Tahir Zaman,1 Frederic Clayton,2 Josephine Abraham.1,2

Introduction: Idiopathic nodular glomerulosclerosis (ING) is a rare but important cause of nephrotic syndrome. There have been case series reported in the literature regarding the association of ING and smoking.

Case Description: A 57-year-old female with a history of rheumatoid arthritis (RA) presented to the hospital with cough and hemoptysis. Her RA treatment consisted of leflunomide, prednisone and folic acid. Her social history is pertinent for a history of smoking (20 pack-years). Urine analysis was with dysmorphic hematuria and proteinuria (spot protein/creatinine ratio 3.2gms). Serologic workup was unremarkable. Renal biopsy revealed nodular glomerulosclerosis with sparse crescents. Due to sparse crescents, hemoptysis, and AKI the patient was started on high dose steroids which exacerbated patient’s nephrotic syndrome. Ultimately steroids were discontinued which lead to an improvement in proteinuria. Smoking cessation was encouraged.

Discussion: ING with crescents has not been described in the literature. In a case series reported by Markowitz et al, patients with ING had renal failure with a mean sCr of 2.4 mg/dl and proteinuria. The main clinical predictors of progression included lack of angiotensin II blockade and continued smoking.1 In retrospect, it is likely the severity of her intra-glomerular pressures which lead to proteinuria was exacerbated with steroid treatment and resolved with discontinuation.

Charcot Foot Syndrome in a Nondiabetic Hemodialysis Patient

Werner Kizogbas,1 2 Behabat Sat,1 Barbara Klein,2 Andreas Westhoff,2,3 Frank Dellanna,1,2 Gerd R. Hetzel.1,2 1MVZ Davita Karlstrasse, Duesseldorf, Germany; 2Univ Med Zentrum Duesseldorf, Germany; 3Heinrich-Heine Univ, Duesseldorf, Germany.

Introduction: The prognosis is very poor for diabetic hemodialysis (HD) patients with foot lesions. Foot lesions are associated with risk of systemic inflammation and cardiovascular (CV) morbidity. Severe cases of diabetic foot with neuropathic arthropathy, microvascular changes from mediasclerosis, and alteration of foot architecture are known as Charcot Foot Syndrome (CFS). Since diabetic and nondiabetic HD patients may experience changes in calcium and phosphate metabolism and secondary hyperparathyroidism, the question arises whether CFS can occur in HD patients in the absence of diabetes.

Case Description: Presented was a decade-long case study of a male HD patient (DOB 1961) who was treated since Dec 1999 for biopsy-proven nephrotic syndrome due to glomerulosclerosis. The patient began thrice weekly HD in Sept 2005 without prior treatment for diabetes mellitus (A1C 4.9%). In Apr 2012 he presented with a painless inflammatory acute foot syndrome, then presented in Apr 2013 with a planar ulceration. After conservative wound management, prophylactic shoes were prescribed. In clinical examination he showed signs of chronic CFS and arthropathic changes in osa metatarsals 2 and 3 with osteolysis and luxation of tarso-metatarsal joints. Lab results indicate secondary hyperparathyroidism: parathyroid hormone 465 pg/mL, phosphate 6 mg/dL, and calcium 2.2 mg/dL.
Discussion: We believe this is the first description of chronic CFS in a nondiabetic HD patient. Acute CFS diagnosis is important because its symptoms (red warm skin, foot edema) are similar to those of phleghmon and osteomyelitis, and thus may be considered a differential diagnosis. Further investigations are necessary to determine whether this is an authentic entity of a foot syndrome, and if it’s associated with CV morbidity.

**Funding:** Pharmaceutical Company Support - Davita

**PUB410**


**Introduction:** Crescentic GN is usually manifested by features of active glomerular disease in the urine and by progressive rapid loss of significant renal function. SLE can present as predominantly crescentic GN often as Class III or IV lupus nephritis (LN) usually resulting in rapid deterioration of renal function requiring RRT.

**Case Description:** 18 y/o female recently diagnosed with SLE, on Plaquenil presented to ER with nausea, vomiting and epigastric pain after consuming “tiny tea” and was found to have serum creatinine (Scr) 4.5 mg/dL, which further increased to 4.74 with 3+ protein (2.5g/day), 3+ blood and RBC casts on urinalysis. Other relevant lab data: ANA 1:600, negative dsDNA, positive RNP, anti-SM Ab and normal complements. She was initiated on IV fluids and Scr normalized within 2 days. Renal biopsy showed Pauci immune Crescentic GN, class IV-S (A/C) with minimal IF staining. The clinical course was complicated by seizures; the diagnostic considerations included lupus cerebritis vs. PRES. She was put on valproate to be started on immunosuppression as outpatient. She was admitted a week later with acute liver failure due to valproate and Tylenol at which time she was pulsed with IV Solu-Medrol and discharged on oral steroids with a plan to start MMF after normalization of LFTs.

**Discussion:** Crescentic and focally necrotizing GN can be infrequently present in the spectrum of diffuse proliferative LN. Such cases are generally ANCA negative. Normalization of SCR after hydration in this case suggest pre renal as the likely etiology which poses a treatment dilemma for biopsy proven crescentic GN. While there is not much literature available regarding the treatment of lupus with crescentic GN and normal SCR, a retrospective case series reported that even <50% crescents portend a significant renal risk despite clinically evident preserved renal function. We believe that intense immunosuppression should be used in patients with crescentic GN and preserved renal function, despite the absence of any controlled studies. Our patient was started on MMF and prednisone with improvement in proteinuria from 2.6 gm to 150 mg with normal SCR.

**PUB411**

Anti-Thymocyte Globulin Induced Non Cardiogenic Pulmonary Edema Jaya Kaia, Amit Lahoti. Nephrology, Univ of Texas MD Anderson Cancer Center, Houston, TX.

**Introduction:** Anti-Thymocyte globulin (ATG) is used in treatment of hematologic malignancies and solid organ transplantation. Immediate local and systemic reactions are known. There has been only one reported case of non cardiogenic pulmonary edema (NCPE) caused by ATG.

**Case Description:** Our patient was a 59-year-old man with Marginal Zone Lymphoma which had progressed to diffuse large B cell lymphoma. Despite Hyper CVAD and Rituximab his disease continued to progress. He received Matched Unrelated Bone marrow transplantation after conditioning with ATG and rituximab. The next day he was admitted to the ICU with respiratory distress and bilateral lung infiltrates initially thought to be pulmonary edema. He was started on Lasix drip but did not improve. His CVP was 5, and his echocardiogram showed normal ejection fraction. Based on these findings he was diagnosed to have NCPE. Bronchoscopy revealed pulmonary hemorrhage. His condition worsened and he was intubated and started on Continuous Renal replacement therapy. He was given additional doses of steroids but without improvement. His died due to respiratory failure after two days of ICU stay.

**Discussion:** Non cardiogenic pulmonary edema is a clinical syndrome characterized by presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiograph without evidence of left atrial hypertension, fluid overload or congestive heart failure. Drug related NCPE is usually diagnosed after other causes of pulmonary infiltrates such as gastric aspiration, sepsis and pneumonia are excluded. The presence of normal echocardiogram and pulmonary hemorrhage within a day of administration of ATG, pulmonary infiltrates which did not resolve after intense attempts of volume removal indicated that the patient had NCPE. ATG is known to cause acute respiratory distress syndrome, alveolar hemorrhage and rapidly progressive interstitial fibrosis likely secondary to Cytokine release syndrome. Providers need to be aware of such complications as even though rare these cause increased morbidity and mortality. It is beneficial to give ATG infusions slowly and accompanied by high dose systemic steroids.

**PUB412**

Hypomagnesemia After Treatment with Pertuzumab Lilian Saro-Nunez,1 Tiffany A. Traina,2 Karen A. Cadoo,1 Teresa Gilewski,3 Ilya Glezerman,4 1Nephrology, NYP-Well Cornell Medical Center, New York, NY; 2Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY; 3Gynecologic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; 4Renal Service, Memorial Sloan Kettering Cancer Center, New York, NY.

**Introduction:** Hypomagnesemia is a known side effect of epidermal growth factor receptor (EGFR) inhibitors such as cetuximab and panitumumab. Pertuzumab blocks HER (human epidermal growth factor receptor) 2 dimerization with HER3 and EGFR, and is used in HER2+ breast cancer. We present two cases of hypomagnesemia with pertuzumab use.

**Case Description:** Case 1 58 year-old woman with history of breast cancer treated with trastuzumab (T), docetaxel, pertuzumab (two doses of 840mg and one dose of 420mg) and carboplatin (AUC6). Patient developed hypomagnesemia with serum magnesium (Mg2+) 0.7 (1.7-2.6) mg/dl and symptomatic hypomagnesemia of 5.9 (8.5-10.5) mg/dl. Since initiation of chemotherapy she experienced diarrhea controlled with loperamide. Fractional excretion of magnesium (FeMg) was 2%. Parathyroid hormone (PTH) was 309.2 (12-88) pg/ml. Pertuzumab and carboplatin were stopped. Mild hypomagnesemia persisted 6 months later.

Case 2 56 year-old woman with history of breast cancer on treatment with T, paclitaxel and pertuzumab (one dose of 840mg and 2 doses of 420mg) was admitted with Mg2+ of 0.3 (1.4-2.2) mg/dL and corrected calcium of 6.1 mg/dL. She complained of chronic diarrhea which improved with loperamide and was receiving proton pump inhibitor (PPI). FeMg was 3%, PTH was 16.1 (12-88) pg/ml. PPI was stopped but patient received another dose of pertuzumab (840mg). She remained hypomagnesemic and required IV supplementation until her death from progression of disease 22 months later.

**Discussion:** Although there were other confounding factors that could have caused hypomagnesemia including diarrhea, PPI and carboplatin, hypocalcemia (a manifestation of hypomagnesemia) did not develop until patients were started on pertuzumab. Carboplatin has been associated with hypomagnesemia but not with the degree of hypomagnesemia seen in these two patients. We postulate that pertuzumab may interfere with reabsorption of Mg2+ similar to EGFR inhibitors.

**PUB413**

Acute Renal Infarction: Case Series Yelda Delipozbuddyagci,1 Rumeyza Kazancioglu,2 1Nephrology, Bezmialem Vakif Univ, Istanbul, Turkey; 2Nephrology, Bezmialem Vakif Univ, Istanbul, Turkey.

**Introduction:** Acute renal infarction (ARI) occurs from interruption of kidney’s blood supply either partially or totally. Causes of renal infarction include: thromboembolism (usually from injured or replaced heart valves, congenital heart defects etc.) vasculitic disorders, trauma to the kidneys or hypercoagulable state. We present five cases of ARI with different etiologies.

**Case Description:** Description of Cases : Two female, three male, mean age 52 (range 26-72) patients presented to the emergency department between 2013 and 2015 in a university based hospital setting. Presenting complaint was severe flank pain lasting 2 to 5 days for all of them. At initial examination all patients had costo-vertebral angle tenderness at the affected side. Contrast enhanced abdominal tomography was useful for showing renal artery occlusion and also renal infarction. Trans thoracic echocardiography were all normal and were not adequate in identifying patients having had heart defects, trans esophageal echocardiography was obviously superior in finding cases with possible paradoxical embolism. All patients were treated with enoxaparin therapy. During follow-up there was neither further complication nor kidney damage.
A Rare Case of Kidney Amyloidosis Caused by Heroin Abuse

Nilson D. Feliz, Roberto L. Collazo

A 40 y/o AA man with no past medical history just 20 years of IVDA. Is a condition characterized by deposition of insoluble fibrils in various organs; most commonly the liver and kidneys.Occurs as a result of chronic inflammatory states such as RA, IBD, chronic osteomyelitis, or familial Mediterranean fever.Kidney involvement in amyloidosis is a significant source of morbidity as it can progress to CKD.

**Case Description:** A 40 y/o AA man with no past medical history just 20 years of IV heroin abuse presented to the ED with the CC: Worsening lower extremity edema and a weight gain of 20 lbs. in the past few months. Patient denied any other medical problems or complains. On PE, afebrile, normotensive, with clear lungs, normal heart at auscultation. He was placed on ethacrynic acid and atovaquone because of a sulfa allergy. His albumin remained < 1.5 mg/dL. Renal function worsened, developed Clostridium difficile diarrhea. He was placed on ethacrynic acid and atovaquone. The UA showed >600mg/dL of protein and no hematuria. A 24 hour urine protein collection was >3 g/day. The creatinine level increased to 3.3 mg/dL, from 1.2 mg/dL on arrival. The UA showed >600 mg/dL of protein and no hematuria. A 24 hour urine protein collection was >3 g/day. The creatinine level increased to 3.3 mg/dL, from 1.2 mg/dL on arrival. The UA showed >600 mg/dL of protein and no hematuria. A 24 hour urine protein collection was >3 g/day. The creatinine level increased to 3.3 mg/dL, from 1.2 mg/dL on arrival.

**Diagnosis:** The UE showed 600 mg/dL of protein and no hematuria. A 24 hour urine protein collection showed 50 g of proteinuria and serum albumin 2.1 g/dL. Cholesterol 232 mg/dL, LDL 192 mg/dL, and Trig 189 mg/dL. The patient was started on prednisone and cyclosporine. The patient was referred for biopsy-proven FSGS with high-dose prednisone and cyclosporine.

**Discussion:** ARI usually is a hidden disease, which can easily be missed without any specific suspicion for patients presenting with flank pain. It should be kept in mind that there is no specific biochemical test for ARI and diagnosis process must involve evaluation of cardiac pathologies preferably with trans esophageal echocardiography.

**PUB414**

Disseminated Cryptococcal Infection in a 24-Year-Old Man with Primary Focal Segmental Glomerulosclerosis

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**Introduction:** Focal segmental glomerulosclerosis (FSGS) is commonly treated with biopsy-proven FSGS with high-dose prednisone and cyclosporine.

**Case Description:** Our patient initially responded to prednisone 80 mg daily with proteinuria reduced to 37 mg/g from 3.5 g/y, but then suffered frequent hospitalizations for infection necessitating interruption of immunosuppression, now with decreased responsiveness to prednisone. Cyclosporine was added but interrupted after he developed classical symptoms of SLE and her ANA was only mildly positive at 1:40. Biopsy of the kidney revealed predominant immunofluorescent staining for IgG and C1q with mesangial deposits of C1q. There was no clear evidence of focal segmental glomerulosclerosis to portend a worse prognosis. Her decision to pursue pregnancy prompted further inquiry into the effects of pregnancy on her renal disease.

Review of existing literature, limited as it may be, suggested that C1q autoimmunogenicity may be associated with normal placentation and development in the context of hormonal changes.

**Discussion:** Therefore, interpretation of typical parameters, including urinary protein excretion alone, may not be sufficient in determining disease status. This case demonstrates the importance of renal biopsy in defining the underlying pathology in young women with evidence of glomerular disease who wish to become pregnant as it can help guide prognosis.

**Funding:** Other NIH Support - NIH T32 award

**PUB415**

A Rare Case of Kidney Amyloidosis Caused by Heroin Abuse

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**Introduction:** Secondary(AA)Amyloidosis nephropathy is a rare manifestation of AA amyloidosis nephropathy is a rare disease that can present in a variety of ways. We present the case of a 26 year-old female with PCOS and borderline diabetes who developed non-nephrotic-range proteinuria with preserved renal function who wished to become pregnant.

**Case Description:** Her serologic workup was unremarkable. She did not have any classical symptoms of SLE and her ANA was only mildly positive at 1:40. Biopsy of the kidney revealed predominant immunofluorescent staining for IgG and C1q with mesangial deposits of C1q. There was no clear evidence of focal segmental glomerulosclerosis to portend a worse prognosis. Her decision to pursue pregnancy prompted further inquiry into the effects of pregnancy on her renal disease.

Review of existing literature, limited as it may be, suggested that C1q autoimmunogenicity may be associated with normal placentation and development in the context of hormonal changes.

**Discussion:** Therefore, interpretation of typical parameters, including urinary protein excretion alone, may not be sufficient in determining disease status. This case demonstrates the importance of renal biopsy in defining the underlying pathology in young women with evidence of glomerular disease who wish to become pregnant as it can help guide prognosis.

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

Underline represents presenting author.

**Figure 1** shows mean CaXPhos product was higher in patients with no response vs. those that remained stable or improved.

**Characteristics**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Range (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>Female</td>
<td>13.76(4.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>4.23(5.5%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>PAD 8 (47.05%)</td>
</tr>
<tr>
<td>African American</td>
<td>16 (49.4%)</td>
</tr>
<tr>
<td>White</td>
<td>1.65(95.9%)</td>
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<tr>
<td>Mean Age</td>
<td>56.68</td>
</tr>
<tr>
<td>Mean PTH</td>
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<tr>
<td>Mean Calcium</td>
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</tr>
<tr>
<td>Mean P04</td>
<td>5.75</td>
</tr>
<tr>
<td>CaXPO4 product</td>
<td>51.3</td>
</tr>
<tr>
<td>Mean Ferritin</td>
<td>829.7</td>
</tr>
<tr>
<td>Mean Transferin Sat%</td>
<td>29%</td>
</tr>
<tr>
<td>Cincalcet use</td>
<td>10(58.8%)</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>1(5.8%)</td>
</tr>
<tr>
<td>Wound Care Consult</td>
<td>14(82.4%)</td>
</tr>
<tr>
<td>Sodium thiosulfate</td>
<td>17(100%)</td>
</tr>
</tbody>
</table>

**Table 1** shows patient characteristics.

**Figure 1** shows mean CaXPhos product was higher in patients with no response vs. those that remained stable or improved.
A Case of Adult-Onset Segmental Membranous Glomerulonephritis
Mao Watanabe, Toshiyuki Imasawa, Takehiko Kawaguchi, Takafumi Yamakawa, Maiko Nagata, Moritoshi Kadomura, Hiroshi Kitamura. Internal Medicine, National Hospital Organization Chiba East Hospital, Chiba, Japan.

Introduction: Generally, adult-onset membranous glomerulonephritis (MN) has diffuse and global glomerular changes. We experienced a rare case of segmental MN (SMN).

Case Description: A 66 years old Japanese male was firstly noted proteinuria in an annual health check-up. Serum creatinine was 0.76 mg/dl, urine protein excretion was 2.1 g/gCr, and 10-19 red blood cells/high-power field were observed in the urine sediment. A percutaneous renal biopsy revealed segmental spike formation on the glomerular basement membrane (GBM) and segmental subepithelial deposits in all glomeruli. Granular deposits of IgG, IgM, IgA, C3, C1q were segmentally positive with granular patterns at the same regions. In electron microscopy, electron dense deposits were also found segmentally. The glomerular tufts with deposits included inflammatory cells (mainly macrophages). Any autoimmune disease, malignancies, and infections were detected by further examinations. Because urine protein decreased less than 1g/gCr during the hospitalization, only temocapril hydrochloride has been prescribed from 67 years old. He has never taken immunosuppressive drugs. In 68 years old, because urine protein increased to 3g/gCr, the second renal biopsy was performed. Similarly to the first biopsy, segmental spike formation on GBM and segmental staining of immunoglobulins and complements were observed. The percentage of glomeruli with subepithelial deposits decreased to 60% (6/10) compared with 100% (20/20) at the first biopsy.

Discussion: Adult-onset SMN was rarely reported in spite of 30% of MN cases in childhood. Here, we firstly reported the sequential pathological changes of adult-onset SMN without any immunosuppressive therapy. We will also discuss about the pathogenesis about SMN.

A Case of Hydronephrosis due to Bilateral Retroperitoneal Fibrosis
Zachary Freestrong, Akron M. Shaaban, Josephine Abraham. Nephrology, Univ of Utah, Salt Lake City, UT.

Introduction: Retroperitoneal fibrosis is characterized by inflammatory and fibrous retroperitoneal tissue. It is believed to be due to an exaggerated inflammatory reaction to aortic atherosclerosis resulting from an immunologic trigger. Retroperitoneal fibrosis can be classified as primary or secondary. Secondary causes include medications, malignancy, infection, radiotherapy, and trauma. Patients diagnosed with retroperitoneal fibrosis should undergo thorough evaluation for infectious causes and malignancy.

Case Description: A 55 year old male presented to the clinic with a chief complaint of left side flank and groin pain. He had additional symptoms of night sweats, left leg edema, and weight loss. He was referred to our clinic after initially presenting to the emergency department and receiving a CT scan of the abdomen identifying left side hydronephrosis and a retroperitoneal mass. His past medical history included melanoma 4 years prior and cutaneous follicular lymphoma of the right mandible one year prior. Repeat ultrasound prior to initiation of therapy showed new left sided hydronephrosis. The patient was started on monotherapy with prednisone 1 mg/kg/day. Imaging after initiation of therapy showed improvement in fibrosis with resolution of ureteral obstruction. The patient’s serum creatinine improved from 1.93 to 1.2 after initiation of therapy.

Discussion: Retroperitoneal fibrosis can present as obstruction of the ureters. It is often idiopathic, but secondary causes should be ruled out. Secondary causes include malignancy, infection, and medications. Recommended therapy includes decompression of obstruction if renal function is compromised. If the cause of the disease is idiopathic, then immunosuppressive therapy is recommended. If the disease is due to secondary causes, the underlying cause should be immediately addressed.
she developed new onset BK viruria. One month later, she had a new onset BK viremia and worsening BK viruria up to 3 million and 67.5 billion copies/mL, respectively (Figure 1). Concurrently, she had AKI with a serum creatinine (SCr) of 4mg/dL from a baseline of 1.4mg/dL. Ultrasound showed moderate hydronephrosis (Figure 2). Allograft biopsy revealed acute tubular injury with negative SV40. A percutaneous nephrostomy (PCN) tube was placed and antegrade nephrostogram showed high-grade ureteral strictures (Figure 3). A ureteral stent was placed. FK and MPA target levels were decreased to 5-7ng/mL and 2-4mg/L, respectively. One week later, a repeat nephrostogram showed no obstruction and PCN tube was removed. SCr trended down to 1.2mg/dL. Ureteral stent was removed 6 weeks later. BK viremia became undetectable 6 months posttransplant with low-level BK viruria. The high-level BK viremia but negative SV40 in the kidney biopsy in the context of ureteric obstruction suggested that there was extensive BK replication within the urothelium leading to ureteral stricture and mechanical obstruction. The obstruction improved with resolution of BK viremia following reduction in immunosuppression.

Discussion: Medical management of BK virus with lowering immunosuppression can be an effective treatment to reverse ureteral obstruction due to BK virus infection, while surgical intervention is used to temporarily relieve obstruction.

Impact of Cannulation Technique on Access-Related Complications in Hemodialysis Patients

A 39-year-old woman with a history of lupus nephritis (class V) for 19 years was treated with methylprednisolone and mycophenolate sodium, with recovery of renal function. After being transplanted with a kidney, she developed complications including infection, pain, bleeding, and aneurysm. The incidence of access-related complications (i.e. pain, infection, bleeding, and aneurysm) were extracted from 70 articles, of which 6 RCT were reviewed and 5 were included in the analysis.

Case Description: Articles cited in PubMed database from 2000 to 2015 using key words “hemodialysis”, “cannulation”, and “buttonhole” were searched. Original articles evaluating hemodialysis access cannulation techniques were reviewed; randomized controlled trials (RCT) were selected.

Relevant data including primary outcomes and access-related complications (i.e. pain, infection, bleeding, and aneurysm) were extracted and compared.

Impact of Cannulation Technique on Access-Related Complications in Hemodialysis Patients

A total of 70 articles were found, of which 6 RCT were reviewed and 5 were included in this study (1 duplication). There were a total of 472 patients (BHCT 227 and RLCT 245) with follow-up periods ranging from 2 to 12 months. Two studies reported more pain with RLCT while it was similar in 2 studies and one found more pain with BHCT. Importantly, there was a significant tendency for infection with BHCT compared to RLCT in all 4 studies that could evaluate this complication and included 73% of the patients; the overall rate of infection being too low in one trial to be conclusive. Bleeding complications were similar in 4 studies while 1 found higher risk with BHCT. Only 2 studies reported higher tendency for increase in the size of the access in the RLCT group while 3 did not report any increase. Two studies reported higher incidence of access-related complications (i.e. pain, infection, bleeding, and aneurysm) were extracted from 70 articles, of which 6 RCT were reviewed and 5 were included in the analysis.

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Acute Interstitial Nephritis Associated with Probiotic Use

A 44-year-old man was found to have a stable baseline Cr of 1.4mg/dL with a measured Cr of in the normal range. 42 d later, to treat infrequent loose bowel movements (2x/wk), he consumed a probiotic regimen of 10 billion cells of Lactobacillus GG bid for 14 d. There was no diarrhea, fever, rash, blood in the stool, or exposure to NSAIDs, antibiotics, herbs, or other medications. 11 d after probiotics use, during routine physical, he was found to have an increase in his Cr to 1.66 mg/dL (an increase of .5mg/dL in 52 d). There was no proteinuria or hematuria, and an ANA was negative. A renal sonogram revealed echogenic, normal-sized kidneys. His Cr remained 1.4-1.6 mg/dL and did not return to baseline. 135 d after exposure to probiotics, a renal biopsy was performed. The biopsy revealed patchy tubular atrophy and interstitial fibrosis affecting 10% of the cortical area with a few monoclonal inflammatory cells and focal mild lymphocytic tubulitis, consistent with resolving AIN.

Discussion: This case, the temporal association between the use of probiotics with kidney injury and the absence of other causes of AIN implicates the probiotic Lactobacillus GG as the etiologic agent. The mechanisms by which probiotics could potentially cause AIN include manipulation of intestinal microbial communities, immunomodulation, alteration of

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responsiveness of intestinal epithelial and immune cells, and altering the immunogenicity of degraded enteric antigens. Given the frequent over-the-counter use of probiotics, multiple potential coexisting etiologies for aIN, the often indolent nature of this disease, the rarity of this association, and the need for a renal biopsy to establish the diagnosis, the association between probiotics and aIN may be under-recognized.

PUB426
Decision-Making for the Critically Ill Un-Befriended Patient
Aparajita Mattoo, Jennifer S. Scherer.
Nephrology, NYU School of Medicine, New York, NY.

Introduction: The “un-befriended” patient is one that lacks decision-making capacity & a surrogate decision-maker (SDM). Nephrologists encounter un-befriended patients often, yet limited literature exists to guide decision-making for these vulnerable patients. This case describes an organized approach to caring for a critically ill un-befriended patient.

Case Description: Mr. S was a 74-year-old wheelchair bound nursing home (NH) resident who underwent an urgent right hemicolectomy for a perforated colon. His post-operative course was complicated by septic shock & multi-organ failure including AKI due to ATN. During this time his serum Cr increased from 0.8 to 3.6 mg/dl, with a urine output of <50cc/day. Mr. S was obtunded & had diffuse anasarca. He lacked advance directives & any SDM. The primary service believed that dialysis (HD) should be withheld given his overall poor prognosis. The consulting renal service utilized the four-topic approach to ethical decision-making to guide their recommendations. An estranged sister was asked to partake in an inter-disciplinary team (IDT) family meeting with renal, palliative care, bioethics, & the primary service to explore Mr. S’s values. It was established that Mr. S cherished his life in the NH & would have appreciated time there even if on HD. Under provisions of the NY State Family Health Care Decisions Act (FHCDA), it was determined to be ethically appropriate to withhold HD & transition Mr. S to comfort care.

Discussion: Utilizing the four-topic approach to decision-making, established legal policies, & an IDT, nephrologists can manage un-befriended patients within an organized, legally sound, & ethically sensitive framework.

PUB427
Persistent Kidney and Alveolar Damage in Patients with Goodpasture's Disease and Negative Anti-GBM Antibodies
Giovanna Y. Arteaga Muller, Lilia Maria Rizo Topete, Elisa Maria Guerrero Gonzalez, Concepcion Sanchez Martinez, Jesus Cruz Valdez, Gabriela Alarcón Galván.
Nephrology, Univ Hospital José E. González UANL, Monterrey, Mexico; 2Anatomic Pathology, Univ Hospital José E. González UANL, Monterrey, Mexico.

Introduction: Goodpasture’s disease is characterized by the presence of basement membrane antibodies which act against type 4 collagen in the glomerular basement membrane (GBM) and alveoli, it represents 20% of all crescentic glomerulonephritis. In patients with positive anti-GBM antibodies, the effective addition of a second potassium-sparing agent to ATN is logical. Despite prompt initiation of therapy with fomepizole and renal replacement therapy, rare cases of central hypotension have been reported.

Case Description: 21-year-old old woman, with anemic syndrome presenting Hb 4.33g/dl, Cr 0.8mg/dl, receiving a red cell transfusion. Is readmitted 15 days later Hb 2.7g/dl and Cr 1.9 mg/dl, whereby three globular packages were transfused and she was referred to our hospital. On admission, the patient was hypertension, lower limb edema and gross hematuria, Hb 11g/dl, Cr 1.7mg/dl, negative ANA's and ANCA'S and positive anti-GBM antibodies. Renal biopsy showed crescentic glomerulonephritis and linear staining deposits of IgG in GBM (4+).

Direct immunofluorescence technique (400X). Linear glomerular basement membrane staining for IgG.

Immunosuppressive therapy begins with methylprednisolone and CYCLOPS protocol. Later hemoptysis which improves with plasmapheresis, negative control anti-GBM antibodies. After presented sudden hypoxemia, bronchoscopy with abundant hemosiderin-laden macrophages, whereby plasmapheresis is performed again together with methylprednisolone, cyclophosphamide and rituximab. Currently the patient is in chronic hemoptysis, with negative anti-GBM antibodies.

Discussion: In patients with positive anti-GBM antibodies renal involvement may occur alone or associated with pulmonary hemorrhage, our patient despite having negative anti-GBM antibodies presented pulmonary hemorrhage. The literature recommends confirm the sustained absence of anti-GBM antibodies and signs of recurrence every 6 months.

PUB428
Gitelman Syndrome: Use of Dual Potassium-Sparing Agents in Refractory Hypokalemia
Maria Bernadette Yballe, Sandeep Aggarwal.
Div of Nephrology, Drexel Univ, Philadelphia, PA.

Introduction: Hypokalemia is one of the most frequently encountered electrolyte disturbances. Chronic hypokalemia with hypomagnesemia should prompt further investigation to include rare genetic disorders such as Gitelman syndrome. Despite the appropriate diagnosis, treatment can be challenging.

Case Description: We present a case of a 49-year-old non-hypertensive Caucasian female who presented to our outpatient clinic for an evaluation of her polyuria, chronic hypokalemia and hypomagnesemia. Her polyclia testing revealed the first distinct heterozygous missense autosomal recessive mutations of the SLC12A3 gene from Athena Diagnostics: c. 1315G>A; p.Gly439Ser and c. 2221G; p.Gly741Arg. She was continued on spironolactone 25mg twice daily along with potassium and magnesium supplements. Despite supplementation, she often required hospital visits which prompted magnesium and potassium infusions. Addition of amiloride improved her electrolyte levels, decreasing the need for hospitalizations and supplementations.

Discussion: Gitelman syndrome occurs in only ~1% of the Caucasian population which presents as chronic, sometimes severe and symptomatic hypokalemia, hypomagnesemia, hypocalciuria, and normotensive aldosteronism. The existence of 2 unique recessive alleles inherited by two siblings makes this case even more of a rarity. Our case also demonstrates the effective addition of a second potassium-sparing agent such as amiloride in ameliorating the need for more supplementation.

PUB429
Cerebral Ethylene Glycol Toxicity Despite Prompt Renal Replacement Therapy
Maria Bernadette Yballe, Sandeep Aggarwal.
Div of Nephrology, Drexel Univ, Philadelphia, PA.

Introduction: Acute cerebral edema is a rare consequence of ethylene glycol toxicity. Despite prompt initiation of therapy with fomepizole and renal replacement therapy, rare case reports of central hypotensions on CT imaging with neurologic abnormalities have been reported.

Case Description: We present a case of a 38-year-old female with PMH of HTN and anxiety who was brought in for agitation. One hour later, the patient became obtunded with significant respiratory distress requiring intubation. Home medications included bupropion. It was unclear if she ingested any toxins but the patient did have a history of marijuana use. On physical examination, the patient was hypertensive 210/114 mm Hg with reactive pupils. She was found to have high anion gap metabolic acidosis with a pH of 6.808, a serum bicarbonate of 4, an osmolal gap of 68, and a lactate acid of 5.6. Levels of ethanol, acetaminophen, phenobarbital, salicylate, and valproic acid levels were undetectable while urine drug screen was only positive for THC. Head CT did not reveal any acute
pathology. Urine microscopy revealed multiple ovoid colorless crystals in rosette formation consistent with monohydrate calcium oxalate crystals. Fomepizole was immediately started and intermittent dialysis initiated promptly within 10 hours of ingestion. However, due to hemodynamic instability, RRT had to be converted to a continuous veno-venous hemodialysis. After 2 days, patient then experienced an acute hypertensive episode with a BP of 172/100 mm Hg from a radial arterial line with pinpoint pupils and a repeat head CT revealing cerebral hypodensities in the basal ganglia, thalami, and brainstem along with surrounding vasogenic edema. Initial serum toxicology screen suggested ethylene glycol toxicity. The patient was intubated and intermittent dialysis initiated promptly within 10 hours of ingestion. However, there was significant focal edema in the basal ganglia with no other electrolyte abnormalities. Toxicology was negative for ethanol or salicylates. 

Discussion: Despite prompt initiation of dialysis, rare case reports of acute cerebral edema from ethylene glycol toxicity have been reported. It is unknown whether these abnormalities are due to direct cellular toxicity or deposition of crystals in the cerebral vasculature causing ischemia and subsequent edema and inflammation. Our case demonstrates a rare neurologic sequela of ethylene glycol toxicity despite appropriate prompt treatment.

**PUB430**

**Encapsulating Peritoneal Sclerosis – Case Reports**

**Introduction:** Encapsulating Peritoneal Sclerosis (EPS) is a rare but serious and potentially lethal complication in peritoneal dialysis (PD), first described in 1980. Intestinal obstruction, serious malnutrition and sepsis are the causes of death for this uncommon condition. The exact incidence is unknown.

**Case Description:** We described outcomes of 6 cases followed in a referral service of PD between 2010 and 2015.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender/ Age (years)</th>
<th>CKD related infection (years)</th>
<th>Previous infection (number)</th>
<th>Clinical Features</th>
<th>Radiologic Findings</th>
<th>Peritoneal Biopsy</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F / 47</td>
<td>SAH</td>
<td>8</td>
<td>Cauda equina</td>
<td>Acute abdominal obstruction + Bloody effluent</td>
<td>Loculated + Peritoneal thickening + Calculations</td>
<td>Chronic peritonitis + Peritoneal thickening + Fibron deposition</td>
</tr>
<tr>
<td>2</td>
<td>F / 47</td>
<td>SAH</td>
<td>4</td>
<td>Pseudomonas aeruginosa</td>
<td>Partial bowel obstruction + Bloody effluent</td>
<td>Loculated + Bowel thickening</td>
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</tr>
<tr>
<td>3</td>
<td>F / 18</td>
<td>PIGN</td>
<td>10</td>
<td>Staphylococcus coagulase negative</td>
<td>Partial bowel obstruction + pain</td>
<td>Moderate ascites + Peritoneal/Bowel calcifications</td>
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</tr>
<tr>
<td>4</td>
<td>M / 68</td>
<td>TZDM</td>
<td>2.5</td>
<td>Escherichia coli / Klebsiella oxytoca</td>
<td>Partial bowel obstruction + pain</td>
<td>High volume localized ascites + bowel tetherring</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>F / 39</td>
<td>SLE</td>
<td>1</td>
<td>Enterococcus sp</td>
<td>Bowel obstruction + Severe malnutrition + Chronic abdominal pain + Bloody effluent</td>
<td>Peritoneal calcification + Bowel distention + High volume ascites</td>
<td>Death for sepsis after 8 months</td>
</tr>
<tr>
<td>6</td>
<td>M / 53</td>
<td>TZDM</td>
<td>2.5</td>
<td>Streptococcus viridans</td>
<td>Abdominal distension + pain</td>
<td>High volume unique peritoneal collection + Intestinal cocon</td>
<td>--</td>
</tr>
</tbody>
</table>

SAH: Sistemic Arterial Hypertension; SLE: Sistemic Lupus Eritematosus; TZDM: Type 2 Diabetes Mellitus; PIGN: Post Infectious Glomerulonephritis/CKD: Chronic Kidney Disease.

**Discussion:** EPS is a severe event related a long term on peritoneal dialysis or severe cases of peritonitis.

**PUB431**

**AM Tolvlantop to Avert Hypotensive Seizures in a Patient with Primary Polydipsia and New Mildly Impaired Free Water Excretion**

**Introduction:** A former pilot with a history of primary polydipsia PP (past urines >6 l/day) complicated by confusion. Plasma (P_on) and urine sodium were 123 and 37 mEq/l, and plasma (P_off) and urine osmolalities were 251 and 207 mOsm/kg H2O. With cessation of Prozac and advised fluid restriction (FR) P_on corrected. Interim P_on was 286 mOsm/kg and urine SG 1.005. Following multiple surgeries (decompensatory laparotomy, subtotal colectomy, ileostomy, feeding gastrostomy), for complex postoperative syndrome/pancreatitis, AM Tolvlantop was avert hypotensive seizure (HS). No cause for impaired free water excretion (iFWE) was found. Her PP made FR difficult, as she was thirsty at P_on <125 mEq/l, and caused repeat HSs.

**Case Description:** After her 4th seizure, we replaced FR and salt tablets with AM Tolvlantop. This normalized PNa, abolished her recurrent HSs, and was tailored to her new dreadful PP/SIADH combination.

Indeed, since thirst is constant in DI but only diurnal in PP, the AM tolvlantop-induced daytime DI allowed her to quench her thirst without fear of HSs, if since WE were required by us, when the drug effect wore off, and her PP abided. She was reluctant giving up this diurnal/nocturnal PP/DESIADH, for fear of seizures.

**Discussion:** Given the high capacity for FWE, a syndrome of inappropriate antidiuresis (SIAD) or impaired diuresis-aquaresis (SIDA), due or not to ADH (SIAD/H or SIDA/H) must coexist in PP, for HS to occur; conversely some PP or other source of free H2O must exist in the SIAD/H – SIDA/H spectrum of iFWE to cause HS, since FR alone increases the low P_on and prevents HS despite depot ADH in man, or chronic diAVP infusion in rats. This is the first report of successful compassionate off label use of AM tolvlantop, instead of FR, to prevent HS in a patient where PP is the culprit. However FR instead of vaptans is the first line treatment of low P_on in SIAD/H, yet here ADH is the culprit. In that PP and SIAD/H (or iFWE state) must coexist to cause HS, and that ADH, as assessed by sensitive assays is rarely totally suppressed, resolves this paradox.

**PUB432**

**Atypical Presentation of Calcium Oxalate Nephropathy**

**Introduction:** Ethylene glycol ingestion can cause multi-organ dysfunction including acute kidney injury (AKI) and death. The diagnosis can be made based on history, a high anion gap metabolic acidosis with an elevated osmol gap, oxalate crystalluria and an elevated ethylene glycol level. The diagnosis may be challenging with the concurrent use of other substances such as cocaine as it causes vasomotor AKI or ANCA vasculitis. To elucidate the diagnosis, a renal biopsy may be required. Herein, we present a patient with biopsy proven calcium oxalate nephropathy who presented with unexplained AKI likely related to unintentional low dose regular ethylene glycol use. She did not have any symptoms or classic biochemical features of ethylene glycol intoxication.

**Case Description:** A 57-year-old homeless woman with a history of rheumatoid arthritis, COPD presented with a productive cough and dyspnea and was found to have a Cr of 3.9 mg/dl, elevated from a recent baseline of 0.9 mg/dl. Her anion gap was 17, with no other electrolyte abnormalities. Toxicology was negative for ethanol or salicylates. Her BP was 157/77 mm Hg and physical exam was unremarkable. Her last use of cocaine was 3 days prior to admission. She was initially given normal saline and maintained an adequate urine output, but her Cr continued to rise to 13.0 mg/dl. Urine sediment showed a few isomorphic RBCs only. A renal ultrasound revealed normal sized kidneys. Serological tests for autoimmune, post-infectious and dysproteinemic causes of AKI were normal or negative. Renal biopsy revealed acute tubular injury with calcium oxalate deposition. An in depth history did not reveal a high oxalate diet nor a medical history predisposing her to hyperoxaluria, however she admitted to the regular ingestion of “juiced” street alcohol. She did not require dialysis. Her follow-up Cr was 1.8 mg/dl two months later.

**Discussion:** In conclusion, a thorough history is required when encountering unknown AKI, in patients with a history of drug abuse or homelessness, while keeping a high index of suspicion for drug intoxications including ethylene glycol.

**PUB433**

**Thrombotic Microangiopathy (Hemolytic-Uremic Syndrome) Induced Acute Kidney Injury Associated with Brucella Infection**

**Introduction:** Thrombotic microangiopathies (HUS, TTP and DIC) have been associated with a host of infectious agents. Its association with Brucellosis is uncommon.

We present a case of a patient who developed TMA associated with a case of Brucellosis.

**Case Description:** 52-year-old woman with minimal past medical history presented to the hospital with abdominal pain, fever/chills and general body aches. History was significant for intermittent bloody diarrhea approximately 2 weeks prior to ED presentation. Physical examination revealed epigastric and right upper quadrant tenderness to palpation and patient was started on broad-spectrum, empiric IV antiobiotic therapy with...
Vancomycin, Piperacillin-Tazobactam, and Ciprofloxacin. Shortly thereafter, her clinical status continued to deteriorate resulting in acute respiratory failure requiring intubation and mechanical ventilation. CBC was notable for a white blood cell count of 27,000, hemoglobin of 7.3 g/dL and a platelet count 80,000. Other labs were notable for total bilirubin 2.3 mg/dL, LDH 509 U/L, lactate dehydrogenase less than 10, procalcitonin 5.7 nmol/L and elevated transaminases. Peripheral Smear was notable to be positive for numerous schistocytes. Patient was anuria and Nephrology consulted to begin CRRT in setting of sepsis requiring three vasoressors.

Patient had a rapid improvement in symptoms after initiation of sepsis protocol and was weaned off all vasoressors by 72 hours. Initial workup including abdominal imaging and blood cultures were negative for a source of infection. Patient had remarkable spontaneous clinical recovery and was later found to be positive for Brucellosis by immunoglobulin assay.

Discussion: Brucella infection has uncommonly been associated with the development of Hemolytic Uremic Syndrome. In addition, clinical course is widely variable, ranging from spontaneous recovery, as occurred with this patient, to disease requiring long-term renal replacement therapy.

**PUB434**

**Patient with Clinical Diagnosis of Scleroderma Presenting with Sjögren’s Associated Renal Disease:** Aasim Jaberi, Javvinder S. Bhatia. Nephrology, Boston Medical Center, Boston, MA.

**Introduction:** Overlap rheumatologic syndromes occur in a substantial number of patients with renal disease. The clinical manifestations often favor one diagnosis over another, which can make diagnosing and treating the renal disease very challenging.

**Case Description:** 69-year-old female with no known history of previous rheumatologic disease presented with cough, fever and AKI and was diagnosed with mCTD-related pneumonia. Initial laboratory tests revealed a creatinine level of 2.2 mg/dL and persistent non-anion gap metabolic acidosis. On further history, she complained of long standing heartburn and Raynaud’s symptoms in her fingers. Her physical examination disclosed telangiectasias on palms and skin thickening of the face and PIP joint. These features were consistent with systemic sclerosis, which prompted a rheumatologic work-up. Serologies were significant for a positive ANA and SSA antibody as well as hypocomplementemia. Urine sediment revealed many WBCs with no casts and some non-dysmorphic RBCs. A decision was made to proceed with kidney biopsy to identify the cause of her renal disease since the sediment was not supportive of Scleroderma associated renal disease. She was commenced on corticosteroid therapy and two months post-initiation, her renal function has stabilized.

**Discussion:** This case demonstrated the importance of kidney biopsy in elucidating a diagnosis in a challenging case of overlap syndrome. The rapid diagnosis of interstitial nephritis was particularly important in this patient since most cases of renal associated Sjögren’s go unrecognized until significant renal dysfunction has occurred. It has been proposed to consider kidney biopsy findings of tubulointerstitial disease as additional supportive criteria in the classification of Primary Sjögren’s syndrome, which is a sentiment we also support.

**PUB435**


**Introduction:** Acute post infectious glomerulonephritis (APIGN) most frequently be expected in just over half of patients, and prognosis is dismal in those with underlying diabetic glomerulosclerosis.

**Case Description:** A 69-year-old male with medical history of uncontrolled diabetes, Hypertension and chronic alcohol abuse presented to the emergency department due to shortness of breath and swelling of his legs since one week. Patient was afibrile, blood pressure 200/102 mm Hg. On exam he had clear signs of fluid overload. Pitting edema was seen over the lower extremities bilaterally, up to the shins. He also had an oval ulcer on his right leg anteriorly measuring 2 cm discharging pus. The remainder of the physical exam was grossly normal. Relevant laboratory results potassium of 6.4 meq/L, BUN 51 mg/dl, Creatinine 1.7 mg/dL (Baseline unidentified) and Albumin 2.8 g/dL. Arterialization: protein 300 mg/dL, blood MOD, WBC 61/hpf, RBC 87/hpf, Hyaline casts 7/hpf. Urine eosinophils present. Urine 24 Hr Protein: 6.7 g. Wound cultures positive for Beta Hemolytic Streptococcus Group A. Complement C3: 10.950 <10, C4:34 Antistreptolysin O:400 <200 IU/ml Anti DNAs B Titre: 967. Kidney biopsy results: acute post-infectious glomerulonephritis superimposed on background changes of moderate nodular diabetic glomerulosclerosis.

Discussion: Most children with APIGN recover completely, but there is general agreement that the prognosis is more guarded in adults. Full recovery of renal function can be expected in just over half of patients, and prognosis is dismal in those with underlying diabetic glomerulosclerosis.

**PUB436**

**Two Cases of Kidney Injury Induced by Anti-VEGF Therapy for Carcinoma** Yudai Isozaki, Youse Okagawa, Takuya Isegawa, Masahiro Koizumi, Masafumi Fukagawa. Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.

**Introduction:** Anti-vascular endothelial growth factor (VEGF) agents have been widely used in the treatment of various types of advanced-stage malignant tumor, including lung carcinoma and renal cell carcinoma. Although these agents are generally well tolerated, there are increasing reports of renal adverse events, especially proteinuria.

**Case Description: Case 1: A 69 year-old male started chemotherapy including bevacizumab (monoclonal antibody of VEGF) with a diagnosis of advanced lung adenocarcinoma of left upper lobe. The completion of four-course chemotherapy resulted in reduction of tumor volume, and then converted to bevacizumab monotherapy. At one year after the start of therapy, proteinuria with renal insufficiency developed. He was referred to our service for further evaluation and management. Renal biopsy demonstrated microthrombi in the loop wall with duplication of GBM, which was consistent with thrombotic microangiopathy (TMA). Thereafter, with cessation of anti-VEGF agent, proteinuria was gradually ameliorated to less than 1.0 g/day and renal function returned to normal range. Case 2: A 56 year-old male with renal cell carcinoma, who had undergone nephrectomy and diabetes. After the introduction of therapy, he exhibited progression of kidney disease with nephrotic-range proteinuria in a short time. In addition to the cessation of sutinib, hemodialysis was initiated because of fluid overload. After several times of dialysis, urine output was gradually increased and renal function returned to the baseline level.

**Discussion:** The renal adverse effects of anti-VEGF agents are supposed to arise from inhibition of podocyte-endothelial VEGF signaling pathway. VEGF signaling pathway plays an essential part in glomerular development and endothelial maintenance. We need to pay attention to renal adverse effects with anti-VEGF therapy.

**PUB437**

**Concurrent Development of Eculizumab (ECU) (Anti-C5 Antibody) - Responsive Atypical Hemolytic Uremic Syndrome (aHUS) and Siltuximab (SLT) (Anti-IL-6 Antibody) -Sensitive Multicentric Castleman Disease (MCD): Evidence for the Pathogenic Role of Inflammatory Cytokines Joe Ghata,13 Abdulmawla Albiniri,1 Kai Lau.

**Introduction:** The literature has a few cases on the association of MCD with thrombotic microangiopathy (TMA), but the pathogenesis & therapy are unknown.

**Case Description:** We describe a 29-year-old previously healthy man initially presented with non-specific symptoms of what later proved to be MCD. Diagnosis was delayed due to explosive full-blown systemic & biopsy-proven renal TMA, producing dialysis-dependent ARF, severe thrombocytopenia & transfusion-dependent hemolytic anemia tail eculizumab (ECU). The appearance of diffuse lymphadenopathy 8 weeks after acute renal failure (ARF) led to node-biopsy proven MCD diagnosis & therapy with SLT. We postulate MCD was the trigger for TMA & full resolution needs both ECU & SLT directed at the etiology.

10 days before ARF, patient had abdominal pain, treated as cholecystitis by cholecystectomy. Mild splenomegaly & trace ascites were overlooked. Day 7 after ARF, bilateral pleural & peri-cardial effusion & moderate ascites emerged but overlooked as serum creatinine rose.
Severe Hypercalcemia Presenting During Recovery Phase of Ischemic Acute Kidney Injury
Buthavna A. Dinari,1 Fazel Dinari,1 Lavinia A. Negrea.1

Introduction: AKI is frequently complicated by multiple electrolyte abnormalities, including hyperkalemia, hyperphosphatemia, and hypo/hypercalcemia. Hypercalcemia is often seen in the recovery phase of rhabdomyolysis associated AKI, can be severe, including mobilization of calcium deposits out of the recovering muscles, secondary hyperparathyroidism, increase in calcitriol, and resolution of hyperphosphatemia. Immobilization during the oliguric phase he developed severe symptomatic hypercalcemia. Improved with volume replacement and administration of calcitonin, and bisphosphonates are some of the methods used for its treatment.

Case Description: A 31 yo Caucasian male with recently diagnosed Type I DM. A case of hyponatremia from adrenal insufficiency mimicking SIADH

Kappa and lambda light chain staining was negative.1 mg/kg metilprednisolone therapy was initiated and given for 1 month. No regression was observed and hemodialysis therapy was continued. After 2 months steroid therapy was reintiated again but there was no clinical and biochemical response. On follow-up, after 7 months from renal biopsy hypercalcemia, anemia, high sedimentation rate, hypergobulinemia and lytic bone lesions were detected. 16% monoclonal plasma cells were present in bone marrow. With further examinations MM diagnosis was made.

Discussion: Renal biopsies revealing acute tubulointerstitial nephritis pattern which are unresponsive to steroid therapy should always be deeply investigated for alternative diagnoses. MM may have obscure presentations.

Sleep Disturbances in an ESRD Patient Soon After Initiation on Hemodialysis: An Atypical Presentation of ESRD-Related Sleep Disorders
Desiree Garcia Anton, Franco H. Cabeza Rivera, Alexandre Abreu, Marco A. LodinoAvellaneda. Nephrology, Univ of Miami, Miami, FL.

Introduction: Sleep disorders including obstructive sleep apnea (OSA), restless legs syndrome (RLS) and insomnia are highly prevalent in ESRD patients undergoing dialysis, however, these remain stable or tend to improve after initiation of dialysis. There is scarce evidence of new-onset sleep complaints or disorders after initiation of dialysis.

Case Description: We present a case of a 64 year-old male with HTN, DM, ESRD and no previous sleep problems who developed insomnia, RLS, sleepwalking and other sleep disturbances within a month after initiation of continuous hemodialysis. He presented to the nephrology clinic with secondary complications from uncontrolled diabetes (neuropathy, retinopathy and nephropathy); he had been followed by the nephrology service for 4 years before requiring dialysis for uremia and volume overload. Intermittent HD was well tolerated during first month of treatment, achieving good metabolic clearance and volume control; his Kt/V was 1.16, phosphorus was controlled at 4.6 mg/dl and his anemia improved to a hematocrite of 30%. Despite clinical and laboratory improvement, disabling sleep symptoms were reported and he was referred to the Sleep clinic for further evaluation. On his initial actigraphy, a bedtime or rise time pattern was unable to be determined as it showed continuous movements 24 hours per day for the 14 days monitored. Overnight Polysomnography (PSG) revealed normal size kidneys without hydronephrosis. Renal biopsy was compatible with acute tubulointerstitial nephritis.

Reduced Serum Anion Gap due to Lithium Overdose
Tanmoy Sahai,1 Josef Bautista.1 Internal Medicine, Roger Williams Medical Center, Providence, RI; 2Nephrology, Brown Univ/Rhode Island Hospital, Providence, RI.

Introduction: This case demonstrates the clinical presentation and corresponding laboratory results of lithium overdose as well as further discuss management of overdose with intermittent hemodialysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Case Description: A 32-year-old man with a history of bipolar disorder came to the hospital with altered mental status and worsening lethargy. He was subsequently intubated for airway protection. Patient’s lithium level was ~20 mmol/L. CT head showed no injury. The rest of the toxicology screen was negative. His basic metabolic panel (including calcium and albumin) was within normal limits however his bicarbonate was 32 mmol/L and anion gap was elevated. Patient was intubated 24 hours later as patient was awake, alert and arousable with dramatic improvement in mental status. Creatinine also trended down to 0.9 after 48 hours. Patient was extubated 48 hours after initial presentation.

Discussion: Lithium has a narrow therapeutic window and therefore in cases of overdose toxicity have many symptoms including altered levels of consciousness as seen in this patient. Low anion gap is a diagnostic clue to lithium intoxication however other causes include hyperkalemia, hypermagnesemia, and monoclonal gammopathies. Although serum osmolality was not measured in our patient, this can also be a helpful indicator noted in previous case reports. Elevated osmolar gaps with low anion gaps are useful in diagnosing lithium overdose. The standard management for lithium overdose is intermittent hemodialysis and maintaining water balance. The theory behind using intermittent hemodialysis versus continuous venovenous hemodiafiltration is that higher clearance of lithium can be achieved from faster blood flow rates in intermittent hemodialysis if it can be tolerated hemodynamically.

PUB443
Episodes of Hypertensive Crises in a Tetraplegic Dialysis Patient due to Catheter-Associated Endocarditis
Martin Russoorum, Joachim Hoyer, Ivica Gregic, Dept of Internal Medicine and Nephrology, Philips-Univers Marburg, Marburg, Germany.

Introduction: Hypertensive emergencies are a life-threatening condition associated with organ damage including acute heart failure, seizures and coma. Pre-existing arterial hypertension and non-adherence to anti-hypertensive treatment as well as volume overload particularly in dialysis patients are considered major triggers of HC. ESRD patients have a high prevalence (>70%) for hypertension and are at high risk for the development of cardiovascular disease and related complications. Early assessment and treatment of hypertensive states including HC is therefore imperative.

Case Description: Here, we report a case of a 34-year-old patient with sudden onset of repeated episodes of hypertensive emergencies on dialysis. The first episodes of spiking blood pressure of >240/120 mmHg occurred several weeks prior to admission and had become increasingly difficult to manage forcing early termination of dialysis sessions. The patient had been on hemodialysis, via tunneled catheter, for one year. Laboratory findings showed elevated inflammation parameters. Blood cultures were positive for gram-negative rods which were later identified as Pseudomonas aerugiiosa (Pa.). We performed transesophageal echocardiography which showed echodense masses at the tip of the catheter and right cardiac atrium. Hemodialysis via an alternative vascular access instantly resulted in normal blood pressures during dialysis. Subsequently, the patient underwent heart surgery. The tunneled catheter and a large (5.2 x 3.5cm), PA-infected thrombus were removed from the right atrium and the patient put on a targeted antibiotics. Following recovery, a forearm fistula was created and used without major complications.

Discussion: To our knowledge, there is no report in the current literature of hypertensive crises associated with CAE infection. While one may question whether or not it is theoretically possible that the infected catheter may have led to transient bacteremia triggering hypertensive episodes via an unclear mechanism. This case demonstrates that catheter-associated infections should be included in the differentials of causes and triggers of HC.

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PUB444
Adipsic Nephrogenic Diabetes Insipidus a Possibility? Nivin Haroon, Zeenat Youssuf Bhat. Dept Nephrology, Wayne State Univ, Detroit, MI.

Introduction: Adipsic diabetes insipidus (DI) is a rare syndrome where the patient has central DI and lack of thirst response due to presence of central lesion. We describe a patient who developed nephrogenic DI following a contrast exposure and acute kidney injury (AKI).

Case Description: The patient is a 47 yr old African American female with significant past medical history of mild diabetes mellitus. Her baseline kidney function was stable with a creatinine of 1.0 mg/dl. She had developed progressive non-infarctive inflammatory breast cancer. She completed 2 cycles of paclitaxel and doxorubicin and cyclophosphomide. During this time she was admitted to the hospital following incision and drainage of a rectal abscess and treated with vancomycin and zosyn. Patient had received contrast exposure from computed tomography imaging for the abscess. Two days later the patient started to have rise in Cr with level going from 0.7 to 1.5. Nephrology was consulted for the same.

There was no overt septic shock or blood pressure fluctuation. Urine microscopy was bland and ultrasound showed no pathology. Acute kidney injury was possible from the contrast exposure due to the time to Cr bump within 48 to 72 hour period and history of other overt evidence. Along with the AKI patient was found to have rise in sodium levels. She was having increased urine output in the range of over 4 Liters every day. Sodium was going up from baseline 140 up to 152. Initially patient was not having increased thirst response to give a 5% glucose in D5W (DDAVP) challenge test with no change in the urine output. An MRI imaging of brain was negative for pathology. She was instructed to drink water to match her urine out even if not thirsty. Initially the sodium levelled off and later trended down along with AKI.

Discussion: The case is very much as the contrast injury resulted in nephrogenic DI. The patient lack of thirst response and rise in sodium was even more peculiar as the DI was clearly nephrogenic due to lack of response to DDAVP. It is still unclear why the thirst response in this patient was affected. More studies in future will unravel the complex relation between thirst response and osmolarity.

PUB445
Frailty Modifies the Association Between Age and Dysnatremia in Community-Dwelling Adults
Amanda Jean Miller, 1 Susan E. Howlett, 2 Kenneth John Rockwood, 2 Karthik K. Tennankore. 1 Nephrology, Dalhousie Univ, Halifax, NS, Canada; 2Geriatrics, Dalhousie Univ, Halifax, NS, Canada.

Background: Frailty represents a state of increased risk to adverse health outcomes, reflecting some combination of increased damage and compromised repair processes. Dysnatremia is more common with age and can occur in many settings, suggesting that it may reflect not simply a specific renal problem, but a more general imbalance in damage and repair. The aims of this study were to establish whether frailty severity is associated with a higher rate of dysnatremia and to determine whether frailty explains the previously established association between age and dysnatremia.

Methods: The relationship between age, frailty severity and dysnatremia was investigated across the adult life course in 8898 respondents from the 2003-2004 and 2005-2006 cross-sectional National Health and Nutrition Examination Survey (NHANES) datasets. Respondents were assigned a frailty index (FI) and assessed for dysnatremia (a deviation of serum sodium from the 135-144 mmol/L normal range). The coefficient of variation in serum sodium was used as a systems measure of the response repertoire.

Results: In the overall population, there was a significant positive association between increasing frailty severity and the proportion of patients with dysnatremia (chi-square trend p = 0.001). Increasing frailty severity was also associated with more variability in serum sodium. There was a significant association between advancing age and dysnatremia (p < 0.001); however after stratifying by frailty (FI <0.100, 0.100-0.199, 0.200-0.299, 0.300-0.399, >=0.400), the association between increasing age and dysnatremia became non-significant in all categories.

Conclusions: Increasing frailty severity is associated with dysnatremia and greater variability in serum sodium. Furthermore, frailty appears to modify the earlier association between age and dysnatremia.

PUB446
Approach to Hyponatremia in Congestive Heart Failure: A Survey of Canadian Physicians and Trainees
Amanda Jean Miller1, Bonnie Kuehl, 2 Karthik K. Tennankore. 1 Nephrology, Dalhousie Univ, Halifax, NS, Canada; 2Research, Scientific Insights Consulting Group Inc., Mississauga, ON, Canada.

Background: Hyponatremia is a complication of congestive heart failure (CHF) and is associated with reduced survival, however there are no consensus guidelines for the treatment of hyponatremia in CHF. The aim of this study was to determine the approach to hyponatremia in CHF among Canadian Nephrologists, Cardiologists, Internists and trainees in each of two domains; pathophysiology and management. Management topics included use of diuretic therapy, hypertonic saline, oral urea tablets, vasopressin receptor antagonists (vaptans) and rate of sodium correction. Correct answers were determined by an expert panel of Canadian Nephrologists and Cardiologists.

Methods: Respondents completed 15 multiple-choice style questions surrounding three cases of hyponatremia complicating CHF using an online survey on UKiN.com between December 2012-May 2013. Results were summarized as the proportion of correct/ incorrect responses among Canadian Nephrologists, Cardiologists, Internists and trainees in each of two domains; pathophysiology and management. Management topics included use of diuretic therapy, hypertonic saline, oral urea tablets, vasopressin receptor antagonists (vaptans) and rate of sodium correction. Correct answers were determined by an expert panel of Canadian Nephrologists and Cardiologists.

Results: There were 1097 responses to survey questions among 455 Canadian respondents. Pathophysiology governing hyponatremia in CHF was correctly identified in 68.7% of responses (n = 380). Overall, hyponatremia was managed inappropriately in 53.6% of responses (n = 759). The proportion of incorrect responses among specialists and trainees is depicted in Figure 1. Importantly, an incorrect rate for sodium correction was selected 61.1% of the time (n = 211).

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

991A
Sorafenib Induced Hyponatremia

Evan Gorshein,1 Catherine K. Wei,1 Jasmeet S. Bajaj,2 Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; 2Critical Care Unit, Univ Medical Center of Princeton at Plainsboro, Plainsboro, NJ.

Background: Sorafenib treats unresectable hepatocellular carcinoma (HCC). It is a multi-targeted tyrosine kinase inhibitor (TKI), which prevents tumor cell proliferation. Their use, however, has been limited by adverse events. Hyponatremia has been reported as one of the most common adverse events associated with sorafenib.

Methods: A 58 year-old female presented with lethargy and edema. Patient was diagnosed with HCC 6 months earlier. She underwent transcatheter arterial chemoembolization and was noted on repeat imaging to have metastatic disease. Patient began sorafenib two weeks prior to admission, with a dose of 200 mg daily. A week later, the dose was increased to 200 mg twice daily. Three days later, the patient increased her dose to 400 mg in the AM and 200 mg in the PM. A day thereafter, patient became lethargic, with generalized swelling. The serum sodium was 106 mmol/L, with a baseline of 134 mmol/L three weeks prior to admission. Urine osmolality was 542 mOsm/kg, and the urine random sodium was less than 25 mEq/L. Patient’s TSH was 6.82, with a normal FT4. AM cortisol was measured at 20.2. Her total protein and lipid profile were normal.

Conclusions: TKI agents may enhance the effects or increase the action of ADH. Time to onset of hyponatremia may be within ten days. Our patient took sorafenib for two weeks. Upon admission, her serum sodium was 106. It was noted that she had a prolonged diuresis and fluid restriction, her sodium reached 128. Other etiologies of hyponatremia were excluded. Sorafenib has been associated with hyponatremia, which may be related to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. We present a case of sorafenib induced hyponatremia.

PUB447

Current Trends in Etiologic Factors Responsible for the Development of Hyponatremia in Hospitalized Patients

Sandor Win,1 Maria V. DeVita,1 Diana Dreyer,2 Samuel J. Wahl,2 Sandor Win,1 Maria V. DeVita,1 Diana Dreyer,2 Samuel J. Wahl,2 Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; 2Critical Care Unit, Univ Medical Center of Princeton at Plainsboro, Plainsboro, NJ.

Background: Hyponatremia remains the most common electrolyte disorder seen in hospitalized patients. The prevalence has been reported to range from 5% to 15% and to be as high as 29.6% depending on the hospital setting.

Methods: New data were obtained on 2 separate days to evaluate the prevalence and etiologies of hyponatremia in hospitalized patients in a large metropolitan hospital. Hyponatremia was defined as less than 135mmol/L.

Results: Hyponatremia was recognized in 41 of 879 patients (4.6%). The mean serum sodium level in the hyponatremia group was 132.0±3.2 mmol/L. Eighty-five percent of the patients exhibited a serum sodium level of <130 mmol/L. Individuals aged 65 years old or greater made up 58.5% of the patients. Etiologic factors identified in the total number of hyponatremic patients included 9.7% with ESRD, 4.8% post op, 14.6% dehydration, 24.3% with pulmonary disorders, 26.8% with a diagnosis of cancer. The majority of patients were noted, however, to be receiving related drug therapies 63.4%. They were distributed between diuretic therapy (36.6%) and psychiatric drug therapy (26.8%).

Conclusions: This study suggests that hyponatremia often is mild, is commonly associated with drug therapy, affects a significant number of younger patients, and now includes novel conditions such as patients receiving renal replacement therapy.

PUB449

Development of Metabolic Acidosis After Neobladder Replacement in Korea

Shina Lee,1 Dong-Ryeeol Ryu, Kyu Bok Choi, Suk-Hae Kang, Seung-Jung Kim. 1Department of Internal Medicine, School of Medicine, Ewha Womans Univ, Seoul, Korea.

Background: Metabolic acidosis frequently develops in patients after neobladder replacement. However, the incidence of metabolic acidosis in patients with neobladder and the factors associated with the development of metabolic acidosis have not been well elucidated. We aimed to investigate the incidence and the potential predictors for the development of metabolic acidosis after neobladder replacement with intestinal segment.

Methods: We included all patients who underwent neobladder replacement using intestinal segment at Mokdong Hospital between January 1, 2005 and December 31, 2014. Metabolic acidosis was defined as serum CO2 below 22 mEq/L at any visit during the follow up period. Patients’ biologic data was presented using t-test and student t test. Subgroups according to the time of metabolic acidosis occurrence was further analyzed in order to characterize predictors for metabolic acidosis by ANOVA tests and multiple regression.

Results: Metabolic acidosis was encountered in 79.4% of patients with neobladder during follow up period. When patients were divided into 2 groups according to anion gap (AG), total CO2(18.9±2.1 mEq/L vs. 20.9±1.3 mEq/L, p<0.001) and chloride(106.6±4 mEq/L vs. 109.4±3.6 mEq/L, p<0.001) were significant different between groups with AG<12 and AG≥12 respectively. Furthermore, when patients were divided into 3 groups; patients with metabolic acidosis at post operative day 1; within a 14days; after 14days, there was significant difference of postoperative laboratory findings among the those subgroups.

Conclusions: Our study showed the rate of development of metabolic acidosis in patients underwent neobladder replacement and the difference between patients with metabolic acidosis and those without metabolic acidosis after neobladder replacement for the first time in Korea. In the future, well designed prospective study will be needed to prevent metabolic acidosis after neobladder replacement.

PUB450

Potassium Abnormalities and Acute Kidney Injury Are Common Complications After Colectomy

Lindsay M. Smith,1 Robert M. Perkins,2 Andrea Lynn Berger,1 H. Lester Kirchner,3 Morgan Grams,1 Alex R. Chang,1 Geisinger Health System; 2Bayer Healthcare; 3Johns Hopkins Bloomberg School of Public Health.

Background: Patients undergoing colectomy may be predisposed to disturbed potassium homeostasis, since the colon has a role in potassium excretion, and volume depletion due to diarrhea occurs frequently after colectomy.

Methods: We examined the frequency of incident mild (<5 mmol/L) and severe hyperkalemia (>6 mmol/L), mild (<3.5 mmol/L) and severe (<2.5 mmol/L) hypokalemia, and impaired AKI, stratified by estimated glomerular filtration rate (eGFR) using creatinine only and potassium (impaired/outpatient) data from 1,762 patients who underwent colectomy surgery at Geisinger Health System between 2004-2013. Results: Median age was 66 and mean baseline eGFR was 79 ml/min/1.73m2. Colonic conditions included inflammatory bowel disease (8%), bowel obstruction (8%), incontinence (2%), diverticulitis (23%), and colorectal cancer (20%). During the surgery hospitalization, post-operative AKI occurred in 32% of patients ; mild and severe hyperkalemia occurred in 18% and 3% of patients. Over a median of 4.0 years post discharge after colectomy, mild and severe hyperkalemia occurred at a rate of 13.4 events/100 person-years and 1.8 events/100 person-years; mild hyperkalemia and severe hyperkalemia occurred at a rate of 15.4 events/100 person-years and 0.7 events per person-years. Rates of impaired AKI after discharge were high (9.1 events/100 person-years). Risks for AKI, mild and severe hyperkalemia increased as eGFR declined (p-values<0.001, Table). Conclusions: Patients who undergo colectomy are at high risk for hyperkalemia, hypokalemia, and AKI, particularly when eGFR is decreased. Comparison to a control group is needed to determine whether the high incidence of hyperkalemia is related to removal of the colon or frequent AKI episodes.

Table. Event Rates for Hyperkalemia, Hypokalemia, and AKI Events after Colectomy by Baseline eGFR Category

<table>
<thead>
<tr>
<th>eGFR Category</th>
<th>Number of Events per 100 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (eGFR &gt;60)</td>
<td>11.6 (59.1% of cases)</td>
</tr>
<tr>
<td>60-89 (eGFR 40-59)</td>
<td>26.7 (32.0)</td>
</tr>
<tr>
<td>30-39 (eGFR 20-29)</td>
<td>32.0 (34.6)</td>
</tr>
<tr>
<td>10-19 (eGFR &lt;20)</td>
<td>35.4 (43.3)</td>
</tr>
</tbody>
</table>

Funding: Private Foundation Support

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

Underline represents presenting author.
Identify the Causes of the Chronic Hypokalemia: Importance of Urinary Sodium and Chloride Excretion

Chi-Hsien Sung, Kun-Lin Wu, Chih-Jen Cheng, Yu-Juei Hsu, Sung-Sen Yang, Shih-Hua P. Lin

Methods: The patients referred for evaluation of chronic hypokalemia in a medical center were enrolled prospectively for five years.

Results: Ninety-nine patients with chronic hypokalemia (serum K⁺: 2.8±0.4 mmol/L) were enrolled. The major presentations were diziness, fatigue, palpitation, abdominal fullness and muscle weakness/weakness. The plasma renin activities were increased in all patients along with normal-to-high serum aldosterone level. The main imaging findings were nephrocalcinosis/renal stones (n=25). Although Gitelman’s/Bartter’s syndrome (n=32/13) and renal tubular acidosis (n=10) were major renal tubular disorders, forty-four patients were identified with anorexia/bulimia nervosa (n=24), surreptitious use of laxatives (n=10) and diuretics (n=10). The urinary K⁺ excretion rates in patients with renal versus non-renal tubular disorders were significantly overlapped for making the diagnosis alone. Of note, unparalled urinary sodium (Na⁺) and chloride (Cl⁻) excretion with normal Na⁺/Cl⁻ ratio are unique to non-renal tubular disorders. Furthermore, body mass index, serum bicarbonate and magnesium levels, and urine pH were also helpful for the differential diagnosis.

Conclusions: Chronic hypokalemia due to non-renal tubular disorders is emerging and often clinically indistinguishable from those with renal tubular disorders. The integrative interpretation of urine electrolytes excretion rates, especially Na⁺ versus Cl⁻, is important to make a prompt and accurate diagnosis.

Funding: Private Foundation Support

Effect of Arterial pH and Bicarbonate Level on Survival of Lactic Acidosis

Disorders of Plasma Sodium in Hospitalized Patients and Effect of Total Plasma Protein Concentration on Its Measurement
Pedro J. Labrador, Silvia Gonzalez S, Santiago Polanco Candelario, Elena Davin Carrero, Jesus P. Marin, Ines Castellano, Juan R. Gomez-Martino. Nephrology, San Pedro de Alcantara Hospital, Cáceres, Spain.

Background: The aim of the study was the analysis of the prevalence of hyponatremia in hospitalized patients, and the effect of total plasma protein concentration on plasma sodium measurements.

Methods: We registered all biochemical analysis from in-hospital patients during one year. Data from age, sex, and department was recorded. Plasma Na was measured by an indirect ion selective electrode measuring system (Cobas 8000 analyzer, Roche Diagnostics). Hyponatremia was defined as plasma Na concentration lower than 135 mmol/L. Hyponatremia was classified based on plasma Na concentration. Mild hyponatremia was defined as 130-134 mmol/L, moderate as 125-129 mmol/L and profound as lower than 125 mmol/L. When TPP was measured, plasma Na concentration was corrected according to: Plasma Na (mmol/L) = Na (mmol/L) / [1 + 0.7 x (TPP concentration)] and by Plasma Na – indirect Na = 0.7 x (TPP concentration – 10).

Results: Our hospital is a 520 in-hospital beds. Plasma Na was measured in 26,904 biochemical analyses from 6,873 patients. Median age was 67 (IQR 50-79). 55.9% were men. Median plasma Na measurement was 5 (IQR 2-11). Hyponatremia was present in 1,514 patients (22%), mild hyponatremia 1,114 (16.2%), moderate 287 (4.2%) and profound 113 (1.6%). Plasma Na could be corrected to TPP in 3,122 patients, using the first formula hyponatremia was present in 29.4% (mild 19.6%, moderate 6.8% and profound 3%) while using the second one, 27.9% (mild 18.7%, moderate 6.4% and profound 2.8%).

Conclusions: Hyponatremia is present in one fifth of in-hospital patients. Correction of plasma Na concentration according to TPP concentration increase hyponatremia diagnostic up to 25%.

An Unusual Cause of Hyponatremia
Mohanad A. Hanounah, James F. Simon. Internal Medicine, Cleveland Clinic, Cleveland, OH; 2Glickman Urologic and Kidney Inst, Cleveland Clinic, Cleveland, OH.

Methods: A 59-year-old woman presented as a self-referral for a second opinion regarding hyponatremia. She had long-standing resistant hypertension currently treated with a diuretic and calcium channel blocker. Medical history included hypertension, type 2 diabetes, and hyperlipidemia.She had been treated for depression and developed depression complications during this hospitalization. She had chronic kidney disease along with mild hyponatremia. She was admitted due to possible hypokalemic polydipsia. She denied any use of diuretics, lithium or diuretic abuse, the last of which was most likely in this clinical situation. Suppression of both renin and aldosterone secretion after IVF confirmed the initial abnormalities were due to volume depletion.

Conclusions: Diuretic abuse should be considered when patients present with hyponatremia and hyponatremia. This case provides a rare insight into physiologic response of the renin-angiotensin system to diuretic abuse and volume resuscitation.
mortality adjusted for patients' characteristics and co-morbid conditions. We used random effects meta-analysis to derive pooled estimates of effect in medical, surgical and mixed admission settings.

Results: We evaluated 135 full text publications from 2,105 reviewed abstracts, of which 32 studies met the inclusion criteria (19, 13, and 5 reported aOR, proportion and both respectively). Patients with hyponatremia were at increased risk of hospital mortality (OR=2.59, 95% CI 1.5-4.47, P=0.001).

Figure 4: Mean serum Na levels before and after the activity.

Conclusions: Admission with serum Na of ≥145 mg/dl is significantly associated with twice the odds of hospital mortality. Protocols towards increasing awareness of hyponatremia and studies evaluating the efficacy of early intervention are warranted.

PUB446

Diagnostic Workup of Hyponatremia in Hospitalized Patients: Does Education Have an Impact? Farai Karimol. Ladan Golestaneh. Dept of Nephrology, Montefiore Medical Center, Bronx, NY.

Background: Hyponatremia is associated with poor outcomes. Studies show that hospitalized hyponatremic patients seldom get adequate diagnostic workups. This study tests the effects of a CME activity on physician’s behavior in the diagnostic workup of hyponatremia.

Methods: This is a cross-sectional analysis of patients admitted to the Internal medicine department at Montefiore Medical center between 05/01/2014 and 12/01/2014. Demographic and clinical data were collected retrospectively. Patients were included if they were admitted under the service of 24 hospitalist attendings. These attendings were implemented to improve hyponatremia workup as defined by the frequency of the following tests: serum osmolality, urine osmolality, and urine sodium. Hyponatremia was defined as the earliest serum sodium less than 135 mEq/dL. There was further subclassification into three groups based on the severity: mild- 130-135 mEq/dL, moderate- 125-130 mEq/ dL and severe: less than 125 mEq/L. Frequency of the diagnostic orders was stratified to be calculated after the activity.

Results: There were 358 patients with hyponatremia: 176 hyponatremia admissions occurred before the live lectures and 182 occurred after. Average age was 63±17, average length of stay was 5.2 days ± 2.9. The severity of hyponatremia was 82%, 14% and 3.4% for mild, moderate and severe, respectively. Forty eight percent of all patients who had hyponatremia at admission were discharged with hyponatremia. There was an increase in serum sodium between admission and discharge with a mean difference of 3.06 (95%CI, 2.63-5.5mg/dL). The mean duration of the 3 orders was 3.2, 19% and 50% in the pre-activity compared to 5.6% in the post-activity. The p value was <0.0001. The effect of activity was 130-135 mEq/dL, moderate- 125-130 mEq/ dL and severe: less than 125 mEq/L.

Funding: Pharmaceutical Company Support - Rockpoint LLC

PUB465

Characteristics and Initial Outcomes of a Multidisciplinary Renal Genetics Clinic (RGC) Andrew John Mallett,1,2,3 Helen G. Healy,1,2,3 Julie M. McQuaughan,1,3 Melissa H. Little,1,3,5 Chirag Patel,1,3,5 ‘Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane & Women’s Hospital, Brisbane, QLD, Australia; ‘School of Medicine, The Univ of Queensland, St Lucia, QLD, Australia; ‘School of Population Health, The Univ of Queensland, St Lucia, QLD, Australia; ‘Genetic Health Queensland, RBWH, Brisbane, QLD, Australia; ‘Murdoch Children’s Research Inst, Melbourne, VIC, Australia.

Background: Genetic Renal Disease (GRD) accounts for 10% of adults and 50% of children with end stage kidney disease. Advances in molecular genetic diagnostic testing and multidisciplinary renal clinic models suggest opportunities for clinical redesign. Here we describe the initial characteristics, experience and outcomes of the first Australian multidisciplinary RGC.

Methods: A retrospective audit was undertaken of the RBWH Adult Conjoint RGC (1st year of operation; Aug 13-Jul 14). Each encounter involved a nephrologist, clinical geneticist and genetic counselor.

Results: 278 patients (56%) encountered had a known GRD, 9/48 (19%) had a suspected GRD and 12/48 (25%) had an unknown GRD with positive family history (FHs). Patients were most commonly referred by nephrologists (66%). The most common GRD category & diagnosis were cystic kidney disease (49%) and Autosomal Dominant Tubular Aldosteronism (42%). The impact of clinical genetics was associated with GRD in 12/26 (48%). During consultations differential diagnoses were explored (54%), management

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

Underline represents presenting author.

PUB466

OTC Medication Leading to Chronic Salicylate Toxicity. Muhammad Deen, Roozi Khan. Nephrology, CHI St. Luke’s Health, Houston, TX.

Background: OTC medication containing salicylate leading to intoxication.

Methods: 60 YO F with PMH significant for chronic migraines, PUD s/p partial gastrectomy, presented to the ED with complains of nausea, vomiting, AMS, confusion and lethargy with headaches, timmness and decreased bilateral hearing. Patient was found to be tachyphic, diaphoretic with respiratory alkalosis and anion gap metabolic acidosis with normal renal function.

Vitals: BP 114/67mmHg, Pulse 90/min, Temp 97.6 °F, RR 22/min and SpO2 100%.

Examination: Unremarkable examination except AMS.

Figure 3: Admission with serum Na of ≥145 mg/dl is significantly associated with twice the odds of hospital mortality. Protocols towards increasing awareness of hyponatremia

Figure 4: Mean serum Na levels before and after the activity.

Conclusions: Admission with serum Na of ≥145 mg/dl is significantly associated with twice the odds of hospital mortality. Protocols towards increasing awareness of hyponatremia and studies evaluating the efficacy of early intervention are warranted.
advice provided (83%) and genetic counseling undertaken (79%). A genetic test was requested in 58.3%, most commonly being induced by combined diagnostic and genetic counseling reasons (78.6%). Of 12 returned genetic test results, 7 were positive and 1 was a variant of uncertain significance. Two negative results have prompted additional genetic testing. Of 27 patients referred with a known GRD, 6 now have a new suspected GRD. The majority of those referred with either a suspected (69) or unknown GRD diagnosis (10/12) now have a new suspected or confirmed GRD.

Conclusions: These findings demonstrate the early successful operation of this RGC model including diagnostic and genetic counseling benefit. Future assessment of clinical outcomes and expansion to telehealth and paediatric settings is anticipated.

PUB466
Characteristics and Clinicopathological Analysis of Japanese Nephronophthisis Patients Keisuke Sugimoto, Tomoki Miyazawa, Takuji Enya, Hitomi Nishi, Kohei Miyazaki, Hidehiko Yanagida, Mitsuura Okuda, Tsukasa Takeamura, Pediatrics, Kindai Univ Faculty of Medicine, Osaka, Osaka, Japan; 2Pediatrics, Kindai Univ Faculty of Medicine, Medulla Osaka, Osaka, Japan; 3Pediatrics, Kindai Univ Faculty of Medicine, Sakai, Osaka, Japan.

Background: Nephronophthisis (NPHP) accounts for 4 to 5% of end-stage renal disease (ESRD) occurring in childhood. Disease subtypes include infantile NPH1, which progresses to ESRD around the age of 3 years; juvenile NPH, which develops from early childhood to school age and usually progresses to ESRD by an age of 13 14 years; and adolescent NPH, with development of ESRD at an average age of 19 years. Juvenile NPH is reported to be the most common subtype.

Methods: We investigated clinical, histologic, and genetic features in 35 Japanese patients clinically and histologically suspected to have NPHP, aiming to promote early diagnosis. We studied many exons as many as 13 NPHP genes. Since such genetic analysis involves significant cost and time, we also screened biopsy specimens by immunohisto metric methods employing antibodies against relevant peptides.

Results: NPHP occurred fairly uniformly throughout Japan irrespective of region or gender. In 3 families, NPHP affected siblings. The median age of patients was 12.5 years. Renal abnormalities attributable to NPHP discovered through mass screening, such as urine tests in school, however, NPHP accounted for less than 50% of children with abnormal findings, including incidentally discovered renal dysfunction during evaluation of extrarenal symptoms or during routine check-ups. Typical extrarenal manifestations led to discovery including anemia and delayed physical development. The urine often showed low gravity specific density and low-molecular-weight proteinuria. Renal frequent histologic findings included cys tic dilation of tubules, mainly in the medulla, and irregularity of tubular basement membranes. Genetically abnormalities of NPH1 were not common, with large deletions found in heterozygotes showing single abnormalities in each of NPH1, NPH3, NPH4 were observed.

Conclusions: Our findings resemble those reported in Western populations.

PUB467
The Functional Role of the ARHGAP32 L405V Mutation on Cytoskeleton Guisun Li, Li Wang. Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, China.

Background: A site-directed mutagenesis for ARHGAP32 was developed to whether the mutation of ARHGAP32 has the effect on the related factors of cytoskeleton in vitro and to understand the functional role of ARHGAP32 in FSGS.

Methods: 1. Blood DNA of 110 FSGS patients proved by renal biopsy were sequenced and screened for the mutation of ARHGAP32. 2. Total exons sequencing were performed in 28 DNA samples to find out whether mutation of ARHGAP2and other genes were existed. 2.1 site-directed mutagenesis primers of ARHGAP32 was designed and amplified by PCR, obtaining the mutations of ARHGAP32 plasmids. 2.2 Transform the wild type and mutant plasmids of ARHGAP32 into Escherichia Coli respectively, sequenced the plasmids to identify whether the site-directed mutagenesis of ARHGAP32 was successful constructed. (3) Transfected the mutated plasmid of ARHGAP32 into 293T cells and real time RT-PCR. 3.1 Detected the expression of ARHGAP32 in FSGS, IgAN, MN, normal change disease and diabetic disease by IHC. 2.2) (2) The expression of ARHGAP32 in FSGS, IgAN, MN, minimal change disease and diabetic disease by IHC.

Results: 1. No mutation of ARHGAP32 was detected while 6 candidate genes were selected by sequencing all exons. 2. (1) ARHGAP32 gene was expressed mainly in glomerular in kidney tissue by IHC. 2. (2) The expression of ARHGAP32 and β-catenin by real time RT-PCR and western blots in 293T cells which were transfected with the wild type and mutant plasmids of ARHGAP32. 2.2) (2) The expression of Cdc42 and -catenin by real time RT-PCR and western blots in 293T cells which were transfected with the wild type and mutant plasmids of ARHGAP32.

Conclusions: 1. No mutation was detected in sporadic FSGS currently. 2. The mutation of ARHGAP32 had effect on the distribution of cytoskeletal protein of F-actin.

PUB468

Background: Hyponatraemia is the commonest electrolyte abnormality found in elderly hospitalized patients defined as a serum sodium concentration <135 mmol/L with a mean prevalence of 5%. (NDT 2003; 18: 2466). It is a risk factor for fractures due to unsteady gait as well as osteoporosis and bone fragility. Fractured necks of femurs (NOF) are a significant cause of morbidity and mortality in the elderly with an estimated 24% mortality at 1 year (JAMA 2001; 285: 2736).

Methods: Retrospective analysis of 501 patients from fractured NOF database from 1/1/2014 to 31/12/2014 to identify the incidence and severity of hyponatraemia, Chronic Kidney Disease(CKD) Stage and mortality at 30 days and 1 year.

Results: Mean age was 83 years and M:F ratio of 1:3. Mild-moderate hyponatraemia was found in 48% of patients (serum sodium of 126-134mmol/L) with only 3% suffering with severe hyponatraemia (< 126mmol/L). 31% of patients had CKD Stage 3, 5% Stage 4 and 2% Stage 5. 30-day and 1-year mortality was 7% and 18% respectively. Patients were separated into 3 groups based on natrema status.

Natraema status (mmol/L) 1 year survival (%)
<126 (severe) 0.643
126-134 (mild-moderate) 0.809
≥135 (normal) 0.841

Kaplan-Meier survival functions were calculated looking at 1-year mortality.

Those with hyponatraemia at the time of presentation appeared to have a worse 1-year survival. Log-rank test was performed. Using a chi-squared value of 3.521, a p value of 0.172 was obtained (not significant).

Conclusions: From our analysis it is clear that nearly half of patients on admission with fractured NOF have at least mild hyponatraemia with evidence to suggest reduction in 1-year survival. We propose more rigorous investigation of this subtle electrolyte disturbance in primary care which carries with it a significant morbidity and mortality.

PUB469
The Effect of Age on Mitochondrial Protein Levels in Rat Kidney Cortex and Medulla Marianna J. Zamauskis-Tucker, Natalya Mezenina, Cameron M. Behringer. Physiology & Health Science, Ball State Univ, Muncie, IN.

Background: The present study was undertaken to determine the effect of rat age on total protein levels in mitochondria from kidney cortex and medulla.

Methods: Young (3 months of age) and Old (22 months of age) female Lewis rats were used. The kidneys were harvested from anesthetized rats after being perfused with isotonic saline via a catheter in the abdominal aorta. The kidneys were separated into cortical and medullary sections and homogenized in isotonic saline. Differential centrifugation was used to isolate the mitochondrial pellet. The mitochondrial pellet was dissolved in distilled water and spun again at 10,000 rpm to isolate the mitochondrial protein pellet. The mitochondrial protein pellet was dissolved in 1 ml of 0.1 M sodium hydroxide. The protein concentration of the sodium hydroxide solution was measured using the Lowry Protein Assay. The protein concentration was expressed as mg protein/g kidney wet weight. Differences were evaluated using a Student’s t test.

Results: A significant decrease in the total mitochondrial protein level was observed in kidney cortex from Old rats. The total mitochondrial protein level in kidney medulla from Old rats was not significantly decreased.

<table>
<thead>
<tr>
<th>Mitochondrial Protein</th>
<th>Young (n=5)</th>
<th>Old (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>2.02 ± 0.42</td>
<td>0.59 ±0.30 *</td>
</tr>
<tr>
<td>mg/g kidney wet wt</td>
<td>Medulla</td>
<td>2.43 ±0.42</td>
</tr>
</tbody>
</table>

* Significantly different from the Young.
Conclusions: Total mitochondrial protein levels decrease in the cortex but not in the medulla of the rat kidney with age.

PUB470

Background: Prior research suggests that functional status in ESRD patients declines after initiation of dialysis, implicating the dialysis process in contributing to functional decline. We evaluated a dialysis-specific risk factor of intradialytic change in blood pressure (BP) in relation to changes in physical performance, a component of functional status.

Methods: We enrolled 29 dialysis patients aged ≥50 years. Participants completed a 4m timed walk to measure gait speed both pre and post predialysis and a Falls Efficacy Survey, a measure of concern for falls. Dialytic variables included BP measurements from pre, post and during dialysis along with ultrafiltration rate. Demographics and comorbid data was collected. Analysis evaluated for association between dialytic BP variables and change in gait speed and score on Falls Survey. Multivariate analysis was done to adjust for age, race, sex, diabetes and congestive heart failure.

Results: 28 participants completed the study. The mean age was 62.7 (12.3) years. The majority were male (70.4%) and hypertensive (86.2%). Diabetes was present in 55.2%. The mean (SD) change in gait speed from pre to post dialysis was -0.10 (1.01) m/s. The mean (SD) change in systolic and diastolic BP from pre to post dialysis was -10.6 (25.8) mmHg and -4.6 (10.5) mmHg, respectively. Participants with diabetes had greater intradialytic change with mean (SD) change of SBP + DBP of -26.9 (23.5) and -7.9 (11.3) and -4.6 (10.5) mmHg, respectively. Univariate analysis showed that every 10mmHg decrease in systolic BP and every 5mmHg decrease in diastolic BP was associated with a change in gait speed of -0.01m/s (p = 0.02) and -0.02m/s (p = 0.01), respectively. This association was no longer significant in multivariate analysis, likely due to correlation of change in BP with diabetes status. There was no association between BP change and Falls Survey score.

Conclusions: Decline in physical performance, as measured by gait speed, can be seen post dialysis and is associated with hemodynamic changes during dialysis. Patients with diabetes may be most susceptible to hemodynamic changes. Improving dialytic hemodynamic stability may be a way to reduce the significant functional impairment that occurs post-dialysis.

Funding: Private Foundation Support

PUB471
Sirtuin1 Expression in Kidney Tissue Specimens in Patients with IgA Nephropathy. Cetin Ozemre,1 Izret Hakki Arıkan,2 Ceren Ozcan,2 Derya Guler,2 Serhan Tuglular,2 Finlife Denizli.1 *Internal Medicine, Marmara Univ Hospital, Istanbul, Turkey; Nephrology, Marmara Univ Hospital, Istanbul, Turkey; Pathology, Marmara Univ Hospital, Istanbul, Turkey.*

Background: SIRT1 immune expression in renal biopsies samples of the patients with IgA nephropathy were evaluated to identify the possible role of SIRT1 on the pathogenesis of SIRT1 in IgA nephropathy.

Methods: Twenty eight patients 28 patients (16 women, mean age 37±13.8 years) were included. Biopsy specimens of the patients were evaluated according to Oxford Classification. Immunexpression of SIRT1, TNF-α, IL-10 and TGF-β were evaluated on kidney tissue specimens by immunohistochemical staining.

Results: Older age, and higher serum creatinine and uric acid levels were the predictors of a greater decline of the kidney function. There was a positive correlation between mesangial hypercellularity and uric acid levels. TGF-β (nuclear) and IL-10 (cytoplasmic) expressions were shown in 20 (71.4%) and 25 (89.3%) of the patients, respectively. Expression of the IL-10 was higher in patients who had a high average mesangial score. Tubular and weak (+) SIRT1 expression was present only in 7 patients.

Conclusions: A positive correlation was shown between mesangial hypercellularity with uric acid levels in the first time. These results suggest that SIRT1 does not play a direct role in the pathogenesis of IgA nephropathy.

Funding: NIDDK Support

PUB472
Response of Human Primary Renal Proximal Tubular Epithelial Cells to Different LPS Strains. Hong Wang, Margaret M. O’Neill, Carine Boustany, Steven S. Pullen. *CardioMetabolic Diseases Research, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.*

Background: Toll-like receptors are expressed on leukocytes and renal tubular epithelial cells where they regulate immune responses. Recent evidence has implicated renal TLR4 signaling in the pro-inflammatory response in diabetic nephropathy. Ligands for TLR4 include lipopolysaccharide (LPS) and HMGB1. We sought to explore the response of renal proximal tubular epithelial cells (PTEC) to different strains of LPS and HMGB1 as well as modulation by TLR4 antagonists.

Methods: The HK-2 human proximal tubular cell line was stimulated with 3 strains of LPS (S. minnesota, E. coli K12, E. coli 0111:B4) and HMGB1. Primary human PTEC were stimulated with 5 strains of LPS (S. minnesota, E. coli 0111:B4, E. coli 055:B5, E. coli K12, S. typhosa) and HMGB1. Supernatants were harvested and IL-1β, IL-6, IL-8, TNFα, and MCP-1 were detected. TLR4 antagonists EX 76233 and EX 76824 were tested for the ability to modulate cytokine production induced by LPS stimulation.

Results: In HK-2 cells, LPS from E. coli 0111:B4 induced IL-6 and IL-8 production, whereas, S. minnesota and E. coli K12 did not stimulate cytokine production. In PTEC, IL-6 and IL-8 production increased upon S. typhosa, and S. minnesota stimulation. Other strains of LPS did not stimulate production of IL-6 and IL-8 in PTEC. There was little detectable production of IL-1β, TNFα or MCP-1 under the conditions tested in both PTEC and HK-2 cells. HMGB1 induced IL-8 production in PTEC whereas HK-2 cells did not produce any of the cytokines or chemokines tested upon HMGB1 stimulation. The TLR4 antagonists EX 76233 and EX 76824 blocked cytokine production stimulated by S. typhosa in PTEC. EX 76824 inhibited IL-6 and IL-8 production stimulated by E. coli 0111:B4 in HK-2 cells.

Conclusions: Primary PTEC have unique responses to different strains of LPS, and this response profile differs from that of the HK-2 cell line. HMGB1 induced IL-8 production in PTEC whereas HK-2 cells did not respond to HMGB1 stimulation. These results highlight a limitation of using the HK-2 cell line in lieu of primary PTEC for interrogating the role of TLR4 in renal inflammation.

PUB473
Assessment of Serum Transforming Growth Factor-Beta 1 in Patients with Diabetic Nephropathy. Om Prakash Kalra,1 Avanish Shukla,1 Ashok Kumar Tripathi,1 Alpana Raizada.2 *Medicine, UCMS & GTB Hospital, Delhi, India; 1Biochemistry, UCMS & GTB Hospital, Delhi, India.*

Background: Diabetes mellitus is the leading cause of chronic kidney disease (CKD) worldwide. The pathogenesis and initial molecular events leading to diabetic nephropathy are still elusive. Chronic low grade inflammation plays an important role in pathogenesis of diabetic nephropathy. Ubiquitous cytokines like transforming growth factor-beta (TGF-β) function in an autocrine or paracrine fashion to elicit extra cellular matrix (ECM) accumulation and cellular hypertrophy in several cell types. TGF-β may play an important role in the pathogenesis of diabetic nephropathy by influencing ECM accumulation.

Methods: This was a case control, cross sectional study. 75 subjects aged 30 – 65 years of either sex were recruited and divided into three groups: Group I: healthy controls (n=25), Group II: patients of T2DM without nephropathy (n=25), Group III: patients of T2DM with nephropathy (n=25). Detailed history, complete physical examination, routine investigations, urine albumin creatinine ratio (ACR) estimation was done. Serum levels of hs-CRP and TGF-β1 were estimated by ELISA.

Results: A statistically significant difference in serum TGF-β1 and hs-CRP levels was observed between all the 3 groups (p<0.001), where highest levels were found in group III and lowest in group I. A positive correlation was observed between serum TGF-β1 and duration of diabetes, FBs, PPBS, HbA1c levels, serum creatinine, urinary ACR and serum hs-CRP. Similarly serum hs-CRP levels positively correlated with the duration of diabetes, FBs, PPBS, HbA1c levels, serum creatinine, and urinary ACR. Serum TGF-β1 and serum hs-CRP showed negative correlation with eGFR.

Conclusions: Overall, TGF-β1 and hs-CRP levels were significantly higher in diabetics as compared to non-diabetic subjects. They were higher in diabetic subjects with nephropathy as compared to those without nephropathy. Serum TGF-β1 and hs-CRP levels in diabetic subjects appear to be dependent on duration of diabetes, glycemic control and degree of renal dysfunction. Thus cytokines like TGF-β1 may play a role in the etiopathogenesis of diabetic nephropathy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PUB474

Daptomycin Antibiotic Lock Therapy for Hemodialysis Patients with Gram-Positive Bloodstream Infections following Use of Tunneled, Cuffed Hemodialysis Catheters. Retropective Single Center Analysis Hsung-Wen Yen, Szu-yuan Li. Dept of Medicine, Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Catheter-related blood stream infection (CRBSI) is a major complication in hemodialysis patients. We assessed the efficacy of systemic daptomycin (DPT) plus DPT antibiotic lock therapy (DPT-ALT) for catheter-salvage in patients with gram-positive CRBSI.

Methods: Study Design: Retrospective study of hemodialysis patients with tunneled, cuffed hemodialysis catheters. Setting & Participants: All patients were from a single institution in Taipei and received systemic DPT plus DPT-ALT for treatment of gram-positive CRBSI. Outcome: Successful resolution of CRBSI. Measurements: Resolution of fever within 48 h, negative result of repeated blood cultures after resolution of fever, no clinical evidence of CRBSI relapse, and no need for catheter removal.

Results: Fifteen hemodialysis patients received DPT-ALT for CRBSI, 9 with coagulase-negative Staphylococcus (CONS), 2 with methicillin-resistant Staphylococcus aureus (MRSA), 3 with methicillin-sensitive Staphylococcus aureus (MSSA), and 1 with polymicrobial infections. Systemic DPT plus DPT-ALT cured 11 patients (73.3%). Treatment failed in all 3 MRSA cases (2 with MRSA and 1 with MRSA + Enterococcus faecalis).

Conclusion: Daptomycin antibiotic lock therapy (DPT-ALT) appears to be a promising treatment for CRBSI from CONS and MSSA, but not for MRSA CRBSI. Systemic DPT plus DPT-ALT should be considered for patients with CRBSIs caused by certain species.

PUB475

The Association of the Type of Vascular Access and Erythropoietin Dose in Maintenance Hemodialysis Patients with Targeted Hemoglobin Level Fanoping Lu.1 Nephrology, First Hospital of Tsinghua Univ, Beijing, China; 2Blood Purification, Beijing Chaoyang Hospital, Beijing, China; 3Nephrology, The Third Hospital of Beijing Hospital, Beijing, China.

Background: Arteriovenous Fistula (AVF) is considered to be the preferential access for patients needing hemodialysis. It is called the “line of life” for these patients. Complications may occur even in autologous AVF or grafts (PTFE). Stenosis is the most frequent complication. Therefore thrombolysis is used for high morbidity, mortality, hospitalization, interruption of the treatment and access loss. The patient must go to angiography study immediately. We want to show that endovascular percutaneous technique with transluminal angioplasty through trans radial access (TRA) results in quick recovery, particularly in AVF thrombosis.

Methods: A 81-year-old man with a left brachiocephalic AVF for 5 years visited the ER with uremic symptoms, and right upper arm swelling, and pain. There was a thrombus in the brachiocephalic vein. Results: Successful cannulation was not possible through the arm. TRA was carried out with a 6Fr sheath and a 0.035” guide wire. A 6F sheath was used to perform an angiography which showed an AVF thrombosis. A 6F sheath was used for the TRA, a 2.5/8 mm angioplasty balloon was used, and it was inflated twice. There was no further AVF thrombosis. The patient was discharged 5 days later with improved symptoms.

Conclusion: Trans Radial Access for Percutaneous Treatment of Arteriovenous Fistula Thrombosis – 2 Cases

PUB476

Trans Radial Access for Percutaneous Treatment of Arteriovenous Fistula Thrombosis – 2 Cases Gunhila Sohal Velly,1 Enio Ziemiecki Junior,2 Heloísa Maria Chagas Rego,2 Maurício Da Silva Telles,1 Hemodialysis Unit, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil; 2Interventional Radiology Service, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.

Background: Arteriovenous Fistula (AVF) is considered to be the preferential access for patients needing hemodialysis. It is called the “line of life” for these patients. Complications may occur even in autologous AVF or grafts (PTFE). Stenosis is the most frequent complication. Therefore thrombolysis is used for high morbidity, mortality, hospitalization, interruption of the treatment and access loss. The patient must go to angiography study immediately. We want to show that endovascular percutaneous technique with transluminal angioplasty through trans radial access (TRA) results in quick recovery, particularly in AVF thrombosis.

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Conclusion: Trans Radial Access for Percutaneous Treatment of Arteriovenous Fistula Thrombosis – 2 Cases

PUB477

Incidence and Risk Factors for Cather Related Infections (CRI) and Their Antibiotics in Hemodialysis Patients – A South Indian Study Shruti Gupta,1 Shikara P. Mallya.2 1Microbiology, SGPJIMS, Lucknow, India; 2Microbiology, KMC, Mangalore, India.

Background: Bacterial infections particularly Staphylococcus species often complicate the vascular access in dialysis patients. This study was aimed to determine the incidence and associated risk factors for catheter related infections in patients on maintenance hemodialysis in a tertiary Hospital in South India.

Methods: Eighty-seven hemodialysis patients (56 M; 31 F) were enrolled in the study. After insertion of dual lumen catheter, patients were followed up till its removal. Nasal swabs were also collected before insertion. At each dialysis session, catheters were examined for any evidence of local infection or sepsis. In case of suspicion, the catheter tip was sent to microbiology laboratory and patients were empirically administered vancomycin. Data obtained was examined for relationship of CRI with clinical and socio-demographic risk factors.

Results: Fifty-three catheters (61%) showed colonization (<15 CFU). Twenty-four (45.2%) catheter tips were found to be colonized by S. aureus, 9 (17%) by P. aeruginosa, 5 (9%) by Acinetobacter, 4 (7.5%) by Enterobacter, 3 (5.6%) by Klebsiella, 2 (3.7%) each by E. coli and Citrobacter spp and one (1.9%) each by S. epidermidis, S. maltophilia, S. marcescens and C. albicans. Bacteremia was positive in 18(20.7%) patients and P. aeruginosa was the organism isolated in 17 (73.8%) episodes. Staphylococcal nasal carriage was seen in 60 (69%) patients, and 36 (41.4%) of these isolates were MRSA. Positive Statistically significant factors associated with CRI included history of bacteremia, presence of diabetes mellitus, long duration (>15 days) of catheterization and antibiotic use within 3 months (p < 0.05 for all). However, the age, gender and staphylococcal nasal carriage did not correlate with increased rate of infection.

Conclusion: P. aeruginosa is the most common organism in catheter related bacteremia which may have a bearing on our current antibiotic policy. Also, early initiation of hemodialysis through fistula may help reduce the CRI rate.
Analysis of Risk Factors of Death in Patients of Maintenance Hemodialysis with Tunneled Cuffed Venous Catheter

Li Zhou, Min Shi, Ping Fu
Nephrology/Medicine, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.

Background: To analyze the causes of death in patients of maintenance hemodialysis with tunneled cuffed catheter, and explore the risk factors of death.

Methods: All patients of maintenance hemodialysis with tunneled cuffed venous catheter starting hemodialysis from January 1, 2009 to December 1, 2014 in West China hospital were included and observed until June 1, 2015. The patients were divided into observation (death) and control group (survival). Multivariate logistic regression analysis was used.

Results: In total 94 hemodialysis patients who met the inclusion criteria, 24 cases died in the study period. The median age of dead patients was 73.4 years (51.5–96.4). The median time of hemodialysis was 19.20 months (3.17–56.27). Just 1 case replaced tunneled cuffed catheter for twenty three times in total. The main primary causes of renal disease were: CGN 54.3%, JDK 25.7%, HTN 43.3%, polycystic kidney disease 4.3%. Multivariate logistic regression analysis showed that elder age, infection, low serum albumin were risk factors of death. Replacement of tunneled cuffed catheter was not the risk factors for death.

Conclusions: The main causes of death of patients with maintenance hemodialysis by tunneled cuffed venous catheter were cardiovascular and cerebrovascular diseases and infection. Elder age, infection, lower level of serum albumin were risk factors of death in patients of maintenance hemodialysis with tunneled cuffed venous catheter. Replacement of DM (38.3% vs. 58.4%; p = 0.01), more AKI rather than ESRD as a cause of catheter insertion (42.6% vs. 25%; p = 0.02). The immediate complication rate including suturing at exit site for bleeding control was higher in the exchange group (19.1% vs. 8.7%; p = 0.03), but the late complication rate including infection and catheter dysfunction was higher in the de novo placement group (21.6% vs. 8.5%; p = 0.04). The catheter survival rates between two groups were comparable (p = 0.58) and multivariate Cox regression analysis for catheter survival showed the development of late complication was the only risk factor (odds ratio [OR] 1.391, 95% confidence interval [CI]: 1.017–1.901; p = 0.039) rather than the exchange procedure was not a risk factor (OR 0.878, 95% CI: 0.554–1.393; p = 0.582).

Conclusions: The exchange over the guidewire from a previous tunneled catheter to a new one should be positively considered and performed when the new tunneled catheter placement is required.

Exchange Technique Using Previous Venotomy Site Over the Guidewire From Non-Tunneled to Tunneled Hemodialysis Catheter Can Be Performed without Compromising Catheter Long Term Patency

Woo Jeong Kim, Min Seok Choi, Hoong Soh Park, Sung Jun Kim, Byeong Ha Chung, Hyoung Wook Kim, Bum Soon Choi, Cheol Whee Park, Chul Woy Yang, Dong-Chan Jin
Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ. Korea.

Background: The exchange from non-tunneled HD catheter to tunneled one over the guidewire using previous venotomy site does not require time for hemostasis for a new tunneled catheter insertion after its removal. It also does not require a new venipuncture so that it can prevent additional vessel wall injury. However, some concerns that it may be associated with increased risk of infection and bleeding after procedure prevention is required.

Methods: From March in 2009 to March in 2013, 47 cases where the exchange from non-tunneled to tunneled catheter and 310 cases with de novo placement groups were respectively assigned to exchange and de novo placement groups and they were compared.

Results: Compared with the de novo placement group, the exchange group over the guidewire had a higher hemoglobin level (10.6 ± 1.6 g/dl vs. 10.3 ± 1.7 g/dl; p = 0.001), more females (69.6% vs. 48.1%; p = 0.006), more ESRD rather than AKI as a cause of catheter insertion (95.7% vs. 74.8%; p = 0.002). Both immediate complication rate including suturing at exit site for bleeding control (19.6% vs. 8.7%; p = 0.02) and late one including infection and catheter dysfunction were higher in the exchange group (21.6% vs. 8.5%; p = 0.04). The catheter survival rates between two groups were comparable (p = 0.58) and multivariate Cox regression analysis for catheter survival showed the development of late complication was the only risk factor (odds ratio [OR] 1.391, 95% confidence interval [CI]: 1.017–1.901; p = 0.039) rather than the exchange procedure was not a risk factor (OR 0.878, 95% CI: 0.554–1.393; p = 0.582).

Conclusions: The exchange over the guidewire from a previous tunneled catheter to a new one should be positively considered and performed when the new tunneled catheter placement is required.
Utility of Arterio-Venous Fistula Flow and Doppler Ultrasound in the Prevention of Thrombosis of the Vascular Access

Background: A Multidisciplinary Unit for attention to the vascular access was established in our hospital in December 2010. The main role of the nephrologist consists in monitoring the functioning of the vascular access by determining the arterio-venous flow (AVF) and undertaking the doppler ultrasound. The objectives for initiating this program were to reduce the thrombosis rate by diagnosis and treatment of a non clinically detected pathology and to decrease the percentage of patients with a tunnelled catheter.

Methods: The prevalence of haemodialysis patients on 31st December 2014 was 65 patients in the Hospital Unit and 90 patients in the Dialysis Center. In the Hospital Unit we supervise the functioning of the vascular access by measuring the AVF flow and we perform a Doppler ultrasound study if the flow is less than 500 ml/min, if there are significant decreases in comparison with previous controls or if there is any clinical dysfunction. The Dialysis Center uses first generation methods for monitoring (increase in venous pressure, pump flow decrease, recirculation) and requests the Hospital Unit to undertake a Doppler ultrasound study whenever there is any type of dysfunction.

Results: We have observed differences in the results between both centers: 1° Incidence of patients with a tunnelled catheter was lower in the Hospital Unit (14 vs 22%). 2° Thrombosis rate was 40% lower in the Hospital Unit (7.9 vs 12/100 patients-year). 3° Doppler ultrasound detected 25 patients with haemodynamically significant stenosis, confirmed by radiologic study, which were successfully treated.

Conclusions: The combined use of AVF flow measuring and doppler ultrasound studies for monitoring the vascular access is an efficient method for reducing the rates of thrombosis and the number of tunnelled catheters due to the early detection of stenosis and its preventive treatment.

Females Have Less Arteriovenous Fistula and More Grafts Compared to Men: Data from the Slovenian Renal Replacement Therapy Registry

Background: The aim of our study was to compare prevalence of arteriovenous fistula (AVF) and graft in female and male chronic haemodialysis (HD) patients.

Methods: Data on vascular access in prevalent HD patients on December 31, from 2009-2013, were analyzed, in addition to sex, age, dry body weight and blood flow (QB) during HD, from database of the Slovenian Renal Replacement Therapy Registry. The use of preoperative ultrasonography mapping before AVF and graft construction in standard practice in the country.

Results:

<table>
<thead>
<tr>
<th>Year</th>
<th>2013</th>
<th>2012</th>
<th>2011</th>
<th>2010</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HD (No)</td>
<td>1375</td>
<td>1361</td>
<td>1346</td>
<td>1375</td>
<td>1397</td>
</tr>
<tr>
<td>Males</td>
<td>831</td>
<td>837</td>
<td>824</td>
<td>818</td>
<td>827</td>
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<tr>
<td>Males age (years)</td>
<td>64±14</td>
<td>64±14</td>
<td>63±14</td>
<td>63±14</td>
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</tr>
<tr>
<td>Males % AVF</td>
<td>82.8</td>
<td>81.8</td>
<td>83.5</td>
<td>85.0</td>
<td>84.6</td>
</tr>
<tr>
<td>Males % grafts</td>
<td>7.2</td>
<td>7.1</td>
<td>5.0</td>
<td>5.5</td>
<td>4.5</td>
</tr>
<tr>
<td>QB (ml/min)</td>
<td>287±35</td>
<td>287±39</td>
<td>290±39</td>
<td>290±44</td>
<td>295±44</td>
</tr>
<tr>
<td>Females</td>
<td>544</td>
<td>524</td>
<td>522</td>
<td>557</td>
<td>570</td>
</tr>
<tr>
<td>Females age (years)</td>
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<td>67±15</td>
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<tr>
<td>Females % AVF</td>
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<tr>
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<td>7.9</td>
<td>7.5</td>
<td>7.5</td>
<td>7.7</td>
</tr>
<tr>
<td>QB (ml/min)</td>
<td>273±35</td>
<td>274±38</td>
<td>275±38</td>
<td>271±40</td>
<td>277±41</td>
</tr>
</tbody>
</table>

The difference between percentage of AVF comparing females and males is persistent and highly significant during the observation period (p<0.001), with females having less AVF. Females had persistently slightly more grafts. Males had higher mean dry body weight (77.1±11.6 kg vs. 64.7±14.7 kg, end of 2013, p<0.001). Although absolute blood flow during HD was higher in males, females had higher blood flow when standardised to body weight (4.41±1.03 vs. 3.83±0.83 ml/min/kg, p=0.001, end of 2013).

Conclusion: Females chronically have significantly less arteriovenous fistula and slightly more grafts compared to males, with the difference being persistent during five years. Blood flow during HD, when standardised to body weight, was significantly higher in females than in males. Potential clinical consequence of higher blood flow during HD in females is the lack of unexplained variation which is increasingly had seen in patients on AVF where we are waiting to intervene.

Waiting Too Long to Intervene

Background: A number of patients with newly created arteriovenous fistulae (AVF) require tunnelled dialysis catheter (TDC) for dialysis until their AVF is deemed mature. Although data have emphasized that the AVF maturation period is 4-6 weeks long, providers often wait up to 6 months hoping the AVF will eventually mature. During this maturation period if dialysis is required, patients frequently use TDC and can experience complications associated with these devices. This retrospective study evaluated 43 ESRD patients with a maturing AVF who were dialyzing with a coexisting TDC placed within 3 months of AVF creation. The patient population was divided based on dual access (DA) duration: DA<42 days (n=10), DA=42-90 days (n=13), and DA>90 days (n=20). An analysis of DA duration and follow-up visits were performed. All patients had surgical follow-up at least once within the first 42 days of AVF placement regardless of DA duration. Additionally, patients with a DA duration greater than 90 days were evaluated consistently by a surgeon once within the first 42 days of AVF placement regardless of DA duration. Despite this, patient with DA period of greater than 42 days had increasing propensity to undergo avoidable exposure to the risks of prolonged TDC use (p<0.01). Specifically patients with DA>42 days, DA=42-90 days, and DA>90 days were unnecessarily exposed to the risks of dual access for an additional 2.5, 11.7, and 46 days, respectively (p<0.01). This discrepancy between regular surveillance and delayed TDC removal raises concerns that there is a lack of timely intervention after assessment. A more thorough documentation of reasons for prolonged TDC use and analysis of such data are required to verify this hypothesis and get a better idea of etiology of delayed TDC removal.

Methods: Retrospective collection of data from outpatient dialysis units on patients who have AVF/Graft and TDC.

Results: The delayed TDC removal in patients with AVF/Graft the risk of infection in these patients with both devices.

Conclusions: TDC should be removed at an appropriate period once AVF/Graft are mature enough to be used.

Gene Methylation Profile of Human Vein Tissues Taken at the Time of Surgery: Correlation with AVF Maturation

Background: Early arteriovenous fistula (AVF) failure remains an important cause of hemodialysis vascular access dysfunction and a major impediment to the Fistula First initiative. Despite the magnitude of the clinical problem, there are currently no effective therapeutic interventions for early AVF failure. In order to better understand the cellular and molecular mechanisms involved in early AVF failure we have evaluated the gene methylation profile of venous segment tissue samples obtained at the time of AVF creation. DNA methylation of Cpg islands (regions of the genome that are rich in cytosine and guanine sequences), influences gene expression (turns off the gene). An increasing number of diverse factors are now known to epigenetically regulate genes, including stress, inflammation, nutrition, metabolism, drugs and infection (all of which are prominent in the biological milieu of patients with CKD and ESRD). In this study we compare the overall methylation profiles of non-maturing AVFs at 6 months as compared to AVFs that are able to support dialysis.

Methods: gDNA was isolated from venous segments collected at the time of AVF creation. Deep sequencing technologies were used to identify genes with the greatest differences in methylation between the two groups. Gene networks focused on inflammation, oxidative stress and endothelial dysfunction were evaluated. Standard bioinformatic techniques were used to identify/interrogate both the gene list and the network analyses.

Results: We were able to identify approximately 300 genes that were significantly different in the overall methylation profiles of non-maturing AVFs at 6 months as compared to AVFs that were able to support dialysis.

Conclusions: Our results suggest that epigenetic regulation (DNA methylation) could play an important role in AVF maturation, and also in the identification of novel druggable targets. This latter point could result in the development of novel therapies for dialysis vascular access dysfunction as a whole.

Development of a Uremic Pig Model of Arteriovenous Fistula Stenosis (AVF): A Surgical Approach

Background: AVF stenosis remains an important cause of hemodialysis vascular access dysfunction for which there are no truly effective therapies. We and others have previously described well characterized large animal models of AVF stenosis. An important flaw in these models is that the pigs are not uremic, which is an important factor in the pathogenesis of AVF stenosis.

Methods: Chronic renal insufficiency was created by initially removing one of the kidneys through a midline incision. Following this the contralateral kidney underwent a dissection of the renal vasculature to expose all the major branches of the renal vasculature. A selective ligation of the renal vasculature in the pelvis,
which allowed for the viability of less than 20% of the renal mass on one side was then performed (upper figure = a, b, c). Of note the differential backbleeding/motting of the kidney following ligation of vessels in the renal pelvis, allows us to perform a real time assessment in terms of the amount of viable renal tissue. BUN and creatinine estimations were then made biweekly for 6 weeks.

Results: The described surgical technique has allowed us to achieve a stable creatinine of 4 mg/dL over a four week period (lower figure = d). This stable period of uremia will allow us test out the impact of “downstream uremic vescular biology” on AVF maturation.

Conclusions: We have developed a unique, innovative and surgically created pig model of uremia with potential logistic and financial benefits. The availability of this animal model will put us in a unique position to be able to tease out the relative contributions of hemodynamics and uremia to AVF stenosis both in our experimental pig model and also in CKD and ESRD patients.

Multimedia Education Tools for Dialysis Vascular Access Monitoring

Tushar J. Vachharajani, 1 Claudia L. Poole, 2 Victoria L. Cash, 2 Joseph A. Vassalotti, 1 Nephrology, W. G. (Bill) Hefner VAMC, Salisbury, NC; 2Fistula First Catheter Last Workgroup Coalition, ESRD National Coordinating Center; 1Nephrology, Icahn School of Medicine at Mount Sinai & National Kidney Foundation, NY.

Background: From 2005 to 2012, the Fistula First Breakthrough Initiative (FFBI) of the Centers for Medicare & Medicaid Services focused on improving the arteriovenous fistula (AVF) rate in the hemodialysis (HD) patients. Since the transition to Fistula First Catheter Last (FFCL) in 2013, the workgroup has created multimedia tools to help dialysis facilities and clinicians reduce the use of central venous catheters (CVCs) and further increase AVF use. The key focus for FFCL remains access planning, access monitoring (physical examination) and the multidisciplinary dialysis care team (DCT) with the ultimate goal of achieving freedom from CVC. Two separate toolkits available on the FFCL website (http://esrdncc.org/ffcl) highlight patient-level and DCT-level education.

Results: The multimedia toolkits are interactive and easily accessible from any mobile device. Conventional handout/poster formats are also available. The impact of these educational tools will be evaluated once these resources are widely utilized in clinical practice. The primary goal is to develop and disseminate tools to educate and create awareness to increase AV fistula utilization to 68% of appropriate patients, decrease the use of long term catheters (<90 days) to <10%. FFCL is currently collecting metrics on professionals that are aware and using these tools.

Conclusions: The purpose of this presentation is to achieve wider dissemination of these tools and increase awareness among patients/professionals.

Multimedia Access Planning Tools to Attain Catheter Freedom

Tushar J. Vachharajani, 1 Claudia L. Poole, 2 Victoria L. Cash, 2 Joseph A. Vassalotti, 1 Nephrology, W. G. (Bill) Hefner VAMC, Salisbury, NC; 2Fistula First Catheter Last Workgroup Coalition, ESRD National Coordinating Center; 1Icahn School of Medicine at Mount Sinai & National Kidney Foundation, NY.

Background: From 2005 to 2012, the Fistula First Breakthrough Initiative (FFBI) of the Centers for Medicare & Medicaid Services focused on improving the arteriovenous fistula (AVF) rate in the hemodialysis (HD) patients. Since the transition to Fistula First Catheter Last (FFCL) in 2013, the workgroup has created multimedia tools to help dialysis facilities and clinicians reduce the use of central venous catheters (CVCs) and further increase AVF use. The key focus for FFCL remains access planning, access monitoring (physical examination) and prevention of access infection.

Methods: Why the need for change? FFBI Change Concepts over the past decade resulted in an increase in the AVF rate in the prevalent HD population from 23% to 61% of eligible patients. The impact on the incident HD population has remained suboptimal, with >78% HD patients initiating dialysis with a tunneled CVC. Moreover, the percentage of patients in the prevalent HD population with CVCs in use for 90 days or longer has remained stagnant. Access planning tools: FFCL tools are created to educate the patient and the multidisciplinary dialysis care team (DCT) with the ultimate goal of achieving freedom from CVC. Two separate toolkits available on the FFCL website (http://esrdncc.org/ffcl) highlight patient-level and DCT-level education.

Results: The multimedia toolkits are interactive and easily accessible from any mobile device. Conventional handout/poster formats are also available. The impact of these educational tools will be evaluated once these resources are widely utilized in clinical practice. The primary goal is to develop and disseminate tools to educate and create awareness to increase AV fistula utilization to 68% of appropriate patients, decrease the use of long term catheters (<90 days) to <10%. FFCL is currently collecting metrics on professionals that are aware and using these tools.

Conclusions: The purpose of this presentation is to achieve wider dissemination of these tools and increase awareness among patients/professionals.
There was a steep relationship between weekly Kt/V and B2M in all three modalities. The steepness of this relationship was similar between HD and SF across RRF values, but differed for RRF=4ml/min in LD. At any given level of Kt/V the B2M level depended on RRF and dialysis modality.

Conclusions: Weekly B2M Kt/V, a simple measure of middle molecule dialysis adequacy, tracks middle molecule exposure in conventional and daily dialysis. The interpretation of a given Kt/V value requires knowledge of RRF in all dialysis modalities. Future studies should determine whether RRF, diaclytic Kt/V or both are predictors of survival in daily dialysis.

PUB492

A Test Battery to Establish Changes in Physical Performance and Protein Energy Wasting in Nocturnal Hemodialysis: The DiapriFIT Study

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Background: Nocturnal hemodialysis (NHD) improves volume control and phosphate and middle molecule removal. Observational data show increases in body weight and protein intake upon switching to NHD. Other aspects of protein energy wasting (PEW) remain underexplored and also little is known about functional outcomes, such as physical performance and muscle strength. Therefore, the aim of this study is to investigate whether physical performance improves and PEW decreases in patients who change from conventional hemodialysis (CHD) to NHD, compared to patients who continue their treatment on CHD.

Methods: The DiapriFIT study plans to include 25 patients on CHD (2-4x/wk, 3-4 hours) and 25 patients on CHD who switch to NHD (3-4x/wk, 8 hours) with 1-year physical performance and PEW as endpoints. They were submitted to a Visual Appetite Score (VAS), Handgrip Strength (HGS), upper arm circumference (UAC), Short Physical Performance Battery (SPPB) and 6 minute walk test (6MWT), baseline results are reported here. As in NHD weight increases, we tested associations of the outcome parameters with dry weight.

Results: At present, 23 patients were included, aged 58.3±16.0 years, 30.4% males, with a dry weight of 87.6±17.2 in males and 74.3±17.2 in females. Mean VAS was 7.3±2.3, HGS 22.7±5.6 cm, UAC 8.0±2.3, SPPB 8.0±1.9 and 6MWT 576±328 meters. Only HGS and UAC were correlated with HD dry weight (r 0.43, p<0.05 for HGS, r 0.79, p<0.001 for UAC).

Conclusions: The DiapriFIT Study measures a great variety of parameters regarding physical performance and PEW. As some, but not all parameters correlate with HD dry weight, we expect them to differentiate between CHD and NHD during follow-up of the study. Other results of physical performance and PEW, such as subjective global assessment, physical activity, sleep, and QOL-questionnaires, activity monitoring, body composition measurement, nutritional diary, DEXA and lab tests will provide additional information on these patient-relevant outcomes of NHD.

Funding: Pharmaceutical Company Support - Baxter U.S.

PUB493

Anti-Thymocyte Serum Nephritis Rats Developed Augmented Circadian Rhythm of the Intrarenal Renin-Angiotensin System

Rats were sacrificed every 6 hour and the levels of the intrarenal RAS components were evaluated.

| protein expression levels of intrarenal AGT, AngII and AT1R proteins were made| increased in A group compared with C group and attenuated in AO and AH group (Peak trough ratios of AGT in C: 1.13, A: 1.47, AO 1.24, AH 1.17, AngII in C: 1.03, A: 1.26, AO: 1.14, AH: 1.17 and AT1R in C: 1.36, A: 1.51, AO: 1.37, AH: 1.26). However, renal function, proteinuria and augmentation of intrarenal RAS components were attenuated only in AO group. The protein expression levels of intrarenal renin and protein were the same tendency as AGT, AngII and AT1R, though fluctuation of them was attenuated in AO group. The protein expression levels and fluctuation of angiotsin converting enzyme and (pro)renin receptor were not different among groups.

Conclusions: Intrarenal AGT, AngII and AT1R proteins were increased and the amplitude of oscillations of these proteins was augmented in ATP-knell nephritis rats. Furthermore, renal damage may be linked to the activation of the intrarenal RAS independent of amplitude of its oscillation and BP.

PUB494

Do KCNQ1 Channels Contribute to Control of Arterial Vascular Tone?

Dmitry Tsvetkov,1 Ian Chan,1,2 Mario Kassmann,1 Jean-Yves Tan,1 Johanna Schliebenbaum,1 Jakob Volkl,1 Florian C. Lang,1 Yu Huang,4 Maik Gollasch,1 1Experimental and Clinical Research Center (ECRC), a Joint Cooperation between the Charité Medical Faculty and the Max Delbrück Center for Molecular Medicine (MDC), Berlin, Germany; 2Xiamen Zhongshan Hospital, Xiamen Univ, Xiamen, Fujian Province, China; 3Dept of Physiology, Univ of Tübingen, Tübingen, Germany; 4School of Biomedical Sciences, Lo Kwee-Seong Integrated Biomedical Sciences Building, Area 39, Chinese Univ of Hong Kong, Hong Kong, Hong Kong.

Background: Recent data suggest that the KCNQ family of voltage activated K+ (K7) channels represents a new therapeutic target in cardiovascular disease. We used KCnq1-/- mice to determine whether KCNQ1 (K7.1) play a role in the regulation of arterial tone.

Methods: Wire-myography, pharmacology approach and patch-clamp techniques were used.

Results: We found that R-L3 produces similar concentration-dependent relaxations (EC50 =1.6 µM in wild-type (Kcnq1+/+) and KCnq1-/- arteries pre-contracted with either phenylephrine or 60 mM KCl. This relaxation was not affected by 10 µM chromanol-B293, 10 µM HMR1556, 30 µM XE991 or 500 µM 4-aminopyridine. Chromanol-B293 and HMR1556 did not affect the anti-contraction effects of perivascular adipose tissue (PVAT). The anti-contraction effects of PVAT were normal in Kcnq1-/- arteries. Whole-cell recordings showed normal peak K, currents, capacity and their blockade by XE991 in Kcnq1-/- VSMCs. The pan KCNQ2-5 opener retigabine lead to a similar relaxations in Kcnq1-/- and wild-type vessels.

Conclusions: We conclude that KCNQ1 channels are apparently not involved in the control of arterial tone by alpha, adrenergic vasoconstrictors and PVAT. R-L3 is an appropriate pharmacological tool for studying the function of native vascular KCNQ1 channels in mice.

PUB495

The Role of Renal AT1 Receptor-Associated Protein in Salt-Sensitive Blood Pressure Regulation

Hiromichi Waku,1 Kouichi Tamura,1 Ryu Kobayashi,1 Kazuaki Ueseda,1 Masato Ohawa,1 Toru Dejima,1 Akinobu Maeda,1 Yoshiyuki Toya,1 Kotoro Haruhara,1 Satoshi Umemura.1 1The Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan; 2Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.

Background: The intrarenal renin-angiotensin system plays a role in the regulation of renal hemodynamics and the maintenance of water electrolyte balance, and is also involved in the pathophysiology of hypertension and target organ damages. We previously identified an angiotensin II type 1 receptor-associated protein (ATRAP), which interacts with the C-terminal domain of angiotensin II type 1 receptor (AT1R) and attenuates AT1R-mediated pathological responses. The present study was designed to investigate the putative functional role of ATRAP in the blood pressure regulation by high salt loading in vivo.

Methods: We generated transgenic mice expressing ATRAP dominantly on renal tubules on a C57BL/6J background. Renal ATRAP transgenic mice and their wild-type littermate mice on a normal salt diet at baseline were subjected to dietary high salt loading for 7 days. Results: In renal ATRAP transgenic mice, the development of high blood pressure was suppressed when salt loaded, thereby suggesting ATRAP to be an interesting target in hypertension.

Funding: Private Foundation Support, Government Support - Non-U.S.
**PUB496**

**Carbonic Anhydrase II Inactivation Confers Salt Appetite and Elicits Salt Sensitive Hypertension**

Mujian Varashteh kia, Sharon L. Barone, Saeed Alishahrami, Marybeth Brooks, Kaymar A. Zahedi, Jie Xu, Manoocher Soleimani, Center on Genetics of Transport, Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; Research Services, VA Medical Center, Cincinnati, OH.

**Background:** Salt appetite or salt intake in excess of physiological needs is a major health problem and a risk factor in the pathogenesis of hypertension, which consequently can lead to heart disease and stroke. Few genetic factors are implicated in the pathogenesis of salt appetite.

**Methods:** Wild-type and CAII null mice were given a choice of regular water or 140mM NaCl dissolved in their drinking water. Balance studies were performed and blood pressure was measured via the CODA tail cuff system. Western blots and Northern Hybridizations were performed.

**Results:** Our results indicate that CAII null mice display significant salt appetite as judged by their preference for salted water (140 mM NaCl) over regular water, when both options are provided. In age and gender matched mice (n=4 per each group), daily salted water intake was 2.89 ml in WT vs. 5.71 ml in CAII null mice, while daily regular water intake was 5.05 ml in WT and 3.6 ml in CAII null mice. Kidney renin expression and blood creatinine concentration were comparable in WT and CAII null mice. When given only salted water, CAII null animals showed a robust increase in their daily salt intake (12.21ml in CAII null vs. 7.80ml in WT mice) and urine volume (4.62ml/day in CAII null vs. 2.62ml/day in WT mice). Expression of sodium and water absorbing channels, ENaC and AQP-2, increased by ~100 to 200% in both cortex and medulla in CAII null vs. WT mice in response to salt intake for 10 days. Consequently, CAII null mice developed hypertension (systolic BP of 155 +/- 3.9 in CAII null vs. 138 +/- 3.2 in WT, p<0.003). The protein expression levels of ENaC in taste buds were not different between the two genotypes. Male CAII null mice exhibited a remarkable propensity toward salted water intake vs. regular water intake as compared to female null mice.

**Conclusions:** We propose that CAII plays an important role in regulating salt intake and its inactivation can cause salt appetite, specifically in male animals, and provoke salt sensitive hypertension.

**Funding:** Veterans Administration Support

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**PUB497**

**Ambulatory Blood Pressure in Chronic Kidney Disease: An International Collaborative Study**

Paul E. Drazner, Luca De Nicolia, Naohiko Fujii, Francis B. Gabbai, Jennifer J. Gassman, Satoshi Iimuro, Roberto Minutolo, Robert A. Phillips, Luis M. Ruijope, Raymond R. Townsend, Mahboob Rahman, Div of Renal Diseases & Hypertension, Univ of Minnesota; Italian Cohort; CKD-JAC; AASK; Spanish Cohort; CRIC.

**Background:** In chronic kidney disease (CKD), ambulatory blood pressure (BP) is a better measure of hypertension related risk for cardiovascular disease and ESRD than clinic BP. The International Ambulatory Blood Pressure in Chronic Kidney Disease Collaborative Group is a collaboration among investigators from different countries interested in ambulatory BP in patients with CKD. The main aims of the research facilitated by this collaboration will be to evaluate: 1) the clinical and demographic characteristics associated with elevated ambulatory BP, 2) the prognostic role of ambulatory BP on cardiovascular and renal outcomes, and 3) ethnic and geographic differences in these associations.

**Methods:** This group will establish a large database derived from individual databases in the various countries to allow for powerful individual participant data meta-analyses of the relationship between clinical and demographic characteristics, CKD severity, ambulatory BP, and clinical outcomes.

**Results:** Investigators from 5 cohort studies have already agreed to participate. Characteristics of the cohorts are shown below.

<table>
<thead>
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<td>Age (years)</td>
<td>64.4</td>
<td>69.3</td>
<td>60.3</td>
<td>63.1</td>
<td>60.7</td>
</tr>
<tr>
<td>Male/Female</td>
<td>290 / 199</td>
<td>2630 / 1804</td>
<td>382 / 235</td>
<td>853 / 659</td>
<td>682 / 393</td>
</tr>
<tr>
<td>eGFR</td>
<td>44.8</td>
<td>45.5</td>
<td>43.5</td>
<td>46.1</td>
<td>28.8</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>63%</td>
<td>16%</td>
<td>30%</td>
<td>42%</td>
<td>86%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>176 (36%)</td>
<td>1385 (31%)</td>
<td>63 (19%)</td>
<td>626 (42%)</td>
<td>381 (35%)</td>
</tr>
<tr>
<td>a. Urine protein /015g/day</td>
<td>b. Urine albCr /50mg/g</td>
<td>c. Urine proCr /0.22mg/mg</td>
<td></td>
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</tr>
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</table>

**Conclusions:** This multi-national collaboration will provide greater insights than possible from within-country analyses into the etiology and consequences of high risk ambulatory BP profiles. This information will be instrumental in helping us design prospective international large scale multicenter trials aimed at reducing renal and cardiovascular events in patients with CKD.

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**PUB498**

**Clinical Study of Pregnancy Related Kidney Injury**

Yumei Liu, Ying Fan, Yang Fei, Hongda Bao, Yajuan Huang, Niansong Wang, Nephrology and Rhenumatology, Shanghai Jiao Tong Univ Affiliated Sixth People’s Hospital, Shanghai, China; Obstetrics and Gynecology, Shanghai Jiao Tong Univ Affiliated Sixth People’s Hospital, Shanghai, China.

**Background:** The diagnosis and treatment of pregnancy related kidney injury is a complicated clinical problem for obstetricians and nephrologists. However, information regarding this topic in China is insufficient.

**Methods:** Totally 18589 women hospitalized between August 2004 and January 2013 from Obstetric and Nephrology Department in Shanghai Jiao Tong University Affiliated Sixth People’s Hospital were screened. 569 women were enrolled for the pregnancy related kidney injury, including 494 cases from 2008 to 2013 and 75 cases from 2004 to 2007. The inclusive criteria was women with a history of kidney disease or Scr >= 70mmol/L or proteinuria >= 0.3g/24hour before the termination of pregnancy, or the diagnosis of kidney disease made during or after 6-month delivery.

**Results:** The prevalence of pregnancy related kidney injury was 3.1%. The incidence of kidney injury caused by obstetric disease was 3.1%, with the most common reason for pre-eclampsia (88.9%). The incidence of chronic kidney disease women with pregnancy is 0.74%, with the most common reason for chronic glomerular nephritis (36.2%). The incidence of kidney disease onset related to pregnancy was 1.5%. The incidence of proceeding to end stage renal disease for pregnancy was 0.21%. Kidney injury in pregnant women with obstetric disease may be more severe than that in pregnant women with kidney disease (with higher maternal blood pressure and proteinuria, lower birth weight and higher proportion of pre-term babies, P<0.05). Most women with pregnancy related kidney injury underwent cesarean section (>60%). Their proportion of stillbirth, pre-term and low birth weight babies were higher than healthy parturient, and the proportion of follow-up was low (9.9%). Neonatal death rate was 0.63% and pare-natal death rate was 2.1% in all.

**Conclusions:** Prevalence of pregnancy related kidney injury increases due to the foundation of Shanghai First-Aid Center for High-risk Pregnant Women in 2007. Serum creatinine, proteinuria and blood pressure have different indication for maternal condition and pregnancy outcome.

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

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**PUB499**

**A New Vasculo-Renal Marker Enhances Accuracy of Hypertensive Nephropathy Recognition**

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**Background:** Latent and slow beginning of chronic kidney disease (CKD) coexisting with well tolerated, usually not recognized previously hypertension makes difficult to recognize hypertensive nephropathy (HN) from CKD of others origins. The aim of the study was to investigate the best marker helpful in differentiating HN from other causes of CKD.

**Methods:** Forty patients (4; 36 M; age 52.7 ± 14.4) with stable CKD (CKD-EPI 53.1 ±27.6 ml/min/1.73m2) and a history of hypertension (26 with HN) were enrolled in the study. Serum Creatinine (Cre), Cystatin C (Cys), NT-pro brain natriuretic peptide (NTproBNP), Troponin 1 (TNI) and urinary albumin to creatinine ratio (UACR) were tested. Renal function was estimated according to Cre and Cys based CKD-EPI formula. Echocardiographic examination, carotid Intima-Media Thickness (IMT), ABPM, Renal Resistive Index (RRI) were performed. Vasculo-Renal Index (VRI) was calculated as IMT to UACR ratio.

**Results:** Groups with HN and CKD of other origins did not differ in renal function (CKD-EPI 46.2 vs 57.1 ml/min/1.73m2, p =0.22), NTproBNP: TNI, left ventricular (LV) ejection fraction, LV mass index and mean arterial pressure. Patients with HN were older (56.4 ±15.1 vs 45.9 ±14.1; p <0.039), had lower UACR (0.264 ±0.484 vs 0.814 ±0.564 mg/mg; p=0.001), but higher IMT (0.858 ±0.217 vs 0.652 ±0.380; p<0.009) and VRI (m. 28.8 ±0.36; 1030.00) vs m. 0.78 ±0.34; 12.50 ±0.0001). In ROC analysis VRI ≥ 1.91, UACR ≤ 0.199, and IMT ≥ 0.87 could recognize HN with sensitivity of 85%, 73% and 62% respectively, specificity of 79%, 93% and 86% and of accuracy of 82.5%, 80% and 70% (AUC 0.874, 0.849 and 0.749; p<0.05).

**Conclusions:** A new Vasculo-Renal Index recognizes HN more accurately, but UACR and IMT are not significantly worse.

**Funding:** Government Support - Non-U.S.
Glomerular collapse and hyper-
Akihiro Tsuchimoto, 2 Takehiko Kawaguchi, Mao Watanabe,1,2 Akihiro Tsuchimoto, 2 Hisako Yoshida, 2
Toshiyuki Imasawa, 1,2,3 Ritsuko Katafuchi, 1,2,3 Takanari Kitazono. 2 Kidney Unit, Fukuoka Higashi Medical
School of Medical Sciences, Kyusu Univ, Fukuoka; 1 Dept of Medicine and Clinical Science, Graduate
School of Medical Sciences, Kyusu Univ, Fukuoka; 2 Dept of Integrated Therapy for Chronic Kidney Disease,
Graduate School of Medical Sciences, Kyusu Univ, Fukuoka, Japan.

Background: In patients with chronic kidney disease (CKD), impaired urinary sodium excretion (UNa) may cause nocturnal hypertension and pressure natriuresis to compensate for daytime sodium retention. The aim of this study was to determine the renal histological lesions which associated with nocturnal blood pressure (BP) and UNa in patients with CKD.

Methods: We analyzed patients biopsyed in our institutions from Sep 2010 to Apr 2014 (Forty Iga nephropathy, 6 Purpura nephritis, 4 membranous nephropathy and 14 the others). During the same hospitalization period of renal biopsy, ambulatory BP monitoring and evaluation of UNa were performed simultaneously. The association of histological findings such as global sclerosis (%GS), arteriolar hyalinosis (%hyaline), and interstitial fibrosis (IF), with nocturnal BP and night/day ratio of UNa were assessed using linear regression analysis.

Results: Twenty three patients were male, mean age was 40.5 ± 15.9 years, and mean estimated glomerular filtration rate (eGFR) was 79.0 ± 28.9 ml/min/1.73m². Both nocturnal BP and night/day ration of UNa positively associated with %GS, %hyaline, and IF, and negatively associated with eGFR. Multiple regression analysis adjusted for age, sex, eGFR, and usage of antihypertensive drugs showed that %GS was significantly associated with nocturnal systolic BP (β = 0.38, p = 0.012), nocturnal diastolic BP (β = 0.34, p = 0.031) and night/day ratio of UNa (β = 0.52, p = 0.005).

Conclusions: We found that night/day ratio of UNa and nocturnal BP closely related to the percentage of global sclerosis. These findings could be the morphological evidence that increase in the number of functioning glomeruli causes increase in nocturnal UNa to compensate for daytime sodium retention resulting in elevation of nocturnal BP in patients with CKD.

Conclusion: This meta-analysis suggests that the bedtime dosing regimen drug therapy benefits CKD patients in terms of hypertension especially those with non-diaper BP pattern.

Funding: Government Support - Non-U.S.

The Impact of Glomerular Collapse in Hypertensive Emergency Patients Tukafumi Yamakawa, Yoshihiko Imasawa, Takeliko Kawaguchi, Mao Watanabe, Maiko Nagata, Hiroki Kitamura. Dept of Internal Medicine, National Hospital Organization Chiba East Hospital, Chiba City, Japan.

Background: The prognosis of kidney disease with hypertensive emergency (malignant glomerulosclerosis) is still worse compared with benign nephrosclerosis. Here, further to assess the reasons of worse prognosis and to reconsider more appropriate therapy for malignant nephrosclerosis, we compared pathological parameters between malignant and benign nephrosclerosis.

Methods: 8 patients diagnosed as hypertensive emergency with acute renal failure were performed renal biopsies from October 2005 to May 2015. We selected all patients with benign nephrosclerosis (n=20), who were performed renal biopsies during same period, as controls. We compared changes in clinical and pathological data using the paired t-test and the Mann-Whitney U-test.

Results: All 8 patients with hypertensive emergency had characteristic pathological changes of malignant hypertension, such as fibrinoid necrosis, onion-skin thickening and edematous-appearing matrix in arterioles. These changes were never observed in benign nephrosclerosis. The rates of global sclerosis and segmental sclerosis had no statistical differences between these two groups. Interestingly, when glomerular collapsing rate was counted by GCR (GCR=number of glomerular collapse/ total number of glomeruli), GCR scores were much higher in hypertensive emergency cases compared with those in benign nephrosclerosis cases (42.9 ± 23.8 vs. 6.5 ± 7.4 %; p < 0.05). These patient's clinical characteristics showed a high level of plasma renin activity (PRA) (14.9 ± 5.8 ng/ml/h) and a high level of aldosterone (263 ± 256 ng/dl).

Conclusions: Glomerular collapse and hyper-renin mean glomerular hyperperfusion. Therefore, if therapy accelerate this glomerular hyperperfusion, it might affect renal outcome. We should reconsider the way of therapy, such as the selection of anti-hypertensive drugs, and the speed of declining blood pressure and volume control by thinking glomerular hyperperfusion.
Conclusions: This study shows that high dosage ACEI and super high dosage ACEI all can decrease blood pressure, reduce proteinuria, depress the expressions of TGF-β and PAI-1 protein in SHR, and delay glomerulosclerosis. But super high dosage ACEI can not reverse glomerulosclerosis in SHR.

PUB505
Hemolytic Uremic Syndrome Associated with Scleroderma Renal Crisis: The Challenge for Timely and Accurate Diagnosis
Amro Elshoury, Syed S. Haqiqie, Daniel Sedhom, Arif Asif. Albany Medical Center, Albany, NY.

Background: Scleroderma renal crisis (SRC) is a rare cause of atypical hemolytic uremic syndrome (aHUS) and differentiating it from other causes of thrombotic microangiopathies can be challenging. A 53-year old Caucasian male, with no past medical history was found unresponsive. BP was elevated to 207/141 mm Hg. Skin examination showed diffuse telangectasia and edema of his extremities with bilateral sclerodactyly (Figure 1). Fundoscopy revealed bilateral retinal hemorrhage and exudates. Labs showed a hemoglobin=5gm/dl, platelet=25×10^9/μl, creatinine=6mg/dl. LDH=1122U/L, bilirubin=1.6mg/dl, haptoglobin<5%, reticulocyte count<10.4% and schistocytes. ANA and anti-RNA Polymerase III antibody were positive (C3 and C4, coagulation profile, fibrinogen were normal; Coombs negative). CT head showed severe microvascular changes throughout the white matter of the cerebrum and MRI showed evidence of punctuate chronic micro-hemorrhages in the left thalamus and cerebellar tonsils. The presence of MAH, acute renal failure and thrombocytopenia raised suspicion for possible aHUS/TPP. Serum ADAMTS 13 was ordered. Because of the possibility of SRC, the patient was started on caprornil. A dramatic improvement in BP, hemoglobin and platelets count along with the normalization of LDH and schistocytes disappearance was observed. However, there was no improvement in kidney function requiring hemodialysis. ADAMT-13 activity returned at 40% (cut-off for TTP is <5%). Patient did not pursue eculizumab therapy. A significant portion of patients with Scleroderma can develop aHUS. In this case, hypertension might have served as a complement amplifying condition.

Methods: Clinical presentation/course of the patient.
Results: Despite therapy with ACEI inhibitors patient ended up on RRT.
Conclusions: Patient presenting with Malignant HTN and MAH was found to be in scleroderma crisis.

PUB506
The Impact of Neck Irradiation on Baroreceptor Reflex and Hypertension

Background: Only a few studies with a very limited sample size have evaluated the impact of neck irradiation on baroreceptor reflex failure and blood pressure (BP) abnormalities. We investigated 60-patients, with head/neck cancer, who received neck irradiation between 2005 to 2010. IRB approval was obtained. Median for age was 61.5 years (range 24-90 years). We used the same cohort of patients, before they received neck irradiation between 2005 to 2010. IRB approval was obtained. Median for age was 61.5 years (range 24-90 years). We used the same cohort of patients, before they received neck irradiation between 2005 to 2010. IRB approval was obtained.

Results:
Blood pressure before and after radiation showed no increase.

Conclusions: The study suggests that carotid baroreceptors might not have been damaged by radiation or baroreceptors.

PUB507
Sympathetic Nervous System Activity Reflected by Renalase and Catecholamines in Different Aged Patients with and without Chronic Kidney Disease
Edyta Zbroszlav, Dominika Maciorowska, Ewa Koc-Zorawska, Jolanta Malczewska, 1 2nd Dept of Nephrology and Hypertension with Dialysis Centre, Medical Univ, Bialystok, Poland; 1 1st Dept of Nephrology and Transplantation, Medical Univ, Bialystok, Poland.

Background: Sympathetic nervous system activity is elevated in patients with chronic kidney disease (CKD) as well as in older persons. It contributes to hypertension and cardiovascular diseases. It is due to a reduction of catecholamines clearance and in elderly also to an increased sympathetic discharge from different organs. Renalase may play a role in the regulation of catecholamines degradation. The aim of the study was to assess the sympathetic nervous system activity, according to serum renalase and catecholamines concentration in a cohort of 211 patients with hypertension and or with chronic kidney disease.

Methods: The study group was divided according to age below and above 65 years. The older persons (61) was also divided into group with (75%) and without CKD stage 5. The serum renalase, dopamine and norepinephrine concentration as well as pressure control, residual renal function rate and echocardiography were assessed.

Results: The older group had higher renalase (p=0.02) and dopamine (p=0.001) concentration and it was elevated in patients with CKD comparing to those without. They also had advanced abnormalities in echocardiography, like thicker interventricular septum (p=0.03) and lower ejection fraction (p=0.001) as well as CKD patients comparing to those without CKD – pronounced left ventricular hypertrophy (p=0.007) and lower ejection fraction (p=0.004). They more often suffered from coronary artery disease. The residual renal function was less in older patients with CKD. The main used hypotensive drugs in studied group were beta-blockers. There was the significant correlation between age and renalase, norpinephrine and dopamine concentration.

Conclusions: The advanced aged especially combined with chronic kidney disease is associated with elevated renalase and dopamine level. It may reflect the sympathetic nervous system hyperactivity due to impaired kidney function and reduction of residual diuresis. It may have an impact on the development of cardiovascular complications.

PUB508
Heart Rate Variabilities During Day and Night Can Alter the Circadian Blood Pressure (BP) Rhythm
Toshinuki Miura,1 Michio Fukuda,1 Yoshiaki Ogizama,2 Ken Kiyono,3 Junichiro Hayano,3 Nobuyuki Ohte.1 1 Nagoya City Univ, Japan; 2 Osaka Univ, Japan; 3 Tokoyo Univ, Japan.

Background: We previously reported in patients with chronic kidney disease (CKD) that the circadian rhythms of BP and urinary sodium excretion (Un/Ur) were both impaired into non-dipper pattern as renal function deteriorated. Elevated salt-sensitivity of BP and inappropriate activation of the renin-angiotensin-aldosterone system and the sympathetic nerve system play important roles in high BP and the high incidence of cardiovascular diseases in patients with CKD.

Methods: In 39 patients with CKD, we analyzed HRV in 24-h electrocardiography, BP monitoring and urine collection, separately for daytime and nighttime. Patients, who took antihypertensive agents, were excluded. We evaluated the relationship between systolic blood pressure (SBP) and Un/Ur, the Non-Gaussianity index of HRV(Un), which reflects the probability of intermittent large deviations of heart rate (HR) from the trend, and the power of high frequency (HF, 0.15–0.40 Hz) obtained by frequency domain analysis of HRV as well as GFR was reduced.

Results: In 39 patients with CKD, we analyzed HRV in 24-h electrocardiography, BP monitoring and urine collection, separately for daytime and nighttime. Patients, who took antihypertensive agents, were excluded. We evaluated the relationship between systolic blood pressure (SBP) and Un/Ur, the Non-Gaussianity index of HRV(Un), which reflects the probability of intermittent large deviations of heart rate (HR) from the trend, and the power of high frequency (HF, 0.15–0.40 Hz) obtained by frequency domain analysis of HRV as well as GFR was reduced.

Conclusions: Our study clearly demonstrated that as renal function deteriorated, sympathetic nerve activity is activated during the day, and vagal activation was impaired during the night, both of which can contributes to high BP in patients with CKD. However, the type of circadian BP rhythm was associated with the circadian Un/Ur rhythm rather than sympathetic or vagal nerve activity, even though the sympathetic activity can stimulate tubular sodium reabsorption.

PUB509
The Effects of the Insight Meditation Practice on Blood Pressure Reduction in Buddhist Exemplary People
Kriengsak Vareesangthip,1 Jutamas Vareesangthip,2 1 Dhamma Communication Div, Graduate School, Mahachulalongkornrajavidyalaya Univ, Bangkok, Thailand; 2 Renal Div, Dept of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand.

Background: Hypertension (HTN) is a leading risk factor for preventative cardiovascular disease, with over one in five adults affected worldwide. Lifestyle modification is an important strategy for the prevention and treatment of HTN. Contemplative interventions are associated with greater cardiovascular risk, and stress management is a recommended intervention for hypertension. For many patients, maximal medical therapy is insufficient.
to adequately treat refractory hypertension. Lifestyle modification remains an important approach in management. Buddhist meditation encompasses a variety of meditation techniques that aim to develop mindfulness, concentration, and insight.

Methods: We aimed to study whether Buddhist Insight Meditation (IM) Practice, composing of Walking Meditation and Sitting Meditation, could reduce the level of blood pressure in the Buddhist Exemplary People. 65 exemplary people were divided into 3 groups according to the schedule they performed IM Practice. Group 1 (n=25) performed 30 minutes of the Walking and 30 minutes of the Sitting Meditation, group 2 (n=20) performed 45 minutes in each Meditation and group 3 (n=20) performed 60 minutes in each Meditation. Their blood pressures (BP), pulse pressures (PP) and pulses (P) were measured before and after Walking and Sitting Meditations.

Results: The results clearly showed that systolic BP, PP and P were significantly decreased after the Walking Meditation at 30-45-60 minutes. After IM Practice schedule, an artsy-duced decrease was significantly increased in all 3 groups, PP has been significantly decreased in group 2 and systolic BP has been significantly reduced in group 3.

Conclusions: In conclusion, the Buddhist IM Practice could meaningfully reduce the sympathetic activities including systolic BP, PP and P. Therefore, this Buddhist Practice should be added to be one modality of the standard hypertensive treatments.

**PUB510**

**ENA as a Novel Mechanism for Hypertension and Volume Expansion in Type 2 Diabetes**

Mark L. Unruh,¹ V. Shane Pankratz,¹ Evan C. Ray,¹ Rebecca P. Hughey,² Thomas R. Kleyman.³ Div of Nephrology, Univ of New Mexico; ²Renal-Electrolyte Div, UPMC.

Background: Renal Na retention and extracellular fluid volume expansion are hallmark features of type 2 diabetes. There is evidence that this occurs even in the absence of activation of hormones that are known to stimulate renal Na transporters. Recent studies suggest that plasmin-dependent activation of ENA may be responsible for renal Na retention in the setting of nephrotic syndrome. We hypothesized that the ENA inhibitor amiloride would be an effective therapeutic agent in inducing a natriuresis and lowering blood pressure in individuals with macroscopic proteinuria.

Methods: We conducted a pilot double-blind randomized cross-over study comparing the effects of daily administration of either oral amiloride (10 (low dose) followed by 20 (high dose) mg/d) or HCTZ (Na,Cl co-transporter inhibitor) to patients with type 2 diabetes and macroscopic proteinuria. We examined safety and feasibility of amiloride by monitoring kidney function, adherence, blood pressure, weight, urinary Na excretion and serum electrolytes during diuretic administration.

Results: 9 subjects were enrolled in the trial. Systolic blood pressure (SBP) decreased in both treatment groups, but there was not a significant difference between HCTZ and amiloride (p=0.53). Amiloride treatment was associated with a 1.1±0.4 kg decline in weight (p=0.02), and a 0.78 ± 0.18 mmol/L greater increase in serum potassium (p=0.002) over the low dose portion of the study. 2 subjects developed acute kidney injury and hyperkalemia when treated with amiloride. 5 subjects had readily detectable levels of urinary plasminogen/plasmin, and 4 did not. Among those receiving amiloride, the low plasmian group experienced a change of 1.1±4.6 mmol/L in SBP and the high plasmian group experienced a change of -13.9±8.7 mmol/L, although there was insufficient evidence to conclude that there were differential treatment effects by high/low plasminogen status (p=0.113).

Conclusions: Among patients with type 2 diabetes, normal renal function, and proteinuria, there was suggestion of increased natriuresis for those treated with amiloride vs. HCTZ. However, acute kidney injury and severe hyperkalemia was a safety concern.

_Funding:_ Private Foundation Support

**PUB511**

**Serum Phosphorus Control and Reduced Phosphate Binder Pill Burden Among Hemodialysis Patients Who Switched from Sevelamer to Sucroferric Oxyhydroxide**

Vidhya Parameswaran, Lin Ma, Linda H. Ficociello, Claudy Mullon, Franklin W. Maddux, Robert J. Kossman. Fresenius Medical Care North America, Waltham, MA.

Background: Clinical management of hyperphosphatemia among hemodialysis (HD) patients (pts) can present challenges. A retrospective database analysis was conducted to study the effectiveness of sucroferric oxyhydroxide (SO) among in-center HD pts who switched from sevelamer to SO as part of routine clinical care.

Methods: Pts who switched from sevelamer and had 1 serum phosphorus (sPshos) measured during SO treatment were included. Changes in sPshos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and pill burden were assessed at baseline (3-months prior to SO) and at follow-up (3-months during SO treatment).

Results: Pts (n=1487) were, on average, 54 years old, with dialysis vintage of 4.4 years and hyperphosphatemia (baseline sPshos=6.94 mg/dL). Figure shows sPshos distribution at baseline and follow-up. Pts with in-range sPshos (3.5-5.5 mg/dL) increased from 12% to 20.1% (68% increase). Mean sPshos decreased from 6.94 to 6.7 mg/dL (p<0.001) and mean sCa decreased from 9.3 to 9.25 mg/dL (p<0.001). There was a significant decrease (4.7 pills/day, p=0.001) in pill burden (8.5 to 3.7 pills). No significant change in iPTH levels was seen in Baseline 1 to 67.6 pg/mL). TSAT and FER significantly increased (p=0.001) from 33.7% to 35.3% and 98.3 to 105.1 ng/mL, respectively. In pts not receiving IV iron (n=149), there were no significant changes in TSAT (36.3% to 35.9%) or FER (1221.5 to 1177.4 ng/mL).

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

*Underline represents presenting author.*

1006A

Conclusions: Changes of y-variables with FE_3 were examined. Other x-variables correlated inversely with E_P|C_rx or were unrelated to E_P|C_rx. None of the y-variables correlated with [PTH] or [FGF23].

_Funding:_ Veterans Administration Support, Pharmaceutical Company Support

**PUB512**

An Investigation of the Inverse Relationship Between Fractional Excretion of Phosphate and the Tubular Maximum for Phosphate per Volume of Filtrate

Kenneth R. Phelps,¹ Darius Mazon.² ² Strattion VAMC, Albany, NY; ³Albany Medical College, Albany, NY; ⁴Albany College of Pharmacy and Health Sciences, Albany, NY.

Background: The serum P concentration ([P]) is the sum of urinary excretion and tubular reabsorption rates of [P] per volume of filtrate (E_P|C_rx and Tm_P/C_rx). The two ratios could determine fractional excretion of P (FEP) [Clin Nephrol 85:167] and E_P|C_rx is approximately proportionally to the concentration of [P] (P) in the cortical distal nephron (CDN) [Clin Nephrol 82:191]. Maximal TR_P/C_rx (i.e. Tm_P/GFR) exceeds actual TR_P/C_rx when FE_P is < 20%; as FE_P falls, Tm_P/GFR and (Tm_P/GFR - FEP) rise [Clin Chim Acta 26:15]. We investigated these phenomena.

Methods: We measured [cr] and [P] in fasting serum (s) and urine (u), and [PTH]1-84 (Scantibodies) and intact [FGF23] (Immunotops) in plasma from 28 subjects without renal or parathyroid disease. We calculated E_P|C_rx as [P] [cr] / [cr] and TR_P/C_rx as [P] - E_P|C_rx and FE_P as ([P] - [cr]) / [cr]. We then determined Tm_P/GFR from the Walton-Bijvoet nomogram.

Results: All x-variables correlated inversely with FEP, Tm_P/GFR correlated directly with TR_P/C_rx but was unrelated to E_P|C_rx. Other x-variables correlated inversely with E_P|C_rx but were unrelated to TR_P/C_rx. None of the y-variables correlated with [PTH] or [FGF23].

_Funding:_ Pharmaceutical Company Support - Fresenius Medical Care North America
PUB513
Observational Study at the Mexican Institute for Social Security and Services for State Worker’s National Medical Center 20 de Noviembre Nephrology Department Outpatient Clinic Using Cinacalcet as Renal Replacement Therapy for Secondary Hyperparathyroidism Caused by Chronic Kidney Disease poster

Elvira González, Jesús Alejandro Nava Martínez, Juana Eugenia Amador Sánchez, Edgar Alejandro Fragoso, LM Valeria Espinosa, CRISCUA, Hospital General, Mexico, D.F., Mexico, Nephrology, CMN 20 de Noviembre, Mexico, D.F., Mexico.

Background: Secondary hyperparathyroidism is a highly prevalent clinical condition in persons with advanced chronic kidney disease (CKD). It can be seen in the early stages of the disease and consists of disorders in bone metabolism.

Methods: A descriptive, retrospective observational study was done using patient records at the Institute for Social Security and Services for State Worker’s (ISSSTE) National Medical Center 20 de Noviembre Nephrology outpatient clinic, located in Mexico City, Mexico. 50 cases of adult patients with advanced chronic kidney disease were reviewed in renal replacement treatment, dentopetalal dialysis and/or hemodialysis who were managed with Cinacalcet for Secondary Hyperparathyroidism, with PTHi > 300 pg/ml.

Results: The baseline level of serum parathyroid hormone of the 42 patients was 137.1 pg/ml prior to the use of cinacalcet, with a percentage reduction of 33% per month and 6 months of treatment 55% with a mean of 1133 pg/ml and 615.48 pg/ml respectively. A total of 42 patients; 19 (45%) achieved targets at the end of the 6-month study. 36 patients underwent to scintigraphy of parathyroid gland, because they did not obtain parathyroid hormone decreased over 30% at the 3rd month of treatment; 5 patients showed hyperplasia and 11 parathyroid adenoma.

Conclusions: Cinacalcet combined with conventional treatment succeeds in reaching goals compared to standard treatment only. Hypocalcemia is a common side effect however when administered together with calcium salts and/or vitamin D or its analogues decrease side effects According to previous studies cinacalcet it increases the achievement of goals in mild hyperparathyroidism. In our study was more important for the response time in the RRT than the severity of hyperparathyroidism.

Funding: Government Support - Non-U.S.

PUB514
“Binder Reminders” for Persistent Hyperphosphatemia in Hemodialysis Patients: A Fellow’s Quality Improvement Project poster

Divyakam Jammalamadaka, N. Stanley Nahman, John Jason White. Medicine, Georgia Regents Univ, Augusta, GA.

Background: Despite regular quality improvement (Qa) processes, control of mineral metabolism remains poor. One root cause is patient non-adherence to phosphate (Pho) binders. Evolving data suggest SMS/text reminders improve medication adherence in a wide range of chronic illnesses. Here, we report our initial experience with text reminders on Pho control in HD patients.

Methods: 40 patients with Pho > 5.5 mg/dL for 2 of last 3 months, and possessing cell-phones with texting capabilities were studied. We randomly assigned 20 to receive the phrase “Binder Reminder” at mealtimes x 7 days prior to their monthly lab draw. The remaining 20 received usual care. Group assignment and messaging was communicated by a nephrology fellow, not part of the multidisciplinary team. Patients were excluded if they declined participation, missed any dialysis sessions during the 7 day period, or if they were unable to obtain their binders. Pho level after intervention was the primary outcome.

Results: After exclusions, 13 patients received the intervention and were compared to 14 controls. Pre-intervention Pho levels were 6.81 +/- 0.88 and 6.60 +/- 0.93 mg/dL (Mean +/- SD) in the control and intervention groups respectively. After intervention, Pho levels declined in the intervention group to 6.00 +/- 1.2 mg/dL (P= 0.10). Pho also declined in the control group to 6.19 +/- 0.76 mg/dL. Hence there was no difference between the groups (P = 0.76). Each group had 8 patients with improved Pho levels, and 5 patients at goal.

Conclusions: Our initial QA project utilizing SMS/text messaging appears to have no effect on short-term Pho control in a group of HDs patients with chronic hyperphosphatemia. A major drawback is the small number of patients and the number excluded (33%). However, this study does provide useful preliminary data for the planning of a larger pilot project, highlights the importance of contemporary control groups in QA to exclude the Hawthorne effect, and, given its simplicity, may be a model for fellow-driven QA projects and education.

Funding: Clinical Revenue Support

PUB515
Niacin Improves Cardiac Function in Alport Mice with Progressive Chronic Kidney Disease and Hyperphosphatemia poster

Kelly Ambell1, Evgenia Dubovy2, Veronica A. Hogg-Correa1, Xiaoxiong Wang3, Yuhan Liu1, Jason R. Stubbs2, Moshe Levi1,1 University of Colorado Denver, 2Univ of Kansas Medical Center.

Background: Increase in serum phosphate (Pi) level (hyperphosphatemia) is a common clinical problem in chronic kidney disease (CKD). Systemic Pi homeostasis is balanced through three major mechanisms: intestinal uptake, retention or release from bone, and renal reabsorption. Sodium-phosphate co-transporter type 2b (NaPi2b) is a major phosphate transport system in the small intestine. Alport syndrome is a genetic disorder characterized by CKD, hearing loss and cardiac dysfunction.

Methods: By 9-10 weeks of age Alport mice, which have a mutation in a COL4A3 gene on the SvEv129 background, develop signs of CKD and hyperphosphatemia.

Results: We have found by western blot that there is an increase in intestinal NaPi2b protein abundance and Evcertel Sac studies showed increased NaPi transport in the Alport Helem compared to the WT littermate controls. Cardiac echo studies revealed that Alport mice have decreased ejection fraction (EF: 67±2% compared to 75±3% in the WT littermate) and diastolic dysfunction (mitral Doppler flow E/A ratio: 1.2±0.1 compared to 1.6±0.1 in the WT littermate, p<0.05), which could be corrected by treatment with Niacin (intestinal phosphate uptake inhibitor). In the treated Alport mice EF increased to 78±2% (p<0.05) and E/A ratio improved to 1.3±0.1 (p<0.05). In addition, there were significant decreases mRNA relative expression in β-MHC (0.08±0.02 in control vs. 2.19±0.34 in Alport, p<0.001, vs. 0.2±0.001 in Alport+Niacin, p<0.05), PAI-1 (0.12±0.01 in control vs. 1.05±0.15 in Alport, p<0.05, vs. 0.15±0.05 in Alport+Niacin, p<0.05), and TGF-β (0.03±0.01 in control vs. 0.77±0.23 in Alport, p<0.01, vs. 0.07±0.23 in Alport+Niacin, p<0.01), markers of heart failure and cardiac fibrosis.

Conclusions: Inhibition of intestinal phosphate transport with Niacin therefore improves systolic and diastolic cardiac dysfunction in CKD.

Funding: Pharmaceutical Company Support - Daichi Sankyo

PUB516
Establishing Regulatory Networks of Phosphorus Metabolism in HD Patients – A New Path of Treating Hyperphosphatemia poster

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Background: The clinical efficiency of current treatment of hyperphosphatemia in HD varies widely on different patients. We assume that it is due to phosphorus regulation in vivo. In physiological conditions, phosphorus is regulated by a biological network consisting of interacting hormones and minerals. In HD, the networks change dramatically and affect serum phosphorus. This study aims to establish the regulatory networks of phosphorus in HD and identify the key factors that may have a causal effect on circulating concentrations of phosphorus.

Methods: 50 HDH patients were enrolled and divided into three groups (n=10, PTH≤300 ng/ml; n=10, 300 ng/ml<PTH≤600 ng/ml; n=10, PTH>600 ng/ml). Predialysis blood samples were obtained on the mid-week dialysis day for detection of PTH, FGF23, 25(OH)D3, Klotho, and Ca every week for 12 weeks every patient. Caused adherence, we would used process of concluding a causal connection, was adopted to establish the regulatory networks of phosphorus metabolism within different PTH levels.

Results: The networks show that when PTH≤600 ng/ml, FGF23 can stimulate the increase of serum Pi, Ca, and PTH, in turn, serum Ca and Pi can also stimulate the increase of FGF23. When PTH>600 ng/ml, FGF23 becomes the stimulator of only serum Ca, and serum Pi has a positive causal effect on PTH, besides, the rise of PTH increases serum Pi level, too. Serum Pi is affect by FGF23 when PTH>600 ng/ml and by PTH when PTH>600 ng/ml. Since FGF23 promotes the increase of PTH when PTH>600 ng/ml, FGF23 becomes the key factor in disorders of phosphorus metabolism. The figures also shows that Klotho and 25(OH)D3 may be not important in the therapy of hyperphosphatemia.

Conclusions: Reducing FGF23 levels might contribute to the control of phosphorus.

PUB517
Evolution of Renal Calcium Excretion Throughout Chronic Kidney Disease poster

Carmen Gonzalez Corvillo1, Paula Batalla-Castano,2 Silvia Ros-Ruiz,2 Fernando Callejo,3,4 José G. Heras,5 Mercedes Salgueira Lazo,5 Nephrology, Hospitales Virgen Macarena-Rocio, Sevilla, Spain; 4Nephrology, Hospital Regional, Malaga, Spain; 5Nephrology, Hospital Puerto Real, Cadiz, Spain; 6Nephrology, Universidad, Granada, Spain.

Background: Chronic kidney disease(CKD)patients have a normal serum calcium(Ca) concentration until the end of renal disease(ESRD).The decrease of VitaminD levels, and that a percentage of patients develops hypocalcemia at ESRD, lead us to think that our Ca networks change dramatically in vivo. In physiological conditions, phosphorus is regulated by a biological network consisting of interacting hormones and minerals. In HD, the networks change dramatically and affect serum phosphorus. Since Klotho and 25(OH)D3 may be not important in the therapy of hyperphosphatemia.

Methods: Observational multicenter,retrospective and transversal study,with the participation of Hospitales 63 patients were included,in different stages of disease(66,7%men,mean age 66years).None on renal replacement therapy. Variables:blood,urine analysis and treatment. The sample was stratified by stage of the disease and urine Ca(>or<100 mg/dl).

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

Underline represents presenting author.
Results: Sample:6,3%/CKD1,4,8%/CKD2,28,6%/CKD3,38,1%/CKD4 and 22,2%/CKD5. Mean serum Ca: 4,77 mg/dl mean serum phosphate(P): 3,77 mg/dl PTH level 1749 dl/ul M0: 27mg/ml Mean Ca excretion: 126mg/day Mean P excretion:477mg/d/day was on Ca based binders, 22,2% on calcium, 12,7% on calcium and 28,6% on paricalcitol. 70% of the sample had Ca excretion<100mg/d. When classifying by stages of the disease, increases the amount of patients with Ca excretion<100 mg/d CKD1 25%, CKD2 50%, CKD3 50%, CKD4 80%, CKD5 83%, decreasing the mean Ca excretion. The group of patients with lower Ca excretion had a higher PTH level (155 vs 111 pg/dl) p<0,05. 94% of patients treated with Ca based binders had a Ca excretion<100 ng/dl, with no difference in serum Ca. Patients on calcium carbonate, paricalcitol or calcium had lower Ca excretion than those without treatment.

Conclusions: According to our results, patients within CKD show a decrease in renal Ca excretion that become exacerbated as the renal disease progresses. Supplementation with hypercalcemic drugs is not balanced out with the expected increase of renal Ca excretion. Therefore, we think that CKD patients are exposed to a chronic Ca overload, sometimes underestimated, with the resulting negative impact in morbidity and mortality.

PUB518

Effect of Parathyroid Hormone on Serum Magnesium Level: The Neglected Relationship in Hemodialysis Patients with Secondary Hyperparathyroidism Bing Tang, Li Fang, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Chronic kidney disease–mineral and bone disorder (CKD–MBD) is an important complication in patients with end-stage kidney disease which is associated with cardiovascular morbidity and mortality. Since recent studies have shown that serum magnesium play an important role in secondary hyperparathyroidism, vascular calcification and in cardiovascular mortality, the interest on magnesium has grown.

Methods: This cross-sectional study was conducted on 111 patients with end-stage renal disease on maintenance hemodialysis who was hospitalized for secondary hyperparathyroidism. The interventional study was conducted on 23 patients underwent total parathyroidectomy.

Results: In our study, hypermagnesaemia (>2.5mg/dl) occurs in up to 44% of cases and hypomagnesemia did not present. No significant correlations were found between serum magnesium and parathyroid hormone (r = 0.143, p = 0.134). Correlation analysis and logistic regression analysis suggested that the derangement of magnesium homeostasis was correlated with the derangement of calcium/phosphate homeostasis. After parathyroidectomy, serum magnesium levels dropped immediately and reached the lowest level at one day after surgery; however, it gradually restored three days later. The changes of serum magnesium after surgery was positive correlated with the changes of serum phosphorus (r=0.558, p=0.003).

Conclusions: The effect of PTH on magnesium metabolism could not be neglected, especially in hemodialysis patients with secondary hyperparathyroidism. The role of magnesium metabolism and therapeutic strategies to achieve optimum serum magnesium levels in CKD-MBD should take into account the varying stages of disease development.

Funding: Government Support - Non-U.S.

PUB519

Calciphylaxis in Patient with Chronic Renal Disease Not Dialytic and Multiple Myeloma Patricia Junqueira Freitas, Aline Lourencio Baptista, Clovis Antonio lopes Pinto, Joubert Araujo Alves, Pedro Caruso, Benedito Jorge Pereira, Germana Alves Brito. Nephrology, AC CAMARGO, Sao Paulo, Brazil.

Background: Calciphylaxis, also known as calcifying uremic arteriolopathy, is a rare medical condition, which is normally diagnosed in patients with terminal CKD who are already in renal replacement therapy (RRT). Objective: report the presence of calciphylaxis in patients with chronic renal disease which is associated with end stage renal disease on maintenance hemodialysis who was hospitalized for secondary hyperparathyroidism.

Methods: The presence of calciphylaxis was diagnosed in a patient with chronic renal disease who was not on dialysis, and multiple myeloma, with a reduced renal function and a hyperparathyroidism. The diagnosis of calciphylaxis was based on the presence of calcific plaques, necrosis, of acute and progressive installation. It must be paid attention to its presence even in non dialytic stages of CKD as happened in the described case.

Funding: Private Foundation Support

PUB520

Calcium Binders Are They All Equal? Comparison Calcium Acetate (CA) versus Carbonate Calcium (CC) in CKD 5D: Multicentric Study Philippe Brugere, David Attaf, Laurent Juillard. 1Nephrology - Dialysis, Conception Hospital, Marseille, Bouches-du-Rhône, France; 2Dialyse, Fresenius, Paris, IDF, France; 3Nephrology - Dialysis, Edouard Herriot Hospital, Lyon, Rhone, France.

Background: CA’s phosphate binder is available since 2010 in France. A monocentric study indicates that CA is equivalent to CC based on phosphatemia reduction while reducing calcium intake by 60%. This study compare CA to CC in different dialysis centers i.e different CKD MBD protocols.

Methods: 28 hemodialysis centers are involved. CC is switched to CA at M6 with 6 months follow up (M0, M6). We compared M0’s, biologic data with M6’s data.

Results: 293 patients (70+/14 y) in 28 centers. At M0, CA dosage was 3.8 +/- 2 pills/day. Demographic characteristics are consistent with our National French registry. At M6 mineral values are similar to M0 : Ph mEq/l (1.54 +/- 0.55 vs 1.52 +/- 0.65, NS), Ca mM (2.23 +/- 0.17 vs 2.21 +/- 0.15, NS), PEx mg/dl (221 +/- 204 vs 262 +/- 217, NS), Vit. D (75 +/- 32 vs 79 +/- 24, NS), % pts with no calcium binder (43 vs 49, NS), % pts w. Ca > 2.6 mM (2 vs 1, NS), % pts w. Ph > 1.5 mM (39 vs 38, NS). The only difference is related to a decrease of Calcium Intake (g/d) from M0 (1.51 +/- 1.13) to M6 (0, 63 +/- 0.31, P<0.05).

Conclusions: At M6, Calcium intake is reduced by 57% vs M0 while Ph is similar vs M0. Mean serum calcium is not altered. The frequency of Ca > 2.60 mM and Ph > 1.5 mM are not modified at M6. Calcium based binders had a Ca excretion<100mg/d with no difference in serum Ca. Patients on calcium carbonate, paricalcitol or calcium had lower Ca excretion than those without treatment.

Funding: Private Foundation Support

PUB521

Hemodynamic Changes in Maintenance Hemodialysis Patients with Hypotension After Parathyroidectomy Meijuan Meng, Bing Tang, Hong Ye, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Parathyroidectomy (PTX) is applied to treat secondary hyperparathyroidism in hemodialysis patients. Some patients suffered from hypotension after PTX although hypocalcemia was corrected. The aim of this study was to demonstrate the hemodynamic changes in hemodialysis patients after PTX.

Methods: Twelve patients were included in this study. Among them 4 have hypotension after PTX (Group 1) and the other have their blood pressure remained after PTX (Group 2). Before PTX, systolic blood pressures (SBP) of all the 12 patients were above 90 mmHg. Noninvasive hemodynamic evaluation was performed before, during and after dialysis.

Results: Comparing with group 2, cardiac index (CI) was higher (P=0.252) while systemic vascular resistance index (SVRI) was lower (P=0.05) in group 1. The mean thoracic fluid capacity (TFC) of the two groups were similar (P=0.424) before dialysis. Serum Ca, PTH, ALP, ventricular ejection fraction and vascular calcification score of thoracic aorta, abdominal aorta and heart valve before PTX, as well as the weight of the removed parathyroid glands, serum Ca, ALP, hemoglobin after PTX of the patients were determined. No statistical differences were found. However, the phosphorus level was lower in group 1 both before and after PTX. CI, SVRI and TFC were similar in both groups during hemodialysis.

Conclusions: Patients with hypotension after PTX have a lower systemic vascular resistance index and a higher cardiac index, which might be associated with serum phosphorus level.

Funding: Government Support - Non-U.S.
PUB522

Cost of Medications Used in the Management of Secondary Hyperparathyroidism (SHPT) in Patients with End Stage Renal Disease (ESRD)  1  Leigh Darryl Quarles, 2  Vasily Belozeroff, 1  Kerry Cooper, 1  Jonathan D. Campbell. 3  Amgen Inc., Thousand Oaks, CA; 4  Univ of Tennessee, Memphis, TN; 5  Univ of Colorado, Aurora, CO.

Background: Management of SHPT associated with ESRD is complex, typically requiring combinations of medications. Eighty-two percent of the ESRD population is covered by Medicare with detailed drug expenditures reported annually by the US Renal Data System. For the remaining 18% covered by commercial health plans, drug expenditure information is unknown. The purpose of this study is to estimate the cost of medications used in the management of SHPT in ESRD patients from the US commercial health plan perspective.

Methods: Economic analysis with one-year time horizon to estimate per-member-per-month (PMPM) cost for SHPT related medications: calcium and non-calcium-based phosphate binders, calcitriol or active vitamin D analogs, and calcimimetics. Input parameters include: prevalence of ESRD in commercial health plans (MarketScan®); medication utilization and non-adherence (IMS Health for oral medications and Outcomes Plus for intravenous [IV] medications); and medication wholesale acquisition costs (WAC) (AnaSource.com) with one-way sensitivity analysis.

Results: The total PMPM (2014 US Dollars) cost of SHPT-related medications is $0.34: cinacalcet $0.06, phosphate binders $0.16, oral vitamin D $0.02, and IV vitamin D $0.10.

Figure 1. Total PMPM Cost Breakdown

Results are most sensitive to variation in ESRD prevalence and cinacalcet WAC parameters.

Conclusions: Results indicate that the collective cost of medications for the management of SHPT in commercial health plans is substantial with the cost of cinacalcet being lower compared to phosphate binders and IV vitamin D, but higher compared to oral vitamin D.

Funding: Pharmaceutical Company Support - Amgen Inc.

PUB523

Medullar Compression by Bone Tumor: Case Report  1  Cinthia Sobral Vieira, Nicole D.T. Carvalho. 2  Nephrology Unit-Cliniefero, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.

Background: The presentation of vertebral tumors may have different kinds of manifestation. They can mimic neoplastic, inflammatory and congenital diseases. The presentation of vertebral tumors may have different kinds of manifestation. They can mimic neoplastic, inflammatory and congenital diseases. The presentation of vertebral tumors may have different kinds of manifestation. They can mimic neoplastic, inflammatory and congenital diseases. The presentation of vertebral tumors may have different kinds of manifestation. They can mimic neoplastic, inflammatory and congenital diseases.

Methods: A 66 years old masculine patient, with chronic renal disease in hemodialysis for 5 years, non-adherent to treatment or diet, had his levels of phosphate, calcium/phosphorus, alkaline phosphatase and parathyroid hormone (PTH) elevated in the last year. He did not take the medication prescription: Calcitriol and Sevelamer. The patient came to the ER of a general hospital referring constipation and abdominal distention. During the hospitalization, he started to refer paresthesia in inferior members with progressive march dysfunction. The neurological exam showed ataxic/calcaneal gait and strength reduction (4+/5+) in the inferior members.

Results: At first, an angiotomography study of the mesenteric vessels were made, thinking of the possibility of mesenteric ischemia, but the exam showed multiple lytic lesions in the corps of lumbar vertebrae and in the hipbones, mimicking secondary implants. The bone MIR demonstrated one lytic bone lesion at the level of D6 and D7 causing medullar compression. The bone scintigraphy was suggestive of a metastatic bone disease and the parathyroid scintigraphy showed a hyperfunctioning tissue, in the parathyroid left pole. The patient was submitted to a compressive laminectomy, the biopsy revealed a Brown Tumor. Then, it was indicated a parathyreodectomy. The pathological result showed no evidence of malign disease. Nowadays, the patient is still in hemodialysis, receiving calcium and under physiotherapy to recover muscle strength, already walking.

Conclusions: Brown Tumor or osteoclastoma is a rare bone lesion, an incidence of 1.4 to 13% in chronic renal patient due to a secondary hyperparathyroidism and less than 5% in primary hyperparathyroidism. It is more frequent in women. The vertebral involvement is uncommon. This case report has its importance for calling attention to importance to include brown tumor as a differential diagnosis in compressive spine lesions especially in chronic renal patients.

PUB524

Rescue-Therapy with Lanthanum-Carbonate (LC) in Uncontrolled Hyperphosphatemia in Dialysis  1  Nicola Giotta, Angela maria Marino. 2  Dept of Medicine, Nephrology and Dialysis Unit, Cardinal Massaia Hospital, Asti, AT, Italy.

Background: Control of hyperphosphatemia in hemodialysis provides an approach based on changes in diet, dialysis efficiency improvement, and use of phosphate binders. The latter, however, in some patients do not prove effective, conditioning the indirect increase of mortality and morbidity of the subject on dialysis. The objective of this study was to evaluate the difference in efficacy of a regimen of lanthanum carbonate plus standard therapy (LTS) compared to standard therapy alone (TS) in the treatment of patients with persistent hyperphosphatemia, as rescue-therapy.

Methods: We conducted an observational study of data on consecutive patients in hemodialysis who have presented more than four phosphorus values greater than 6 mg/dL in three months. Patients treated with TS, have varied therapeutic scheme introducing LC. Patients treated with sevelamer have outstanding this therapy and were treated with LC. The data analysis has been done considering a retrospective phase (FR) of three months and a prospective phase (FP) of six months, for each subject analyzing the effectiveness of therapy before and after enrollment.

Results: In a cohort of 163 patients on hemodialysis, we have selected for the study, 14 patients who had a mean age of about 65 years and length of dialysis than 6 years. The combination of LC plus TS produced a significant increase in the proportion of patients achieving the therapeutic targets as defined by the K/DOQI Guidelines. Reduction of 2.12 mg/dL (-32.7%) than the average of the P phase prospective (4.55 mg/dL) than the retrospective phase (6.27 mg/dL), was statistically significant (p < 0.01), associated with the reduction of 19:21 mg2/dl2 (-32.9%) of the average value of CaXP in the prospective phase (39.07 mg2/dl2) compared to the retrospective phase (58.28 mg2/dl2), also statistically significant (p < 0.001). The patients at the target of the FP accounted for 92.31% for P and 100% for the CaXP, respectively vs. the 7.14% and 50% of FR.

Conclusions: The introduction of the LC-as rescue therapy in the treatment of hemodialysis patients with uncontrolled hyperphosphatemia resulted very effective allowing more easily reach the therapeutic objectives.

PUB525

Glucocorticoid-Induced Osteoporosis in Renal Patients  1  Gabrielle Goldet, George Greenhall,2  Alan D. Salama. 3  Basildon and Thurrock Univ Hospital; 4  Royal Free Hospital, London; 5  Royal Free Hospital, London.

Background: Glucocorticoid-induced osteoporosis (GIO) is associated with severe morbidity due to fragility fractures as well traumatic fractures and 50-90% of patients on long term steroids are affected by GIO. GIO is relevant in the renal context as steroids are widely used to treat renal disease and as part of immunosuppression in transplant. Also, renal patients are already at higher risk of fractures in association with renal bone disease.

Methods: We designed and undertook an audit to assess screening and management of GIO in nephrology outpatients in a university hospital in London, using national guidelines as a benchmark for our performance. We then presented the results at a local meeting, produced posters and leaflets on GIO to be placed in the outpatient waiting area for patients so as to raise awareness of this issue and provided a simple algorithm to be followed by clinicians in all the clinic rooms. We then re-audited after 6 months.

Results: 100 patients were audited in each audit cycle. Measures audited were a) whether all patients over 65 were treated with bone-sparing agents (BSA); b) whether all patients with documented fragility fracture were treated with BSA; c) whether all patients under 65 without fragility fracture underwent DXA scan; d) whether all patients with T-score below -2.5 were treated with BSA; e) whether all patients with T-score 0 to -1.5 underwent repeat DXA within 3 years; f) whether BSA was prescribed for all patients where indicated; g) whether all patients were managed according to national guideline (cycle 1: 29%; cycle 2: 41%). See table for breakdown of results.

<table>
<thead>
<tr>
<th>Audit measure</th>
<th>Audit 1 percentage (%)</th>
<th>Audit 2 proportion of patients meeting target</th>
<th>Audit 2 percentage (%)</th>
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<td>29/100</td>
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<td>41/100</td>
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Conclusions: Our intervention has improved performance as measured against national guidelines, though the rate of GIO screening remains low. Many patients could potentially benefit from bone protection, though larger studies would be needed to demonstrate an effect on fracture incidence.

Funding: Government Support - Non-U.S.
The Kidney Stone and Increased Water Intake Trial in Steel Workers: Results from a Pilot Study
Hakam Gharbi,1 Yair Lotan,2 Jodi Antonelli,2 Inmaculada Buendia Jimenez,3 Allison Ahrens Beaver,4 Aphril Dennis-Barrie,4 Dendra K. Von merveldt,5 Suzie Carter,3 Adam B. Cohen,2 John Pointdexter,6 Orson W. Moe,7 Margaret S. Pearl.1 1Urology, Dallas, TX; 2Mineral Metabolism, Univ of Texas Southern Medical Center, Dallas, TX; 3Mineral Metabolism, Univ of Texas Southern Medical Center, Dallas, TX; 4Mineral Metabolism, Univ of Texas Southern Medical Center, Dallas, TX; 5Mineral Metabolism, Univ of Texas Southern Medical Center, Dallas, TX; 6Mineral Metabolism, Univ of Texas Southern Medical Center, Dallas, TX; 7Mineral Metabolism, Univ of Texas Southern Medical Center, Dallas, TX.

Background: Preventing dehydration in subjects at risk may provide a means of primary prevention of kidney stones. The purpose of this pilot study was to assess the hydration status of an at-risk group of steel plant workers based on end-of-shift ("post-shift") spot urine osmolality and 24-hour urinary stone risk parameters.

Methods: 100 volunteers were recruited from Gerdau Midlantic steel mill in Texas on 11/14/14 and 12/5/14. Clinical data was recorded and a post-shift spot urine sample was obtained for measurement of urine osmolality. In addition, participants were invited to submit a 24-hr urine sample within 4 weeks of enrollment.

Results: Mean age was 41 and 95% were men. The majority of subjects were white (75%), followed by 10% Hispanic and 9% Black. Mean body mass index was 30.1 kg/m2 and overall 16% had past history of stone disease. Mean post-shift urine spot osmolality was 704.5 mOsm (169-1165 mOsm) and was >800 mOsm and >700 mOsm in 39% and 57%, respectively. Among 59 24-hour urine samples, mean volume was 1.89 ± 0.92 l/day, with 56% <2 liters and 17% <1 liter. Elevated levels of urinary analytes were found in 29% of subjects for calcium (>250mg/TV), 39% for uric acid (>700 mg/TV), 25% for oxalate (>45mg/TV) and 50% for sodium (>200 meq/TV).

Conclusions: The prevalence of stone disease in this population of steel workers is higher than the published prevalence of stone disease in the general population. A significant number of workers had concentrated post-shift and 24-hour urines and elevated levels of urinary analytes.

chronic renal pain in medullary sponge kidney
Giovanni Gambaro,1 Jackie Hirsch,2 Rocco Baccaro,1 Nicole Topilow,2 Matteo Bargagli,1 David S. Goldfarb,3 Pietro Manuel Ferraro.1 1Nephrology, Catholic Univ, Rome, Italy; 2NY Univ, School of Medicine, New York, NY.

Background: MSK usually occurs with recurrent stones; less frequently it is asymptomatic; very rarely the main manifestation is severe chronic flank pain. Often these pts are accused of seeking pain medications. Because of the rarity of such a presentation it is not clear whether pain is due to intense lithogenic activity or is independent of it, something like a form of the “loin pain hematuria syndrome”. Three Facebook support groups exist for North American patients with MSK and chronic pain. Their cooperation allowed us to investigate chronic pain in MSK.

Methods: An ad hoc questionnaire and the Brief Pain Inventory were administered through a dedicated web site; 92 patients (89 females) participated after verification of the diagnosis of MSK (imaging and diagnosis certified by a nephrologist or urologist).

Results: Mean age of patients was 39.8y (range 24-66). Age at onset of manifestations and MSK diagnosis were 23y (4-47) and 31y (7-57), respectively. Manifestations at onset were: flank pain (31%), reno-ureteric colic (RUC) (26%), hematuria (19%), cystitis (14%), pyelonephritis (10%). 71% of pts had daily pain, 76.5% have taken painkillers in the past week and 69.1% needed them at the time of questionnaire administration; 58% take them 1 time/day. The strong pain (5.4 in a scale from 0 to 10), jeopardizes general activities, mood and sleep. Only 4.6% of pts have RUC like pain; in 52.9% it is non-radiating flank pain with manifestations of possible UTI or stone passage (painful micturition, urgency, frequent uriination, hematuria, fever); in 42.5% it is non-radiating lumbar pain without other manifestations (however only in 3 cases the pain was a unilateral flank pain). Pain is frequently associated with stone (67%) or sand passage (46%), hydronephrosis (42%), hematuria (42.4%).

Conclusions: Although in these MSK pts the chronic pain that dominates the clinical manifestations is usually associated with some of the typical symptoms of stone passage, in a fraction of pts this is not the case and pain is not associated with lithogenic activity. The etiology of this pain syndrome remains uncertain and merits investigation.

Funding: Government Support - Non-U.S.

Difference in Vitamin D Level Between Older and Younger Kidney Transplant Recipients
Mohamed Amin Elesnawi, Abdullah Hamad, Fadwa S. Al-Ali. Nephrology, Fahd Bin Jasim Kidney Center, Hamad General Hospital, Doha, Qatar.

Background: Vitamin D deficiency is more common in older than younger people. In kidney transplant recipients, vitamin D deficiency has a high prevalence of up to 80% according to recent studies. We compared vitamin D status in older versus younger patients with kidney transplant.

Methods: We reviewed all available record of kidney transplant recipients that came to our clinic at Hamad General Hospital in Qatar between September 1st 2013 and March 1st 2014. We recorded background data and laboratory tests. Patients divided into 2 groups younger and older (below and above 60 years old respectively). All patients were receiving vitamin D supplement.

Results: 102 patients were included. 52 patients in the younger group and 50 patients in the older. Age was 68.6±5.9 years in the older versus 41.9±10.4 years in the younger group. Table (1) compare laboratory values between the two groups. Vitamin D status was classified (normal above 30, mild 20-29, moderate 10-19 and severe below 10 ng/mL) figure (1).

Vitamin D status in elderly versus young kidney transplant patients

<table>
<thead>
<tr>
<th>Vitamin D Status</th>
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<th>Older (n=50)</th>
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</thead>
<tbody>
<tr>
<td>vitamin d</td>
<td>21.2±16.8 ng/mL</td>
<td>21±9.3 ng/mL</td>
</tr>
<tr>
<td>calcium</td>
<td>2.3±0.16 mmol/L</td>
<td>2.27±0.12 mmol/L</td>
</tr>
<tr>
<td>phosphorus</td>
<td>1.4±0.29 mmol/L</td>
<td>1.22±0.2 mmol/L</td>
</tr>
<tr>
<td>alkaline phosphatase</td>
<td>90±39.2 u/L</td>
<td>74.1±41 u/L</td>
</tr>
<tr>
<td>intact parathyroid hormone</td>
<td>120±142 pg/mL</td>
<td>140.8±223 pg/mL</td>
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</table>

Conclusions: In a comparative study, we found that older transplant recipient group had more male patients (pValue<0.05), lower alkaline phosphatase and higher intact parathyroid hormone (not statistically significant) but similar vitamin D, calcium and phosphorus level. There was a trend towards milder vitamin D deficiency in the older group that could be due to better compliance with vitamin D supplement. Despite vitamin D supplement protocol and long sunny days in Qatar we still found high rate of vitamin D deficiency in transplant recipients (81.4%).

Efficacy of Low Dose, Alternate Day Cinacalcet for Treatment of Secondary Hyperparathyroidism in Hemodialysis Patients: A Randomized Controlled Trial
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Background: Secondary hyperparathyroidism (SHPT) is common in hemodialysis patients and has been associated with increased mortality. Cinacalcet, a modulator of calcium-sensing receptor, effectively reduced serum parathyroid hormone (PTH) in clinical studies. We tested whether prescription of low dose, alternate day cinacalcet could be an option for treatment of SHPT.

Methods: An open-labeled, randomized controlled trial enrolled hemodialysis patients with severe secondary hyperparathyroidism (intact PTH > 550 pg/ml). Patients were randomized to received low-dose cinacalcet (25 mg alternate day) or standard-dose (25 mg daily) for 16 weeks. At 8 weeks, doses of cinacalcet could be increased to achieve KDIGO PTH target of less than 585 pg/ml. The primary outcome was the difference in percentage of patients achieving KDIGO target at 16 weeks. The changes of serum iPTH, other biochemical data were also tested.

Results: Between July 2014 and January 2015, a total of 30 hemodialysis patients (15 females, 15 males) were randomly assigned to a treatment group: 16 to low-dose and 14 to standard-dose. Baseline iPTH in low-dose and standard-dose group was 1,065.9 ± 477.7 and 1,211 ± 466.5 pg/ml respectively (p = 0.409). During study period, 4 patients (2 from each group) were dropout from study due to adverse events. Intention to treat analysis showing that the percentage of patients who achieving KDIGO PTH target was not different (38.5% in low-dose group compared with 30.8% in standard-dose group, p = 1.0). Serum iPTH reduction during 16 weeks of study period in low-dose and standard-dose group was 253.5 ± 316.1 and 330.6 ± 698.2 respectively (p = 0.731). The adverse events were not different between both groups except hypocalcemia that tend to be higher in standard-dose (38.5% vs 13.3%, p = 0.274).

Conclusions: Among patients with SHPT, cinacalcet 25 mg alternate day may be sufficient effectively decrease serum iPTH levels with low incidence of hypocalcemia. The role of low dose cinacalcet in SHPT should be determined in large-scale, adequately powered randomized controlled trials.

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Underline represents presenting author.

1010A
Parathyroid Hormone Stability in Hemodialyzed Patients: Comparison on Non-Centrifuged EDTA and Serum Samples with 2nd and 3rd Generation Assays

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Background: PTH stability is of importance. Many studies have shown divergent results between EDTA and serum, mainly linked to differences in protocols or cut-offs used to decipher whether PTH remained stable or not. No studies have yet compared PTH as measured by 2nd and 3rd generation assays on the same samples in hemodialyzed (HD) patients.

Methods: Five pairs of samples (EDTA and gel tubes) were obtained in 10 HD patients before session. One pair was centrifuged and run immediately to establish the “T0”. Two pairs were kept at -4°C and +25°C. They were centrifuged after 4 and 18 hours. Supernatant was kept at -80°C for one week. Then, all samples were measured in a single batch, on Roche Cobas andDiaSorin XL. 2nd and 3rd generation PTH assays. Samples were considered as stable if 90% of subjects had a decrease lower than a total change limit (TCL) that takes both analytical and biological variability into consideration. All determinations were run in duplicates.

Results: At T0, no difference was observed between plasma and serum for any of the methods. PTH decreased in all samples and degradation was the same with 2nd or 3rd generation assays, whatever the method used. Percentages of decrease were systematically lower in EDTA plasma compared to serum and none of our subjects presented a decrease higher than the TCL with EDTA plasma. In serum, PTH was not considered as stable, but only when kept at 25°C for 18 hours.

Conclusions: PTH stability is of paramount importance for correct interpretation of the results. Many studies have tried to evaluate this stability but are not free from criticism, mainly due to a poorly defined T0 and questionable acceptance limits. In this study, we used an unfrozen T0 and decision limits based on analytical and biological variations. Moreover, we tested 2nd and 3rd generation PTH on two automated platforms. Our results show that, if PTH is basically more stable in EDTA plasma than in serum, this advantage is only clinically significant when samples are stored for a long period (18h) at +25°C.

Conclusion: Vitamin D insufficiency is highly prevalent in patients on dialysis and in hypertensive controls, and only partially resolves after kidney transplantation.

Vitamin D Metabolism Is Incompletely Restored After Kidney Transplantation

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Background: Vitamin D deficiency is widely reported in patients with renal impairment and is associated with adverse outcomes. The extent and rate of recovery of vitamin D metabolism after kidney transplantation is uncertain.

Methods: We enrolled 175 dialysis patients (HD) listed for kidney transplantation, and 85 hypertensive but otherwise healthy controls (HTN). We determined blood markers of mineral metabolism including intact FGF23 and vitamin D metabolites at entry (or immediately pre-transplantation), and 2 months. As a surrogate for vitamin D deficiency, we assessed the 25(OH)D3: 24,25(OH)2D3 ratio (D-ratio, normal 5-25).

Results: Of 175 dialysis patients, 76 were transplanted (TXR) during the study. TXR were younger with a lower BMI than controls. FGF23 was higher in HD patients than HTN at baseline, but normalised after 12 months (p=0.13). At baseline, vitamin D insufficiency (defined as 25(OH)D <30 ng/mL) was present in 82 of subjects and did not differ between groups. However, vitamin D deficiency (defined as 25(OH)D <10 ng/mL) was more common in dialysis (15% versus 4%, p=0.49). The baseline D-ratio was higher in HD (48, IQR 27-67) than in HTN (16, IQR 14-18, p<0.0001) patients. Transplantation resulted in significant reduction in D-ratio after 2 and 12 months compared to HD (p=0.0008 and p=0.005 respectively). The slope of D-ratio vs 25(OH)D3 increased after transplantation, but remained lower than for HTN controls, suggesting reduced expression or activity of the cataboly CYP24A1 (25-OH-D3-24-hydroxylase) in kidney failure.

Conclusion: Low TA-iPTH levels during the first 12 months after initiation of dialysis (group 1: <65pg/ml, group 2: 65 to 300 pg/ml, group 3: >300pg/ml). Cox regression analysis was performed to determine the prognostic value of TA-iPTH on overall mortality and MACCEs.

Results: The mean age was 56.5 + 14.5 years and 222 patients (53.8%) were male. During a median follow-up of 50.8 months, 49 patients (11.9%) were dead and MACCEs were occurred in 55 patients (13.3%). Multivariate Cox regression analysis demonstrated that low TA-iPTH level was an independent risk factor for both overall mortality [group 2 as reference; group 1, hazard ratio (HR)=2.08, 95% confidence interval (CI)=1.2-3.85, P=0.02] and MACCEs (HR=1.88, 95% CI=1.04-3.40, P=0.04) in incident dialysis patients after adjusting confounding factors.

Conclusion: This study demonstrates that low TA-iPTH is an independent risk factor for overall mortality and MACCEs in incident dialysis patients.

Combined Analysis of Hypercalcemia and PTH Levels as Clue to Unveil Persistent Transplant Hyperparathyroidism

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Background: Mineral and bone metabolism disorders in chronic kidney disease (CKD-MBD) are not always corrected after kidney transplantation (TxR). The persistence of hyperparathyroidism may have a negative impact on patient and graft outcome. Our objective was to evaluate the evolution off CKD-MBD and the incidence of hyperparathyroidism after 12 months of TxR.

Methods: In this study, we included all consecutive patients submitted to a TxR during the period between Jan 2010 and Dec 2014 in a University based center. We excluded patients with a PTH <300 pg/ml before TxR, multi-organ transplants, patients with an eGFR<30mL/min and those who underwent parathyroidectomy after TxR. Twelve-month eGFR, plasma levels of total calcium (Ca), phosphorus (P), alkaline phosphatase (AlkP), magnesium (Mg), parathormone (PTH), and 25-hydroxy vitamin D (25-OH vit D) were compared to baseline values. A PTH >100pg/mL and a total calcium >10.2mg/dL were considered abnormal. We defined high PTH, with or without hypercalcemia as the primary endpoints for the analysis.
Results: During the observation period, 408 patients were evaluated. There was a significant increase in gFR and in calcium levels 12 months after the TxR. Compared to the baseline, PTH, AlkP, and P significantly decreased. 25-OH VitD did not change during the period. Fifteen percent of patients presented both PTH and Ca above the reference levels, while 37% presented isolated high PTH and 8% hypercalcemia only. Multivariate analysis disclosed that post-TxR hyperparathyroidism was dependent on pre-transplant PTH (OR 1.001; CI 95%: 1.001-1.002) and Ca (OR 1.23; CI 95%: 1.036-1.468).

Conclusions: Monitoring Ca and PTH before and after TxR may be important to detect patients at high risk of persistent hyperparathyroidism, and to identify patients in need of treatment to prevent its complications.

PUB534
Predictors of FGF23 and Soluble Klotho in HIV Infection Rubin Wang,1 Michael Shlipak,2 Joachim H. Ix,1,2 Michelle M. Estrella.1 Johns Hopkins Univ: 1UCSF, 2UCSD.

Background: In the general population, FGF23 and its co-receptor, soluble klotho (sKlotho), have been implicated in the aging process. HIV+ individuals are at higher risk of age-related comorbidities compared with HIV- persons. We evaluated whether FGF23 and sKlotho levels differed by HIV status and determined clinical factors associated with each hormone in HIV+ men.

Methods: 384 HIV+ and 225 HIV- men in the Multicenter AIDS Cohort Study (MACS) were randomly selected for FGF23 and sKlotho measurements from samples stored in 2008-2010. We compared FGF23 and sKlotho levels by HIV status, adjusted for age and race. Multivariable linear regression models were used to determine predictors of FGF23 and sKlotho levels among HIV+ men.

Results: Mean age was 53±20 years; 34% were black; median eGFR was 35.7 mL/min/1.73m². FGF23 levels were 94 [73–141] RU/mL. FGF23 did not change significantly after adding either HCT (99 [74–148] RU/mL) or low sodium diet (98 [57–135 RU/mL]) to HIV- counterparts. Among HIV+ men, clinical predictors associated with FGF23 differed from those associated with sKlotho. Mechanisms by which HIV treatment and co-morbidities impact these hormones need further study.

Conclusions: HIV+ individuals had similar FGF23 but higher sKlotho levels compared to HIV- counterparts. Among HIV+ men, clinical predictors associated with FGF23 differed from those associated with sKlotho. Mechanisms by which HIV treatment and co-morbidities impact these hormones need further study.

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PUB535
Response of Fibroblast Growth Factor 23 to Sodium Interventions in Diabetic Nephropathy and Arterial Hypertension Jolmer K. Humalda,1 Sahoo Arjun,2 Veggeloe,2,3 Gunnar H. Heinc;2 Martin H. De Borst.1 Nephrology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia; 2Nephrology and Hypertension, Saarland Univ Medical Center, Homburg, Germany; 3Nephrology, VU Medical Center, for NiGrAm, Amsterdam, Netherlands.

Background: Fibroblast growth factor 23 (FGF23) rises progressively in chronic kidney disease (CKD) and is associated with adverse cardiac outcomes. Both CKD patients with diabetic nephropathy (DN) and patients with hypertension are vulnerable to the effects of excess sodium. We hypothesized that renin-angiotensin system (RAS) inhibition (ACEi) with four 6-week trial in 45 DN patients on background ACE inhibition would inhibit tubular phosphate reabsorption. Chronic kidney disease (CKD) leads to FGF23 excess and deficiency of sKlotho. Mechanisms by which HIV treatment and co-morbidities impact these hormones need further study.

Methods: We performed a post-hoc analysis of a randomized controlled 2x2 crossover trial in 45 DN patients on background ACE-Inhibition (ACE) with four 6-week treatment periods with add-on hydrochlorothiazide (HCT) or placebo, combined with regular (RS) or low sodium (LS) diet. Plasma C-terminal FGF23 was measured by ELISA (Immutopics). Additionally, FGF23 was measured in 12 patients with arterial hypertension but without overt CKD before and after 4 hours of intravenous administration of 2 liters sodium-chloride 0.9%. Changes in FGF23 were assessed by Friedman’s test and Wilcoxon Signed Rank test as appropriate.

Results: DN patients were 65±9 years old (mean±SD). During ACE+RS eGFR was 65±25 mL/min/1.73m², HbA1c 7.1±0.8% and albuminuria 649 mg/d median [1st- 3rd quartile: 230-2008 mg/d]. FGF23 levels were 94 [73–141] RU/mL . FGF23 did not change significantly after adding either HCT (99 [74–148] RU/mL) or low sodium diet (99 [75–135 RU/mL]) or both HCT and low sodium diet (111 [81–160] RU/mL) P=0.15. The FGF23 response with arterial hypertension were 45/13 years old with an eGFR of 101±18 mL/min/1.73m². Sodium-chloride infusion did not affect FGF23 (before: 68 [58–97] RU/mL, after: 67 [57–77] RU/mL, P=0.4).

Conclusions: Chronic and acute changes in sodium status did not materially change FGF23 in DN and hypertensive patients, respectively. Our data thus do not support a direct feedback loop between volume status and FGF23 in diabetic nephropathy or hypertension.

PUB536
Hypocalcaemia Management Post Parathyroidectomy in Renal Patients – On Experience and Change in Practice Rajkumar Chirnadhar, Maharajan Raman, Constantin Chrysochou, Smeeta Sinha. Dept of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom.

Background: Hypocalcaemia is common post parathyroidectomy in renal patients with secondary hyperparathyroidism due to hungry bone syndrome with an incidence as high as 51%. Hypocalcaemia can be prevented by effectively preloading patient with Vitamin D supplements and close monitoring of calcium levels post operatively. Currently there is no clear guidance on the preloading dose of one-alcacidol in literature. Our current practice is to preload all patients with 2 mcg one-alcacidol for 5 days pre operatively. Our aim was to study the management of hypocalcaemia post parathyroidectomy in renal patients and factors influencing length of hospital stay (LOS). To identify if any changes in current practice could improve outcome.

Methods: Retrospective observational study of all renal patients who underwent parathyroidectomy under a single surgeon over 6 years (April 2008 to September 2014). Data was collected from the Electronic Patient Record. Data were analysed using Stats direct and Fisher Exact test was used for testing statistical significance.

Results: 72% of our sample (n = 25) were male with a mean age of 54. Of the 25 there were 13 transplant, 9 haemodialysis and 3 CKD patients. The mean hospital stay was 5 days shorter than quoted in the literature (5.6 Days). 3 of 25 patients were not preloaded with one-alcacidol and 3 had secondary hyperparathyroidism due to hungry bone syndrome with an incidence as high as 51%. Hypocalcaemia can be prevented by effectively preloading patient with Vitamin D supplements and close monitoring of calcium levels post operatively. Currently there is no clear guidance on the preloading dose of one-alcacidol in literature. Our current practice is to preload all patients with 2 mcg one-alcacidol for 5 days pre operatively.

Conclusions: Insufficient preloading was identified as a major risk factor for hypocalcaemia, which significantly increased LOS. Further to consensus between renal and surgical teams we have increased the preloading dose of one-alcacidol to 5 mcg for 5 days pre operatively. A follow up study is planned in 12 months to observe the outcome of this change.

Funding: Private Foundation Support

PUB537
Links Between Urinary Phosphate Handling, FGF23 and Klotho: An Australian Single-Centre Cross-Sectional Study Sven-Jean Tan,1,2 Edward Robert Smith,1 Stephen G. Holt,1,2 Tim Hewlton,1,2 Nigel David Toussaint.1,2 1Nephrology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia; 2Medicine (RMH), The Univ of Melbourne, Melbourne, Victoria, Australia.

Background: Aim: To examine the links between measured phosphate parameters and regulators of phosphate homeostasis (fibroblast growth factor-23 [FGF23] and soluble α-klotho [sKlotho]). Background: FGF23, via the FGF-Receptor/Klotho complex, reduces expression of sodium-phosphate co-transporters thereby inhibiting tubular phosphate reabsorption. Chronic kidney disease (CKD) leads to FGF23 excess and deficiency of sKlotho. Elevated serum phosphate (sP) results as remaining function nephrons are unable to compensate for reduction in total phosphate excretion. Complex relationships between these parameters in health and disease, and the impact on phosphate handling, are not fully understood.

Methods: Blood samples and spot and 24-hour urine were collected from patients with CKD (Stages 1-5) and healthy volunteers. Serum and urine biochemistry, intact FGF23 and sKlotho were analysed. FGF-23 and sKlotho were log-transformed (Ln). Fractional excretion of phosphate (FEp) and maximal tubular phosphate reabsorption (TmP) were calculated. Pearson correlation coefficients were used to assess correlation between phosphate handling and regulatory hormones.

Results: 116 participants (77 CKD and 39 controls) were recruited. 74 (63.8%) were male. Median (IQR) age of all participants was 61 (49-71) years. FGF23 and FEPi were higher, while sKlotho and TmP were lower, in CKD compared to controls (all p<0.005). Adjusting for eGFR, LnFGF23 correlated with FEp (R=0.22, p=0.026) and sP and FEp (R=0.26, p=0.003). Notably, higher FEp was associated with lower sKlotho (R=-0.328, p=0.001) and sP (R=0.309, p=0.002). There was no association between LnFGF23 and LnKlotho.

Conclusions: Disruption of phosphate regulatory mechanisms is characteristic of CKD. In this small cohort, we established that FGF23 contributes to phosphate excretion. However, sKlotho may provide insight into a greater physiological role of Klotho in regulating TmP at a cellular level. Causal relationships should be explored further in vitro.

Funding: Private Foundation Support

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1012A
**PUB538**

**Fibroblast Growth Factor 23 Can Predict the Progress of Aortic Artery Calcification in Dialysis Patients**  
Zijin Chen, Xiaonong Chen, Xiaobo Ma, Bei Ding, Huawei Ling, Nan Chen.  
Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong Univ School of Medicine, Shanghai, China; Department of Radiology, Ruijin Hospital, Shanghai Jiaotong Univ School of Medicine, Shanghai, China.

**Background:** To investigate the factors associated with progress of aortic artery calcification in maintenance haemodialysis (MHD) patients and to determine whether plasma FGF23 level is related to progress of aortic artery calcification.

**Methods:** MHD patients from Ruijin Hospital from July 1st 2011 to July 31th 2011 were involved in our study. Follow up 36 months. Aortic artery calcification (AAC) was detected by a lateral lumbar X-ray plain and read by two radiologists.

**Results:** 120 MHD patients were enrolled and followed up for 36 months. To July 2014, a total of 67 MHD patients finished the study. Among 67 patients, 32 were male, mean age 53.9±13.1 years old, mean dialysis vintage 44.1±31.8 months, median FGF23 level 48052 (11372-35750.4)Ru/ml, LgFGF23 3.79±0.83. In July 2011, 53.7% of patients had visible calcification in the abdominal aorta and mean involved segment was 1.42 with mean AAC scores(AACS) 3.96. In July 2014, 73.1% had AAC and mean involved segment was 2.34 with mean AACS 10.7. There are significant differences between two AAC involved segments and AACS (both P<0.001). Age, dialysis vintage and FGF23 level had significant difference between AAC progress group and no AAC progress group (P = 0.007, <0.001 and 0.020, separately). Logistic analysis showed that the independent parameters associated with AAC progress were age (OR=1.114, CI:1.045-1.186) and LgFGF23 (P = 0.007, <0.001 and 0.020, separately). The severity of vascular calcification progress yearly in maintenance haemodialysis patients. Age and FGF23 are independently associated with the progress of AAC. FGF23 level could predict the progress of AAC in MHD patients.

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

**Conclusions:** The severity of vascular calcification progress yearly in maintain haemodialysis patients. Age and FGF23 are independently associated with the progress of AAC. FGF23 level could predict the progress of AAC in MHD patients. Funding: Government Support - Non-U.S.

**PUB539**

**Could FGF23 Be a Regulator of Hepcidin in Liver Cells?**  
Justine Bacchetta, Nathalie Domencheaux, David Duranent. Hospices Civils de Lyon and INSERM, Univ Claude Bernard Lyon 1, Lyon, France.

**Background:** Hepcidin is a 25-amino-acid protein synthesized in hepatocytes and macrophages that acts as a post-translational inhibitor of ferroportin, the only receptor known to export iron from intracellular compartments to systemic circulation. Thus, higher hepcidin levels are associated with greater intracellular sequestration of iron, and increased risk of anemia. Vitamin D is an inhibitor of hepcidin expression; the working hypothesis is that FGF23 could be an “inverse” regulator of iron metabolism in comparison to vitamin D, with a stimulation of hepcidin expression, an increase of intracellular ferritin and an inhibition of ferroportin expression on the cell membrane, leading to a further intracellular sequestration of iron.

**Methods:** Three different types of liver cells were used: HepG2, HepaRG and primary human hepatocytes (PHH). Cells were exposed to FGF23 (1, 10 or 100-ng/mL), at different time points (0, 24, 48, 72 h). Cultures were performed in triplicates, and qRT-PCR in duplicates (StepOne Plus Real-Time PCR). Western Blots were also performed (Erk and Akt phosphorylation pathways, FGF1, FGF2, ferritin).  
**Results:** In HepG2, even though FGF1-expression was found by Western blot analysis, FGF23 did not modify hepcidin expression by qRT-PCR, and Erk/Akt pathways were not activated by FGF23. In HepaRG cells, hepcidin expression was modified with FGF23 by qRT-PCR, i.e. increased at 6 hours and decreased at 24 hours.

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

**PUB540**

**Prevalence of Hyperparathyroidism and Its Correlates in a Large Cohort of Hemodialysis Patients**  
Pusquale Esposito, Fabio Malberti, Elena Caramella, Marta Calatroni, Edoardo La Porta, Marina Foramitti, Rosanna Coppo, Antonio Dal Canton. Department of Nephrology, Istituti Ospitalieri di Cremona, Cremona, Italy; Department of Nephrology, Istituti Ospitalieri di Cremona, Cremona, Italy; Department of Nephrology, Regina Margherita Children’s Hospital, Turin, Italy.

**Background:** Beyond experimental setting of randomized trials, little is known about the occurrence of mineral bone disorders (MBD) in the real-life clinical practice of hemodialysis (HD). This is the reason why we designed this observational study to define the prevalence of hyperparathyroidism (HPT) and its correlates in a large cohort of HD patients.

**Methods:** We enrolled HD prevalent patients from 38 Dialysis Units collecting data on: clinical information, dialysis parameters, biochemical and instrumental evaluations and pharmacological therapy. According to the KDIGO guidelines we divided the patients in: patients affected by HPT (i.e. PTH> 9 the upper reference limit of each laboratory) vs patients on target.

**Results:** Out of 495 patients, 34 (6.8%- 59.9±15.5 years, 53%M) presented HPT with mean PTH of 1064±536 pg/ml, while 461 patients resulted OT (93.2%- 66.9±13.7 years, 66%M), mean PTH 242±151 pg/ml (p<0.0001). HPTs were younger than OT (59.9±15 vs 69.9±13.7 years, p=0.008), with a longer HD history (126.2±125 vs 64.3±69.4 months, p=0.0003). There were not significant differences in both clinical and dialysis parameters. Similarly, there were not differences in laboratory examination except from serum ALP that resulted higher in HPTs (194.8±142 vs 144.1±108 U/l, OT, p<0.01). Moreover, there were not differences in the use of phosphate binders, whereas a significantly higher percentage of HPTs was taking paricalcitol and calcimetics and the prescribed vitamin D doses (both as calcitriol and paracalcitriol) were significantly higher in HPT patients.

**Conclusions:** The prevalence of HPT in our population was surprisingly lower, compared to that reported in previous studies. This finding could be due to the general application of KDIGO guidelines, which recommend more permissive PTH levels compared to the previous K-DQOI guidelines, especially those to the availability of effective drugs, probably used more appropriately than in the past.

**PUB541**

**Effect of Vitamin D Receptor Activators on Glomerular Filtration Rate: A Meta-Analysis and Systematic Review**  
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**Background:** Vitamin D receptor activators (VDRAs) can protect against mineral bone disease, but they may also elevate serum creatinine and reduce glomerular filtration rate (GFR).

**Methods:** We conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) to evaluate the effect of VDRAs on kidney function and adverse events. MEDLINE, EMBASE, the Cochrane Controlled Trials Register were searched for RCTs that evaluate vitamin D receptor activators (alfacalcidol, calcitriol, doxercalciferol, falcalcitriol, maxacalcitol and paricalcitol) up to March 2015.

**Results:** We included 31 studies, all of which were performed between 1976 and 2015, which enrolled 2621 patients. Patients receiving VDRAs had lower eGFR (weighted mean difference WMD -1.29 mL/min/1.73m², 95% CI -2.42–(-0.17) and elevated serum creatinine (WMD 7.03 μmol/L, 95% CI 0.61–13.46) in sensitivity analysis excluding studies with dropout rate more than 30%. The VDRAs and control groups had no significant differences in all-cause mortality (relative risk RR 1.41, 95% CI 0.58–3.80), cardiovascular disease (RR 0.84, 95% CI 0.42–1.71), and severe adverse events (RR 1.15, 95% CI 0.75–1.77). Episodes of hypercalcemia (RR 3.29, 95% CI 2.02–5.38) were more common in the VDRAs group than in the control group.

**Conclusions:** Although administration of VDRAs slightly reduced the eGFR, all-cause mortality and severe adverse events were comparable between the groups. Future RCTs with larger sample sizes are needed to assess whether the mild reduction of eGFR is of clinical significance.
This study was an one-year intervention study for hemodialysis patients with hypovitaminosis D. During the first six months, patients received 3,000 IU of cholecalciferol after each hemodialysis (9,000 IU/week), thereafter, they stopped taking supplements. Serum levels of 25(OH)D and 1,25(OH)₂D, and other biological variables were measured every 3 months for one year. We investigated the effects of cholecalciferol supplementation on the biological variables and inflammatory markers. In addition, the effective factors on the levels of 25(OH)D and 1,25(OH)₂D after cholecalciferol supplementation were assessed by multivariate regression analysis.

Results: Twenty-nine patients with hypovitaminosis D participated in our study. During cholecalciferol supplementation, the 25(OH)D and 1,25(OH)₂D concentration significantly increased from baseline to six months (9.9 to 34.3 ng/mL, p = 0.001 and 19.7 to 22.9 ng/mL, p = 0.05, respectively). At 6 months, 65.5% of the patients had 25(OH)D levels within the target range [30 ng/mL] with a low dose of cholecalciferol supplementation. Also, serum calcium and phosphorus levels did not increase above the normal range. However, the inflammation markers, hsCRP, e-selectin, VEGF-A, were not shown significant effects of cholecalciferol supplementation on the biological variables and inflammatory markers. In addition, the effective factors on the levels of 25(OH)D and 1,25(OH)₂D after cholecalciferol supplementation were assessed by multivariate regression analysis.

Conclusions: The low dose cholecalciferol supplementation was effective in correcting serum vitamin D deficiency or insufficiency and safe for hemodialysis patients. However, 6 months of low dose cholecalciferol supplementation in these patients did not improve the levels of inflammatory markers.

Funding: Government Support - Non-U.S.
Methods: We performed a cross sectional study in 80 Tx (5510.5;49M/31W) with CKD stage 2-4 (GFR 47±16 ml/min). 30 healthy subjects (3412;43;30GFR95±19 ml/min) were the control group. We evaluated in all patients SOST, Ca, P, PTH, FGF23 and Alkaline Phosphatase (AP).

Results: SOST was not different between Tx and controls (27.6±10.2; 10.1±0.8; 3.0±0.7; 178.65±59; 51; 26±1 142±17 45.73±28.8). Serum levels of FGF23 were increased compared to controls (473±28.8 vs 30.31;00;0 pg/ml; p<0.05). SOST showed a negative correlation with AP (R=-0.75; p<0.05) and a positive correlation with FGF23 (R=0.23; p<0.05) and 25D (R=0.23; p<0.05). No correlation existed with other parameters.

Conclusions: eGFR does not seem to affect serum levels of SOST in Tx. The negative correlation with AP indicates that SOST maintains its modulatory role of osteoblastic activity in this population. The correlation with FGF23, which is in agreement with low FGF23 in SOST null mice, suggests modulatory effects of both proteins on osteoblastic direct, through Wnt inhibition, for SOST, indirect, through effects on 1,25D, levels for FGF23. Serum SOST may be an additional marker of bone metabolism, useful to understand metabolic pathways in normal subjects and in CRF.

PUB547

Comparison of Cholecalciferol Supplementation Dosing with a Bolus Dose Versus Daily Administration in Chronic Hemodialysis Patients

Background: The aim of this study was to assess the safety profile of bolus cholecalciferol supplementation and compare its effectiveness to daily oral administration in hemodialysis (HD) patients.

Methods: This 6-month prospective, intervention study enrolled 60 stable HD patients with 25-hydroxyvitamin D [25(OH)D] levels <30ng/ml, who received cholecalciferol 25,000 IU once or twice monthly (n=30) or 700 IU daily (n=30). Differences in biochemical parameters, including 25(OH)D, calcium, phosphorous, parathyroid hormone (PTH), alkaline phosphatase and C-reactive protein levels, were analyzed monthly. Primary outcome was 25OHD3 level at 6 months. For safety purposes, in the subgroup of patients with hypertension, hypokalemia, metabolic alkalosis and low plasma renin and aldosterone levels, were low. Given the clinical picture and autosomal recessive inheritance pattern, a provisional diagnosis of AME was made. 24 hour urinary cortisol and cortisone estimation was unavailable. We decided to confirm the diagnosis using next generation gene sequencing.

Methods: Whole blood was collected from the parents and the affected members after informed consent. 30 ng of the isolated high quality DNA was used to prepare library and sequencing. Sequencing was performed using the Illumina HiSeq platform. Variations were called using the GATK Unified Genotyper and analysed using ANNOVAR and annotated ClinVar.

Results: Analysis revealed the presence of homozygous variation p.R337C in HSD11B2 gene annotated to be pathogenic in ClinVar and confirmed to be deleterious using Sanger sequencing of the amplicons, confirming the diagnosis. All the patients were negative for GCKR gene which is known to be associated with hyperglycemia. In addition, the patient was not found to be positive for CYP2C9 and CYP2C19 which are known to be associated with drugs metabolism. The patient showed normal serum levels of vitamin D and calcium, consistent with the diagnosis of AME. The patient was treated with a combination of glucocorticoids and mineralocorticoids and the patient showed an improvement in his symptoms.

Conclusions: A homozygous mutation (p.R337C) variation in the HSD11B2 gene was demonstrated in the family using whole-exome sequencing. This is the first genetically demonstrated case of AME in an Indian population. Our study underscores the utility of next generation sequencing in the diagnosis of rare inherited diseases.

Funding: Government Support - Non-U.S.

PUB550

Genetics of Thrombotic Microangiopathies – The Viennese TMA Cohort

Background: Thrombotic microangiopathies (TMA) classified as hemolytic uremic syndrome (HUS) are characterized by acute kidney injury (AKI), mechanical hemolysis and thrombocytopenia, caused by an excessively activated alternative pathway of the complement cascade. The pathogenesis of TMA is still not fully understood. The aim of this study was to identify genetic variations associated with the risk of TMA in the Viennese population.

Methods: A total of 150 patients with TMA were enrolled in this study. Whole-exome sequencing was performed using Illumina HiSeq 2500 platform. Variations were called using the GATK Unified Genotyper and analysed using ANNOVAR and annotated ClinVar.

Results: Analysis revealed the presence of homozygous variation p.R337C in HSD11B2 gene annotated to be pathogenic in ClinVar and confirmed to be deleterious using Sanger sequencing of the amplicons, confirming the diagnosis. All the patients were negative for GCKR gene which is known to be associated with hyperglycemia. In addition, the patient was not found to be positive for CYP2C9 and CYP2C19 which are known to be associated with drugs metabolism. The patient showed normal serum levels of vitamin D and calcium, consistent with the diagnosis of AME. The patient was treated with a combination of glucocorticoids and mineralocorticoids and the patient showed an improvement in his symptoms.

Conclusions: A homozygous mutation (p.R337C) variation in the HSD11B2 gene was demonstrated in the family using whole-exome sequencing. This is the first genetically characterized case of AME in an Indian population. Our study underscores the utility of next generation sequencing in the diagnosis of rare inherited diseases.

Funding: Government Support - Non-U.S.
Under-Diagnosis of Alport Syndrome in First-Degree Relatives of Affected Individuals Clifford E. Kashtan, 1,2 Theresa F. Cassidy, 1,2 Michelle N. Rheault, 1,2 1Pediatrics, Univ of Minnesota, Minneapolis, MN; 2Alport Syndrome Treatments and Outcomes Registry (ASTOR).

Background: Alport syndrome (AS) is an important inherited cause of progressive renal disease. Hematuria, the cardinal feature of AS, is highly penetrant in affected individuals. Urinalysis is a sensitive method for detecting AS in relatives of AS patients. This report describes a cohort of at-risk individuals (first-degree relatives of known AS patients) who underwent a first urinalysis as part of a clinical trial feasibility study.

Methods: For a study entitled “Multi-center Controlled Clinical Trials in Alport Syndrome – A Feasibility Study” (R21 DK91480, Clinicaltrials.gov #NCT01696253) conducted during 2013-14, first morning urine collection kits were sent to 104 people registered with ASTOR who carried a diagnosis of AS or were first-degree relatives of people known to have AS. 45/104 participants (43%) had been classified as unknown because a urinalysis had not been performed previously.

Results: 17/45 unknowns did not return the urine kit. Of the 28 who returned a urine kit, 11 had hematuria and 17 had normal urinalyses. Of the 11 who were reclassified from unknown to affected, 6 were siblings of a known affected child, 3 were sons of a known affected mother and 2 were mothers of known affected children. 3/11 had microalbuminuria (urine microalbumin:creatinine ratio > 30 mg/g); none had overt proteinuria.

Conclusions: The results are consistent with the following conclusions: 1) it is not unusual for first-degree relatives of known AS patients to have never been screened by urinalysis; 2) screening of first-degree relatives of known AS patients frequently identifies individuals affected individually (39% [11/28] of those who returned urine kits) who may benefit from early intervention. Early initiation of ACE-inhibitor therapy appears to slow renal disease progression in AS (Gross et al, Kidney Int 2012). It is recommended that treatment be initiated when urinary protein is >100 mg/day (n=5), hypertension (n=2), surgery, diabetes and renal transplantation (each n=1). Thirteen and 3 showed a CHF-1 and a MCGPigaac risk haplotype, respectively; potentially disease-causing mutations were identified in 22 patients (7 CFHI, 6 CD46, 3 CFI, 4 C3, 2 CF1, 1 THBD; 4 of them with more than 1 mutation); 7 showed wild-types and no data existed for 1 patient.

Conclusions: In our cohort of TMA patients we identified 30 cases of aHUS. In 22 patients (74%) we identified a mutation within genes of the complement regulatory proteins CFB, thrombomodulin (THBD) and C3, and medical history for triggering factors were analyzed.

Results: Out of 92 patients with TMA we classified 30 as atypical HUS (aHUS), 1 as typical HUS, and 61 as secondary HUS. At onset of disease patients with aHUS had a mean age of 25 years (range: 1-47), 20 were female (65%), and 13 (43%) were kidney transplant recipients. First presentation of 24 patients was AKI, 3 showed hemolysis, 2 had pre-eclampsia and 1 HELLP-syndrome. Distinct triggering factors in 20 patients were: UTIs (n=10), infections (n=5), hypertension (n=2), surgery, diabetes and renal transplantation (each n=1). Thirteen and 3 showed a CHF-1 and a MCGPigaac risk haplotype, respectively; potentially disease-causing mutations were identified in 22 patients (7 CFHI, 6 CD46, 3 CFI, 4 C3, 2 CF1, 1 THBD; 4 of them with more than 1 mutation); 7 showed wild-types and no data existed for 1 patient.

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Keisuke Yatsu, Sanae Saka, Gen Yasuda, Satoshi Amit Gupta.

The DS3 Scores and Quality of Life in Japanese Patients with Fabry Disease Nobuhito Hiraga, Keisuke Yatsu, Sanae Saka, Gen Yasuda, Satoshi Umemura. 1 Dept of Nephrology and Hypertension, Yokohama City Univ Medical Center, Yokohama, Kanagawa, Japan; 2 Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan.

Background: Fabry disease (FD) is the lysosomal storage disorder, caused by the deficiency of lysosomal hydrolase alpha-galactosidase A activity. Various symptoms associated with renal disease, heart lesion and cerebrovascular disease occur in Fabry disease patients. Thus, the quality of life (QoL) would be altered with the disease progressed. We evaluated the clinical severity and the QoL in a sample of Japanese patients with Fabry (FD) disease using the Disease Severity Scoring System (DS3) and the SF-36 survey in male and in female.

Methods: Observational cross-sectional study. The DS3 and SF-36 survey was administered to the patients of the hospitals, which belong to the research group of Kanagawa enzyme replacement therapy. Participants were treated with agalsidase-alpha or agalsidase-beta. Disease activity was assessed by the Disease Severity Scoring System (DS3). The QoL was measured by Short form-36 (SF-36) and the Kidney Disease QoL. Short Form version 1.3 (KDQoL).

Results: Fifteen patients were included in the study. Mean age was 45 years (M/ F=10/5), and all patients were receiving ERT. The mean serum Cr was 2.9 mg/dl. The DS3 scores were follows; mean assessment score: 26.5 +/- 10.1, average domains: 10.5 +/- 9. The renal domain and the cardiac domain showed relatively high score compared to PNS and CNS scores. The QoL scores of the FD patients were lower than those of general population, but the scores were better than the previous reports of FD from U.S. or EU. The mental component summaries of women were similar to those of the general population. The physical component summaries of QoL were negatively associated with the age (r=-0.545, p<0.001).

Conclusions: Japanese patients with FD receiving ERT had a relatively good QoL beyond anticipation. DS3 score is useful for assessing disease severity, and may predict some components of QoL.

PUB556

Two Cases of Fabry Disease in Women with Proteinuria Diagnosed by Molecular Analysis of α-Galactosidase A Gene and Kidney Biopsy Jong Oh Yang, Eun-Young Lee. 1 Internal Medicine, Soonchunhyang Univ, Cheonan, Chungcheongnam-do, Korea; 2 Internal Medicine, Soonchunhyang Univ, Cheonan, Chungcheongnam-do, Korea.

Background: Fabry disease is a X-linked lysosomal storage disorder caused by deficiency of α-galactosidase A. This abnormality in enzyme results intracellular accumulation of globotriaosylceramide and leads to severe painful neuropathy with progressive renal, cardiovascular, and cerebrovascular dysfunction and early death. We report 52 and 55 year-old women with proteinuria and hematuria, which were proven to be due to Fabry disease.

Methods: A52 and 55 year-old women was admitted to the hospital due to proteinuria. They denied previous histories of hypertension, diabetes mellitus, pulmonary tuberculosis, and hepatitis. Their sister and cousin diagnosed fabry disease. Physical examination revealed nonspecific findings. On admission, blood pressure 110/60 mmHg, heart rate 64/min, respiratory rate 16/min, body temperature 36.5°C. Lungs were clear and heart was normal. The extremities showed no edema, cyanosis or skin rashs. The laboratory data showed the WBC 3650/mm², Hb 13.2 g/dL, Platelet 212,000/mm², BUN 10.2 mg/dl, serum creatinine 0.7 mg/dL. Urinalysis showed pH 5.0 SG 1.023 protein 2+ RBC 5-9/HPF WBC 5-9/HPF. 24-hour urine protein was 533 mg. Abdomen & Pelvic CT and echocardiography were normal. The serologic study was normal. The kidney biopsy showed expansion of mesangial matrix and glomerular hypertrophy. The cytoplasm of podocytes was vaculoated, which consisted of multiple, variable-sized, concentric electron-dense lamellated structures, by electron microscopy.

The DS3 Scores and Quality of Life in Japanese Patients with Fabry Disease Nobuhito Hiraga, Keisuke Yatsu, Sanae Saka, Gen Yasuda, Satoshi Umemura. 1 Dept of Nephrology and Hypertension, Yokohama City Univ Medical Center, Yokohama, Kanagawa, Japan; 2 Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan.

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Conclusions: Japanese patients with FD receiving ERT had a relatively good QoL beyond anticipation. DS3 score is useful for assessing disease severity, and may predict some components of QoL.

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

Underline represents presenting author.

1017A
Appetite was average 14.46%±4.13% poor 9.7%±18.18%, anorexic 13.2%±7.4% in males and females. Income correlated with BMI (p<0.001), dietary protein (p<0.001) energy (p<0.001), and carbohydrate (p<0.001). Appetite correlated with creatinine (p<0.01), dietary energy, protein, carbohydrate, and fat (p<0.001). BMI correlated (p<0.001) with fat, carbohydrate, energy and creatinine clearance. Anova showed significant difference among baseline appetite groups in energy, protein, fat, carbohydrate, and creatinine clearance (p<0.001) and serum albumin (p<0.01) in severely malnourished (SGA 1-2, C) and creatinine clearance (p<0.038) between BMI groups. Based on income there was significant difference between groups in BMI (0.001), energy (p<0.019), protein (p=0.031), albumin (0.001).

Conclusions: With decline in renal function, appetite worsened and nutritional intake decreased. Energy intake was significantly deficient. 84% patients had reduced appetite and 69.2% had PEW. Low income is a risk factor for PEW in CKD.

PUB589
Study on Correlation Between Serum Creatinine, Cystatin-C, Uinary Albumin Creatinine Ratio and Body Composition Xuemei Li, Jie Ma.

Background: Based on an epidemiological study in Peking, China, to study the correlation between serum creatinine, Cystatin-C and urinary albumin creatinine ratio (ACR) and body composition.

Methods: Residues over the age of 35 of the Beijing Pingshu District by random sampling method. Laboratory test: taking morning ACR, blood samples were taken for blood routine, kidney function. Test body composition after emptying the bladder by using INBODY-720 machine.Use SPSS 17.0 software for data statistical analysis, count data were analysed by using multivariate linear regression .

Results: A total of 9283 people participated in the survey, which 4324 males, age 54.7±10.7 years, 4599 females, age 53.4±11.2 years. Male: 1) Human body cell mass (BCM) and ACR, Cystatin-C, no correlation, was positively correlated with height (B=0.43, P<0.01), and serum creatinine was that positive correlation (B=0.01, P<0.01). 2) Lean body mass (FFM) and ACR, serum creatinine, Cystatin-C, no correlation. 3) Skeletal muscle content and ACR, serum creatinine, Cystatin-C, no correlation. 4) Body fat mass and ACR, no correlation, and Cystatin-C was positively correlated with (B=0.79, P < 0.01). Female: 1) Human body cell mass (BCM) with height and cystatin-C, no correlation, but positively correlated with serum creatinine (B=0.035, P<0.01), and ACR was negative correlation (B=−0.005, P<0.05). 2) Lean body mass (FFM) and ACR, Cystatin-C, no correlation, and serum creatinine were positively related (B=0.035, P<0.01). 3) Skeletal muscle content and ACR, Cystatin-C, no correlation, and was positively correlated with height (B=0.031, P<0.01), and serum creatinine were positively related (B=0.035, P<0.01). 4) Body fat mass and ACR was negative correlation (B=−0.01, P<0.05). Cystatin-C were positively correlated (B=12.3, P<0.01), and age negatively correlated (B=0.13, P<0.01), and serum creatinine was negative correlation (B=−0.092, P<0.01).

Conclusions: There was a positive correlation between serum creatinine and the human body cell mass (BCM), lean body mass (FFM) in men, and skeletal muscle content, body fat weight in women, but the correlation is not strong. The blood cystatin-C and body fat weight was positively correlated.

PUB560
Worsening Nutritional Status Assessed Is an Independent Predictor of All-Cause Mortality in Incident Dialysis Patients Jong Hyun Jhee, Young Eun Kwon, Tae-Hyun Yoo, Shin-Wook Kang.

Department of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Malnutrition is closely associated with mortality in end-stage renal disease (ESRD) patients. However, little is known whether improvement or deterioration of nutritional status after dialysis initiation affects clinical outcome. This study was aimed to elucidate the association between the changes of subjective global assessment (SGA) after dialysis initiation and mortality in ESRD patients.

Methods: Data were collected from the Clinical Research Center for ESRD cohort. SGA score was measured by trained investigators at the time of dialysis initiation and after 12 months. Nutritional status was defined as well-nourished (SGA 6-7, A), mildly to moderately malnourished (SGA 3-5, B), or severely malnourished (SGA 1-2, C). Severely malnourished patients (SGA C) were excluded due to small sample size. The patients were divided into four groups according to the change of SGA: group 1, A to A; group 2, B to B; group 3, A to B; and, group 4, B to B.

Results: A total of 911 patients were enrolled. The mean age was 54.6±14.1 years, 554 patients (60.0%) were male. During a median follow-up duration of 30 months, 109 patients (12.0%) died. Survival rate of group 1 were the highest, and that of group 4 was the lowest (group 1, 1.77%; group 4, 7.41%; P<0.001). Worsening nutritional status was a significant risk factor for mortality (group 3 vs. 1, HR=3.15, CI=1.51-6.54, P=0.002), while baseline nutritional status at dialysis initiation was not (group 1 vs. 2, P=0.063; group 3 vs. 4, P=0.107).

Conclusions: Improvement of nutritional status after dialysis initiation could be beneficial for patient outcomes regardless of baseline status, suggesting that intervention to improve nutritional status after dialysis initiation might be a strategy to reduce mortality in ESRD patients.

Background: This study was performed to evaluate whether increasing hemoglobin before ascent by prophyactic erythropoietin injections prevents acute mountain sickness (AMS).

Methods: This open label, randomized, controlled trial involved 39 healthy volunteers with hemoglobin £15.5g/dl who were divided randomly into erythropoietin (n = 20; control (n = 19) groups. Epoetin alpha 10,000 IU injections were given weekly for four consecutive weeks. On day 1, and 7 days after the last injection (day 29), oxygen saturation (SatO2), and hemoglobin were measured. The subjects departed Seoul on day 30 and arrived at Annapurna base camp (ABC, 4,130 m) on day 34. AMS was diagnosed when headache and Lake Louise score (LLS) of ± 3 were present. Immediate descent criteria followed US Army recommendations.

Results: Two groups differ in hemoglobin levels on day 29 (15.4 ± 1.1 vs 14.2 ± 1.0 g/dl, P<0.001). At ABC, erythropoietin group had a significantly lower mean LLS, AMS incidence, and number of subjects who met immediate descent criteria. Multiple logistic regression analysis showed that SatO2<87% and control group, but no hemoglobin<15.0 g/dl, independently predicted satisfaction of immediate descent criteria.

Erythropoietin-related adverse effects were not observed. In conclusion, erythropoietin may be an effective prophylaxis for AMS.

PUB562
Nutritional Assessment for the Chronic Dialysis Patients with/witout Sarcopenia Miho Suzuki, Yuya Sakai, Ikuto Masakane. Tabuki Hospital.

Background: A recent arising problem of chronic dialysis patients is sarcopenia closely related to malnutrition. Muscle loss deteriorates daily activities of dialysis patients and ultimately worsens the QOL and prognosis of the patients. The aim of this study was to clarify the relationship between the nutritional status and sarcopenia and to analyze the status of nutrient intake in these patients.

Methods: 90 chronic hemodialysis patients were enrolled to the current study. (age 62.8yrs. Men were 76%, DM 41%).Skeletal muscle mass (SMM) was estimated by bioimpedence analysis and a low muscle mass was defined by the SMM index (SMI: SMM [kg]/ height [m]2 as < men: 7.0kg, women: 5.7kg).Muscle function was evaluated by grip strength and walking speed as the Timed up and go test (TUG).A low grip strength was defined as less than 26 kg (men) or 18 kg (women). TUG less than 11 second was diagnosed as a low walking speed.Malnutrition was defined as by the Malnutrition-Inflammation Score(MIS):<36point), GNRI(<92) and the criteria of protein energy wasting (PEW).The dietary assessment was performed by the food frequency questionnaire.

Results: Sarcopenia was identified in 22% of the subjects. The sensitivity to detect sarcopenia was not sufficient as 35% in MIS, 50% in GNRI and 10% in PEW. In the patients with sarcopenia, the average of total energy intake and protein was significantly lower than those in non-sarcopenia, 1618±122kcal vs 2041±165kcal in energy, 52±4g vs 68±2g in protein. The intake of fishes and meats (110±15g vs 153±8g),beans (313±11g vs 61±6g ),confectionery, beverages and sugar (126±77g vs 306±41g ) were significantly lower in sarcopenia than non-sarcopenia.

Conclusions: Malnutrition-related sarcopenia was only 10-50% among sarcopenia. It is important to measure muscle mass and muscle function regularly for dialysis patients because it is not enough to screen sarcopenia only by nutritional measurements. Sufficient protein and energy intake are essential for the prevention of sarcopenia. If patients don’t have appetite,confectionery or a beverage or sugar may be acceptable for the prevention of muscle loss.
Stomach Acid Reducers May Predict Nutritional Deficiency in Dialysis Patients

**Methods:** This is a cross sectional study of 103 patients undergoing chronic hemodialysis in Budapest, Hungary at a university hospital based dialysis unit. The patients’ nutritional indicators such as serum albumin, phosphorus, nPCR and whether they were on dialysis, chronic kidney disease (CKD) stage were evaluated. The study group included patients who did not take an acid reducing agent, such as a Proton Pump Inhibitor (PPI) or H2 blocker.

**Results:** Six patients were excluded because data were incomplete or the patients had not been on dialysis for more than 2 months. Of the 96 patients 44.9% took an acid reducer on a daily basis. The serum albumin (3.76±0.02 mg/dL vs. 3.56±0.01 mg/dL; p=0.008); phosphates (1.88±0.49 mmol/L vs. 1.64±0.54 mmol/L; p=0.04) and nPCR (1.00±0.20 vs. 0.91±0.25: p=0.06) were lower among PPI takers. PPI takers were much more likely to be taking cholecalciferol measured 25-OH-vitamin D deficiency (1.8% vs. 18.1% p=0.01). While PPI takers were older (59.7±16.2 years vs. 65.7±13.3 p=0.04), there was no difference in the two populations in the presence of a AV Fistula, delivered Kt/V, calcium or serum bicarbonate.

**Conclusions:** We conclude that taking PPI’s or H2 Blockers in dialysis patients may be an indicator of being at risk for malnutrition.

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Impact of the Potassium Additives on the Total Content of This Element in Processed Foods

**Results:** Processed foods contained high potassium values than expected from the food label were, beverages 102.6 to 125.3; type of cream cheese 80.3 to 194.4; margarine 21.6 to 37.3; tomato powder 253.3 to 258.2; salad dressing 78.5 to 128.4; powdered juices 33 to 240.8. Processed food that had higher potassium values than expected included beef jerky, milk beverages, yogurt, a type of cream cheese, margarine, tomato sauce, salad dressing, powdered juices, and had potassium sorbate or others potassium salts. The concentration of potassium (mg K/100g of food) was determined by flame photometry according to the Adolfo Lutz Institute methodology, and in triplicate. The comparison of the potassium obtained with the expected potassium was based on two national reference tables.

**Conclusions:** Processed foods with potassium additives contain higher levels of potassium than those listed in reference tables.

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Differences in Eating Patterns Between Maintenance Hemodialysis Patients from the U.S. and the UK

**Results:** Patients from the US consumed more energy on DD (24.9±2.1 vs. 18.5±1.1 kcal/kg/d; p=0.004) and HDD (24.5±1.5 vs. 20.5±1.2 kcal/kg/d; p=0.048) than US patients. Additionally, US patients had lower energy intake on DD than HDD (p=0.007), while there were no differences in UK patients. UK patients consumed more dairy products and breads, whereas US patients consumed more energy from beverages, entrees, and deli items.

**Conclusions:** HD patients from the US had lower energy intake on DD and HDD compared to UK patients. Furthermore, US patients had lower dietary intake on DD. This might be in part due to US clinics’ restrictive policy on eating during dialysis. Furthermore, there were differences in food pattern consumption and food insecurity. These differences may help explain global differences in nutritional status and outcomes. Further studies are needed to assess the contribution of eating patterns and socioeconomic status on clinical outcomes in HD patients.
Obese Donors: The Multidisciplinary Approach in Improving Outcomes
Giselle Guerra,1 Ian Thomas,1 Panagiotsis Tryphonopoulos,2 Linda J. Chen,2 Gaetano Ciancio.2 1Department of Medicine, Miami Transplant Inst, Miami, FL; 2Department of Surgery, Miami Transplant Inst, Miami, FL.

Background: Living donation appears safe over the years but concerns still exist long-term. Small analyses under similar nephrectomies have resulted in proteinuria and slight decrease in renal function (eGFR) if patient tended to be obese; thus raising a concern for accepting living kidney donors (LKD) with body mass index (BMI) greater than 30 but less than 35: Aim: determine the outcomes of obese LKD with BMI greater than 30 but less than 35.

Methods: A single center retrospective analysis was performed at transplant center during the period January 1, 2010 – November 30, 2014. LKD ages 18-65 were assessed: 1. Study Arm (SA): obese LKD with BMI>30 who were enrolled into a nutritional program; and 2. Control arm (CA): non-obese living donor candidates at the time of referral. Weight loss prior to surgery and afterwards, surgical complications, loss of kidney function (eGFR), and proteinuria (spot urine protein/spot urine creatinine ratio) after 6 months from donation were reviewed.

Results: Patient demographics - SA: 15African Americans (AA), 13 Hispanics (H), 7 White, 1 Other, 3 Unknown versus CA: 55 H; 49 Whites; 20 AA; 5 Other [figure1]. In the SA, 24/40 had BMI>35 at time of referral and placed in nutritional program; 8/24 dropped BMI to less than 35 prior to surgery and 3/24 pending surgery now; 4/24 ruled out due to medical issues & (8/24) were non-compliant. Surgical complications 1/8: Parasthesia. After donation in SA, blood pressure remained stable, 2/8 gained weight. Kidney function at 6 months: 47% of obese donors had a decrease in eGFR at 6 months of 40% or greater. The mean decrease in eGFR was 33.9% in the study arm. In the control arm: 55 Hispanics; 49 Whites; 20 AA; 5 Other. 15% had a decrease in eGFR at 6 months 40% or greater and the mean decrease in eGFR was 28.9.

Conclusions: Obesity among donors needs careful analysis especially in minority populations since there is a trend to have a greater loss in kidney function after donation. Donor nephrectomy is possible but strict nutritional and guidelines and medical evaluation need to persist for the wellness of these patients long-term.

PUB569
The Role of Renal Pharmacist in Prescribing Immunosuppressant Medication for Renal Transplant Patients to Improve Safety
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Background: This paper describes the safe and efficient repatriation of renal immunosuppressant prescribing from General Practitioners (GPs) to secondary care using hospital Pharmacist Independent Prescribers (PIPs).

Methods: From March 2015 the UK commissioner NHS England required all renal immunosuppressant medication, which was traditionally prescribed by GPs following nephrologists’ advice, to be prescribed by hospital renal prescribers. Gloucestershire hospitals NHS Foundation Trust decided to use Pharmacist Independent Prescribers to implement this change and provide the ongoing service using commercial Homecare Companies. All Patients were initially sent detailed information about the changes and asked to consent. On receipt of the completed consent form the PIP wrote the initial homecare prescription which was then processed by the pharmacy homecare team. Patients continued to be reviewed at regular intervals by their nephrologists. Details of these consultations were documented using a central renal database which included graft function, drug levels and communication with GPs. The Pharmacist Prescribers subsequently reviewed the renal database prior to generating the homecare prescriptions and, when necessary, contacted the nephrologist for clarification and interventions.

Results: This service reconfiguration has resulted in safe and robust pathway. The use of Pharmacist Independent Prescribers has insured the whole pathway is efficient and closely monitored. Patients are satisfied with the new homecare service and clinicians value the pharmacists’ input. Pharmacist prescribers have made a number of interventions which have included patient compliance issues, changes to doses in response to serum drug levels and appropriate brand changes to improve cost effectiveness.

Conclusions: The use of Pharmacist Independent Prescribers to prescribe and manage the renal immunosuppressant homecare service at Gloucestershire Hospitals NHS Foundation Trust has been shown to be safe and efficient.

PUB570
Tools for Adverse Events Prevention in a Hemodialysis Facility: A Local Experience
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Background: After the publication “To err is human” there has been a new approach to prevent risks in health system. According to the International Patient Safety Goals there are six steps to be followed like patient identification, proper communication, right surgery in the right side, fall prevention, high alert medication and infection prevention. The goal is to show how a hemodialysis unit, for ambulatory and hospitalized patients leads with adverse event prevention.

Methods: This experience happens in a hemodialysis unit with 101 patients, 3 shifts of 4 hours. It is located in a general hospital in Porto Alegre, south Brazil.

PUB571
Zinc Deficiency Correction and Phosphaturia in Children with CKD – A Pilot Study
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Background: There are no guidelines for correction of Zinc (Zn) deficiency in Chronic Kidney Disease (CKD). Experimental data (Morishita 2001) suggests that Zn modulates the phosphaturic effect of parathyroid hormone and can potentially increase phosphatase. Aim: To identify Zn deficiency and determine whether 3 months of oral Zn therapy normalizes Zn status in children with CKD. To assess feasibility of conducting a clinical trial similar to Morishita’s in mice and gather information on clinical outcomes and relationship between Zn status and correction of Zn deficiency and phosphatase (P) excretion.

Methods: 40 patients (pt) 4-18 yr with primary CKD and CKD due to declining graft function were enrolled from 2 tertiary pediatric nephrology centers. Plasma Zn was measured by High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry at baseline and at 3 months with routine blood and urine parameters. Pt with Zn<11.5 mmol/L were treated for 3 months with Zn citrate tablets (10mg Zn/day for 4-8 yr and 20 mg/day for 9-18 yr). Statistical analysis was done using nonparametric methods and relative risk ratio.

Results: Of 21 pt (M-13, F-8) with completed data, Zn deficiency was found in 10. Stages of CKD were: 2-11 pt, 3-5 pt, 4-5 pt. One pt was hyperphosphatemic. 2 Zn deficient pt had abdominal discomfort whilst taking Zn. Plasma Zn improved in 8 out of the 10 treatment pt (4.4 times more frequently than in control pt) after 3 months of Zn therapy. Zn therapy over 3 months did not change serum P (median 1.23 mmol/L to 1.25 mmol/L) or its fractional excretion (median 24.08% and 21.71%).

Conclusions: Zn deficiency occurred in about 50% of CKD pt. Preliminary analysis indicates that 3 months of oral Zn supplementation is likely beneficial in Zn deficient pt but a larger sample size is required to evaluate the impact of correction of Zn deficiency on other metabolic parameters. Correction of Zn deficiency does not alter P excretion in pt with normal blood P. Similar studies are feasible to perform in hyperphosphatemic pt.

Funding: Private Foundation Support

PUB572
Proteinuria as a Marker of Severe Unilateral Ureteral Obstruction in Infants
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Background: Unilateral ureteral obstruction (UUO) is a common congenital anomaly in infants. Controversies remain regarding clinical indications for timely surgery. The objective was to compare the radiologic and laboratory parameters of a cohort presenting with significant unilateral hydronephrosis that were managed either conservatively or surgically.

Methods: This retrospective analysis included 81 infants during a 10 year period with high grade hydronephrosis designated by renal ultrasound. Further assessment included renal function by nuclear scintigraphy and proteinuria. Proteinuria was determined by random urine total protein to creatinine ratio (U/pr) and albuminuria by random urine albumin to creatinine ratio (U/alb). Receiver operator characteristic (ROC) area under the curve (AUC) statistics were applied to U/pr and U/alb cr ratios with determination of likelihood ratios (LR) for requiring surgery.

Results: In this cohort, 22/81 (27%) were operated, including 21 pyeloplasties and 1 nephrectomy for severe UUO. Initial proteinuria was significantly greater in UUO patients who underwent surgery compared to those without surgery (p=0.02). ROC-AUC demonstrated that both U/pr and U/alb cr predicted the presence of severe UUO requiring surgery (U/pr: AUC=0.71; p=0.01 and U/alb cr: AUC=0.75; p=0.02). U/pr and U/alb cr was similar in normal control infants and those with non-surgical UUO.
Conclusions: Proteinuria and albuminuria were significantly elevated in UUO infants who required surgery compared to normal term infants and those with non-surgical UUO. Although both were sensitive markers of renal injury, albuminuria was superior in predicting who required surgery compared to normal term infants and those with non-surgical UUO.

PUB574
Familial Lecithin-Cholesterol Acetyltansferase Deficiency Masquerading as Membranous Nephropathy in Childhood

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Background: Familial Lecithin-cholesterol acetyltransferase (LCAT) deficiency is a rare autosomal recessive disorder of lipid metabolism characterised by severely reduced HDL concentrations and impaired esterification of cholesterol. It is characterised clinically by glomerulopathy and mild haemolytic anaemia presenting in adulthood leading to ESRD by the fourth decade of life through the deposition of abnormal lipoproteins in the renal stroma. Paediatric cases are rarely described.

Methods: 2 siblings aged 8 and 11 years presented with asymptomatic non-nephrotic range proteinuria detected on routine testing. There was no family history of renal disease, although parents were consanguineous. Initial screens revealed normal renal function and normal serum albumin. Other investigations demonstrated raised lipid profiles but in keeping with nephrotic syndrome. A renal biopsy was performed in view of escalating protein and albumin creatinine ratios.

Results: Renal biopsy initially demonstrated light microscopic features of membranous nephropathy. However, electron microscopy demonstrated inclusions that were not typical of the adult form of the disease but clearly lipid filled (Figure 1). Confirmation of the diagnosis was by demonstration of significantly reduced HDL-cholesterol, and detection of a novel LCAT gene missense mutation G54V as well as reduced LCAT enzyme activity on assay.

Conclusions: LCAT deficiency may present with mild symptomatic proteinuria in childhood. Although rare, it should be considered in a differential in paediatric membranous nephropathy. However, electron microscopy demonstrated inclusions that were not typical of the adult form of the disease but clearly lipid filled (Figure 1). Confirmation of the diagnosis was by demonstration of significantly reduced HDL-cholesterol, and detection of a novel LCAT gene missense mutation G54V as well as reduced LCAT enzyme activity on assay.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
1021A
Insulin-Like Growth Factor/Growth Hormone and Insulin-Like Growth Factor Binding Proteins in Normal Height and Short Children with CKD

Methods: 232 children in CKD (206 normal height: 26 short stature; none on GH therapy) were matched by gender, age and GFR. Short stature = Height Standard Deviation Score (SDS) < -1.88. GH, IGF-1, and IGFBP-1 and 3 were determined by chemiluminometer and ELISA.

Results: Normal height CKD children had higher serum IGF-1/GH, higher IGF-1/IGF-1 BP1 and similar IGF-1/IGF-1 BP3 compared to short CKD children.

Conclusions: Differences in IGF-1, IGF-1/GH, and IGF-1/IGFBP-1 may explain some variance in growth in CKD children. Height is more highly correlated to IGF-1 in normal height than short children. Analyses in paired subjects may provide further evidence to explain and/or predict growth in children with CKD.

Funding: NIDDK Support, Private Foundation Support

PUB579

Acute Lymphoctic Leukemia with Bilateral Renal Masses Masquerading as Nephroblastomatosis

Background: While leukemia has a wide spectrum of presenting features, renal involvement in the presentation of disease is relatively rare. We report a case of acute lymphocytic leukemia (ALL) with bilateral renal masses that presented as nephroblastomatosis.

Methods: A 4 year old boy was presented with low grade fever and abdominal pain for few days. A complete blood count (CBC) and abdominal CT scan were done to rule out appendicitis. WBC of 8.1 K/UL, hemoglobin of 13.3 g/dL, Platelets of 170 K/UL, neutrophils 22%. Lymphocytes of 68.9% and absolute neutrophil count of 1.8 K/UL. CT scan showed bilateral renal enlargement with multiple hypodense lesions in the corticomedullary regions. Blood urea nitrogen of 7 mg/dL and creatinine of 0.38 mg/dL. The patient was diagnosed with viral gastritis and sent home on supportive treatment. CT scan was later interpreted as nephroblastomatosis by pediatric radiologist as an incidental finding advised follow up with the pediatric nephrologist. After 14 days he again had low grade fever with abdominal pain. CBC showed WBC of 3.5 K/UL, hemoglobin of 11.1 g/dL, platelets count of 21 K/UL, neutrophils 6% and lymphocyte 85% Absolute neutrophil count was 351 and ESR of 71 mm/hr. The pediatric oncology service was consulted for possible malignancy. Peripheral blood smear showed the presence of abundant immature lymphoid cells representing 90% of the total white cells. Bone marrow aspirate and biopsy, flow cytometry and cytogenetic studies showed early B cell leukemia. Treatment was initiated following the guidelines of COG AALL1092. After one week of induction therapy, the CT scan showed a complete interval resolution of all renal hypodense lesions.

Conclusions: Renal involvement in leukemia is challenging to diagnose due to its variable presentation on imaging. On CT scan, it may present as enlargement of kidneys (unilateral or bilateral), or a low-attenuation focal parenchymal. These focal lesions can be difficult to distinguish from nephroblastomatosis which has a similar radiological picture on CT scan.

PUB577

Assessment of Cochlear Sensitivity of the Pediatric Chronic Kidney Disease and Hemodialysis Patients

Conclusions: UAH links an adverse and/or competitive intrauterine environment with nephrogenesis independent of GA. An enhanced umbilical artery muscle area reflects an increased renal mass while increased vascular collagen parallels decreased renal mass in discordant twins and singletons of PE mothers.

Funding: Private Foundation Support

PUB578

Percutaneous Renal Biopsy at OPD Level

Background: Renal biopsy is a prerequisite procedure for the final diagnosis and to evaluate the treatment effect or to determine the prognosis, however due to serious complication of the procedure, should be done by nephrologist and has been performed at admission state.

Methods: Our center performed percutaneous renal biopsy 3,000 cases without major complications during last 30 years, when patients were admitted for 3 days. During last 18 months, we performed percutaneous renal biopsy at OPD level under the ultrasound guide (LOGIQ E9).

Results: The youngest one is 1 year old male and the oldest was 64 years old. Mean age was 26 years old. Male to female ratio was 3:2. Mean glomerular numbers were 31. We used disposable kidney biopsy needle (TSK ASECUT). We checked ultrasound 3 times after renal biopsy for checking AV fistula, hematoma formation during 6 hours hospital stay. Of the 100 case 8 cases received follow up biopsies. Among 100 samples renal medulla was not detected. Two patients(2%) among 100 biopsies showed small(less than 1cm) hematomas. No AV fistula were detected. All patients went home 6 hours after renal biopsy without any problems. Renal biopsy results showed IgAN(23%), Non_specific GN(21%), Diffuse mesangial proliferative GN(17%),JSSP(6.7%),MGN(5.6%),FSGS(5.6%).Others were Alport,Lupus nephritis,DM nephropathy,MPGN type I,Thin GBM nephropathy.

Conclusions: In conclusion, percutaneous renal biopsy under the ultra-guide sound at OPD level with 6 hour ABR is safe and effective if performed at renal cortex level.
Malodity of Treatment of Pediatric Patients with Diarrheal HUS in Acute Renal Failure Does Not Affect Long Term Outcome and Survival

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Background: Diarrheal HUS is a disease process usually resulting from infection by E. coli H7:0157 and leading to the development of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Acute renal failure typically follows in five days from presentation, with resolution of the majority of the renal replacement therapy (RRT) in the first week. Long-term studies have demonstrated that these patients are at risk for long-term renal insufficiency and end-stage renal disease. Indications to start dialysis and the mode of dialysis vary from institution to institution. There is no current study comparing which mode of dialysis, hemodialysis or peritoneal dialysis, has better benefit and less complications. The aim of this study is to compare dialysis modalities and determine whether one modality will result in less complications and better outcomes.

Methods: This is single center, retrospective review. We studied a total of 102 patients from January 2010 to 2014. We compared the number of complications and the types of complications from each modality. Long-term outcomes were measured by each patient’s CKD staging at least one year after diagnosis. EGFR was calculated using the Schwartz formula. Fisher’s exact statistical test was used to assess statistical significance.

Results: No statistical significance was found between the mode of dialysis and associated complications (p>0.4). There was also no statistical significance between kidney and long term outcome (p>0.9). Complications of PD were catheter malfunction (p=0.6), peritonitis (p=0.5), and the need to switch to HD or CVVHDF (p=0.3). Complications of HD included central line infections (p=1).

Conclusions: PD and HD are equally effective in treating patients with diHUS in renal failure and have comparable long term outcome and risks for complications. An important complication to consider for patients on PD is the potential need to switch to HD or CVVHFH; this exposes the patient to an additional surgical procedure that may result in further complications.

Self-Reported Health Care Transition Readiness Among Mexican Adolescents with Chronic or End-Stage Kidney Disease

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Background: 90% of pediatric patients with chronic disease live more than 20 years after being diagnosed. When pediatric patients are transferred to adult-focused health services, generally they do not have the skills and abilities to manage their disease. Adolescents tend to have poor adherence to treatment, and there is a period when there may be complications and increased morbidity-mortality. Performance on self-reported health care transition readiness (HCTR) needs to be assessed in patients with chronic or end-stage kidney disease. The aim of the study was to measure self-reported HCTR using the STARs (Self-management and Transition to Adulthood with Rx=Transition) Questionnaires, among adolescents in the Nephrology Service at Hospital Infantil de Mexico Federico Gomez. The Spanish version of the STAR, Questionnaire was translated and back translated for validity. The tool evaluates adolescents with chronic or end-stage kidney disease in the outpatient nephrology department over a 9-month period. The 18-question tool diagnoses difficulties in the transition, and end-stage kidney disease differs by sex and treatment modality.

Methods: The Spanish version of the STAR, Questionnaire was translated and back translated for validity. The tool evaluates adolescents with chronic or end-stage kidney disease. The aim of the study was to measure self-reported HCTR using the STARs (Self-management and Transition to Adulthood with Rx=Transition) Questionnaires, among adolescents in the Nephrology Service at Hospital Infantil de Mexico Federico Gomez.

Results: We enrolled 68 adolescents (53% males) who had a mean age of 15.75 years (± 1.87). Patients who received hemodialysis in the past 22 (34%). Females had significantly greater scores than males in the “action” category. Those who received hemodialysis in the past had greater knowledge about the disease (p=0.013).

Conclusions: The self-reported HCTR among Mexican adolescents with chronic or end-stage kidney disease differs by sex and treatment modality.

Funding: Government Support - Non-U.S.
A retrospective database study on the real-world effectiveness of sucroferric oxyhydroxide (SO) use among peritoneal dialysis (PD) patients (pts) who self-selected as Black or African American (AA).

**Methods:** A retrospective database analysis was conducted on a cohort of AA PD pts who were prescribed SO as part of standard care at FMCNA clinics. Pts had 1 serum phosphorus (sPhos) measured while using SO and had been on sevelamer, calcium-based phosphate binders or had no phosphate binder specified prior to SO treatment. Differences in sPhos, pill burden (PB), serum calcium (Ca), ferritin, transferrin saturation (TSAT), and intact parathyroid hormone (iPTH) were noted between baseline (BL; 3 months prior to SO) and follow-up (SO-TX; 3 months during SO).

**Results:** 117 AA PD pts (mean age=50 years, dialysis vintage=4.2 years) were included. At BL, 37% were on sevelamer, 31% on calcium-based phosphate binders, 2% on dual phosphate binders or had no phosphate binder specified. Figure shows increase in pts who have in-range sPhos (20% to 31.6%, 58% increase). Mean sPhos dropped from 6.55-6.38 mg/dl (p=0.06). A significant decrease in PB was observed (4.5 pills/day; p<0.001) between BL (8.8 pills) and SO-TX (4.3 pills). No significant differences were observed between BL and SO-TX for sCa (BL=9.1 mg/dl, SO-TX=9.1 mg/dl), ferritin (BL=861.9 ng/ml, SO-TX=870 ng/ml), TSATs (BL=34.7%, SO-TX=36.8%) and iPTH (BL=729.5 pg/ml, SO-TX=696.4 pg/ml).

**Conclusions:** In a cohort of African American peritoneal dialysis patients who were prescribed sucroferric oxyhydroxide as part of routine clinical care, there was a 58% increase in the number of patients with serum phosphorus levels in-range (p<0.006). Furthermore, there was a significant reduction in pill burden (4.5 fewer pills, p<0.001).

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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**Peritoneal Dialysis Patients Who Switch Phosphate Binders from Sevelamer to Sucroferric Oxyhydroxide As Part of Routine Clinical Practice: A Retrospective Database Study**

**Background:** A retrospective database study on the real-world effectiveness of sucroferric oxyhydroxide (SO), an iron-based phosphate binder (PB), in a cohort of adult peritoneal dialysis (PD) patients (pts) was conducted. This analysis examines PD pts from that cohort who switched from sevelamer (SEV) to SO (n=183).

**Methods:** All pts were prescribed SO as part of routine clinical practice at FMCNA clinics. Pts eligible for analysis had 1 serum phosphorus (sPhos) during SO and the most recent PB used during the 3 months before SO was SEV. Changes in sPhos, serum calcium (Ca), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and PB pills per day were assessed 3-months before starting SO (baseline) and 3-months during SO treatment (follow-up).

**Results:** Pts (n=183) were, on average, 53 years old with a dialysis vintage of 3.9 years. Pts with in-range sPhos increased from 14.8% to 25.7% (74% increase). There was a significant reduction in sPhos (6.8 to 6.5 mg/dl; p=0.005), sCa (9.2 to 9.1 mg/dl; p=0.02), and PB pills per day were assessed 3-months before starting SO (baseline) and 3-months during SO treatment (follow-up).

**Conclusions:** Our single-center experience demonstrated similar PD catheter survival rate and a better 2-year survival for catheters placed by peritoneoscopy. Our predominant use of the curvy PD catheters suggests no significant difference in outcome compared to the straight catheters.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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**Peritoneal Dialysis for Management of Refractory Heart Failure**

**Background:** Refractory heart failure (RHF) is associated with significant morbidity and mortality. There is growing interest in the use of peritoneal dialysis (PD) for management of patients with RHF. In this study, we explored the currently available data on the safety and efficacy of PD in this setting.

**Methods:** A search of PubMed database using key words “peritoneal dialysis” and “‘heart failure’” from 1985 to 2015 was performed by two of the authors independently and found 763 articles, from which those including at least 20 patients who had initiated PD for cardiac indication were selected. Relevant data on efficacy and safety such as changes in the quality of life and cardiac function as well as the rate of hospitalization were extracted and compared.

**Results:** Seven studies (4 prospective and 3 retrospective) met the inclusion criteria with a total of 398 patients and a mean age of 70.4 years. PD was associated with improvement in functional status (1 to 2 NYHA class reductions) in 5 of the 7 studies (not reported in 2) as well as an increase in the ejection fraction in 6 studies. A variety of PD regimens were used that in general showed efficacy in removal of fluid as suggested by notable reduction in patients’ weight in 6 studies by up to 8.3 kg (unavailable in 1). It was also shown to significantly reduce the number of days of hospitalization for acute HF in 6 studies by up to 90%. Five studies reported increase in responsiveness to diuretics as well as perceived improvement in the quality of life. The PD-related complications were found to be minimal in 6 studies while one reported 0.75 episode/patient/year of peritonitis.

**Conclusions:** Currently available evidence suggests that PD is an efficacious option for management of patients with RHF that can result in significant improvement in their functional status, hospitalization rate, and the quality of life. Based on the findings of these studies PD is safe in this population and its related morbidity does not replace HF-
associated morbidity. Larger controlled trials are warranted to explore the potential impact of PD on the mortality of patients with RHF and to define those subgroups most likely to benefit from this therapy.

PUB888

Procalcitonin, Is It a Useful Biomarker for Peritoneal Dialysis Peritonitis? Shinshan Song, Hyeyeon-Chool Park, Jae Seok Kim, Jae Won Yang, Byoung Geun Han, Seung-Ok Choi. Internal Medicine, Yonsei Wonju College of Medicine, Wonju, Korea.

Background: Peritonitis is a common complication in peritoneal dialysis (PD). Procalcitonin is a peptide hormone which has been used as a biomarker for the diagnosis of bacterial infection. We aimed to investigate the usefulness of procalcitonin in the patients with PD peritonitis.

Methods: This study included 33 episodes of peritonitis in 27 patients for follow-up period of 450 days. In addition, we collected samples of PD effluents from 7 PD patients without peritonitis to compare with those of peritonitis. We investigated clinical characteristics, serum and PD effluent levels of procalcitonin at the time of initial visit and discharge.

Results: The mean value of dialysis vintage of patients with peritonitis was 1774 days, incidence of total peritonitis for period of PD maintenance: 4.3 times, interval from symptom onset to visit: 13.6 hours, duration of intraperitoneal antibiotic treatment: 8.2 days, and interval from clinical improvement to recurrence: 80.7 days. Initial serum procalcitonin increased to 0.97 ± 3.67 ng/mL (mean ± standard deviation) compared with reference values (healthy <0.05, PD patients <0.50 ng/mL), and PD effluent procalcitonin also increased compared with the subjects without peritonitis, but not significantly (0.07 ± 0.19 vs. 0.01 ± 0.01 ng/mL, p=0.505). The serum procalcitonin decreased to 0.33 ± 0.54 ng/mL with clinical improvement but not significantly (p=0.308), and the PD effluent procalcitonin also showed the decreased level of 0.03 ± 0.08 ng/mL, but not the statistical significance (p=0.360). Pearson’s correlation analysis showed that the serum and PD effluent procalcitonin did not have relationships with existing inflammatory markers such as ESR, CRP. Lastly, procalcitonin could not predict recurrence and mortality of peritonitis.

Conclusions: Collectively, procalcitonin showed the tendencies corresponding to the clinical course of PD peritonitis, but not statistical significance. We believe that procalcitonin is not superior biomarker in PD peritonitis compared with other existing markers.

PUB889

Epidemiological Survey of Maintenance Peritoneal Dialysis in China Xiang-Mei Chen, Xueying Cao, Delong Zhao, Guangyan Cai. Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases.

Background: To analysis epidemiology and trend of peritoneal dialysis during 2011 - 2014 in China.

Methods: Patient-reported outcome data from the peritoneal dialysis centers were collected online during the study.

Results: (1)By the end of 2014, there were 55373 cases of maintenance peritoneal dialysis patients in China, had increased by 17% per year over this time period. The annual incidence rate was 5.81/100 million people. The prevalence was 34.3/100 million. (2)The average age was 53 years. Male to female ratio was 1.2:1. The average age at initiation of dialysis was about 30 years old. The average residual renal function was 3ml/min. The average dialysis time was 2 years. The primary causes were primary glomerular disease 54%, diabetic nephropathy 16%, hypertensive renal damage 14%. (3)In 2014, DOR fell to 6.6%. TOT was 27.2 months. The death patients accounted for about 51.3% of exit patients. The average death age was 64.8 years. The average therapy time was more than 28.6 months. The cause of death was the cardiovascular and cerebrovascular events (4) Peritoneal dialysis access was the two cufis, no gooseneck, straight. 78% patients were the continuous ambulatory peritoneal dialysis patients. The therapeutic dose was 6L to 8L. High peritoneal transport type was the largest. (5)PD patients with hemoglobin 100g/L ratio was raised every year. The albumin level in plasma was greater than or equal to 35g/L in peritoneal dialysis (PD) patients. We studied the effects of chlorhexidine-impregnated patches (Biopatch), which are used as central-line dressings or drain site dressings, on PD catheter exit site infection and tunnel infections.

Conclusions: In a cohort of PD patients who switch from calcium-based binders to sucoraf er oxyhydroxide as part of routine clinical practice, there was a 78% increase in patients achieving in-range serum phosphorus (p=0.003). Additionally, phosphate binder pill burden was lessened from 7.4 to 3.6 pills per day (3.7 fewer pills, p=0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB890

Peritoneal Dialysis Patients Who Switch from Calcium-Based Binders to Sucroferric Oxyhydroxide as Part of Routine Clinical Practice: A Retrospective Database Study Linda H. Fioceciello, Vidhya Parameswaran, Phaneth Keo, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. Fresenius Medical Care North America (FMCNA), Waltham, MA.

Background: A retrospective database study on the real-world effectiveness of sucorfer oxyhydroxide (SO), an iron-based phosphate binder (PB), was conducted in a cohort of adult peritoneal dialysis (PD) patients. This analysis examines pts who switched from a calcium-based phosphate binder (CaPB); either calcium acetate (n=95) or calcium carbonate (n=35) to SO.

Methods: All pts were prescribed SO as part of routine clinical practice at FMCNA clinics, had 1 serum phosphorus (sPhos) measured during SO, and the most recent PB used was a CaPB. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), % transferrin saturation (TSAT), ferritin (FER), and PB pills per day were assessed 3-months before starting SO baseline and 3-months during SO treatment (follow-up).

Results: Pts who had in-range sPhos increased from 12.5% to 22.3% (78% increase) between baseline and follow-up (Figure). There were significant reductions in sPhos (7.1 to 6.8 mg/dL, p=0.004) and PB pills per day (7.4 to 3.6 pills, p<0.001). Minimal change in sCa (8.9 to 8.95 mg/dL, p=0.5) and iPTH (519.2 to 544.4 mg/mL, p=0.4) was observed. There was significant change in FER (708.5 to 788.5 mg/mL, p=0.008, but not TSAT (35.8 to 35.5%, p=0.8) when pts treated with IV iron were included. There was minimal increase in FER (733.6 to 735.0 mg/mL, p=0.98) or TSAT (38.0 to 39.1%, p=0.61) in pts not administered IV iron (n=45).

Serum phosphorus during baseline compared to sucorfer oxyhydroxide[SO]-treated follow-up for patients who switched from calcium-based binders to SO (N=130)

Conclusions: In a cohort of PD patients who switch from calcium-based binders to sucorfer oxyhydroxide as part of routine clinical practice, there was a 78% increase in patients achieving in-range serum phosphorus (p=0.003). Additionally, phosphate binder pill burden was lessened from 7.4 to 3.6 pills per day (3.7 fewer pills, p=0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB891

Effects of Chlorhexidine-Impregnated Patches on Catheter Exit Site and Tunnel Infections in Peritoneal Dialysis Patients Chiiki Kawabata, General Internal Medicine, Japanese Red Cross Kaminomoto Hospital, Kaminomoto, Japan.

Background: Exit-site infections and tunnel infections are major causes of catheter loss in peritoneal dialysis (PD) patients. We studied the effects of chlorhexidine-impregnated patches (Biopatch), which are used as central-line dressings or drain site dressings, on PD catheter exit site infection and tunnel infections.

Methods: A retrospective review was conducted of 45 patients whose PD catheter exit site was made between January 2007 and December 2014. We compared acute exit site infections, chronic exit site infections, and tunnel infections of the two groups, (the Biopatch Group and the Non-Biopatch Group), 6 months after the exit site was created.

Results: The Biopatch was used until the exit site had healed perfectly. The mean time of using the Biopatch was 63±26 days. The two groups had no significant differences in age (49.6±12.0 years vs 52.3±16.3 years), diabetes mellitus co-morbidity or pattern of peritoneal dialysis. There were no statistical differences in acute exit site infections [15.4% vs 6.1% (p=0.27)]. chronic exit site infections [0% vs 9.1% (p=0.28)] or tunnel infections [15.4% vs 15.2% (p=0.901)] during the 6 months. A cohort Using the Biopatch until the exit site has healed perfectly does not reduce either exit site infections or tunnel infections.

Funding: Non-U.S.
When to Remove the Peritoneal Dialysis (PD) Catheter After Renal Transplantation? (RT) 

Results: 108 patients transplanted from PD, 32 women/76 men with a mean age at the time of transplantation 58.0±13.3 years were analyzed. Two patients received RT due to a tunnel infection by Staphylococcus aureus or Pseudomonas aeruginosa. The withdrawal was delayed in 91 patients (84%) and 8 has not yet been removed. The average withdrawal time was 4.1±2.7 months. The indication of withdrawal was: stable renal function in 85 (93%), stable pancreatic and renal function in 4 and exit site infection in 2 (2%). Mean survival at the time of withdrawal was 2.1 months and 4.1 months for catheters were removed surgically under local anesthesia. The mean duration of hospitalization was 2.1±0.8 days (0-12). Four patients (3.7%) had complications during withdrawal (one hemotoma, two hemorrhagic shock and one surgical wound infection). 18% patients shared complications before withdrawal: 13 exit site infection, one peritonitis associated with urinary fistula and one spontaneous peritonitis.

Conclusions: In our experience the removal of the peritoneal catheter may be delayed until renal graft function were stabilize since the rate of complication is low compared with another studies.

Funding: Other NIH Support - Spanish Public Health Service

When to Remove the Peritoneal Dialysis Catheter (PD) Catheter After Renal Transplantation? (RT) 

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Background: There seems to be consensus that the time of removal of the peritoneal catheter after RT may be delayed until renal function and the patient is stabilized, but there are few publications about.

Methods: We analyzed retrospectively patients on peritoneal Dialysis Unit (PD) who have received a RT between May 1995 and March 2015 gathering medical history data relating to the peritoneal catheter removal and complications.
Conclusions: The combination of serum albumin, hs-CRP, and BMI at the time of PD commencement was a significant independent risk factor for the composite outcome of all-cause death and unplanned hospitalization in incident PD patients. 

Funding: Government Support - Non-U.S.

PUB597


Background: Learning proper device use and clinical concepts of care must be internalized by patients to successfully perform PD at home. With increasingly diverse patients going on PD and increasing adoption of urgent start PD, there is a need for simpler techniques. Enhancing the user educational environment with methods including visual, graphical and voice will improve the educational experience leaving the patient with better understanding of the procedure.

Methods: Automated PD training was undertaken at a university based home dialysis program using a novel APD device (AMIA). 5 patients were trained on the device in a 1:1 nurse to patient ratio. The cyclers provided on screen instructions using a touch screen interface with voice guidance, text instructions and animation. Each patient was trained according to standardized outlines and sequential training progression from CAPD to APD techniques. Training included RN demonstration followed by patient direct interaction with the device. Instruction was displayed on a touch screen.

Results: Patient training completion required consistency of error free setup.

Results:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Etiology of renal disease</th>
<th>Incident (/P)</th>
<th>Urgent (U)/Routine (R)</th>
<th>Training Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>F</td>
<td>Hypertension/NSAID</td>
<td>U</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>F</td>
<td>FSFS</td>
<td>U</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>F</td>
<td>Calcineurin Inshb Toxicity</td>
<td>P-HD</td>
<td>R</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>M</td>
<td>FSFS</td>
<td>P-HD</td>
<td>R</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>F</td>
<td>Lupus Nephritis</td>
<td>P-APD</td>
<td>R</td>
<td>4</td>
</tr>
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5 patients aged 30-68 yrs (mean 47), 80% female with a minimum of HS education completed training. Device training ranged from 2-3 days for urgent start patients and 4-5 days for routine start patients.

Conclusions: From our experience, training times were similar or reduced using the AMIA cycler and allowed the ability to efficiently train urgent start patients. Observed advantages of the new cycler included: 1) less need for memorization 2) distinction of a beginner vs advanced mode 3) online alarm troubleshooting 4) presence of an air detector in the device. Instruction was displayed on a touch screen.

PUB598

Peritoneal Dialysis-Related Peritonitis in a Single Center: 10 Years Experience Patricia O. Costa, Carla M V Melo, Jardordon P. Oliveira, Flavia A. Nobrega, Jandson P. Oliveira, Kleyton Andrade Bastos. Dept of Medicine, Federal Univ of Sergipe, Aracaju, Sergipe, Brazil.

Background: Peritonitis remains as the main Peritoneal Dialysis (PD)-related complication. It is estimated that it contributes directly to 20% of dropout and is related to 16% of all deaths. This study proposes to evaluate episodes of PD-related peritonitis and describe its incidence, causative organisms and possible predictors in patients belonging to a DP program from a reference center in Aracaju-Sergipe-Brazil.

Methods: Retrospective cohort study that evaluated 565 patients who stayed for at least 30 days in the technique, between 01/01/2003 and 12/31/2012, with a mean age of 54 ± 19 years, 55% male, 62% less than 8 years of regular study and 88% with monthly income less than 5 national minimum wages. They remained in DP by an average of 713.5 days. Among the 565 patients, 348 had at least an episode of peritonitis, resulting in 494 episodes of peritonitis, with an incidence of 8.7 episodes/100 patient-months.

Results:

Patient Age

<table>
<thead>
<tr>
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<th>Gender</th>
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Conclusions: From our experience, training times were similar or reduced using the AMIA cycler and allowed the ability to efficiently train urgent start patients. Observed advantages of the new cycler included: 1) less need for memorization 2) distinction of a beginner vs advanced mode 3) online alarm troubleshooting 4) presence of an air detector in the device. Instruction was displayed on a touch screen.

PUB600

Body Composition and Cardiovascular Outcomes Using Continuous Automated Peritoneal Dialysis – A Prospective Cohort Study Carlos Alberto Garza, Gabriela Leal, Bernard Moguel. Dept of Nephrology, National Inst of Cardiology, Mexico City, Federal District, Mexico.

Background: Fluid overload (FO) due to compliance in Continuous Ambulatory Peritoneal Dialysis (CAPD) is common. Efforts to achieve dry weight and avoid cardiovascular outcomes (CO) are lessen from inaccurate body composition (BC) estimations despite best clinical assessment.

Methods: We’ll follow BC, multiple frequency bioelectrical impedance (InBody S10, InBody Co), standard laboratories and CO, in all new patients to continuous Automated Peritoneal Dialysis (APD) previously in a CAPD. Measurements at baseline (CAPD), 1 month and every visit to the dialysis clinic thereafter (APD) for a 5 year period.

Results: These are the first data of BODY cohort study. Initial 10 subjects are described, 4 men and 6 women, median age 27 years (17-46), height 159.5cm(146-166), baseline and first follow up variables are in Table 1. Wilcoxon rank test for related samples was performed. We found that PD modality switch to APD, at 1 month, reflected a body composition transition with statistical significance (P<0.05), within the EBW/TBW ratio at expense of trunk compartment. Most likely from improved dialysis adherence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Baseline</th>
<th>30 days</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Kilogram (K)</td>
<td>60.75(42.7-104.2)</td>
<td>58.6(45.2-108.4)</td>
<td>-</td>
</tr>
<tr>
<td>BMI</td>
<td>Kg/m²</td>
<td>23.4(17.2-39.7)</td>
<td>23.4(18.6-41.3)</td>
<td>-</td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>mmHg</td>
<td>152(110-175)</td>
<td>136(117-180)</td>
<td>-</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>mmHg</td>
<td>97.5(64-108)</td>
<td>91(59-127)</td>
<td>-</td>
</tr>
<tr>
<td>Body water (TBW)</td>
<td>Liter(L)</td>
<td>31.5(22.4-53.5)</td>
<td>31.5(24.8-45.2)</td>
<td>-</td>
</tr>
<tr>
<td>Extracellular water (EBW)</td>
<td>L</td>
<td>12.9(3.7-17.9)</td>
<td>12.2(9.4-17.5)</td>
<td>-</td>
</tr>
<tr>
<td>Intracellular water (IBW)</td>
<td>L</td>
<td>19.0(12.9-27.4)</td>
<td>19.4(14.7-27.7)</td>
<td>-</td>
</tr>
<tr>
<td>E BV/T BW Ratio</td>
<td>0.39(0.38-0.42)</td>
<td>0.38(0.38-0.41)</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>E BV/IBW Trunk Ratio</td>
<td>0.39(0.38-0.42)</td>
<td>0.38(0.38-0.41)</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Lean Muscle</td>
<td>Kg</td>
<td>43.5(30.1-60.6)</td>
<td>43.5(30.1-60.6)</td>
<td>-</td>
</tr>
<tr>
<td>Body Fat</td>
<td>Kg</td>
<td>15.5(3.4-34.6)</td>
<td>16.2(5.7-47.8)</td>
<td>-</td>
</tr>
<tr>
<td>Metabolic Rate (IMR)</td>
<td>Kcal/day</td>
<td>131(1019-1679)</td>
<td>1298(1091-1678)</td>
<td>-</td>
</tr>
<tr>
<td>Dialysis</td>
<td>L</td>
<td>71(2.10)</td>
<td>81(8.12)</td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>

**"not statistically significant**
Conclusions: We consider that APD, on the ground of increased, uninterrupted and rigorously performed therapy, is an appropriate and effective treatment to optimize FO and aim for dry weight in PD. Further recruitment of patients and follow up of the BODY Cohort study is expected to confirm this hypothesis.

Funding: Pharmaceutical Company Support - HiTec Medical

PREVENTION OF PD GROWTH USING MODIFIED PET

PB601

The Changes in Bicarbonate Level and Ionized Ca/Corrected Ca Ratio of Patients Receiving Peritoneal Dialysis Using Bicarbonate/Lactate-Buffered Solution Emi Kimoto, Nanae Matsuo, Masamitsu Morishita, Mami Nakamura, Yukio Maruyama, Yuayuki Nakada, Masatsugu Nakao, Yudo Tanno, Ichiro Ohkido, Hiroyasu Yamamoto, Keitaro Yokoyama, Takashi Yokoi. Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.

Background: Recently, PD solution which contains 25mEq/L bicarbonate and 10mEq/L lactate (Bicarbonate/Lactate-buffered peritoneal dialysis solution; B/L solution) is developed in Japan. Because of high concentration of lactate (40mEq/L) of conventional peritoneal dialysis (PD) solution, patients have generally higher serum bicarbonate level than those of patients receiving hemodialysis (HD). The new B/L solution is expected not only its biocompatibility but also improving excess correction of acids. Under the metabolic alkalosis environment, we reported that PD patients have lower levels of ionized Ca (iCa) at the same corrected Ca (cCa) levels. Thus, we hypothesized that iCa / cCa ratio increased after switching PD solution from Lactate-buffered to B/L solution.

Methods: We recruited 28 patients (55 ± 13 years, male 82%, PD duration 42 ± 21 months) who switched from Lactate-buffered to B/L solution, and investigated changes in serum bicarbonate, iCa, and cCa levels.

Results: After switching solution, serum bicarbonate decreased (26.7 ± 3.2 vs 24.8 ± 2.5, P<0.01), and cCa did not change (9.3 ± 0.5 vs 9.3 ± 0.5, P=0.63). Neither iCa nor iCa/cCa ratio increased significantly (1.12 ± 0.09 vs 1.11 ± 0.09, P=0.48; 0.12 ± 0.007 vs 0.119 ± 0.006, P=0.54, respectively).

Conclusions: Conversion to B/L solution from lactate solution was associated with lower serum bicarbonate. Unfortunately, iCa did not change. Further investigations are needed to confirm the utility of the monitoring of iCa for the management of chronic kidney disease - mineral and bone disorder (CKD-MBD) in PD patients.

PB602

Road to Success: One Academic Medical Center’s Experience Building a Peritoneal Dialysis Clinic Yazar M. Ali, William A. Schlueter, Erwin E. Morales, Maria A. Gavino, Shubhada N. Ahya, Robin E. Watson. Nephrology, Northwestern Memorial Hospital, Chicago, IL.

Background: Peritoneal Dialysis (PD) is an option for renal replacement therapy. The US Renal Data System 2012 Annual Report states that the annual per-patient HD cost is approximately $87,500 whereas for PD it is $66,750. In addition, studies have demonstrated that some aspects of quality of life are improved in PD patients compared with HD patients. Despite this, PD is underutilized in the US. Northwestern Medicine’s PD Program was initiated in 01/2014 with 4 nephrologists and 10 patients who transferred from a neighboring PD Unit. From 02/2014 to 04/2015, Northwestern’s Peritoneal Dialysis Clinic grew to 50 peritoneal dialysis patients.

Methods: We included all patients who started on PD (or transferred to PD) in PD Clinic between the periods of 2/14 and 4/15. Patients excluded from this analysis stopped PD within this period for the following reasons: switched to HD, expired, recovered kidney function, or underwent transplantation.

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

1028A
Results: There were significant differences between group B and A (Hazard Ratio: 2.611, \(p = 0.016\), 95% CI: 1.223-6.009), group B and C (Hazard Ratio: 6.031, \(p = 0.001\), 95% CI: 2.975-13.53), group C and A (Hazard Ratio: 2.390, \(p = 0.009\), 95% CI: 1.33-4.09). In addition, these groups were analysed by adjustment factor such as age, sex, blood pressure, hemoglobin, Ca, P, whole PTH, TC with multivariable analysis. The results proved that there were tended to be correlation between group B and A (Hazard Ratio: 1.963, \(p = 0.09\), 95% CI: 0.901-4.61). There were significant differences between group B and C (Hazard Ratio: 4.00, \(p = 0.003\), 95% CI: 1.866-9.35), group C and A (Hazard Ratio: 2.037, \(p = 0.002\), 95% CI: 1.165-3.63).

Conclusions: Low level of albumin increases the mortality of PD patients gradually. Therefore we may decrease mortality of PD patients by improving nutritional condition and infection control when PD patients are introduced.

PUB605

The Effect of Neutral pH versus Conventional Peritoneal Dialysis Solutions on Peritoneal Permeability

Atsushi Ueda, Kei Nagai, Toshiaki Usui, Joichi Usui, Kunhiro Yamagata, Chie Saito. Univ of Tsukuba, Tsukuba, Japan.

Background: Biocompatible peritoneal dialysis (PD) solutions have been anticipated to reduce oxidative stress against peritoneal PD solutions. However, previous reports suggested peritoneal permeability have not been changed. This study was undertaken to investigate the peritoneal transport status from PD initiation, using biocompatible or conventional PD solutions.

Methods: We employed retrospectively 101 patients who started PD and divided into three groups. Group A was consisted of 76 patients who used only conventional low pH solutions, and neutral pH group was consisted of 19 patients who used only biocompatible neutral pH solutions during the subsequent two years. The rest of six patients used low pH solutions at the initial phase of PD, then switched to neutral pH solutions. The ratios of diolysate to plasma creatinine concentration at 4 hour (D/Pcre) in peritoneal equilibration test were measured at every year. We evaluated D/Pcre levels at the initiation and two years after between acid and neutral pH groups, and also the D/Pcre movements before and after switching PD solutions of the six patients.

Results: There was no significant difference on the D/Pcre values between at the start and two years after in the acid and neutral pH groups respectively. D/Pcre change between at the start and two years after in the acid group was not significant different compared to that of the neutral pH group. However, D/Pcre declined significantly one year after switching PD solutions from acid to neutral pH.

Conclusions: It was not observed obvious beneficial effects of neutral pH solutions on peritoneal permeability within two years PD duration. However, the transient effect in decreasing peritoneal permeability was found, and suggested that biocompatible solutions may preserve peritoneal functions compared to conventional solutions in a long time period.

PUB606

Predictive Power of Serum Cystatin C Assessing Residual Renal Function in Patients on Peritoneal Dialysis

Jung Min Park,1 Song-Hoon Song,1 Eun Young Seong,1 Harin Reeh,1 Ihm Soo Kwak,1 Il Young Kim,1 Dong Won Lee,1 Soo Bong Lee,2 Woo Jin Jung,1 Su Min Park,1 Min Jung Kim,2 Joo Hui Kim.1 1Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea; 2Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea.

Background: Residual renal function (RRF) is of considerable importance for patient survival on peritoneal dialysis. In clinical practice, the RRF is usually measured by assessing the urine concentrations of urea and creatinine and total urine output and the process is cumbersome and time consuming. Cystatin C has proposed to be used in place of RRF measurement. This study aims to investigate the predictive power of serum cystatin C in peritoneal dialysis patients.

Methods: This study included 54 patients on peritoneal dialysis who had evaluated RRF, serum cystatin C and serum creatinine. RRF was measured using the 24-hour urea-creatinine clearance method and cystatin C based glomerular filtration rate (eGFRcysC) was estimated using the Hoek’s formula. RRF and cystatin C were followed up for 6 months at least. The rate of RRF decline and slope of serum cystatin C were assessed by regression.

Results: Patients were on peritoneal dialysis for a median of 30 months and average serum concentrations of cystatin C was 5.41 ± 1.06 mg/L. Among the 54 patients, sixteen was anuric and seven became anuric during follow up. The patients with RRF had significantly lower cystatin C levels (\(p = 0.001\)). RRF was correlated with cystatin C (\(r = -0.687\), \(p < 0.01\)). In simple linear regression, RRF was associated with cystatin C (\(r = 0.687\), \(p < 0.001\), eGFRcysC (\(r = 0.741\), \(p < 0.001\)) and creatinine (\(r = 0.662\), \(p < 0.001\)). The slope of serum cystatin C was correlated with the rate of RRF decline (\(r = 0.616\), \(p < 0.001\)) during follow up. The overall small loss of RRF group had a higher level of serum cystatin C at the point of dialysis initiation (\(p = 0.017\)).

Conclusions: Serum cystatin C level might be convenient parameter for estimating the RRF and serum cystatin C at the point of dialysis initiation might be a predictive marker of preservation of RRF. Further studies about the cystatin C based equations are required to replace creatinine/urea clearance measured RRF.

PUB607

Peritoneal Dialysis: A Decade Experience at a Reference Centre in Brazil

Patricia O. Costa, Carla M.V. Melo, Flavia A. Nobrega, Jordanno P. Oliveira, Jандson P. Oliveira, Kleyton Andrade Bastos. Dept of Medicine, Federal Univ of Sergipe, Aracaju, Sergipe, Brazil.

Background: Peritoneal Dialysis (PD) is underutilized in most countries. The Brazilian prevalence is around 9%. This study aims to describe the ten years experience on PD in a dialysis center in Northeast of Brazil (Aracaju-Sergipe). Unlike other national programs, negative selection for DP is not an attribute of this dialysis unit.

Methods: Retrospective cohort study that evaluated the sociodemographic and clinical profiles, comorbidities, peritonitis, hospitalizations and death causes of 565 patients who remained in PD for at least 30 days from 01/01/2003 to 12/31/2012.

Results: Patients were mostly men (55%), living outside Sergipe’s capital (56%), had a mean age of 54 ± 19 years old when started on dialysis, were illiterate or had less than 4 school years (62%) and had a family income less than 5 national minimum wages per month (88%). The etiology of nephropathy was identified in 54% of cases, diabetic nephropathy (46%) and hypertensive nephrosclerosis (22%) were the most prevalent. Hypertension was associated with immobility (77%), diabetes (29%), D/Pcre was the initial dialysis modality for 53% of patients, mainly as an emergency (58%), and only 9% of patients had undergone peritoneal dialysis care for at least six months. Patients remained in PD by an average of 710.5 ± 714.2 days, and 61% of them also underwent hemodialysis (HD) at some point during their dialysis treatment. 676 peritoneal catheters were implanted (1.19 patient), 75% by trocar, by nephrologist, mostly Tenckhoff (58%). The main cause of dropout were infectious complications related to therapy (17%). The peritoneal index was 1 episode every 27.03 months, and S. aureus was the most prevalent etiological agent (22%). There were 1045 hospitalizations during follow up, most frequently due to infections (48%). The cause of death was identified in 64% of cases, mostly from cardiovascular diseases (50%).

Conclusions: In this study, patients had predominantly low socioeconomic status and did not have access to predialysis treatment, however, peritonitis rates and catheter complications are similar to those reported in other international series. HD and PD are shown as complementary techniques.

PUB608

Implementation of Clinical Practice Guidelines on Antimicrobial Prophylaxis in Peritoneal Dialysis Patients

Denise Campbell,1 Fiona Brown,2 Jonathan C. Craig,1 Martin P. Gallagher,4 David W. Johnson,4 Geoffrey S. Kirkland,4 Subramanian K. Kumar,4 Wai Hoi Lim,3 Dwarakanathan Ranganathan,4 Walaa W. Saweirs,6 Germaine Wong,7 David Mudge. 1School of Public Health, Univ of Sydney, Sydney, New South Wales, Australia; 2Nephrology, Monash Univ, Clayton, Victoria, Australia; 3Renal Medicine, Auckland City Hospital, Auckland, New Zealand; 4Renal and Metabolic Div, George Inst for Global Health, Sydney, New South Wales, Australia; 5Nephrology, Princess Alexandra Hospital, Wooloongabba, Queensland, Australia; 6Nephrology, Royal Hobart Hospital, Hobart, Tasmania, Australia; 7Renal Unit, Gosford Hospital, Gosford, New South Wales, Australia; 8Renal Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; 9Nephrology, Royal Brisbane & Women’s Hospital, Herston, Queensland, Australia; 10Renal Unit, Whangarei Hospital, Whangarei, New Zealand.

Background: Despite the existence of international guidelines, peritoneal dialysis (PD)-related infections vary widely across Australia and New Zealand units, with multiple units reporting suboptimal rates and variable practice.

Methods: The current practice and barriers to guideline uptake were evaluated in eight PD units located in Australia and New Zealand in 2011. A multifaceted intervention was developed which included case report forms, a patient diary, a ‘Preventing Peritonitis Checklist’, an Emergency Department flyer, a letter to the patient’s general practitioner, a medical card, and a poster summarizing ISPD and KHA-CARI guidelines.

Results: At baseline (1 Jan-31 Dec 2011), exit-site infection (ESI) rates ranged from 0.06-0.53 episodes/patient-year; peritonitis from 0.31-0.86 episodes/patient-year; and fungal peritonitis from 0.00-0.50 episodes/patient-year. After implementation (9 Dec 2013-8 Dec 2014), the ESI rates were 0.00-0.22 episodes/patient-year; peritonitis was 0.06-0.53 episodes/patient-year; and fungal peritonitis was 0.00-0.14 episodes/patient-year.

Conclusions: Implementing the various tools resulted in improvement in the ESI and peritonitis rates but the difference was not statistically significant (P=0.15 and P=0.08). There was no statistically significant difference in the fungal peritonitis rate (P=0.64).

Funding: Government Support - Non-U.S.
Survival Analysis of 326 Continuous Ambulatory Peritoneal Dialysis (CAPD) Patients  

Hao Zhang, Liu Li, Bin Yi, Wei Li. The Third Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: This study aimed to identify clinical outcomes and risk factors that may affect potential prognosis of ESRD (end-stage renal disease) patients who receiving continuous ambulatory peritoneal dialysis(CAPD) in Southern China.

Methods: A total of 326 CAPD patients were initiated Cycler in the Third Xiangya Hospital, Central South Univ, from August 1st 2002 to Mar 31st 2015. The patients were divided into two groups according to the baseline PET. Gender (r = 0.299, p = 0.299), serum albumin (r = 0.199, p = 0.199) and TG level (r = 0.140, p = 0.140) were correlated with the baseline PET respectively. Multiple stepwise linear regression analysis showed that gender (β = 0.085), serum albumin (β = -0.005, p = 0.005) were associated with baseline PET independently. Multivariate Logistic analysis showed that men (OR = 3.314, p = 0.001), hypoalbuminemia (OR = 2.552, p = 0.001) and TG levels (1.11±0.62 mmol/L vs 1.28±0.57 mmol/L, p = 0.047) compared to the low baseline PET. Gender (r = 0.299, p = 0.299), serum albumin (r = 0.199, p = 0.199) and TG level (r = 0.140, p = 0.140) were correlated with the baseline PET respectively. The high transport rate is a contributory factor in low serum albumin levels. This result is similar to what several large studies had reported in the literature. For diabetic PD patients, PET should be carefully evaluated and accordingly the prescription of short dwells, which have found their natural application in APD, should be kept in mind as a treatment option. The high transport rate is a contributory factor in low serum albumin levels.

Results: A total of 326 CAPD patients (199 male and 127 female) were identified in this study. The mean age was 50.73±14.99 years, median dialysis vintage was 46(2-144) months. Primary glomerulonephritis was the most common cause of ESRD (50.6%). The overall 1-, 3- and 5- patient survival rate were 95.4%, 79.3% and 46.2%, and 1-, 3- and 5- technique survival rates were 78%, 62% and 42% respectively. Technique survival rates were 64%, 52% and 24% respectively. Only 10% of the patients could perform their PD therapy without the assistance of any family member or nurses. Only 70% of the patients were on APD among those using CAPD. Albumin levels were significantly associated with the commencement were independent risk factors for technique survival in diabetic patients on peritoneal dialysis (PD).

Conclusions: Our data suggest that diabetic PD patients tend to be significantly high transporters with worse prognosis in terms of patient and technique survival.

Factors Influence the Baseline Peritoneal Transport Status  

Hao Zhang, Bin Yi, Cuiling Hou. The Third Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: Baseline peritoneal solute transport rate (PSTR) is an independent risk factor for total and cardiovascular (CV) mortality in the PD (peritoneal dialysis) population. The determinants of PSTR in incident PD patients are still under debate. Our objective was to explore the influence factors of baseline PSTR.

Methods: (1) 205 incident PD patients who had a standard peritoneal equilibration test (PET) within 3 months after commencing PD and without peritonitis history were enrolled. Pre-dialysis clinical parameters and biochemical indexes were assessed. 205 individuals were divided into two groups according to the baseline PET. High transport group: PET > 0.65, Low transport group: PET < 0.65. (2) Pre-dialysis serum advanced oxidation protein products (AOPP) and dialysate AOPP, GPx, hsCRP, IL-1beta, TGF-beta1 and eGFR were collected from medical records. Outcome of death or technique failure from any causes were selected. All-cause mortality and survival rate were analyzed using variance analysis and COX regression.

Results: A total of 326 CAPD patients (199 male and 127 female) were identified in this study. The mean age was 50.73±14.99 years, median dialysis vintage was 46(2-144) months. Primary glomerulonephritis was the most common cause of ESRD (50.6%). The overall 1-, 3- and 5- patient survival rate were 95.4%, 79.3% and 46.2%, and 1-, 3- and 5- technique survival rates were 78%, 62% and 42% respectively. Technique survival rates were 64%, 52% and 24% respectively. Only 10% of the patients could perform their PD therapy without the assistance of any family member or nurses. Only 70% of the patients were on APD among those using CAPD. Albumin levels were significantly associated with the commencement were independent risk factors for technique survival in diabetic patients on peritoneal dialysis (PD).

Conclusions: A strong adherence to PD method in all 15 patients. All patients were educated 2-3 weeks after the start of acute PD regimen and we observed a strong adherence to PD method in all 15 patients.

Causes of Failure in Chronic Peritoneal Dialysis Catheters  

Elizabeth Huerta calistis. Nephrology, Hospital Angeles Puebla, Puebla, Mexico.

Background: One of most common treatment of end stage kidney failure is peritoneal dialysis. Encapsulating peritoneal sclerosis is a complication in wich the osmotic capacity of the peritoneal barrier is lost, mainly due to infections. This pathology has different clinical presentations that oblige to use different diagnostic and therapeutic methods.

Methods: I was a survey conducted retrospective, descriptive and cross that included June 1, 2008 to May 30, 2014 in nephrology department of Angeles Hospital.

Results: Clinical and imagine presentation in three different patients, we analyze each separately as well as their solutions. These include delimitation of the affected zone, sterilization of the cavity and its collapse, even the renal transplantation.

Conclusions: Different clinical presentations of the encapsulating peritoneal sclerosis oblige to design evaluation and treatment for each patient in particular, using all the imagine and laparoscopic methods.

Take on Characteristics of Incident PD Patients in a Multicentre Multinational Integrated Care Setting  

Belen Maroni, Marieta Torro, Delia Timofio, Janusz Ostrowski, Jose C. Divino-Filho. 1 Diaverum Home Therapies. Medical Office, Diaverum, Munich, Germany; 2 Segged Diaverum Clinic, Diaverum, Szeged, Hungary; 3 Sena Diaverum Clinic, Diaverum, Bucharest, Romania; 4 Wloclawek Diaverum Clinic, Diaverum, Wloclawek, Poland.

Background: Our institution as a Renal Service provider is committed to integrated care, offering all types of RRT and focusing in patient’s choice. Objectives: To analyze HD and PD take on and its relationship with the type of previous referral and provided care. Methods: A retrospective analysis of 547 incident patients starting dialysis in 23 HD/PD clinics in 2012. Early referral (ER) considered if patient known ≥3months in Nephrology, and scheduled initiation of dialysis with a permanent access was considered planned (P).

Results: Population: 30% diabetes, mean age 64 years, 84% with previous medical care of renal disease, 49 % late referral, 80% modality informed, 58% unplanned start, 11% PD (3% early switch from urgent HD). PD therapy in non-planned start applied in 5/59 PD patients. No differences in HD/PD take on were observed for gender, diabetes, initial renal and predialysis follow up, at structured units or in elapsed time between early

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
follow up and dialysis start. PD patients (p=0.02) received more modality information than HD (92% vs. 78%) and were mainly under 50 years (p = 0.001). Incidence varied according with different studied groups

<table>
<thead>
<tr>
<th>Studied groups: n (% vs.col.)</th>
<th>All patients n=547</th>
<th>HD n=488</th>
<th>PD n=59</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER + P</td>
<td>168 (31)</td>
<td>133 (27)</td>
<td>35 (59)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Late referral + P</td>
<td>63 (12)</td>
<td>58 (12)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>ER + Unplanned start</td>
<td>113 (20)</td>
<td>104 (21)</td>
<td>9 (15)</td>
<td></td>
</tr>
<tr>
<td>Late referral + Unplanned start</td>
<td>203 (37)</td>
<td>193 (40)</td>
<td>10 (17)</td>
<td></td>
</tr>
<tr>
<td>Optimal care: ER + modality informed + P</td>
<td>121 (22)</td>
<td>96 (20)</td>
<td>25 (42)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Despite commitment to offer PD/HD as complementary treatments, PD incidence is still low. Optimal care provision is important to improve outcomes but also to involve patients in their therapy choice.

PUB615

The Adsorption Kinetics Profile of Aminoglycoside Antibiotics During Lixelle S-35 Cartridge Hemoperfusion

Marco Sartori, 1,2 Angela Casas, 1 Silvia De Rosa, 1 Mirella Zancato, 1 Leopolda Zampieri, 1 Davide Giavarina, 1 Claudio Ronco. 1 Internal Medical Research Inst of Vicenza, St. Bortolo Hospital, Vicenza, Italy; 2Dept of Pharmaceutical and Pharmacological Sciences, Univ of Padua, Padua, Italy.

Background: The bactericidal activity against Gram(-)-to of Tobramycin(TOB)and Gentamicin(GEN)is concentration-dependent. It is therefore fundamental achieving the maximum drug plasma levels. Lixelle-S-35 is a physiological hydrophilic interaction liquid chromatography (HILIC)-tandem MS/MS. A small volume (150mL) of plasma spiked with six drugs was diluted with 350mL of acetonitrile containing 0.1% formic acid. After centrifugation, 100uL of the clear supernatant was directly injected into the HILIC-MS/MS, without any solvent evaporation and reconstitution step. The chromatographic separation of the AG AMBs was achieved on Unison UHPLC-HILIC column (50m x 3mm i.d., particle size 3um) with a linear gradient elution system composed of 0.1% formic acid and acetonitrile.

Methods: We performed mock direct hemoperfusion (DHP;Q B =1.06mg/L; n=3) then it was circulated into the system. Samples were taken from arterial(Cpin) and venous(Cpout) lines at 5, 10, 60, 120 min. Sample levels were measured by TOBR and GENT Flex methods (Siemens). The adsorption kinetics profiles were calculated. Results: The mob mass adsorption was 37.20% whereas GEN was 46.20%.

Conclusions: Our in vitro study indicates an high adsorption rate for both aminoglycosides. This should be considered when TOB or GEN are used in pts treated with Lixelle S-35 cartridge. A supplemental dose may be needed to maximize efficacy.

PUB616

Analysis of Some Aminoglycoside Antimicrobials in Human Plasma by HILIC-MS/MS

Shinya Omika, 1,2 Xiao-Piao Lee, 1 Takeshi Kumazawa, 1 Keiko Sato, 1 Kyoko Inui, 1 Tomoki Miyazaki, 1 Yoshitivo Inoue, 1 Ashio Yoshimura, 1 Daichi Medicine, Div of Nephrology, Showa Univ Fujigaoka Hospital, Kanagawa, Japan; 2Dept of Legal Medicine, Showa Univ School of Medicine, Tokyo, Japan.

Background: Aminoglycoside(AG) antimicrobials(AMBs) have been used for a treatment of bacterial infections especially by acid-fast bacteria. However, their acute overdose or chronic abuse can cause serious side effects, such as difficulty in hearing, interstitial nephritis resulting in renal failure and even sudden death from anaphylactic shock. In such cases, there is a great need to identify and quantify AG AMBs in the blood from patients or cadavers. We earlier reported an analytical procedure for nine AG AMBs in human serum by capillary HILIC mass spectrometry (MS). Although this method works well for identification of the drug, it is semi-quantitative unless a suitable isotopic internal standard is used.

Methods: A simple, rapid, sensitive and quantitative method is presented for the analysis of six AG AMBs (streptomycin, ribostamycin, kanamycin, amikacin, dibekacin, arbekacin) in human plasma samples by hydrophilic interaction liquid chromatography (HILIC)-tandem MS/MS. A small volume (150mL) of plasma spiked with six drugs was diluted with 350mL of acetonitrile containing 0.1% formic acid. After centrifugation, 100uL of the clear supernatant was directly injected into the HILIC-MS/MS, without any solvent evaporation and reconstitution step. The chromatographic separation of the AG AMBs was achieved on Unison UHPLC-HILIC column (50m x 3mm i.d., particle size 3um) with a linear gradient elution system composed of 0.1% formic acid and acetonitrile.

Results: All drugs showed base peaks due to [M+H]+ ions by HILIC-MS with positive ion electrospray ionization, and the product ions were produced from each drug ion as a product ion by HILIC-MS/MS quantification was made by selected reaction monitoring. The data obtained from actual determination of the AG antimicrobials in human plasma after their oral or intramuscular administration are also presented for validation of the methods.

Conclusions: This method would seem to be useful in clinical and forensic medicine because of its ability in both identification and quantification of the drugs.

PUB617

Prevalence of Chronic Musculoskeletal Pain Among Hemodialysis Patients

Magdy F. Elshankawy, 1 Cherry Reda, 1 Haitham Ezzat, 1 Amr Mohab. 1 Nephrology Dept, Ain Shams Univ, Egypt.

Background: Chronic musculoskeletal pain is common in patients with end stage renal disease (ESRD) undergoing hemodialysis; however information regarding its frequency and prevalence is relatively scarce.

Methods: A cross-sectional study was conducted on 100 ESRD patients on maintenance hemodialysis three times per week for at least 3 months. Chronic musculoskeletal pain was evaluated using the VON KRAEEFUHRENS scale for grading the severity of musculoskeletal pain. Correlation was done between chronic MS pain and physical findings of motor and sensory systems examination. In addition, correlation was also done between chronic MS pain and intact Parathormone (PTH), serum corrected calcium, serum phosphorus, serum alkaline phosphatase, serum albumin and hemoglobin level.

Results: Mean age was 57.46 years. Mean dialysis duration was 3.80 years. 42% were females and 58% were males. In our study, 37% of the patients had low disability low intensity of pain i.e. little affection on the daily, social & work activity (grade 1), 37% of the patients had low disability high intensity of pain (grade 2) while 26% of them had high disability high intensity of pain i.e. moderate limitation of the daily, social, recreational & work activities (grade 3). Chronic musculoskeletal pain showed positive correlation with muscle state, tenderness and power (p<0.001, p<0.001, p=0.001 respectively). Grade 3 disability patients had the highest level of serum Ca and PTH which were significantly different from grade 1 and 2 patients (p<0.001, p=0.013 respectively). While serum albumin level was lowest in grade 3 patients (p=0.025).

Conclusions: Chronic MS pain is common in ESRD patients. Disturbed mineral metabolism is strongly associated with chronic MS pain in long-term HD patients. Musculoskeletal system involvement remains a common problem that limits the physical function of patients with ESRD.

PUB618

Practice Patterns of United States Nephrologists in Blood Pressure Medication Use when Transitioning Patients to Dialysis

Mary C. Mallapalli, 1 Steven Fishbane, 2 Rimda Wanchoo, 2 Andrea Roche-Recinos, 1 Subodh J. Saggi, 2 Moro O. Salifu. 1 Internal Medicine: Div of Nephrology, SUNY Downstate School of Medicine, Brooklyn, NY; 2Internal Medicine -Div of Nephrology, Hofstra North Shore LIJ School of Medicine, Great Neck, NY.

Background: As there is no standard approach to transitioning a patient in chronic kidney disease (CKD)-5 to CKD5-Dialysis in regards to adjustment of diuretics, BP medication, optimal frequency of medication reconciliation (MR) and determination of dry weight (DW) we conducted a survey to determine how US nephrologists transition a patient from CKD5 to CKD5-D in these aspects.

Methods: We designed an anonymous electronic survey with 39 questions and sent it to practicing nephrologists in the US after IRB approval.

Results: 120 US Nephrologists replied to the survey; 60% were in Nephrology for more than 10 years. (79%) used furosemide in CKD5 (66%) used a combination of furosemide and metolazone. The first choice of diuretics in CKD5 was furosemide (79%), in CKD5-D was torsemide (9%) and torsemide (9%) (p=0.005). In CKD5, 45% used diuretics daily, 29% on non-dialysis days and 26% discontinued them(p<0.002). In CKD 5, 63% would continue ACEI or ARB. In CKD5D, 84% of responders had at least 30% of patients on ACEI/ARB and most (64%) would not stop these medications despite hyperkalemia. The majority (79%) did not change ACEI to those that were not dialyzed out. The perceived most effective BP medication in CKD5 decreasing order: Nifedipine/mladipine (36%), ACEI/ARB (29%), beta blockers (17%), diuretics (13%) and others (4%); (p=0.0005). Most responders (79%) prescribed BP medication on non-dialysis days only and 88% thought that BP should be monitored with ultrasound in the first month. The first choice of BP medication in CKD5 was monthly (78%), weekly (12%) and as needed only (8%). DW was determined in the first week (31%) and the first month(52%). Of those surveyed, 59% felt HTN in CKD5 had multiple causes.

Conclusions: Transitioning patients from CKD5 to CKD5-D continues to remain challenging in terms of adjustment of BP medication. Variations in practice regarding the frequency of medication use may benefit from guidelines.
First Dialysis Prescription and Access Use: A Survey of United States Nephrologists  
Mary C. Mallapallil,1 Steven Fishbane,2 Rinda Wanchoo,2 Andrea Roche-Recinos,1 Subodh J. Saggi,1 Moro O. Salifu.1 1Internal Medicine-Nephrol, SUNY Downstate School of Medicine, Brooklyn, NY; 2Div of Nephrology, Hofstra North Shore LIJ School of Medicine, Great Neck, NY.

Background: As there is no standard approach to initiate renal replacement therapy in CKD5 patients in regard to location of first treatment, access and dialysis prescription we conducted a survey of US nephrologists to better identify current practice patterns.

Methods: We created an anonymous electronic survey with 39 questions that was validated then approved by the IRB. Aggregate data was analyzed using descriptive statistics, avoiding duplicate responses.

Results: 120 US nephrologists replied to the survey, 60% were in nephrology practice for more than 10 years. The first hemodialysis (HD) treatment was as inpatient (22%), outpatient (29%) or either (49.5%). At the first HD, most nephrologists (92%) used a blood flow (BF) >300 mL/min. 65% would use lower than usual dialysate flow rates (DFR) and 47% would use another access. Ninety six percent prescribed less than twice the usual dose, even with blood area nitrogen less than 100 mg/dL. About 45% replied that only 10-50% of patients meeting criteria for peritoneal dialysis were actually started on this modality (p<0.005). Of the participants 47% noted that only 10-50% of patients who were eligible for transplant were listed, and the majority of responders noted less than 10% of their patients got a preemptive transplant (p<0.0005). A patient educator was available to educate 64% of the participants. First dialysis with a permanent access was noted among 30-60% of patients by 43% of responders and in more than 60% of patients by 22% of responders. Of the participants 73% replied that the majority (>60%) of their patients got vein mapping before access creation. The time between vein mapping and access creation was one week to one month (61%) and more than one month (26%), (p<0.005). The number of angioplasties that were acceptable prior to primary access failure was noted as 2, (25%) or more than 4 (24%).

Conclusions: There is variation in practice in several areas in regard to the initial dialysis session in CKD5 which may benefit from guidelines.

Association Among Calcium, Phosphorus, and Parathyroid Hormone with Aortic Ring Calcification in a Cohort of Hemodialysis Patients  
Arturo Reyes Marin. Nephrology, Hospital Juzre de Mexico, DF, Mexico.

Background: The prevalence of vascular calcification in dialytic therapy is 40-92%, values increased in serum levels of calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) have been associated with high calcification progression and cardiovascular mortality. It has been described association among serum levels of Ca, P, Ca-P product and PTH with aortic ring calcification in patients with chronic renal disease (CRD). We did an observational and descriptive study, in the nephrology department of Hospital Juzre de Mexico, with a cohort of 95 hemodialysis patients, the aim of study was to evaluate the association among aortic ring calcification by torax radiography with the serum levels of Ca, P and PTH.

Methods: Adult patients in hemodialysis were included, patients with severe malnutrition, cancer and mental abnormalities were excluded. We used 2 scales (torax radiography), in order to assess the aortic ring calcification and we did correlation coefficient among Ca, P, PTH and 2 scales. We used Pearson correlation coefficient for analysis and Bland-Altman test for analysis of concordance among Ca, P, PTH and 2 scales.

Results: They were 95 adult patients: 50 (52%) men and 45 (48%) women, average age was 40.7 years old. We found weak negative correlation between Ca and PTH (r = -0.21, p > 0.05), weak positive association was found between P and PTH (r = 0.30, p < 0.05), correlation between PTH and CaSP (r = -0.36, p > 0.05), PTH and 2 scales (r = 0.5, p < 0.05). In the scales that we used to evaluate vascular calcification (torax radiography) showed high scores, however the intraclass correlation coefficient between scales and PTH, Ca and P (0.33) showed not statistical significance.

Conclusions: Despite that vascular calcification was high by torax radiography, the association among scales (torax radiography) and serum levels of Ca, P and PTH was not statistical significant. There are other important factors that can explain the progression of vascular calcification and the traditional markers for calcification: Ca, P and PTH are not enough for explain it.

Funding: Government Support - Non-U.S.

How to Dialyze a Patient with Left Ventricular Assist Device in a Chronic Dialysis Unit? A Practical Protocol  
Sadiq Ahmed,1 Debbie Baker,2 1Univ of Kentucky; 2Univ of Padua, Padua, Italy.

Background: To provide chronic HD treatments to ESRD patients with LVAD in a chronic unit in the community is a challenge and a relatively new experience for nephrologists. As LVADs have revolutionized the treatment of advanced heart failure there are rising numbers of these patients developing ESRD need for HD in the community. Development of a practical, simple and safe protocol is needed to dialyse these patients in the chronic units.

Methods: This protocol and safety check list is developed to provide routine HD treatment for patients with LVAD and successfully implemented in a chronic dialysis unit in the community setting. The special policy and procedure relevant to this protocol, safety check list and standing orders for the dialysis nurses were approved by the governing body in the community setting. The special policy and procedure relevant to this protocol, safety check list and standing orders for the dialysis nurses were approved by the governing body in the community setting.

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Conclusions: This protocol to provide incenter HD to patients with LVAD in a chronic unit is simple & safe. It can be implemented in a chronic HD unit.

Funding: Private Foundation Support

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Funding: Private Foundation Support
PUB623

Does Dialysis Influence Treg Cells? A Meta-Analysis  Carlotta Caprara, 1 Gilbert R. Kinsey, 1 Wenxin Xin, 1 Jennie Z. Ma, 1 Valentina Corradia, 1 Elisa Scalzotti, 1 Francesca K. Martino, 1 Mark D. Okusa, 2 Mitchell H. Rosner, 2 Fiorenza Ferrara, 2 Claudio Ronco, 2 1International Renal Research Inst Vicenza (IRRV), Dept of Nephrology, Dialysis & Transplantation, St. Bortolo Hospital, Vicenza, Italy; 2Medicine, Univ of Virginia, Charlottesville; 3Public Health Sciences, Univ of Virginia, Charlottesville.

Background: The immunological state of patients with ESRD is dysregulated. Regulatory T (Treg) cells comprise a small proportion of the total lymphocyte population yet regulate key immune responses across a variety of disease settings. Contrasting results have been reported about the influence of dialysis on Treg cells. Our aim is to determine whether the available literature support a positive or negative influence of dialysis on Treg cells.

Methods: After screening 84 published studies (PubMed and Web of Science) we included 10 that evaluated Treg cells in ESRD patients. Of these, 5 studies included comparable healthy controls (HCs) and hemodialysis (HD) patients and used similar criteria for determining the percentage of Treg cells in total CD4 T cells were subjects included to a meta-analysis.

Results: A total of 99 HD patients and 88 age-matched HCs were included in these 5 studies. Using the fixed effect model a significant difference in the percentage of Treg cells in total CD4 T between HD and HCs was observed (P<0.001). The mean difference in Treg percentage was -2.34% in HD patients vs. HCs. Several discrepancies were noted between studies that may be due to the lack of consistent criteria for Treg cell identification and use of different type of dialysis membranes which was not specified in all articles.

Conclusions: The available literature comparing Tregs in HD patients and HCs suggested HD is associated with a reduction in Tregs. A limitation is that only a few articles consider uremic patients (ESRD not on dialysis) as a control group for HD. Furthermore, no studies have investigated Treg cells in the same patient before and then after initiating dialysis. This type of study will be critical to understanding the influence of dialysis on Treg cells. Furthermore, the clinical significance of these changes in Treg cell numbers will need to be elucidated.

PUB624

Combination of Insulin Degludec (IDeg) and Liraglutide (Lira) (IDeg+Lira) Is Potentially Superior to Basal-Bolus Insulin Therapy (BB) in Hemodialysis (HD) Patients with Type 2 Diabetes (T2DM) – An Assessment by Continuous Glucose Monitoring (CGM)  Satoshi Funakoshi, 1 Jyunichiro Hashiguchii, 1 Kenji Sawase, 1 Osamu Sasaki, 1 Hiroshi Ichinose, 1 Miwa Shirahama, 1 Miki Yano, 1 Yutaka Morii, 2 Takahisa Uchino, 1 Kazunori Usunomiya, 1 Yoko Obata, 1 Tomoya Nishino, 1 Takashi Harada. 1 1Osamu Sasaki, 1 Hiroshi Ichinose, 1 Miwa Shirahama, 1 Miki Yano, 1 Yutaka Morii, 2 Takahisa Uchino, 1 Kazunori Usunomiya, 1 Yoko Obata, 1 Tomoya Nishino, 1 Takashi Harada. 1

Background: Glycemic fluctuations in HD with T2DM.

Methods: After screening 84 published studies (PubMed and Web of Science) we included 10 that evaluated Treg cells in ESRD patients. Of these, 5 studies included comparable healthy controls (HCs) and hemodialysis (HD) patients and used similar criteria for determining the percentage of Treg cells in total CD4 T cells were subjects included to a meta-analysis.

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PUB625

More Nephrologist Visits Are Associated with Lower Cost of Care for Dialysis Patients  Hao Hang, Jane Brzozowski, Sheetal Chaudhuri, John W. Larkin, Mahathi Mothali, 1 Len A. Usvyat, Terry Ketchersid, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: Medicare patients with end stage renal disease (ESRD) are treated by nephrologists, primary care providers (PCPs), cardiologists and other specialists on a regular basis. We investigated the relationship of visits to these providers and total costs of care.

Methods: Medicare 100% ESRD data for patients with evidence of dialysis at any time during January 1, 2010 through December 31, 2011 were analyzed. Nephrologist, PCP and cardiologist visits were determined by specialty codes of Part B claims including both in- and out-patient visits. All data was aggregated at the Metropolitan Statistical Area level (MSA). We computed a ratio of nephrologist visits to PCP visits per MSA as well as nephrologist visits to cardiologist visits per MSA during the above period (visits were calculated on a per patient per month basis). Total costs of care (per member per month [PMPM]) were determined by aggregating Medicare Part A and B costs. Comparisons of ratios were performed using t-tests for quartiles of PMPM for two specialty visit ratios.

Results: Claims for 368,711 patients were analyzed. Patients in the lower quartiles of total cost had significantly more nephrologist visits relative to PCPs and cardiologists.

PUB626

Prediction of Non-Adherence to Hemodialysis Treatment Regimens  Yue Jiao, 1 Daniel E. Geary, 2 Theresa J. Hetzel, 1 Sheetal Chaudhuril, 1 Mahathi Mothali, 1 Terry Ketchersid, 1 Dugan Maddux, 1 John W. Larkin, 1 Peter Kotanko, 1,2 Brian Scott Ash, 2 Len A. Usvyat, 1 Franklin W. Maddux. 1Fresenius Medical Care North America, Waltham, MA; 2Renal Research Inst, New York, NY; 1Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Non-adherence with hemodialysis (HD) treatment regimens is known to be associated with increased morbidity and mortality. The aim of this project was to develop a predictive model (PM) to identify HD patients who will likely have unexcused no shows to routine dialysis treatments within the next week.

Methods: Using data between 1/1/2014 and 12/31/2014 from the Fresenius Medical Care Knowledge Center and 2014 weather data from the National Oceanic and Atmospheric Administration’s National Centers for Environmental Information, PMs were designed and developed for prediction of unexcused no shows in patients not residing in a nursing home. Various PMs were investigated and included the generalized linear model, partitioning and regression trees, artificial neural networks, and generalized additive model (GAM). In all, 1,554,833 records stratified in weekly intervals on 60 variables from 172,854 patients were utilized. Variables included data on the patient’s history of unexcused no shows, demographics, comorbidities, laboratories, holidays, sporting events, and weather. A multi-tier prediction process was performed with respect to the availability of data. The area under the curve (AUC), sensitivities and specificities were investigated to determine the model with the highest performance.

Results: Best performing model had AUC of 0.87 for the multi-tier PMs utilizing a 30% test dataset. A small pilot test on 860 patients for three weeks utilizing optimal Yoden index as the cutoff value to predict the high probability of the unexcused no show events achieved an average sensitivity of 0.57 and specificity of 0.95.

Conclusions: These results indicate that higher ratios of nephrologist visits to cardiologist/PCP visits are significantly associated with decreased cost on a MSA level. Taken that nephrologist visits tend to be constant (due to the monthly capped payment), these results may be reveling a “sicker” and therefore more expensive population of patients on a MSA level that require more medical attention from a cardiologist or PCP, likely due to hospitalizations. Adjustments for underlying disease should be considered.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America
Conclusions: This pilot test of the developed modeling demonstrates that PM can assist in identifying patients with a high probability for unexcused missed HD treatments. Additional studies are needed to further analyze the potential of predictions for and interventions associated with reducing unexcused no show events.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB627
Factors Influencing Residual Renal Function Decrease in Hemodialysis Treated Patients

Bobby C. Lee, 1 John Duffy, 2

Background: We have shown in previous studies that maintenance of residual renal function in hemodialysis treated patients is conditioned by the number of weekly sessions, and is better in patients who start treatment with a twice weekly schedule. The aim of this study is to analyse the influence of other variables in the preservation of residual renal function.

Methods: Of the 174 consecutive patients who started hemodialysis treatment in the hospital, 98 began with 2-weekly sessions (2HD group), and 76 with 3-weekly sessions (3HD group). Residual renal function was measured every two months (mean urea and creatinine clearance).

Results: Decrease in residual renal function was lower in the 2HD group (median 0.19 vs 0.46 ml/min/month, p=0.005). In both groups the residual renal function decrease was higher in the patients from the transplant program than in those from predialysis: 2HD group: median 0.93 vs 0.17 ml/min/month, p=0.003; 3HD group: median 0.76 vs 0.32 ml/min/ month, p=0.005. Neither the initial schedule, sex or etiology of the renal disease influenced the decrease in residual renal function in either of the two groups of patients. Moreover we found no correlation between the decrease in residual renal function with age, the residual renal function at the start of dialysis or with the Charlson comorbidity index. Of the 98 patients who began with the 2HD schedule, 45 went on to dialysis three times a week when the residual renal function was less than 3 ml/min: these patients had a mean of 10.8 months on the 2HD schedule. The length of time on this model was not influenced either by age, sex, etiology of the nephropathy, comorbidity index, scheduled start or basal renal function.

Conclusions: The decrease in residual renal function in the patient treated with hemodialysis depends basically on the number of weekly sessions with which the dialysis treatment was started. Of the variables analysed only the return to dialysis due to graft loss conditioned a higher decrease in residual renal function in both groups of patients.

PUB628
Circadian Blood Pressure Behaviour in Hemodialysis Patients

Dimitrios Petras, 1 Kyriakos Dimitriadis, 2 Panagioti E. Giannouli, 1 Eirini Andrikou, 2 Konstantinos Tsioufs. 2

Background: Blood pressure (BP) evaluation and management in haemodialysis (HD) patients is often a matter of debate. During HD hypotension as well as a paradoxical rise in BP pattern are at high risk for coronary artery disease, especially if other comorbidities are present. The riser pattern is high and further increases during the interdialytic period. Patients with this BP pattern are at high risk for coronary artery disease, especially if other comorbidities coexist. Ambulatory BP monitoring in ERSD patients is a promising non-invasive technique for the recognition of future heart disease.

PUB629
In Vitro Dialysability of SNF472, a Novel Inhibitor of Vascular Calcification, Using Conventional Hemodialysis and Hemodiafiltration

Joan Perelló, 1 Miquel Gomez Humbert, 2 Nestor Yesid Rodriguez, 2 Carolina Salcedo, 1 Miquel D. Ferrer, 1 Juan Manuel Buaides, 3 Maria de mar Perez, 2 Eva Martin Becerra, 4 Francisco Maduell, 1 Sanijet, Palma, Spain; 2Nephrol. and Renal Transpl., Hosp. Clinic, Barcelona, Spain; 3Nephrol., Hosp. Son Llàtzer, Palma, Spain; 4Kürol, Madrid, Spain.

Background: SNF472 is being developed for the treatment of calciphylaxis and cardiovascular calcification in end stage renal disease patients on hemodialysis. The intended use of SNF472 is intravenous infusion during dialysis; therefore our aim was to assess its possible dialyzability and its effects on calcium (Ca) chelation.

Methods: Dialysability of SNF472 was assessed using online hemodiafiltration (OL-HDF) and conventional hemodialysis (HD) systems. The interaction of SNF472 with Ca was studied under bypass conditions (dialysis in off-mode). One liter of heparinized fresh blood spiked with 8 mg/dl creatinine was introduced in a container maintained at 37 ºC and a one hour dialysis session was simulated. 66.6, 30 and 10 ml/liter SNF472 were infused during the first 20 minutes of dialysis. Samples were obtained at different time points and creatinine, total and ionized Ca and SNF472 levels were quantified.

Results: No dialyzation of SNF472 was detected at 30 and 66.6 mg/liter neither in OL-HDF nor in HD systems. Dialyzation was measured at 10 ml/liter SNF472 both in OL-HDF and in HD, with an estimated clearance (Cl) of 30 and 18 ml/min, respectively. Creatinine showed a Cl of 231 and 220 ml/min, respectively. In bypass conditions, blood Ca was chelated during the 20 minutes of SNF472 infusion when added at 66.6 mg/ml. However, when the system was switched to the dialysis mode, the Ca in the dialysis bath compensated the chelating effect of SNF472 and Ca levels remained unaltered.

Conclusions: SNF472 dialyzes with a low Cl. SNF472 levels increase in blood during infusion and dialysis does not prevent from attaining potentially therapeutic levels. As SNF472 will be infused during the whole dialysis session, this low Cl is not expected to affect systemic exposure. The chelating effects of SNF472 on Ca are compensated by the Ca in the dialysis bath, so no hypercalcemia is expected. Supported by REDINREN RD012/0021 and RETOS COLABORACIÓN RTC-2014-2460-1 grants.

Funding: Pharmaceutical Company Support - Laboratoris Sanijet, Government Support - Non-U.S.

PUB630
A Simple and Cost Effective Approach to Ultra-Pure Dialysate

Anthony M. Valeri, 1 Bobby C. Lee, 2 John Duffy, 3 Robin Ferrer, 4 Ronald Villota, 5 Greg C. Riccardi, 5 Edmond P. Wong. 3

Background: Ultrapure dialysate has been shown to reduce inflammation and improve nutritional and anemia parameters in patients on chronic maintenance hemodialysis. The Nephros 9 HDU (Dual Stage Ultrafilter, Nephros Inc, River Edge, NJ) has been shown to reduce bacterial counts and endotoxin levels by at least a 5 log order of magnitude.

Methods: We performed an observational trial of this filter in a hospital-based acute dialysis facility in the USA.

Results: There were 23 chronic stable hemodialysis outpatients treated during the 6 month period after the installation of the filters to the preceding 6 months, there was an increase in the mean hemoglobin level of 0.5 g/dl (p=0.010) with a reduction in the mean weekly darbopoietin dose of 14.6 mcg or 40% (P<0.001) translating to a reduction in the ESA resistance index (weekly ESA dose/hemoglobin level) of 1.52 (p<0.001). During this time period, indirect inflammatory markers showed a reduction in the mean WBC count from 7,000 to 6,600 x 10³/ L (p=0.008) and an increase in serum albumin from 3.6 to 3.7 (p=0.024). The mean sPκt/V was unchanged during the 2 time periods (from 1.699 to 1.607, p=0.30).

Conclusions: In conclusion, the use of the Nephros® DSU filter to further reduce endotoxin exposure in chronic hemodialysis patients can result in improved ESA responsiveness and a lower ESA dose.
**PUB631**

Care Delivery Models for End Stage Renal Disease: A Systematic Review
María Lourdes Gonzalez-Suárez,1 Priya Ramar,2 Sagar Chawla,2 Adriano Luiz Ammirati, Thais Nemoto Matsui, Maria C.C. Andreoli, Fabiana Dias Carneiro, Ana C M S Ramos, Bento C. Santos. Dialysis Center, Hospital Israelita Albert Einstein, Brazil.

**Background:** Reimbursement for dialysis care has led the way for the broader transition to a value-based payment model. As payment policy for dialysis evolves, a better understanding of the evidence regarding care delivery models that optimize outcomes and increase the value of care for dialysis patients is essential. Limited evidence exists about which care delivery models are most effective.

**Methods:** Multiple databases were searched for comparative studies of care delivery models. Included were studies published between 2000 and 2014. The intervention had to include >5 dialysis patients over age 18 years and receiving treatment; >6 months follow up, and reported patient important outcomes i.e. mortality, important clinical outcomes, hospitalizations and quality of life. Data was abstracted by reviewer pairs; study quality was evaluated using Cochrane and Newcastle-Ottawa criteria: a) diagnosis of cognitive dementia, b) survival rates, c) hospitalization rates, d) quality of life.

**Results:** 1841 abstracts were screened, 59 full text articles were reviewed, and 23 studies with 87,281 patients were included for final analysis. The interventions included nutritional care (n=4), multidisciplinary care (n=6), satellite programs (n=3), home dialysis (n=3), access monitoring (n=2), physician contact (n=4), and nocturnal dialysis (n=1).

Most were observational studies of decent quality with representativeness and incomplete follow up being the main potential sources of bias. Two randomized studies on home dialysis and pharmacist care, had attention as the main risk of bias. Most interventions showed positive effect raising concern of publication bias. Overall, hospitalizations were significantly lower in the intervention group despite large heterogeneity: RR: 0.824, 95% CI 0.781, 0.868, p=0.001, I²=95.96%.

**Conclusions:** Multiple interventions have the potential to improve the outcomes of dialysis patients but have not been compared in terms of safety and effectiveness. Limited evidence is available to inform dialysis practice redesign to adapt to new payment structures. Further studies are needed to define best delivery models for dialysis care.

**PUB632**

Symetrical Dimethylarginine (SDMA) Is Poorly Cleared by Standard Hemodialysis
Mirela A. Dobra,1 Peter B. De Oro,2 Timothy W. Meyer,3 Thomas H. Hostetter.1 Case Western Reserve Univ; 2Centers for Dialysis Care, Cleveland; 3Stanford Univ School of Medicine.

**Background:** High SDMA levels have been associated with an increased risk for cardiovascular disease in patients with normal or reduced renal function. The effect of hemodialysis on SDMA has not been thoroughly studied.

**Methods:** We measured SDMA levels and its handling by hemodialysis and by the normal kidney in subjects with ESRD on chronic hemodialysis (n=7) and in normal controls (n=6).

**Results:** The mean (SD) SDMA levels in ESRD were six times higher than in normal controls, 3.350(6.5) vs 0.530(2.5) μM, p<0.001. For comparison pre-dialysis BUN levels was 44.123(1 ml)/dl in ESRD, and 14.9(3.2) mg/dl in controls. The fractional reduction of SDMA was significantly lower than that of urea, 47.4(1.5)%, vs 76.7(4.7), p<0.001; and the volume of distribution was much higher 58.5(14.5) ml vs 35.10(4) ml. For urea. Also the urinary clearance of SDMA 17.82(33.5) ml/min in normal controls was higher than that of urea 55.2(13.7) ml/min. SDMA production rates were similar 46.7(9.4) vs 52.3(13.9) mmole/day, ESRD vs normals, p<0.05.

**Conclusions:** In summary, SDMA circulates at high levels in hemodialysis patients due at least in part to its relative high clearance by the high kidney, relative to urea, and its larger volume of distribution. The latter suggests that SDMA is likely to be localized in the intracellular compartment, and therefore less available for clearance by standard hemodialysis.

**Funding:** NIDDK Support, Private Foundation Support

**PUB633**

On-Line Hemodiafiltration Is Efficient for Inflammation and Phosphorus Control
Nadia Guimaraes-Souza,1 Thais Nemoto Matsui, Adriano Luiz Ammirati, Maria C.C. Andreoli, Fabiana Dias Carneiro, Ana C M S Ramos, Bento C. Santos. Dialysis Center, Hospital Israelita Albert Einstein, Brazil.

**Background:** High efficiency on-line hemodiafiltration is the best method for middle molecules and phosphorus removal. Many studies have demonstrated the efficiency of this method in mortality reduction. The main objective of this study was to compare the three filters available for on-line HDF comparing the ability to remove urea, phosphorus and beta2-microglobulin.

**Methods:** Prospective cross-over study including four patients and three available filters for hemodiafiltration. All section of on-line hemodiafiltration was made with high efficiency (23-25%). Filters HDF 100, FX100 and HDF80COR were compared. Urea, phosphorus and beta-2-microglobulin were collected before and after first use of each filter A reduction ratio was computed for each.

**Results:** 95% surveys of the total population comprised 111 patients were taken; of which 85 are for patients undergoing hemodialysis and 10 patients on CAPD. By studying the “General Satisfaction” in all aspect of the service that is offered to the patients responses they expressed their overall dissatisfaction. Prospective, descriptive study conducted at the Dialysis Unit of the Military Hospital Córdoba, conducted between 15/11/2014 to 15/12/2014. Methods: All patients attending the service, who received some form of dialysis (hemodiafiltration) in the period. Exclusion criteria: a) diagnosos of cognitive dementia, b) Carrying less than three month of treatment c) not be psychological and physical conditions to answer the survey. A qualitative survey, structured ajar, applied voluntary and anonymous.

**Conclusions:** FX100 and HDF100 filter were similar for urea remotion ratio. There were no differences for other molecules.

**PUB635**

Satisfaction of Patients on Dialysis Unit
Jorge Nicolas Abadla. Nephrology, Militar Hospital, Cordoba, Capital, Argentina.

**Background:** The assessment of the satisfaction of patients in Dialysis, is a useful tool to meet patient needs; axis on which the care service is based.In turn it allows to identify the deficient areas.

**Methods:** Objective 1) To know the views of patients about the service that is offered in each of the areas of focus. 2) To analyze the profile of satisfaction of patients they expressed their overall dissatisfaction. Prospective, descriptive study conducted at the Dialysis Unit of the Military Hospital Córdoba, conducted between 15/11/2014 to 15/12/2014. Methods: All patients attending the service, with received some form of dialysis (hemodiafiltration) in the period. Exclusion criteria: a) MSN diagnostic of cognitive dementia, b) Carrying less than three month of treatment c) not be psychological and physical conditions to answer the survey. A qualitative survey, structured ajar, applied voluntary and anonymous.

**Conclusions:** FX100 and HDF100 filter were similar for urea remotion ratio. There were no differences for other molecules.

**PUB636**

Correlation Between Calcium Phosphorus Product and Hypertension in ESRD Patients on Maintenance Hemodialysis
Shoua Islam1, Hafiz I. Ahmad1, Syed Rizwan Bokhari2, Arif Asif1. 1Dept of Nephrology, Allama Iqbal Medical College/ Jinnah Hospital, Lahore, Pakistan; 2Div of Nephrology and Hypertension, Albany Medical College, Albany, NY.

**Background:** Increased levels of serum calcium, phosphorus and product of serum calcium and phosphorus (Ca x P) in end stage renal disease (ESRD) patients has been shown to be associated with increased mean arterial blood pressure (MAP). The available data is limited and no study has been done in Pakistan. We conducted a cross sectional study to determine the correlation between mean arterial blood pressure (MAP) and serum calcium-phosphorus product in our ESRD patients on hemodialysis.

**Methods:** Blood Pressure of all the prevalent ESRD patients in a single dialysis center was recorded and mean arterial blood pressure (MAP) was calculated pre and post dialysis. All patients were clinically euvalmic. Serum calcium and phosphorous levels were measured and Calcium-phosphorus product (CaP) was calculated. The product above 50 and the MAP above 93 were taken as high.

**Conclusions:** High efficiency on-line hemodiafiltration is an efficient method of reduction of reactive C protein and may reduce costs due to reduced doses of erythropoietin analogs.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Urinary miR, Makoto Tonsho, Philip,1 Omkar U. Vaidya. 1,2

Behavior of Ankle-Brachial Index During Hemodialysis: Effect of Calcium Dialysate Concentration. Zaida Noemy Cabrera Jimenez,1 Rosa M. A. Moyes,1,2 Bruno C. Silva,1 Luciene dos Reis,1 Wagner Dominguez,1 Fabiana Gracioli,1 Rosilene M. Elias.1 Nephrology, Univ of Sao Paulo, Sao Paulo, SP, Brazil; 2Univ de Nole Juho-UNINOVE, Sao Paulo, SP, Brazil.

Background: Ankle-brachial index (ABI) is a simple way to access cardiovascular risk. Both low (<0.9) and high (>1.3) ABI are associated with increased mortality risk in patients on hemodialysis (HD). However, little is known regarding the acute variation of ABI (from pre to post hemodialysis), and also whether the calcium dialysate content [Ca] may interfere with this variability. We aimed to investigate the impact of [Ca] 3.5 vs. 2.5 on the variability of ABI during HD.

Methods: Incident patients on HD for up to 90days were included. ABI was evaluated pre- and post-HD in the midweek session of two consecutive weeks with [Ca] 3.5 and 2.5, respectively. Biochemical variables, electrical bioimpedance and non-invasive hemodynamic (Finapress®) were assessed.

Results: 17 patients (10 men) aged 42 ± 17 years were included. ABI pre- and post-HD with [Ca] 3.5 and 2.5 were 1.2 ± 0.1, 1.1 ± 0.1, 1.1 ± 0.2, and 1.2 ± 0.1, respectively. Although the mean ABI values were within normal range, there was a great variability in the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing

Conclusions: ABI presents great variability during a conventional HD. However, whether an acute decrease in ABI by using a [Ca] 2.5 may impact the long-term mortality deserves further investigation.

Variation in the Intracranial Pressure During Hemodialysis in a Patient with Subdural Hematoma on Propofol. Rho-Phe Bhargava,1 Omkar U. Vaidya.1,2

1Dept of Internal Medicine, Univ of Missouri-Kansas City, Kansas City, MO; 2Dept of Nephrology and Hypertension, Univ of Missouri-Kansas City, Kansas City, MO; 3Dept of Critical Care, Saint Lukes Hospital, Kansas City, MO.

Background: Disseminated intravascular coagulation (DIC) is a rare but potentially serious complication of hemodialysis. Pathophysiology of this disorder is explained by the ‘reverse urea effect’. This can be difficult to detect in patients in the neuro-intensive care unit given their compromised CNS status. However it is imperative to diagnose DIC especially in this population as intracranial pressure (ICP) instability during hemodialysis can lead to microcirculatory defects.

Methods: 60 y/o male with ESRD admitted for left frontal subdural hematoma, underwent evacuation with ventricular drain placement. He was intubated and sedated, BP 142/69 mmHg, Pulse 122 bpm, Temp of 37.3 °C, RR of 34 and SpO2 100%. The remaining physical examination was unremarkable. Hemodialysis (HD) was performed on 3 contiguous days. ICP and the changes in cerebral perfusion pressure (CPP) were monitored every 15 minutes during hemodialysis. Sedation with propofol which was started on Day 1, was weaned off completely by the session on day three. The patient seized after the third hemodialysis session. CT scan of the head was unremarkable. He was eventually discharged on day 14 and made full recovery.

Conclusions: ICP and CPP during hemodialysis decreased in the first 30 minutes and maximum variation was between 45-120 minutes. Peak ICP pressure during HD: Day 1: 5 mmHg; Day 2: 1.5 mmHg and Day 3: 25 mm Hg. Maximum change in CPP from baseline during HD: Day 1: 20 mm Hg; Day 2: 22 mm Hg and Day 3: 47 mmHg.

Cerebrovascular disease is a major cause of hospital death in patients with ESRD. Therefore it is vital to prevent and manage the ICP during HD. In this case, the acute variation in ICP and CPP makes it feasible to perform HD while monitoring the physiological parameters.
**Methods:** PBMCs were isolated from blood of patients with Delay graft function (DGF) and early graft function (EGF, n=10) at T0 and T24h from transplant. Gene expression profiles of PBMCs from both groups were assessed by Affymetrix technologies. Results were evaluated by statistical analysis and functional pathway analysis and validated by confocal analysis on a swine model of IR injury. Renal I was induced in 5 pigs by arterial clamping for 30 min and tissues were analyzed at different time points after R (T15, 30′ , 60′).

**Results:** Microarray analysis (FDR<5% and a FC>1.5) revealed that the expression of PTX3 and C3 were downregulated in EGF compared to DGF patients. On the contrary, the gene CR1 was upregulated in DGF. Furthermore, in the pig model, confocal laser microscopy showed that deposits already present at 15 R, localized at peritubular (7.7±1.1;p=0.005) and glomerular (8.2±2.5;p<0.03) capillary levels. We found a significant increase in infiltrating interstitial leucocytes such as CD163+/PTX3+ monocyte-macrophages (6.2±1.2;p=0.05) and SWC3a+/PTX3+ dendritic cells (3.7±0.5;p=0.05) compared to T0. Finally, we identified tubulo-interstitial FSP1+/PTX3+ myofibroblasts (4.1±1.3;p=0.04). Co-localization between C5b-9/PTX3, PTX3/C1g and PTX3/MBL clearly demonstrated the activation of Classical and Lectin Complement pathways in presence of PTX3 deposits.

**Conclusions:** Our data would suggest a key role of PTX3 synthesized by peripheral blood mononuclear cells (PBMCs) during DGF leading to an early activation of complement in transplant kidney.

**PUB642**

**The Effect of Combined Treatment of Dipeptidyl Peptidase Inhibitor and Metformin in Sirolimus-Induced Diabetes Mellitus** Long Jin, Jian Jin, Sun WOo Lim, Byung Ha Chung, Chul Wooy Yang. **Transplant Research Center & Div of Nephrology, Dept of Internal Medicine, Seoul, St Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.**

**Background:** Optimal treatment of post-transplant diabetes mellitus is still controversial. This study was performed to evaluate whether the combined treatment of DPP IV inhibitor with metformin (MET) is effective in sirolimus (SRL)-induced diabetes mellitus.

**Methods:** SRL-induced diabetes mellitus was made by treating SRL (0.3 mg/kg) for 3 weeks in rats, and then started to treat DPP IV inhibitor (LC15-0444[Lc], 5 mg/kg), and/or MET (200 mg/kg) for further 3 weeks. The effect of combined treatment of LC and MET on SRL-induced diabetes mellitus was evaluated by IPGTT and islet size. The oxidative stress was evaluated by measuring 8-OHdG, 4-HHE, M3SOd, and catalase in samples. Insulin secretion capacity was evaluated by glucose-stimulated insulin secretion (GSIS) test using normal isolated rat islets treated with SRL, exendin-4 and/or MET.

**Results:** SRL treatment for 6 weeks decreased body weight and increased water intake and urine volume compared with vehicle group. SRL treatment significantly increased AUCG from the values obtained during the IPGTT, but LC or MET treatment recovered these value compared with the SRL treatment alone. Combined treatment with LC and MET has more significantly decreased blood glucose level than LC or MET treatment alone. Combined treatment with LC and MET showed higher insulin level than exendin-4 or MET treatment alone.

**Conclusions:** Combined treatment with LC and MET exerts better glucose control by decreasing oxidative stress by SRL. This provides the rationales of the combined use of DPP IV inhibitor and MET in SRL-induced diabetes mellitus.

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

**PUB643**

**Incidence and Outcomes of Hyponatremia Early Post Lung Transplantation** Ekamol Tantisattamo, 1 Aneesa Shetty, 1 Bing Ho, 1 John J. Friedewald, 1 Opas Traitannon, 1 Sangeeta Bhorade, 2 Alexander Haynes, 2 Amber Nieland, 2 Lorenzo G. Gallon. 1 *Div of Nephrology and Hypertension; Pulmonary and Critical Care, Dept of Medicine, Northwestern Univ Feinberg School of Medicine.*

**Background:** Outcomes of in-hospital hyponatremia in lung transplant recipients are unclear. The aim of this study is to describe the frequency of hyponatremia and outcomes associated with hyponatremia during the early postoperative period.

**Methods:** We performed a retrospective chart review of all lung transplant recipients at Northwestern Memorial Hospital since the first case performed in July 2014 until May 2015. The severity of hyponatremia was defined as mild, moderate, and severe with serum sodium of 135 to 130, 120 to 125, and less than 120 mEq/L, respectively.

**Results:** A total of 13 lung transplant recipients were included. Age at the time of transplantation was 61.5±2.2 (SEM) years and 69% was female. The most common indication for transplantation was severe COPD (54%). Serum creatinine at the time of transplantation and at hospital discharge was 0.8±0.6 and 1.1±0.2 mg/dL, respectively. Seven out of 13 lung transplant recipients developed acute kidney injury (AKI) with AKI severity ranging from Stage 1 to Stage 3. Co-morbidities like chronic obstructive pulmonary disease (COPD) (66%) and hypertension (67%) were common. Hyponatremia was present in 6 (46.2%) recipients at time of discharge. Table 1. Of the 6 recipients with hyponatremia, the incidence was up to 46% at the time of discharge (Table 1). Almost half of the patients had persistent hyponatremia during month follow-up.

**Conclusions:** Lung transplant recipients commonly develop hyponatremia during the immediate postoperative period and are more likely to be readmitted with hyponatremia. The incidence of hyponatremia remains high up to 1 month post transplantation. AKI is also a risk for readmission and predicts longer length of hospital stay.

**PUB644**

**Motivations, Challenges, and Attitudes to Self-Management in Kidney Transplant Recipients: A Systematic Review of Qualitative Studies** Nathan Jamieson, 1,2 Camilla Sara Hanson, 1,2 Michelle A. Josephson, 1,2 Elisa J. Gordon, 1,2 Jonathan C. Craig, 1,2 Fabian Halleck, 1,2 Klemens Budde, 1 Allison Tong, 1,2 1 Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; 2School of Public Health, Univ of Sydney, Sydney, New South Wales, Australia; 2Dept of Medicine, The Univ of Chicago, Chicago, IL; 1Centre for Healthcare Studies and Comprehensive Transplant Centre, Northwestern Univ Feinberg School of Medicine, Chicago, IL; 2Dept of Nephrology, Charite, Universitaetsmedizin Berlin, Berlin, Germany.

**Background:** Kidney transplantation offers superior life expectancy and quality of life outcomes compared to other renal replacement therapy modalities. However, the complex and ongoing medication and self-management regimes impose a treatement burden on patients, and non-adherence remains a leading cause of graft loss.

**Methods:** MEDLINE, Embase, PsycINFO, and CINAHL were searched from database inception to October 2014. We used thematic synthesis to analyse the findings.

**Results:** Fifty studies involving 1238 participants aged from 18 to 82 years across 19 countries were included. We identified five themes: empowerment through autonomy (achieving mastery, tracking against tangible targets, developing bodily autonomy, routinisng and problem-solving, adaptive coping), prevailing fear of consequences (inescapable rejection anxiety, aversion to dialysis, minimising future morbidity, trivialisation and denial, defining acceptable risks), burdensome treatment and responsibilities (frustrating ambiguities, inadvertent forgetfulness, intrusive side-effects, reversing ingrained behaviours, financial hardship), over-medicalising life (dominating focus, evading patienthood, succumbing to burnout), and social accountability and motivation (demonstrating gratitude towards medical team, indebtedness to donor, peer learning).

**Conclusions:** Self-efficacy and social accountability are motivators for self-management, but ongoing adherence can be mentally and physiologically taxing. Multi-component interventions that incorporate education, psychosocial support, decision aids, and self-monitoring tools may foster self-management capacity and improve transplant outcomes.

**PUB645**

**Abstract Withdrawn**

**PUB646**

**Characteristics of Patients with Vitamin D Deficiency After Kidney Transplantation in Qatar** Mohamed Amin Elesawy, 1,2 Abdullah Hamad, 1,2 Fadwa S. Al-Ali. Nephrology, Fahd Bin Jasim Kidney Center, Hamad General Hospital, Doha, Qatar.

**Background:** Vitamin D deficiency is common among normal people and in patients with chronic kidney disease including dialysis patients. Vitamin D deficiency continues to be prevalent after kidney transplantation (studies showed prevalence of 50-80%) especially with immunosuppression use and sun protection needed for elevated risk of skin cancer. We studied characteristics of kidney transplant patients with vitamin D deficiency in Qatar.

**Methods:** We reviewed all available records of kidney transplant patients presented to our clinic at Hamad General Hospital in Doha, Qatar between 1/9/2013 and 1/3/2014 and have vitamin D level less than 30 ng/mL. Background data and laboratory tests of patients were obtained. All patients were receiving vitamin D supplements and prednisone within the immunosuppression per institution protocol.

**Results:** We studied 83 patients. Mean age was 55.5 ± 16.1 years. There were 55 males (66%) and 28 females (34%). Vitamin D deficiency was severe (level than 10 ng/mL) in 15 patients (18%), moderate in 38 (45.7 ng/mL) and mild in 30 patients (20)-9 ng/mL). Duration of transplant was 7.9 ± 2.5 years. Glomerular Filtration Rate was 65.5 ± 20.6 ml/min. We found no correlation between vitamin D and PTH levels or between vitamin D and GFR levels. Table 1 summarize bone mineral panel in our patients.
Table 1

<table>
<thead>
<tr>
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<th>Plasma Level +/- SD</th>
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<tbody>
<tr>
<td>Vitamin D</td>
<td>16.4 +/- 6.7 ng/mL</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.28 +/- 0.14 mmol/L</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.2 +/- 0.26 mmol/L</td>
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<tr>
<td>Alkaline Phosphatase</td>
<td>86.9 +/- 37.8 u/L</td>
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<tr>
<td>Intact Parathyroid Hormone</td>
<td>146 +/- 2.1 pg/mL</td>
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### Conclusion:
In a study of kidney transplant patients with vitamin D deficiency in Qatar, we found that they were predominantly males, had normal calcium, phosphorus, and alkaline phosphatase levels, while they have variable degree of elevated PTH with no correlation to vitamin D level. Most patients have mild to moderate vitamin D deficiency (82%) despite receiving vitamin D supplement although the supplement could have decreased the number of patients with severe vitamin D deficiency (18%). Further study could help to evaluate the role of vitamin D supplement in improving vitamin D level in kidney transplant recipients.

**Methods:** We reviewed the medical records of 86 renal transplant recipients, 45 patients with 51 acute graft rejection episodes and 41 patients with 54 AGPN episodes, at the Univ of College of Medicine, Seoul, Republic of Korea.

**Funding:** This work was supported by the Ministry of Health and Welfare of Korea (H11011008001-09), the Ministry of Science, ICT, and Future Planning (2010-0028874), and the National Research Foundation of Korea (2011-0019406).

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In a study of kidney transplant patients with vitamin D deficiency in Qatar, we found that they were predominantly males, had normal calcium, phosphorus, and alkaline phosphatase levels, while they have variable degree of elevated PTH with no correlation to vitamin D level. Most patients have mild to moderate vitamin D deficiency (82%) despite receiving vitamin D supplement although the supplement could have decreased the number of patients with severe vitamin D deficiency (18%). Further study could help to evaluate the role of vitamin D supplement in improving vitamin D level in kidney transplant recipients.

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A DNI value of 2.7% was selected as cut-off value for AGPN, and renal transplant recipients with a DNI ≥ 2.7% were found to be at a higher risk of infection than those with a DNI < 2.7% (odd ratio [OR] 40.50; 95% CI 8.68-189.08; P <0.001). In a multivariate logistic regression analysis, DNI was a significant independent factor for predicting AGPN after adjusting age, sex, log WBC count, log neutrophil count, log lymphocyte count, DNI value, CRP concentration and procalcitonin concentration (OR 4.32; 95% CI 1.81-10.34, P = 0.001).

Conclusions: The present study demonstrated that a DNI value above 2.7% was an independent predictive marker for AGPN and an effective marker to differentiate between AGPN and acute graft rejection. Thus, these finding suggest that DNI may be a useful marker in the management of these patients.

PUB652

Effect of Pre-Transplant Dialysis Modality on Outcomes of Living-Donor Kidney Transplantation Recipients Chiaki Kawabata, General Internal Medicine, Japanese Red Cross Kumamoto Hospital, Kumamoto, Japan.

Background: There are few studies on living-donor kidney transplantation that compare the outcomes after pre-transplant dialysis modality. We examined the short-term outcomes of living-donor kidney transplantation recipients after peritoneal dialysis (PD) and hemodialysis (HD), respectively.

Methods: 112 patients have undergone living-donor kidney transplantation procedures in our hospital between January 2001 and May 2014. We studied 40 patients, under 40 years of age, with dialysis durations of less than 5 years. We compared 13 PD patients with 27 HD patients and investigated the short-term outcomes.

Results: These two groups showed no significant differences as regards baseline characteristics including dialysis duration, body mass index, type of calcineurin inhibitor or ABO blood type compatibility. The PD group was younger than the HD group as regards dialysis duration, body mass index, type of calcineurin inhibitor or ABO blood type compatibility (data not shown).

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Conclusions: The present study demonstrated that a DNI value above 2.7% was an independent predictive marker for AGPN and an effective marker to differentiate between AGPN and acute graft rejection. Thus, these finding suggest that DNI may be a useful marker in the management of these patients.

PUB654

Intravenous Immunoglobulin in the Management of Pneumocystis Pneumonia: A Case Series Musab Elgaali, Muhammad Inman, Matthew Edey. Hull Royal Infirmary, Hull, United Kingdom.

Background: Pneumocystis pneumonia (PCP) is a well-recognized complication of renal transplantation. We present 2 cases of severe PCP treated successfully with intravenous immunoglobulin (IVIg), trimethoprim-sulfamethoxazole (TMP-SMX) and withdrawal of immunosuppression. Graft function was maintained despite a high baseline immunosuppression.

Methods: Case A: A 32-year-old woman presented 2 years post-transplant with acute cellular rejection treated with steroids. 2 months later she was admitted with respiratory failure due to PCP. She required intubation and ultimately oscillatory ventilation. CMV DNA was detected at low levels in bronchoalveolar lavage (BAL) fluid. IVlg 30g on alternate days (10 doses) was added, in addition to withdrawal of immunosuppression and hydrocortisone replacement. She made a full recovery, with preservation of transplant function. She was discharged on prednisolone, mycophenolate and tacrolimus. 9 months later she was admitted with respiratory failure and Pneumocystis jirovecii in BAL. She required invasive ventilation and inotropic support. She was treated with intravenous TMP-SMX, but her clinical condition deteriorated with acute kidney injury (AKI) requiring hemofiltration and escalating ventilator requirements. She received IVlg 25g/day for 5 days, replacement hydrocortisone and immunosuppression was withdrawn. Her AKI resolved and later she became ventilator-independent. Graft function was at baseline on discharge. Maintenance immunosuppression was recommenced.

Conclusions: It is understood that immunity against Pneumocystis jirovecii is both B- and T-cell mediated. This pooled immunoglobulin might be expected to have some anti-Pneumocystis activity. It is also recognized that IVlg has immunomodulatory properties. In both cases the administration of IVlg allowed withdrawal of immunosuppression apart from replacement steroid without graft rejection despite high immunological risk. Both patients survived life-threatening PCP. We suggest adjunctive therapy with IVlg be considered in severe PCP.
A 12/20 (60%) were on statin therapy. Almost all (6/7 = 85.7%) of patients with vascular risk clinically, however, further analysis will be required to determine whether valid reasons exist to support decisions to omit statins or renin inhibitors. Significant proteinuria (uPCR >50) was not common (6/68 = 8.8%), but of these patients (63.6%) have not had a follow up HbA1c. 20/69 (29.0%) of patients were calculated to have a >20% cardiovascular risk on the basis of comorbidities or using JBS2. Of these only 9/12 (75%) achieved target HBa1c of <48 mmol/mol. Prescription of statins, antihypertensives and aspirin were audited against guidelines from the UK Renal Association (RA) and KDIGO. Cardiovascular risk management of all transplant patients in our region by comparing new policies and practices. This spurred the current study which addressed the perspective of doctors regarding emerging ethical issues pertaining to kidney donation/transplantation. Our sample consisted of 140 doctors from Mumbai (Age Range=21-80 years, M=38.1, SD=17.95, Males=44.3%, Females=55.7%). A questionnaire, presenting ethical issues related to kidney donation/transplantation, in an agree/disagree format with supporting reasons was employed. The research design was exploratory; data was analyzed quantitatively and qualitatively.

**Results:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Agree (%)</th>
<th>Reasons (%)</th>
<th>Dis-agree (%)</th>
<th>Reasons (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated transplant patients should be governed by the government</td>
<td>75.7</td>
<td>Serves lives (16.4) Remedies organ donor shortages (16.4)</td>
<td>24.3</td>
<td>Misuse of organs (7.1) Higher chances of mismatch/organ rejection (7.1)</td>
</tr>
<tr>
<td>Kidney selling should be made legal</td>
<td>22.9</td>
<td>Greater donor availability (21.7) Avoidance of malpractice (4.4)</td>
<td>77.1</td>
<td>May lead to illegal/ unethical practices (41.4)</td>
</tr>
<tr>
<td>Handicapped should not be kidney donors</td>
<td>24.3</td>
<td>Should not burden them as already challenged healthwise (10.7)</td>
<td>75.7</td>
<td>If informed consent given (20) If kidney is effectively functioning (14.3)</td>
</tr>
<tr>
<td>Substance abusers should not be transplant recipients</td>
<td>50.7</td>
<td>Close to bring deterioration in life (10) Might abuse the transplant (15.7)</td>
<td>49.3</td>
<td>All are entitled to be kidney recipients (22.1)</td>
</tr>
<tr>
<td>Younger individuals should be given transplantation preference</td>
<td>60</td>
<td>Longer life expectancy (20) Greater transplantation success (12.9)</td>
<td>40</td>
<td>Need-based rather than age-based preference (11.4)</td>
</tr>
<tr>
<td>Families of cadaver donors should be given incentives</td>
<td>45.7</td>
<td>Motivates donation (22.9)</td>
<td>54.3</td>
<td>Would lead to commercialization and criminal activities (20.7)</td>
</tr>
<tr>
<td>Kidney donation should be made compulsory after death</td>
<td>44.3</td>
<td>Serves live (26.4)</td>
<td>55.7</td>
<td>Donation is individual's choice, coercion is unethical (44.4)</td>
</tr>
</tbody>
</table>

*Representative

**Conclusions:** This study is relevant in view of the dearth of Indian research. Educating doctors about medico-ethical issues is the need of the hour.

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**PUB656**

Cardiovascular Risk Management of Renal Transplant Patients

Joseph C. Newton, Thalakunte M. Muniraju, Dumfries and Galloway Royal Infirmary, Dumfries, United Kingdom.

**Background:** There is a high burden of cardiovascular disease amongst renal transplant recipients, and it is the most common cause of death with a functioning graft. We have assessed the medical management of all transplant patients in our region by comparing regular monitoring of glycaemia, blood pressure and serum lipids, with appropriate prescription of medicines based on their cardiovascular risk.

**Methods:** Using the electronic health record information was collected on detergent dysfunction in patients with CAD. Notably, taurine was increased in serum after the initiation of dialysis. Nephrologists should prepare patients to PKT rather than to dialysis.

**Funding:** Private Foundation Support

**Results:**

- among the major determinants of poor long-term graft survival. Metabolic abnormalities in serum and kidney graft parenchyma may worsen allograft function, while alterations of urinary metabolites may be used as diagnostic biomarkers. To explore this hypothesis, we recruited individuals with stable allograft function (n=20), chronic allograft dysfunction (n=20) and healthy controls (n=10), and analyzed their metabolomic profile by ex vivo liquid/gas chromatography-mass spectrometry (LC/MS-MS) of serum and urine in vivo two dimensional correlated spectroscopy (2D-COSY) of the kidney graft.

**Results:** LC/MS-MS revealed serum and urine abnormalities of amino acids, biogenic amines and acylcarnitines in individuals with worse allograft function (T3) compared to preserved graft function (T1). Novel potential theranostics targets have been identified with an unbiased

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

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**PUB657**

Preemptive Transplantation Is Associated with Improved Graft Survival: Results from the French Transplant Database

Mathilde Revist,1,2 Christian Comec,2 Jerome Haraamb,2 Christian Jacqueline,2 Pierre Merville,2 Lionel Couzi,2 Karen Leffondré,1 INSERM U897, Bordeaux School of Public Health, Bordeaux, France; 1Nephrology and Transplantation, Bordeaux Univ Hospital, Bordeaux, France; 2Agence de la Biomedecine, Paris, France.

**Background:** Kidney transplantation (KT) is the treatment of choice for end-stage renal disease. In France, preemptive kidney transplantation (PKT) should be considered when glomerular filtration rate is under 20 ml/min/1.73m² but European reports on the results of PKT are scarce. Our objective was to evaluate the impact of PKT on graft and patient survival.

**Methods:** We analyzed all first kidney-only transplants performed in adults in France between 2002 and 2012. A Cox multivariable model was used to study the impact of PKT on the hazard of graft failure defined as death, return to dialysis, or retransplantation, whichever came first.

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

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**PUB658**

Novel Potential Theranostics Targets in Individuals with Kidney Allograft Dysfunction

Roberto Bassi,1,2 Monika A. Niewczas,1 Nirmala Almeida,1 Karen Almeida,1 Alan F. Almeida,2 1LifeSupporters Inst of Heath Sciences; 2Human Development, Nirmala Niketan College of Home Science; Psychology, Mumbai Univ; 1Nephrology, PD Hinduja Hospital, Mumbai, India.

Ethical Issues Related to Kidney Donation/Transplantation: Perspective of Indian Doctors

Richard S. Fernandes Almeida,1 Nirmala Almeida,1 Karen Almeida,1 Alan F. Almeida,2 1LifeSupporters Inst of Heath Sciences; 2Human Development, Nirmala Niketan College of Home Science; Psychology, Mumbai Univ; 1Nephrology, PD Hinduja Hospital, Mumbai, India.

**Background:** Dearth of kidneys for transplantation has provoked the need to evaluate new policies and practices. This spurred the current study which addressed the perspective of doctors regarding emerging ethical issues pertaining to kidney donation/transplantation.

**Methods:** The sample consisted of 140 doctors from Mumbai (Age Range=21-80 years, M=38.1, SD=17.95, Males=44.3%, Females=55.7%). A questionnaire, presenting ethical issues related to kidney donation/transplantation, in an agree/disagree format with supporting reasons was employed. The research design was exploratory; data was analyzed quantitatively and qualitatively.

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**Methods:** We analyzed all first kidney-only transplants performed in adults in France between 2002 and 2012. A Cox multivariable model was used to study the impact of PKT on the hazard of graft failure defined as death, return to dialysis, or retransplantation, whichever came first.

**Results:** Between 2002 and 2012, 22 288 patients received a first KT, including 3112 (14%) who had a PKT. Mean recipient age at KT was 50 ± 13.4 years, 61% were men. Median follow-up was 4.7 years. In addition, 493 patients were recruited for the UK Renal Association (RA) and KDIGO. Cardiovascular risk management of all transplant patients in our region by comparing new policies and practices. This spurred the current study which addressed the perspective of doctors regarding emerging ethical issues pertaining to kidney donation/transplantation.

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**Funding:** Government Support - Non-U.S.
Good Patient and Graft Survival in Recipients of Kidney Transplantation due to Diabetic Nephropathy  
Amjad E. El Agroudy. Internal Medicine Dept, College of Medicine and Medical Sciences, Arabian Gulf Univ, Manama, Bahrain. 

Background: Compared with non-diabetic subjects, patients with type 2 diabetes and end-stage renal disease (ESRD) have seldom been selected for renal transplantation. The aim of this study is to compare patient and graft outcome in kidney transplant patients with diabetes mellitus. 

Methods: We retrospectively studied 358 patients who underwent kidney transplantation between 1979 and 2014, including 88 with diabetic ESRD (DM group) (type 1, n = 8; type 2, n = 80) and 270 with non-diabetic ESRD (NDM group). Mean follow-up was 92 ± (1.389) months. 

Results: Mean age was higher in the DM group (52.8 ± 44.6 years; P < .0001), and there was no significant difference in recipient gender, donor age or donor source. At the end of follow-up, there was no difference between the groups in terms of blood pressure (DM 139 ± 16.7/81 ± 7.376 vs NDM 138 ± 15.7/82 ± 1.81 mmHG; P = 0.83 ± 0.80) and renal function (creatinine, 115±4.71 vs 133±4.80 μmol/L, P = 0.18; calculated creatinine clearance, 66±24 vs 68±42 ml/min/1.73 m², respectively, P = 0.9). In total, 26 patients had acute transplant rejections [8 patients with diabetes vs 18 patients without diabetes, P = 0.11]. There was no significant difference in post transplant surgical complications as wound dehiscence or infections. There was a significant high incidence of the urinary tract infection rate in DM group (17 vs 32 patients; P = 0.02). Four out of 22 patients died (18.2%) in the DM group and 10 out of 47 patients died (21.3%) in the NDM group died from cardiovascular disease (P = 0.17). The 1-, and 10-year patient survival rates in the DM and NDM groups were 97.5% vs 99% (ns), and 56.8% vs 58.8% (ns), respectively. The 1- and 10-year graft survival rates were 97.5% vs 70.7% (ns) and 58.9% vs 66.1% (ns), respectively. 

Conclusions: Renal transplantation in diabetic ESRD patients yields good results in terms of patient survival and complications, suggesting that renal transplantation can be performed in these patients and should become a more established treatment option. 

PUB660 
Impact of Pre-Transplant Peritoneal Dialysis Compared with Hemodialysis on the Incidence of Delayed Graft Function in Kidney Transplant Recipients with Lupus 
Gabriel Contreras, Javier Pagan, Antonio A. Armstrong, Jorge M. Diego, Ian Thomas, Patricia Marie Byers, Alberto J. Sabucedo, Jair Munoz Mendoza, David Roth. Univ of Miami Miller School of Medicine. 

Background: Delayed graft function (DGF) increases the risk of allograft failure in recipients of kidney transplants. 

Methods: In this study we assessed the impact of pre-transplant peritoneal dialysis (PD) compared with hemodialysis (HD) on the risk of DGF in patients with lupus using logistic regression models. 

Results: Three hundred-fifty three of 2513 (14 %) recipients transplanted between 3/22/1994 and 9/27/2006 with complete records in the United Network for Organ Sharing files had DGF. The incidence of DGF was lower in recipients who used PD (68.6±13.1%) compared with HD (285/1900 = 15%) prior to transplantation (P = 0.013). After adjusting for donor and recipient age, gender and race-ethnicity, type of donor, recipient education and insurance, time of dialysis prior to transplantation, panel reactive antibodies (PRA), human leukocyte antigen (HLA) mismatch, and ABO blood type compatibility, the lower risk for DGF associated with the use of PD compared with HD remained significant (Odds-ratio 0.70 [95% confidence interval 0.53-0.94]; P = 0.015). Donor age (1.01 [1.00-1.02] per 1 year), deceased donor transplantation (1.64 [2.59-9.12] living donor as reference), HLA mismatch (1.08 [1.01-1.15] per 1 antigen mismatch), and PRA (1.01 [1.00-1.01] per 1%)) were also independently associated with DGF. 

Conclusions: In lupus recipients of kidney transplants, the use of PD compared with HD is associated with lower risk of DGF after adjusting for important predictors. 

Funding: Other NIH Support - This work was supported in part by Health Resources and Services Administration contract 231‑00‑0115. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. 

PUB661 
Association Between Dipstick Proteinuria and Allograft Outcomes in Living Donor Kidney Transplant Recipients 
Joon-young Park, Joon Wook Choi, Chang Hyun Lee, Gang-Hyun Kim. Dept of Internal Medicine, Hanyang Univ College of Medicine, Seoul, Republic of Korea. 

Background: Proteinuria is one of the important factors suggestive of kidney function impairment. Previous epidemiologic studies had demonstrated that greater than trace amounts of protein on a casual urine dipstick may be an important predictor of long-term clinical outcomes in general population. In kidney transplant (KT) recipients, there were few data concerning it. 

Methods: We retrospectively analyzed 238 living donor KT recipients to investigate impact of dipstick proteinuria on allograft outcomes. All KT recipients were divided into 2 groups according to dipstick proteinuria: control group (n=190); negative; case group (n=48), ≥ trace. Cox’s proportional hazard model with time-dependent covariates was used to encompass compounding effect of covariates that change over time, including vintage and allograft survival time. 

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only 
Underline represents presenting author. 
1041A
While cytomegalovirus (CMV) infection is associated with Guillain-Barré syndrome (GBS), the development of CMV disease shortly after transplantation was not expected. This vignette details a case of CMV disease in a renal transplant recipient, focusing on the clinical presentation, diagnosis, and management.

**Background:**

BK nephropathy (BKN) is a relevant cause of graft dysfunction in kidney transplantation. mTOR inhibitors (mTORi) have been suggested as the best immunosuppression in BKN. However, CMV-free therapy could increase the risk of rejection. Since 2009 in patients with BKVN we conducted a protocol discontinuing Mycophenolate and decreasing Tacrolimus (TAC) dose in association with mTORi, both with target levels of 5 ng/mL.

**Methods:**

From 2007 to 2013 we diagnosed 22 BKVN. Patients diagnosed since 2009 (n = 14, group 1) were treated beginning mTORi and decreasing TAC dose. The others 8 patients suffered significant reduction of immunosuppression (group 2). We analyze renal function, plasma quantitative BK PCR, antiHLA antibodies, reactions and dialysis mortality. We calculate follow-up.

**Results:**

22 patients were identified. The BKVN was diagnosed at 7 months after transplantation (range 2-55). The medium duration of follow-up was 53 months (685). Baseline characteristics and evolution are listed in table 1.

<table>
<thead>
<tr>
<th>Group 1 (n=14)</th>
<th>Group 2 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine at baseline (mg/dl)</td>
<td>1.3 ± 0.36</td>
</tr>
<tr>
<td>AntiHLA antibodies positive at BKVN diagnosis</td>
<td>43% (6)</td>
</tr>
<tr>
<td>Serum Creatinine at BKVN diagnosis (mg/dl)</td>
<td>1.93 ± 0.37</td>
</tr>
<tr>
<td>Serum Creatinine at final follow-up (mg/dl)</td>
<td>1.6 ± 0.7</td>
</tr>
<tr>
<td>Dialysis at final follow-up</td>
<td>7.1% (1)</td>
</tr>
<tr>
<td>Plasma BK viral load at diagnosis (copies/ml)</td>
<td>84369 (10035-8234680)</td>
</tr>
<tr>
<td>Patients with negative plasma BK viral load at final follow-up</td>
<td>78.6% (11)</td>
</tr>
<tr>
<td>Acute rejection after BKVN</td>
<td>0%</td>
</tr>
</tbody>
</table>

Although group 1 had a greater immunologic risk and a higher plasma BK viral load at diagnosis, the renal function during follow-up was more favorable than patients from group 2. No rejection episodes were diagnosis in group 1. Only one patient in each group started chronic dialysis at the end of the follow-up (52 and 85 months after BKVN diagnosis).

**Conclusions:**

An immunosuppression regimen based in TAC and mTORi is an effective treatment for BKVN. This treatment reduces viral load and increases graft survival without increasing the rejection risk.

**PUB665**

A Rare Case of Guillain-Barré Syndrome Associated with Cytomegalovirus Disease in a Renal Transplant Patient

Jessica Bian, George P. Bayliss, Medicine, Rhode Island Hospital, Providence, RI.

**Background:**

While cytomegalovirus (CMV) infection is associated with Guillain-Barré syndrome (GBS) in the general population, there are few reports of GBS associated with CMV disease in the renal transplant patients. We describe the case of a renal transplant patient who developed GBS after treatment for documented CMV disease.

**Methods:**

The patient is a 62-year-old woman with ESRD from polycystic kidney disease status post deceased donor renal transplant (CMV donor positive/recipient seronegative) on tacrolimus and prednisone. She developed ascending motor weakness, sensory loss, and areflexia without progression to respiratory compromise, improving with IVIG therapy. She was started on treatment with CMV disease (serum CMV PCR 2200 copies; CSF CMV PCR undetectable) and prednisone. Fourteen days after stopping valgancyclovir, she presented with fevers, chills, and myalgias, consistent with GBS. She developed ascending motor weakness, sensory loss, and areflexia. CSF studies were notable for albuminocytologic dissociation. MRI brain showed T2-weighted hyperintensities, consistent with GBS. She was started on treatment with CMV disease (serum CMV PCR 2200 copies; CSF CMV PCR undetectable) and prednisone.

**Results:**

She returned 7 days later with compartment syndrome of her right arm due to deep venous thrombosis of her right subclavian, axillary, and brachial veins with associated hematoma requiring emergent fasciotomy and hematoma evacuation. This was attributed to recent IVIG therapy, as thromboses may occur even in the absence of other risk factors (US boxed warning). She was bridged to warfarin prior to discharge. Of note, she maintained excellent alloreactive function throughout this complicated course.

**Conclusions:**

This vignette details a case of CMV-associated GBS after renal transplantation. The case is notable for the development of CMV disease shortly after cessation of valgancyclovir prophylaxis in a CMV donor positive/recipient negative renal transplant despite only being on only being on a two-drug immunosuppressive regimen. This may support a longer course of CMV prophylaxis in donor positive/reipient negative renal transplants.

**Funding:** Clinical Research Support

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**PUB667**

Clinical Significance of Pre-Transplant 25-Hydroxyvitamin D Levels on Acute Rejection and Infection in Kidney Transplant Recipients

Jessica Kiberd, 1
decision of Nephrology, Dalhousie Univ, Halifax, NS, Canada; 2Medicine, Div of Nephrology, Univ of Toronto, Toronto, ON, Canada; 3Dept of Surgery, Multi-Organ Transplant Program, Dalhousie Univ, Halifax, NS, Canada.

**Background:**

It is well known that vitamin D shows immune modulating effects. However, vitamin D levels in transplant serum 25(OH)D levels are independent predictor of acute rejection or infection in kidney transplant recipients.

**Methods:**

We included 174 kidney transplant recipients with low immunologic risk between 2011 and 2013. We measured 25(OH)D levels right before transplantation, and investigated whether the level of 25(OH)D predicts the development of acute rejection or infection in kidney transplant recipients.

**Results:**

During the first year after the KT, a total 27 cases of biopsy proven acute rejection was detected. 25(OH)D levels showed significant association with the development of acute rejection within the first year from KT. In the high tertile, the rate of acute rejection was 6.9 % (p=0.012). It was significantly lower incidence toward the high tertile. There was significant distinction between each tertile (low and second, p=0.032; second and high, p=0.002). For the prediction of infectious complications, after the 1 year predictive limits of 25(OH)D levels were dissipated. During the first year after KT, a total of 62 (47.5%) cases of infectious complications were detected. Most common causes were 23 (33.2%) cases of CMV and UTI respectively. 25(OH)D levels did not show significant association with either the overall or different types of infectious complications.

**Conclusions:**

Clinical transplant serum 25(OH)D levels are independent predictor of acute rejection after the first year from kidney transplantation. However, they were not associated with infectious episode.
Mammalian Target of Rapamycin Inhibitors Withdrawal in Kidney Transplant Recipients: Risk Factors and Related Transplant Outcomes

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Background: With its antiproliferative and antineoplastic properties, Mammalian Target of Rapamycin Inhibitors (MTORi) potentially have important long-term therapeutic consideration in kidney transplantation. Treatment cessation frequently occurs following its unique adverse effects. The objective of this study was to investigate the risk factors for MTORi withdrawal and its impacts on transplant outcomes.

Methods: This retrospective observational study consisted of kidney transplant recipients followed up from January 1999 till May 2015. We examined the risk factor for MTORi withdrawal using multivariate logistic regression analysis. The impacts of MTORi withdrawal on transplant outcomes were analyzed using multivariate Cox regression and logistic regression. P<0.05 was considered as statistically significant.

Results: A total of 111 kidney transplant recipients who received MTORi treatments were included, with 46 patients withdrew (41.0%). The risk factors for MTORi withdrawal included initial proteinuria (adjusted OR=4.61, P=0.007), higher initial serum creatinine (per 1mg/dl increment, adjusted OR=2.73, P=0.035), and glomerulonephritis as primary renal disease (adjusted OR=5.00, P=0.035). MTORi withdrawal was associated with an increased risk of graft failure (adjusted HR=3.79, P=0.027), but not with patient survival (adjusted HR=0.61, P=0.595).

Conclusions: MTORi withdrawal is a strong risk factor for renal graft failure. Proteinuria, poor initial graft function and primary renal disease of glomerulonephritis are predictors for MTORi withdrawal. Earlier identification of risk factors may assist physician to decide the best candidate for MTORi conversion in order to optimize transplantation outcomes.

Impact of Donor Age on Longterm Outcomes in Living Donor Kidney Transplants: A Propensity Score Matched Analysis Using Multicenter Cohort

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Background: The use of steroid withdrawal protocols after kidney transplantation has been increasing because of well-known adverse effects of steroids and the introduction of new effective immunosuppressants. Long-term efficacy and safety of tacrolimus plus mycophenolate mofetil (TAC) group compared with cyclosporine A plus MMF (Csa group) for 10 years were analyzed in renal transplantation patients with low immunologic risk who underwent steroid withdrawal at 6 months after transplantation.

Methods: Overall 10-year follow-up data of patients who underwent their first living-donor renal transplantation at Samsung Medical Center between September 2000 and August 2003 were retrospectively analyzed. Patients were randomized to CsA or TAC groups and underwent steroid withdrawal at 6 months after renal transplantation. End points were patient and graft survival, and the incidence of acute rejection and post-transplant de-novo comorbidity such as diabetes mellitus.

Results: A total of 117 patients who successfully discontinued steroid treatment were included (55 in Csa group vs. 62 in TAC group). The 10-year patient survival was 96.2% in the Csa group and 98.4% (61/62) in the TAC group (p=0.495). The 10-year graft survival rate did not differ between groups (81.3% in Csa vs 91.2% in TAC; p=0.412). The cumulative incidence of acute rejection for 10 years after transplantation was 24.5% and 15.6% in the Csa and TAC groups, respectively (p=0.201). The incidence of post-transplantation diabetes mellitus was higher in the Csa group compared to the Csa group (10.0% vs 23.3%, respectively; p=0.046).

Conclusions: Long-term graft and patient survival, and the incidence of acute rejection were similar between CsA- and TAC-based regimens combined with MMF in low immunologic risk patients who underwent steroid withdrawal 6 months after kidney transplantation.

Impact of Donor Age on Longterm Outcomes in Living Donor Kidney Transplants: A Propensity Score Matched Analysis Using Multicenter Cohort

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: 10 CV events occurred in the overall group, and 7 events in the post KT bacterial group, and 3 events in the post KT viral group. All affected CV events of these group were diabetes, high body mass index (BMI) and high baPWV. Overall arterial stiffness measured by baPWV after KT showed significant improvement (1417.5 ± 234.5 cm/s) compared to those of before KT (1503.5 ± 252.2 cm/s) (p=0.05 vs after KT).55 out of 79 patients (69.6%) showed improvement of baPWV after KT, but 24 patients did not. Between two groups, improvement group showed higher pre-transplant baPWV than no-improvement group (1561.0 ± 263.9 vs. 1371.6 ± 177.1), and multivariate analysis revealed that gender and BMI, degree of decrement of calcium level were an independent risk factor of change of baPWV.

Conclusions: We could expect CV event risk in KT recipients by diabetes, BMI and baPWV, and these were very strong prediction marker of CV event. Arterial stiffness in ESRD patients improves after transplantation, and lower BMI, the amount of calcium decreased, gender affected the improvement of baPWV. PUB673

The Correlation of Donor:Recipient Body-Mass Index (BMI) Ratio and 6-Month Post-Transplant Kidney Function in Known End-Stage Renal Disease (ESRD) Patients

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Background: Kidney Transplant (KT) is the preferred treatment for ESRD. The challenge rests in finding appropriate donors. Donor-recipient size mismatch was shown to correspond to donor-recipient nephron supply mismatch, affecting prognosis. Matching nephron supply to recipient needs was proposed to improve outcomes. Patients with a higher BMI relative to their donors were shown to have poorer post-KT graft function. Determining whether measures such as BMI are valid predictors of outcomes is a legitimate area of study. This research sought to determine the association and correlation between Donor-Recipient BMI Ratio and the 6-month post-KT creatine (crea).

Methods: A review of patients who underwent KT in 2005-2014 at the CSMC was done. Inclusion criteria were Filipinos aged 18 years and above with a graft, coming from a Living Donor, functioning for at least 6 months post-KT (25 Donor-Recipient pairs). Association using Chi-Square and correlation using Multiple Regression analysis between Donor-Recipient BMI and renal function based on 6 months post-KT crea were determined.

Results: Data showed no statistically significant association (p=0.64) and correlation (p=0.77) between Donor-Recipient BMI ratio and post-KT crea. Statistically significant correlations (p<0.10) were noted between the post-KT crea and the recipient and donor BMI. For every 1.00-point increase in post-KT crea per 1 point increase in the donor BMI, and a 13.51umol/L decrease in post-KT crea per 1 point increase in recipient BMI.

Conclusions: The data support two schools of thought on donor-recipient selection in improving outcomes. First, recipients are to lose weight to improve BMI before KT due to the increased risk of graft damage from hyperfiltration and lipotoxicity. Second, donors with larger BMI’s are better due to a higher nephron reserve. It could be surmised from the study that the donor and recipient BMI’s influence the 6-month post-KT crea. The appropriate mathematical instrument defining the relationship between these measures predicting KT outcomes more accurately, however, is yet to be universally established.

PUB674

Incidence of Malignancies in Kidney Transplant Patients – Report from Eastern Province of Saudi Arabia

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Background: Renal transplant patients have a higher incidence of malignancies due to the use of immunosuppressive medications and concomitant infections.

Methods: Based on the follow up of a single center in Saudi Arabia, the incidence of malignancies patients who underwent kidney transplantation was analyzed.

Results: During the 15 years study period, a total of 221 patients underwent renal transplantation. Eleven patients developed post-transplant malignancies with an average incidence of 4.9%. Two patients had Kaposi sarcoma (0.9%) and two developed Non-Hodgkin lymphoma (0.9%). One case was reported to have transitional cell carcinoma of the bladder (0.45%), one had breast cancer (0.45%), one had cervical cancer (0.45%), one developed angiosarcoma (0.45%), and one had hepatocellular carcinoma (0.45%). In addition, two patients developed renal cell carcinoma, one in the native kidney (0.45%), and the other in the transplanted kidney (0.45%). The duration to cancer development ranged from 6-120 months. Mortality rate in renal transplant patients with cancer was higher (55%) than those who did not develop cancer. Risk factors that determined cancer development included patient age, gender, duration of the transplantation and type of immunosuppression. Type of transplant was not found to be a determining factor of cancer development.

Conclusions: The incidence of malignancies in post renal transplant patients in the Kingdom of Saudi Arabia is evidently comparable to that reported in literature. In addition, the data highlights the importance of long term close follow up of renal transplant patients.
seen more in non-desensitized patients at 3 months, but significance was not sustained after 3 months (Table). The leukopenia effect was not significant when adjusted for steroid. There was no difference in eGFR in either group, however mean eGFR was higher in those desensitized. Incidence of rejection was very low in both groups (5% vs 8%). When living donor recipients from both groups were compared, the eGFR and leukopenia effect was similar in both groups, and there was no significant difference in BK Viremia.

Conclusions: Desensitization with IV Ig appears to be safe and effective. The lower incidence of leukopenia in desensitized group can be explained by greater use of steroids.

PUB678

Results of Chinese Renal Transplant Recipients with Post-Transplant Malignancies Lihui Ou, Hong Jiang, Jianghua Chen. The Kidney Disease Center, The First Affiliated Hospital, Medical College, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: Malignancies are a severe complication of immunosuppressive therapy among renal transplant recipients, representing an important cause of long-term morbidity and mortality.

Methods: A retrospective study of 2700 recipients who underwent renal transplantation between July 1977 and July 2013 was carried out. 51 patients developed the following malignancies at a mean of 55.2 months (range = 1–207) after kidney transplantation. According to the regimen of immunosuppressive agents, all the recipients occurred malignancies were divided into azathioprine group (Aza group, n = 21) and mycophenolate mofetil group (MMF group, n = 30). The recipient age, gender, interval from renal transplantation to tumor development, long term survival of patient and graft and the ratio of converting to rapamycin of patients were made a comparison in detail between two groups.

Results: 29 patients survived without a recurrence including 28 with graft function (Survival group, n=29), and 22 patients died of malignancies including 21 with graft function (Death group, n=22). In the survival group, only one patient lost the graft after 26 months after immunosuppressant adjustment due to chronic rejection. Renal graft function remained stable in all other patients from diagnosis throughout follow-up. Moreover, 10 patients in the survival group were switched from calcineurin inhibitor-based immunosuppression to rapamycin after the diagnoses of malignancy, otherwise no patient in death group switched to rapamycin. At a mean follow-up of 34.0 months (range: 4–74), all the 10 patients are cancer-free and survived with functional graft. The incidence of death was similar in the Aza group and MMF group.

Conclusions: Our results demonstrate that the incidence of malignancy in renal allograft recipients is much higher than normal population, closely related to the long term use of immunosuppressant. Treating cancer thoroughly and maintaining the function of the transplanted kidney can decrease the risk of death with functional graft. Rapamycin-based immunosuppression blocks the recurrence of nonmetastatic tumors.

PUB679


Background: Basiliximab is widely used in clinical practice for induction therapy of renal transplant recipients, expecting to reduce the incidence of acute rejection and improved graft function without increasing adverse events. We evaluate the impact of induction therapy using Basiliximab on relevant clinical outcomes: graft and patient survival, incidence of acute rejection (AR) and incidence of infectious or malignancy complications.

Methods: This retrospective study included all renal allograft recipients who were transplanted between January 2010 and April 2014 and who received Basiliximab as induction therapy. We collected the baseline characteristic of recipients, type of donor, donor’s age, HLA matches and immunosuppression at the time of transplantation. The clinical outcomes were evaluated at the first year of transplantation and include: AR incidence, infectious or malignancy complications, serum creatinine and estimated glomerular filtration rate (eGFR) using the 4-variable MDRD formula, as well as graft and recipient survivals.

Results: The demographic characteristics of recipients and donors are in Table 1. Among 662 renal transplant recipients including in this study, only 10.6% (n=70) experienced AR during the first year follow up. The incidence of infectious complications in the first year after transplantation was 32.3%, mostly urinary tract infection (82%). No episode of malignancy was reported. Graft and patient survival rates were 96.9% and 98.5% respectively.

Conclusions: Our findings support previous studies, with similar incidence of AR episodes during the first year, and less incidence of infectious and malignant complications, similar patient and graft survivals at 1 year follow up. We can conclude that basiliximab is associated with excellent graft and patient survival and low rates of AR episodes.

PUB680


Background: A successful kidney transplant improves the quality of life and reduces the risk of death in most patients when compared with staying on dialysis, however, the survival of transplant patients is lower than general population patients of the same age. In our analysis we calculated, the causes of death and characteristics of deceased patients were identified.

Methods: This was a retrospective observational study that included all kidney transplant patients between January 1, 2010 to April 30, 2014, at HE-CMNO, IMSS, Guadalajara, Jalisco, Mexico. The follow-up time was one year. Mortality was calculated, the causes of death and characteristics of deceased patients were identified.

Results: During this time 1,047 transplants were performed. 30 deaths (2.86%) were recorded during the first year after transplantation. Regarding the type of donor: 12/102 (11.76%) patients with brain death donor died, and 18/945 (1.9%) patients with living donor died. The causes of death were 20 (66.6%) infections, 6 (20%) cardiovascular events, 2 (6.6%) related to graft rejection event and 2 (6.6%) unknown. The average time of transplantation to death was 2 months 27.4 days with a SD of ± 2.9 months 21.9 days; 70% of deaths occurred in the first 3 months after transplantation. The average time in dialysis was 5 years, with a SD ± 3 years 4.4 months; 83.3% of patients had more than two years on dialysis. Most patients who died had thymoglobulin induction, but patients were older, had more comorbidities, more time on dialysis, increased immunological risk and they had a brain death donor. Finally, 76.7% of patients who died had functional graft.

Conclusions: In our hospital, 1 year mortality postkidney transplantation is low, but there are many individual patient factors that contribute to the risk of mortality increases significantly in them and there we could intervene.

PUB681

Granzyme B Level and Acute Kidney Allograft Rejection: Impact on One Year Survival in Mexican Population Perlà Edith Simancas Ruiz,1 Caridad Aurea Leal,2 Benjamin Gomez-Navarro.1 1Nephrology and Transplant, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico; 2Surgical Research, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico.

Background: Exposure to insufficient levels or discontinuation of immunosuppressants often increases the risk of rejection. Granzyme B is the most useful test to monitor graft function. However, it is a poor predictor of rejection and often raises only after significant damage has occurred to the allograft. Granzyme B has been tested as a marker of acute rejection, with high specificity and sensitivity in different types of sample and has also enabled the identification of subclinical
rejection. The elevation of both the mRNA and protein has been associated with a worse prognosis.  

Methods: Kidney recipients transplanted between January 2008 and March 2009. Donors (n=38) and healthy subjects (n=6) were also included. The relation of granzyme B levels determined by ELISA with graft function and rejection was studied.  

Results:  

<table>
<thead>
<tr>
<th>Receptor age (n=94)</th>
<th>26±10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction therapy:</td>
<td>46%</td>
</tr>
<tr>
<td>Basiliximab</td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td></td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>21%</td>
</tr>
<tr>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>One year creatinine</td>
<td>1.66 mg/dL</td>
</tr>
<tr>
<td>Rejection:</td>
<td>46%</td>
</tr>
<tr>
<td>Borderline</td>
<td></td>
</tr>
<tr>
<td>Banff IA</td>
<td>56%</td>
</tr>
<tr>
<td>Banff Ib</td>
<td></td>
</tr>
<tr>
<td>Chronic nephropathy</td>
<td>46%</td>
</tr>
</tbody>
</table>

Granulocyte levels in patients (n=43) was 12.5 pg/mL while the reference group (n=6) was 1.5 pg/mL (p<0.001). Comparison between patients with rejection (n=14) and non-rejection (n=20) was not statistically significant, nor the development of interstitial fibrosis year. The correlation between creatinine, GFT and granzyme level showed a trend to significance (n=66, r=0.30, p=0.06).  

Conclusions: The level of granzyme B was not associated with one year post-transplant rejection. However immune system activation is suggested by the higher level of granulocyte in patients vs control group. Continuous analysis of patients.

PUB684

Prediction of Recipients Survival in Deceased Donor Kidney Transplant Using Korean Network for Organ Sharing Database  

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1Seoul National Univ College of Medicine; 2Seoul National Univ College of Engineering; 3Univ of Ulsan.  

Background: The Korean Network for Organ Sharing (KONOS) was founded in 2000 for organ allocation in Korea. It has been allowed medical doctors and researchers to fully access the national population-based raw data about KT recipients. We propose a novel prediction approach of recipient survival based on machine learning techniques using KONOS data.  

Methods: Our dataset is collected from 2000 to 2014 by the KONOS. We design a novel prediction model that uses all of the follow-up recipients’ data including censored ones, on which estimated death risks are weighted accordingly. We compare this approach with the baseline model that uses only uncensored data by the CART (Classification And Regression Trees) modeling.  

Results: We analyze 5,430 recipients’ records with more than 10 attributes, among which we use 15 independent attributes to learn our models. The proposed weighted algorithm leads a better performance when predicting survival rates of transplant recipients within 6 years, but fails to show any significant difference from the baseline for those more than 7 years after transplantation. Using the decision-tree models, we find that the inotropic agent usage of donor management is the most important predictor, which estimates in 51.3% of 10-year mortality. In the age ≥51.5 group, non-diabetes recipients, waiting period < 4years, and donor age < 23.5 years show significant associations with better 10YRS. The results are consistent with our hypothesis that poor donor status, recipients’ longer waiting time and advanced age are associated with poor prognosis.

PUB685

Perforin Expression in Renal Allograft Biopsies  

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Background: Perforin is a cytotoxic protein in effector lymphocytes that facilitates targeted cell killing and it has an established role in allograft rejection. A diagnostic value has not been delineated. We examined perforin expression in renal transplant biopsies by immunohistochemistry (IHC) and found that positive lymphocytes are confined largely to the microvasculature in cases of active cellular rejection (ACR). The goal of this study is to investigate whether perforin IHC is a useful metric in identifying and classifying acute rejection in renal transplant biopsies.  

Methods: Renal transplant biopsies accessioned over a one-year period were selected to include cases showing no acute rejection, acute tubular injury, BK nephritis, ACR types 1 and 2, and C4d+ antibody-mediated rejection (AMR), according to the 2013 revised Banff Classification. IHC using a mouse monoclonal anti-perforin antibody was performed on each case. Perforin positive cells/10 high power (400X) fields (hpf) were counted from slides identified by number only.  

Results: Most rejection-negative cases had < 10 perforin-positive cells/10 hpf. Biopsies showing type 1 ACR, excluding one outlier, did not exhibit a significant increase in perforin-positive cells relative to rejection-negative cases. In contrast, cases of type 1B and 2 ACR, and C4d+ AMR displayed significantly increased perforin-positive cells (p < 0.0001) with most showing > 40/10 hpf. Cases of AMR contained the highest number of perforin-positive cells (p < 0.052). Cases of BK nephritis varied widely from < 10 to > 50/10 hpf. 2 of 3 cases with > 50 had a recent history of ACR developing BK infection upon increasing immunosuppression, raising the possibility of coexisting BK and rejection.  

Conclusions: Further study is needed, but our data suggests that increased numbers of perforin-positive lymphocytes correlate with more aggressive forms of rejection, and that perforin IHC may be a useful ancillary test for acute allograft rejection of type 1B or higher.

PUB638

Impact of Hemoglobin Concentration on Mortality After Renal Transplantation  

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Background: Kidney transplant recipients have chronic anemia, irrespective of the time from transplantation. Objective: To assess the impact of hemoglobin concentration on mortality in renal transplantation.  

Methods: A total of 233 patients who underwent renal allograft biopsy between January 2010 to January 2014, for graft dysfunction, proteinuria or active urinary sediments. All protocol biopsies were excluded from the study. Graft biopsies were evaluated by light microscopy and indirect immunofluorescence study. Out of 285 graft biopsy biopsies 242 were taken into study. Biopsies showing evidences of glomerulonephritis were further evaluated for incidence of individual types of glomerulonephritisand their outcome at the end of one year post diagnosis.  

Results: Based on biopsy findings among 242 renal allograft biopsies taken in study 42(17.35%) had post-transplant glomerulonephritis. Further the incidence of individual types of glomerulonephritisand their outcome at the end of one year post diagnosis.  

<table>
<thead>
<tr>
<th>Year after transplantation</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline model AUC</td>
<td>0.644</td>
<td>0.665</td>
<td>0.759</td>
<td>0.832</td>
</tr>
<tr>
<td>Weighted Model AUC</td>
<td>0.653</td>
<td>0.678</td>
<td>0.777</td>
<td>0.822</td>
</tr>
</tbody>
</table>

Conclusions: In this study, we show that the proposed machine learning based models with weights of estimated-death risks can present more accurate and flexible than baseline models for predicting in long-term survival rates of kidney transplant recipients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Due to TS were identified. Incidence rates and standardized incidence ratios (SIR) were computed using Poisson distribution and standardized using 2001-2002 as reference. Hazards ratios adjusting for age, sex, race and ethnicity (AHR) were calculated for outcomes.

Results: In 2001-2002, the overall incidence rate of ESRD due to TS was 1 per 10 million person years (MPY) and the SIR remained largely unchanged over the observation period. Of those with ESRD due to TS were more likely to be < 40 years (23.2% vs 9.2%), white ethnicity (81.5% vs 65.5%), and lack diabetes (81.2% vs 48.1%). Compared to those with ESRD due to other causes, odds ratios adjusted for age, sex, race and ethnicity (AOR) were highest for females (1.83) and those with eGFR > 15mL/min/1.73. Factors associated with ESRD included age 40-64 years (0.29), age ≥ 65 years (0.25), and black race (0.33). Over the study period, 53.7% of TS patients died, 27.3% were listed and 10.6% were transplanted. The AHR for outcomes demonstrated those < 40 years of age were more likely to be listed for renal transplant, receive renal transplant and survive.

Conclusions: The incidence of ESRD due to TS remained largely unchanged from 2001 through 2010. Our results indicated gender and racial differences in the odds of ESRD due to TS.

PUB689

The Impact of Hepatitis C Virus Infection on the Clinical Course, Short-term and Long-term Outcome in Renal Transplant Recipients – A Retrospective Study

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Background: Hepatitis C infection is common in patients of end stage renal disease with increased morbidity and mortality post-transplant. The aim of the study was to find out the impact of HCV infection on graft and patient outcome and compare it with the non HCV infected post-transplant cohort.

Methods: We retrospectively analysed patient and graft survival of HCV infected (after virological remission) post renal transplant patients from 2008 to 2014 with a median follow up of 24 months and compared them with our HCV negative statistically matched cohort.

Results: Outcome analysis was done at 6, 12, 18 and 24 months in terms of liver dysfunction, acute rejections, infections, hospitalization and death. Results were further tabulated as shown.

Conclusions: HCV infected end stage renal disease patients may undergo renal transplantation safely after virological remission and outcome is not different from other renal transplant recipients.

PUB690

Patient and Graft Survival in Pediatric Kidney Transplantation: A Single-Center Experience According to Transplant Era

Marta Monteverde, Juan Carlos Lopez,1 Gerardo Nyman,1 Liliana Briones. 1Nephrology Unit, Hospital JP Garrahan, Buenos Aires, CABA, Argentina; 2Urology Unit, Hospital JP Garrahan, Buenos Aires, CABA, Argentina.

Background: Improvements in the management of kidney transplantation has improved in the last 20 years. However the long term results in terms of graft survival and morbidity still require more research.

Methods: We evaluated 744 pediatric renal transplants (RTX), 551 with deceased donor (DD) and 222 with living-related donor (LRD), between 1988-2015. We divided this time into 2 periods: 1988-2000 and 2001-2015. Patient and graft survival were calculated for each period for LD and DD recipient. We analyzed causes of mortality, causes of graft failure and risk factors for graft loss. Mean age at RTX was 3.6 y (r: 0.5-19.5). Mean time of follow-up was 54.5 months (IQR: 22.4-90.1) months.

Results: Patient and graft survival for DD have significantly increased in the recent era (p=0.0002; p=0.0013 resp). Chronic rejection was the first cause of graft loss in both eras (43.9% vs 61.1%). Vascular thrombosis decreased (14.9% vs 5.5%; p=0.001), and also Death with a Functioning Graft (15.8% vs 8.3%; p=0.001). Acute rejection during the first 30 days post RTX + relapse of the original disease increased (0% vs 7.1%). First cause of death in both eras was bacterial infection (77% vs 66%). No death due to PFTD were seen in 2001-2015. Independent Risk factors for graft loss for DD recipients were: FSGS

VARIABLES
HCV positive patients
HCV negative patients

Patient(s) 51
2. Induction with ATG 26(50%) 700(50.68%)
3. Tacrolimus 34(66.67%) 1196(86.9%) <0.05
4. Cyclosporin 17(33.3%) 185(13.1%) <0.05
5. Infection 05(9.8%) 117(8.5%) NS
6. Abnormal LFT 08(15.6%) NA
7. 1 year patient survival 96.1% 97% NS
8. 2 year patient survival 92% 93.2% NS
9. Hospitalization 24 episodes 621 episodes NS

Results were found not to be statistically different from non HCV infected renal allograft recipients.

Conclusions: HCV infected end stage renal disease patients may undergo renal transplantation safely after virological remission and outcome is not different from other renal transplant recipients.

PUB686

Is It Safe to Transplant Sensitized Patients? Analysis of 1,002 Consecutive Kidney Transplants

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Background: From 2009-13, 24% of kidney recipients in our center had antiHLA antibodies (aHLA abs). Obj: To compare the risks of rejection, patient and graft survival when transplant recipients were performed with or without aHLA abs and with or without DSAs. To compare morbidity between patients transplanted with aHLA abs to mortality in the waiting list.

Methods: Retrospective study, which included all isolated kidney Tx in patients older than 18 and performed between 2009 and 2015. We analysed the incidence of TCMBR and ABMR in the first year after Tx. Median follow-up time was 32mo. Graft and patient survival were evaluated by Kaplan Meyer estimates.

Results: In 741 Tx (74%), no aHLA abs were detected (AHR=0) and 261(26%) had PrA+ with or without DSAs (AHR=0). Tx with PrA+ and DSA(6.6%, 129(86.6%; 0.11%) did not have rejection, 16(11%) had TCMBR and 7(4.7%) had ABMR. In Tx with PrA-0 with DSA(91, 56:10.2%) did not have rejection, 7(5.5%) had TCMBR and 3(33.4%) had ABMR. ABMR was more frequent when there was a DSA(p=0.001).

Graft survival did not differ according to ARP or DSA in groups with no rejection. TCMBR and ABMR. There were more graft losses in the whole sample when a DSA was detected(p<0.0001) or when Rama occurred, in comparison to no rejection(p=0.001) and TCMBR(p 0.0143). Regarding patient survival, there was no influence of aHLA abs and DSAs, nor influence of TCMBR or ABMR. In recipients with aHLA abs, mortality was 11% in 32mo, or 4.12% per year, smaller than in the waiting list in our state, which was 5.6% in the same period.

Conclusions: There was no difference in patient survival after 32 mo between patients with or without aHLA abs or DSAs, or even between patients with or without ABM.

However, there were more graft losses in recipients with aHLA abs and with ABM.

Mortality after Tx among sensitized patients hasn’t been larger than in the waiting list. We conclude that transplanting the sensitized patient does not increase mortality risk.
as cause of ESRD (HR: 3.1; CI 95%: 2.4-4.8), DGF (HR: 2.8; CI 95%: 2.4-4.8) and Receiving no induction therapy (HR: 2.1; CI 95%: 1.3-3.5). For the recipients: DGF (HR: 5.2; CI 95%: 2.9-9.3) and Age at RTX = 12y (HR: 2.2; CI; 0.9-1.3-2.9).

Conclusions: Patient and graft survival has significantly improved for DD in the recent era. Chronic rejection remains a major cause of graft failure. No death from malignancy were observed in the recent era.

Graft Survival 1y (% SE) 3y (%SE) 5y (%SE) 7y (% SE) 10y (%SE)
LD(1988-2000) 97.0 (0.01) 95.0 (0.02) 95.0 (0.03) 95.0 (0.03) 95.0 (0.03)
LD(2001-2015) 96.0 (0.02) 95.0 (0.03) 97.0 (0.03) 97.0 (0.03) 97.0 (0.03)
LD(1988-2000) 93.2 (0.03) 74.5 (0.03) 67.9 (0.03) 62.6 (0.03) 51 (0.04)
LD(2001-2015) 94.7 (0.01) 86.8 (0.02) 82.7 (0.02) 74.5 (0.03) 58.6 (0.07)

PUB691
Impact of Rituximab Induction on Short Term Outcome of Kidney Transplant Recipients

Background: Rituximab (rATG) induction has proven efficacy. However, it remains unclear what is the best dosing regimen.

Methods: From August 8th, 2014 immunosuppression protocol was changed at our institution to induction with single dose thymoglobulin to all deceased donor kidney transplant recipients. This retrospective study evaluated the incidence of acute rejection (AR) in deceased kidney transplant recipients with delayed donor graft function (DDGF) before and after the adoption of a new induction protocol.

Results: Pre-protocol Group 1 - 96 patients transplanted between 12/31/2013 and 08/08/2014: Standard criteria deceased donors (SCD) (without induction, tacrolimus 0.1-0.3 mg/kg or prednisone and methylprednisolone) or expanded criteria (EC) (induction with thymoglobulin 6mg / kg, tacrolimus 0.05 mg/Kg/dose, prednisone and mycophenolate sodium) versus Group 2 (new protocol), 87 patients transplanted between 08/08/2014 and 03/31/2015, subdivided in the same way, receiving the same maintenance therapy and thymoglobulin induction 3mg/kg single dose. In both groups, the population was overwhelmingly male (63% vs. 55%), young (47 vs 46 years) and low immunological risk. The incidence of AR in G1 vs. G2, SCD subgroup was 13%, vs. 4% (p = 0.09). When compared ECD recipients, the incidence of rejection was similar between G1 vs. G2 (15% vs. 15%, respectively), respectively. Inclusions: In the SCD kidney transplant recipients, the incidence of AR was numerically lower in the group that received induction with single dose rATG 3mg/kg and induction with a reduced dose of rATG was not inferior in the ECD group.

PUB694
Cardiovascular Changes After Kidney Donation
Fernando H. Marquis, Nefrologia y Transplante Renal, Hospital General de Agudos Cosme Argerich, CABA, Buenos Aires, Argentina.

Background: The aim of our study is to investigate the changes in cardiovascular structure and endothelial function after donation in kidney donors.

Methods: Fourteen living kidney donors (both genders) without history of kidney disease, diabetes, cardiovascular events or hypertension, who participated in the donor screening protocol with subsequent donation, were included. Office blood pressure (OBP), ambulatory blood pressure monitoring (ABPM), left ventricular mass index (LVMI), arterial stiffness (AS) and endothelial function (EF) were measured before and one year after the donation. AS was assessed from the left index finger using a digital photoplethysmograph (Pulse Trace; Micro Medical), that uses a simplified analysis of the digital volume pulse stiffness (AS) and endothelial function (EF) were measured before and one year after the donation. AS was assessed from the left index finger using a digital photoplethysmograph (Pulse Trace; Micro Medical), that uses a simplified analysis of the digital volume pulse.

Results: Reduced nephron mass (0.7; 0.9, P<0.001), mean BMI (27.1 ± 4, P<0.001), mean SBP (127 ± 8, P<0.001), mean DBP (80 ± 10, P<0.001), mean OBP (88.6 ± 7, P<0.001), mean LVMI (76.3 ± 13.7, P=0.004), mean OBP (90 ± 10, P=0.004), mean DBP (61.4 ± 4, P=0.004), mean OBP (71 ± 9, P=0.004), mean DBP (41 ± 10, P=0.004). The isolated estimated glomerular filtration rate levels by MDRD 4 formula at 1 year (57.4 ± 12ml/min/1.73 m², P<0.001) were significantly increased as compared to baseline (26.4 ± 3; 85 (76, 92) and 0.78 (0.74, 0.97), respectively). The estimated glomerular filtration rate levels by MDRD 4 formula at 1 year (57.4 ± 12ml/min/1.73 m², P<0.001) were significantly decreased as compared to baseline (82.8 ± 10 ml/min/1.73 m²). We did not find significantly differences in mean 24hs ABPM (84.8 ± 15 mmHg, P=0.940), mean LVMII (6.6 ± 1.7 mm, P=0.727), mean AS (7.7 ± 2.3 m/s, P=0.210) and median EF (5.1% ± 18.3, P=0.374) compared to baseline (85 ± 7 mmHg. 99.8 ± 31 ml/g; 9.03 ± 2.3 m/s and 10% ± 1.6, 34.6), respectively.

Conclusions: Our study demonstrated that after an year, reduced nephron mass because of kidney donation was not associated with changes in cardiovascular structure and endothelial function.

Funding: Government Support - Non-U.S.
viral, fungal and bacterial cultures. Cytologic and serologic studies were unremarkable. Flow cytometry analysis of the spinal fluid showed no evidence of lymphoma. A brain biopsy was performed revealing non-specific perivascular lymphoplasmocytic infiltrate with no evidence of lymphoma or infection. Additionally, myelain stain was positive ruling out demyelinating disease. Our patient was started on high-dose steroids with remarkable improvement of his symptoms. Diagnosis of CLIPPERS was made.

Conclusions: CLIPPERS is a rare and poorly recognized CNS inflammatory condition. To our knowledge, this is the first case reported after renal transplantation. More studies are needed to determine the pathophysiology of CLIPPERS in immunosuppressed patients and whether it could represent a pre-malignant state. Duration of treatment and follow up is yet to be determined. In this case, treatment with steroids has led to symptomatic improvement over a month and close follow-up continues.

PUB696
The Impact of Post-Transplant Hemoglobin and Creatinine Level on Renal Allograft Survival
Luis Fernando Christiani, Fernanda Paula Feres Rios Da Costa, Ana Flavia Baldoni, Alicia Imada, Kelly Rodrigues, Maria Izabel Neves de Holanda Barbosa, Géssika Marcelo Gomes, Cláudia Fagundes. Nephrology, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil.

Background: Anemia is a common finding after kidney transplantation. The roll and the prevalence of Posttransplantation anemia (PTA) in predicting renal allograft outcomes still vary between different studies. In this study, we aim to assess the prevalence of anemia at one and six months post transplant and its correlation with 1 year renal allograft survival.

Methods: Anemia was defined by an absolute level of hemoglobin less than 11 g/dL. Hemoglobin and creatinine level were assessed at one, six and twelve-month after transplantation.

Results: We included 261 consecutive patients who underwent renal transplant from January/2010 to June/2012. Mean recipient age was 42±10 years and 56% were male. Prevalence of anemia was 42% at 1 month, 16% at 6 months and 9% at 12 months. Hemoglobin and creatinine level at first month of transplantation were 11.2±1.0 and 56% were >2.25 mg/dL. Hemoglobin and creatinine level were assessed at one, six and twelve-month after transplantation.

Results: We included 261 consecutive patients who underwent renal transplant from January/2010 to June/2012. Mean recipient age was 42±10 years and 56% were male. Prevalence of anemia was 42% at 1 month, 16% at 6 months and 9% at 12 months. Hemoglobin and creatinine level at first month of transplantation were 11.2±1.0 and 56% were >2.25 mg/dL. Hemoglobin and creatinine level were independently associated with poor graft survival at 12 months. The best cut-off selected by receiver operating characteristic curve analysis was 10.8 g/dL for Hemoglobin level, (AUROC 0.74 (0.63-0.86), p: 0.001), and 2.25 mg/dL, for serum creatinine (AUROC 0.77 (0.62-0.91), p: 0.001). Combining the best points of those two variables could identify patients at risk of graft loss. Patients who met both criteria ( Hb < 10.8 g/dL and Creatinine ≥2.25 mg/dL) had 59% graft survival at 1-year, whereas allograft survival was 98.5% for patients without any criteria ( Hb ≥10.8 g/dL and Creatinine < 2.25 mg/dL).

Conclusions: Prevalence of anemia was high in the first month after transplant and persisted in a substantial proportion of functioning kidney transplant recipients. Early (1-month) hemoglobin and creatinine level can predict 1-year graft survival.

PUB697
Examining Adverse Weight Gain After Kidney Transplantation
Birah Workeh,
1 Linda W. Moore,
2 William E. Mitchell.
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Background: Between 15,000-17,000 patients with end-stage renal disease (ESRD) receive a kidney transplant in the United States every year. Among the most consequential complications to these patients are adverse weight gain and the development of diabetes, commonly termed New-Onset Diabetes After Transplantation (NODAT) with consequent complications to these patients are adverse weight gain and the development of diabetes. The impact of post-transplant reveals there is significant gain in adipose weight gain in all cases.

Methods: We are conducting a longitudinal study in ESRD patients anticipating receiving a live donor kidney transplant. We are studying subjects before kidney transplant, at 12 weeks and 1 year after they have received living donor kidney transplant to measure changes body composition and other indices. Body composition was characterized by DEXA as well as total body potassium (a gold standard measure of muscle mass).

Results: Results from 5 subjects who completed baseline assessment and 3 months post-transplant reveals there is significant gain in adipose weight gain in all cases.

Additionally, we discovered there is significant loss in skeletal muscle mass (p=0.032) measured by total body potassium.

Conclusions: We have not studied enough to conclude whether changes in energy expenditure and diet contribute to adipose weight gain and whether there is acute nitrogen (muscle) loss peroperatively. Ultimately, methods to identify patients at high risk for adverse weight gain and related metabolic disorders before transplant are greatly needed.

Funding: Private Foundation Support

PUB698
Effect of Mycophenolate Mofetil Dose on BK Virus Infection in Kidney Transplant Recipients
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Background: Intensity of overall immunosuppression is a risk factor for BK virus infection (BKVI). However, the exact impact of exposure to tacrolimus and mycophenolate mofetil (MMF) to BKVI is unclear. The aim of this study was to determine if BKVI in kidney transplant (KT) recipients is associated with drug exposure to MMF.

Methods: This prospective randomised controlled clinical trial (NCT01860183) included 36 KT who underwent KT from May 2013 to February 2015 at Clinical Hospital Merkur. Immunosuppression consisted of basiliximab induction, with tacrolimus, MMF±steroid maintenance. KTR were randomized in two groups, with respect to MMF dose (2g or 3 g daily). Urine cytology for decoy cells was performed at prespecified time-points posttransplant. KTR were followed up to 12 months post KT. Graft biopsy was performed per protocol at 2, 6 and 12 months, or in case of graft dysfunction. Kaplan-Meier analysis with log-rank test was used to assess graft survival. A Cox regression was used to determine variables associated with graft survival.

Results: 13 (37.1%) KTR had decoy cells in urine, 4 (11.1%) KTR had biopsy-proven BK virus-associated nephropathy (BKVAN). The mean time-to-occurrence was 4.8 months for decoy cells and 4.3 months for BKVAN. Cumulative one-year overall graft survival was 93.5%. Incidence of decoy cells, BKVAN, or acute rejection was similar in the two MMF groups. Rejection was not a risk factor for decoy cell positivity or for BKVAN.

Conclusions: MMF dose may not increase risk for BKVI after kidney transplantation.

Funding: Government Support - Non-U.S.

PUB699
Malignancy following Renal Transplantation
Louloures de la Vara Iniesta,1 Francisco Llamas Fuentes,2 Inmaculada Lorenzo Gonzalez,2 Carmen Gomez Roldan.2 1Virgen de la Luz Hospital, Cuenca; 2Univ Hospital of Albacete, Albacete.

Background: There is retrospective experience in many reports about the association between the intensity of immunosuppression and the higher frequency of malignancy. Objective: Analyse and describe our centre’s experience.

Methods: 275 transplant patients were analyzed. A record was made of the frequency, anatomic-pathological diagnostics, location, the mean interval between transplantation and diagnosis (latency time), follow-up time, use of antilymphocyte-antibodies, affection by cytomegalovirus, rejection and immunosuppressive therapy.

Results: Of 273 patients, 9.52% (26) were diagnosed of cancer. The majority, 93.43% (24), corresponded to De novo malignancy. 7.7% (2) were recurrences of pre-existing disease. The mean age at diagnosis was 63.19±9.43 years. The most frequent malignancies were skin cancers, predominantly Basal-cell and Squamous-cell carcinomas. The incidence of other tumors was similar to the general population. The most common causes of chronic renal failure was the glomerular and interstitial disorders.

Conclusions: Of 273 patients, 9.52% (26) were diagnosed of cancer. The majority, 93.43% (24), corresponded to De novo malignancy. 7.7% (2) were recurrences of pre-existing disease. The mean age at diagnosis was 63.19±9.43 years. The most frequent malignancies were skin cancers, predominantly Basal-cell and Squamous-cell carcinomas. The incidence of other tumors was similar to the general population. The most common causes of chronic renal failure was the glomerular and interstitial disorders.
Conclusions: Our experience is similar to what is reported in the literature. The incidence of cancer is higher than expected in the general population and increases according to the duration of the immunosuppression. Skin cancers were the most frequent malignancies. Unlike other studies, there was a low incidence of lymphoproliferative disorder and Kaposi’s sarcoma, and the incidence of other solid malignancies being similar to that of the general population. To reduce the development of malignancies must be one of our objectives.

PUB700
Lipidapheresis in 3 Sisters with Familial Hypercholesterolemia
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1Pediatric Nephrology, Univesity Hospital of Cologne, Cologne, Germany; 2Dept of Pediatrics, Neuroradiology and Cardiology, Univesity Hospital of Duesseldorf, Duesseldorf, Germany.

Background: Familial hypercholesterolemia (FH) is the most common monogenic form of hypercholesterolemia. It carries the risk of premature coronary heart disease. As the atherosclerotic burden is dependent on the degree and duration of exposure to raised LDL-cholesterol levels, early diagnosis and effective treatment are imperative. Statins are the mainstay in the management of these patients. Lipoprotein-apheresis becomes recently more established in patients with severe dyslipidemia. Together these treatments improve the prognosis of FH. Most children fail to attain targeted lipid goals owing to persistent shortcomings in diagnosis and treatment.

Methods: Three siblings with a LDLR mutation (p.Trp577Arg) being on statins (20 mg/d Atorvastatin) and Ezetimib (10 mg/d) for 12 months with still LDL-C plasma concentrations of above 300-500 mg/dl started once a week a double filtration plasmaphoresis (DFPP) with with a single plasma volume to be treated.

Results: After each LDL-apheresis LDL-C concentration of 100-150 mg/dl could be reached. (66-70% reduction). After 6 months plasma volume to treat was doubled because of a rebound within 7 days with LDL-C concentration up to 300-350 mg/dl. But though after each session LDL-C concentration decreased to 50-100 mg/dl the rebound was still evident after 7 days of therapy pause. With a treatment regime with twice plasma volume every 3-4 days the children finally attained a stable pre-treatment LDL-C concentration of 120-170 mg/dl. Another 2 months later statin therapy was stopped because of underlying mutation with assumed non receptor function. Neither the effectiveness of each apheresis nor the LDL-C concentration after 4 days showed any change.

Conclusions: In pediatric FH patients with high levels of LDL-cholesterol plasma concentration it might be necessary to treat instead of conservative medication with apoaferesis in high frequency and with high plasma volumes to reach a durable decrease in LDL-cholesterol plasma concentration. The use of cholesterol uptake-inhibitors should be considered.

PUB702
Cadmium Induces Matrix Metalloproteinase-9 Expression via NADPH Oxidase/Ros-Dependent Egfr Signals in Human Endothelial Cells
Nam ho Kim. Internal Medicine, Chonnam National Univesial Hospital, Gwangju, Korea.

Background: Cadmium, a widespread cumulative pollutant, is a known human carcinogen, associated with inflammation and tumor. Matrix metalloproteinase-9(MMP-9) plays a pivotal role in inflammatory reaction and tumor metastasis, however, the mechanisms underlying MMP-9 expression induced by cadmium remains obscure in human endothelial cells.

Methods: Here, cadmium elevated MMP-9 expression and enzyme activity, as well as MMP-9 promoter-driven luciferase activity, in a dose and time dependent manner in ECs. Moreover, cadmium activated phosphorylation of EGF, Akt, Erk1/2, JNK1/2, P38MAPK and promoted NF-kB and AP-1 binding.

Results: Specific inhibition and mutation studies show that EGFR, Akt, Erk1/2, JNK1/2 and transcription factor NF-kB and AP-1 were related to cadmium-induced matrix metalloproteinase expression in ECs. Furthermore, cadmium increased ROS production and the ROS-producing NADPH oxidase. Cadmium translocates p47phox, a key subunit of NADPH oxidase, to the cell membrane. The exogenous H2O2 increased MMP-9 mRNA expression. And that, inhibition of ROS by ROS scavenger (NAC) or NADPH oxidase inhibitor (DPI) attenuated EGF, Akt, MAP/ERK1/2,JNK1/2,p38MAPK activation, and MMP-9 expression. Likewise, inhibition of EGFR phosphorylation prevented the activation of AKT,MAP/ERK1/2,JNK1/2,p38MAPK activation, and MMP-9 expression. These findings provide further insight into the molecular mechanisms in the carcinogenesis effect of cadmium.

PUB703
Exosomes from Activated Kidney Fibroblast Have Ambivalent Potential Effects on Atherosclerosis
Fumitoshi Nishio, Noritoshi Kato, Yoshio Funahashi, Takuji Ishimoto, Tomoki Kosugi, Naotake Tsuobi, Shoichi Maruyama, Seichi Matsuo. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi-Pref., Japan.

Background: Exosomes are small (50-140nm) membrane vesicles of endosomal origin that contain host cell’s proteins, mRNAs, and microRNAs (miRNAs). The body of the cell secretes vesicles or exosomes which have been biologically active, and had roles in intracellular communication. Especially tumor-derived exosomes has been intensively explored and proven to be associated with distant metastasis. On the other hand, it is well known that CKD patients are at risk of cardiovascular diseases, but the mechanism of this distant organ crosstalk is not fully understood. Under the hypothesis that exosomes are involved in cardiovascular correction (CRS), the aim of this study is to explore the role of exosomes from kidney fibroblasts, which are activated in diseased kidney, on cardiovascular endothelial cells.

Methods: We isolated Exosomes from culture media of TGF-β stimulated rat kidney fibroblasts line (NRK-49F), by ultracentrifugation technique. Cured vascular endothelial cells (RAOEC; Rat Aortic Endothelial Cells) were stimulated by these exosomes or exosomes from unstimulated fibroblast. Then we evaluated the expression of genes, which associated with atherosclerosis by qPCR.

Results: RAOE-C stimulated with exosome from TGF-β activated kidney fibroblasts (RAOE-T) showed higher expression of PIGF and lower expression of FB-1, ABCA-1 than control (RAOE-C). This expression pattern is compatible with atherosclerotic change. On the other hand, RAOEC-T showed reduced expression of adhesion molecules such as ICAM-1/VCAM-1 and E-selectin compare with RAOE-C.

Conclusions: So far, CRS is supposed to caused by uremic factor, RAS system, chronic inflammation, and so on. From this study, we showed that exosomes from activated kidney fibroblasts have ambivalent roles in atherosclerosis by modulating the expression of adhesion molecules, metabolic factor, and VEGF system on endothelial cells. Further studies are needed to elucidate the contribution level of exosomes on CRS.

PUB704
Prevalence of Metabolic Syndrome in Patients with End Stage Renal Disease: Relevance of Biomarkers Vinod K. Bansal, Jennifer Sakl, Debra Hoppensteadt, Danyal Syed, Schubaatraz Abro, Jawed Fareed. Nephrology, Loyola Univ Medical Center, Maywood, IL; Pathology, Loyola Univ Medical Center, Maywood, IL.

Background: Since the metabolic syndrome (MetS) and chronic kidney disease (CKD) share many of the same risk factors and similar inflammatory pathogenesis, many studies have suggested a correlation between CKD and MetS, and that patients with MetS are more likely to develop CKD. The purpose is to investigate metabolic biomarker levels in ESRD patients to evaluate their relevance to ESRD and to provide insight into the pathological ESRD processes and the development of associated comorbidities.

Methods: Plasma samples were retrospectively collected from 89 ESRD patients prior to maintenance hemodialysis. Normal human plasma samples (female & male, 18-35 years old) were purchased from George King Biomedical Inc. (Overland Park, KS).
were stored at -80°C. Biochips were purchased from RANDOX (Co. Antrim, Northern Ireland) to test C peptide, ferritin, IL-6, resistin, insulin, TNFα, IL-1α, leptin, PAI-1. These biomarkers were tested on 82 ESRD and 17 normal samples.

Results: All biomarkers, except insulin, were significantly elevated in Patients with ESRD compared to normal (p values are 0.05 - 0.0001). MetS patients with ESRD, as compared to non-MetS Patients with ESRD, had significantly elevated Leptin (P=0.002), and the correlation between MetS and Leptin levels was significant (P=0.0001, r=0.43). All other biomarkers showed no significant difference between ESRD+MetS and ESRD-MetS patients. Furthermore, when leptin levels for Patients with ESRD were broken down into ESRD+MetS and ESRD-MetS, ESRD+MetS vs. normal was significant (P=0.003), but ESRD-MetS vs. normal was not (P=0.6).

Conclusions: Elevated biomarkers suggest an ongoing inflammatory process in ESRD patients. Insulin levels were not significantly elevated in ESRD patients, possibly attributable to the high Leptin levels, which can interfere with insulin secretion and signaling. ESRD+MetS and ESRD-MetS populations are not statistically different for all other biomarkers. This suggests that biomarker elevation is due to ESRD pathogenesis, rather than due to MetS as a comorbidity.

PUB705
Decreased Mitochondrial Membrane Potential in Monocyte Subsets from Patients with Chronic Kidney Disease Ying Wang,† Eric Joseph Lai,† Annie Febus,† Yuan Zhang, Linda Vernocchi,† Anjali Ganda,† 1 Div of Nephrology, Dept of Medicine, Columbia Univ Medical Center, New York, NY; 2 Dept of Biostatistics, Mailman School of Public Health, Columbia Univ, New York, NY.

Background: Particular monocyte subsets are associated with future cardiovascular events in patients with chronic kidney disease (CKD), and the underlying mechanisms require further investigation. Previous studies have suggested impaired mitochondrial function in patients on dialysis, while little is known about mitochondrial functionality in monocyte subsets from non-dialyzed patients with CKD. Given that mitochondrial dysfunction has been linked to atherosclerosis, we hypothesized that non-dialyzed patients with CKD would have mitochondrial dysfunction in monocyte subsets which could accelerate atherosclerosis in patients with CKD.

Methods: Monocyte subsets from 18 adult CKD patients (eGFR<30 ml/min/1.73 m²) and 26 matched controls (eGFR ≥60 ml/min/1.73 m²) were freshly analyzed by flow cytometry. Mitochondrial membrane potential (ΔYm), as a measure of mitochondrial functionality, was determined by the mean fluorescence intensity (MFI) of TMRM (tetramethylrhodamine methyl ester).

Results: ΔYm was significantly reduced by 10% in patients with CKD vs. controls in total monocytes (P<0.05). Interestingly, the intermediate monocyte subset (CD14++CD16+), which has the highest ΔYm among all the monocyte subsets and has been shown to predict accelerated atherosclerosis in patients with CKD.

Conclusions: Patients with CKD demonstrate mitochondrial dysfunction in total monocytes and monocyte subsets. Mechanistic and prospective studies are needed to examine the relationship between monocyte mitochondrial dysfunction, atherosclerosis, and future cardiovascular events in CKD patients.

Funding: NIDDK Support, Private Foundation Support

PUB706
Paricalcitol Uregulates Renal Klotho and Restores Uremia-Induced Endothelial Integrity Disruption Marc Vila Cuéllar,1 Robert H.j. Beelen,† Marc G. Vervloet.† 1 Molecular Cell Biology & Immunology, YU Univ Medical Center, Amsterdam, Netherlands; 2 Nephrology, YU Univ Medical Center, Amsterdam, Netherlands.

Background: Klotho deficiency in chronic kidney disease (CKD) is associated with the disruption of the endothelial integrity. Active vitamin D induces klotho expression. Hence, active vitamin D may limit endothelial layer disruption.

Methods: Male wistar rats were assigned into one of four groups: Control; Vitamin D deficiency, induced with Vitamin D deficient diet; Uremic, developed after ½ nephrectomy; Uremic + Vitamin D deficiency. Animals were treated with Paricalcitol or vehicle control during 7 weeks. Serum samples were analyzed for 25D and 1,25D. Evans Blue was injected for estimation of the endothelial thoracic aorta and lung permeability and quantified using spectrophotometry. To determine the levels of Klotho, qPCR and WesternBlot was performed in kidney tissue.

Results: Average 25D levels were 9.83 nmol/L while 1,25D levels were below the detection levels (20pmol/L) after the induction Vitamin D deficiency. mRNA and protein levels of Klotho in the kidney were decreased in Vitamin D deficient and uremic rats and restored after Paricalcitol treatment. Aortic Evans blue leakage increased in all uremic rats regardless of vitamin D level, compared with the control group and restored after Paricalcitol treatment (p<0.03). Uremia did not induce pulmonary leakage, but paricalcitol lowered it compared to control and uremic condition (p<0.04). Figure shows uremic without D-deficiency together.

Funding: Pharmaceutical Company Support - Abbvie

PUB707
Altered Intra-Aortic Expression of the Renin-Angiotensin System Is Associated with Arterial Aging in Mice Hye Eun Yoon,‡ Eun Niam Kim,† Min Young Kim,† Ji Hee Lim,‡ Cheol Whee Park,‡ Bum Soon Choi.‡ 1 Internal Medicine, The Catholic Univ of Korea, Seoul, Korea; 2 Internal Medicine, Incheon St. Mary’s Hospital, Incheon, Korea.

Background: Aging is the major risk factor of cardiovascular disease and results in progressive decline in physiological function and structural abnormalities of vasculature. The renin-angiotensin system (RAS) is the key player in cardiovascular diseases. This study evaluated whether the change in the RAS is associated with arterial aging.

Methods: Histologic changes and expressions of angiotensin, angiotensin converting enzyme 1 (ACE1), angiotensin II type 1 receptor (AT1R), angiotensin II type 2 receptor (AT2R), and antioxidant enzymes, superoxide dismutase 1 (SOD1) and superoxide dismutase 2 (SOD2), were measured in the thoracic aortas from 2-month-old, 12-month-old, and 24-month-old C57BL/6 mice.

Results: Twenty-four-month-old mice showed significantly increased aortic media thickness compared to 2-month-old mice (1.6-fold). The aortic expression of angiotensin was increased in 12-month-old (1.2-fold) and 24-month-old mice (1.6-fold) compared to 2-month-old mice. Similarly, the expression of ACE1 was increased in 12-month-old (1.2-fold) and 24-month-old mice (3-fold) compared to 2-month-old mice. The AT1R/AT2R ratios were increased in 12-month-old (1.3-fold) and 24-month-old mice (1.5-fold) compared with 2-month-old mice. The expressions of SOD1 and SOD2 were decreased in 12-month-old (0.8-fold and 0.6-fold, respectively) and 24-month-old mice (0.6-fold and 0.5-fold, respectively) compared with 2-month-old mice.

Conclusions: Age-related intra-aortic activation of the RAS was associated with reduced antioxidant enzymes and hypertrophy of the aorta. These results suggest that the altered expression of the RAS contributes to the increased susceptibility to vascular injury in the elderly population.

Funding: Government Support - Non-U.S.

PUB708
Upregulation of Microparticles, Tissue Factor, Adhesion Molecules, Nitric Oxide and Adiponectin in End Stage Renal Disease Vinod K. Bansal,† Daneyal Syed,† Debra Hoppensteadt,† Jawed Fareed.† 1Nephrology, Loyola Univ Medical Center, Maywood, IL; 2Pathology, Loyola Univ Medical Center, Maywood, IL.

Background: End stage renal disease (ESRD) represents the final stage of chronic kidney disease characterized by kidney failure (GFR <15 ml/min/1.73 m²). To understand the pathophysiology of ESRD, we measured the circulating levels of microparticles (MP), tissue factor (TF), adhesion molecules, such as p-selectin (P-select), soluble ICAM (s-ICAM), nitric oxide (NO) and adiponectin (AD).

Methods: Plasma samples were collected from 119 ESRD patients undergoing maintenance hemodialysis to profile various inflammatory biomarkers. 100 normal plasma samples were collected from healthy individuals. MP levels were measured using an annexin

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

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binding method (Hyphen Biomedical, Paris, France). NO was measured using a kit from R&D systems (Minneapolis, Minnesota) and ELISA methods for TF, P-Sel, s-ICAM and adiponectin were obtained from R&D systems. A chromogenic substrate method was used to measure heparin.

Results: MP levels were elevated in the ESRD group (28.1nm ± 6.1nm vs. the control 8.9nm ±1.3nm). Tissue factor levels were found to be increased in the ESRD group (20.4±1.6 ipg/ml vs the control (11.9±2.8ipg/ml). The nitric oxide level was markedly higher in the ESRD group (32±17μM) vs the controls (7±3μM). The p-selectin levels were elevated in the ESRD group (46±20ng/ml) vs the control (31±3ng/ml). The soluble ICAM levels were higher in the ESRD group (250±112ng/ml) vs the control (180±19ng/ml). Interestingly, the adiponectin levels were also increased in the ESRD group (19.2±11.2ug/ml) vs the control (11.2±9.3ug/ml). The nitric oxide level was markedly higher in the ESRD group (46 ± 20 ng/ml) vs the control (31 ± 3 ng/ml).

Conclusions: These studies suggest that MP, TF, NO, P-selectin and s-ICAM levels are increased in the ESRD patient. It is of interest to note that despite that a significant number of ESRD patients were diabetic; the AD levels were increased. These results also suggest that while ESRD represents a pro-inflammatory/ hypercoaguable state, the repeated administration of heparin and other drugs may contribute to the regulation of the hemostatic process and inflammatory balance.

PUB709
Coronary Artery Calcification and All-Cause Mortality in RRT Patients with Diabetes: 5 Year Survival Analysis
Ramin Tolouian, 1 Sean M. Connery, 2 Kyari Sumayin Ngamdu. 2 Internal Medicine, Eastern Virginia Medical School, Norfolk, VA; *Internal Medicine, Texas Tech Univ HSC El Paso, El Paso, TX.

Background: Vascular calcification is a significant sequela of ESRD. A Coronary Artery Calcification (CAC) Agatston score ≥ 300 has been associated with adverse cardiovascular events & increased mortality. The purpose was to evaluate all-cause mortality rates in patients with diabetes.

Methods: 113 diabetic pts undergoing RRT had CAC scoring by sub-second gated helical CT standard Agatston scoring system, slice thickness 3mm. Patients were categorized into 3 groups according to CAC score: 0, 1-299, ≥ 300 (Low, Medium, High Risk). Survival of 3 groups was calculated using Kaplan-Meier curves for all-cause mortality for 5 year period after CAC. Unadjusted and risk-factor adjusted for age & length of time on dialysis Cox proportional hazard modeling was used to estimate time to all-cause mortality.

Results: 5 year survival was 92%, 60%, 46% for Low, Medium, High Risk CAC groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Low (n=25)</th>
<th>Medium (n=46)</th>
<th>High (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>57 ±11</td>
<td>61 ±9*</td>
<td></td>
</tr>
<tr>
<td>Months on Dialysis</td>
<td>40 ±35</td>
<td>23 ±20</td>
<td>40 ±35</td>
</tr>
</tbody>
</table>

Mean ±SD, *p<0.05 Low vs Medium, **Medium vs High, *Medium vs High ANOVA

Conclusions: There was a statistically significant difference between survival curves, Gehan-Breslow p = 0.031, but no difference between Medium & High Risk curves pairwise multiple comparison procedures Holm-Sidak method (p=0.1). Adjusting for covariates of age & length of time on dialysis at time of scan did not make a significant difference in survival curves, Age HR = 1.034 (0.99-1.0795% CI), time on dialysis HR = 1.004 (0.99-1.0195%).

PUB710
Elevated Toll Like Receptor 4 Expression and Macrophage Infiltration Is Found in High Dose Vitamin D-Induced Non-Uremic Vascular Calcification
Jianpeng Zhou, 1,2 Yuan Min Wang, 1 Helen Williams, 1 Anne M. Durkan, 1 Geoff yu Zhang, 1 Huiling Wu, 1 Andrew Sawyer, 1 Stephen I. Alexander, 1 David C. Harris, 1 Vincent W.S. Lee. 3 *Centre for Kidney Research, Children’s Hospital at Westmead, NSW, Australia; 3Centre for Transplantation and Renal Research, Univ of Sydney at Westmead Millennium Inst, Westmead, Sydney, NSW, Australia; 2 Vascular Biology Research Centre, Surgery, Univ of Sydney, Westmead Hospital, Sydney, NSW, Australia; 4 Transplant Research Group, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia.

Background: Vascular calcification is strongly associated with cardiovascular morbidity and mortality. Several studies have suggested that monocytes/macrophages are involved in arterial vascular calcification, while the involvement of the TLR4 pathway in vascular calcification has also been proposed.

Methods: Male C57BL/6 mice aged 8 weeks were injected with a high dose of vitamin D (50000IU/kg/day) subcutaneously for 3 days at 0, 24 and 48 hours. All mice were sacrificed 3 days after the final administration of vitamin D. Kidneys were assessed histologically. Whole aortas were dissected. Macrophage infiltration and TLR4 expression was assessed by immunohistochemistry and histology and vascular calcification by Von Kossa staining.

Results: High dose vitamin D treatment did not induce kidney fibrosis or injury in C57BL/6 mice within the short time frame, as assessed by GT fibrosis score and PAS tubular damage score. High dose vitamin D treated mice demonstrated significantly higher calcium deposition in the aortic arteries (17.45% of vessel area) compared to controls (1.2% p<0.05). This was accompanied by a greater level of macrophage infiltration and TLR4 expression in these arteries compared to controls.

Conclusions: Accelerated vascular calcification was induced in mice with high dose vitamin D treatment. These data also identify a potential role for macrophages and the TLR4 pathway in vascular calcification.

PUB711
Lack of Correlation of Pyrophosphate Levels with Survival and Coronary Artery Calcification in Hemodialysis Patients
Ramin Tolouian, 1 Sean M. Connery. 1 *Internal Medicine, Div of Nephrology, Eastern Virginia Medical School; *Internal Medicine, Texas Tech Univ HSC El Paso.

Background: Vascular calcification is an important predictor of cardiovascular mortality in ESRD. Decreased levels of inorganic pyrophosphate (PPi) are thought to increase vascular calcification. The purpose of this study was to evaluate the association of PPi & coronary calcification scores in maintenance HD patients and all-cause mortality over 5 years.

Methods: 98 maintenance HD patients were studied (mean ± SD): Age (yr) 57 ±10.7, HD vintage (month) 36 ±37.6. Platelet free plasma PPi was measured by radiometric, enzymatic method as described by Tolouian. Coronary arterial calcification score (CACS) was measured by sub-second gated helical computed tomography with an Imatron C-150 XL ultra fast CT scanner using a standard protocol for vascular calcification. Patients were categorized into 3 groups according to their CAC score: 0, 1-300, and > 300.

Results:

<table>
<thead>
<tr>
<th>Groups</th>
<th>CACS 0 (n=27)</th>
<th>CACS 1-299 (n=40)</th>
<th>CACS ≥300 (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPi (μM)</td>
<td>1.49 ±0.37</td>
<td>1.60 ±0.56</td>
<td>1.56 ±0.46</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>51 ±11.0</td>
<td>58 ±11.3</td>
<td>60 ±0.9*</td>
</tr>
<tr>
<td>Months on HD</td>
<td>32 ±27.2</td>
<td>25 ±21.5</td>
<td>47 ±49.5*</td>
</tr>
</tbody>
</table>

*p<0.05 Low vs High, †Medium vs High ANOVA, Dunnett T3

The covariate PPi had no significant effect on the hazard rate, log rank p=0.61. After adjusting for covariates of PPi, age, length of time on HD at time of measurement the log rank statistic for the survival curves is not great enough to exclude the possibility that the difference is due to random sampling variability; there is not a statistically significant difference (P = 0.614).
Conclusions: The difference in 5 year survival rate in dialysis patients based on the severity of vascular calcification is not influenced by pyrophosphate levels. This supports the multi-factorial nature of vascular calcification.

PUB712

Aortic Artery Calcification and Cardiac Valve Calcification Is Associated with Mortality in Chinese Hemodialysis Patients: A 3.5 Year Follow-Up

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Background: Aim to investigate the relationship among aortic artery calcification (AAC), cardiac valve calcification (CVC) and mortality in maintenance haemodialysis (MHD) patients.

Methods: The study included 110 MHD patients. All MHD patients were treated in Shanghai Ruijin Hospital in July 2011. Follow-up these patients for 42 months.

Results: Totally 110 MHD patients were involved in this study, 64(58.2%) patients were male, and the mean age was 55.2±15.0 years old, the mean dialysis duration was 41.7±38.1 months. 25.5% patients had cardiac valve calcification, while 61.8% had visible calcification. After 42 months follow-up, 26(22.7%) patients died, including 16 cases death from cardiovascular events, 5 cases respiratory failure, 3 cases tumor metastasis, 1 case deep venous thrombosis and 1 case abandon treatment. Kaplan-Meier analysis showed that patients with AAC or CVC had a significant greater number of all-cause and cardiovascular deaths than those without. In multivariate analyses, the presence of AAC was a significant factor associated with all-cause mortality (HR 3.149, P=0.025) in addition to lower albumin level and lower 25(OH)D level. The presence of CVC was a significant factor associated with cardiovascular mortality (HR 3.800, P=0.029) in addition to lower albumin level and lower 25(OH)D level.

Conclusions: The presence of AAC and CVC were independently associated with mortality in MHD patients. Regular follow-up by X-ray and echocardiography could be useful method to stratify mortality risk in MHD patients.

Funding: Government Support - Non-U.S.

PUB713

Beneficial Effect of the Vasopressin AV1a and AV2 Receptor Blocker Conivaptan (C) on the Renal Alterations Resulting from Mild Heat-Induced Dehydration (MHID) and Rehydration with a 10% Fructose (F) Beverage

L. Gabriela Sanchez-Lozada, Fernando E. Garcia-arroyo, Monica Gabriela Bias-Marron, Jose Pedraza-chaverrí, Cecilia Zazueta, Magdalena Cristobal, Edilia Tapia. Renal Physiopathology, INCICh, Mexico City, DF, Mexico; Biology, UNAM, Mexico City, DF, Mexico; Cardiovasc BioMed, INCICH, Mexico City, DF, Mexico.

Background: The aims of this study were: 1. To define a possible synergistic effect between fructose and vasopressin during MHID, and 2. To evaluate the potential therapeutic benefit of C (3mg/kg BW) on this condition.

Methods: Six groups of male Wistar rats were MHID (37°C/1 h/day) and rehydrated with the selected beverage during 30 days: Water (W)+Veh, W+C, F+Veh, F+C, Stevia (S)+Veh and S+C. A group of normal control (NC) rats was studied as reference. After 30 days plasma and urine parameters were evaluated, renal cortex mitochondria were isolated and respiratory control rate (RCR) was evaluated with malate/glutamate (M/G) and succinate/rotenone (S/R) substrates.

Conclusion: The presence of AAC and CVC were independently associated with mortality in MHD patients. Regular follow-up by X-ray and echocardiography could be useful method to stratify mortality risk in MHD patients.

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

<table>
<thead>
<tr>
<th>Group/parameter</th>
<th>POProt (mg/dL)</th>
<th>PCR (mg/dL)</th>
<th>PCCo-peptin (ng/mL)</th>
<th>Renal/Ox-Proteome (sM/μg prot)</th>
<th>Urine NAG</th>
<th>RCR MG</th>
<th>RCR S/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>295±4</td>
<td>0.7± .1</td>
<td>0.03± .01</td>
<td>5±4</td>
<td>0</td>
<td>4.4± 0.2</td>
<td>3.4± 0.2</td>
</tr>
<tr>
<td>W+V</td>
<td>303±4</td>
<td>0.8±.0.1</td>
<td>24±3</td>
<td>16±3</td>
<td>0.51±0.03</td>
<td>3.9±0.3</td>
<td>3.2±0.1</td>
</tr>
<tr>
<td>W+C</td>
<td>301±4</td>
<td>0.8±0.1</td>
<td>24±2</td>
<td>14±1</td>
<td>0.41±0.02</td>
<td>3.9±0.2</td>
<td>3.2±0.2</td>
</tr>
<tr>
<td>F+V</td>
<td>317±4</td>
<td>1±.1</td>
<td>5±7</td>
<td>49±3</td>
<td>1.1±0.1</td>
<td>3.6±0.3</td>
<td>2.5±0.2</td>
</tr>
<tr>
<td>F+C</td>
<td>308±3**</td>
<td>0.8±0.2***</td>
<td>85±4</td>
<td>33±3*</td>
<td>0.72±0.30**</td>
<td>3.6±0.3</td>
<td>3.4±0.2**</td>
</tr>
<tr>
<td>S+V</td>
<td>303±3</td>
<td>0.7±0.1</td>
<td>16±2</td>
<td>11±1</td>
<td>0.42±0.04</td>
<td>4.0±0.3</td>
<td>3.1±0.2</td>
</tr>
<tr>
<td>S+C</td>
<td>304±4</td>
<td>0.8±0.1</td>
<td>12±2</td>
<td>12±2</td>
<td>0.41±0.02</td>
<td>4.0±0.2</td>
<td>2.9±0.2</td>
</tr>
<tr>
<td>BEVERAGE</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>****</td>
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<td>TX</td>
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<td>***</td>
</tr>
<tr>
<td>INTERACTION</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

Oxpro: oxidized protein; *p<0.05 vs V; **p<0.01 vs V; ***p<0.001 vs V; ****p<0.0001 vs V.

Conclusions: These data suggest a crosstalk between F and vasopressin on this particular condition. In addition, C treatment prevented renal and mitochondrial alterations induced by rehydration with F.

Funding: Pharmaceutical Company Support - Danone Nutricia Research

PUB714

Lack of Aquaretic Effects of the Kappa Opioid Agonist Nalbuphine following Multiple Ascending Oral Doses in Healthy Volunteers

Amale Hawi, Thomas Sciscia, Vandana S. Mathur, Haiw Consulting, Ridgefield, CT; Trevi Therapeutics, New Haven, CT; Mathur Consulting, Woodside, CA.

Background: Nalbuphine is a mixed µ-antagonist and κ-agonist opioid drug that may suppress thirst in hemodialysis patients with pruritus following oral administration of nalbuphine HCl extended release (ER) tablets. However, as a class, kappa opioid agonists have aquaretic effects in both animals and humans, which can be treatment-limiting. In this Phase 1 study, the potential of nalbuphine to induce aquaretic effects was explored in healthy subjects.

Methods: Healthy male and female subjects (n=9) were administered oral doses of nalbuphine escalating every 2-3 days from 30 mg QD on Day 1 to 30 mg BID, 60 mg BID, 180 mg (Day 10, PM) to 180 mg QD on Day 13.

Results: There was no evidence of an aquaretic effect at nalbuphine oral doses up to 180 mg BID in healthy subjects, the most sensitive population in which such effects have been reported to selectively contain renal functional proteins, including AQP2. In this study, we examined whether the level of urinary exosomal AQP2 excretion was altered in pcy mice.

Conclusions: Urinary volume in pcy mice was not altered at 7 weeks of age, those significantly increased at 16 and 21 weeks of age in comparison with age-matched control mice. Urine osmolality was significantly decreased in pcy mice at all ages examined in this study. Urinary exosomal AQP2 protein levels in pcy mice were dramatically increased at 16 weeks of age, whereas those at 7 and 21 weeks of age were not significantly increased. Similarly, a transient increase in urinary excretion of exosomal tumor susceptibility gene 101 protein (TSG101), frequently used as an exosome marker protein, was observed in pcy mice at 16 weeks of age. The levels of renal AQP2 protein in pcy mice at 16 weeks of age or older were significantly higher than those in the control mice.

Conclusions: Urinary exosomal AQP2 protein excretion was transiently increased in pcy mice and this increase appeared to be related to both the number of exosomes excreted into the urine and its renal abundance.

Funding: NIHDK Support

PUB716

Low Osmolar Diet and Adjusted Water Intake for Vasopressin Suppression in ADPKD


Background: Autosomal dominant polycystic kidney disease (ADPKD) affects 12.5 million persons worldwide and accounts for 10% of patients with end-stage renal disease in the United States. Vasopressin is a known detrimental factor in disease progression and cyst enlargement.

Methods: This randomized controlled trial examined the effect of a novel approach of combining low osmolar diet and adjusted water intake on vasopressin, measured by change in urinary osmolality, and total daily urinary solute in 34 patients with early ADPKD. Participants were randomized to receive a low osmolar diet (low sodium (1500 mg/day), low protein (0.8 gram/kg body weight) diet) followed by adjusted water intake to achieve a urine osmolality of 280 mOsm/kg versus no intervention for two weeks duration, with equal (1:1) allocation. Permutated block randomization was performed within strata of age and sex.

Results: Baseline characteristics of the two groups were similar. Compared with baseline, the mean urine osmolality significantly declined from 426 (±193) to 258 (±110) mOsm/kg (P=0.007) but not in the control group. At 2 weeks, levels significantly differed between groups (P=0.04).

Funding: NIDDK Support
Crispr-Cas9-Mediated Deletion of Myosin Light Chain Kinase in Cultured Collecting Duct Cells

Viswanathan Raghuram, 1,2,3 Naoyuki Otani, 1 Promsuk Jutabha, 1 Motoshi Ouchi, 1 Naohiko Anzai. 1

Background: Regulation of osmotic water transport in the renal cortical collecting duct by vasopressin is in part dependent on membrane trafficking of aquaporin-2 (AQP2) to the apical plasma membrane of the principal cells. It is known that trafficking of AQP2 is in part dependent on changes in AQP2 phosphorylation. We previously proposed that AQP2 trafficking is dependent on the protein kinase Myosin Light Chain Kinase (MLCK; gene symbol: Mylk). Here, we test the role of MLCK in AQP2 phosphorylation and trafficking, utilizing Crispr-Cas9-mediated gene editing to mutate the catalytic region of the Mylk gene. Clones were generated with 4 different guide RNAs and were characterized by genomic sequencing and immunoblotting. Effects of the deletions were assessed by immunoblotting and immunofluorescence immunocytochemistry of AQP2.

Results: Multiple clones with mutations in the catalytic domain of MLCK were generated. Western blots showed absence of MLCK protein in MLCK-deleted clones. Controls were clones that express MLCK without mutations in the catalytic domain, but may contain off-target modifications. AQP2 protein abundance varied over a broad range, among all MLCK-deleted (n=4) and control (n=4) lines, but, on average, was not affected by the deletion. Immunocytochemistry showed that vasopressin stimulates redistribution of AQP2 to the apical plasma membrane in both control cells and MLCK-deleted cells. Vasopressin-dependent phosphorylation of AQP2 at Ser256 and Ser269 was not significantly reduced in MLCK-deleted AQP2 clones.

Conclusions: The results demonstrate the feasibility of Crispr-Cas9-mediated genome editing in mouse mpkCCD cells. Our experiments in mouse cultured collecting duct cells provide evidence that vasopressin-induced phosphorylation of AQP2 and redistribution of AQP2 to the apical plasma membrane can occur independently of myosin light chain kinase.

Funding: Other NIH Support - NHLBI Intramural

The PDZ Domain-Containing Protein Harmonin Is a Binding Partner of Sodium-Coupled Monocarboxylate Transporter 2

Naoyuki Otani, 1 Promsuk Jutabha, 1 Motoshi Ouchi, 1 Hajime Hasegawa, 2 Naohiko Anzai. 1

1Dept of Pharmacology and Toxicology, Dokkyo Medical University School of Medicine, Hitawari, Tochigi, Japan; 2Dept of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama, Japan.

Background: Lactate is freely filtered and extensively reabsorbed in the proximal tubule to prevent the loss of this valuable metabolite from the body. Sodium-coupled monocarboxylate transporters SMCt2 (SLC5A12) mediates the transport of pyruvate, lactate, and lactate (Gopal et al., BBA. 2007). In contrast to its well characterized transport properties, less information is available on the regulatory mechanism of SMCt2.

Methods: We used Crispr-Cas9-genome-editing to mutate the catalytic region of the Mylk gene. Clones were generated with 4 different guide RNAs and were characterized by genomic sequencing and immunoblotting. Effects of the deletions were assessed by immunoblotting and immunofluorescence immunocytochemistry of AQP2.

Results: The catalytic domain of SMCt2 was exposed to the cytoplasmic compartment and contains thePDZ domain, one of the famous protein-protein interaction modules, suggesting that it may interact with PDZ proteins.

Methods: We used the yeast two-hybrid screening to investigate the putative SMCt2-associated proteins that modulate its transport function. Using the SMCt2 C-terminal tail (SMCt2-CT) as bait, we performed a yeast two-hybrid screen of a cDNA library constructed from the human adult kidney. Next, to further confirm the interaction between SMCt2 and harmonin, we performed a co-immunoprecipitation study using anti-harmonin antibodies.

Results: In the yeast two-hybrid screening, 34 positive clones were obtained from a total of 1.2 × 107 independent colonies screened. Of these, 8 yielded an identical sequence encoding the gene for the PDZ protein PPDK1 (manuscript in preparation), and 1 yielded an identical sequence encoding the gene for the PDZ protein Harmonin. Deletion of C-terminal PDZ motif abolished the interaction with harmonin in the yeast two-hybrid system. Furthermore, co-immunoprecipitation studies revealed that the SMCt2 interacted directly with harmonin.

Conclusions: Harmonin was identified as the binding partner for SMCt2. The elucidation of these interactions may further our understanding of the function and regulation of monocarboxylate (e.g., lactate) transport in the human kidney.

Stimulation of V1a Receptor Increases Renal Uric Acid Clearance via Abcg2 Transporter - Insight into Hypouricemia in SIADH

Yoshifuru Tamura, Shigeru Shibata, Shunya Uchida. Dept of Internal Medicine, Teikyo Univ School of Medicine, Ithabashi, Tokyo, Japan.

Background: Hypouricemia seen in the subjects with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is pathogenicomicohthe mechanism of hypouricemia remains to be clarified. V2 receptor agonist ‘desmopressin’ induced hyponatremia but not hypouricemia in human unlike SIADH (G Decca, JASN, 1996). Therefore, we hypothesized that V1 receptor but not V2 receptor may play a role in inducing hypouricemia. In the present study, we examined the changes in serum uric acid, urinary uric acid excretionand expression of uric acid transporters in response to V1a receptor agonist ‘terlipressin’.

Methods: Terlipressin was subcutaneously infused by osmotic mini pump to 7-weeks-old male Wistar rats (n = 9). Control rats were infused with normal saline (n = 9). The rats were sacrificed to obtain renal cortical tissues at 3 days.

Results: Serum uric acid significantly decreased and the excretion of urinary uric acid significantly increased in the terlipressin group. Thus, fractional excretion of uric acid increased from 1.20% ± 0.28% to 3.10 ± 0.56% (P < 0.001). The expression of ATP-binding cassette transporter, sub-family G, member 2 (ABCG2) significantly increased in the terlipressin group. Other uric acid transportersdid not significantly change.

Conclusions: These results suggest that stimulation of V1a receptor increases renal uric acid clearance probably via upregulation of ABCG2, leading to hypouricemia seen in SIADH patients.

Fluorescein Angiography and the Kidney: Friend or Foe?


Background: Fluorescein angiography (FA) is an indispensable tool for diagnosis and management of diabetic retinopathy (DR). However, safety of fluorescein sodium on renal functions is not fully understood.

Methods: 100 type 2 diabetic patients presenting to the ophthalmology outpatient clinic at Alexandria main university hospital were included in our study. Serum creatinine and cystatin-C were measured just before and 2 days after FA. Urinary NGAL as a tubular biomarker was measured also before and 4 hours after FA. Renal injury was defined as 25 % increase in serum creatinine or cystatin-C.

Results: The mean of serum creatinine was 0.99 ± 0.36 mg/dL and 1.0 ± 0.36 mg/dL before and after FA respectively with no statistically significant change (P=0.061). Only one patient (out of 100) experienced more than 25% rise in serum creatinine from baseline. Cystatin-C and urinary NGAL increased significantly after FA (P<0.001). Mean of serum Cystatin-C was 0.89 ± 0.34 mg/L and 0.95 ± 0.36 mg/L before and after FA respectively. 11 patients experienced more than 25% rise in serum cystatin-C from baseline. Mean of urinary NGAL was 21.78 ± 23.90 ng/ml and 27.15 ± 28.17 ng/ml before and after FA respectively.

Conclusions: Using ordinary renal biomarkers as serum creatinine, FA was thought to be kidney friendly. Nevertheless, using more sensitive early biomarkers as serum cystatin-C and urine NGAL, FA is not as innocent as previously thought. A creatinine negative, biomarker positive change may implicate a form of subclinical AKI.

Transcultural Adaptation and Validation of the Mexican Version of the Kidney Disease Questionnaire KDQOL-SF36 Version 1.3

Edgar Dehesa Lopez, 1 Ricardo Correa-Rotter, 2,3 David Olvera, 2,4 Carlos Gonzalez Parra, 3 Rafael Bazaldua, 2,4 1Dept of Nephrology, Research and Teaching Center in Health Sciences (CJIDOC), Culiacan, Sinaloa, Mexico; 2Dept of Nephrology, National Inst of Medical Sciences and Nutrition Salvador Zubiran, Mexico, D.F, Mexico; 3Dept of Nephrology, Hospital ISSSTE, Ciudad Valles, San Luis Potosi, Mexico; 4Department of Nephrology, Christus Merguez UPAEP, Puebla, Mexico; 1Dept of Nephrology, Hospital ISSSTE, Xalapa, Veracruz, Mexico.

Background: The evaluation of health-related quality of life through the application of efficient, reliable and simple instruments is a relatively new concept in the practice of nephrology. The aim of the study was to translate the Kidney Disease Quality of Life Short Form 36 (KDQOL-SF36) into the Spanish language, to adapt it culturally and to validate it in the Mexican population.

Methods: The translation, transcultural adaptation and validation of the Mexican version of KDQOL-SF36 was performed according to the recommendations of RAND Health. The validity was evaluated using Cronbach’s α. The test-retest reliability was evaluated using interobserver and intraobserver intraclass correlation coefficients (ICCs).

Results: The questionnaires were applied to 194 Mexican patients with end stage chronic kidney disease in chronic hemodialysis. The average age was 54±16 years and 54.6.1% were males. The Mexican version proved reliable with intra-and interobserver ICCs ≥ 0.7 in most of the dimensions evaluated, with a range between 0.5 and 0.9. The validity of the questionnaire was acceptable, with an internal items-dimensions consistency between 0.4 and 0.9, dimensions-total of 0.725 and items-total of 0.921.

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

1055A
AKI was a frequent diagnosis on hospital admission or during the hospitalization. The epidemiological characteristics and prognosis of patients with AKI and H-AKI have not been thoroughly studied.

Methods: A total of 192 patients admitted to internal medicine service were studied. AKI was diagnosed and classified at time of admission (C-AKI) or posteriorly during hospitalization. AKI was defined according to the Acute Kidney Injury Network (AKIN) criteria and serum sCr. The etiology, severity and evolution of the AKI episodes were compared among patients with C-AKI and H-AKI.

Results: C-AKI incidence was 22.4% (n=43) and H-AKI was 5.7% (n=11), giving an overall incidence of 28.1%. AKI stage 1 was present in 51.7%, AKI stage 2 in 12.9% and AKI stage 3 in 35.4%. Renal factors were the most frequent etiology of AKI in 55.6%, preterminal in 38.9% and obstructive in 5.6%. Oliguric AKI was observed in 75.9% of cases, among them 34.5% required dialysis, 24.1% reached the third stage of AKI and 31.8% were referred to additional treatment after ICU discharge. Eleven (9%) patients died and 63.6% of them developed AKI. The bivariate analysis showed that age (p = 0.006) and APACHE II score (p = 0.003) had a higher median among patients who developed AKI compared to those who did not develop AKI. In the logistic regression, the number of medications (OR: 1.15; 95% CI: 1.05 to 1.26) presented a statistically significant correlation with the development of AKI.

Conclusions: These results demonstrate that the identification of factors associated with AKI in ICU patients is very important for the early identification of renal dysfunction induced by drugs, providing conditions for appropriate prevention and treatment of the extent of kidney damage.

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

1056A
Clinical, Dialytic and Laboratorial Factors Associated with Poor Health Related Quality of Life in Mexicans Hemodialysis Patients

Edgar Dehesa Lopez,1 David Olvera,2 Carlos Gonzalez parra,3 Rafael Baizabal.4
1Dept of Nephrology, Research and Teaching Center in Health Sciences (CIDOCS), Culiacan, Sinaloa, Mexico; 2Dept of Nephrology, Hospital ISSSTE, Ciudad Valles, San Luis Potosi, Mexico; 3Dept of Nephrology, IMSS, Puebla, Mexico; 4Deparment of Nephrology, Hospital ISSSTE, Xalapa, Veracruz, Mexico.

Background: The evaluation of health related quality of life (HRQOL) in hemodialysis patients has recently gained great importance because it has proven to be an independent predictor of clinical outcomes.

Methods: Cross-sectional study. The validated Mexican version of the KDQOL-SF36 v1.3 questionnaire were applied to 194 adult patients with ESRD on hemodialysis in different regions of Mexico. According to the global score of questionnaire, patients were grouped in: patients with poor HRQOL (global score below the median) and patients with good HRQOL (global score greater than the median). Logistic regression was used to investigate the effects of clinical, dialytic and laboratorial factors on HRQOL.

Results: The average age was 54±16 with 54.6.1% male. Comorbidities were: hypertension in 86.6%, diabetes mellitus 2 in 57.2% and dyslipidemia in 7.2%. The vascular access was a catheter in 55.2% and fistula in 44.8% of the cases. Diabetes mellitus and the use of catheters as vascular access were more frequent in patients with poor quality of life. On the other hand, phosphorus >5.5 mg/dl and albumin >4g/dl were more frequent in patients with good quality of life. There were no differences in age, Kt/V, hemoglobin and calcium between groups. Table 1 shown the clinical, dialytic and laboratorial factors studied in the multivariate logistic analysis.

Table 1-Multivariate logistic regression analysis of clinical, dialytic and laboratorial factors associated with poor HRQOL.

<table>
<thead>
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<th>Variables</th>
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<tr>
<td>Age (years)</td>
<td>1.02</td>
<td>0.99</td>
<td>1.05</td>
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<td>Gender (male vs female)</td>
<td>0.87</td>
<td>0.40</td>
<td>1.89</td>
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<tr>
<td>Diabetes mellitus (yes/no)</td>
<td>1.35</td>
<td>0.56</td>
<td>3.24</td>
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<td>Vascular access (catheter vs fistula)</td>
<td>3.03</td>
<td>1.30</td>
<td>7.09</td>
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<td>Hemoglobin (&lt;9 g/dl vs &gt;9 g/dl)</td>
<td>1.23</td>
<td>0.46</td>
<td>3.26</td>
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<tr>
<td>Albumin (&lt;4 g/dl vs &gt;4 g/dl)</td>
<td>3.30</td>
<td>1.37</td>
<td>7.98</td>
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<tr>
<td>Kt/V (&lt;1.4 vs &gt;1.4)</td>
<td>1.02</td>
<td>0.40</td>
<td>2.60</td>
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<td>Calcium (&lt;8.5 mg/dl reference)</td>
<td>1.56</td>
<td>0.65</td>
<td>3.78</td>
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<td>Calcium (&gt;8-10 mg/dl)</td>
<td>0.55</td>
<td>0.18</td>
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<tr>
<td>Phosphorus (&lt;4.5 mg/dl reference)</td>
<td>2.45</td>
<td>0.30</td>
<td>19.77</td>
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<tr>
<td>Phosphorus (4.5-5.5 mg/dl)</td>
<td>1.15</td>
<td>0.14</td>
<td>9.28</td>
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<tr>
<td>Hemodialysis stay (months)</td>
<td>1.02</td>
<td>1.00</td>
<td>1.04</td>
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Conclusions: The associated factors with poor HRQOL in Mexicans hemodialysis patients were: the time spent in hemodialysis, serum albumin <4 g/dl and use of catheter for vascular access.

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

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ACE inhibitors

ACE inhibitors

acut...
ANCA (continued)...... SA-P039, SA-P041, SA-P011, SA-P049, SA-P051, SA-P055, PUB071, PUB077, PUB213, PUB221, PUB224, PUB325, PUB231, PUB251, PUB402
angiotensin...... TH-PO240, TH-P0390, TH-P0409, TH-P0411, TH-P0438, TH-P0563, TH-P0611, TH-P0657, TH-P0728, FR-P0116, FR-P0125, FR-P0126, FR-P0127, FR-P0128, FR-P0138, FR-P0147, FR-P0288, FR-P0339, SA-OR043, SA-P0286, SA-P0321, SA-P0324, SA-P0356, SA-P0389, SA-P0390, SA-P0392, SA-P0936, SA-P0957, PUB032, PUB036
anti-GBM disease...... TH-P0143, TH-P0681, TH-P0684, TH-P01099, FR-P0407, FR-P0418, FR-P0962, FR-P0963, FR-P0970, FR-P0999, PUB071, PUB427
apolipoprotein E...... TH-P0406, FR-P0167, PUB230
apoptosis...... TH-OR088, TH-P0015, TH-P0017, TH-P0018, TH-P0019, TH-P0020, TH-P0021, TH-P0263, TH-P0264, TH-P0361, TH-P0365, TH-P0387, FR-OR085, FR-OR089, FR-P0218, FR-P0219, FR-P0231, FR-P0258, FR-P0306, FR-P0354, FR-P0523, FR-P0828, FR-P0969, SA-P0240, SA-P0243, SA-P0273, SA-P0279, SA-P0286, SA-P0287, SA-P0293, SA-P0296, SA-P0301, SA-P0303, SA-P0304, SA-P0305, SA-P0307, SA-P0311, SA-P0312, SA-P0313, SA-P0359, SA-P0365, SA-P0409, SA-P0867, PUB022, PUB066, PUB076, PUB471
arteries...... TH-P0257, FR-P0127, FR-P0194, SA-P0555, PUB694
arteriosclerosis...... TH-P0381, TH-P0386, TH-P0391, TH-P0406, TH-P0416, TH-P0888, TH-P0889, TH-P0891, TH-P0895, TH-P0971, FR-P01064, FR-P0545, FR-P0625, FR-P0863, SA-P0314, SA-P0592, PUB187, PUB201, PUB705
arteriovenous access...... TH-OR062, TH-P0536, TH-P0842, TH-P0851, TH-P0858, TH-P0869, TH-P0870, TH-P0873, FR-P0382, FR-P0693, FR-P0694, FR-P0703, FR-P0713, SA-P0845, PUB486, PUB488
arteriovenous fistula...... TH-OR059, TH-P0334, TH-P0383, TH-P0389, TH-P0841, TH-P0842, TH-P0843, TH-P0846, TH-P0851, TH-P0855, TH-P0859, TH-P0860, TH-P0862, TH-P0864, TH-P0866, TH-P0869, TH-P0871, TH-P0874, TH-P0875, TH-P0876, FR-P0693, FR-P0697, FR-P0717, FR-P0720, FR-P0723, SA-P0555, SA-P0147, SA-P0165, SA-P0576, PUB475, PUB476, PUB479, PUB483, PUB484, PUB485, PUB486, PUB487, PUB489, PUB490
arteriovenous graft...... TH-P0850, TH-P0855, TH-P0859, TH-P0866, TH-P0879, FR-P0693, PUB484, PUB485
arteriovenous shunt...... TH-P0854
Barter syndrome...... TH-OR076, TH-P0425, FR-P0011, FR-P0040, SA-P0904

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TH‑PO278, TH‑PO288, TH‑PO319,
TH‑PO356, TH‑PO394, TH‑PO395,
TH‑PO415, TH‑PO892, FR‑OR058,
FR‑OR059, FR‑PO117, FR‑PO163,
FR‑PO247, FR‑PO400, FR‑PO831,
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PUB472
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PUB665, PUB676
cytoskeleton.................... TH‑PO038, TH‑PO302,
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FR‑PO336, FR‑PO359, SA‑OR045,
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SA‑PO839, SA‑PO841, PUB491
delayed graft function........................TH‑PO263,
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SA‑PO952, SA‑PO953, SA‑PO986,
SA‑PO996, SA‑PO1028, PUB660
dementia......................... TH‑OR015, TH‑OR017,
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SA‑PO631, PUB367
Dent disease..................... FR‑OR051, SA‑PO053
depression.......................TH‑OR016, TH‑PO997,
TH‑PO1024, FR‑PO600, FR‑PO667,
FR‑PO800, FR‑PO1037, SA‑PO168,
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TH‑PO805, TH‑PO904, TH‑PO965,
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FR‑PO637, FR‑PO648, FR‑PO793,
FR‑PO894, FR‑PO948, FR‑PO1105,
SA‑OR006, SA‑OR093, SA‑OR095,
SA‑PO299, SA‑PO301, SA‑PO348,
SA‑PO367, SA‑PO379, SA‑PO385,
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diabetes insipidus........... FR‑OR003, FR‑OR004,
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diabetic glomerulosclerosis...............TH‑PO249,
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PUB301, PUB302, PUB303, PUB305,
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FR‑PO901, FR‑PO905, FR‑PO907,
FR‑PO908, FR‑PO1001, FR‑PO1034,
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SA‑PO011, SA‑PO091, SA‑PO113,
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SA‑PO780, SA‑PO781, SA‑PO788,
SA‑PO789, SA‑PO794, SA‑PO799,
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SA‑PO843, SA‑PO908, SA‑PO910,
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PUB307, PUB324, PUB327, PUB330,


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expression family history familial nephropathy Fabry disease Fabry disease familial nephropathy fibrosis (continued)......FR-PO1080, SA-OR044, SA-OR059, SA-OR081, SA-OR085, SA-OR086, SA-OR087, SA-P0074, SA-P0253, SA-P0277, SA-P0288, SA-P0298, SA-P0304, SA-P0328, SA-P0329, SA-P0330, SA-P0331, SA-P0332, SA-P0373, SA-P0378, SA-P0416, SA-P0422, SA-P0433, SA-P0444, SA-P0461, SA-P0463, SA-P0465, SA-P0468, SA-P0471, SA-P0472, SA-P0477, SA-P0479, SA-P0480, SA-P0483, SA-P0486, SA-P0487, SA-P0488, SA-P0495, SA-P0503, SA-P0884, SA-P0984, SA-P0999, PUB014, PUB015, PUB067, PUB089, PUB178, PUB389, PUB391, PUB392, PUB393, PUB420.

focal segmental glomerulosclerosis......TH-OR043, TH-OR094, TH-PO174, TH-PO224, TH-PO240, TH-PO398, TH-PO465, TH-PO701, TH-PO1106, TH-PO1108, FR-OR049, FR-OR051, FR-OR052, FR-OR053, FR-OR060, FR-PO621, FR-PO659, FR-PO152, FR-PO153, FR-PO155, FR-PO175, FR-PO308, FR-PO316, FR-PO322, FR-PO326, FR-PO327, FR-PO335, FR-PO342, FR-PO349, FR-PO356, FR-P0433, FR-P0477, FR-P0513, FR-P0986, SA-OR020, SA-OR045, SA-OR053, SA-OR054, SA-PO002, SA-PO017, SA-PO093, SA-PO100, SA-PO295, SA-PO347, SA-PO442, SA-PO512, SA-PO1079, SA-PO1080, PUB072, PUB077, PUB078, PUB203, PUB245, PUB257, PUB467.
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gastrointestinal medications......TH-OR114, TH-PO655, FR-PO878, SA-PO547.
gender difference......TH-PO212, TH-PO553, TH-PO863, TH-PO933, FR-PO395, FR-PO701, SA-PO542, PUB190, PB-P0198, PB-P0610.
gene expression......TH-OR041, TH-OR042, TH-OR047, TH-OR048, TH-OR049, TH-OR030, TH-OR0154, TH-OR0172, TH-OR0186, TH-OR0187, TH-OR0197, TH-OR0230, TH-OR0256, TH-PO261, TH-PO276, TH-PO279, TH-PO304, TH-PO325, TH-PO408, TH-PO483, TH-PO492, TH-PO522, TH-PO683, TH-PO706, TH-PO709, FR-OR083, FR-OR076, FR-OR078, FR-PO094, FR-PO183, FR-PO397, FR-PO421, FR-PO813, FR-PO818, FR-PO827, FR-PO954, FR-PO978, FR-PO1077, SA-OR095, SA-PO171, SA-PO274, SA-PO282, SA-PO393, SA-PO492, SA-PO504, SA-PO510, SA-PO512, SA-PO587, SA-PO588, SA-PO982, SA-PO997, SA-PO1089, PB-P0397, PB-P0398.
glomerular disease (continued)......TH‑PO693, TH‑PO696, TH‑PO700, TH‑PO716, TH‑PO722, TH‑PO724, TH‑PO735, TH‑PO751, TH‑PO755, TH‑PO760, TH‑PO769, TH‑PO782, TH‑PO786, TH‑PO1071, TH‑PO1072, TH‑PO1077, TH‑PO1086, TH‑PO1112, FR‑OR066, FR‑PO149, FR‑PO150, FR‑PO154, FR‑PO157, FR‑PO159, FR‑PO160, FR‑PO164, FR‑PO206, FR‑PO315, FR‑PO318, FR‑PO321, FR‑PO330, FR‑PO333, FR‑PO348, FR‑PO352, FR‑PO362, FR‑PO363, FR‑PO419, FR‑PO426, FR‑PO436, FR‑PO440, FR‑PO441, FR‑PO449, FR‑PO450, FR‑PO451, FR‑PO514, FR‑PO964, FR‑Po966, SA‑OR013, SA‑OR025, SA‑OR028, SA‑PO306, SA‑PO308, SA‑PO157, SA‑PO297, SA‑PO343, SA‑PO350, SA‑PO427, SA‑PO428, SA‑PO430, SA‑PO434, SA‑PO505, SA‑PO508, SA‑PO509, SA‑PO538, PUB050, PUB082, PUB084, PUB088, PUB089, PUB209, PUB210, PUB213, PUB214, PUB216, PUB222, PUB232, PUB236, PUB238, PUB256, PUB399, PUB553, PUB554, PUB574, PUB682

glomerular endothelial cells........TH‑PO273, TH‑PO298, TH‑PO315, TH‑PO346, TH‑PO369, SA‑PO353, SA‑PO466, PUB091, PUB701
glomerular epithelial cells............TH‑OR085, TH‑PO366, TH‑PO1031, FR‑PO324, FR‑PO328, FR‑PO329, SA‑PO335

glomerular filtration barrier............TH‑PO239, TH‑PO246, TH‑PO303, FR‑PO154, FR‑PO162, FR‑PO324, FR‑PO334, FR‑PO337, FR‑PO341, FR‑PO352, SA‑OR038, SA‑PO351, SA‑PO448, SA‑PO454, PUB081, PUB091, PUB094

glomerular filtration rate............TH‑OR001, TH‑OR013, TH‑OR037, TH‑PO199, TH‑PO607, TH‑PO608, TH‑PO666, TH‑PO675, TH‑PO705, TH‑PO712, TH‑PO739, TH‑PO740, TH‑PO771, FR‑OR068, FR‑OR114, FR‑PO070, FR‑PO132, FR‑PO149, FR‑PO227, FR‑PO375, FR‑PO376, FR‑PO526, FR‑PO544, FR‑PO550, FR‑PO551, FR‑PO557, FR‑PO578, FR‑PO583, FR‑PO628, FR‑PO633, FR‑PO638, FR‑PO645, FR‑PO847, FR‑PO853, FR‑POP1003, FR‑PO1018, FR‑PO1023, FR‑PO1062, SA‑OR010, SA‑OR043, SA‑OR063, SA‑PO257, SA‑PO258, SA‑PO455, SA‑PO545, SA‑PO642, SA‑PO672, SA‑PO673, SA‑PO674, SA‑PO675, SA‑PO676, SA‑PO677, SA‑PO680, SA‑PO737, SA‑PO740, SA‑PO765, SA‑PO767, SA‑PO773, SA‑PO856, SA‑PO877, SA‑PO892, SA‑PO1011, SA‑PO1022, SA‑PO1025, PUB044, PUB119, PUB124, PUB133, PUB160, PUB161, PUB162, PUB177, PUB180, PUB189, PUB190, PUB193, PUB194, PUB195, PUB300, PUB377, PUB661
glomerular hyperfiltration............TH‑PO372, TH‑PO705, FR‑PO122, FR‑PO320, FR‑PO605, SA‑PO345, PUB088, PUB573

glomerulonephritis............TH‑OR024, TH‑OR072, TH‑OR093, TH‑PO126, TH‑PO131, TH‑PO237, TH‑PO252, TH‑PO254, TH‑PO683, TH‑PO689, TH‑PO703, TH‑PO709, TH‑PO713, TH‑PO725, TH‑PO736, TH‑PO747, TH‑PO749, TH‑PO761, TH‑PO788, TH‑PO794, TH‑PO797, TH‑PO1078, TH‑PO1080, TH‑PO1100, TH‑PO1109, TH‑PO1117, TH‑PO1119, TH‑PO1120, FR‑OR067, FR‑PO017, FR‑PO024, FR‑PO336, FR‑PO386, FR‑PO403, FR‑PO408, FR‑PO410, FR‑PO414, FR‑PO424, FR‑PO427, FR‑PO442, FR‑PO449, FR‑PO452, FR‑PO453, FR‑PO970, FR‑PO971, FR‑PO973, FR‑PO976, FR‑PO979, FR‑PO981, FR‑PO984, FR‑PO992, FR‑PO993, FR‑PO996, FR‑OR014, SA‑PO014, SA‑PO019, SA‑PO033, SA‑PO035, SA‑PO039, SA‑PO040, SA‑PO041, SA‑PO064, SA‑PO068, SA‑PO076, SA‑PO078, SA‑PO104, SA‑PO109, SA‑PO110, SA‑PO111, SA‑PO123, SA‑PO349, SA‑PO426, SA‑PO440, SA‑PO441, SA‑PO534, SA‑PO647, SA‑PO687, SA‑PO1055, PUB074, PUB077, PUB101, PUB208, PUB215, PUB221, PUB241, PUB254, PUB255, PUB258, PUB407, PUB408, PUB410, PUB415, PUB435

glomerulopathy............TH‑OR138, TH‑OR230, TH‑PO700, TH‑PO718, TH‑PO726, TH‑PO762, TH‑PO1043, FR‑PO425, FR‑PO957, FR‑PO958, SA‑OR017, SA‑OR050, SA‑PO003, SA‑PO027, SA‑PO042, SA‑PO059, SA‑PO344, SA‑PO359, SA‑PO454, SA‑PO457, SA‑PO522, SA‑PO526, PUB069, PUB074

glomerulosclerosis............TH‑OR088, TH‑OR092, TH‑PO235, TH‑PO309, TH‑PO750, FR‑OR101, FR‑PO286, FR‑PO302, FR‑PO338, FR‑PO352, FR‑PO353, FR‑PO435, FR‑PO438, FR‑PO512, FR‑PO534, FR‑PO582, FR‑PO623, FR‑PO624, SA‑OR052, SA‑OR103, SA‑PO051, SA‑PO121, SA‑PO360, SA‑PO427, SA‑PO983, PUB246, PUB290, PUB409, PUB584, PUB663

glomerulus............TH‑PO133, TH‑PO223, TH‑PO338, FR‑PO187, FR‑PO189, FR‑PO193, FR‑PO304, FR‑PO317, FR‑PO339, FR‑PO359, FR‑PO396, FR‑PO996, SA‑OR046, SA‑OR336, SA‑PO339, SA‑PO345, SA‑PO352, SA‑PO355, SA‑PO388, SA‑PO453, PUB083, PUB090, PUB092, PUB282, PUB293
glycation............TH‑PO248, FR‑PO963, SA‑PO397, SA‑PO692

Goodpasture syndrome............TH‑PO1122, TH‑PO407, FR‑PO962, FR‑PO965, SA‑PO222
multiple myeloma

mycophenolate mofetil

nephrectomy

nephrology

nephrosis

nephrotic syndrome

nephrotic syndrome (continued)

nephrotoxicity

nitric oxide

nocturnal hypoxemia

nutrition

obesity

mRNA
renal stem cell
renat transplantation
renal tubular acidosis
renin angiotensin system
rhabdomyolysis
rheumatology

risk factors

renal transplantation

systolic blood pressure

tacrolimus

tGF-beta

statins

stem cell

stress factors

tolerance

theophylline

thrombosis
vasopressin............... TH-PO213, TH-PO795,
TH-PO1056, FR-PO028, FR-PO031,
FR-PO095, FR-PO097, FR-PO100,
FR-PO106, FR-PO108, SA-OR111,
SA-OR112, SA-OR113, SA-OR114,
SA-OR115, SA-OR116, SA-PO010,
SA-PO379, SA-PO852, SA-PO853,
SA-PO857, SA-PO863, SA-PO880,
SA-PO916, PUB095, PUB713, PUB717,
PUB719
VEGF ........ TH-PO016, TH-PO241, FR-PO148,
FR-PO350, FR-PO831, SA-PO116,
SA-PO215, SA-PO317
vesico-ureteral reflux .... TH-PO462, TH-PO737,
FR-PO018, FR-PO455
virology ...... TH-PO1031, FR-PO052, FR-PO332,
FR-PO778, SA-PO106, SA-PO181,
SA-PO1058, SA-PO1062, SA-PO1063,
SA-PO1064, SA-PO1065, SA-PO1069,
PUB689
vitamin B1 ...................... FR-PO596
vitamin C .... TH-PO1095, FR-PO890, SA-PO807
vitamin D .... TH-PO394, TH-PO485, TH-PO488,
TH-PO505, TH-PO506, TH-PO507,
TH-PO508, TH-PO510, TH-PO511,
TH-PO512, TH-PO513, TH-PO514,
TH-PO515, TH-PO522, TH-PO523,
TH-PO524, TH-PO601, TH-PO623,
TH-PO641, TH-PO645, TH-PO822,
TH-PO914, TH-PO1019, FR-PO029,
FR-PO343, FR-PO229, FR-PO311,
FR-PO615, FR-PO696, FR-PO800,
FR-PO815, FR-PO841, FR-PO926,
FR-PO943, FR-PO944, FR-PO1009,
SA-OR028, SA-PO106, SA-PO665,
SA-PO365, SA-PO398, SA-PO558,
SA-PO580, SA-PO597, SA-PO611,
SA-PO633, SA-PO655, SA-PO660,
SA-PO743, SA-PO1067, PUB073, PUB525,
PUB528, PUB531, PUB540, PUB542,
PUB544, PUB547, PUB548, PUB646,
PUB647, PUB667
water channels ........ FR-OR038, FR-PO096,
FR-PO098, FR-PO099, FR-PO100,
FR-PO101, FR-PO102, FR-PO104,
FR-PO105, FR-PO109, FR-PO140,
FR-PO611, FR-PO945, SA-OR115,
SA-OR117, SA-OR118, SA-PO285,
SA-PO928, SA-PO972, PUB268,
PUB715, PUB717
water transport ........ FR-OR004, FR-OR038,
FR-PO095, FR-PO107, FR-PO109,
FR-PO808, SA-OR118, PUB714
water-electrolyte balance .......... TH-OR082,
TH-OR084, TH-PO120, TH-PO423,
TH-PO428, TH-PO832, TH-PO1056,
FR-OR004, FR-OR009, FR-PO007,
FR-PO026, FR-PO050, FR-PO097,
FR-PO099, FR-PO100, FR-PO106,
FR-PO118, FR-PO122, FR-PO506,
FR-PO923, SA-OR110, SA-OR111,
SA-OR112, SA-PO257, SA-PO417,
SA-PO637, SA-PO902, SA-PO903,
SA-PO906, SA-PO907, SA-PO909,
SA-PO913, SA-PO916, SA-PO932, PUB362,
PUB431, PUB446, PUB600
HI-OR01

Empagliflozin and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Chronic Kidney Disease
Christopher Wanner, 1 John M. Lachin, 2 David H. Fitchett, 3 Silvio E. Inzucchi, 4 Maximilian von Eynatten, 5 Michaela Matthaeus, 6 Odd Erik Johannsen, 7 Hans-Juergen Woerle, 8 Uli Christian Broedl, 9 Bernard Zinman, 10 1 Dept of Medicine, Wurzburg Univ Clinic, Wurzburg, Germany; 2 The Biostatistics Center, The George Washington Univ, Rockville, MD; 3 St Michael's Hospital, Div of Cardiology, Univ of Toronto, Toronto, Canada; 4 Section of Endocrinology, Yale Univ School of Medicine, New Haven, CT; 5 Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 6 Boehringer Ingelheim Norway KS, Asker, Norway; 7 Lunenburg-Tannhaeuser Research Inst, Mount Sinai Hospital, Toronto, Canada; 8 Div of Endocrinology, Univ of Toronto, Toronto, Canada.

Background: Patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) are at high risk of cardiovascular (CV) events and premature death. Empagliflozin is a sodium-glucose co-transporter (SGLT)-2 inhibitor used in the treatment of T2D.

Methods: In EMPA-REG OUTCOME®, we explored long-term CV outcomes with empagliflozin vs placebo when added to standard of care in 7020 T2D patients with established CV disease. Inclusion criteria included eGFR ≥30ml/min/1.73m². Patients (mean age 63 years, male 71%, mean HbA1c 8.1%) were randomized 1:1:1 to empagliflozin 10mg, 25mg or placebo.

Results: Most patients had impaired kidney function (52.2% stage 2, 17.8% stage 3a, 7.7% stage 3b CKD) while 28.7% and 11.0%, respectively, had moderately (30-300mg/g) or severely (>300mg/g) increased urine albumin to creatinine excretion. At a median follow-up of 3.1 years, the primary outcome (first occurrence of non-fatal myocardial infarction, non-fatal stroke, or CV death) occurred in a lower percentage of patients on empagliflozin (10.5%) than placebo (12.1%) (HR 0.86 [0.74-0.99]; p=0.04). This result was driven by a 38% reduction in CV death vs placebo (HR 0.62 [0.49-0.77]; p<0.001), with no difference in the risk of heart attack or stroke. Empagliflozin reduced hospitalization for heart failure by 35% (HR 0.65 [0.50-0.85]; p=0.0017). Pre-defined subgroup analyses on CV outcomes in patients with T2D and CKD will be presented.

Conclusions: Empagliflozin reduces CV morbidity and mortality in patients with T2D and various degrees of CKD.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim and Eli Lilly and Company.

HI-OR02

High Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery
Federic Tremaine Billings, Chad E. Wagner, Patty Hendricks, Yaping Shi, Michael R. Petracek, Nancy J. Brown. Vanderbilt Univ, Nashville, TN.

Background: Hydroxy-methylglutaryl-coenzyme A reductase inhibitors (statins) affect several mechanisms underlying acute kidney injury (AKI), a common and dangerous complication after cardiac surgery. We hypothesized that short-term high-dose perioperative atorvastatin would reduce AKI following cardiac surgery.

Methods: We randomized elective cardiac surgery patients, stratified by chronic kidney disease (CKD), to atorvastatin or matching-placebo starting the day prior to surgery until 14 days following surgery, or new dialysis in the 30 days following surgery. Patients, care givers and outcome-assessors were blinded to allocation. Acute kidney injury was defined as ≥2.50% or ≥26.5 mmol/l increase in the postoperative serum creatinine concentration from the preoperative concentration in the 14 days following surgery, or new dialysis in the 30 days following surgery.

Results: Methylprednisolone (n=3,647) vs placebo (n=3,639) did not alter the risk of acute kidney injury (40.9% vs 39.5%, respectively; relative risk 1.03 [95% CI, 0.96 to 1.11]). Results were consistent with multiple alternate continuous and categorical definitions of acute kidney injury, and in the subgroup with baseline chronic kidney disease.

Conclusions: Amongst patients undergoing cardiac surgery with cardiopulmonary bypass, the use of corticosteroids during the perioperative period did not alter the risk of acute kidney injury. Trial Registration: NCT00427388

Funding: Government Support - Non-U.S.

HI-OR04

The NEFILGAN Trial: NEFCON, a Novel Targeted Release Formulation of Budesonide, Reduces Proteinuria and Stabilizes eGFR in IgA Nephropathy Patients at Risk of ESRD
Benet C. Feliu-strom, 1 Rosanna Coppo, 2 John Feehally, 3 Jürgen Floege, 4 Johan W. De Fijter, 5 Alan G. Jardine, 6 Francesco Locatelli, 7 Bart D. Maes, 8 Alex Merce, 9 Fernanda Ortiz, 10 Manuel Praga, 11 Soren Schwartz-Sorensen, 12 Vladimir Tesar. 13

Background: In IgA nephropathy (IgAN) nephropathy, patients at risk for end-stage renal disease (ESRD) are often treated with oral corticosteroids. However, the frequent side effects of long-term corticosteroid therapy limit their use. NEFCON is a novel targeted release formulation of budesonide which allows for sustained release of drug directly to the glomerulus, effectively reducing proteinuria with minimal systemic glucocorticoid side effects.

Methods: A double-blind, placebo-controlled study in 150 patients (62 sites, 10 EU countries) with primary IgAN, proteinuria (UPCR >0.5 g/G or urinary protein >0.75 g/d) and eGFR ≥30ml/min/1.73m² randomized to NEFCON (n=75) vs placebo (n=75). Primary endpoint was renal function at 12 months.

Results: At baseline, patients in the NEFCON and placebo groups were well matched with comparable baseline characteristics, and mean UPCR was 4.77±1.73 mg/dl. Mean UPCR decreased to 1.09±0.79 mg/dl in the NEFCON group compared to 1.13±0.75 mg/dl in the placebo group (p=0.0036), after 12 months of follow-up. NEFCON was generally well-tolerated.

Conclusions: NEFCON reduced proteinuria in IgAN patients with a risk of transitioning to ESRD, with minimal systemic glucocorticoid side effects. NEFCON is a promising new treatment for IgAN.

Funding: Pharmaceutical Company Support - Pharmalink AB

Underline represents presenting author/disclosure.
HI-OR05

Randomized Trial on Efficacy of Mycophenolate Mofetil versus Tacrolimus in Maintaining Remission in Children with Steroid Resistant Nephrotic Syndrome

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Background: Since prolonged therapy with tacrolimus (Tac) causes nephrotoxicity, this RCT examined non-inferiority of mycophenolate mofetil (MMF) to Tac in maintaining remission in patients with steroid resistant nephrotic syndrome (SRNS).

Methods: Following approvals, 84 patients with SRNS (1-18 yr; minimal change 48, FSGS 36) & eGFR >60 ml/min/1.73m2 were randomized to Tac (0.15 mg/kg/d; trough 4-8 ng/ml) for 6 months. Stratifying for histology & type of response, patients with complete (Up/Uc <0.2 mg/mg) or partial remission (Up/Uc 0.2-2, albumin >2.5 g/dl) were randomized to continue Tac or receive MMF (0.75-1 g/m2/d), prednisone & enalapril. Primary outcome, at 12-mo, was proportion with remission or infrequent relapses. Therapy failure was recurrent SRNS, frequent relapses or >1 SAE. Enrolment was closed after interim intention-to-treat analysis of outcome in 1/2 sample.

Results: Baseline features were similar. Therapy with MMF led to significantly higher treatment failure, prednisone dose & SAE; eGFR change was similar. On multivariate regression, hazards of treatment failure were high with MMF (HR 9.7, adjusted for histology, type of resistance & remission; P<0.0001).

HI-OR06

Prevention of Bone Mineral Density Loss in De Novo Kidney Transplant Recipients with Twice-Yearly Denosumab: A Randomized Controlled Trial

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Div of Nephrology; 2Div of Visceral and Transplantation Surgery; 3Inst of Clinical Chemistry, Univ Hospital, Zurich, Switzerland; 4Graf Biostatistics, Winterthur, Switzerland.

Background: Kidney transplantation is associated with bone loss and an increased risk of fracture. Since current therapeutic options to prevent bone loss are limited we assessed the efficacy and safety of Receptor Activator of Nuclear Factor k B Ligand (RANKL) inhibition with denosumab to improve bone mineralization in the first year after kidney transplantation.

Methods: We enrolled 108 kidney transplant recipients and randomized 90 patients two weeks after surgery in a 1:1 ratio to receive denosumab (subcutaneous injections of 60 mg denosumab at baseline and after 6 months) or no treatment. The primary endpoint was the percentage change in bone mineral density (BMD) measured by DXA at the lumbar spine at 12 months.

Results: After 12 months, the primary outcome of total lumbar spine BMD increased by 4.6% (95% CI 3.3-5.9%) in 46 patients in the denosumab group and decreased by -0.5% (95% CI -1.8-0.9%) in 44 patients in the control group (between-group difference 5.1%, 95% CI 1.7-8.5%, p=0.001). Denosumab also significantly increased BMD at the total hip by 1.9% (95% CI 0.1 to 3.7%; p=0.035) over that in the control group at 12 months. HR-pQCT in a subgroup of 24 patients showed that denosumab also significantly increased BMD and cortical thickness at the distal tibia and radius (p<0.05). Biomarkers of bone resorption (β-Cr, urine deoxypyridinoline) and bone formation (P1NP, BSAP) markedly decreased with denosumab (p<0.0001). Episodes of cystitis and asymptomatic hypocalcaemia occurred more often with denosumab, whereas graft function, rate of rejections and incidence of opportunistic infections were similar.

Conclusions: Antagonizing RANKL with denosumab effectively increased BMD in de novo kidney transplant recipients, but was associated with more frequent episodes of urinary tract infection and decreased calcium.

Funding: Government Support - Non-U.S.
Methods: This international, randomised, double-blind, placebo-controlled trial examined whether 3 months therapy with w3FA (Ag/day) reduced primary AVF failure at 12 months after AVF creation. AVF failure was defined as AVF thrombosis and/or abandonment and/or cannulation failure. A subset of patients received aspirin (100mg/day) or matching placebo in addition to w3FA or placebo in a factorial design (n=388).

Results: The 567 randomised participants had a mean age of 55 years, 63% were male and 46% diabetic. AVF failure occurred in 128/270 (47%) participants assigned to w3FA compared with 125/266 (47%) assigned to placebo (relative risk adjusted for aspirin use [RR] 1.03, 95% confidence interval [CI] 0.86-1.23, p = 0.78). Regarding each component of AVF failure, w3FA did not reduce the risk of thrombosis (22% vs 23%, RR 0.98, 95% CI 0.72-1.34, p=0.90), AVF abandonment (19% vs 22%, RR 0.87, CI 0.62-1.22, p=0.43) or cannulation failure (40% vs 39%, RR 1.03, 0.83-1.26, p=0.81). A subgroup difference was observed for diabetes mellitus (interaction p=0.038; RR 1.30 v.0.78; diabetics vs non-diabetics) but not for age, gender, AVF site, dialysis modality and cardiovascular disease. There was no difference in any serious adverse event (AE) (9.2% vs 13.0%, p=0.14; bleeding, 8.1% vs 10.9%; p=0.26, or gastrointestinal AE, 4.9% vs 5.4%; p=0.86. The risk of AVF failure was similar (45% vs 45%, RR 1.05, 95% CI 0.95-1.15) in the subset of participants randomised to aspirin or placebo-aspirin as part of the factorial design.

Conclusions: Three months of w3FA intake was ineffective in reducing primary AVF failure at 12 months. Aspirin may be similarly ineffective. There was no increased risk of bleeding. Neither w3FA nor aspirin increased the proportion of useable de novo AVF.

Funding: Other NIH Support - NHMRC Project Grant, Pharmaceutical Company Support - AMGEN Australia

SA-PO1091
The Remote Ischemic Preconditioning in Cardiac Surgery Trial (Remote IMPACT) Michael Walsh,1,2 McMaster Univ; 3Population Health Research Inst.

Background: Cardiac surgery is frequently complicated by ischemia-reperfusion injury which can lead to kidney and myocardial injury. Preoperative Remote Ischemic Preconditioning (RIPC), cycles of brief ischemia to a limb alternating with reperfusion, may reduce the frequency or severity of organ injury after cardiac surgery.

Methods: We randomly allocated 258 patients at high risk for death after cardiac surgery to receive either RIPC or a sham procedure immediately after induction of anesthesia. RIPC consisted of 3 cycles of thigh tourniquet inflation to 300 mmHg for 5 minutes followed by 5 minutes reperfusion. The sham group tourniquets were inflated to 15 mmHg. Patients and care providers were blinded. The main clinical outcomes were change in creatinine over the first 4 postoperative days and the peak CK-MB within 24 hours of surgery. Other outcomes were assessed 30 days after randomization. Analyses were performed according to the intention-to-treat principle.

Results: We randomized 128 patients to RIPC and 130 to sham. No patients were lost to follow-up. There was no significant difference in postoperative change in creatinine (p=0.79) or peak CK-MB (p=0.18) (Figure 1). We found no significant differences in the frequency of acute kidney injury (34% vs 31%), myocardial injury (24% vs 24%), stroke (4% vs 3%) or mortality (6% vs 5%) at 30 days.

Figure 1. Mean and 95% confidence intervals of creatinine over time for the RIPC (green diamonds) and sham (blue circles) groups.

Conclusions: In this trial RIPC did not affect markers of kidney and myocardial injury. These results fail to provide proof-of-concept that RIPC may impact clinically important outcomes in the cardiac surgery setting.

SA-PO1092
Nephrotoxicity of Invasive and Noninvasive Coronary Angiography: Randomized Controlled Study of Intracoronary and Intravenous Contrast Agent Administration Eva Schönberger,1 Patricia D. Bady,2 Peter Martus,2 Elke Zimmermann,2 Michael Laule,3 Marc Dewey,4 Anesthesiology, Charité, Berlin, Germany; 2Radiology, Charité, Berlin, Germany; 4Inst for Clinical Epidemiology and Applied Biostatistics, Eberhard Karls Univ, Tübingen, Germany; 5Cardiology, Charité, Berlin, Germany.

Background: Intradialytic contrast agent administration is known to cause nephrotoxicity. We compared the effects of intracoronary contrast agent administration (ICA) vs intravenous contrast agent administration (CTA). We hypothesized that ICA will cause less nephrotoxicity than CTA.

Methods: We randomly assigned patients with suspected coronary disease to either intracoronary contrast agent for invasive coronary angiography (ICA) or an alternative diagnostic test (CTA). The 302 patients were randomised to receive either ICA or CTA. In ICA group, the intracoronary contrast agent was used for ICA and CTA. Blood samples were taken before and at two time points after ICA and CTA (18 to 24 hours and 46 to 50 hours) to identify contrast-induced acute kidney injury defined according to the KDOQI definition of at least 0.5 mg per deciliter or 25%.

Results: 218 patients of whom 10 and 4 dropped out from the ICA and CTA group, respectively, leaving 161 and 165 patients who underwent ICA and CTA until September 8, 2015. Baseline creatinine levels in the ICA group (0.85±0.19) and the CTA group (0.87±0.21 mg per deciliter) were similar (P=0.34). Follow-up creatinine was not available in 3 and 5 patients in the ICA and CTA group, respectively. Twenty-one of the 158 patients in the ICA group (13%) had an increase in creatinine of at least 0.5 mg per deciliter or 25%, as compared with 9 of the 160 patients in the CTA group (6%; P=0.05). In patients without coronary disease on ICA or CTA, such a creatinine increase was found in 17 of the 134 patients in the ICA group (13%) and 6 of the 139 patients in the CTA group (4%; P<0.05). No patient without coronary disease in the CTA group had an increase in creatinine according to the KDOQI definition of at least 0.5 mg per deciliter or 50%, but 6 of the 134 patients in the ICA group (4%; P<0.05).

Conclusions: Nephrotoxicity may be more likely after intracoronary than after intravenous contrast agent administration.

Funding: Government Support - Non-U.S.

SA-PO1093
Efficacy and Safety of Bosutinib in Autosomal Dominant Polycystic Kidney Disease: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Ewa Rzepczynska,1 Katarzyna Biechowicz,1 Marcin Wronski,1 Barbara Truszczyńska,2 York P. Ingwersen,3 Andreas L. Serra,4 Pomeranian Medical Univ, Szczecin, Poland; 3Charles Univ, Prague, Czech Republic; 4Univ Health Network, Toronto, Ontario, Canada; 5Ichsan School of Medicine at Mount Sinai, New York, NY; 2Pfizer Inc, San Diego, CA; 3Pfizer Inc, Cambridge, MA; 7Sanofi US, Bridgewater, NJ; 8Roche Pharma Research and Development, Basel, Switzerland; 9Inst for Allgemeine Inneren Medizin und Nephropathie, Suisse ADPKD Hirslanden, Zurich, Switzerland.

Background: Src overactivation has been linked to the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). We assessed efficacy and safety of bosutinib (BOS), an oral dual Src/Abl tyrosine kinase inhibitor, in ADPKD patients (pts).

Methods: In this phase 2, multicenter study (NCT01233869), ADPKD pts with estimated glomerular filtration rate ≥60 mL/min/1.73 m2 and magnetic resonance image (MRI) confirmed total kidney volume (TKV) ≥750 cc were randomized 1:1:1 to placebo (PBO), 200 mg/d, or 400 mg/d of oral BOS for ≥24 mo. The primary endpoint was annualized TKV % change. Pts treated for ≥2 wk who had an MRI after a 30-d washout period were included in the modified intent-to-treat (mITT) analysis.

Results: 169 of 172 enrolled pts received ≥1 dose of treatment. 24 pts who initially received 400 mg/d BOS were later reduced to 200 mg/d BOS per protocol. 88 pts (52%) were in the mITT population (200 mg/d, n=27; 400 mg/d, n=7; 400 mg/d to 200 mg/d, n=21; PBO, n=33) after discontinuations (unrelated to study drug, 27%; study drug-related adverse events, 17%; consent withdrawal, 14%). Annual rate of kidney enlargement was significantly reduced for pooled BOS vs PBO (0.84% vs 4.74%, respectively, 95% CI for difference in annualized rates [2.02-5.74]; p<0.0001) and was 65.2% lower for BOS 200 mg/d vs PBO (1.63% vs 4.74%, respectively, 95% CI [0.93 to 5.27]; p<0.005). Gastrointestinal (GI) effects were dose-dependent for BOS; the overall safety profile, including GI toxicities, was consistent with the known profile of BOS.

Conclusions: BOS reduced the annual rate of kidney enlargement vs PBO in ADPKD pts, and the safety profile was consistent with the BOS label.

Funding: Pharmaceutical Company Support - Pfizer Inc

SA-PO1094
Low Osmolar Diet and Adjusted Water Intake for Vasopressin Suppression in ADPKD: A Randomized Controlled Trial Osama W. Amro,1,2 Jessica K. Paulus,2 Farzad Nourbary,1 Ronald D. Perrone.3 Nephrology, Tufts Medical Center, Boston, MA; 2Tufts Univ School of Medicine.

Background: Autosomal dominant polycystic kidney disease (ADPKD) affects 12.5 million persons worldwide. Vasopressin promotes disease progression.

Methods: This randomized trial examined the effect of combining a low osmolar diet and adjusted water intake on vasopressin as measured by change in plasma copeptin, and

underline represents presenting author/disclosure.
urinary osmolality in 34 ADPKD patients. Participants were randomized to receive a low osmolar diet (low sodium (1500 mg/day), low protein (0.8 gram/kg body weight) diet) followed by adjusted water intake to achieve a urine osmolality of ≥280 mOsm/L versus no intervention for two weeks.

**Results:** Change from baseline to two weeks between intervention and control groups was statistically significant for the primary outcome of copeptin and urinary osmolality (-3.86 ±1.3 pmol/L versus +0.39 ±1.2 pmol/L; p=0.009) and -167±264 mOsm/L versus +20.80 mOsm/L (0.007) respectively. Mean plasma copeptin and urinary osmolality declined from 6.2 ±0.5 to 5.3 ±2.5 pmol/L (p=0.3) and from 426 ±193 to 258 ±117 mOsm/L (p=0.003) respectively in the intervention group compared to a non-significant increase from 4.7 ±3.6 to 5.07±5.4 pmol/L (p=0.7) and from 329 ±159 to 349 ±139 mOsm/L (p=0.6) in the control group.

Total urinary solute decreased only in the intervention group and significantly differed between groups at week one (p=0.03) reducing mean water prescription from 3.2 to 2.6 liter/day.

**Conclusions:** We developed a step wise dietary intervention that led to significant reduction in vasopressin in ADPKD patients. Furthermore, this intervention led to reduction in water required for vasopressin suppression. Long-term studies are needed to determine if vasopressin suppression slows ADPKD progression.

**Funding:** Other NHI Support - Dr. Amro is supported by NIH 5T32DK007777 institutional training grant. This project was performed and Dr. Perrone were supported in part by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH), Grant Number UL1 TR001064.

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**SA-PO1095**

**A Phase 2, Double-Blind, Randomized Study of Fresolimumab or Placebo in Patients with Steroid-Resistant Primary Focal Segmental Glomerulosclerosis**

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**Background:** Steroid-resistant primary FSGS confers substantial risk of morbidity & progressive kidney failure. Fresolimumab (freso), a neutralizing mAb to all 3 isoforms of TGF-β, is a potential new treatment.

**Methods:** 36 pts with biopsy-proven nephrotic-range FSGS randomized to freso 1mg/kg (n=14) v 4mg/kg (n=12) v placebo (PL) (n=10) for D112, allowed immunosuppressives (IMM). IMM-patients with an eGFR >60 ml/min/1.73m² received a non-stereoid (NSI) IMM. All 7 remission (>50% Up/c decrease from BL to <3mg/mg): 3 pts, 1mg/kg; 2 pts, 4mg/kg; 1 pt, PL; 1 additional pt on 1mg/kg had steep & consistent Up/c decline from 17–4mg/mg. All 7 freso responders were Black/Hispanic. Mean Up/c changes at D112: -18.5% (1mg/kg, PL; 1 additional pt on 1mg/kg had steep & consistent Up/c decline from 17–4mg/mg. All 7 freso responders were Black/Hispanic. Mean Up/c changes at D112: -18.5% (1mg/kg, +10.5% (4mg/kg, P=0.008), +10.5% (4mg/kg, P=0.02), +9.0% (PL, P=0.91). eGFR showed nonsignificant trend for stability in freso v decline in PL. Freso was generally well tolerated with no significant difference in AEs in low v high doses.

**Conclusions:** In steroid-resistant FSGS, freso may be associated with proteinuria remission. Black & Hispanic pts may have higher response rates. Freso merits continued evaluation in FSGS.

**Funding:** Pharmaceutical Company Support - Genzyme-Sanofi

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**SA-PO1096**

**Effects of Sustained-Release Beraprost Sodium in Patients with Primary Glomerular Disease or Nephrosclerosis: The CASSIOPEIR Study**

**Toshiro Fujita,1 Xueqing Yu,2 Suhyngwon Kim,3 Hidetomi Ogita,3 Hajimu Kurumurata,4 Takashi Kiriyama,5 ’The Univ of Tokyo, Tokyo, Japan; ’The First Affiliated Hospital, Sun Yat-sen Univ, Guangzhou, Guangdong, China; ’Seoul National Univ Hospital, Seoul, Korea; ’Saitama Medical Univ, Saitama, Japan; ’The Univ of Toyama, Toyama, Japan; ’Toray Industries, Inc, Tokyo, Japan; ’Astellas Pharma Inc., Tokyo, Japan.

**Background:** No single treatment, except RAS inhibitors, can delay progression of CKD. TRK-100STP, a sustained-release tablet of an orally-active prostacyclin analogue, beraprost sodium, is suggested to suppress worsening of renal filtration function. We aimed to demonstrate superiority of TRK-100STP over placebo in patients with CKD, either as primary glomerular disease or nephrosclerosis; determine the recommended dose of TRK-100STP; and evaluate its safety profile.

**Methods:** We performed a randomized, double-blind, placebo-controlled, parallel-group comparative study at 160 sites in seven Asian-Pacific countries and regions (CASSIOPEIR: CRF Asian Study with Oral PG2; Derivative for Evaluating Improvement of Renal Function). Patients entered a run-in phase with oral administration of placebo twice daily for two to eight weeks. Patients meeting the inclusion/exclusion criteria at the end of the run-in period (n=892) were randomized to TRK-100STP 120 mg, TRK-100STP 240 mg, or placebo for a treatment period of two to four years. The primary efficacy endpoint was the time to first occurrence of a renal composite endpoint: doubling of Scr or occurrence of end-stage renal disease. ClinicalTrials.gov identifier: NCT01090037.

**Results:** No significant differences were evident observed in renal composite endpoints between TRK-100STP and placebo (2-sided 5% significance level, P=0.5674). The overall incidence of adverse events and adverse drug reactions was comparable between the two treatment arms.

**Conclusions:** TRK-100STP did not demonstrate superiority over placebo, and the recommended therapeutic dose for patients with CKD either primary glomerular disease or nephrosclerosis was not determined. However, no findings raised safety concerns in the comparison between TRK-100STP and placebo.

**Funding:** Pharmaceutical Company Support - Toray Industries, Inc., Astellas Parma Inc.

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**SA-PO1097**

**Corticosteroid Monotherapy versus Combined Immunosuppression in IgA Nephropathy: Insights from the STOP-IgAN Trial**

**Jürgen Floege,1 Thomas Rauen,1 Frank Eitner,1 Christina Fitzner,2 Ralf-Dieter Hilger,2 ’Nephrology, RWTH Aachen Univ, Aachen, Germany; ’Biostatistics, RWTH Aachen Univ, Aachen, Germany; ’Bayer AG, Wuppertal, Germany; ’For the STOP-IgAN Investigators.

**Background:** In high-risk IgA nephropathy (IgAN) the value of immunosuppression is controversial.

**Methods:** We recently reported a randomized, controlled trial in IgAN patients (STOP-IgAN trial). Following 6 months of optimized supportive treatment 162 trial participants, who still displayed a proteinuria ≥0.75 g/d, entered a 3 year study phase and were randomized to continue on supportive therapy (SUT) or to receive additional immunosuppression (IMM). IMM-patients with an eGFR ≤60 ml/min/1.73 m² received a 6-month corticosteroid monotherapy (“Pozzi-protocol”). Patients with an eGFR of 30 to
59 ml/min/1.73m² received cyclophosphamide for 3 months, followed by azathioprine, plus oral prednisolone (“Ballardie protocol”). Primary endpoints were (i) full clinical remission (proteinuria < 0.2 g/g and eGFR loss of < 5 ml/min) and (ii) eGFR loss >15 ml/min from baseline to trial end.

Results: Here we report a secondary analysis of the two IMM subgroups versus corresponding SUP patients matched for eGFR. The intention-to-treat (ITT) analysis assuming a worst-case scenario at 3 years is shown in the table.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>GFR &gt;60 ml/min/1.73m²</th>
<th>GFR 30-59 ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMM vs. SUP (n = 55 vs. 54)</td>
<td>OR 5.23 (95%-CI 1.29-21.15), p=0.020</td>
<td>OR 2.77 (95%-CI 0.38-22.29), p=0.319</td>
</tr>
<tr>
<td>IMM vs. SUP (n = 27 vs. 26)</td>
<td>OR 0.65 (95%-CI 0.27-1.56), p=0.333</td>
<td>OR 1.62 (95%-CI 0.49-5.61), p=0.428</td>
</tr>
</tbody>
</table>

eGFR loss >15 ml/min

Patients treated with the Pozzi protocol had a transient decrease in proteinuria after 12 months and significantly less microhematuria at trial end compared to matched SUP patients. In the group with the low eGFR range, there were no significant differences between both arms. Compared to supportive care, more patients receiving immunosuppression developed severe infections, impaired glucose tolerance and weight gain in year one.

Conclusions: Our secondary analyses provide little evidence for a stabilization of renal function with immunosuppression in the group with an eGFR >60 ml/min and no evidence for a benefit in patients with a lower eGFR.

Funding: Government Support - Non-U.S.

SA-PO1098
A Randomized Trial of Rituximab in Advanced IgA Nephropathy
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Background: IgA nephropathy (IgAN) frequently leads to progressive renal dysfunction. Present immunosuppressive treatment remains uncertain in terms of benefit and risks side effects. B cells are an attractive target in IgAN so we performed a pilot trial of rituximab in subjects at high risk of progression.

Methods: Patients with biopsy proven IgAN, more than 1 g/d of proteinuria despite RAASi (or 0.5 g/d if on dual RAASi), well controlled blood pressure (BP) and eGFR <90ml/min were randomized to 1 year of rituximab therapy (4g total) vs ongoing BP control, fish oil and use of RAASi. They were followed for B cell depletion, effects on proteinuria and changes in eGFR. Safety signals were also followed.

Results: 14 patients were randomized. Baseline serum creatinine was 1.5±0.5 mg/dl and proteinuria was 2.1, 0.6-5.5 g/dl. There was no change in BP during the study. Treatment with rituximab resulted in significant B cell depletion and was generally well tolerated. There was no change in renal function during the study in either group. Rituximab treatment had no significant effect on proteinuria compared to baseline or control patients, and 3/17 patients in each group experienced a ≥50% reduction in proteinuria during the study.

Figure 1: Proteinuria (A) Control vs. (B) Rituximab Groups. The heavy weight red line represents median data.

Conclusions: In this small study, rituximab therapy had no influence on renal function or proteinuria in subjects with advanced disease due to IgA nephropathy. There were numerically greater reductions in proteinuria, but this did not reach significance. Few patients had substantial responses in either group. These results do not support the use of rituximab as treatment for patients with IgA nephropathy.

Funding: Pharmaceutical Company Support - Roche, Inc.

SA-PO1099
Establishing Endpoints for Lupus Nephritis Clinical Trials: Progress by the Kidney Health Initiative/Lupus Nephritis Trials Network Collaboration
Brad H. Rovin,1 Meggan Mackay,2 Joanna Stein,3 Kenneth Kalunian,4 Martin L. Lesser,5 Melissa West 5 Ohio State Univ;3 Feinstein Inst;3 Univ Calif San Diego;4 Univ Calif San Francisco;3 American Society of Nephrology.

Background: There are no universally accepted endpoints for lupus nephritis (LN) clinical drug trials. To obtain approval of new therapies a uniform endpoint that can be applied to future LN trials is needed. The optimal endpoint is a short-term measurement that accurately reflects long-term kidney survival. The present work was undertaken to define LN trial endpoints.

Methods: Clinical data at LN flare (baseline) and during serial follow-up (minimum 22 months) from 751 patients were analyzed. Clinical variables at baseline and after 6 and 12 months were tested as predictors of adverse long-term renal outcomes, in this case time to new chronic kidney disease (CKD), defined as a sustained increase in serum creatinine (Scr) ≥30%. Multivariable Cox regression analysis was used to model time to CKD.

Results: After accounting for missing data 507 patients were included in the final analysis. This cohort was 89% female, 56% White, 20% Asian and 14% Black. The average baseline serum creatinine was 1.2±0.7 mg/dl, proteinuria was 4.1±3.4 g/d, and eGFR by CKD-MDRD was 81.35 ml/min. Median follow-up was 42 months (range: 22-147 months). By univariate analysis urine RBCs, race, complement C3, C4, eGFR and proteinuria were potential significant predictors of time to CKD. By multivariate modeling the significant predictors of future CKD were: Scr at 12 months (p=0.0005, Hazard Ratio (HR) 1.8 (95%-CI 1.3-2.5)); proteinuria at 12 months (p=0.0001; HR 1.6 (1.3-1.8)); and an increase in eGFR>10% from baseline to 12 months compared to no change in eGFR (p=0.0001; HR 0.4 (0.3-0.6)).

Conclusions: We have identified 3 highly significant predictors of time to CKD in LN patients that can be measured during the first 12 months of treatment for flare. These were developed into a composite endpoint for future LN therapeutic trials. Unexpectedly, small improvements in eGFR appear to predict renal survival. Also, because urine RBCs do not appear to predict time to CKD, it may be possible to exclude urinalysis as an endpoint component in future clinical trials.

Funding: Private Foundation Support

SA-PO1100
Grazoprevir (GZR)/Elbasvir (EBR) Treatment of Hepatitis C Virus (HCV) Infection in Patients with Chronic Kidney Disease Stage 4/5: Final Results of the C-SURFER Phase 3 Study
David Roth,1 Annette Bruchfeld,2 Paul Martin,1 David R. Nelson,2 Marcelo Silva,4 Howard Monsour,1 Laurent Alric,3 Shuyan Wan,1 Beth Jackson,1 Bach-Yen Nguyen,1 Janice Wahl,1 Eliav Barr,1 Wayne L. Greaves.7 Univ of Miami, Miami, FL; Karlolinstit Ut, Stockholm, Sweden;7 Univ of Florida, Gainesville, FL; Hospital Univ Austral, Pilar, Buenos Aires, Argentina;7 Houston Methodist Hospital, Houston, TX;5 Hôpital de Purpan, Toulouse, France;3 Merck & Co., Inc., Kenilworth, NJ.

Background: Limited options are available for treating HCV infection in patients with advanced kidney disease. C-SURFER is the first randomized, placebo-controlled phase 3 study to evaluate an all-oral, ribavirin-free regimen in CKD 4/5 patients.

Methods: 224 patients with HCV genotype (G1 and CKD 4/5 ± hemodialysis (HD) were randomized to GZR/EBR 100/50mg (Immediate Treatment Group, ITG; n=111) or placebo for 12 weeks. Placebo subjects (deferred treatment group, DTC, n=113) received GZR/EBR after placebo therapy. 11 additional subjects received GZR/EBR with intensive pharmacokinetic (PK) sampling. The primary safety comparison was GZR/EBR vs. placebo. The primary efficacy endpoint, sustained virologic response (SVR) 12 weeks post-therapy in the ITG vs PK group, was reported previously. Here we report the final results, including data from subjects who received GZR/EBR after placebo.

Results: In the placebo-controlled phase, serious adverse events (AEs) occurred in 16 (14%) GZR/EBR and 17 (15%) placebo subjects; discontinuation due to an AE in GZR/EBR and placebo subjects was 0% and 4%. SVR12 in all subjects who received GZR/EBR was 94.6% (ITG) vs. 94.3% [115/122, DTG after placebo. 95.0% [96/101]). 12 subjects failed to attain SVR12: virologic relapse, n=3; discontinuation for AE, n=1; admin reason, n=8. Excluding subjects who discontinued for reasons unrelated to study drug, overall SVR12 was 98.6% (211/214). PK data indicate no need for dose adjustment in HD patients (geometric mean ratio [HD/non-HD] ranged from 0.67-0.85 for GZR and 1.43-1.67 for EBR).

Conclusions: Once-daily GZR/EBR for 12 weeks was highly effective with a low rate of adverse events in patients with advanced kidney disease and HCV G1 infection.

Funding: Pharmaceutical Company Support - Merck Sharp & Dohme Corp.
SA-PO1101

Long-Term (52-Week) Efficacy and Safety of ZS-9 in the Treatment of Hyperkaemia: Interim Results From a Phase 3 Open-Label, Multi-Center, Multi-Dose Maintenance Study

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Background: Hyperkalemia (HK) is a common and potentially lethal electrolyte disorder, often induced with the use of renin-angiotensin-aldosterone inhibitors (RAASi). Currently, the use of RAASi is prevented by HK and thus the potential for cardiac and renal protective effects of these agents is limited. In previous studies, ZS-9 (sodium zirconium cyclosilicate), a selective K+ ion trap, significantly lowered serum K+ and maintained normokalemia (NK) for up to 28 days. We present the results to date of the largest ever phase 3 trial examining the efficacy of ZS-9 in treating HK patients for up to 52wks.

Methods: ZS-9 (target N=750) is a multicenter, ongoing, open-label study evaluating ZS-9 treatment for 52wks in ambulatory pts with HK (K+ ≥5.1 mEq/L) with or without concurrent RAASi therapy. In the acute phase (AP), pts with HK received 10g ZS-9 TID over a 24-72hr period until NK (K+ <5.5 mEq/L) was achieved. Pts achieving NK were enrolled in a 52wk maintenance phase (MP) starting at 5g ZS-9 QD. There were no restrictions on diet and ZS-9 could be titrated to maintain NK. Primary outcomes were proportion of pts with mean K+ ≤5.1 mEq/L during AP and safety of ZS-9.

Results: To date, 583 pts with a mean baseline K+ of 5.6 mEq/L (15% ≥6.0 mEq/L) entered the study. Overall, 575 (99%) normalized K+ in AP and transitioned to the MP. To date, K+ was maintained at ≤5.1 and <5.5 mEq/L in 87% and 99% of patients, respectively. The incidence and severity of adverse events were similar to that of previous studies.

Conclusions: ZS-9 acutely reduced K+ levels in pts with HK and maintained NK for up to 52wks irrespective of RAASi use. ZS-9 may control HK, both emergent and long-term, while allowing continued use of cardio- and renoprotective RAASi.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.

SA-PO1102

Interleukin-1 Inhibition and Vascular Function in Patients with Chronic Kidney Disease (CKD): A Randomized Controlled Trial

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Background: Vascular endothelial dysfunction and increased arterial stiffness contribute to increased cardiovascular risk in CKD patients who exhibit chronic systemic inflammation. As chronic inflammation is a key mechanism contributing to vascular dysfunction, blocking inflammation may reduce cardiovascular risk in CKD.

Methods: In a two-site, double-blind trial, n=42 patients with stage 3-4 CKD were randomized to receive either the interleukin-1 (IL-1) trap rilonacept (subcutaneous injection; loading dose of 320 mg followed by 160 mg/wk) or placebo for 12 weeks. All patients were receiving optimal treatment of hypertension, diabetes, and/or hypercholesterolemia, with 64% and 62% receiving a statin and an ACE inhibitor or ARB, respectively. The co-primary endpoints were change in aortic pulse-wave velocity (aPWV) and transitioned to the MP. To date, K+ was maintained at ≤5.1 and <5.5 mEq/L in 87% and 99% of patients, respectively. The incidence and severity of adverse events were similar to that of previous studies.

Conclusions: ZS-9 acutely reduced K+ levels in pts with HK and maintained NK for up to 52wks irrespective of RAASi use. ZS-9 may control HK, both emergent and long-term, while allowing continued use of cardio- and renoprotective RAASi.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.

SA-PO1103

Abstract Withdrawn

SA-PO1104

Impact of Vitamin D Supplementation on Endothelial and Vascular Function in Patients with Chronic Kidney Disease: A Randomized, Double Blind, Placebo-Controlled Trial

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Background: Vitamin D deficiency is associated with mortality in CKD patients. We investigated the effect of Vitamin D supplementation on endothelial and vascular function in patients with non-diabetic CKD stage 3-4.

Methods: In a prospective, randomized, double blind, placebo-controlled trial, 120 patients with non-diabetic CKD stage 3-4 and vitamin D deficiency [serum 25(OH)D <20ng/ml] aged 18-70 years were randomized (1:1) to receive either two directly observed oral doses of 300 IU of cholecalciferol at 0 and 8 weeks or matching placebo. The pre-specified primary outcome was 40% change in endothelium dependent brachial artery flow mediated dilation (FMD) at 16 weeks. Secondary outcome measures included changes in pulse wave velocity (PWV), augmentation index (AI), and serum biomarkers.

Results: Baseline FMD was identical in both arms (7.6±2.24% vs 7.8±2.34%). Intervention arm showed a significant increase in serum 25(OH)D (+ 24.9 ng/ml, 95% CI: 21.8 to 28.06, p=0.0001), and the number of subjects meeting the primary end point (70% vs 5%, p=0.0001). FMD change was 5.42% (95% CI: 4.44 to 6.40%) in the intervention arm and -0.72% (95% CI: -0.30 to -0.58%) in placebo arm. Intervention led to favorable changes in PWV (-0.94 m/s, 95% CI: -1.30 to -0.58, p=0.0001), E-selectin (3.68 mg/ml, 95% CI: 8.1 to 0.7 p=0.01), IL-6 (-2.96 to 0-p=0.01), FGF-23 (-14.7 pg/ml, 95% CI -28.5 to -1.0 p=0.036) and 1,25(OH)D (+ 15.5 pg/ml, 95% CI: 5.4 to 25.5, p=0.003). These did not change significantly in the control group. No changes were observed in AI, sPWV and hs-CRP in either group.

Conclusions: In non-diabetic patients with stage 3-4 CKD and vitamin D deficiency, vitamin D supplementation leads to improvement in endothelial function, markers of inflammation and arterial stiffness.

Funding: Government Support - Non-U.S.

SA-PO1105

Effect of Cholecalciferol versus Calcitriol on Vascular Endothelial Function in CKD: A Randomized Active-Controlled Trial

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Background: Epidemiological studies have shown that vitamin D is associated with decreased cardiovascular morbidity and mortality, but effect of vitamin D administration on patient outcomes in chronic kidney disease (CKD) are lacking. We conducted a prospective, double-blinded, randomized trial to determine the effects of oral cholecalciferol vs. calcitriol on vascular endothelial function over 24 weeks in patients with CKD stage 3-4.

Methods: 128 patients with CKD stage 3-4 (estimated GFR 15-44 ml/min/1.73m²) with vitamin D deficiency, defined as serum 25-hydroxyvitamin D level (25(OH)D) <30 ng/mL, were randomly assigned to receive either cholecalciferol (4000 IU daily x 4 weeks then 2000 IU daily x 20 weeks) or calcitriol (0.25 mcg daily x 4 weeks then 0.5 mcg daily x 20 weeks). The primary endpoint was change in brachial artery flow mediated dilation (FMDa) over 24 weeks. Secondary endpoints included changes in parameters of mineral bone disease and plasma concentrations of inflammatory cytokines (C-reactive protein and interleukin-6).

Results: 115 patients completed the study. The mean (SD) age and eGFR was 58.1 ± 12.4 years and 33.1 ± 10.2 ml/min/1.73m², respectively. In the cholecalciferol group, mean 25(OH)D levels increased from 22.7 ± 7.5 ng/mL to 33.5 ± 7.9 ng/mL. There was no change in 25(OH)D levels in the calcitriol group. Parathyroid hormone levels decreased significantly in the calcitriol group compared to the cholecalciferol group (p=0.001). At 24 weeks, the change in FMDa did not differ significantly between treatment groups (cholecalciferol group -0.72%, 95% CI -1.97 to 0.54 vs calcitriol group 0.29%, 95% CI -0.72 to 1.29, p=0.44). There was no significant change in C-reactive protein or interleukin-6 concentrations between the two groups. Episodes of hypercalcemia were more frequent in the calcitriol group (n=4) compared with the cholecalciferol group (n=1).

Conclusions: Twenty-four week therapy with cholecalciferol or calcitriol did not improve vascular endothelial function or reduce inflammation in patients with CKD.

Funding: NIDDK Support
SA-PO1106

Vitamin D Receptor Activation and Dietary Sodium Restriction to Reduce Residual Albuminuria in Chronic Kidney Disease

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Background: Reduction of residual albuminuria during single-agent RAAS-blockade is associated with improved cardioress outcomes in CKD. Both vitamin D receptor activators (VDRA) and dietary sodium restriction reduce residual albuminuria. Previous data suggested that sodium restriction is not required for optimal albuminuria reduction by VDRA. We studied the individual and combined effects of paricalcitol and sodium restriction on residual albuminuria during optimally dosed ACEi in CKD.

Methods: In a multi-center, randomized, placebo-controlled cross-over trial, 45 patients with non-diabetic CKD stage 1-3 and residual albuminuria >300 mg/24h despite ramipril 10 mg/d and BP ≤140/90 mmHg were treated during four 8-week periods with paricalcitol (PARI, 2 µg/day) or placebo (PLAC), each combined with a low (LS, 2.5 gr Na+/d) or regular sodium (RS, 4 gr Na+/d) diet, in random order. Linear mixed-effect models for repeated measurements were used to determine treatment effect.

Results: In the intention-to-treat analysis, albuminuria was 1,060 [778 to 1,443] (geometric mean [95% CI]) mg/24h (-12.5% [-26.0% to 26.3%] vs. RS+PLAC, P=0.2). LS+PARI reduced albuminuria to 717 [512 to 1,005] mg/24h (-25.4% [-52.6% to -2.3%] vs. RS+PLAC, P=0.001). LS+PARI provided the strongest albuminuria reduction to 683 [502 to 929] mg/24h (-31.7% [-55.0% to -0.9%], P=0.001 vs. RS+PLAC, although the additional reduction by PARI beyond the effect of LS was non-significant (P=0.6). However, in a per protocol analysis (≥95% compliance, N=34) PARI did reduce residual albuminuria beyond the effect of LS (P=0.04).

Conclusions: The combination of paricalcitol and moderate dietary sodium restriction provided the strongest reduction of residual albuminuria during optimal ACEi; the effect was mainly driven by sodium restriction. Our findings underline the relevance of sodium restriction, possibly combined with paricalcitol, to optimize albuminuria reduction.

SA-PO1107

Vascular Function and Uric Acid Lowering via Allopurinol in Stage III CKD: Results of a Double-Blinded Randomized Placebo-Controlled Study

Diana I. Jalal,1 Emily Decker,1 Loni J. Perrenoud,1 Nina Bispham,2 Tapan Mehta,2 Gerard John Smits,3 Richard J. Johnson. 1UMC Groningen, 2VUMc Amsterdam, 3ZGT Almelo.

Background: Observational studies suggest that asymptomatic hyperuricemia associates with vascular disease in chronic kidney disease (CKD). A recent study suggested that lowering serum urate with allopurinol improves endothelial function in elderly adults with stage III CKD. It remains unknown if lowering serum urate improves endothelial function in adult subjects with stage III CKD.

Methods: 80 adult subjects (18-70) years of age with stage III CKD and asymptomatic hyperuricemia (>7 mg/dL in men and >6 mg/dL in women) were randomized to receive placebo or allopurinol (100 mg tablets) for 12 weeks. The study was double-blinded and subjects were instructed to take 1 tablet for 1 week, 2 tablets for another week, and 3 tablets thereafter. Changes (from baseline) between both groups were compared by Wilcoxon rank-sum test.

Results: No significant differences existed between both groups at baseline. After 12 weeks, allopurinol lowered serum urate significantly. FMD increased in the allopurinol group compared to placebo; but this was not statistically significant. NMD increased with allopurinol but decreased with placebo; p value = 0.14. These data are shown in Table 1. There were no significant differences between allopurinol and placebo for systolic or diastolic blood pressure, markers of inflammation, or markers of oxidative stress. 10 subjects withdrew from the study. A few adverse events were noted in both groups including 1 gout attack in each group. 1 subject died during the study due to a cardiac event.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Allopurinol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Urate(mg/dL)</td>
<td>0.05(1.54)</td>
<td>-3.24(1.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FMD (%change)</td>
<td>0.16(4.05)</td>
<td>0.91(3.9)</td>
<td>0.47</td>
</tr>
<tr>
<td>NMD (%change)</td>
<td>-1.29(5.33)</td>
<td>0.97(6.05)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Conclusions: Allopurinol effectively and safely lowered serum urate in adults with stage III CKD and asymptomatic hyperuricemia but this did not improve endothelial function significantly. There was tendency towards improved NMD suggesting that hyperuricemia may negatively impact vascular smooth muscle function in stage III CKD.

Funding: NIDDK Support

SA-PO1108

Podocyturia Is an Earlier and Superior Predictor of Cardiovascular Outcomes Than Is Albuminuria

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Background: Increased urinary albumin excretion rate (AER), a predictor of cardiovascular events, results from abnormally increased albumin filtration accompanying injury to glomerular endothelial and epithelial cells (“podocytes”). Since AER is modified by renal proximal tubule albumin filtration, we hypothesized that urinary podocyte shedding, podocyturia, would be a more relevant and earlier biomarker of endothelial injury (and CVD) than moderate albuminuria.

Methods: In 106 Type II diabetic subjects (mean age: 46/60 men/women) with normal AER (<2.26 mg/mmol (20 µg/mg) creatinine) and free of overt cardiovascular disease (CVD) were enrolled. AER and podocyte-specific proteins (podocin and nephrin) mRNA were measured at baseline (visit 1), 3-4 years later (visit 2) and at 7 years (visit 3). Development of cardiovascular diseases VD - defined as coronary disease, cerebrovascular disease and/or peripheral vascular disease (can be removed to fit words counting) was collected as outcome. 7-year Kaplan-Meier time-to-event (log rank) data were compared in baseline biomarker tercile groups (low, intermediate, high).

Results: All three biomarkers increased significantly between visits (P<0.001). ARExhibit similar time to CVD (P=0.127), which was in contrast with the step-wise and substantial increase in CVD events with increasing podocin and nephrin levels (P<0.001). Considering all three biomarkers as continuous factors, the covariate-adjusted hazard ratios (95% confidence intervals) [HR] were highest for podocin mRNA [HR=15.9 (6.1-41.8); p<0.001], intermediate for nephrin mRNA [HR=7.61 (3.75-15.5); p<0.001] and lowest for ARE [HR=1.17 (1.01-1.36); P=0.041].

Conclusions: Compared to traditional ARE, podocyturia predicts more accurately and a longer time point the presence of silent systemic vascular injury, that manifests as overt cardiovascular events.

SA-PO1109

Empagliflozin Reduces Microalbuminuria and Macroalbuminuria in Patients with Type 2 Diabetes

David Cherry,1 Soren Sogaard Lund,1 Bruce A. Perkins,1 Per-Henrik Groop,2 Mark E. Cooper,3 Stefan Kaspers,4 Susanne Crowe,5 Hans-Juergen Woerle,6 Maximilian von Eynatten.7 1Toronto General Hospital, Univ of Toronto, Canada; 2Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 3Mount Sinai Hospital, Univ of Toronto, Canada; 4Univ of Helsinki and Helsinki Univ Hospital, Folkhalsan Research Center, Helsinki, Finland; 5Baker IDI Heart and Diabetes Inst, Melbourne, Australia.

Background: Reductions in HbA1c, systolic blood pressure (SBP), and weight with the highly selective SGLT2 inhibitor empagliflozin in patients with type 2 diabetes (T2D) may favorably impact albuminuria.

Methods: Using data pooled from 5 Phase III, randomized clinical trials, we assessed the effect of empagliflozin 10 or 25 mg for 24 weeks on urine albumin to creatinine ratio (UACR) in patients with T2D and prevalent microalbuminuria (UACR 30–300 mg/g; n=636) or macroalbuminuria (UACR >300 mg/g; n=215) at baseline.

Results: Empagliflozin reduced UACR vs placebo in patients with T2D and microalbuminuria (-32%; p<0.001) or macroalbuminuria (-41%; p<0.001) after controlling for baseline log (UACR), HbA1c, SBP, estimated glomerular filtration rate (MDRD), region, study and treatment (Figure). Adjusted mean (SE) changes in HbA1c, weight, SBP and diastolic BP with empagliflozin vs placebo were -0.50 (0.07) %, -1.6 (0.2) kg, -4.4 (1.1) mmHg and -2.3 (0.6) mmHg, respectively, in patients with microalbuminuria (all p<0.001), and -0.53 (0.13) %, -1.8 (0.4) kg, -6.3 (2.0) mmHg and -2.2 (1.1) mmHg, respectively, in patients with macroalbuminuria (all p<0.05). Linear regression analyses showed that changes in HbA1c, weight and SBP accounted for a maximum of half the UACR-lowering effect.

Conclusions: Empagliflozin reduced microalbuminuria and macroalbuminuria in patients with type 2 diabetes (T2D) and may favorably impact albuminuria.

Funding: NIHDK Support

Underline represents presenting author/disclosure.
SA-PO1110
Vadadustat, a Novel Oral Treatment for Anemia of Chronic Kidney Disease, Maintains Stable Hemoglobin Levels in Dialysis Patients Converting from Erythropoiesis-Stimulating Agents

Methods: A multi-center, open-label, 16-week trial was designed to assess Hb response, safety, and tolerability of vadadustat. The trial enrolled 94 hemodialysis patients (Hb 9 - 12 g/dL), who were maintained on erythropoiesis-stimulating agents (ESAs) prior to study entry. Patients were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300 mg once daily (QD); 450 mg QD; or 450 mg three times weekly (TIW). The primary entry. Patients were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300 mg once daily (QD); 450 mg QD; or 450 mg three times weekly (TIW). The primary

Vadadustat safely and effectively maintained Hb levels in dialysis patients who were converted from injectable ESAs.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim and Eli Lilly and Company

Conclusions: SGLT2 inhibition with empagliflozin reduced UACR by >30% in patients with T2D and prevalent microalbuminuria or macroalbuminuria, independent of its known metabolic and hemodynamic effects.

SA-PO1112
Monitoring in Dialysis (MiD) Study: Exploring the Timeline and Etiology of Increased Arrhythmias in Hemodialysis (HD) Patients

Methods: We present initial results from 3 ongoing open label ascending dose studies of TARGT in patients with anemia due to CKD undergoing either Hemo or Peritoneal Dialysis.

Results: Thus far 14 patients were enrolled in all protocols. Follow up is ongoing with the first implanted patient being followed with stable EPO secretion and stable Hb for over 14 months from a single implantation without the need for rHuEPO or blood transfusion. Concentrations of serum EPO levels revealed significantly lower Cmax compared to rHuEPO and an order of magnitude less overall EPO exposure as calculated by Area Under the Curve which may confer significant clinical benefit. No treatment related serious adverse events have been reported.

Conclusions: TARGT™ is a promising novel therapy for the treatment of anemia of CKD and potentially for other protein deficient diseases.

Funding: Pharmaceutical Company Support - Medgenics Inc.

SA-PO1111
Autologous Erythropoietin Production by the TARGT Gene Therapy Platform Maintains Stable Hb for 6-12 Month in ESRD Patients without the Need for ESA Administration

Background: Recombinant human erythropoietin (rHuEPO) administration to iron replete patients corrects anemia in most patients with ESRD, but doses result in supra-physiological peak serum concentration (Cmax) of EPO that may cause thromboembolic complications. The Transduced Autologous Restorative Gene Therapy system (TARGT™) is an ex-vivo gene therapy, providing autologous, continuous protein therapies at physiological ranges that was used encoding for the human erythropoietin gene (TARGT™) for these studies. Patient dermal tissue biopsies (MOs) are transduced with a Helper-Dependent Adenoviral Vector containing the EPO gene and then re-implemented subcutaneously to deliver the required EPO dose.

Methods: We present initial results from 3 ongoing open label ascending dose studies of TARGT in patients with anemia due to CKD undergoing either Hemo or Peritoneal Dialysis.

Results: Thus far 14 patients were enrolled in all protocols. Follow up is ongoing with the first implanted patient being followed with stable EPO secretion and stable Hb for over 14 months from a single implantation without the need for rHuEPO or blood transfusion. Comparative analysis of serum EPO levels revealed significantly lower Cmax with TARGT compared to rHuEPO and an order of magnitude less overall EPO exposure as calculated by Area Under the Curve which may confer significant clinical benefit. No treatment related serious adverse events have been reported.

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Funding: Pharmaceutical Company Support - Medgenics Inc.

Mean Hb levels (g/dL) in Modified Intent-To-Treat (MITT) population

<table>
<thead>
<tr>
<th>Mean Hb levels (g/dL) in Modified Intent-To-Treat (MITT) population</th>
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<th>Baseline</th>
<th>Week 7/8</th>
<th>Week 15/16</th>
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<td>10.4</td>
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<td>10.5</td>
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One subject in the 300mg QD cohort had a single Hb excursion to 13.1 g/dL. Adverse events were balanced across the 3 cohorts. Serious adverse events (SAEs) were reported in 13 subjects (13.8%), which was within the expected range (13 – 17 subjects). No drug-related SAEs, nor deaths, were reported.

Conclusions: Vadadustat is a novel, oral agent that stimulates erythropoiesis by stabilizing hypoxia-inducible factor (HIF). Prior studies in patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) have shown that vadadustat results in metabolic and hemodynamic effects. The trial enrolled 94 hemodialysis patients (Hb 9 - 12 g/dL), who were maintained on erythropoiesis-stimulating agents (ESAs) prior to study entry. Patients were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300 mg once daily (QD); 450 mg QD; or 450 mg three times weekly (TIW). The primary

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Results: Vadadustat maintained stable Hb levels in all 3 dose cohorts during the 16 week treatment period following conversion from ESA.

Mean Hb levels (g/dL) in Modified Intent-To-Treat (MITT) population

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Results: Vadadustat maintained stable Hb levels in all 3 dose cohorts during the 16 week treatment period following conversion from ESA.
Conclusions: These data establish linkages between intra-dialytic CSA and the long interdialytic period, and also identify a unique interaction between fluid removal and K in the generation of RCA. This suggests for the first time, that future data driving targeted of these parameters might reduce CA and potentially SCF in HD pts.

Funding: Pharmaceutical Company Support - Medtronic

SA-PO1113

The Occurrence of Cardiac Arrhythmias in Hemodialysis Patients is Linked to the Hemodialysis Procedure and to Electrolyte Abnormalities as Recorded by Implantable Loop Recorders

Christian Combe, 1 Antoine Benard, 1 Hélène Savel, 1 F. Sacher, 1, 2 CHU & Univ: Bordeaux, Bordeaux, France; 2 Rhythmical Study Group.

Background: Sudden cardiac death (SCD) is the most common mode of death among hemodialysis (HD) patients (pts). Little is known about the terminal arrhythmic events in these pts. Our objective was to identify the mechanisms which may lead to SCD in HD pts by using an implantable loop recorder (ILR, Reveal XT®, Medtronic).

Methods: Pts from 9 HD centers have been included in the study. Continuous monitoring of the cardiac rhythm has been performed using the remote monitoring capability of the ILR device (CardiLink®). Clinical, biological, and technical HD parameters and medications have been recorded for at least 1 year. General joint frailty model for recurrent event data were used to analyze associations between these parameters and the occurrence of cardiac rhythm events.

Results: 72 pts (65 18±6.6 yrs, 52M) have been included. Causes of ESRD were diabetes (n=32) and hypertension (n=19). 22 pts had an ischemic cardiomyopathy. In multivariate analyses, the occurrence of conduction abnormalities (n=64) was associated to diabetes (n=32) and hypertension (n=19). 22 pts had an ischemic cardiomyopathy. In SA-PO1114

Abstract Withdrawn

SA-PO1115

Comparison of the Efficacy and Safety of Intravenous (IV) Etecalcetide (AMG 416) and Oral Cinacalcet (CIN) in Patients on Hemodialysis (HD) with Secondary Hyperparathyroidism (sHPT)

Kevin J. Martin, 1 Geoffrey A. Block, 2 Sunifa Cheng, 1 Bastian Dehmel, 3 Reshma Kewalramani, 3 David M. Spiegel, 4 Hao Wang, 1 Glenn Matthew C terrct, 1 St Louis Univ SOM, St Louis, MO; 2 Denver Neph, Denver, CO; 3 Amgen; 4 Relypsa.

Background: Approximately 40% of US hemodialysis (HD) patients experience moderate-to-severe itching, which negatively affect their mental and physical health (e.g., sleep loss, depression, higher antibiotic and cytotoxic side effect and increased mortality). The etiology of this condition is likely multi-factorial, including immune system dysfunction and imbalance of mu/kappa endogenous opioids. CR845 is a novel and well-tolerated kappa opioid receptor (KOR) agonist with limited central nervous system entry, thereby preferentially activating peripheral KOR on immune and skin cells and reduces itch.

Methods: In this Phase 2 double-blind, randomized (1:1), placebo-controlled clinical study, 65 prevalent US HD patients with persistent (~5 years) moderate-to-severe pruritus (baseline V AS ~68 mm, 0=no itch; 100 mm =worst itch) were treated with 1 mcg/kg intravenous CR845 or placebo following each HD session for 2 weeks. Antihistamines were discontinued 1 week prior to the study.

Results: The primary endpoint was VAS change in worst itch intensity from Baseline to Days 1-15, with a significant difference in itch intensity between placebo and CR845-treated patients (p<0.01). CR845-treated patients had a 50% mean reduction in itch intensity from baseline. The 1st secondary endpoint was also met with a significant improvement in Skindex-10, a validated patient-reported outcome measure of pruritus-related quality of life (p <0.003). Furthermore, a trend for a sleep improvement was observed (SLEEP).

Conclusions: Short-term treatment with CR845 significantly reduced itch intensity and improved quality of life in HD patients with moderate-to-severe pruritus. Thus, CR845 appears to have substantial potential to alleviate the symptoms and consequences of this frequently incapacitating condition for which existing treatments have often provided little or no relief. These data also support the opioid/immune etiology of this condition.

Funding: Pharmaceutical Company Support - Cara Therapeutics, Inc.
The ASSertID Study: Feasibility Randomised Controlled Trial of Drug Treatment for Depression in Patients on Haemodialysis

Ayan Gunuguri,1,2 Michael K. Almond,3 Joseph Chilcot,4 Andrew Davenport,5 Clara Day,2 Naomi Fineberg,2,3 Karin Friedli,6 Benjamin Spencer,1 David Wellsted,1 Ken Farrington,1 1East & North Hertfordshire NHS Trust, United Kingdom; 2Univ of Hertfordshire, United Kingdom; 3Hertfordshire Partnership Univ NHS Trust, United Kingdom; 4Southend Univ Hospitals NHS Trust, United Kingdom; 5King’s College London, United Kingdom; 6Royal free London NHS Trust, United Kingdom; 7Univ Hospitals Birmingham NHS Trust, United Kingdom.

Background: Major Depressive Disorder (MDD) is common in patients on Haemodialysis (HD) but there is little evidence of benefit from antidepressants. Hence we undertook a multicentre feasibility Randomised Controlled Trial (RCT) of sertraline versus placebo.

Methods: A screening phase identified patients with Beck Depression Inventory (BDI-II) score ≥16. Those meeting eligibility criteria, underwent psychiatric assessment (Mini International Neuropsychiatric Interview). Consenting patients with mild to moderate MDD and Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥18 were randomised to sertraline or placebo. Follow-up by study psychiatrist/week 2, month 2, 4 and 6 and monthly by study nurses. Initial dose was 50 mg with titration to 100 mg if required.

Results: Of 1355 patients approached, 715 consenting for screening. BDI-II ’16 was present in 231(32.3%), 58 (25.1%) were ineligible due to current treatment for MDD. Sixty-three underwent psychiatric assessment. MDD was diagnosed in 37; 30 consented to the RCT (mean age 61±15; 71% male; 60% white). Twenty-one (70%) completed the trial, 8(15) on sertraline and 13(25) on placebo. Over 6 months, BDI-II and MADRS scores decreased ((17±6; t=3.001 and (20(±11.3, t=0.001 respectively). There was no reliable difference between the sertraline and placebo groups. Fewer on sertraline completed (6 withdrawals and one death versus 2 withdrawals on placebo (22±3.97, p=0.046)). There was a trend towards a greater fall in MADRS scores by month 2 on sertraline (effect size 0.37; lower bound 0).

Conclusions: This feasibility study is the largest RCT investigating the use of anti-depressants in HD patients with MDD. Similar significant improvement in MDD occurred over both groups. Recovery may have been quicker on sertraline.

The Effects of Normal Saline and an Acetate-Buffered Crystalloid Solution on Hyperkalemia in Deceased Donor Renal Transplantation: A Randomized Blinded Trial

Laura Elisabeth Harris, Peter F. Mount, Francesco L. Ierino, Laura Legendre, Stephen J. Chadban, J. Grinyo, Nizam Mamode, Gunnar Tufveson, Lionel Couzi, P. Riggoti, 1Y. Lebranthu, S. Sandrini, W. Marks. 1Hôpital Saint-Louis, Paris, France; 2Royal Free Hospital, London, United Kingdom; 3Hôpital Saint-Louis, Paris, France; 4Alexion Pharmaceuticals, Inc., Chesire, CT; The International Eculizumab Transplant Study Group.

Background: Complement activation by preformed DSA is the major mechanism of acute antibody-mediated rejection (aAMR) in sensitized, kidney transplant recipients (SKTR). In a previous interim study report, the C5 inhibitor eculizumab (Ec) appeared effective in preventing aAMR in deceased donor (DD) SKTR compared to historical controls. We now report 12-mo efficacy and safety data from a Sept 2015 update of this ongoing, open-label, single-arm, phase 3 clinical trial.

Methods: SKTR defined as current DSA->3000MF detected by SAB; or Br- or T-cell flow cytometric crossmatch <300 and ≤500 mean channel shift; or historical positive complement-dependent cytotoxicity crossmatch to donor HLA. All recipients received Ec 1200mg perioperative day (POD) 0 prior to reperfusion. 900mg on POD 1, 7, 14, and 28, and 1200mg at wks 5, 7, and 9. Recipients received Rabbit ATG for induction and corticosteroids, tacrolimus, and mycophenolate for maintenance immunosuppression. Plasmapheresis was not allowed following Post- transplant week 9. The primary composite endpoint was clinically significant, biopsy (bx)-proven aAMR grade II/III (Banff 2007, based on centrally read bx), graft loss, death, or loss to follow-up at 9wks. Graft and patient (pt) survival were estimated by K-M.

Results: 80 pts were transplanted (48 F, 32 M); median age 52y (range, 24–70). 7 of 80 SKTR had aAMR (8.8%) compared to 30% expected for historical controls. 11.8 SKTR met the 9wk composite primary endpoint based on local bx (13.8% [95% CI 7.1–23.3]). Graft survival at 6 and 12mwo was 93.7% and 88.7%, respectively; pt survival at 6 and 12mwo was 97.4%. SCR levels (mg/dL) at baseline, 1 and 12mwo were 7.43 (±2.51), n=79; 1.86 (±0.9), n=79; 1.86 (±0.9), n=79. (p=0.37)

Conclusions: Ec appeared to be effective in reducing aAMR in SKTR. Pt and graft survival and kidney function at 12mwo were similar to those expected for non-sensitized KET. Ec was well tolerated. Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

Impact of De Novo Donor Specific Antibodies on Graft Outcomes in Kidney Transplant Recipients following Early Switch from Calcineurin Inhibitor to Everolimus: Analysis of the ELEV ATE Trial

Johan W. De Fijter, Wolfgang Hubdass, Patricia M. Lopez, Peter Bernhardt, Zailong Wang, Frans Claas, Wolfgang Arns, Josep M. Cruzado, Markus van der Giet.

Background: Development of de novo donor specific HLA-antibodies (dnDSA) after kidney transplantation (KTx) is associated with an increased risk of antibody-mediated rejection (AMR) and graft failure. The ELEVATE study evaluated the impact of early conversion from CNIs to everolimus (EVR) after KTxs and prospectively explored the status and development of DNAs.

Methods: In this 24 month (M), multicentre study KTx recipients were randomized at 10–14 weeks post-Tx to convert from CNI to EVR (n=366: C0 6–10 ng/mL) or continue CNI (n=373: C0, tacrolimus 5–10 ng/mL, ciclosporine 100–250 ng/mL); all received enteric-coated mycophenolate sodium (MPS) + corticosteroids. Blood samples were collected at

Underline represents presenting author/disclosure.

SA-PO1118
SA-PO1112
SA-PO1122
SA-PO1119
SA-PO1120
SA-PO1121
baseline, randomization (RND), M12 and M24 or at time of rejection episodes and analysed by Luminex/SAB assay in one central lab. dnDSA was defined by a MFI value $\geq 500$ any time post-RND in patients with MFI $\geq 500$ at RND.

**Results:** Baseline characteristics were comparable between groups. Incidence of preformed DSA (MFI $\geq 500$ at baseline) against HLA class-I or -II was low (table A). Overall, incidence of dnDSA HLA class-I was higher with EVR/MPS treatment vs CNI/MPS at M12 and M24. The incidence of dnHLA Class-II antibodies was dominated by anti-DQ in the CsA/MPS [lrm]group (table B). No association between de novo (either HLA class-I or -II) antibodies and a diagnosis of AMR or tBPAR was evident in this population up to M24 (table C, D).

**Conclusions:** Early conversion to EVR at 3M post-Tx did not increase the risk of dnDSA formation vs CNI continuation. Moreover, no association was observed between development of dnDSA and AMR or tBPAR, even with the lowest detection thresholds.

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**Donor-Derived Cell-Free DNA in Plasma Increases with Rejection and Decreases after Treatment in Kidney Transplant Recipients**

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**Background:** Donor-derived cell-free DNA (dd-cfDNA) is an emerging biomarker of acute cellular rejection in organ transplant recipients. The utility of determining plasma levels of dd-cfDNA aimed at diagnosing rejection and evaluating treatment response was assessed in kidney transplant recipients in a longitudinal observational trial.

**Methods:** Clinical status, biopsy grade (performed in response to elevated serum creatinine) and plasma were collected at 326 routine surveillance visits from 101 patients. Samples from nine patients assigned a biopsy grade I, II or III (NIH criteria) were classified as rejection (R). Samples from seventeen patients assigned a biopsy grade 0 were classified as quiescent (Q). cfDNA extracted from plasma was amplified at targeted SNPs and analyzed using a sensitive and accurate Next Generation Sequencing assay to quantify dd-cfDNA levels without the need to separately genotype the donor. Standard statistical measures of significance were used.

**Results:** dd-cfDNA levels were significantly higher ($p=0.029$) in patients with biopsy-confirmed rejection (R, mean 4.23%) compared to quiescent patients (Q, mean 0.96%). Creatinine levels were not significantly different between R and Q patients ($p=0.69$; mean 4 and 3.1 mg/dL, respectively). Longitudinal sample analysis from 15 patients showed increased dd-cfDNA levels following transplant (mean 2.8%) with reduction to levels below 1% by two weeks post transplantation. In 3 cases with clinically treated biopsy-confirmed rejection and 2 serial samples following the rejection, levels of dd-cfDNA decreased following rejection treatment.

**Conclusions:** dd-cfDNA shows promise as a biomarker of rejection that may be used for non-invasive surveillance of kidney allograft status and treatment response. The ongoing measurement of cfDNA may allow clinicians to better personalize care and improve patient outcomes.

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