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A Registry of Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (NCCR project)

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Background: Autosomal dominant tubulointerstitial kidney diseases (ADTKD) are characterized by progressive renal failure culminating in end-stage renal disease, with non-specific structural changes including interstitial fibrosis and tubular atrophy. Mutations in UMOD, the gene that encodes uromodulin, the most abundant protein in normal urine, are predominantly involved. More recently, mutations in three additional genes, HNF1B, REN and MUC1, have also been associated with ADTKD. The relative prevalence of the underlying genetic defect and the clinical criteria for genetic testing in ADTKD remain to be defined.

Methods: We recruited 133 Belgian and Swiss families presenting tubulointerstitial nephritis with either gout or hyperuricemia before the age of 40 years, renal cysts or a first degree relative with tubulointerstitial nephritis. We included the cases in a comprehensive registry and screened all families for UMOD mutations, followed by screening for HNF1B and REN mutations in UMOD-negative families.

Results: We detected mutations in UMOD in 44 out of 133 (33%) tested families. Among the UMOD-negative families, 5 out of 77 (6.5%) screened positive for HNF1B mutations and none was positive for REN mutations. We analyzed the UMOD mutations and found that 86% of them are clustered in exon 3 and that 43% involve conserved cysteines crucial for the tertiary structure of uromodulin. We retrospectively detected a strong positive correlation between early hyperuricemia/gout and the rate of UMOD mutation detection (fig. 1).

Conclusions: Mutations in UMOD were detected in 33% of tested families with ADTKD, contrasting with low detection rates for HNF1B and REN mutations in UMOD-negative families in this cohort (6.5% and 0%, respectively). The rate of UMOD mutation detection is strongly correlated with early hyperuricemia/gout. The role of MUC1 remains to be ascertained. The creation of this registry will be useful to delineate the genetic and clinical spectrum of ADTKD in Switzerland and beyond.

Long term outcome of membranous glomerulonephritis associated with anti-PLA2R antibodies

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Most cases of primary membranous glomerulonephritis are caused by autoimmunity against the phospholipase A2 receptor (PLA2R). Detection of circulating antibodies against PLA2R and immunohistochemical PLA2R staining can be used to identify these patients. Long term data regarding the outcome have not been reported.

We retrospectively analyzed patients with primary or secondary MGN diagnosed at the University Hospital Basel between 1992 and 2007. Kidney biopsies were stained for PLA2R by immunohistochemistry. Serum taken at the time of biopsy was tested for anti-PLA2R antibodies. Clinical follow-up data were collected and, if possible, patients were retested for anti-PLA2R antibodies.

34 patients (21 male, 13 female, median age 61.9 years) were identified and enrolled in the study. 27 were considered to have primary MGN. By indirect immunofluorescence tests, 18 had circulating anti-PLA2R at the time of diagnosis, 16 of them also showing a positive biopsy staining. Two of 9 patients with negative serum tests still had a positive immunohistochemistry. A positive antibody titer significantly correlated with a positive immunostaining (p <0.01). Follow-up data were available for 21 primary MGN patients. Three of these developed end-stage renal disease. 14 of the remaining patients were retested for anti-PLA2R antibodies after a median follow-up of 9.5 years (5.2–19.3). Only 3 patients still had detectable circulating autoantibodies. Compared to the patients that had turned negative during follow-up, they tended to have higher proteinuria (2.6 g/day vs. 0.45 g/day, p = 0.18). Immunosuppressive treatment had neither a positive effect on GFR nor on proteinuria at the end of follow-up.

Our data show that both detection of antibodies in the serum and immunohistochemistry are useful to identify MGN patients with an autoimmune response against PLA2R. Most of these patients will control the antibody response during the course of the disease with a favorable outcome, even without therapy.
Sleep quality decreases with declining GFR in early stages of chronic kidney disease

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Introduction: Sleep disturbances are a common complaint in end stage renal disease patients. We assessed sleep quality in early CKD stages in comparison to the non-CKD subjects, and evaluated their association with kidney function.

Methods: 1747 participants in the population-based HypnOLaus study (857 men, 890 women) underwent full polysomnography at home and answered a questionnaire on their sleep quality. Glomerular filtration rate (GFR) was estimated by CKD-EPI equation and categorized according to KDIGO2012 guidelines. Only subjects with GFR ≥30 ml/min were considered. Associations of SSQ and sleep efficiency with GFR categories were explored by logistic and linear regression, respectively.

Results: Mean age of the population was 59.2 ±11.3 years and mean GFR 62.1 ±14.7 ml/min/1.73 m², 269 (15.4%) subjects had a CKD: 3.5% St1-2, 71% St3.

48% of patients with CKD-St3 vs 39% with no-CKD reported poor subjective sleep quality (SSQ, p = 0.05). They had shorter total sleep time (TST: 384 ± 80 min vs 402 ± 71, p = 0.008) and lower sleep efficiency (SE: 78 ± 12% vs 85 ± 11, p <0.001) compared to non-CKD. CKD-St1-2 patients showed intermediate features (p <0.001 for trend across CKD stages, for both TST and SE). The use of sleep medication increased across CKD stages (9.6%, 11.1% and 14.9% for no-CKD, St1-2 and St3 respectively, p = 0.02 for trend).

Older age and the severity of sleep apnea were the strongest predictors of both poor SSQ scores, and SE in multivariate regression analysis adjusting for gender, periodic leg movements during sleep and restless legs syndrome; CKD-St3 was significantly associated with a reduced SE (p = 0.03) but not with subjective sleep quality in the preceding models.

Conclusion: Low GFR in early stages of CKD is associated with impaired subjective and objective sleep quality, and with increased consumption of sleep medication. Besides classical factors, such as age and sleep apnea, kidney function level below CKD-stage3 seems to negatively affect sleep quality.

Correlation of Transcriptome Sequencing Data from Formalin-Fixed, Paraffin-Embedded vs. RNAAlater® stored Kidney Biopsies

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Background: Archival, formalin-fixed, paraffin-embedded (FFPE) kidney biopsies are a readily available although underused resource for molecular diagnostics. This feasibility study aimed to establish next generation sequencing (NGS) from these biopsies.

Methods: Core biopsies were obtained with a 16 g needle from 6 patients undergoing (partial) nephrectomy at time of surgery in Trondheim, Norway; Molecular Medicine, Norwegian University of Science and Technology, Bergen, Norway; Bergen, Norway

Methods: 15 patients with histologically-confirmed clear cell renal cell carcinoma (cRCC) and non-tumorous ("normal") tissue were either FFPE or stored in an RNA-stabilizing agent (RNAAlater®; Qiagen, Germany). Total RNA was extracted with the miRNAasy FFPE kit or the miRNAasy micro kit (Qiagen), respectively. NGS libraries were prepared using the illumina TruSeq® RNA Access protocol and sequenced on an illumina HiSeq 2500 instrument. Assembly of reads and alignment of the contigs was guided by TopHat and Bowtie. Comparative analysis was done using voom/Limma R-package. Pathway analysis was performed with Ingenuity Pathway Analysis.

Results: Analysis of the FFPE and the RNAAlater® datasets yielded similar numbers of detected transcript species, differentially expressed transcripts and significantly affected pathways. The average expression of detected transcripts in both datasets correlated very well (R² = 0.96), and log2 fold changes of the transcripts which were significantly altered in both datasets (pad <0.05, fold changes ≥2; n = 920) correlated with R² = 0.94. Among the transcripts with the highest fold changes in both datasets were NPTX2 and CA9, both higher expressed in tumor, and UMOD, higher expressed in non-tumor tissue. All three genes are known to be differentially regulated in ccRCC. In both datasets, pathway analysis reveals the presence of gene signatures of cancer, renal damage and immune response. Immunohistochemistry confirmed the down-regulation of uromodulin (UMOD) in ccRCC. In essence, we have obtained a ccRCC signature according to the literature in both data sets.

Conclusions: NGS is feasible in FFPE kidney biopsies and expands the utility of these tissue specimens.

Effect of SGLT-2 inhibitor Dapagliflozin on Cystic Disease Progression in PCK Rats with Autosomal Recessive Polycystic Kidney Disease (ARPKD)

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Background: Autosomal dominant polycystic kidney disease (ADPKD) accounts for 5% of patients with end stage renal disease (ESRD). As specific treatment options are likely becoming available in the near future, predicting disease course would be of utmost importance to select high risk patients for treatment. We have previously identified ADPKD-specific patterns of urine peptide excretion but have not been able to predict disease course so far. Here, based on extended follow up time, we identified a set of urinary peptides that predict progression to ESRD and thus allow early detection of high risk ADPKD patients.

Methods: Baseline urine samples from all patients in the CRISP cohort were analyzed by capillary electrophoresis online coupled to mass spectrometry (CE-MS). All patients were followed for up to 12 (minimum 7) years and the urine peptide of those reaching ESRD was compared to control patients with relatively slow progression during follow up (defined as an annual GFR loss of no more than 4 ml/min/1.73 m²). Two thirds of both cases and controls were used to identify a prognostic biomarker score, the remaining patients served as validation cohort.

Results: During follow up, 22 patients reached ESRD, and 46 patients matched for baseline GFR had a low progression rate. A prognostic biomarker score based on 52 urinary peptides, applied to the validation cohort, reached an AUC of 0.94 in the training cohort upon cross validation and an AUC of 0.81 in the validation cohort to identify patients reaching ESRD during follow up (sensitivity 83% and specificity 71% at a predetermined cut-off level).

Conclusions: We identified a biomarker score based on the urine peptide at a single timepoint that allows to identify ADPKD patients with high risk for future progression to ESRD.
Blood and urine were collected at baseline and after 3 and 6 weeks of treatment to assess parameters of renal function. After 6 weeks of treatment, kidney growth was performed and rats were immediately sacrificed and kidneys were excised for analysis of cyst growth.

**Results:** DAPA significantly increased urine output (DAPA 573 ± 19.2, CON 19.3 ± 2.3 ml/day at week 6 of treatment) and resulted in higher osmolal clearance in DAPA group (462 ± 5.7 versus 40.8 ± 5.8 ml/min/1.73 m², p < 0.005) compared to predonation versus 61 ± 11 ml/min/1.73 m². 3 months after treatment, DAPA-treated PCK rats displayed higher creatinine clearance (DAPA 3.08 ± 0.40, CON 2.56 ± 0.54 ml/min) and BUN (DAPA 1.71 ± 0.34, CON 1.23 ± 0.31 mmol/l) whereas after 6 weeks there was no difference between DAPA and CON. Furthermore, DAPA-treated PCK rats displayed a 3.5-fold increase in albumin excretion after 6 weeks of treatment. Surprisingly, there was a 23% higher total kidney weight after 6 weeks of treatment with DAPA. In vivo ultrasound imaging and histological analysis also showed an increase in the cyst growth, although there was no change in the level of renal AMP content between both groups.

**Conclusions:** Inhibition of glucose reabsorption with the SGLT2-specific inhibitor DAPA caused significant glycuria, hyperfiltration and albuminuria in PCK rats. Unexpectedly, the cyst growth was enhanced, suggesting that the factors which regulate cyst growth in this model act independently from the factors which control GFR. The mechanisms which link glycuria and hyperfiltration to distal cyst growth remain to be elucidated.

**OC 07**
Calciprotein Particles Induce Calcification of Vascular Smooth Muscle Cells In Vitro
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**Background:** Vascular calcification is prevalent in patients with chronic kidney disease (CKD) and is associated with significant cardiovascular morbidity and mortality. Calciprotein particles (CPP) are calcium phosphate-containing nano-aggregates which have been found in the blood of CKD patients. The effect of CPP on vascular smooth muscle cells (VSMC) mineralization has yet to be evaluated.

**Methods:** Synthetic primary and secondary CPP were generated using phosphate-enriched culture medium (DMEM/10% FBS) incubated at 37°C for either one day (primary CPP) or seven days (secondary CPP). Human VSMC were cultured with these media and mineralization was assessed qualitatively with Alizarin red staining and quantitatively by measurement of calcium and phosphate content.

**Results:** The supplementation of culture medium with 3.5 mM phosphate and 1 mM calcium resulted in a time- and temperature-dependent generation of primary and secondary CPP, as identified by TEM. Exposure of VSMC to secondary CPP led to a pronounced and consistent dose-related accumulation of calcium and phosphate mineral (i.e. calcification) within 5 days, whereas exposure to primary CPP did not. Furthermore, the amount of FBS used for the generation of morphologically indistinguishable secondary CPP corresponded to the extent of VSMC calcification.

**Conclusion:** CPP form spontaneously in cell culture medium containing high phosphate. Secondary CPP induce VSMC calcifications in vitro, whereas primary do not. This indicates that controlling CPP transformation may be an important determinant of VSMC calcification in vitro.

**OC 08**
The sodium/proton exchanger NHA2 is a novel regulator of sodium and calcium homeostasis in the distal convoluted tubule
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NHA2 is a recently cloned sodium/hydrogen exchanger present in all metazoan genomes with unknown biological function. We recently demonstrated that NHA2 is critical for insulin secretion in β-cells (Deisl et al., PNAS 2013). Here we find that NHA2 is expressed in distal convoluted tubules of mice and humans, a tubular segment that is paramount for the regulation of sodium, calcium and blood pressure homeostasis. To test the physiological role of NHA2 in the kidney, we performed telemetric blood pressure measurements and metabolic balance studies in NHA2 WT and KO mice. NHA2 was dispensable for the renal adaptation to acute metabolic acidosis and water deprivation. Blood pressure, however, was lower in NHA2 KO mice compared to WT mice under high sodium diet, but not under low sodium diet. In addition, NHA2 KO mice exhibited normocalcemia and normoglycemia. Furthermore, NHA2 KO mice displayed a 3.5-fold lower total kidney weight levels while 1, 25-OH Vitamin D3 levels remained unaltered. Interestingly, immunoblotting of kidney tissue lysates revealed decreased NCC phosphorylation (Thr324/Thr325) in the proximal tubules of mice and humans, a tubular segment that is paramount for the regulation of sodium, calcium and blood pressure homeostasis in the distal convoluted tubule of the kidney. In conclusion, our data reveal the sodium/hydrogen exchanger NHA2 as a novel regulator of calcium, sodium and blood pressure homeostasis in the distal convoluted tubule of the kidney.

**OC 09**
Calcification propensity after kidney donation: a one year prospective study
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**Background:** The question of increased cardiovascular risk after kidney donation is still a matter of debate. Recently, a novel nanoparticulate test was developed to measure overall calcification propensity in serum. When applied to predialysis CKD patients, high calcification propensity (i.e. low T50) was associated with progressive aortic stiffness and increased all-cause mortality at a follow up of 5 years. In this work, we investigated the impact of kidney donation on serum calcification propensity (T50).

**Methods:** We included 21 living kidney donors (LKD) in a prospective study. We measured T50, augmented T50 (AT50) and serum mineralisation index (RII) and pulse wave velocity (PWV) before donation, and at 12 months after donation.

**Results:** LKO showed a significant decline in renal function (95 ± 10 versus 61 ± 11 ml/min/1.73 m², p < 0.001) and plasma phosphate levels (1.2 ± 0.2 versus 1.1 ± 0.2 mmol/l, p < 0.005) compared to predonation after one year of follow up. T50 measurement increased slightly one year after donation (290 ± 53 versus 312 ± 38 min, p = 0.046). AT50, PWV as well as RRI were not changed significantly by kidney donation. Correlation analyses revealed no significant associations between T50, AT50 and PWV (all p >0.09), neither at baseline nor at 1 year. However, T50 was inversely correlated to plasma phosphate level (R = -0.64; p = 0.002 at day 0 and R = -0.48; p = 0.03 at 1 year).

**Conclusion:** We demonstrate that one year after kidney donation, calcification propensity slightly improves whereas PWV and RRI are unchanged in kidney donors compared to predonation. This supports the notion that the loss of GFR associated with kidney donation does not per se enhance cardiovascular risk.

**OC 10**
Final Results from the Long-term Extension (LTE) of the Belatacept Phase 2 Study in Kidney Transplantation
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**Background:** At 5 years post-transplant, data from the Phase 2 MI03-100 LTE study of belatacept (belatacept) in kidney transplantation demonstrated a favorable safety profile and improved renal function vs cyclosporine (CsA) (Vincenti F et al., JASN 2010;21(9):1587–96).

**Methods:** This was a post hoc analysis of the Phase 2 MI03-100 LTE study of belatacept in kidney transplantation. The primary endpoint was the incidence of biopsy-proven acute rejection (BPAR) in patients receiving belatacept versus CsA. The primary end point was defined as the percentage of patients with at least one BPAR in the first 12 months from 5 years post-transplant. The BPAR rate was compared using Kaplan-Meier survival analysis and log-rank test. Secondary endpoints included the incidence of infection and death. A total of 472 patients were randomized to the study (239 belatacept; 233 CsA) and 431 patients completed the 5-year extension. Baseline patient characteristics were similar in the two groups. The incidence of death and infection was comparable in both groups. The incidence of BPAR was lower in the belatacept group compared to the CsA group (6.6% vs 11.5%, respectively, Log-rank p = 0.02). The incidence of death and infection was comparable in both groups. The incidence of BPAR was lower in the belatacept group compared to the CsA group (6.6% vs 11.5%, respectively, Log-rank p = 0.02).

**Conclusion:** In conclusion, the results of the long-term extension (LTE) study confirm the benefits of belatacept over CsA in terms of improved renal function and reduced BPAR rates in kidney transplantation.
Here we report outcomes in all randomized and treated patients through study close (approximately 10 years).

Methods: 218 patients were randomized to receive bela (n = 145) or CsA (n = 73). After 6 months, bela patients were randomized to 4-week (n = 62) or 8-week (n = 60) dosing intervals (5 mg/kg). Here we focus on the results from randomization to study end in bela patients randomized to 4- or 8-week treatment groups and all CsA patients.

Results: At month 3, mean MDRD cGFR was 66 (bela 4-week), 65 (bela 8-week), and 60 (CsA) mL/min/1.73 m²; and at 10 years mean cGFR was 72 (bela 4-week), 67 (bela 8-week), and 52 (CsA) mL/min/1.73 m² (figure). From randomization to end of study, acute rejection occurred in 4, 4, and 5 patients in the bela 4-week, bela 8-week, and CsA groups, respectively. Death or graft loss occurred in 14 bela patients (10%) and 8 CsA patients (11%). The incidence rate of serious adverse events was 33 (bela 4-week), 48 (bela 8-week), and 55 (CsA) per 100 person-years; incidence of serious infections was 6 (bela 4-week), 10 (bela 8-week), and 15 (CsA) per 100 person-years. There were 3 cases of PTLD in bela-treated patients (2 EBV-negative, 1 EBV-unknown) that occurred by Month 13 and 1 case in a CsA-treated patient in Year 4 (EBV-unknown).

Conclusions: Data from this limited cohort suggest that the profile of bela is consistent over approximately 10 years of treatment: patients maintained renal function with no new safety findings, and long-term outcomes were similar between 4-week and 8-week treatment groups. Results should be validated in a larger cohort.
Fetal hypoxia induces ectopic Fetuin A expression in renal tubular cells
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Background: In previous experiments, we demonstrated that hypoxia during fetal development induces intrauterine growth restriction. Further, microarray analysis showed upregulation of Fetuin A in the kidneys of hypoxic embryos. In this study, we examined whether Fetuin A, which is normally secreted only by the liver, is produced locally in the hypoxic kidney.

Methods: Pregnant mice were exposed to hypoxic condition (9.5% O2) from E14.5 until E18.5. Sacrificed, and Fetuin A mRNA, immunohistochemistry (IHC), Western blot and qRT-PCR were collected for analysis: Whole mount in situ hybridization (ISH) using 2 different riboprobes directed against the 3’ or 5’ half of Fetuin A mRNA, immunohistochemistry (IHC), Western blot and qRT-PCR.

Results: Fetuin A was detected by Western blot and qRT-PCR only in hypoxic kidneys, but not in normoxic controls. Both riboprobes gave a similar expression pattern of Fetuin A in tubular structures traversing the renal cortex and extending into the deeper layers of whole mount hypoxic kidneys. In ISH or IHC sections, these structures were identified as distal tubules and collecting ducts. Analysis of the Fetuin A promoter region identified two potential binding sites for Hif-1.

Conclusions: Hypoxia imposes a severe stress condition on the developing renal cells. Fetuin A is a serum protein, normally secreted by the liver, which is the major anti-calcification agent in the serum. Based on our data that in response to hypoxia, renal tubular cells produce Fetuin A, which might protect the developing kidney from calcification. Further studies using Fetuin A knock-out animals are planned to substantiate this hypothesis.

Conclusion: We established a reliable hanging-drop protocol to obtain kidney microtissues with different PT cell lines. Microtissues obtained by this approach could be used for the development of high throughput drug and toxicity screenings, using endocytosis as a functional readout.
Stone formers with the V-ATPase B1 subunit polymorphism p.E161K have a mild urinary acidification deficit with an increased prevalence of CaP containing kidney stones.

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Background: Mutations in the V-ATPase B1 subunit gene ATP6V1B1 cause autosomal-recessive distal renal tubular acidosis. We previously demonstrated that a common single nucleotide polymorphism (SNP) in ATP6V1B1 (c.481G>A; p.E161K) greatly diminishes pump function when tested in vitro. To study the impact of the p.E161K SNP on urinary acidification in humans, we conducted a cross-sectional study in the Dallas and Bern kidney stone registries.

Methods: Inclusion criteria: Informed consent and at least one stone episode. Exclusion criteria: Hyperparathyroidism, cystinuria, sarcoidosis, malignancy, thyroid dysfunction, short bowel syndrome or bariatric surgery, urinary tract infection, anorexia nervosa or patients on medications interfering with urinary acidification during investigation.

We conducted a multivariate analysis, adjusting for the two major determinants of urinary acidification, BMI and animal protein intake (24 hr sulfate excretion).

Results: 550 stone formers (SF) could be included. 32 of the 550 SF (5.8%) were heterozygous for the SNP. No patient in these cohorts was homozygous for the SNP. Mean age at presentation was 43.6 years in wild-type and 38.5 years in heterozygous SF (p < 0.05). Plasma HCO3- was not different between the two groups. However, on a random outpatient diet, heterozygous SF had significantly higher 24 hr urinary pH (6.31 vs 6.09; p < 0.05). On an outpatient diet restricted in Na+ and Ca++, the difference in 24 hr urinary pH became even more pronounced (6.44 vs 6.04; p < 0.001). Compatible with the findings of increased urinary pH, calcui of heterozygous SF were significantly more likely to contain calcium phosphate (CaP) (p < 0.05).

Conclusions: SF with the V-ATPase B1 subunit p.E161K SNP are younger at presentation and exhibit a urinary acidification deficit with an increased prevalence of CaP containing kidney stones. The burden of E161K heterozygosity may be a forme fruste of distal RTA.

Dietary phosphate intake increases blood pressure via the NCC cotransporter ("NCCR Project")

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Background: The thiazide-sensitive Na+-Cl- cotransporter NCC, plays a key role in renal salt reabsorption and blood pressure control. High intake of dietary phosphate has been linked to increased cardiovascular morbidity and mortality in healthy subjects and patients with kidney diseases. We tested whether altered NCC activity may contribute to these negative effects of a high phosphate diet.

Methods: Mice were kept for 1–5 days on low (0.1%) or high (1.2%) phosphate (Pi) diets. Plasma PTH, FGF23 and urinary aldosterone level were measured by ELISA. Cardiac hypertrophy markers and urinary aldosterone excretion (24 hr) were determined. Plasma PTH, FGF23 and urinary aldosterone were also measured in aldosterone-treated rats subjected to either low or high dietary sodium. In this setting, higher levels of sodium reabsorption in the CD were associated with increased claudin-8 protein abundance.

Results: The high Pi diet increased plasma FGF23, PTH, urinary aldosterone and renal renin expression, Systolic blood pressure and the expression of cardiac hypertrophy markers were elevated by high Pi diet and this effect was blunted by thiazide diuretics. Thiazide diuretics on high Pi diet increased urinary NaCl excretion more than low Pi diet. The high Pi diet increased NCC abundance and phosphorylation. Similar to the high Pi diet in control mice, mice over expressing FGF23 or treated with recombinant FGF23 showed increased NCC abundance and phosphorylation. However, while the high Pi diet stimulated phosphorylation of SPAK, a possible regulator of NCC, isolated FGF23 overexpression or administration did not stimulate SPAK phosphorylation, suggesting that high Pi intake and FGF23 activate NCC by distinct pathways. The expression of other Na+-transporters like as NHE3, NKCC2 and ENaC remained unchanged.

Conclusion: Dietary intake of Pi stimulates NCC activity, increases systolic blood pressure and promotes cardiac hypertrophy. Thus, high Pi may increase cardiovascular morbidity through activation of NCC, which might be related to a renin and aldosterone mediated activation of the SPAK kinase.

Chronic hydrochlorothiazide treatment up-regulates sodium chloride co-transporter (NCC) expression within urinary exosomes.

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Background: The thiazide-sensitive NaCl cotransporter (NCC) is located in the apical membrane of epithelial cells lining the distal convoluted tubule of the kidney and is important for fine-tuning of renal sodium excretion. Salt-sensitive hypertension can result from increased renal sodium reabsorption via NCC and therefore detection of renal NCC abundance is of great interest.

Methods: The aim of the present study was to investigate the effect of antihypertensive treatment on NCC abundance. Firstly using novel technique of analyzing urinary exosomes we characterized expressions of the NCC in six healthy subjects. Furthermore, urinary exosomes of patients with essential hypertension (n = 23) before and after hydrochlorothiazide (HCT) and Valsartan treatment were characterized for NCC and its phosphorylated form (pNCC) expression.

Results: NCC was detected in urinary exosomes as a glycosylated protein forming an oligomeric structure. It comprised of dimer (≈130 kDa) and monomer (≈130 kDa). Despite of its inhibitory nature, HCT treatment led to a more than 2 fold increase in NCC and pNCC expression. On the other hand, Valsartan treatment did not significantly affect exosomal NCC or pNCC abundance. The amount of C09, an exosomal marker, was similar after all treatments.

Conclusions: We found that chronic HCT treatment in hypertensive patients enhanced NCC and pNCC expression within urinary exosomes. Our results support the notion that NCC abundance in urinary exosomes can be employed as a clinical biomarker for the detection of salt-sensitive hypertension.
Activation of the transcription factor Nrf2 attenuates the pro-inflammatory response of mouse macrophage following CPP exposure: Potential therapeutic target in vascular calcification (NCCR Project)

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Background: Fetuin-A-containing calciprotein particles (CPP) clear calcium phosphate nanocrystals from the extracellular fluid via the reticuloendothelial system, thus preventing soft tissue mineralization. Increased levels of CPP in pathological situations can trigger the generation of reactive oxygen species (ROS) and inflammation, two of the underlying causes leading to vascular calcification. The transcription factor, nuclear-factor-E2-related factor 2 (Nrf2) is a master regulator of cell defense and can protect against oxidative and electrophilic stress. Under normal basal conditions, Nrf2 is repressed in the cytoplasm by its inhibitor Keap1, which subsequently targets Nrf2 for ubiquitination and proteosomal degradation. We hypothesized that the induction of Nrf2 in macrophage may be a beneficial target to inhibit the progression of calcification by preventing CPP driven inflammation.

Methods: The mouse Raw 264.7 cell line was used as a model macrophage. We exposed the cells to CPP and measured the expression of the pro-inflammatory M1 markers MCP1, IL-1β and TNF-α by quantitative RT-PCR and ELISA. We manipulated the Nrf2/Keap1 system using a well characterized synthetic Nrf2 inducer, CDDO-Me, and also knocked down the expression of Nrf2 and Keap1 using specific siRNA targeting molecules.

Results: We show that CPP induce a strong proinflammatory response in Raw 264.7 cells increasing the transcription and secretion of MCP1, IL-1β and TNF-α. The expression of MCP1 and IL1-β, but not that of TNF-α, was strongly suppressed by CDDO-Me and Keap1 knockdown via the Nrf2 pathway.

Conclusions: Macrophage-specific Nrf2 induction may ameliorate the secondary CPP driven inflammatory response and therefore delay the progression of calcification.
Trice weekly post-dialysis Cefepime prescription in patients on maintenance hemodialysis

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Introduction: In chronic hemodialysis patients the post-dialysis prescription of intravenous antibiotics allows to manage even severe infections on an outpatient basis. Cefepime is a 4th generation cephalosporin with a broad spectrum and bactericidal activity in monotherapy. We report here the pharmacokinetic of cefepime after post-dialysis prescription.

Methods: 12 infectious episodes occurring in 9 patients (mean age = 69 ± 7 y) were treated with post-dialysis cefepime. The sites of infection were: lungs (4), urinary tract (3), catheter-related (2), skin, bone and digestive tract. The causal pathogen was identified in seven episodes. The initial post-dialysis dose of cefepime ranged from 750 to 1500 mg and was thereafter adapted according to the trough serum levels obtained before the subsequent dialysis in order to be above the breakpoints/MIC90 of susceptible organisms. Cefepime concentrations were determined before (n = 30) and after (n = 17) dialysis by liquid chromatography–mass spectrometry (LC-MS/MS).

Results: The mean ± SD dose of cefepime used was 920 ± 270 mg (14.5 ± 5.1 mg/kg). The mean through pre-dialysis concentrations were 10.7 ± 3.9 mg/ml and 11.3 ± 5.6 mg/ml at 48 and 72 hours, respectively. These levels always exceeded largely the EUCAST breakpoints for susceptibility of all the targeted bacteria (>1 mg/ml), with the exception of Pseudomonas aeruginosa for which the susceptibility breakpoint is higher (>8 mg/l). Pre-dialysis cefepime concentrations were significantly higher in anuric patients compared to those with a conserved diuresis (15.6 ± 3.5 vs 9.25 ± 3.6 mg/l; p <0.001). The mean post-dialysis cefepime concentration was 1.96 ± 1.7 mg/l. The clinical evolution of all patients was favorable.

Conclusion: Outpatient treatment with cefepime administered post-dialysis proved to be safe and effective in our patients, while reducing hospital stay and improving quality of life. According to our data, the initial dose of cefepime should be 1 g/48 h and 1.5 g/72 h, to be adapted thereafter according to the pre-dialysis trough serum levels. Higher doses may be necessary in patients having a residual renal function or with Pseudomonas infection.

Calcitriol concentrations increase significantly in patients on maintenance hemodialysis (HD) receiving long-term cholecalciferol supplementation

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Background: All HD patients of our center having low baseline vitamin D levels receive cholecalciferol supplementation in order to maintain the 25(OH)D levels within the optimal range of 75–150 nmol/l.

Methods: 104 patients from 6 HD centers in Canton Vaud were assessed by home polygraphy to measure the apneas-hypopneas index (AHI) and completed 3 SDB screening scores: STOP-BANG, Berlin’s Questionnaire (BQ) and Adjusted Neck Circumference (ANC). Age, neck circumference and time on renal replacement therapy were identified as the best predictors of moderate to severe SBD in the derivation population and were used to develop a new screening score, specific to the HD population: the ANT (age–neck–time)-score.

We therefore propose a simple screening score specific to the HD population and were used to develop a new screening score, specific to the HD population: the ANT (age–neck–time)-score.

The patients were divided in a derivation and an independent validation population, based on readily available clinical data (the ANT-score), for SDB screening in HD patients.

Results: Classical screening tools were not reliable for SDB screening in HD patients with a sensitivity/specificity of 52/54% for BQ, 85/54% for STOP-BANG and 30/91% for ANC respectively.

Calcitriol concentrations increase significantly to identify the patients who need further investigation. This score, specific to the HD population: the ANT (age–neck–time)-score.

Results are given as mean±SD; * p<0.05 compared to anuric patients; ** p<0.05 compared to non-diabetic patients.

Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
<th>Baseline</th>
<th>24 month</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium</td>
<td>2.20–2.55 mmol/l</td>
<td>2.32±0.17</td>
<td>2.37±0.16</td>
<td>p= NS</td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>1.12–1.32 mmol/l</td>
<td>1.14±0.09</td>
<td>1.15±0.07</td>
<td>p= NS</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.90–1.45 mmol/l</td>
<td>1.55±0.39</td>
<td>1.68±0.49</td>
<td>p= NS</td>
</tr>
<tr>
<td>i-PTH</td>
<td>15–65 ng/l</td>
<td>241±174</td>
<td>311±204</td>
<td>p= NS</td>
</tr>
<tr>
<td>25-DH vitamin D</td>
<td>75–150 nmol/l</td>
<td>32.2±17</td>
<td>109.9±23</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

1,25-DihydroxyVitaminD (calcitriol)

- all patients 43–149 pmol/l | 28.7±11.9 | 42.1±22.1 | p<0.01 |
- with conserved diuresis (n=24) 43–149 pmol/l | 32.8±15.9 | 56.8±28.3 | p<0.05 |
- anuric patients (n=11) 43–149 pmol/l | 26.9±9.4 | 35.3±15.3 | p<0.05 |
- non-diabetic patients (n=21) 43–149 pmol/l | 30.3±11.5 | 48.9±24.6 | p<0.01 |
- diabetic patients (n=14) 43–149 pmol/l | 26.4±12.6 | 31.9±12.8 | p= NS |

Results are given as mean±SD; * p<0.05 compared to anuric patients; ** p<0.05 compared to non-diabetic patients.
Results: After 24 months, the mean dose of the cholecalciferol supplement was 10400 ± 5980 IU/week. The main results are reported in table 1. Under cholecalciferol supplementation the 25(OH)D and the calcitriol concentrations increased significantly, with 12 out of the 35 patients (35%) achieving calcitriol concentrations within normal range (≥43 pmol/l). The calcitriol concentrations increased by 73% in patients having a non-diuretic history of CKD. However, only by 31% in the anuric ones (p <0.05) and only slightly in diabetic patients (p = NS).

Conclusions: In patients on maintenance HD the long-term prescription of cholecalciferol is associated to a significant increase of the calcitriol levels – particularly in non-diabetic patients – suggesting the persistence of a 1-alfa hydroxylation activity. The higher increase observed in patients with conserved diuresis supports renal synthesis; however extrarenal synthesis may be present as well, as also suggested by the calcitriol levels observed in anephric HD patients. Overall, our data suggest that the calcitriol deficiency developing with progressive CKD may be partly due to vitamin D deficiency and thus could be partially corrected or prevented by cholecalciferol supplementation.

Women, none of the measures were associated with increased risk of mortality events.
Hypertension, kidney function and proteinuria were selected as criteria for long-term outcome.

Results: Prominent clinical findings during acute NE were fever (90%), back pain (67%), limb pain (71%) and nausea and vomiting (47%). In total 88% of the patients had AKI by RIFLE criteria, severe thrombocytopenia (platelets ≤ 50 x 10^9/L) was found in 49 patients (12%), none of whom required platelet transfusion. At the time of follow-up (17 (7–35) months) all patients had detectable Hantavirus-specific IgG; 8.5% had persistent IgM antibodies; 25% had hematuria; 23% had hypertension (33% pre-existing and 67% newly diagnosed); 7% had proteinuria.

Conclusions: NE causes AKI in a high proportion of patients. Hypertension and proteinuria do not seem to be long-term consequences of NE, whereas Hematuria might be. All patients had Hantavirus-specific IgG antibodies years after the infection.

New anthropometry-based age- and sex-specific reference values of the urinary 24-h creatinine excretion based on the adult Swiss population

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Background: Urinary creatinine excretion is used as a marker of completeness of timed urine collections. The current reference values for 24-h urinary creatinine excretion are poorly representative of the general European population.

The aim of this study was to establish and validate anthropometry-based age- and sex-specific reference values of the urinary 24-h creatinine excretion on two independent adult populations.

Methods: We used data from two independent Swiss cross-sectional population-based studies with standardized 24-h urine collection and measured anthropometric variables. Only data from adults of European descent, with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m² and reported completeness of the urinary collection were retained. A prediction model for the completeness of 24-h urinary creatinine excretion was developed in 1137 participants from the Swiss Survey on Salt (SSS) and validated in 994 participants from the Swiss Kidney Project on Genes in Hypertension (SKIPGKH).

Results: The mean urinary creatinine excretion was 193 ± 41 µmol/kg/24 h in men and 151 ± 38 µmol/kg/24 h in women in SSS. The values were inversely correlated with age and body mass index (BMI). Based on current reference values (177–251 µmol/kg/24 h in men and 133–177 µmol/kg/24 h in women), 56% of the urinary collections in the whole population and 67% in subjects >60 years would have been considered as inaccurate. A linear regression model with sex, BMI and age as predictor variables was found to provide the best prediction of the observed values.

Conclusions: We propose a validated prediction equation for 24-h urinary creatinine excretion in a general Swiss population, based on readily available variables such as sex, BMI and age, and few derived normograms to ease its clinical application. This should help healthcare providers to interpret the completeness of a 24-h urine collection in the daily clinical practice and in epidemiological population studies.

Primary antiphospholipid syndrome presenting as renal vein thrombosis and membranous nephropathy

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Background: Antiphospholipid syndrome (APS) is a multisystem autoimmune disorder characterized by thrombotic events and/or recurrent pregnancy complications in the presence of circulating antiphospholipid-antibodies (APL). APS may be primary or associated with other autoimmune disease. Commonly described renal findings are major vessel thrombosis, renal artery stenosis and thrombotic microangiopathy. Non-thrombotic glomerulonephritis are however increasingly recognized in patients with primary APS.

Case report: We report a case of a 28 year-old female who presented with left flank pain for a few weeks. Medical history and physical examination revealed otherwise unremarkable. Initial laboratory examination revealed increased serum creatinine (136 µmol/L) and LDH (602 UI), hypoalbuminemia (16 g/l) and mild proteinuria (spot urine protein-creatinine ratio 51 mg/mmol). Further evaluation showed complete obliteration of the left renal vein (MRI) and positive APL. Persistant positive APL 3 months later confirmed the diagnosis. During the hospitalisation, she developed a nephrotic syndrome with edema and heavy proteinuria (5 g/d). A 99mTc-MAG3-scintigraphy revealed a non-functioning left kidney. Due to the persistent nephrotic syndrome despite anticoagulation and antiproteinuric therapy for 3 months, a biopsy of the single functioning kidney was performed, which revealed membranous nephropathy stage 3. Given the persistent nephrotic syndrome and impaired renal function, prednisone and tacrolimus were added to the therapeutic regimen.

Conclusion: Recently, non-thrombotic glomerulonephritides in association with PAPS, in particular membranous nephropathy have been reported. The pathogenic role of APL in the causation of
glomerular disease in general and in membranous nephropathy is not clear. Our report highlights the impact of circulating APL on the kidney of a previously healthy young female and illustrates a rare potential clinical presentation of APS.

The changing pattern of postinfectious glomerulonephritis
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Background: The classical form of poststreptococcal disease is decreasing worldwide but remains a significant health care problem in developing countries, especially in children. In industrialised countries postinfectious glomerulonephritis is now primarily due to non-streptococcal disease and affects elderly patients.

Case report: A 71 year old patient with diabetc foot syndrome presented with severe renal failure, nephritic urinanalysis and signs of inflammation (CRP 407 g/l). Complement C3 and C4 were normal. Urine culture was positive for methicillin-sensitive staphylococcus aureus. Despite adequate antibiotic therapy renal function worsened and haemodialysis was started. Renal biopsy showed a mesangio proliferative and endocapillary glomerulonephritis with concomittant acute tubular injury and chronic lesions due to beginning diabetic nephropathy. Subepithelial humps were demonstrated on electron microscopy. Screening for endocarditis was negative. One week after cessation of flucloxacillin lower back pain developed and recurrence of the inflammatory syndrome was observed. Blood cultures were positive for staphylococcus aureus. An acute spondylodiscitis L3/L4 with peridural abcess was diagnosed on MRT. Haemodialysis was stopped after 2 months, but stage 5 CKD persists 8 months after presentation.

Conclusions: In elderly patients with risk factors such as diabetes mellitus and in intravenous drug users postinfectious glomerulonephritis is most often associated with staphylococcal infections. Compared to the good outcome of classical poststreptococcal glomerulonephritis the severity of the nephritic syndrome is increased and the prognosis is worse, especially if pre-existing renal disease such as diabetic or vascular nephropathy is present. Adequate treatment, including prolonged antibiotic therapy and often surgical measures, of the primary focus of infection is of utmost importance to improve the outcome of this condition.

Renal tissue oxygenation as measured with BOLD-MRI in children with vesico-ureteral reflux or a solitary kidney in comparison with healthy controls
Hassib Chehade1, Maciej Piskunowicz2, Bastien Milani3, Isabelle Bassi4, Christiane Anex5, Matthias Stub4, Bruno Vogt1, Michel Burnier1, Menno Pruijm1, Nephrology, University Hospital Lausanne CHUV; 2Radiology, University Hospital Ghent; 3Radiology, University Hospital Lausanne (CHUV); 4Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Department of Clinical Research, University of Bern, Switzerland

Background: Vesico-ureteral reflux (VUR) in children is a risk factor for the development of renal scarring and chronic kidney disease (CKD), yet the underlying pathophysiology is incompletely understood. Similarly, the renal outcome of children with a congenital solitary kidney (SK) or unilateral nephrectomy (UN) differs significantly. Renal hypoxia might be one of the underlying mechanism contributing to the progression of CKD in these children, yet this has not been assessed so far. We measured cortical and medullary oxygenation in children with VUR, SK or UN, and compared the results with those of healthy controls using blood oxygenation level dependent magnetic resonance imaging (BOLD-MRI).

Methods: BOLD-MRI was performed under standardized hydration conditions, before and after the administration of furosemide. Four coronal slices were selected in each kidney, and combination sequence was used to acquire T2* weighted images. The mean R2* values (=1/T2*) were calculated for each kidney, a low R2* indicating a high tissue oxygenation.

Results: A total of 51 children (26 controls and 25 patients) participated to the study, corresponding to 95 kidneys. Baseline characteristics and results of MR-measurements are shown in the table. In all groups, cortical oxygenation was higher (R2* lower) in girls than in boys. Medullary and cortical R2* levels were significantly higher (p = 0.003 and 0.02 respectively) and medullary R2* decreased more under stimulated conditions (furosemide injection) in healthy controls than in reflux kidneys (p = 0.02). The highest medullary R2* values and furosemide-induced decreases were seen in the UN and SK groups.

Conclusion: These data suggest that VUR is not associated with chronic hypoxia in children. The large furosemide-induced decreases in medullary R2* levels in the solitary kidney- and unilateral nephrectomy- groups point towards intense renal sodium transport and a high metabolic workload in children with one kidney.

Should we care about the sequela of preeclampsia?
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Background: Preeclampsia is characterized by the onset of hypertension and either proteinuria or organ dysfunction after 20 weeks of gestation. Epidemiological data on sequela in the first year after preeclampsia are scarce. We investigated kidney function, hypertension, proteinuria and urine sediment in women with preeclampsia six month after delivery.

Methods: From January 2007 to July 2014 women with preeclampsia and 6-moths follow up at the university hospital Basel were analyzed. Hypertension was defined as a blood pressure ≥140/90 or the use of antihypertensive medication. Proteinuria was defined as a protein-to-creatinine ratio in a spot urine >11.0 mg/mmol. Urine sediment was evaluated by a nephrologist.

Results: 202 women were included into the analysis. The mean time of the follow up visit was 172 days (± 39.6) after delivery. Mean age of the 202 women was 32 years (± 5.9). The mean blood pressure at follow up was 124/76 mm Hg (± 14/11, range 116-182/63-110) and the
mean serum-creatinine was 61.8 umol/l (± 11.6). Mean estimated glomerular filtration rate using CKD-EPI was 110.7 ml/min/1.73 m² (range 59.6-197.3 ml/min/1.73 m²). 203% (n = 41) had at blood pressure of 140/90 or higher (mean 143/89 mm Hg) or were receiving antihypertensive medication (5.5%, n = 11). Proteinuria was present in 33.1% (n = 66) (mean 27.5 mg/mmol, range 12-261 mg/mmol). Proteinuria and hypertension was present in 8% (n = 16). No active urine sediment (e.g. signs of glomerulonephritis) was observed.

Conclusion: Hypertension and proteinuria are frequent in women 6-months after preeclampsia and delivery. The findings stress the importance of a close follow up to identify those women who need further care.

Transjugular renal biopsy in high-risk patients.

Experience in 138 cases

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Background: Transjugular renal biopsy (TJRB) is an essential tool in the diagnosis and treatment of high-risk patients with underlying kidney disease. Technical advances have simplified and improved TJRB by increasing safety concerning tissue yielding and diagnostic efficacy was reported in various studies. The objective of this study was to evaluate the indications, complications and sample-adequacy of TJRB in high-risk patients.

Methods: We analyzed TJRB of native kidneys in 138 adults (>15 yr) patients consecutively from Mai 2008 through Mai 2014 at the University Hospital of Bern-Inselspital. CT-Imaging and TJRB were performed by an experienced interventional radiologist. A rapid percutaneous nephropathological assessment of biopsy samples was introduced in Mai 2011. All patients were observed for at least 24 h after intervention for the presence and severity of complications.

We collected data, including indication for biopsy, technical eligibility, tissue cores, number of glomeruli harvest, histological diagnosis and major complications.

Results: The mean common indication for TJRB was bleeding diathesis. The procedure was technically successful in all but one patient. A mean of 3.32 ± 2.0 cores were obtained, with 9.83 ± 9.05 glomeruli. The renal tissue was sufficient for pathological assessment and diagnosis in 110/138 (80%) of patients. Major complications occurred in 2 patients (1.45%).

Conclusion: TJRB is a minimally invasive procedure and an excellent diagnostic tool for adequate tissue sampling in high-risk patients who require renal biopsies.

Prevalence and predictors of sleep disordered breathing in early stages of chronic kidney disease

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Introduction: Sleep disordered breathing (SDB) is a common finding in end stage renal disease (ESRD) patients, and represents a risk factor for perioperative complications. The prevalence of SDB in the patients on waiting list for renal transplantation is poorly described and there are no guidelines about its screening before transplantation surgery.

Our aim was to assess the prevalence of SDB in a Swiss HD population and to evaluate the predictive value of classical screening scores.

Methods: Patients on the Lausanne renal transplantation's waiting list were screened for SDB using home nocturnal polysomnography to measure the Index of Apneic-Hypopneas per hour of sleep (AHI). Participants also completed 3 SDB screening scores: STOP-BANG questionnaire, Berlin’s Questionnaire (BQ) and Adjusted Neck Circumference (ANC).

Results: 44 men and 16 women were assessed; mean age was 55.5 (±11.5) years and BMI 26.8 (±4.2) kg/m². 68% were on hemodialysis, 11% on peritoneal dialysis and 17% had no renal replacement therapy. 76% of the participants had a SDB (AHI >5/h); 30% had mild (AHI 5–15/h), 18% moderate (AHI 15–30/h) and 30% severe SDB (AHI ≥30/h). SBD had been previously diagnosed in 11% of patients and was treated in 5%.

Positive (PPV) and negative predictive values (NPV) for moderate to severe SDB were 55% and 64% respectively for BQ, 63%/64% for STOP-BANG and 60%/65% for ANC.

Conclusion: We observed a high prevalence of SDB among patients on waiting list for renal transplantation, which is largely underdiagnosed and undertreated. Classical screening scores do not seem to be reliable to screen for SDB in this population. Given the increased perioperative complication risk associated with SDB, the implementation of SDB screening using home sleep recordings in the pre-operative assessment of renal transplantation candidates should be considered.

Acknowledgements: This study was supported by grants of the Schweizerische Nierenstiftung and the Ligue Pulmonaire Vaudoise.

Screening for sleep disordered breathing in ESRD patients scheduled for renal transplantation

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Rationale: Sleep disordered breathing (SDB) is a common finding in end-stage renal disease (ESRD) patients. Its occurrence in early stages of CKD and SBD had been previously diagnosed in 11% of patients and was treated in 5%.

Positive (PPV) and negative predictive values (NPV) for moderate to severe SDB were 55% and 64% respectively for BQ, 63%/64% for STOP-BANG and 60%/65% for ANC.

Conclusion: We observed a high prevalence of SDB among patients on waiting list for renal transplantation, which is largely underdiagnosed and undertreated. Classical screening scores do not seem to be reliable to screen for SDB in this population. Given the increased perioperative complication risk associated with SDB, the implementation of SDB screening using home sleep recordings in the pre-operative assessment of renal transplantation candidates should be considered.

Acknowledgements: This study was supported by grants of the Schweizerische Nierenstiftung and the Ligue Pulmonaire Vaudoise.

Outcome of acute kidney injury in a base hospital in Ticino, Southern Switzerland: Experience of a single center

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Background: Acute kidney injury (AKI) is defined as a rapid loss of kidney function. Even small increments of serum creatinine are associated with worst outcomes. The spectrum of AKI ranges from less severe to acute kidney failure requiring renal replacement therapy (RRT). Since AKI is common in hospitalized patients, with a mortality rate of up to 80% in critically ill patients, we evaluated the short-term outcome of AKI in one of the base hospitals of Southern Switzerland.

Methods: We retrospectively analyzed the outcome of 28 patients who presented AKI in our base hospital during a one year period, from September 2012 to August 2013.

Results: Of all 28 patients who presented AKI, 90% of these had an underlying chronic kidney disease (CKD). Among these 28 patients, 18 (64%) showed a recovery of the renal function of 78% (16/20 patients) had spontaneous recoveries and 22% (4/18 patients) needed temporary RRT. Among these four patients, two (50%) died after renal function recovery. Of the remaining ten patients (10/28 or 36%), who did not show any renal function improvement, six patients died and...
Extradigitation in the electrophoresis of a patient with ARF caused by penicilline-overdosing

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1Nephrology, Kantonsspital Basel, Liestal; 2Laboratory Medicine, Kantonsspital Basel

History: (Background) A 86-year-old man with a history of back pain and fever (39.0 °C), was referred to our hospital. The MRI of the lumbar spine was suspicious for a spondylodiscitis. In the blood cultures staphylococcus aureus could be detected. An intravenous treatment with penicillin (3×5 million units/day) was started. After ten days of treatment the serum creatinine started to increase continuously.

Clinical Examination and Laboratory Examination: (Methods) After four weeks of treatment the patient was free of pain and afebrile but became progressively weak – heart rate 76 bpm and RR 170/80 mmHg. C-reactive protein (CRP) was 91 mg/l, s-Cr 437 µmol/l, albumin 29 g/l; haemoglobin 102 g/l; urinary protein-creatinine ratio was 65 mg/1.73 m². Urin sediment showed only a non-glomerular microhematuria.

Penicillin treatment was changed immediately to levofloxacin and rifampicin. Additionally an oral treatment with prednisolone was started to prevent the side effects of long-term corticosteroid therapy. A patient with ARF caused by penicillin (estimated 56%), also known as bisalbuminemia.

Renal biopsy revealed a heavy acute eosinophilic interstitial nephritis. Clinical Examination and Laboratory Examination: (Results) We assumed that the interstitial nephritis was caused by penicillin.

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Renal biopsy revealed a heavy acute eosinophilic interstitial nephritis.
Severe cobalamin deficiency mimicking thrombotic microangiopathy – a sheep in wolf’s clothing?

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Thrombotic microangiopathy (TMA) carries a morbidity and mortality. The classic treatment includes aggressive therapies including plasma exchange. Rarely in severe cobalamin deficiency young patients mimicking TMA.

First patient is a 37-year-old female from Sri Lanka with a two weeks history of fatigue, mild headache, epigastric pain and dyspnoea on exertion. She has coeliac disease and chronic hepatitis C. Prior to this admission, she had a deep vein thrombosis, but no hypercoagulable states were identified. The patient was started on low molecular weight heparin. Her prothrombin time was normal, but D-dimers were elevated. After evaluating potential causes for her livedo reticularis and 1 month later, she was referred to nephrology for the ongoing dyspnoea.

Hb was 58 g/l, WBC 3.6 G/l, Tc 61 G/l, Hct 16 %, Schistoc 12 %, LDH 5883 U/l, Hapt 0.15, eGFR (CKD-EPI) 116 ml/min/1.73 m². A renal biopsy was performed. The pathology showed multi-organ involvement, including the kidney, with characteristic fibrin thrombi in the renal vessels. The patient was started on supportive care, including plasma relocations and folic acid. The patient recovered and was discharged.

Second patient was a 56-year-old kidney transplant recipient with a past medical history of arterial hypertension. She presented with dyspnoea, fatigue, and proteinuria. Her Hb was 82 g/l, WBC 3.5 G/l, Tc 85 G/l, Hct 18 %, Schistoc 20 %, LDH 3295 U/l, Hapt 0.15, eGFR (CKD-EPI) 126 ml/min/1.73 m². A renal biopsy was performed. The pathology showed multi-organ involvement, including the kidney, with characteristic fibrin thrombi in the renal vessels. The patient was started on supportive care, including plasma relocations and folic acid. The patient recovered and was discharged.

Conclusion: Severe cobalamin deficiency may present with symptoms mimicking TMA. Further studies are needed to better understand the pathophysiology of TMA in patients with severe cobalamin deficiency.

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<th>Hb (g/l)</th>
<th>WBC (G/l)</th>
<th>Tc (G/l)</th>
<th>Reti (%)</th>
<th>Schistoc (%)</th>
<th>LDH (U/l)</th>
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<th>eGFR (CKD-EPI)</th>
<th>Vit B12 (ng/l)</th>
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<td>58</td>
<td>3.6</td>
<td>61</td>
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<td>3295</td>
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Progressive renal failure after resection of a neuroendocrine tumor of the small intestine

Michael Girsberger1, Stefan Kalbermatter1, Thomas Menter1, Helmut Hoyer2, Danes Kiss3
1Nephrology, Kantonsspital Baselland, Liestal; 2Pathology University of Basel

A 70-year old man was referred to our clinic with a history of recurring nephrolithiasis, renal insufficiency and metastatic neuroendocrine cancer of the small intestine. The patient was suffering of diarrhoea, night sweats and flushing for 15 years before being diagnosed with a neuroendocrine tumor of the small intestine and metastatic liver disease by computer tomography during evaluation of an episode of urolithiasis. After 145 cm ileoceleal resection of the tumor recurrent nephrolithiasis with urinary tract obstruction and renal insufficiency occurred.

On examination the patient was afebrile, the blood pressure 129/80 mm Hg and the pulse 78 bpm. S-Creatinine was 181 µmol/l with an estimated glomerular filtration rate (GFR) of 34 ml/min/1.73 m² (MDRD). S-Calcium 2.27 mmol/l, albumin 38 g/l, uric acid 469 µmol/l and haemoglobin 144 g/l, 24-hour urine collection revealed heavy hyperoxaluria (2.89 mmol/24h). Renal biopsy showed acute tubular injury with moderate oxalosis and nephrocalcinosis (picture). We diagnosed nephrocalcinosis due to heavy hyperoxaluria after short bowel resection with short bowel syndrome. Acute tubular injury was assumed consecutive to recurring urinary tract obstruction. We initiated a treatment of colestyramin, calcimimcrtat and pankreatin leading to a significant reduction of oxate excretion from 2.89 mmol/24h to 0.97 mmol/24h and continuous improvement of renal function (S-Creatinine 237 umol/l to 135 umol/l).

Conclusion: Renal resection leads to malabsorption of bile acids what induces a compensatory increase of liver production. But when losses exceed production, malabsorption of bile acids causes excessive absorption of oxate, leading to hyperoxaluria and kidney stone formation. The increase in oxate absorption is due to binding of free calcium to fatty acids in the intestinal lumen and to increased colonic permeability to small molecules such as oxate induced by exposure of the colon to nonabsorbed bile salts. The treatment with calcimicrat proved to be very effective on oxate absorption and renal function.

Renal tubulopathies: rare patients, typical patterns

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Background: Renal tubulopathies are rare genetic diseases. Clinical presentation is highly variable whereas blood and urine tests often show specific patterns. Genetic testing allows final diagnosis. We present 4 cases with inborn dysfunction along the renal tubule.


Case 3: 2-year old boy with 2 episodes of urolithiasis (100% calciumoxalate-dihydrate). Parents were first cousins. Further tests: Normal plasma creatinine, hypomagnesemia, mildly elevated uric acid and parathyroid hormone, hypercalciuria and normal ultrasound. Genetic analysis revealed a novel homozygous mutation in the CLDN16-gene (c.316T;p.S105P) confirming a tight-junction dysfunction in the loop of Henle.

Case 4: 7-month old boy: Incidental finding of repeated hypokalaemia. Uneventful family history. Further evaluation: Metabolic alkalosis, hypomagnesemia, hypocalciuria and normal ultrasound, all findings consistent with Gitelman’s syndrome in the distal tubule. Genetic analysis is pending.

Conclusion: Diagnostic algorithm in renal tubulopathies includes precise history, clinical examination, renal ultrasound and targeted analysis of blood/urine metabolites. Specific patterns lead to a clinical hypothesis which can be confirmed by genetic analysis.

Simply medullary cystic kidney disease?!

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Case report: A 26-year old caucasian man presented with paraesthesia and cramps paralleled by stupor and hyperventilation. In his medical history he was suffering from chronic kidney disease KDIGO G3b A1 due to medullary cystic kidney disease. Blood chemistry demonstrated hypocalciuria (Calcium ionized 0.98 mmol/l (1.15–1.27)), severe hypomagnesemia (0.38 mmol/l (0.65–1.10)), slight hypophosphatemia (0.7 mmol/l (0.8–1.6)), and an acute respiratory alkalosis (pH 7.53, pCO2 2.9kPa, Bicarbonate 17.7 mmol/l). The inactive (25-OH-Vit. D3) and active (1,25-(OH)2-Vit. D3) vitamin D3 levels were in the normal range and the parathyroid hormone was slightly elevated (PTH 11.5 pmol/l (1.5–7.6)) due the impaired kidney function (Creatinine 244 µmol/l (eGFR (CKD-EPI) 30.4 ml/min/1.73 m²)). The physical examination revealed muscle cramps in all extremities with lively reflexes. He received intravenously magnesium, calcium and phosphate and all symptoms disappeared. The combination of medullary cystic kidney disease and severe hypomagnesemia revealed a heterozygous mutation in the Hepatocyte Nuclear Factor-1 Beta (HNF1B) gene.

Discussion: HNF1B is a transcription factor, that is expressed in pancreas, liver, and the kidneys. Mutations lead to an early onset diabetes of the young (MODY, Type 5), neonatal diabetes mellitus or cystic dysplasia of the kidneys and mayoccur as de novo or inherited. The association of renal cysts and diabetes with a HNF1B mutation is termed the renal cysts and diabetes (RCAD) syndrome. Our patient also demonstrated an impaired glucose tolerance (HbA1c 5.6%). The most typical renal manifestation presents as cystic kidney disease. The kidney function depends on the phenotype; 15% of the patients develop ESRD. Hypomagnesemia is caused by impaired magnesium reabsorption in the distal convoluted tubule (DCT). Other organ manifestations such as liver abnormalities, hyperuricemia, and genitourinary tract malformations may also occur.

Conclusion: Chronic kidney disease due to cystic dysplasia combined with hypomagnesemia is indicative of HNF1B mutation. Timely diagnosis and therapy increases quality of life and reduces significantly hospitalisations.
C3 glomerulonephritis in a patient with Down’s syndrome: clinicopathological and genetic findings

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An 18-year-old male patient with trisomy 21 presented with acute kidney injury and severe hypertension. Urinalysis showed an active sediment with nephrotic proteinuria. Serum complement C3 levels were decreased with normal C4 concentrations. Ultrasound demonstrated normal kidney size with increased parenchymal echogenicity. A kidney biopsy was performed and mesangial matrix increase with hypercellularity as well as thickening of the glo-merular basement membrane with double contours were detected. Immunofluorescence was positive for granular deposits mainly composed of C3 and focal IgA in the glomerular and mesangial compartment, while IgG was absent. Electron microscopy revealed deposits in the mesangium and glomerulum along with micriviall transformation of the podocyte foot pro-cesses. Based on these findings C3 glomerulonephritis (C3GN) was diagnosed, a recently described disorder and subtype of C3 glomerulopathy. The disorder affects both genders and all ages [1]. The pathogenesis of glomerular injury in C3GN is supposedly resulting from genetic or acquired dysregulation of the complement system, specifically the alternative pathway. The most common acquired abnormality is the C3 Nephritic Factor autoantibody which stabilizes the C3 convertase with a consequent excessive activation of complement. Genetic defects affect mainly mutations of the genes coding for complement factor H (CFH), complement factor I (CFI) and C3 [2]. The presence of these findings in genetic analysis and antibody detection by western immunoblot technique was a heterozygote deletion of CFHR1 and finding in genetic analysis and antibody detection by western immunoblot technique was a heterozygote deletion of CFHR1 and antibody detection by western immunoblot technique was a heterozygote deletion of CFHR1 and C3GN was discussed but not initiated because kidney injury is supposedly resulting from genetic or acquired dysregulation of the complement system, specifically the alternative pathway. The most common acquired abnormality is the C3 Nephritic Factor autoantibody which stabilizes the C3 convertase with a consequent excessive activation of complement. Genetic defects affect mainly mutations of the genes coding for complement factor H (CFH), complement factor I (CFI) and C3 [2]. The presence of these findings in genetic analysis and antibody detection by western immunoblot technique was a heterozygote deletion of CFHR1 and C3GN was discussed but not initiated because kidney injury was supposedly resulting from genetic or acquired dysregulation of the complement system, specifically the alternative pathway. The most common acquired abnormality is the C3 Nephritic Factor autoantibody which stabilizes the C3 convertase with a consequent excessive activation of complement. Genetic defects affect mainly mutations of the genes coding for complement factor H (CFH), complement factor I (CFI) and C3 [2].


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Calciprotein particles induce an inflammatory response in macrophages

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Introduction: Calciprotein particles (CPP) are nanoscale mineral-protein aggregates, which have been found in the blood of patients with chronic kidney disease (CKD). These particles contain amorphous (primary CPP) or crystalline (secondary CPP) calcium phosphate along with serum proteins. We investigated whether CPP might induce inflammatory responses in macrophages.

Methods: Prim. and sec. CPP were generated using phosphate- and calcium-enriched cell culture media with varying amounts of FBS. The particles were characterized morphologically by transmission electron microscopy (TEM). Murine RAW-264.7 macrophage-like cells were exposed to increasing amounts of CPP for 24 hrs. RT-PCR was performed to assess interleukin (IL)-6, IL-1β, TNF-α and NLRP3. The involvement of toll-like receptor (TLR)-4, nuclear factor-kappa B (NF-κB) and NLRP3 was measured using selective chemical inhibitors.

Results: TEM imaging of synthetic CPP revealed populations of amorphous spherical (prim. CPP) and larger crystalline sphindle-shaped particles (sec. CPP). Exposure of RAW-264.7 cells to sec. CPP resulted in a dose-dependent increase in the expression of pro-inflammatory cytokine IL-6, IL-1β, MCP-1, TNF-α and NLRP3. The involvement of TLR-4, NF-κB and NLRP3-dependent pathways were assessed using selective chemical inhibitors.

Conclusions: Thus TLR4 signaling is involved in renal injury, mediates a new pathway in parietal epithelial cell activation with crescent formation, and is a new therapeutic target in renal diseases.
Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; 4Hypertension Unit, University Hospitals of Geneva, Geneva, Switzerland.

Background: Matrix Gla protein (MGP) is a vascular calcification inhibitor. Unmodified and inactive MGP, known as dephosphorylated-uncarboxylated MGP (dp-ucMGP), can be measured in plasma and has been associated inconsistently with different cardiovascular (CV) outcomes, CV markers and mortality. Increased pulse wave velocity (PWV) is a marker of aortic stiffness and an independent predictor of CV events and all-cause mortality. Increased renal resistive index (RRI) is a marker of intra-renal vascular resistance and a predictor of progressive renal dysfunction. In this study we hypothesized that high level of dp-ucMGP is associated with increased aortic stiffness and increased kidney vascular resistance.

Methods: We analyzed data on 1070 participants from the Swiss Kidney Project on Genes in Hypertension (SKIPOGH), SKIPOGH is a family-based cross sectional study exploring the role of genes and kidney hemodynamics in blood pressure (BP) regulation in the general population. Dp-ucMGP was quantified in plasma samples by sandwich ELISA. Aortic PWV was determined by applanation tonometry using carotid and femoral pulse waveforms. Renal doppler sonography were performed using standardized protocols to measure RRI on 3 segmental arteries in each kidney. Multiple regression analysis was used to estimate associations between PWV, RRI and dp-ucMGP adjusting for common CV risk factors and age. After backward elimination, only significant covariates were left in the final model.

Results: We included 970 and 974 participants for PWV and RRI analyses, respectively. Mean PWV was 7.94 ± 2.72 m/s, mean RRI 0.63 ± 0.05 and mean dp-ucMGP 456 ± 260 pM. In multivariate analysis adjusted for age, body mass index, systolic BP, heart rate (HR) and diabetes, dp-ucMGP was associated with PWV (p < .01). Dp-ucMGP was associated with RRI (p <.001) adjusted for age, BMI, systolic and diastolic BP, HR, gender and diabetes.

Conclusion: High level of dp-ucMGP is associated with arterial stiffness and kidney vascular resistance after adjustment for common CV risk factors and age.

Identification of renal cell-type-specific dysregulation of hypoxia-associated transcripts by transcriptome-based network analysis

Natalia Shved1, Gregor Warsow2, David Hoogeweg2, Clemens Cohens, Maja Ljubojevic (BP) regulation in the general population.

Methods: To study the cell-type-specific response to hypoxia and the relevance of HIFs proximal tubular cells and conditionally immortalized podocytes with stable HIF1a and/or HIF2a suppression were generated. Gene expression profiles from cell lines and more than 160 renal biopsies from patients with different CKD stages were obtained using Affymetrix arrays. Weighted Correlation Network Analysis (WGCNA) was applied in order to identify modules of genes that showed highly correlated gene expression across cell groups (Wt, HIF1a, HIF2a, HIF1a+2a) and conditions (hypoxia, normoxia). Gene sets from each module underwent GO-enrichment analysis using the topGO library for R, the Pathway System analysis as well as the transcription factor overrepresentation tool from Genomatix.

Results: Microarray analysis of hypoxia-treated renal cells revealed cell-type-specific HIF1/HIF2 dependencies as well as dysregulation of several pathways in the renal cell lines. WGCNA analysis resulted in gene sets (modules) that were highly correlated within the modules. Further characterization of the modules disclosed common as well as cell-type specific pathways, GO-Terms and transcription factors for each cell line. Expression analysis of hypoxia-associated genes in genome-wide expression profiles revealed correlation of established HIF-target genes with eGFR in cortical tubulointerstitial and glomerular biopsy specimens. These correlations were both positive and negative and in part condition specific.

Conclusions: Our gene expression analysis indicates a condition- and cell-type-specific dysregulation of hypoxia-associated transcripts in renal cells.
Inhibition of sodium-glucose Cotransporter 2 with Dapagliflozin in Han:SPRD rats with Polycystic Kidney Disease

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Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common form of renal cystic diseases. It is associated with mutations in PKD1 and PKD2 genes that encode for the proteins polycystin-1 (PC1) and polycystin-2 (PC2). Dapagliflozin is a selective inhibitor of the sodium-glucose cotransporter 2 (SGLT2) which induces renal glycosuria.

We studied the effect of SGLT2 inhibitor Dapagliflozin on renal function and cyst progression in Han:SPRD rat model of ADPKD. Dapagliflozin (DAPA) (10 mg/kg/day) or vehicle (CON) were administered orally via gavage to 5 week old male Han:SPRD rats (n = 8/group) for a total of 5 weeks. At the end of the treatment, rats were sacrificed and kidneys were harvested for histological analysis.

DAPA-treated rats had a significantly higher urine output (37.9 ± 8.9 vs. 25.0 ± 11.2 ml/d), glucose excretion (13.4 ± 6.2 vs. 0.3 ± 0.1 mmol/d) and water intake (72.5 ± 2.9 vs. 55.0 ± 14.7 ml/d) when compared versus controls after 5 weeks of treatment. In contrast, no changes in body weight were observed. There were no differences in urine excretions of Na+ (1.7 ± 0.5 vs. 1.2 ± 0.2 mmol/d) neither Cl- (2.4 ± 0.7 vs. 1.8 ± 0.4 mmol/d) between DAPA- and vehicle-treated rats. DAPA-treated rats showed significantly higher clearances for creatinine (2.4 ± 0.3 vs. 1.1 ± 0.1 ml/min P = 0.01) and BUN (0.7 ± 0.1 vs. 0.4 ± 0.1 ml/min) after 5 weeks when compared to controls. DAPA-treated rats showed a 2 kg/weight body ratio increase (2.3 ± 0.3 vs. 2.0 ± 0.2 P = 0.01). In contrast, there was a reduction of cyst index (6.9%) when compared DAPA-treated with Vehicle-treated rats (20.3 ± 1.4 vs. 21.9 ± 1.2%) p = 0.05).

Inhibition of glucose reabsorption with the SGLT2-specific inhibitor dapagliflozin caused significant glycosuria in Han:SPRD rats. Unexpectedly, even when the kidney weight increased, cyst index seems to decrease slightly and clearances reflect an enhanced function. This suggests that there is dissociation between kidney weight and cyst growth in this model of ADPKD.
Mediator of ErbB2 Induced Cell Motility in Mineral Homeostasis
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1University of Lausanne, Department of Pharmacology and Toxicology, Lausanne; 2Friedrich Miescher Institut for Biomedical Research, Basel
Background: The 33kDa mediator of ErbB2 induced cell motility (Memo) modulates fibroblast growth factor (FGF) receptor, insulin receptor, estrogen receptor and sphingosine-1-phosphate signaling, but its physiological role is poorly understood. Inducible Memo knockout mice showed signs of premature aging, insulin hypersensitivity and a deranged mineral metabolism similar to the phenotype of FGF-23 or klotho mutant mice, including hypercalcermia, elevated 1,25-OH-D3 and suppressed parafformaldehyde (PTH) (Haenzi B, FASEB J 2013). We tested (1) if Memo is expressed in osteocytes that secrete FGF23 and in osteoclasts and (2) if Memo expression can be regulated.
Methods: C57BL/6 bone marrow monocytes were isolated and differentiated to osteoclasts ex vivo by RANK ligand and colony-stimulating factor. MLO-Y4 osteocytes were grown on collagen. C57BL/6 mice were challenged with 1.69% vs 0.89% vs 0.17% dietary calcium over 7 days (group 2), treated with 1 subcutaneous injection of 2ug/kg 1,25(OH)2-D3 (group 3) or 80 ug/kg PTH (group 4), or treated with daily subcutaneous injections of 15ng 17beta-Estradiol or vehicle over 5 days (group 5). Cells and tissues were prepared for qPCR and immunoblotting using specific probes and anti-Memo antibodies respectively.
Results: Memo was present in osteoclasts ex vivo and in osteocytes in vitro. Varying dietary calcium and phosphate load, or treating 1.25(OH)2-D3, PTH, or estradiol treatment altered experimental control gene expression in the kidney and in the tibia, but Memo RNA and protein abundance remained unchanged.
Conclusion: Memo contains a housekeeping gene's function in normal mineral homeostasis but is not a responsive element to calcitropic stimuli. During the next steps, Memo will be studied in the bone of inducible whole-body Memo KO mice.

Neuropilin1 as a novel regulator of glomerular basement membrane
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Background: Neuropilin1 (Nrp1) is a transmembrane co-receptor classically implicated in the regulation of endothelial cell migration during angiogenesis and thus a potential target of anti-tumorigenic therapy. Recently, clinical trial with antiNrp1 antibodies in cancer patients had to be discontinued due to the high grade proteinuria in all subjects. The aim of this study was therefore to unravel the expression pattern and role of Nrp1 in adult kidney.
Methods: AntiNrp1 neutralizing antibodies with different binding properties were applied to 2–3 weeks old mice. Control animals received mouse IgG. Kidney function was monitored following animal sacrifice after 5 weeks of treatment.
Results: In adult mouse kidney, Nrp1 was expressed in mesangial cells and pericytes of kidney peritubular capillaries in addition to already described localization in endothelium. Administration of antiNrp1 antibodies caused progressive proteinuria, however only in male mice. Kidney histology showed mild mesangial expansion, and electron microscopy revealed thickened and folded glomerular basement membrane (GBM). The foot process and endothelial fenestrae showed both, relative intaglio, infiltrative lamellae of laminin5, and agrin and neuregulin were upregulated following Nrp1 blockade, whereas vegf was downregulated. Surprisingly, VEGFR2 receptor was hyperphosphorylated upon Nrp1 inhibition. Further in vitro studies with primary mesangial human and mouse cell lines showed increased cell proliferation upon Nrp1 blockade and abnormal actin reorganization when Nrp1 knock down cells were stimulated with PDGF-Bb.
Conclusions: This study shows an unexpected role of Nrp1 in maintenance of GBM and suggests a critical involvement of mesangial Nrp1 in this process.

Oncostatin M receptor is a sensitive and early marker of kidney injury
Barbara Pedycz1, Pang Young2, Catherine Compston1, Valerie Luoytk1, Julie Hof2, Valeria Mass1, Lin-Fu Zhu1, Donald Gynocho1, Rachel Khadaroo1, Thomas Mueller1
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Background: Early and sensitive biomarkers for acute kidney injury are needed for diagnostic and therapeutic purposes. The IL6-family receptor Oncostatin M (OSMR) was shown to be the most significantly induced acute phase protein in kidney tissues from deceased compared to living donors.
Methods: Microarray-based gene transcription levels of OSMR in 0-hr biopsies of 67 human deceased donor kidneys were compared between groups stratified for normal, mild-to-moderate, and severely impaired function. In mice undergoing unilateral kidney clamping (AKI) induced by local ischemia reperfusion and undergoing cecal ligation and puncture (AKI) induced by systemic infection) kidneys, hearts, livers and lungs were harvested at different time points post-injury and transcript levels of pre-selected injury markers were compared with OSMR expression measured by array or RT-PCR based technologies. Transcriptome changes were analyzed using GeneSpring and Ingenuity software packages.
Results: In the human 0-hr biopsies OSMR-transcript levels compared to established injury markers such as TIMP1 and NGAL changed most significantly according to degree of functional impairment (corr. P <0.001). The transcriptome analysis further identified more than 60 other injury marker genes with similar expression patterns than OSMR (r >0.95).
The mice models also indicated that organ injury induced by renal ischemia or systemic infection/sepsis is associated with increased OSMR levels already at early time points (at least 3 hrs after injury) and in all investigated organs. In addition the severity of injury, as shown on histology, changes in renal function or extent of lesion induced, correlated with the degree of OSMR expression.
Conclusions: Our results indicate that OSMR is a novel, promising biomarker of organ injury, in particular reflecting degree of kidney injury at a very early time point.

Pathophysiology of Chronic Kidney Disease in Methylessalonic Aciduria (MMA)  
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Background: MMA is an inborn error of metabolism caused by mutations in the mitochondrial enzyme Methylaminocarboxy-CoA Mutase (MCM) or by mutations affecting the synthesis of its cofactor adenosylcobalamin. MMA leads to life-threatening metabolic crisis occurring in the neonatal period, with chronic kidney disease (CKD) and end stage renal failure as classical long-term complications. The role of MCM in the kidney and the pathophysiology of CKD associated with MMA are unknown.
Methods: We characterized the expression profile of MCM in mouse kidney and its subcellular distribution in the human proximal tubule cell line HK2 using RT-qPCR, immunoblot analysis and STED microscopy. We next used renal cells obtained from the urine of MMA patients as a disease model to characterize the pathophysiology of MMA.
Results: MCM was detected in the proximal tubule and in distal nephron segments of the mouse kidney identified by co-distribution of specific markers. Co-staining with TOM20, an outer membrane mitochondrial import receptor, evidenced that MCM is localized in the mitochondrial matrix. Enzymatic MCM activity measurements in urinary cells from the MMA patients are in line with the metabolic phenotype of these patients. Differences in mitochondrial morphology and a reduction in mitochondrial mass could be observed in the MMA cells in baseline conditions. Starvation for 48h showed oxidative stress and changes in the mitochondrial morphology in MMA but not in control cells. Analysis of mitochondrial function by live cell imaging showed enhanced ROS production and reduced mobility of swollen mitochondria in MMA versus normal cells.
Conclusions: These studies reveal a complex distribution of MCM in the mitochondria of epithelial cells lining various renal tubular segments. Urinary cells derived from MMA patients show defective handling of starvation, with increased oxidative stress and defective mitochondria. These data provide novel insights into the mechanisms of CKD in MMA.
Proteomic Signature of Hypertension-induced Damage in the Two-Kidney, One-Clip (2K1C) Rat Model

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1 Department of Clinical Medicine, University of Bergen, Bergen, Norway; 2Department of Biomedicine, University of Bergen, Bergen, Norway; 3Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden; 4INSERM U702, Hopital Tenon, Paris, France;

Background: Hypertensive nephrosclerosis is one of the most frequent causes of chronic kidney failure leading to end-stage renal disease (ESRD). Proteome analysis potentially improves the pathophysiological understanding and diagnostic precision of this disorder. In the present exploratory study we investigated experimental nephrosclerosis in the Two-Kidney, One-Clip (2K1C) hypertensive rat model.

Methods: The renal cortex proteome from juxtamedullary cortex (JMC) and outer cortex (OC) of 2K1C male Wistar-Hannover rats (n = 4) was compared with sham-operated controls (n = 6), using mass spectrometry-based quantitative proteomics. We combined a liquid chromatographic gradient to improve peptide and protein identification. Immunohistology was used for independent confirmation of abundance.

Results: We identified 1,724 proteins, of which 1,434 were quantified with ≥2 unique peptides. Comparative proteomics revealed 608 proteins, including the PDGF-R signalling pathway, with different abundances between the non-clipped kidney of hypertensive 2K1C rats and the corresponding kidney of normotensive controls (p <0.05, absolute fold change ≥1.5). Among the most significantly altered proteins in whole cortex were periostin, transgelin, and creatine kinase B-type. Relative abundance of periostin alone allowed clear classification of 2K1C and controls. Enrichment of periostin in 2K1C rats was verified by immunohistology showing positivity especially around fibrotic vessels.

Conclusion: The proteome is altered in hypertension-induced kidney damage. We propose periostin, especially in combination with transgelin and creatine kinase B-type as possible proteomic classifier to distinguish hypertensive nephrosclerosis from normal tissue. This classifier needs to be further validated with respect to early diagnosis of fibrosis, prognosis, and its potential as a novel molecular target for pharmacological interventions.

Poster presentations – Basic science / Genetics

P 38

Sex-specific expression of genes involved in uric acid handling in mice

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Background: In several species, females have lower serum uric acid (SUA) levels compared to males, an observation largely dependent on sex hormones, but independent of the presence of uricase. In human, this is illustrated by the fact that men are more prone to develop gout flares or uric acid kidney stones. The underlying mechanism is however not precisely known and we ask here whether production, degradation or excretion of uric acid may account for the observed difference between genders.

Methods: We used C57BL/6N mice to address the role of the liver, ileum, colon and the kidney in sex-specific difference in SUA levels.

Results: We first confirmed that SUA concentrations are 36.1 ± 18.7% lower in female than male mice. Interestingly, the fractional excretion of uric acid was identical between males and females, suggesting that the overall renal tubular function was similar. We then performed a detailed expression analysis of genes involved in uric acid production (XDH), degradation (UOX) or transport in the liver, ileum, colon and the kidney (MRP4, ABCG2, GLUT9a, GLUT9b, SURAT1, OAT1, OAT3, OAT10, NPT1, NPT4). Several genes were found to display a sex-dependent expression pattern eventually suggesting that females may have increased MRP4-mediated UA excretion in the intestine.

Conclusions: Our results may have consequences beyond uric acid handling as several of these transporters are also involved in drug secretion. Sex-differences in the expression of these transporters should be taken into consideration.

Renal sensitivity to orthostatic stress: a comparison of neural-hormonal and renal hemodynamic responses between obese patients and healthy volunteers

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Objective: Obesity is associated with an increased risk of developing hypertension and chronic kidney disease. However the mechanisms involved in obesity-related hypertension are fully elucidated. Animal studies have suggested that the sympathetic nervous system and the ability to excrete sodium are key factors involved in the development of hypertension.

The objective of the study was to compare neuro-hormonal and renal responses to orthostatic stress induced by lower body negative pressure (LBNP) in healthy volunteers and obese patients.

Method and design: This was a single center prospective study. Healthy volunteers and obese patients were included in a 1:1 ratio. Participants' characteristics, leptin and adiponectin were measured at baseline. Blood pressure (BP), heart rate, plasma renin activity (PRA), plasma aldosterone, norepinephrine (NE), sodium excretion, glomerular filtration rate (GFR, inulin clearance) and renal plasma flow (RPF, PAG clearance) were measured at baseline and after one hour of LBNP.

Results: 48 patients were included in this study, 25 healthy controls (HC) and 23 obese patients (OB). Mean BMI was 22.0 ± 2.2 kg/m² in HC and 34.7 ± 4.6 kg/m² in OB (p <0.05). Hemodynamic, neuro-hormonal and renal responses to LBNP are shown in table 1.

Table 1: hemodynamic, renal and neuro-hormonal responses to LBNP in HC and OB

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HC Baseline</th>
<th>LBNP</th>
<th></th>
<th>OB Baseline</th>
<th>LBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>110 ± 9</td>
<td>113 ± 10*</td>
<td></td>
<td>128 ± 15*</td>
<td>134 ± 15*</td>
</tr>
<tr>
<td><strong>Diasstolic BP (mmHg)</strong></td>
<td>64 ± 6</td>
<td>69 ± 7*</td>
<td></td>
<td>74 ± 11*</td>
<td>84 ± 13*</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>63 ± 8</td>
<td>62 ± 8</td>
<td></td>
<td>65 ± 7</td>
<td>68 ± 9*</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate (ml/min)</strong></td>
<td>102.4 ± 21</td>
<td>90.0 ± 23*</td>
<td></td>
<td>102.0 ± 45</td>
<td>102.1 ± 37</td>
</tr>
<tr>
<td><strong>Renal plasma flow (ml/min)</strong></td>
<td>576 (434-675)</td>
<td>514 (349-605)*</td>
<td></td>
<td>611 (284-715)</td>
<td>562 (415-656)</td>
</tr>
<tr>
<td><strong>Sodium excretion (µmol/min)</strong></td>
<td>236 ± 78</td>
<td>231 ± 192*</td>
<td></td>
<td>234 ± 113</td>
<td>214 ± 49</td>
</tr>
<tr>
<td><strong>NE (nm)</strong></td>
<td>1.14 (0.92-1.37)</td>
<td>1.46 (1.17-2.1)*</td>
<td></td>
<td>1.03 (0.76-1.46)</td>
<td>1.54 (1.07-1.82)*</td>
</tr>
<tr>
<td><strong>PRA (ng/ml/min)</strong></td>
<td>0.35 (0.3-0.5)</td>
<td>0.5 (0.25-0.8)*</td>
<td></td>
<td>0.5 (0.08-0.6)</td>
<td>0.5 (0.2-1.0)*</td>
</tr>
<tr>
<td><strong>Aldosterone (pg/ml)</strong></td>
<td>28.5 (21.0-50.9)</td>
<td>29.5 (20.8-56.1)</td>
<td></td>
<td>39.8 (18.0-57.2)</td>
<td>42.4 (27.3-51.8)</td>
</tr>
</tbody>
</table>

Data are means ± SD or medians and interquartile range. HC: healthy control; OB: obese; LBNP: lower body negative pressure; BP: blood pressure; NE: norepinephrine; PRA: plasma renin activity. * P<0.05 vs baseline, † P<0.05 vs HC.
At baseline, systolic BP, diastolic BP were significantly higher in OB than in HC. During LBNP, systolic and diastolic BP increased in both groups. HR increased in OB but not in HC (+2.9 vs. −1.2 beats/min, p = 0.01). GFR and RPF decreased significantly in HC, respectively (−12 ± 26 ml/min); (−85 ml/min (−152.3), but not in OB patients.

Conclusion: Obese patients seem to be able to maintain GFR and sodium excretion compared to healthy volunteer during an orthostatic stress. This may be secondary to increased systemic blood pressure and/or cardiac output as suggested by increase in heart rate during the LBNP period.

Poster presentations – Transplantation

ABO incompatible kidney transplantation from an anti-hepatitis C virus antibody positive-RNA negative donor into an anti-hepatitis C virus antibody negative recipients

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Background: Due to a decreased number of deceased donors, continuous efforts are needed to avoid discarding potential living donors. Anti-hepatitis C virus (HCV) positive donors are not considered suitable candidates for living kidney donation with little known regarding outcomes of such a procedure.

Methods: A 66 year old male, blood type O, had been on dialysis since 2007. Evaluation of his 62-year old wife, blood type A, showed positive anti-HCV antibodies in serum, undetectable HCV-RNA, normal serum liver enzymes and Fibroscan. A multidisciplinary round agreed on the transplantation and informed consent was obtained from both the donor and the recipient. Immunosuppression consisted of 375 mg/m2 rituximab 4 weeks before the transplantation, tacrolimus, mycophenolate mofetil and prednisolone starting 1 week preoperatively, and basiliximab induction. Specific immunosuppression was not required (low anti-A antibodies).

Results: The transplantation was successful with few complications during the first year and, at one-year post transplant, the recipient’s liver function tests remained normal, anti-HCV antibodies were negative and HCV RNA was undetectable. A liver biopsy was not deemed indicated. Protocol kidney biopsies performed at 3 and 12 months showed no rejection.

Conclusions: To our knowledge, we report the first ABO incompatible kidney transplantation from an anti-HCV antibody positive–HCV RNA negative donor into an anti-HCV antibody negative recipient, advocating that anti-HCV antibody positive-RNA negative people deserve consideration for living kidney donation.

Distinct radiological CT-patterns of Pneumocystis jirovecii pneumonia between Renal transplant recipients and HIV-positive patients

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Background: Pneumocystis jirovecii pneumonia (PCP) is a fungal infection with potentially life-threatening complications. Renal transplant recipients (RTR) and individuals who are immunocompromised (i.e. HIV patients) are at substantial risk for PCP.

Aim: To compare CT patterns of PCP between HIV-positive patients and renal transplant recipients (RTR).

Methods: Retrospective analysis of 40 immunocompromised patients (16 HIV, 24 RTR) presenting with CT-radiographic findings and established PCP diagnosis during hospitalization. Patient data were obtained from the Bernese HIV- and RTR-cohort of the University Hospital of Bern. Classification of the lung patterns was performed according to the Fleischner society recommendations.

Results: In 40 immunocompromised patients we identified a distinct distribution in the lungs of the HIV patients infected with PCP, which showed significantly more areas with a diffuse pattern of scattering (81 ± 10% HIV vs. 23 ± 5% RTR, p = 0.02). Multifocal pattern distribution, central lung parenchyma affection, lung peripheral involvement, cysts and subpleural sparing did not differ significantly between the groups. Ground glass nodules >5 mm were significantly more common in the HIV patients than the RTR (69 ± 12% vs. 4 ± 4%; p = 0.0004). Enlarged hilar lymph nodes were a distinct characteristic of HIV-associated PCP, since no such finding was identified in RTR (0% vs. 44 ± 12%; p = 0.0123).

Conclusions: Radiographic differences in PCP are present between HIV-patients and RTR. Distinct patterns should be considered in the differential diagnosis of pulmonary infiltrates. These differences potentially reflect immunological differences in the host immune response.

Outcome of transitional cell cancer in renal transplant recipients

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Background: Patients after renal transplantation are at increased risk for the development of malignancies. The risk for the development of a transitional cell cancer (TCC) is about 2–4 fold higher for renal/ureter TCC compared to the general population. The impact of TCC after renal transplantation on the patients and
Poster presentations – Transplantation

Outcomes at 3-years in EBV+ Recipients of Deceased Donor Kidneys from Two Randomized Trials (BENEFIT and BENEFIT-EXT) Comparing Belatacept vs Cyclosporine

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Background: Belatacept (bela; less intensive [LI] regimen) is approved to treat EBV+ adult kidney transplant patients (pts). Here we present post-hoc analyses of 3-year outcomes in EBV+ pts in the pooled populations of BENEFIT and BENEFIT-EXT who received a deceased donor kidney.

Methods: In BENEFIT, pts received living donor (n = 385) or SCD kidneys (n = 281). BENEFIT-EXT (N = 543), pts received ECD kidneys (defined as UNOS criteria ECD, cold ischemia time ≥24 hour, or donation after cardiac death). In both trials, pts were randomized to more intensive (MI) or LI bela or CsA. Here we evaluated the pooled cohort for pt and graft survival, cGFR, acute rejection (AR), and a composite end point (EP): death, graft loss or GFR <30.

Results: In this cohort, 250 MI, 247 LI, and 249 CsA pts were EBV+ at the time of transplant and received a deceased donor kidney. Pt/graft survival at Month (M) 36: 211 (84%) MI, 217 (88%) LI, and 205 (82%) CsA. The rate of AR through M36 was 22% MI, 17% LI, 14% CsA. Mean (SD) MDRD cGFR at M36 was 50.5 (30) MI, 51.6 (27) LI, 35.0 (23) mL/min/1.73 m² CsA. Fewer bela-treated pts vs CsA reached the composite EP (figure). Rates of serious adverse events were generally similar across treatment arms.

Conclusions: Results of this post-hoc analysis demonstrate the following for EBV+ pts in BENEFIT and BENEFIT-EXT receiving a deceased donor kidney, vs CsA: similar pt/graft survival with bela, improved renal function for both bela regimens, and similar rate of AR for bela (approved LI regimen only). For both bela regimens, the rate of composite EP was lower with bela vs CsA. The positive outcomes in this subset of EBV+ pts are consistent with results observed with bela in the overall populations of BENEFIT and BENEFIT-EXT.
Outcomes at 3-years in EBV+ Recipients of UNOS Criteria ECD Kidneys from a Randomized Trial (BENEFIT-EXT) Comparing Belatacept vs Cyclosporine

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1Medical University of Vienna, Austria; 2University Hospital of Bicêtre, France.

Background: Prevention of bone mineral density (BMD) loss after kidney transplantation has not been studied. Denosumab targets RANK ligand, inhibits bone resorption and is not nephrotoxic. Whether denosumab is effective to prevent BMD loss after renal transplantation has not been studied.

Methods: In BENEFIT-EXT, 543 pts received ECD kidneys per UNOS criteria, anticipated cold ischemia time (CIT) >24 hrs, or donation after cardiac death. UNOS criteria included age ≥60 years or age 50–59 years with ≥2 other risk factors (cerebrovascular accident, hypertension, or cardiac death. UNOS criteria included age ≥60 years or age 50–59 years with ≥2 other risk factors (cerebrovascular accident, hypertension, or serum creatinine >1.5 mg/dL). Pts were randomized to receive CsA or more intensive (MI) or LI bela. Here we evaluated pt and graft survival, cGFR, acute rejection (AR), and a composite end point (EP) of time to death, graft loss or cGFR<30 mL/min/1.73 m².

Results: Patients (n = 90; mean age 48 ± 13 years; 63% males) had a baseline eGFR of 52.7 ± 15.0 mL/min/1.73 m². By DXA (lumbar spine) 37% were osteopenic and 11% osteoporotic. Baseline calcium (2.32 ± 0.19 mmol/l), phosphate (0.58 ± 0.20 mmol/l) and PTH (153.7 ± 145.2 ng/l) indicated persistent hyperparathyroidism. Denosumab-treated patients had significantly lower plasma levels of the bone resorption marker β-CTX (0.22 ± 0.20 vs 0.79 ± 0.51 µg/l; p <0.001) and the bone formation markers PINP (55 ± 69 vs 150 ± 93 µg/l; p <0.001) and BSAP (10.7 ± 8.9 vs 20.5 ± 11.5 µg/l; p <0.02) at 12 months. Denosumab treatment was well tolerated, except for a higher occurrence of urinary tract infections (60% vs 32% of patients, p = 0.047).

Conclusions: The POSTOP trial represents the first study to investigate whether denosumab prevents BMD loss in the first year after kidney transplantation. Measurements of β-CTX, PINP and BSAP can be used to monitor the effect of denosumab treatment. Further analyses are needed to correlate the changes of these biomarkers with the effect of denosumab on BMD.
Risk stratification for rejection and infection after kidney transplantation

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Background: Current immunosuppressive therapy is very effective in preventing acute renal allograft rejection, but is inevitably related to adverse effects. Keeping the delicate balance between the control of rejection and the risk for infections emerged as a critical aim in modern transplantation medicine. The aim of this study was to establish a risk stratification model for rejection and infection after kidney transplantation.

Methods: In a post-hoc analysis of the ELITE-Symphony trial (n = 1190) we characterized the incidence and pre-transplant predictors of severe infection and biopsy-proven acute rejection episodes in the first year after transplantation with the goal of identifying patient groups that may benefit from tailored immunosuppressive protocols. The approach was validated using two independent data sets as well as an external study population from the FDCC trial (n = 901).

Results: In the first year after kidney transplantation infections were frequent (incidence 25.5%) and the principal cause of death in kidney transplantation patients. Death rate was significantly influenced by recipient age, donor type, HLA mismatches and CMV status were associated with infection; donor type, HLA-mismatches and type of immunosuppressive therapy with rejection. Based on these data we developed a risk model that partitions the two-dimensional risk space for infection and rejection after kidney transplantation. The validation work provided evidence for the applicability of the proposed risk model to an independent cohort.

Conclusions: An integrated assessment of the risk for rejection and infection is necessary to improve clinical management of transplant recipients and to design future transplant studies. The proposed risk stratification approach might help personalize immunosuppressive therapy.

Role of lymphocytes in renal allograft rejection

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Background: Kidney transplantation is the most common form of solid organ transplantation. Recruitment of inflammatory cells is a hallmark of chronic renal allograft injury and may result in the formation of nodular infiltrates (with defined microarchitecture). Lymphocytes (LT) mediate the communication between lymphocytes and stromal cells and play a pivotal role in the formation of lymphoid tissue. The aim of this study was to assess the expression of ligands and receptors of the LT system in renal allograft injury.

Methods and Results: We investigated differentially expressed components of the LT system in cDNA microarrays from human renal allograft biopsies. We were able to demonstrate the upregulation of LTBeta, LIGHT, HVEM and TNF receptors 1 and 2 in acute and chronic rejection in human renal biopsies. In addition we found evidence for the activation of the NFkappaB pathway, most likely a consequence of LTbeta receptor activation. By RT-PCR robust upregulation of LTalpha, LTBeta and LIGHT was shown in borderline and acute rejection. In human leukocytes, Claude Carat, Corrado Berenson7, Thomas Fehr5, University Hospital Zurich, Division of Nephrology and Dialysis; 8Institute of Pathology, University of Zurich, Switzerland; 9Clinical Institute of Pathology, University of Vienna, Austria; 10Institute of Virology, University of Basle, Switzerland

Sarcopenic obesity in male renal transplant recipients

Vasileios Devetzis, Uyen Huynh-Do, Spyridon Arampatzis1, Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Switzerland; 2Department of Dermatology, University Hospital Zurich, Switzerland

Background: Although abnormal body compositions such as sarcopenic obesity (SO), which describes the condition in which high fat mass (obesity) co-exists with low muscle mass (sarcopenia), are clinical relevant phenotypes, data on their prevalence and impact on bone mineral status in renal transplant recipients (RTR) are currently lacking.

Methods: To investigate the prevalence of sarcopenia and obesity after renal transplantation and their impact on bone mineral density, we conducted during a 48 months period a cross sectional analysis in 78 male RTR with a stable renal function (eGFR >30 ml/min). Body composition and bone mineral density were evaluated by dual X-ray absorptiometry (DXA). Obesity was defined as percentage of whole body fat mass >27% and sarcopenia as appendicular skeletal muscle mass ≤7.26 kg/m².

Results: The prevalence rates of sarcopenia and obesity in our cohort were 28% (22/78), and 51% (40/78), respectively. Sarcopenic obesity was present in 15% (12/78) of RTR. Those classified as SO had similar clinical (age, months after transplantation, BMI, glaucorticosteroid doses, rejection episodes) and biochemical (eGFR, serum intact parathyroid hormone and 25-hydroxyvitamin D levels) profiles when compared to non-sarcopenic RTR. Bone mineral density at total body and femur were lower in SO than in NSO (mean ± SD SO lumbar spine: 1.030 ± 0.168 g/cm², femoral neck: 0.764 ± 0.125 g/cm² and proximal femur: 0.916 ± 0.162 g/cm²) compared to non-sarcopenic RTR (lumbar spine: 0.930 ± 0.142 g/cm², p = 0.03, femoral neck: 0.645 ± 0.137 g/cm², p = 0.002 and proximal femur: 0.790 ± 0.154, p = 0.008).

Conclusion: Obesity and sarcopenia are highly prevalent after renal transplantation and may potentiate each other, thus maximizing their deleterious effects on skeletal health.
The inflammatory burden determined by urinary CXCL10 chemokine levels predicts long-term renal allograft outcome

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Background: Even nowadays, graft loss is a clinically evident problem. We have previously demonstrated that the urinary CXCL10 chemokine is a biomarker for clinical and subclinical tubulo-interstitial inflammation. The aim of the current study was to investigate whether urinary CXCL10 levels measured within the first 6 months – reflecting the early inflammatory burden – can predict long-term outcome.

Methods: The study cohort consisted of 154 kidney allograft recipients with two surveillance biopsies/ corresponding urine specimens until six months post-transplant (i.e. performed at three and six months).

Outcomes were prospectively determined during a minimal follow-up of five years (range 5–8.5 y). The sum of urinary CXCL10 concentration obtained at biopsy time-points was calculated and the arithmetic mean used for determining the “inflammatory burden”.

Evaluation endpoints were graft loss; decline of renal function (i.e. >20% decrease of eGFR between six months and last follow-up); clinically evident late rejection (i.e. after six months post-transplant).

Results: After a minimal follow-up of five years 43/154 patients reached the combined graft endpoint (28%). CXCL10 levels were significantly higher in these patients compared to kidney allograft recipients with a stable post-transplant course (median urinary CXCL10/creatinine ratio of 2.0 ng/mmol vs. 0.9 gnmol/mol; p = 0.005).

In a multivariable cox-regression model including baseline and histological variables independent predictors of combined graft endpoint were high CXCL10 levels (HR of 1.14 (95% CI, 1.18–0.89; p = 0.001)) and total HLA-mismatches (HR of 1.36 (95% CI, 1.04–1.79; p = 0.03)), while donor age/height, presence of BKV viremia, proteinuria at six months and occurrence of early acute rejection were not (p ≥0.05).

A CXCL10 inflammatory burden of <1.06 ng/mmol (determined by ROC analysis) was associated with a 90% endpoint-free 5-year survival compared to 60% with urinary CXCL10 >1.06 ng/mmol (p <0.0001).

Conclusion: The early inflammatory burden determined by urinary CXCL10 levels is independent and strong predictor of long-term renal allograft outcome.

What should the post-transplant creatinine be?

An approach to better assess kidney transplant function

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Background: Knowledge of an optimal expected serum creatinine (SCr) would be useful to detect early renal dysfunction after transplantation. Current measurements of post-transplant function rely exclusively on the recipient’s SCr and derived calculations (eGFR), based on recipient age, weight and gender. Renal function post-transplant, however, also depends on the donor supply of functioning nephrons and adaptation in GFR of a single kidney.

Methods: We developed a formula to predict the optimal expected SCr post-transplant derived from donor and recipient Cockroft-Gault GFRs, and adjusted for the single kidney adaptive response, obtained from measurements in 27 living donors pre- and post-donation. We compared the expected SCr with the lowest observed SCr in a cohort of living (79) and deceased (67) donor allograft recipients followed over five years.

Results: The remaining, native kidneys showed a highly reproducible adaptive response of about 36% increase in GFR post-donation in the living donors. At time of transplantation donor and recipient demographics were similar between the living and deceased donor groups. Expected SCr correlated well with the observed SCr in both living and deceased donor kidney recipients, however correlation was stronger between expected and observed SCr in deceased donor kidney recipients.

Recipient to donor body weight ratio was significantly associated with the difference between expected and observed SCr, suggesting that recipient body weight is a major predictor of post-transplant renal function. The difference between expected and observed SCr was significantly greater among deceased donor kidney recipients, suggesting poorer function in these patients, which was not detected by SCr or estimated GFR (CKD-EPI, MDRD or G F formula) alone.

Conclusions: Calculation of expected renal function for a given donor-recipient combination adds relevant information to assessment of allograft function. Future studies will permit determination of a threshold difference between expected and observed SCr that should trigger investigation and potential intervention to improve allograft function.
FGF23 and markers of phosphate and calcium homeostasis in subjects with preserved renal function

Hypomagnesemia, mostly associated with hypocalcemic hypoparathyroidism and hypokalemia, was reported in 53 individuals on long-term proton-pump inhibitors. When measured, hypomagnesemia was always accompanied by hypomagnesuria. Hypomagnesemia recurred following replacement of one proton-pump inhibitor with another but not on treatment with a histamine type 2 receptor antagonist. No significant association between hypomagnesemia and proton-pump inhibitors was noted in 3 out of 4 case-control, cross-sectional studies including less than 500 patients each. On the contrary, a significant association was observed in 4 case-control, cross-sectional studies including less than 500 patients each. On the contrary, a significant association was observed in 5 larger, well-designed studies. Both in case reports as well as in case-control studies, the tendency to hypomagnesemia was more prominent in subjects concurrently managed with agents possibly inducing hypomagnesemia such as cisplatin, carboplatin and diuretics.

Conclusions: Proton-pump inhibitors may cause hypomagnesemia along with hypocalcemia and hypokalemia. The concurrent demonstration of hypomagnesemia and hypomagnesuria suggests intestinal magnesium absorption impairment as the possible mechanism of this adverse drug reaction. Switching to a histamine type 2 receptor antagonist may be attempted.

Why muscle cramps occur at night: Circadian rhythm and factors associated with fractional excretion of magnesium in a population based study

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Background: FGF23 is a bone-derived hormone that causes phosphaturia, inhibition of 1,25-OH Vitamin D synthesis, reduction of PTH secretion and induction of left ventricular hypertrophy. The study of FGF23 regulation in adult subjects with preserved renal function has received little attention thus far.

Methods: We examined cross-sectionally in 1128 participants of the SKIPOGH cohort, a large family-based multi-center observational study, the associations of c-terminal FGF23 levels with markers of diet, mineral metabolism and renal function. For statistical analysis we constructed mixed linear models with log-transformed FGF23 as the dependent variable and family as random effect.

Results: Mean eGFR (CKD-EPI) was 96.3 ml/min/1.73 m^2 (SD 17.8 ml/min/1.73 m^2), mean FGF23 levels were 86.1 fU/ml (SD 79.3 fU/ml). Log FGF23 levels were associated inversely with eGFR (β: –0.01, SE: 0.00; p = 5.62x10^-11). In multivariate analysis adjusting for age, gender, BMI and eGFR, higher FGF23 levels were positively associated with plasma phosphate levels (β: 0.03, SE: 0.09; p = 6.96x10^{-4}) but not with phosphate intake, 24h phosphate excretion or fractional excretion of phosphate. Interestingly, FGF23 was also independently associated with plasma calcium (β: 0.36, SE: 0.16; p = 0.022), 24h calcium excretion (β: –0.02, SE: 0.01; p = 9.07x10^{-4}) and fractional excretion of calcium (β: –0.05, SE: 0.01; p = 1.62x10^{-4}) but not with 25-OH Vitamin D.

Conclusions: We identified a novel association of FGF23 with plasma calcium and excretion of calcium in participants with largely preserved renal function. While FGF23 levels were positively associated with plasma phosphate levels, we surprisingly found no association of FGF23 with fractional excretion of phosphate. Thus, in subjects with preserved renal function, FGF23 may affect plasma phosphate levels independently of renal phosphate excretion.

Poster presentations – Hypertension / Mineral / Electrolytes
Cytochrome P450 3A 4/5 (CYP3A4/5) activity is associated with white coat blood pressure in a Swiss population based study (SKIPOGH STUDY)

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Background: Animal studies suggest that CYP3A (3A4/3A5) activity may play a role in arterial hypertension. 6β-hydroxycortisol/cortisol ratio is a known marker of CYP3A activity, which can be induced by the pregnane X nuclear receptor (PXR). We investigated the association of various blood pressure (BP) traits with CYP3A activity in a Swiss population-based sample.

Methods: SKIPOGH (Swiss Kidney Project on Genes in Hypertension) is a family-based multi-centric cross-sectional study. Office and daytime ambulatory BP were measured using validated devices. We used the urinary 6β-hydroxycortisol/cortisol ratio to estimate CYP3A activity. We analyzed the association of office and ambulatory daytime systolic BP (SBP), diastolic BP (DBP), heart rate (HR), proportional white-coat effect (office BP-mean ambulatory daytime BP)/mean ambulatory daytime BP with log-transformed CYP3A activity using mixed linear regression to account for familial correlations. Analyses were adjusted for age, sex, body mass index (BMI), study centre, renal function, medication and smoking status.

Results: The 254 men and 288 women included in this analysis had mean (±SD) age of 48.0 (18.2) and 49.7 (17.3) years and mean BMI of 26.0(3.8) and 24.3(4.4) kg/m2, respectively. Mean SBP/DBP was 119.3(17.2)/75.2(9.3) mm Hg for office, 120.8(12.7)/79.8(8.4) for daytime and −1.5(12.1)/−4.0(7.9) for the white-coat effect. Office, but not daytime ambulatory SBP, DBP were associated negatively with log-day CYP3A activity (P <0.05). White-coat effects were associated negatively with log-day CYP3A activity (P <0.001).

Conclusions: We found office SBP/DBP and white-coat effects to be associated negatively with estimated day CYP3A activity. These results may reflect regulation of CYP3A activity through cross-talks between glucocorticoid receptor and PXR. Our findings are in line with a potential involvement of detoxification enzymes in blood pressure regulation, in particular when stress-induced.

Taste acceptability of pulverized brand-name and generic drugs containing amlodipine or candesartan

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Background: Trials with pulverized brand-name antihypertensive drugs among children suggest that, from the perspective of taste acceptability, crushed candesartan, chlorthalidone, hydrochlorothiazide, lecanidipine and lisinopril should be preferred to pulverized amlodipine, atenolol, bisoprolol, enalapril, ibersartan, losartan, ramipril, telmisartan and valsartan. Brand-name antihypertensive drugs and the corresponding generic medicines have never been compared with respect to their taste acceptability.

Methods: Many observations indicate that both children and adults dislike drugs with a bitter taste and like those with a neutral taste. We therefore investigated among healthy health care workers the taste acceptability of a pulverized 1 mg-test dose of the brand-name and two generics containing either the dihydropyridine calcium-channel blocker amlodipine (Norvasc®), Amlodipin-Mepha® and Amlodipin Pfizer® or the angiotensin receptor antagonist candesartan (Atacand®, Cansartan-Mepha® and Pernzec®). For this purpose, a smiley-face protocol was combined with pairwise concentration trials and may resist atrial angiotensinergic reflexes via synaptic Ang receptors to control blood pressure.

Results: Between November and December 2013, the taste test was performed among 19 nurses (15 female and 4 male subjects) and 12 physicians (5 female and 7 male subjects) aged between 25 and

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Impact of uninephrectomy on body L-arginine homeostasis and blood pressure control (NCCR project)

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L-arginine plays an important role as precursor for a variety of physiologically important substances including citrulline, urea, ornithine, proline and nitric oxide, and the kidney is a major site for its metabolism. Uninephrectomy (UNX) is observed to cause an increase in the size of the remnant kidney and, to some degree, compensation of the glomerular filtration rate. As very little is known about UNX-induced effects on blood pressure control and expression levels of transporters and enzymes involved in arginine metabolism, we are using mice to test the hypothesis that renal mass reduction impacts on Arg metabolism and possibly thereby affects blood pressure control. C57/B6 female and male mice were subjected to left UNX or sham operated. Blood pressure was measured using a tail-cuff system and verified by telemetry. The concentrations of plasma amino acids and other parameters were analyzed.

Our results show that mice having undergone UNX display an increased systolic blood pressure (120 ± 2.14 vs. 112 ± 1.97 mm Hg by tail cuff measurements, n = 9-18). This effect was more pronounced in females than in males and observed also by telemetry. Plasma levels of asymmetric dimethyl arginine (ADMA), an inhibitor of NOS considered to be a good marker for renal disease, were increased in UNX animals, whereas the level of some proteinogenic amino acids was changed significantly. There were also no changes in the mRNA expression levels of Arg transporters and enzymes involved in arginine metabolism. The amount of urinary nitrate and nitrite was unchanged indicating that the observed changes in blood pressure were not mediated by changes in the NO levels. Our observations suggest that UNX affects blood pressure and the effects are less pronounced in males, possibly due to a more important remnant kidney compensatory growth.

Poster presentations – Dialysis

A rare case of peritoneal dialysis associated peritonitis with Sphingomonas koreensis

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Background: Sphingomonas species is an aerobic gram-negative bacillus which is rarely isolated in human materials and plays an extremely limited role as an infectious agent. PD-associated peritonitis with Sphingomonas species is observed very rarely.

Case presentation: A 51 years old man with end-stage renal disease on continuous ambulatory peritoneal dialysis was admitted due to abdominal pain and cloudy dialysate. Laboratory analysis showed: WBC count 11.3 G/l and C-reactive protein 202 mg/l, Leucocyte count of the peritoneal fluid (LCf) 20.8x10⁷/l (norm: 0–0.1x10⁷/l) confirming PD-associated peritonitis. Cultures of the peritoneal fluid were taken and empiric therapy with Amikacine and Cefazolin was started. Cultures became positive and the isolates were identified as escherichia coli. After rapid drop of LCf to 0.36 G/l and patient improvement, he was discharged on oral Ciprofloxacine 3 days after admission. At follow-up visit two days later LCf rose to 3.4x10⁷/l. A CT-scan of the abdomen was performed without apparent pathologies. Due to further rise of the LCf to 15.3x10⁷/l PD-catheter was removed. Cultures of the peritoneal dialysis fluid and the catheters tip were taken and antibiotic treatment was switched to Piperacillin/Tazobactam. After 40 hours of incubation the cultures now revealed gram negative rods. The gram negative isolates were identified as Sphingomonas koreensis. The antibiogram showed susceptibility to cotrimoxazol and resistance to all the other tested antibiotics. The patient was treated with Cotrimoxazol per orally for 2 weeks with completely resolving. The underlying cause for the polymicrobial peritonitis remained unclear. Sphingomonas koreensis was probably initially missed by culture due to the very high inoculum of E.coli and the very slow growth of itself. WBC count 11.3 G/l and C-reactive protein 202 mg/l, Leucocyte count of the peritoneal fluid (LCf) 20.8x10⁷/l (norm: 0–0.1x10⁷/l) confirming PD-associated peritonitis with Sphingomonas koreensis.
Platelet-derived growth factor receptor β (PDGFRβ) expression in human peritoneum

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Introduction: Simple peritoneal fibrosis and encapsulating peritoneal sclerosis (EPS) are important lesions in the peritoneum of patients on peritoneal dialysis (PD). We previously described a population of podoplanin positive myofibroblasts in peritoneal biopsies from patients with EPS. PDGFR receptor β (PDGFRβ) is a marker of pericytes and PDGFRβ might be involved in the fibrotic response of the peritoneum. This study aimed to describe PDGFRβ in the human peritoneum.

Methods: In this retrospective analysis we localized PDGFRβ in peritoneal biopsies from patients with EPS (n = 6), on PD without signs of EPS (n = 5), and compared them with normal peritoneum (n = 4) and peritoneum from uremic patients (n = 5). Consecutive sections were stained for smooth-muscle actin (SMA) and podoplanin. Slides were scored semiquantitatively by two observers blinded to the diagnosis.

Results: PDGFRβ was expressed by cells of arterial walls in all biopsies. A prominent population of PDGFRβ positive cells was present in the normal peritoneum, which were SMA negative on consecutive sections. In patients on PD a high number of PDGFRβ were also positive for SMA. In EPS the majority of podoplanin positive cells were positive for PDGFRβ. In peritoneal biopsies from normal and uremic patients the expression of SMA was mainly restricted to cells of arterial walls. Podoplanin expression was restricted to lymphatic vessels in normal peritoneum, in uremic patients, and patients on PD without EPS.

Conclusions: As podoplanin positive myofibroblasts express PDGFRβ, these cells might be related to pericytes (rather than other sources of fibroblasts). PDGFRβ might turn out to be a therapeutic target in EPS.

Demographic characteristics of maintenance hemodialysis (HD) patients in Switzerland

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1Stadtpital Waid, Zürich; 2Kantonsspital Baden; 3Kantonsspital Winterthur; Spital Lachen; Kantonsspital Schaffhausen

Background: Knowledge about demographic characteristics of individuals treated by HD in Switzerland is limited.

Methods: 567 patients were evaluated from the monitor! project, a prospective dynamic hemodialysis cohort assessing a wide range of medical data. Mean follow-up of patients was 1.6 years.

Results: Almost two thirds of the study population were male (59.4%). The most common primary renal disease is diabetes mellitus type 2 (20%), followed by hypertensive nephropathy (18.1%). During this follow-up, 40 patients underwent transplantation, 5 patients were switched to peritoneal dialysis, 13 patients stopped treatment and 3 patients recovered from renal failure. 53 patients had already been transplanted once. Death rate was 11.8% per year.

Further analysis was performed after age stratification (A: ≤39 yrs, B: 40–69 yrs, C: 60–79 yrs, D: 80 yrs). Comorbidity correlated clearly with age, older patients having higher CCI. However, no further increase in comorbidity was found for group D vs. C. In contrast, no association was found between age and dialysis vintage.

Cox regression analysis including age, BMI, CCI and dialysis vintage, revealed an increase in mortality of 6.3% for every additional year on dialysis.

Table

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>P</th>
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<tbody>
<tr>
<td>≤39 yrs</td>
<td>0.000</td>
</tr>
<tr>
<td>40–59 yrs</td>
<td>0.000</td>
</tr>
<tr>
<td>≥60 yrs</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Dialysis vintage (yrs)

| ≤1 yrs | 0.008 |
| 1–3 yrs | 0.000 |
| ≥4 yrs | 0.000 |

CCI

| low | average | high |
| 4.0 | 4.3 | 4.3 |
| 4.0 | 4.3 | 4.3 |

Handgrip strength and mortality in a hemodialysis (HD) cohort

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Background: Poor muscular strength has been shown to be associated with increased mortality in healthy people. The aim of this study was to assess muscular strength, its longitudinal change, and its association with mortality in a Swiss HD cohort.

Methods: 340 patients were evaluated from the monitor! project, a prospective dynamic hemodialysis cohort assessing a wide range of clinical, laboratory and anthropometrical data. Muscular strength was measured using a handgrip dynamometer.

Results: Mean handgrip strength was 22.5 kg (male: 26.4 kg, female: 16.5 kg), which is significantly lower compared to age-matched healthy individuals. With every additional kilogram of handgrip strength (adjusted for age, sex, CCI and time on HD), patients probability to die is reduced by 4% (95% C.I.: 0.929–0.993). Patients with an increase in absolute handgrip strength have a significantly better survival compared to individuals with decreased handgrip.
Conclusions: Patients on maintenance HD present with severe reduction in muscle mass compared to healthy individuals. As muscular strength is associated with mortality, measures should be taken to improve muscle capacity in HD patients. An interventional study would be necessary to prove causal relation with mortality.

<table>
<thead>
<tr>
<th>Handgrip strength (kg)</th>
<th>CC (years)</th>
<th>LTM (%)</th>
<th>Time on HD (years)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (N = 126)</td>
<td>71.6 ± 13.3</td>
<td>41.7 ± 12.8</td>
<td>4.3 ± 5.5</td>
<td>68.8 ± 15.6</td>
</tr>
<tr>
<td>Average (N = 101)</td>
<td>70.0 ± 12.8</td>
<td>42.0 ± 12.2</td>
<td>3.3 ± 4.6</td>
<td>75.4 ± 15.4</td>
</tr>
<tr>
<td>High (N = 113)</td>
<td>63.2 ± 16.4</td>
<td>50.1 ± 12.7</td>
<td>3.2 ± 3.8</td>
<td>80.0 ± 14.3</td>
</tr>
</tbody>
</table>

1) *P <0.001 vs. "low handgrip strength" 2) *P <0.001 vs. "average handgrip strength" 3) Charlson Comorbidity Index

Is the nutritional risk screening (NRS) score a useful tool to predict changes in lean tissue mass of maintenance hemodialysis (HD) patients?

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Background: Impaired nutritional status is frequent in hemodialysis (HD) patients. The aim of the present study was to evaluate the prognostic usefulness of the NRS score to predict a change in lean tissue mass (LTM) in HD patients dialyzed in Switzerland.

Methods: 375 patients were evaluated from the monitor! project, 63 patients were excluded from the analysis because of missing data. NRS was calculated at baseline (T1) and 1 year later (T2) and the change in LTM was calculated as the difference between T1 and T2. Results: Mean LTM was 42.8%, indicating very low muscle mass. Stratification of the study population according to direction of LTM changes within 1 year.

Results: Occurrence of LTM changes within 1 year.

Conclusions: Assessment of maintenance HD patients by NRS can be used as a straightforward and accurate tool to identify subjects with negligible risk for substantial muscle loss. However, the screening instrument is unsuitable to detect patients developing sarcopenia within 1 year’s time. No correlation was found for changes in muscle mass and survival, which may be explained by the short follow-up.

Baclofen toxicity in a dialysis patient

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Background: Baclofen, a derivative of γ-aminobutyric acid, is an oral antispasmodic used to treat spasticity of spinal origin. It is eliminated predominantly by the kidneys and patients with impaired renal function are at particular risk for baclofen accumulation. Many investigators suggest that haemodialysis is a reasonable treatment modality in patients with overdose even in patients with normal renal function. We present a case of a dialysis patient who developed unconsciousness after receiving baclofen and was relieved of symptoms after dialysis treatment.

Case: A 70-year old man on dialysis was admitted to our hospital due to loss of consciousness. His sister reported that he had been started on baclofen treatment due to leg muscle pain, two days ago. He had totally received 40 mg of baclofen. On clinical examination, his temperature was 37.5°C, blood pressure 110/70 mm Hg, he was disoriented in a state of confusion, GCS 7, without signs of localization. Laboratory tests showed Hb 15 g/dl, leukocytes 8090/uL, platelets 154 000/μl, potassium 5.4 meq/L, sodium 134 meq/L, urea 190 mg/dl, creatinine 10.3 mg/dl, SGOT 12 IU/L, SGPT 28 IU/L. Brain computed tomography did not show any findings. Haemodialysis was performed and the patient showed clinical improvement. Complete recovery was achieved after two dialysis sessions.

Discussion: Baclofen is a drug, 90% of which, is excreted unchanged by glomerular filtration. Since it is a small molecule, it has a low volume of distribution and low protein binding, dialysis treatment is effective in removing it. In ESRD patients such as our patient was, even low doses can cause serious toxicity. There are a few cases of baclofen toxicity in these patients reported in the literature. Further studies should elucidate if the administration of baclofen in these patients is appropriate.

Comparison of sodium conductivity prescription and dialysate sodium concentration with three different hemodialysis (HD) monitors: not all the monitors are equal

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Background: Individualized sodium prescription and/or sodium modeling have been proposed to improve tolerance to HD, improve blood pressure control or optimize sodium balance. For this purpose it is of course necessary to accurately know if the sodium concentration in the inlet dialysate [Na+] corresponds to what is prescribed. The aim of the present study was to compare on 3 different HD monitors the sodium conductivity prescribed with the measured values of [Na+].

Methods: In our center we use the following monitors: Gambro AK200, Nikkiso DBB-05/07 and Fresenius 5008. During 79 HD an aliquot of dialysate was drawn from the inlet line two times during the session and the conductivity prescribed at the moment of drawing was recorded. The [Na+] was than measured by the indirect ISE method with a COBAS 6000 (Roche). Finally, the prescribed and measured values were compared for each type of monitor.

Results: 178 inlet dialysate specimens were analyzed and the main results are reported in table 1. With all monitors the mean measured [Na+] was higher than the prescribed values. However, while with the Nikkiso and Fresenius monitors the mean difference was rather small (plus 0.56 and 0.70 mmol/l), with the Gambro AK200 it was much higher (+3.5 mmol/l). Passing&Bablock analysis shows that for a same prescription the Gambro monitor delivers a sodium concentration that is much higher (+3.5 mmol/l).

Conclusions: The present data show that for a same prescription not all the dialysis monitors deliver the same sodium concentration of sodium, certainly due to difference in the algorithms and/or procedures used to prepare the dialysate. This discordance may explain some differences in the dialysis tolerance observed when a patient is dialyzed using a different monitor than the usual one. Therefore clinicians should pay attention to this point when prescribing sodium conductivity and/or sodium modeling on different HD monitors.

Table 1.

<table>
<thead>
<tr>
<th>Dialysis monitor</th>
<th>Prescribed Na conductivity</th>
<th>Measured sodium concentration</th>
<th>Difference</th>
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<tbody>
<tr>
<td></td>
<td>mmol/l-equivalent</td>
<td>mmol/l</td>
<td>mmol/l</td>
</tr>
<tr>
<td>G ambro AK 200</td>
<td>139.49 ± 2.92</td>
<td>143.02 ± 3.98</td>
<td>3.53 ± 1.99</td>
</tr>
<tr>
<td>Nikkiso DBB-05/07</td>
<td>139.81 ± 2.53</td>
<td>140.37 ± 2.73</td>
<td>0.56 ± 1.94</td>
</tr>
<tr>
<td>Fresenius 5008</td>
<td>138.49 ± 3.39</td>
<td>139.13 ± 4.08</td>
<td>0.70 ± 1.84</td>
</tr>
</tbody>
</table>
The association between ultrafiltration volume and difference of the pre- and post-dialysis hemoglobin levels in maintenance hemodialysis patients

Michael Moeddel
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Background: The question whether a greater ultrafiltration volume will cause higher hemoglobin/hematocrit levels or not is discussed controversially (1). Aim of the study is to examine the association between ultrafiltration volume and changes in hemoglobin levels during hemodialysis in maintenance hemodialysis patients.

Methods: A multicentre, retrospective/prospective observational survey examining stable hemodialysis patients (n = 56) at the long interval (3d). The association between ultrafiltration volumes and the changes in hemoglobin levels were measured. Subgroups have been defined as diabetic, non-diabetic, low/high ultrafiltration, low/high weight patients. Treatment parameter illustrates patients in the participating dialysis units. Statistical analysis was performed by using Pearson’s correlation and t-Student test.

Results: Pearson’s correlation: Correlation between pre- and postdialytic hemoglobin level are for total patients and all subgroups highly positive (between 0.82 and 0.95) and each very significant (p <0.01). t-Test for paired samples: The differences between arithmetic means for pre- and postdialytic hemoglobin levels lies for total patients, diabetic and non-diabetic patient subgroups between −0.48 and −0.52 g/dl. They are very significant positive for all patient, non-diabetic patients (p <0.1% two-tailed) and significant for diabetic patients (p <5% two-tailed).

Data in edition illustrate patients and treatment.

Conclusion: Our results revealed correlations between ultrafiltration volume and changes in intradialytic hemoglobin levels. The results demonstrate a post-dialysis hemococoncentration effect.

The post-dialysis hemococoncentration seems to be larger in patients with high ultrafiltration and less with low ultrafiltration. Further studies are needed to quantify the complex relationship between hemoglobin and ultrafiltration volume.

Anemia management in hemodialysis patients might be adapted on ultrafiltration volume.

Large variations in pulse wave velocity and reflection patterns occur during a hemodialysis session and are not related to the degree of ultrafiltration

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Background: Arteries of end-stage renal disease patients are characterized by accelerated atherosclerosis and chronically progressive arterial stiffening. The acute effects of hemodialysis sessions on arterial properties have been less intensively studied, with contradictory results, possibly due to lack of standardization. The aim of this study was therefore to assess arterial properties throughout a hemodialysis session performed under standardized conditions, and to compare patients dialyzed at stable body weight with those undergoing ultrafiltration.

Methods: cartoid-radial (cr) and carotid-femoral (cf) Pulse wave velocity (PWV) and the central systolic augmentation index corrected for heart rate (Aix 75) were measured in 13 hemodialysis patients undergoing ultrafiltration (UF) and 8 patients dialyzed at stable body weight (SW). Measurements were taken just before, halfway through, and just after a standardized hemodialysis session.

Results: No significant differences were noted between the groups for Aix, PWV and their changes. When the arterial properties of both groups were analyzed together, median cr-PWV increased slightly (from 8.6 (8.0–8.9) before to 9.8 m/sec (8.7–7.0) after hemodialysis, p = 0.09), cf-PWV did not (from 10.3 (8.8–9.3) to 10.1 m/sec (9.4–9.4), p = 0.7), and Aix 75 decreased significantly (from 28 (20.3–35) to 24.3% (19.3–31.3), p = 0.02). However, large individual fluctuations occurred in arterial properties throughout hemodialysis in each group (see figure).

Conclusion: Independently of ultrafiltration, important changes in arterial wall properties occur during hemodialysis, which may partly account for the heterogeneous hemodynamic responses observed during dialysis sessions.

Poor correlation of 44h blood pressure measurements with in-center blood pressure in hemodialysis patients

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Background/Methods: Antihypertensive treatment in hemodialysis patients is usually guided by pre- and postdialysis blood pressure. To validate this approach, we measured 44h ambulatory blood pressure in 38 stable hemodialysis patients as part of their annual cardiovascular status check. Recordings were taken in 96 four minute intervals from 7–22 h and in 60 minute intervals from 22–7 h during 44 hours of a 2-day interdialytic interval. Results were compared with the weekly average of pre- and postdialytic blood pressure and correlations which were obtained from the blood pressure module of the dialysis machine and electronically recorded.

Results: Recordings of 38 dialysis patients (24 m:14 f; mean age 67y) were analysed. Mean (±SEM) 44h systolic BP (44hBPsyst) was lower than pre- and postdialysis BPsyst (127.6 ± 2.8 versus 131.5 ± 3.5 and 129.9 ± 3.2). In contrast, 44hBpwdias was higher than pre- and postdialytic Bpwdias (75.7 ± 2.0 versus 63.0 ± 2.1 and 65.3 ± 2.0 mm Hg). Of the 38 patients, only 4 (11%) were nocturnal dippers (>10% decrease of BPsyst), whereas 53% were nondippers and 37% reverse dippers. In-center pre-dialysis BPsyst exceeded 44hBPsyst by >20 mm Hg in 10 patients (24%), but was more than 20 mm lower than 44hBPsyst in 16%. Discrepancies were less pronounced for post-dialysis BPsyst(16% too high by >20 mm Hg, 8% too low by <20 mm Hg). There was no correlation of pre-dialysis BDbyps with 44hBPsyst (r = 0.17), and only a weak correlation with post-dialysis BDbys (r = 0.34, p = 0.04). Similar weak correlations were found for pre- and postdialysis MAP with 24h MAP (r = 0.34 and 0.35).

Summary and Conclusions: Pre- and postdialysis in-center blood pressure correlates poorly with 44h blood pressure. Substantial (>20 mm Hg) over- and underestimations of true blood pressure occurred in 40% of the studied population. In-center blood pressure recordings are nearly useless to guide antihypertensive therapy in hemodialysis patients, but 44 hour blood pressure recordings are a feasible alternative.

First experience in Switzerland of the HeRO® graft for arterio-venous access for hemodialysis

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Background: Central vein stenosis or occlusion resulting from long term AV access on the lower limb or placement of long-term catheters is one of the major causes of access failure in dialyzed patients. The initial approach is angioplasty with stent placement but low patency rates at 1 year have been reported. In these situations, creation of arterio-venous (AV) access on the upper arm to the venous component. This 5-mm diameter segment is made endovascularly placed to the right atrium. However, the new HeRO® graft seems to be an alternative.

Method: The HeRO® graft is a fully subcutaneous access system that bypasses central veins and differs from conventional graft since it has no venous anastomosis. It is composed of a 6 mm diameter ePTFE arterial graft that is attached to the brachial artery and tunneled to the deltopectoral groove. It is connected through a titanium connector to the venous component. This 5-mm diameter segment is made of radiopaque silicone with braided nitinol reinforcement and endovascularly placed to the right atrium.

Results: We report the case of a 54 year old man on hemodialysis for years due to diabetic nephropathy. He has a long history of failed native fistulas and prosthetic grafts on both arms. Due to bilateral
subclavian venous stenosis, it was decided to use the HeRO graft to avoid long-term catheter or lower limb access. The intervention was successful. At 6 months, the graft is used without the need of any re-intervention and with a flow of 1400 ml/min.

**Conclusions:** This is the first report in Switzerland of the use of the HeRO graft as AV access. Due to good patency rate at 2 years approaching 90% and reduced risk of infection compared with catheters, this graft seems to appear as an excellent solution in case of central vein stenosis.

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**Fistula First Initiative: Yes, we can**

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**Background:** Complications of access being the leading cause of hospitalisation among patients on haemodialysis, The Fistula First Initiative favours native arteriovenous fistula (AVF) creation. The current study was undertaken to determine whether aggressive work-up of poorly maturing or failing autogenous AVFs would be fruitful in increasing the use of autogenous access.

**Method:** From January 2009 to June 2012, we retrospectively analysed the chart of all patients who underwent new AVF creation in our University Hospital. The outcomes were primary and secondary maturation rates and the loss of AV access during the 3 months following initial surgery.

**Results:** During the study, 144 accesses were created, with 97 (67%) being AVF. There were 71 radiocephalic (group I) and 28 brachiocephalic (group II) AVF. About one third of patients required a permanent tunneled catheter. The mean initial diameter of the vein and the artery was 3.15 and 2.86 mm in group I and 3.9 and 4.6 mm in group II. Blood flow measured after the first week, at 1 and 3 months was respectively 764/864/890 ml/min in the group I, and 1344/1488/1601 ml/min in the group II. In the group I, 80% of patients achieved maturity at 3 months without any additional intervention and 16% needed a proximalisation for stenosis. Two AV accesses were lost. The secondary maturation rate achieved 96%. The only statistically significant difference between the patients who underwent revision and those who did not, was the initial artery diameter. In group II, 84% of patients achieved maturity at 3 months without any additional intervention, 3 needed PTA, and 1 access was lost.

**Conclusions:** The results of the present study confirm that the possibility to fulfill the criteria of the Fistula First Initiative. With a multidisciplinary approach to carefully select the patients, good maturation rates can be achieved through early detection and correction of problems.

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**Is supplementation of water soluble vitamins justified in chronic haemodialysis patients?**

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**Background:** Deficiency of several water soluble vitamins has been reported in patients undergoing chronic haemodialysis (HD). Therefore in many dialysis centers vitamins are routinely supplemented. However no validated supplementation-strategy exists until now. We aimed to characterize the vitamin status in our dialysis population receiving 2 capsules of Diavital® after each HD session.

**Methods:** We analyzed erythrocyte folic acid (EFA), vitamin B1 (V-B1) and Vitamin B6 (V-B6) plasma levels from blood drawn before a dialysis session in 100 patients undergoing chronic HD at the University Hospital of Basel.

**Results:** Mean values of EFA, V-B1 and V-B6 were in 100 patients where 3182, 224 and 377 nmol/l respectively. 91% of these patients serum vitamin levels were under the lower limit of normal, even in those not receiving vitamin supplementation (N = 11). 99, 59, and 90 patients had serum levels over the upper limit of normal for EFA, V-B1 and V-B6 respectively.

**Conclusions:** Based on our data dosage of 2 capsules of Diavital® after each HD session may result in oversubstitution of these water soluble vitamins in many patients. As even patients without vitamin supplementation seem to have sufficient serum vitamin levels it is legitimate to question if general supplementation in HD patients is justified.

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**Sclerostin and other circulating bone remodeling markers in hemodialysis patients**

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**Background:** Cardiovascular calcification contributes to the increased morbidity and mortality in hemodialysis patients. Sclerostin, an osteocyte-secreted protein, was recently identified as an antianabolic bone factor causing soft tissue calcification.

**Methods:** In our multicenter prospective longitudinal observational study following hemodialysis patients, we aimed to assess the associations of the circulating sclerostin and bone remodeling markers with long-term mortality. We also evaluated the relationship between circulating sclerostin, FGF23 and traditional remodeling markers. Sclerostin levels in hemodialysis patients were compared with healthy controls.

**Results:** We enrolled 239 hemodialysis patients with a median follow-up of 1191 [IQR 712-1232] days. In Cox regression analysis, Fibroblast growth factor 23 (FGF23) (HR 1.44; 95% CI 1.14-1.83), parathyroid hormone (PTH) (HR 1.95; 95% CI 1.53–2.49) and alkaline phosphatase (AP) (HR 1.62; 95% CI 1.16–2.25) per SD, 25(OH) vitamin D (HR 0.32 (0.17–0.60) per natural log but not sclerostin (HR 0.97 95% CI 0.68–1.37) per SD increase levels were independently associated with mortality. FGF23 (OR –0.06; 95% CI –0.14 to –0.02), PTH (OR –0.17; 95% CI –0.19 to –0.08) and AP (OR –0.17; 95% CI –0.19 to –0.08) were independently negatively associated with sclerostin levels after adjustments for possible confounders.

Among control and hemodialysis females, sclerostin levels were lower than in men (fig. 1).

**Conclusion:** FGF23, PTH, AP but not sclerostin levels predicted long-term mortality. Sclerostin was negatively associated with FGF23, PTH and AP and lower in female than in male subjects.
Das kompakte Nephrologie-Handbuch


**Dr. P. Hirt-Minkowski**, geb. am 3.5.1974, arbeitet zur Zeit als Oberärztin und wissenschaftliche Mitarbeiterin am Universitätsspital in Basel sowie als Belegärztin am Lindenhofspital in Bern. Die Faszination für die verschiedenen Nierenerkrankheiten und auch die Freude daran, Wissen weiterzugeben, haben sie motiviert, dieses Handbuch zu verfassen.

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