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OC 01

## 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.

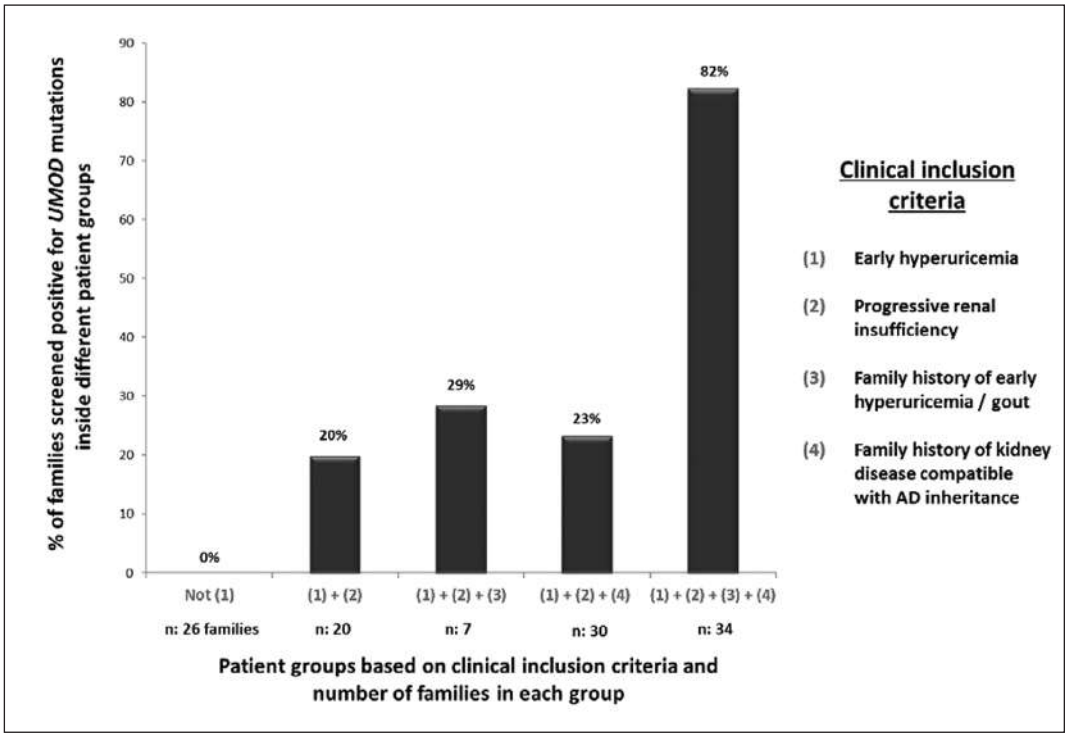


**Figure 1**
Rate of *UMOD* mutation detection according to the number of clinical criteria.

OC 02

## 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.

OC 03

### Sleep quality decreases with declining GFR in early stages of chronic kidney disease

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**Valentina Forni Ogna and Adam Ogna: Joint First Authorship*

**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 82.1 (±14.7) ml/min/1.73 $m^2$. 269 (15.4%) subjects had a CKD: 8.3% St1-2 and 7.1% 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 and low SE in multivariate regression analysis adjusting for gender, periodic legs 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.

OC 04

### A urine peptidome-based score accurately predicts the risk of reaching ESRD in ADPKD patients

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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 peptidome 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 $m^2$). 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 peptidome at a single timepoint that allows to identify ADPKD patients with high risk for future progression to ESRD.

## Oral communications – Basic Science / Genetics

OC 05

### Correlation of Transcriptome Sequencing Data from Formalin-Fixed, Paraffin-Embedded vs. RNAlater® 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 the operating room.
Paired biopsies from each patient with histologically-confirmed clear cell renal cell carcinoma (ccRCC) and non-tumorous ("normal") tissue were either FFPE or stored in an RNA-stabilizing agent (RNAlater®, Qiagen, Germany). Total RNA was extracted with the miRNeasy FFPE kit or the miRNeasy 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 RNAlater® datasets yielded similar numbers of detected RNA 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 (padj <0.05, fold changeabs ≥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.

OC 06

### 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:** The sodium-glucose cotransporter 2 (SGLT-2) inhibitor dapagliflozin (DAPA) induces renal glycosuria. The therapeutic effect of this drug in ARPKD has not been studied. Therefore we examined the effect of DAPA in PCK rats, an orthologous animal model of ARPKD. Methods: DAPA (10 mg/kg/day) or vehicle (CON) were administered via gavage to 6 week-old male PCK rats (n = 8 per group) for 6 weeks.

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, ultrasound was performed and rats were immediately sacrificed and kidneys were excised for analysis of cyst growth.
**Results:** DAPA significantly increased urine output (DAPA 57.3 ± 19.2, CON 19.3 ± 2.3 ml/day at week 6 of treatment) and resulted in higher osmolar excretion (DAPA 62.5 ± 15.8, CON 23.9 ± 2.8 mosm/day) and higher glucose excretion (DAPA 23.4 ± 12.0, CON 0.3 ± 0.3 mmol/day). After 3 weeks of treatment, DAPA-treated PCK rats displayed higher clearances for creatinine (DAPA 3.06 ± 0.40, CON 2.56 ± 0.54 ml/min) and BUN (DAPA 1.71 ± 0.34, CON 1.23 ± 0.31 ml/min) 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 cAMP content between both groups.
**Conclusions:** Inhibition of glucose reabsorption with the SGLT2-specific inhibitor DAPA caused significant glycuresis, 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 glycosuria and hyperfiltration to distal cyst growth remain to be elucidated.

OC 07

### Calciprotein Particles Induce Calcification of Vascular Smooth Muscle Cells In vitro

*Parisa Aghagolzadeh[1], Bijarnia Rakesh Kumar[1], Prakash Chandak[1], Matthias Bachtler[1], Edward R. Smith[2], Andreas Pasch[1]*
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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 particle type and 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 normocalcemic hypocalciuria with lower plasma PTH levels while 1, 25-OH Vitamin D3 levels remained unaltered. Interestingly, immunoblotting of kidney tissue lysates revealed significantly reduced phosphorylation of the thiazide-sensitive sodium/chloride co-transporter (NCC), mutated in Gitelman's syndrome, in the distal convoluted tubules of NHA2 KO mice. Similarly, phosphorylation of the SPS1-related proline/alanine-rich kinase (SPAK), the kinase responsible for NCC phosphorylation, as well as the abundance of WNK4, a kinase further upstream in the regulatory cascade of NCC phosphorylation, was markedly reduced in kidney lysates of KO mice, compared with those of WT mice. In line with these findings, NHA2 KO mice exhibit a reduced natriuretic response to hydrochlorothiazide compared to WT mice. In the distal tubular cell line mpkDCT4, stimulation of NCC phosphorylation is reduced upon siRNA mediated knockdown of NHA2, compared with control siRNA treated cells.
Thus, in summary, 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.

## Oral communications – Transplantation

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 nanoparticle-based 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 stiffening and increased future all-cause mortality at a follow up of five 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, augmentation index (AI) renal resistance index (RRI) and pulse wave velocity (PWV) before donation, and at 12 months after donation.
**Results:** LKD showed a significant decline in renal function (95 ± 10 versus 61 ± 11 ml/min/1.73 $m^2$, p <0.001) and plasma phosphate levels (1.2 ± 0.2 versus 1.1 ± 0.2 mmol/l, p <0.005) compaired to predonation after one year of follow up. T50 measurement increased slightly one year after donation (290 ± 53 versus 312 ± 38 min, p = 0.0495). AI, PWV as well as RRI were not changed significantly by kidney donation. Correlation analyses revealed no significant associations between T50, AI, RRI 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 = –048; 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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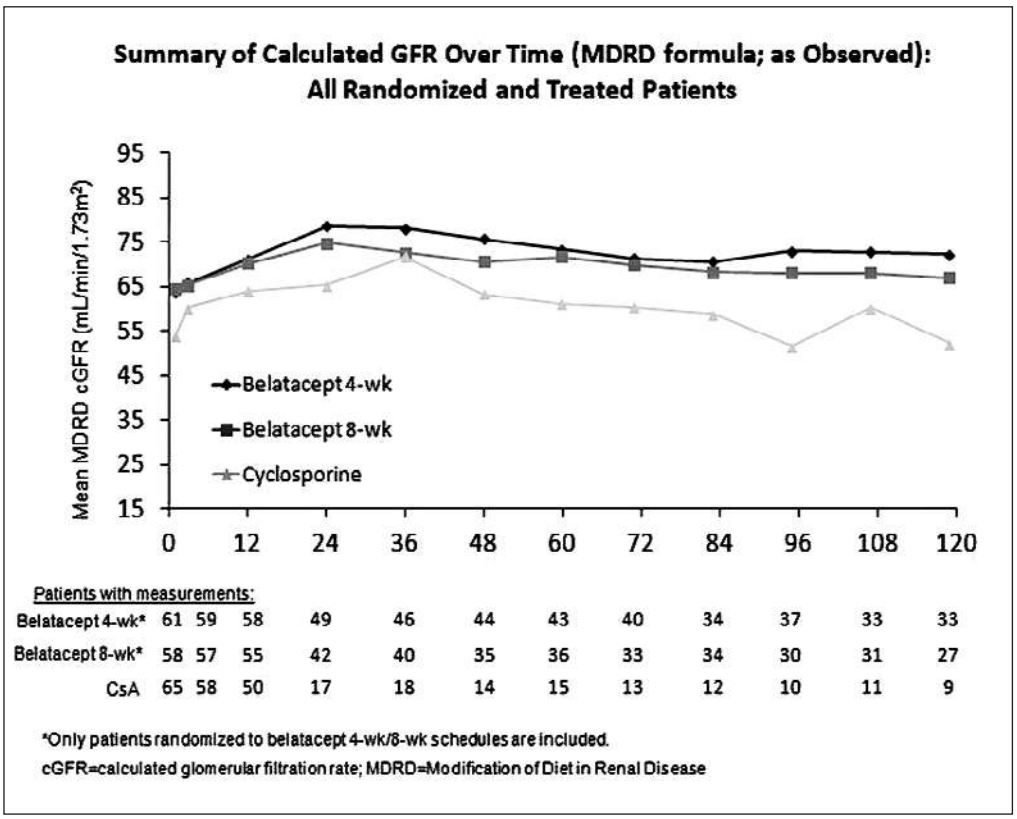
**Background:** At 5 years post-transplant, data from the Phase 2 IM103-100 LTE study of belatacept (bela) in kidney transplantation demonstrated a favorable safety profile and improved renal function vs cyclosporine (CsA) (Vincenti F et al., JASN 2010;21(9):1587–96).

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 $m^2$; and at 10 years mean cGFR was 72 (bela 4-week), 67 (bela 8-week), and 52 (CsA) mL/min/1.73 $m^2$ (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.




OC 11

## Why are potential living kidney donors declined?

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**Background:** Within the last decades living kidney donation has become an important part of every renal transplantation program. As a relevant number of potential donors is declined in the process, we analysed the reasons for not being a suitable donor.
**Methods:** All potential living donors evaluated at our center between 2007 and 2013 were examined, including non-directed donors. Evaluation followed the principles recommended by the SAMW (swiss academy of medical sciences). The reasons for declining donation were recorded prospectively and analysed.
**Results:** A total of 139 potential donors was evaluated, resulting in 33 transplantations and 106 donors being declined. Accepted donors were on average 53 years old and 68% were females. Declined donors were on average 52.5 years and 58% females (not significant vs. accepted donors).
The main reasons for declining were immunological (34%, due to donor specific antibodies and/or positive crossmatch), followed by psycho-social (16%) and renal (13%) conditions. Half of these were due to low GFR (mean 62, 49–75 ml/min), the other half mainly to anatomical reasons. 3 potential donors were diagnosed with relevant kidney disease. Hypertension and meta-bolic syndrome accounted for 11% each and were mostly first diagnosis. In the remaining 14% other medical reasons including obesity (3%) led to declining donation.
**Conclusions:** Despite ABO incompatible transplantion, immunological reasons for declining donation still make up to one third of the cases. This could be in part alleviated by crossover donation, especially if there was a central database for crossover donation. As psycho-social findings are the second most reason for declining a donor, it might be advisable to conduct psycho-social evaluation early in the process.

OC 12

## The C1q-binding assays and clinical outcomes in kidney transplantation

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**Background:** Contradictory conclusions have emerged from clinical trials when testing the predictive value of C1q-binding donor-specific HLA-antibodies (HLA-DSA). The aim of this study was to investigate the association between C1q-binding ability of HLA-DSA and the clinical outcome (i.e. antibody-mediated rejection (AMR) and long-term allograft survival).
**Methods:** Pretransplant sera of 64 patients known to possess preformed HLA-DSA were retrospectively analyzed by the standard and anti-globulin (AHG) enhanced C1q assay.
**Results:** The cumulative incidence of clinical/subclinical AMR within 6 months posttransplant was equal in recipients with and without C1q-binding HLA-DSA when using the standard C1q and the AHG C1q assay with the cut-offs MFI 300, 500, and 1000 for positivity ($p = 0.62$, $p = 0.47$, $p = 0.80$ and $p = 0.58$, $p = 0.40$, $p = 0.42$, respectively). The prevalence of subclinical AMR at 3 and 6 months

posttransplant was also not different between the recipients with and without C1q-binding HLA-DSA: p >0.55, p >0.35, and p >0.35 for the standard C1q assay; p >0.20, p >0.20, and p >0.10 for the AHG C1q assay with the cut-offs MFI 300, 500, and 1000. At a median of 8 years posttransplant, allograft survival was equal in patients with/without C1q-binding HLA-DSA (p >0.57 for the standard and p >0.09 for the AHG enhanced C1q assay). The MFI was a strong and independent factor for C1q-binding in both C1q assays (OR >8.25 for standard and >4.33 for AHG enhanced C1q assay; p <0.0001).
**Conclusion:** Pretransplant C1q-binding HLA-DSA – either detected by the standard or the AHG enhanced C1q assay - were not predictive for any clinical outcome. The MFI of HLA-DSA was strongly influencing C1q-binding.

## Oral communications – NCCR / Experimental Nephrology

OC 13

### 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% $O_2$) from E14.5 until E18.5, sacrificed, and fetal kidneys were collected for analysis: Whole mount in situ hybridization (WISH) using 2 different riboprobes directed against the 3' or 5' half of Fetuin A mRNA, immunohistochemistry (IHC), Western blot and qRT-PCR. Furthermore, the Fetuin A promoter region was analyzed for hypoxia-responsive elements using BIOBASE and TRANSFAC® positional weight matrices with the Patch 1.0 algorithm.
**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 WISH 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 at -2kb and +1.5 kb in relation to the transcription start site.
**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 findings, we hypothesize that in response to hypoxia, renal tubular cells produce Fetuin A, which might protect the developing kidney from calcifying. Further studies using Fetuin A knock-out animals are planned to substantiate this hypothesis.

OC 14

### Human Proximal Tubule Cells Form Functional Microtissues

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**Background:** The epithelial cells lining the proximal tubules (PT) of the kidney mediate complex transport processes that are particularly vulnerable to drug toxicity. Two-dimensional cultures of immortalized PT cells have been used in drug toxicity research, prior to animal trials. Since this approach does not reproduce the physiological conditions (e.g. saturable endocytic uptake) encountered in vivo, generating three-dimension organotypic microtissues has become an important objective for drug efficacy and toxicity studies.
**Methods:** Microtissue cultures of PT cells (immortalized and primary) were done in hanging-drop GravityPLUSÔ culture plates under different serum, cell density and cell composition conditions. Microtissues were characterized morphologically, with a panel of proliferation and differentiation markers, and functionally, by monitoring the endocytic uptake of Alexa 488-labelled albumin.
**Results:** Kidney microtissues were successfully obtained by co-culturing fibroblasts with immortalized human proximal tubular cells (HK-2) or Human Renal Proximal Tubular Epithelial Cells (HRPTEpiC) in hanging-drop plates. The HK2 microtissues formed highly proliferative, but dedifferentiated microtissues within 10 days of culture, while co-culture with fibroblasts yielded spheroid structures already after 2 days. Low passage HRPTEpiC microtissues (pure and co-culture) were less proliferative and expressed tissue-specific differentiation markers important for functional readout. Electron microscopy analysis showed more evident markers of epithelial differentiation (microvilli and tight junctions) in the co-cultured HRPTEpiC microtissues. The functionality of HRPTEpiC microtissues was evidenced by the endocytic uptake of Alexa 488-labelled albumin.
**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 toxicology screenings, using endocytosis as a functional readout.

OC 15

### A role for hypoxia-inducible cytoglobin in chronic kidney disease?

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**Background:** Cytoglobin (CYGB) is a recently discovered globin that belongs to the mammalian globin family, in addition to hemoglobin and myoglobin. Despite extensive research efforts, its physiological role remains unknown, but possible functions include reactive oxygen species (ROS) detoxification and signaling. Accumulating evidence suggests that ROS play a crucial role in podocyte detachment and/or apoptosis during diabetic nephropathy.
**Methods:** To assess the putative anti-oxidative function of CYGB in podocytes, we are using the human podocyte cell line AB8/13, which expresses high endogenous CYGB levels. We generated stable CYGB knock-down and overexpressing cell models and are currently studying CYGB-dependent gene expression, cell viability and oxidative stress response.
**Results:** CYGB deficient cells showed an increase in cell death, up-regulation of pro-apoptotic gene expression and are more sensitive to oxidative stress compared to CYGB overexpressing podocytes. Interestingly, gene array expression analysis of biopsies from CKD patients showed a pronounced CYGB induction in diabetic nephropathy, validated by RT-qPCR in independent nephropathy samples. Moreover, genome-wide association studies (GWAS) revealed that CYGB is potentially implicated in chronic kidney disease (CKD).
**Conclusions:** Data of our study demonstrate for the first time that CYGB (i) is expressed in a human podocyte cell line, (ii) protects podocytes from oxidative stress and apoptosis, and (iii) may be involved in CKD, particularly in diabetic nephropathy. In parallel to validating our findings in an independent podocyte model we will study the CYGB-dependent transcriptome, to gain further functional insight in the molecular mechanism of CYGB in podocytes.

OC 16

### Mechanism of coupling between trancellular sodium transport and paracellular permeability in renal collecting duct cells

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The aldosterone-sensitive distal nephron is responsible for the fine-tuning of sodium balance. According to dietary sodium intake, collecting ducts (CD) are subjected to large variations of sodium transport. In CD, sodium reabsorption occurs mostly through principal cells via a transcellular pathway that involves apical channels (ENaC) and basolateral Na,K-ATPase. Several strands of tight junctions prevent paracellular ion permeability and sodium back flux. We hypothesized that transcellular sodium fluxes cross talk with tight-junctions to prevent back flux of reabsorbed ions.
We analyzed cultured mCCDcl1 cells either subjected to aldosterone treatment or doxycycline-inducible overexpression γ-ENaC to increase transcellular sodium flux. Increased transcellular sodium transport was associated with enhanced transepithelial resistance. Time-course experiments revealed that current increased first followed by increased transepithelial resistance. Total and Triton X-100 insoluble claudin-4 and 8 protein abundance were increased. However, only claudin-8

mRNA levels were increased indicating that a primary increase in claudin-8 protein level may secondarily stabilize claudin-4. The increase in claudins abundance relied on decreased β-catenin signaling and was prevented by inhibition of GSK3. In addition, abundance of membrane associated β-catenin increased thus decreasing availability of cytoplasmic β-catenin for nuclear translocation. These results were confirmed 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.

Our results reveal a new coupling mechanism between transcellular sodium transport and paracellular permeability. This coupling primarily involves the regulation of tight junctions components represented by claudin-8 and claudin-4 and may both increase paracellular chloride reabsorption and prevent sodium back flux to the lumen. We are currently addressing the role of the conserved TCF/β-catenin binding site identified in the sequence of the promoter of the claudin-8 gene.

## Oral communications – Hypertension / Mineral / Electrolytes

OC 17

### 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; $p < 0.05$) and lower 24 hr urinary citrate excretion (2.23 vs 3.00 mmol; $p < 0.05$). 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, calculi 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.

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OC 18

### 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 renal renin expression level were investigated at RNA level by qPCR. Systolic blood pressure was monitored by the tail cuff method. NCC abundance/phosphorylation was analyzed by western blot.
**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 positive 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.

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OC 19

### 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. Patients were monitored for clinical biochemistry and 24-hour ambulatory blood pressure.
**Results:** NCC was detected in urinary exosomes as a glycosylated protein forming an oligomeric structure. It comprised of dimer (≈ 250 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 CD9, 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.

OC 20

### 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, IL1-β 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, IL1-β 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.

## Oral communications – Dialysis

OC 21

### Abdominal CT scan in 30 EPS patients prior to surgery: a tool to predict the intraoperative findings?

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**Background:** The diagnostic pillars of encapsulating peritoneal sclerosis (EPS) are based on clinical symptoms, radiologic findings, macroscopical and histological criteria. Two diagnostic scores for radiologic findings in CT scans of EPS patients have been established in the past (Tarzi et al.,Vlijm et al.). Whether these scores resemble different macroscopical phenotypes, leading to specific surgical techniques with different patient outcome has not been investigated yet.
**Methods:** We retrospectively analyzed 30 late-stage EPS patients of our referral center who underwent major surgery with peritonectomy and enterolysis (PEEL). The preoperative CT scans scored according to the two established systems. The macroscopic phenotype, the surgical procedure and laboratory values at the time of surgery were noted. Correlations were studied between CT findings and the macroscopic phenotype.
**Results:** Using both scoring systems, all patients had highly predictive CT-scores for EPS. The macroscopical Type III had significantly higher CT scores compared to other macroscopic phenotypes. Patients with a macroscopical Type I had significantly higher C-reactive protein (CrP) values compared to EPS Type III. Calcifications were detected in 11 out of 15 in Type III and in 2 out of 9 in Type I ($p < 0.05$). Operation time was significantly longer, requirement for redo surgery was higher ($p < 0.05$) and intraoperative complications were more frequent in EPS Type I compared to EPS Type III ($p < 0.001$).
**Conclusions:** Higher scores were associated with bowel obstruction due to intestinal cocooning. Surgical treatment of EPS Type I is associated with more intraoperative complications and longer operation time requiring different surgical techniques. The combination of CT scores, CrP levels, calcifications and absence of fluid loculation might be a useful tool to separate Type I from Type III. This differentiation is important to plan a proper operation procedure and might influence a decision in favor or against initiation of a medical therapy.

OC 22

### Validation of a specific screening score for sleep disordered breathing in patients undergoing chronic intermittent hemodialysis

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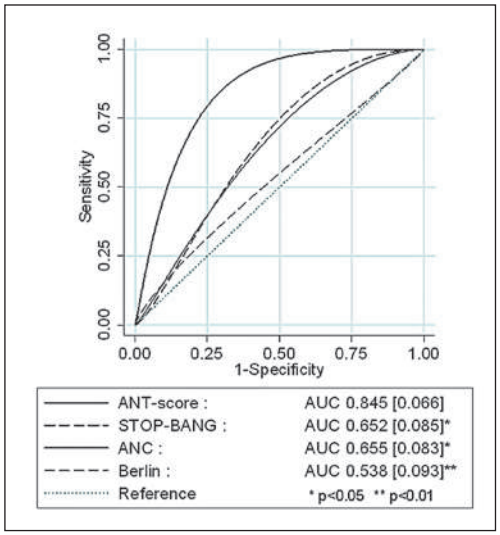
**Introduction:** We previously described a 56% prevalence of sleep disordered breathing (SDB; including obstructive and central sleep apnea) in hemodialysis (HD) patients, which was under-diagnosed and undertreated. The best diagnostic approach currently is undefined, since no screening tool has been validated in this population. We aimed to evaluate the performance of classical screening scores for SDB and to propose a new specific screening score.



**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). The patients were divided in a derivation and an independent validation population, according to the HD-center. Multivariate logistic regression and CART-analysis were used to identify the best predictors of SDB and develop the new score.
**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.
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. The herein proposed ANT-score showed 90% [82–99] sensitivity and 64% [49–78] specificity in the validation population. On ROC-analysis, the ANT-score (ROC-area 0.845 [SE 0.066]) performed better than the 3 classical sores in the validation population (ROC-areas 0.538 [0.093] for BQ, 0.652 [0.085] for STOP-BANG and 0.655 [0.083] for ANC).
**Conclusion:** Classical screening scores showed poor performance for SDB screening in HD patients.
We therefore propose a simple screening score specific to the HD population, based on readily available clinical data (the ANT-score), to identify the patients who need further investigation. This score needs to be validated prospectively.

OC 23

## Trice weekly post-dialysis Cefepime prescription in patients on maintenance hemodialysis

*Filipe Martins[1], Ould Maouloud Hemett[1], Veronique Erard[2], Christian Chuard[2], Eric Descombes[1]*
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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 through 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/l and 11.3 ± 5.6 mg/l at 48 and 72 hours, respectively. These levels always exceeded largely the EUCAST breakpoints for susceptibility of all the targeted bacteria (>1 mg/l), 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 ± 1.17 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 through serum levels. Higher doses may be necessary in patients having a residual renal function or with Pseudomonas infection.

OC 24

## 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. The analysis of our data after 2 years of cholecalciferol supplementation showed an important increase of the calcitriol concentrations and the aim of the present cross-sectional study is to report these long-term results.
**Patients and methods:** Were included all the 35 patients (mean age 69.9 ± 9.5 y; 19 males, 14 diabetics, 1 anephric) who received post-dialysis cholecalciferol for 2 years. The 25(OH)D and 1,25-DihydroxyVitaminD (calcitriol) levels were measured at baseline and after 24 months. Total 25(OH)D was measured with the COBAS 6000 immunoassay (ROCHE) and calcitriol with a RIA kit (Immunodiagnostic system; reader: Wizard gamma Counter, PerkinElmer).

**Table 1.**

| Parameter | Normal range | Baseline | 24 month | p value |
|---|---|---|---|---|
| | | | | |
| Total calcium | 2.20-2.55 mmol/l | 2.32±0.17 | 2.37±0.16 | p= NS |
| Ionized calcium | 1.12-1.32 mmol/l | 1.14±0.09 | 1.15±0.07 | p= NS |
| Phosphate | 0.90-1.45 mmol/l | 1.55±0.39 | 1.68±0.49 | p= NS |
| i-PTH | 15-65 ng/l | 241±174 | 311±204 | p= NS |
| 25-OH vitamin D | 75-150 nmol/l | 32.2±17 | 109.9±23 | p<0.0001 |
| | | | | |
| **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 the 35 patients (35%) achieving calcitriol concentrations within normal range (>43 pmol/l). The calcitriol concentrations increased by 73% in patients having a conserved diuresis (p <0.05) but 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.

## Poster presentations – Clinical Nephrology

**P 01**

### Implementation of nutritional risk screening in daily clinical routine and evaluation of clinical outcome in a tertiary nephrology department

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**Background:** Malnutrition is a debilitating condition among chronic kidney disease (CKD) patients, associated with protein-energy wasting and increased need for medical resources and adverse outcomes. However nutritional screening upon hospital admission is infrequently performed in nephrological wards. The aim of the present study was to evaluate the implementation of a nutritional risk screening in daily routine medical care and explore the impact of malnutrition on the clinical outcome of CKD patients.
**Methods:** We screened all admissions (n = 747) between January and December 2013 at our nephrology department for malnutrition according to the Nutrition Risk Screening 2002 score (NRS-2002). Cases with a score of 3 or more, which denotes severe malnutrition or patient "at risk" for malnutrition were analyzed.
**Results:** Out of 747 admissions, 35% were defined as 'at-risk'. 'At-risk' admissions required longer hospitalization (16 ± 18 vs. 6 ± 6 days, P <0.001) and caused higher treatment costs (41'178 ± 47'158 vs. 14'123 ± 14'188 CHF, P <0.001), than 'not at-risk' patients. After adjusting for several confounders (age, gender, comorbidities, length of hospitalization, readmissions and AKIN stage) multivariate analysis confirmed an independent and significant association between higher in-hospital mortality and NRS ≥3 [OR 1.82 (1.30–2.56), P <0.001] along with functional status assessed by Barthel-Index [OR 3.66 (1.03–13.02), P <0.05].
**Conclusion:** Malnutrition is evident in up to one third of the admissions and is associated with increased cost, length of stay and in-hospital mortality. Our results underscore the need to establish a routine screening and therapeutic nutritional follow-up in CKD patients.

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**P 02**

### Anthropometric measurements and mortality events in chronic kidney disease patients; A decade follow-up in Tehran Lipid and Glucose Study

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**Background:** No study has yet evaluated the effect of different fat distribution measures on risk of all-cause mortality events among chronic kidney disease (CKD) patients.
**Methods:** The present study consisted of 1860 individuals with CKD, aged ≥30 years who participated in Tehran Lipid and Glucose Study. Estimated glomerular filtration rate (eGFR) was estimated using the abbreviated prediction equation, provided by the Modification of Diet in Renal Disease formula and CKD was defined as eGFR ≤60 mL/min/1.73 $m^2$. Cox proportional hazard regression was implemented to estimate the hazard ratios (HRs) of different anthropometric measures for predicting mortality events.
**Results:** During 10.1 years follow up, 221 cases of all-cause mortality events occurred. In confounder adjusted model(age, sex, creatinine, history of cardiovascular disease, smoking), none of the HRs of different anthropometric measures reached the significant level, however, when we also considered mediator variables (hypertension, diabetes, hypercholesterolemia) in the model, there was significant interaction between sex and waist circumference for risk prediction of mortality events. Among men, the HR of mortality for 1 SD increase in anthropometric measures were 0.73 (0.57–0.92) for weight, 0.67 (0.54–0.83) for waist circumference, 0.75 (0.58–0.97) for body mass index and 0.71(0.52–0.96) for hip circumference. However among women, none of the measures were associated with increased risk of all-cause mortality events.
**Conclusion:** In the presence of diabetes or hypertension among CKD patients men, regardless of fat distribution in hip, waist or in whole body, having more fat mass result in better survival.

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**P 03**

### FGF_23 or PTH: which comes first in CKD?

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**Background:** Control of Calcium-Phosphate (Ca-Pi) metabolism represents a good part of a nephrologist's workload. Despite considerable progress in understanding, diagnosing and treating Ca-Pi related problems in patients with chronic kidney disease (CKD), Ca-Pi remain one of the leading risk factors responsible for the excess mortality rate in CKD-patients. This may be due to the complexity of this multihormonal system, where correcting one parameter may trigger considerable variations in other(s)
**Aim of the study:** To evaluate the complexity of a multifactorial system with respect to its importance and chronology of its appearance.
**Patients, material, methods:** Crossectional, single center. New patients consulting the first time during 2012 were enrolled (n:54), as well as all patients on HD (36). CA*Pi + FGF-23,PTHi, VitD were measured
**Results:** This study clearly reveals FGF-23 to be the first factor to rise with doubling of blood levels in CKD-3 (10/11 pts showed high blood levels), whilst PTHi (2/8pts high), Pi (1/8) Ca*Pi and VitD (1-OH, not di(OH) displayed pathological values only as CKD progressed to CKD-4.This study also shows that chronic renal insufficiency of moderate degree (<CKD-3) is not associated with any measurable significant alterations in kidney functions other than increase of creatinine. As progression of CKD continues and reaches CK-5 FGF-23 displays in some pts values mire than 5'000 times the upper norm. On HD FGF-23 level is negatively influenced by the level of vitaminD.
**Conclusions:** This study gives some more evidence that in chronic renal insufficiency, FGF-23 is the first factor to react on a change in Ca*Pi handling, and suggest the importance of this reaction to be dependent of the status of vitaminD.
All this adds to the fact of the importance of individualisation of the treatment of hyperPi, therefore protection of ectopic calcifications. FGF-23 should be included in a regularly in Ca*Pi-work-up

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**P 04**

### Clinical course and long-term outcome in 456 patients with Hantavirus-induced Nephropathia epidemica, Germany, 2001–2012

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**Background:** Puumala virus (PUUV) is the most common species of Hantavirus in Central Europe. Nephropathia Epidemica (NE), caused by PUUV, is characterized by acute kidney injury (AKI) and thrombocytopenia. The major goals of this study were to describe detailed clinical phenotypes of patients with clinically manifest hantavirus infection. Furthermore, we provide data on long-term outcome and humoral immunity to PUUV in this patient cohort.
**Methods:** We performed a cross-sectional prospective survey of 456 adult patients with serologically confirmed NE. Data were collected from medical records and prospectively at follow-up visit.

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 ≤60 109/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.

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**P 05**

### 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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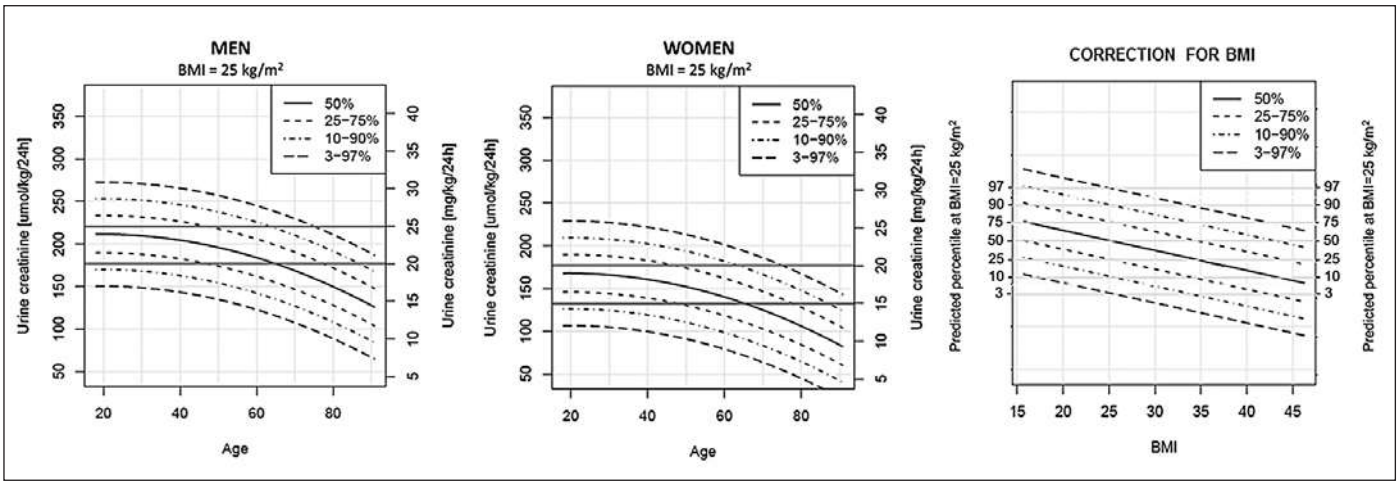
**Background:** Urinary creatinine excretion is used as a marker of the completeness of timed urine collections. The current reference values for 24-h urinary creatinine excretion are poorly representative of the general European population.
The aim of this study was to establish and validate anthropometry-based 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 urinary collection and measured anthropometric variables. Only data from adults of European descent, with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 $m^2$ 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 (SKIPOGH).
**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 (177–221 µmol/kg/24h 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.

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**P 06**

### 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 26 year-old female who presented with left flank pain for a few weeks. Medical history and physical examination were otherwise unremarkable. Initial laboratory examination revealed increased serum creatinine (136 µmol/L) and LDH (602 U/l), 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 in the absence of other autoimmune disorders or malignancy, which led to the diagnosis of primary APS (PAPS). Persistent 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 glomerulopathies 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.

P 07

### 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 diabetic foot syndrome presented with severe renal failure, nephritic urianalysis 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 mesangioproliferative 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. After two neurosurgical interventions and antistaphylococcal therapy for a further 5 months the spondylodiscitis was considered cured. 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.

P 08

### Renal tissue oxygenation as measured with BOLD-MRI in children with vesico-ureteral reflux or a solitary kidney in comparison with healthy controls

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**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.

| | **Reflux** | | **Solitary Kidney** | **Unilateral Nephrectomy** | **Healthy Controls** |
|---|---|---|---|---|---|
| N of patients | 18 | | 5 | 2 | 26 |
| Age (years) | 15.7±1.4 | | 14.4±1.0 | 16.5±1.1 | 14.3±1.6 |
| Sex (% female) | 66.7 | | 60 | 50 | 42.3 |
| eGFR quadratic formula (ml/min/1.73m2) | 88±14 | | 96±9 | 85±2 | 104±10 |
| | *Reflux* | *Healthy Contralateral Kidney* | | | |
| N of kidneys | 29 | 7 | 5 | 2 | 52 |
| Medullary R2* (1/s) | 28.4±3.2 | 28.5±3.2 | 29.9±0.4 | 31.3±2.1 | 30.3±1.9 |
| Cortical R2* (1/s) | 16.4±1.4 | 16.7±1.7 | 15.6±1.6 | 15.2±1.6 | 17.2±1.6 |
| Furosemide-induced decrease in R2* (1/s) | -5.7±3.0 | -7.4±3.2 | -8.6±3.6 | -8.8±0.6 | -6.9±3.4 |

P 09

### 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 mml/min/1.73 m² (range 59.7–142.4 mml/min/1.73 m²). 20.3% (n = 41) had a 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.

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**P 10**

### 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 but a high variability 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 a single center.
**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 perinterventional 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 most common indication for TJRB was bleeding diathesis. The procedure was technically successful in 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, which allows adequate tissue sampling in high-risk patients who require renal biopsies.

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**P 11**

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

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**Introduction:** Sleep disordered breathing (SDB; including obstructive and central sleep apnea) has an increased prevalence in end-stage renal disease (ESRD) patients. Its occurrence in early stages of chronic kidney disease (CKD) is poorly described. We aimed to assess the prevalence of SDB in early stages of CKD and to evaluate its association with kidney function and classical risk factors.
**Methods:** 1747 participants in the population-based HypnoLaus study (857 men, 890 women) underwent full polysomnography at home to assess Apnea-Hypopnea Index (AHI). Glomerular filtration rate (GFR) was estimated by CKD-EPI equation and kidney function classified in risk categories according to KDIGO 2012 guidelines. Only subjects with GFR ≥30 ml/min were considered.
**Results:** Mean age of the population was 59.2 (±11.3) years and mean GFR 82.1 (±14.7)ml/min/1.73 m².
269 (15.4%) subjects had a CKD: 8.3% St1-2 and 7.1% St3. 84.6% were in the low risk category, 13.4% in the moderate risk and 2.0% in the high or very high risk categories.
The prevalence of moderate-severe (AHI ≥15/h) and severe SDB (AHI ≥30/h) were 37.3% and 15.3%, respectively. In univariate logistic regression analysis, SDB prevalence increased with increasing CKD risk categories (p <0.001) and with decreasing GFR quartiles (p <0.001).
In multivariate analysis, age, gender and BMI were the only independent predictors of SDB, whilst the association with CKD risk categories and GFR quartiles became non-significant.
**Conclusion:** Subjects with early stages of CKD have an increased prevalence of SDB, which seems to be explained by classical risk factors, such as age, sex and obesity. We found no independent association between CKD and SDB in this population, suggesting that the increased prevalence of SDB in ESRD patients could be linked to specific mechanisms appearing late in the course of GFR decline, such as uremic toxins accumulation and fluid overload.

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**P 12**

### 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 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 Apnea-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 mean BMI 26.8 (±4.2) kg/m². 68% were on hemodialysis, 11% on peritoneal dialysis and 17% had no renal replacement therapy.
78% 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 SBD 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-operatory assessment of renal transplantation candidates should be considered.

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

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**P 13**

### 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 extends 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 examined the 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 chonic kidney disease (CKD). Among these 28 patients, 18 (64%) showed a recovery of the renal function, of these 78% (14/18 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

four patients entered a chronic RRT program. Overall there was a recovery rate of 57% (16/28), and a total death rate of 32% (9/28), with 11% of the patients (3/28) remaining on chronic RRT.
**Conclusion:** In our base hospital, the overall survival rate of 57% and the mortality rate of 32% due to AKI is comparable to the worldwide reported data.
Regarding chronic RRT our trend is slightly lower than reported worldwide (11% vs 13.8%). Since AKI predominantly occurs in elderly and critically ill patients with underlying comorbidities, such as CKD, a particular attention should be addressed to volume state, administration of nephrotoxic drugs and/or radiocontrast agents in all inpatients at risk.

P 14

### Extragradient in the electrophoresis of a patient with ARF caused by penicilline-overdosing

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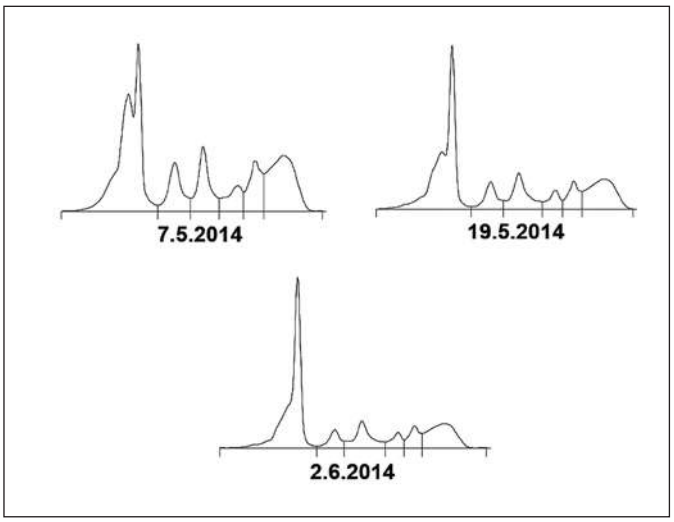
**History:** (Background) A 86-year-old man with a history of back pain and fever (39.0 °C), was referred to our hospital. The MRI of the lumbar spine was suspicious for a spondylodiscitis. In the blood cultures staphylococcus aureus could be detected. An intravenous treatment with penicillin (3x5 million 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 mm Hg. 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/mmol. Urin sediment showed only a non-glomerular microhematuria (catheter).
Serum electrophoresis showed an impressive atypical peak in the albumin region. This atypical peak was interpreted as the albumin bound penicillin (estimated 56%), also known as bisalbuminemia. Renal biopsy revealed a heavy acute eosinophilic interstitial nephritis.
**Course:** (Results) We assumed that the interstitial nephritis was caused by penicillin.
Penicillin treatment was changed immediately to levofloxacin and rifampicin. Additionally an oral treatment with prednisolone was started leading to a continuous improvement of the kidney function. The peak in the albumin range slowly diminished and almost disappeared four weeks after stopping the penicillin treatment (figure). There are several drugs and radio-contrast media which can interfere with the capillary zone electrophoresis, leading to a bisalbumienmia.
**Conclusion:** Overdosing of certain antibiotics can lead to an abnormal electrophoresis pattern in the albumine region.
Careful dosing in renal insufficiency is mandatory.




P15

### Kidneys On Strike

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**Introduction:** The phenomenon of reflex anuria as a rare cause of abrupt anuric renal failure has been described in the literature for decades. Spasms of intrarenal arterioles as well as ureters in both kidneys by the activation of sympathetic nervous system in response to irritation or trauma to one kidney or ureter, or severely painful stimuli to other organs were postulated as underlying mechanism of reflex anuria. Here we report 4 cases of acute anuric renal failure secondary to reflex anuria at the University Hospital Basel between September 2013 and September 2014.
**Case report:** 4 cases are summarized in the table.
**Conclusion:** Our 4 cases of reflex anuria identified within a period of 12 months underline that reflex anuria is not as rare as previously suggested in the literature, and should be considered as diagnosis of exclusion in case of acute anuric renal failure. With respect to the advanced age of the patients reported, reflex anuria might be an increasing phenomenon in elderly patients with polymorbidity as a result of dysfunctional autonomic nervous system.

**Table:**

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| Age / Sex | 69 / m | 71 / f | 62 / f | 81 / f |
| Cause of admission | radical cystectomy for bladder cancer | resection of locally recurrent breast cancer | pacemaker endocarditis | explantation of knee joint prosthesis |
| Baseline creatinine | 105 µmol/l | 45 µmol/l | 62 µmol/l | 78 µmol/l |
| eGFR (CKD-EPI) | 62 ml/min/ 1.73 m² | 96 ml/min/ 1.73 m² | 93 ml/ min/1.73 m² | 61 ml/min/ 1.73 m² |
| Creatinine max. | 821 µmol/l | 648 µmol/l | 559 µmol/l | 277 µmol/l |
| Etiology of reflex anuria | postoperative abdominal pain | unilateral ureteral obstruction | unilateral ureteral obstruction | postoperative local pain |
| Intervention | pain control | double J stent | double J stent | pain control |
| Duration of acute kidney injury[1] | >18 days[2] | 11 days | 11 days | 7 days |
| Dialysis | yes | no | no | no |
| Creatinine at discharge | 147 µmol/l | 53 µmol/l | 44 µmol/l | [3] |
| Creatinine at last follow-up | 117 µmol/l | 61 µmol/l | 54 µmol/l | 93 µmol/l |

[1] Diagnostic criteria according to Acute Kidney Injury Network (AKIN)
[2] Discharge before complete resolution of acute kidney injury
[3] Currently hospitalized

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### A Fribourg case of IgG4-RD (related disease) revealed by IgG4-RKD (related kidney disease), Switzerland

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IgG-4 RD is an old clinopathological entity, newly recognized, characterized by tumefactive lesions, a dense lymphoplasmocytic infiltrate riche in IgG4 positive plasma cells with storiform fibrosis in divers organs and elevated serum IgG4. Characteristic tubulonephritis findings in renal biopsy, high serum IgG and IgG4 and extra-renal histology with IgG4 plasma cells >10HPF and IgG4/IgG >40% definite IgG4-RKD. The incidence of malignancies is 3.5 times higher than that in the general population. We report a case of IgG4-RD occurred after lymph node metastasis of nasopharyngeal lymph epithelial carcinoma cT4N3M1. The clinical manifestations of IgG4-RD have simulated

during several years sometimes of multiple organ metastatic localizations except pancreatic of the primary tumor with heavy treatments and their consequences, sometimes a multiple myeloma unconfirmed by marrow biopsies but treated as such, until the worsening radiological images and the biopsy of solitary right kidney who raises the diagnosis of IgG4-RKD.

P 17

### Hyperprolactinemia in ANCA-Vasculitis

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A 26-year-old woman was admitted with abdominal pain, bloody diarrhea, vomiting and oligoarthitis. Later on she developed galactorrhea and kidney failure. Histology of kidney biopsy was consistent with extracapillary pauci-immune glomerulonephritis. Laboratory features included high p-ANCA-Level (ANCA 1:640, MPO-ANCA 105 U/ml, PR3-ANCA: neg., ANA: neg.); prolactin 2447 mU/L (Norm <530 mU/L); normal TSH, CRP 27 mg/l; ESR 59 mm/h. MR imaging of the pituary gland was normal.
The patient was begun with prednisone pulse therapy and rituximab (1 g, day 1 and day 14). Kidney function recovered, galactorrhea disappeared and ANCA- and prolactin-levels improved. 6 month after the first infusion of rituximab the patient again experienced abdominal discomfort, rise in ANCA-Titer and rising Prolactin-Levels (1133 mU/L). She was again treated with rituximab 1g and she improved clinically and Prolactin level fell to 676 mU/L.
**Discussion:** The hormone Prolactin (PRL) is secreted from the anterior lobe of the pituitary gland and other organs and lymphocytes. Prolactin acts in endocrine, autocrine, and paracrine manner through the prolactin receptor and a large number of cytokine receptors. In addition Prolactin has immunstimulatory effects and is discussed to promote autoimmunity, mainly by inhibition of negative selection of autoreactive B-Lymphocytes. Hyperprolactinemia is observed in autoimmune diseases like Systemic Lupus erythematosus (SLE), rheumatoid arthritis (RA)and ANCA-vasculitis.
**Conclusion:** The correlation of Prolactin Levels to disease activity may be explained to the second Prolactin activity as a cytokine and extra pituitary production. However, its exact role in physiology and pathophysiology of autoimmune disease is not clarified. Data from studies which tried to correlate PRL-Levels and disease activity in SLE and RA are conflicting, however, most studies point to a positive correlation. Hyperprolactinemia in ANCA-vasculitis is mostly seen if the central nervous system is affected. To date no data are available that correlate disease activity in ANCA-vasculitis with hyperprolactinemia.

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### Living without ADAMTS13: Hereditary TTP in a 56-year-old kidney transplant recipient

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**Background:** Hereditary TTP (Upshaw-Schulman syndrome) is characterized by the congenital absence of ADAMTS13 activity without an inhibitory autoantibody. Kidney involvement occurs in up to 10% of patients, and ESRD –unlike in acquired TTP- has been frequently described.
**Case report:** Seven months after kidney transplantation, a 56 yo patient presented with nosebleeds and soft tissue hematomas. Workup revealed mild microangiopathic hemolytic anemia and thrombocytopenia. Plasma ADAMTS13 activity of <5% of normal confirmed a diagnosis of TTP. Plasmapheresis with FFP replacement led to clinical resolution within 1 week. No evidence of TTP was detectable throughout the following year, although ADAMTS13 activity consistently remained <5% in all subsequent plasma samples. No ADAMTS13 inhibitor was detected at any time.
Prior to transplantation, thrombocytopenia or hemolysis had never been observed. After diagnosing arterial hypertension at age 33, CKD3A with proteinuria of ~1 g/d was found at 38y. His GFR decreased at ~3 ml/min/year. Kidney biopsy at GFR of 20 ml/min was nonspecific. At 49 y he developed homonymous hemianopia due to cerebral ischemia. At 56 y, he was preemptively transplanted with a deceased donor kidney. There were two episodes of mild thrombocytopenia without hemolysis in the first month. Four transplant biopsies, one at the time of the plasmapheresis, showed no evidence of thrombotic microangiopathy.
The laboratory findings made congenital ADAMTS13 deficiency a plausible diagnosis, which is due to homozygote or compound heterozygote mutations in the ADAMTS13 gene. In our case, sequence analysis revealed a mutation (p.R1060W) in one allele, further studies are pending.
**Conclusion:** Severe deficiency of ADAMTS13 activity may remain silent for decades, until other factors trigger clinical TTP. Retrospectively, hypertension, renal disease and the cerebrovascular incident in this patient may have been manifestations of TTP. Congenital ADAMTS13 deficiency may explain some cases of cryptogenic CKD, and should be liberally treated with FFP when renal function deteriorates for unknown reasons.

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### Severe cobalamine deficiency mimicking thrombotic microangiopathy – a sheep in wolf's clothing?

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Thrombotic microangiopathy (TMA) carries a high morbidity and mortality. The classic treatment includes aggressive therapies including plasma exchange. Rarely in severe cobalamine deficiency pseudo-TMA is found. This condition is not well described in the literature and in practice often misdiagnosed whereas aggressive PEX is not indicated. We report two cases of severe cobalamine deficiency in 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 had no paraesthesia or other neurological symptoms. Initial laboratory results showed severe schistocyte positive pancytopenia. Kidney function was normal and urine analysis unremarkable. Detailed findings are given in the table below.
Based on the findings of severe Coombs negative haemolysis and thrombocytopenia immediately daily plasma exchange and steroids were started. After receiving serum cobalamine result <50 pg/ml and search of the literature the TMA-treatment was stopped in absence of neurological and renal symptoms. Homocysteine level (35 µmol/l) confirmed severe cobalamine deficiency originating from a vegan diet.
The second patient was a 30-year old man from Eritrea. He was known for atrophic gastritis since five months but had no cobalamine substitution. He had similar findings as the first patient. Under substitution with cobalamine and folic acid, slowly all laboratory results normalized in both patients.
Think about cobalamine deficiency in severe haemolytic schistocyte positive anaemia with thrombocytopenia especially in absence of end organ damage such as kidney failure or neurological symptoms. Vitamin B12 determination should be included in the initial investigation when TMA is suspected.

| | Hb **(g/l)** | WBC **(G/l)** | Tc **(G/l)** | Reti **(‰)** | Schistoc **(‰)** | LDH **(U/l)** | Hapto **(g/l)** | eGFR **(CKD-EPI)** | Vit B12 **(ng/l)** |
|---|---|---|---|---|---|---|---|---|---|
| Case 1 | 58 | 3.6 | 61 | 16 | 12 | 5883 | <0.15 | 116 | <50 |
| Case 2 | 82 | 3.5 | 85 | 18 | 20 | 3295 | <0.15 | 126 | 58 |

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## Progressive renal failure after resection of a neuroendocrine tumor of the small intestine

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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 1.5 years before being diagnosed with a neuroendocrine tumor of the small intestine and metastatic liver disease by computertomography during evaluation of an episode of urolithiasis. After 145 cm ileocoecal 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 puls 78 bpm. S-Creatinine was 181 umol/l with an estimated glomerular filtration rate (GFR) of 34 ml/min/1.73 $m^2$ (MDRD), S-Calcium 2.27 mmol/l, albumin 38 g/l, uric acid 469 umol/l and haemoglobin 144 g/l. 24-hour urine collection revealed heavy hyperoxaluria (2.89 mmol/24h). Renal biopsy showed acute tubulur injury with moderate oxalosis and nephrocalcinosis (picture).
We diagnosed nephrocalcinosis due to heavy hyperoxaluria after short bowel resection with short bowel syndrome. Acute tubulur injury was assumed consecutive to recurring urinary tract obstruction. We initiated a treatment of colestyramin, calciumcitrat and pankreatin leading to a significant reduction of oxalate 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:** Ileal 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 oxalate, leading to hyperoxaluria and kidney stone formation.
The increase in oxalate 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 oxalate induced by exposure of the colon to nonabsorbed bile salts. The treatment with calciumcitrate proved to be very effective on oxalate absorption and renal function.

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## 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 1:** 3-year old boy. Initial findings: Pneumonia with glycosuria and proteinuria. Uneventful family history. Further tests: Normal plasma creatinine, tubular proteinuria, intermittent hypercalciuria and nephrocalcinosis. Genetic analysis revealed a novel nonsense mutation in the X-linked CLCN5-gene (c.1885C>T;p.Q629*; p.Gln629Ter) in the proximal tubule, confirming Dent's disease.
**Case 2:** Preterm female with growth retardation and severe polyuria. Consanguineous parents. Further tests: Hypokalaemic, hypochloraemic metabolic alkalosis with transient prerenal failure, hypercalciuria and nephrocalcinosis. Genetic analysis showed a homozygous mutation in the SLC12A1-gene (c.1685C< T;Ala562Val) of the loop of Henle, consistent with Bartter's syndrome type 1.
**Case 3:** 2-year old boy with 2 episodes of urolithiasis (100% calciumoxalate-dihydrate). Parents were first cousins. Further tests: Normal plasma creatinine, hypomagnesaemia, 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.S106P) 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, hypomagnesaemia, 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.

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## 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 hypocalcemia (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, $paCO_2$ 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 $m^2$)). 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.

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### 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. Immunofluorecence was positive for granular deposits mainly composed of C3 and focal IgA in the glomeruluar and mesangial compartment, while IgG was absent. Electron microscopy revealed deposits in the mesangium and glomerulum along with microvillar 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 consecutive excessive activation of complement. Genetic defects affect mainly mutations of the genes coding for complement factor H (CFH), complement fator I (CFI) and C3 [2]. In our patient the only finding in genetic analysis and antibody detection by western immunoblot technique was a heterozygote deletion of CFHR1 and CFHR3 which frequently occurs in healthy individuals, too. A context with Down's syndrome seems unlikely. Immunosuppressive therapy with Eculizumab was discussed but not initiated because kidney injury with interstitial fibrosis was advanced and Eculizumab has not been established yet as a treatment of C3GN.

1 Sethi S, et al. Kidney Int. 2012;82(4):465–73.
2 D'Agati VD, Bomback AS. Kidney Int. 2012;82(4):379–81. doi: 10.1038/ki.2012.80.

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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 an inflammatory response in macrophages.
**Methods:** Prim. and sec. CPP were generated using phosphate- and calcium-enriched cell culture media with varying amounts of FBS. 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, IL-10, MCP-1, TNF-α and NLRP3. The involvement of toll-like receptor-4 (TLR-4), nuclear factor-kappa B (NF-κB) and NLRP3-dependent pathways were evaluated using selective chemical inhibitors.
**Results:** TEM imaging of synthetic CPP revealed populations of amorphous spherical (prim. CPP) and larger crystalline spindle-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 cytokines IL-6, IL-1β, MCP-1 and TNF-α. IL-10 expression was unaffected by sec. CPP exposure. In contrast, no inflammatory response was detected upon exposure to prim. CPP. Inhibition of TLR-4, NF-κB and NLRP3 pathways reduced the sec. CPP-induced inflammatory response in RAW-264.7 cells.
**Conclusion:** Sec., but not prim. CPP induce pro-inflammatory cytokine expression in the macrophage and this effect may be mediated by activation of TLR-4/NF-κB and NLRP3 pathways. CPP-II might be involved in the induction and maintenance of the chronic inflammatory state commonly encountered in CKD patients.

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### The Lymphotoxin β receptor is a therapeutic target in renal inflammation

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**Background:** Accumulation of inflammatory cells in different renal compartments is a hallmark of progressive kidney diseases including glomerulonephritis (GN). Follicular infiltrates with defined and organized microarchitecture develop during chronic renal inflammation. Lymphotoxin β receptor (LTβR) signaling is important for the formation of secondary and tertiary lymphoid tissue. Thus we hypothesized that LTβR signaling plays a role in renal inflammation.
**Methods:** Microarrays from microdissected renal biopsies with lupus nephritis and IgA nephropathy were mined for LTs, LTβR and for NF-kappaB-regulated genes. The mRNA expression was confirmed by real-time RT-PCR in renal biopsies, and LTβ protein was localized by immunohistochemistry in 36 biopsies from patients with the most common forms of GN. Regulation of LTs and response to LTβR signaling was tested in human mesangial cells, tubular epithelial cells and mouse parietal epithelial cells in-vitro. LTβR signaling was blocked in two mouse models of GN (nephrotoxic nephritis and the adenovirus IFN accelerated NZB F1 lupus model)
**Results:** We show that renal biopsies from patients with GN displayed increased levels of LTβ, the ligand for LTβR, mRNA and protein. LTβ was localized to interstitial lymphocytes, and tubular epithelial cells. Human mesangial and tubular epithelial cells expressed both LTα and LTβ RNA upon stimulation with a proinflammatory cytokine in vitro, and expressed chemokines in response to LTβR signaling. In nephrotoxic nephritis, the blockade of LTβR signaling reduced crescent formation and parietal epithelial cells responded to LTβR signaling with chemokine release. In a lupus model, LTβR blockade improved renal function without reduction of serum autoantibody titers or glomerular immune complex deposition.
**Conclusions:** Thus LTβR 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.

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### Comparative effects of aliskiren and hydrochlorothiazide on renal tissue oxigenation in patients with arterial hypertension: a BOLD-MRI study

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**Background:** Animal studies suggest that arterial hypertension is characterized by reduced renal tissue oxygenation and that the latter increases after the acute administration of renin-angiotensin blockers. Since tubular sodium transport is the main determinant of renal tissue oxygenation, our study aimed at comparing the chronic effect of aliskiren versus hydrochlorothiazide (HCT) on renal tissue oxygenation in patients with essential hypertension.
**Design and method:** This was a single-center, randomized controlled trial. Patients underwent BOLD-MRI (Blood oxygenation level dependent MRI) and renal clearance studies at baseline and 6 weeks after aliskiren (300 mg qd) or HCT (25 mg qd). 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, a low R2* indicating a high tissue oxygenation. Response to therapy was defined as a decrease in supine systolic blood pressure (SBP) >10 mm Hg.

**Results:** 20 hypertensive patients (80% male, age: 53.0 ± 12.3 y) completed the study. Office BP decreased from 147/87 to 142/81 mm Hg in the aliskiren group (n = 11) and from 147/86 to 136/80 mmHg in the HCT group (n = 9), without significant changes in renal plasma flow or inulin clearance. Plasma aldosteron level increased significantly in the aliskiren group (p = 0.03). Neither aliskiren nor HCT modified cortical or medullary R2* levels at 6 weeks (see figure). However, BP responders (n = 8) showed a significant decrease in cortical but not medullary R2* levels when compared with non-responders (p = 0.03).
**Conclusions:** No difference in renal tissue oxygenation as measured with BOLD-MRI was found in patients receiving aliskiren or hydrochlorothiazide for 6 weeks. However, when a decrease of >10 mm Hg occured in SBP, a significant increase in cortical oxygenation occured, providing new evidence for a beneficial effect of BP reduction on renal oxygenation in hypertensive patients.

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### ENaC activity in collecting ducts modulates NCC in cirrhotic mice

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Cirrhosis is a frequent and severe disease, complicated by renal sodium retention with oedema and ascites formation. Although events leading to sodium retention are widely documented, cellular mechanisms unbalancing renal sodium transport are still debated. The aim of this study was to determine the importance of the amiloride-sensitive sodium channel (ENaC) in collecting ducts, during compensate and decompensate cirrhosis induced by bile duct ligation. We compared control mice (CTL) to collecting ducts specific αENaC knock-out mice (KO).
The disruption of ENaC in cortical collecting ducts did not alter Na,K-ATPase abundance in these segments and did not influence ascites development or plasma aldosterone concentrations. However ENaC in the whole kidney was upregulated in CTL and KO cirrhotic mice. Total αENaC abundance increased, while total γENaC did not change in cirrhotic mice of both genotypes. Cleaved forms of α and γ ENaC were significantly higher in CTL and KO ascitic mice. Interestingly, the abundance of the αENaC cleaved form was higher in KO ascitic mice than in CTL. The sodium chloride cotransporter protein (NCC) abundance was lower in non ascitic KO, compared to non ascitic CTL mice, but higher in ascitic KO compared to ascitic CTL mice.
Our study demonstrates that in ascitic mice, the lack of ENaC activity in CDs induced an upregulation of ENaC and NCC in upstream segments and correlated the cleavage of ENaC subunits, with the presence of ascites. In conclusion, ENaC activity was not a limiting factor for sodium retention, observed in decompensated cirrhosis.

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### High level of dephospho-uncarboxylated matrix GLA protein (dp-ucMGP) is associated with arterial stiffness and kidney vascular resistance

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**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 cardio-vascular (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 RRIs 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 ± 2.27 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 diabètes, 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.

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### Identification of renal celltype-specific dysregulation of hypoxia-associated transcripts by transcriptome-based network analysis

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**Background:** The best morphologic indicator of disease progression and development of end-stage renal disease is tubulointerstitial fibrosis and capillary rarefaction. Accumulating evidence suggests that dysregulation of hypoxia-regulated transcriptional mechanisms is involved in the loss of renal function and the development of chronic kidney disease (CKD) and hypoxia-induced transcription factors (HIFs) play a role in the dysregulation of gene expression in different renal cells.
**Methods:** To study the celltype-specific response to hypoxia and the relevance of HIFs,proximal tubular cells and conditionally immortalized podocytes with stable HIF1α and/or HIF2α 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, HIF1α, HIF2α, HIF1α+2α) 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 celltype-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 coregulated within the modules. Further characterization of the modules disclosed common as well as cell group- and condition-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 compartment-specific.
**Conclusions:** Our gene expression analysis indicates a condition- and celltype-specific dysregulation of hypoxia-associated transcripts in renal cells.

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### Improvements in angio-µCT: What the kidney morphometry will look like

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**Background:** Nephron number and glomerular volume are the key characteristics of the morphological substrate of the renal function. The accurate estimation of these parameters has become increasingly important because their alterations may play a significant pathophysiological role in the development or progression of a range of nephropathies and various "kidney-related" pathologies. The golden-standard method of the kidney morphometry at the moment is the exhaustive physical fractionator/dissector method (often combined with Cavalieri for kidney volume estimation). Although accepted as standard, it is extremely time-consuming and laborious, let alone disturbing proceeding artefacts.
**Purpose:** to develop an approach that would allow fast and reliable estimation of such parameters as nephron number, glomerular volume, glomerular size distribution and kidney volume.
**Results:** the developed contrast agent (modified Angiofil) turned out appropriate for µCT ex vivo with superior perfusion and contrast-to-noise features. The obtained µCT datasets were of superior quality and allowed clear visualization of the microvasculature, incl. capillaries. In kidney, modern high-resolution microCT (SkyScan-1172) provided the whole mouse kidney vasculature in 3D with the spatial resolution of approx. 2 µm. Quality of the obtained datasets allows both exhaustive and µCT-based stereological kidney morphometry. The sample treatment protocol was improved allowing the fixation of kidney tissue prior µCT-scan. This circumstance brings multiple advantages, including much easier localization of the µCT-findings in the post-scan histological sections or possibility to harvest the samples at one time-point and scan them at convenience etc.
**Conclusions:** the developed angio-µCT-based approach will substitute the existing golden-standard. Besides classical kidney morphometry, it provides the data on the vasculature what makes the technique even more beneficial for pathological processes with involvement of the vasculature. Possibility of further histological analysis is another major advantage of the technique, which could also lead to reduction of the number of animals needed for the study.

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### Inhibition of aerobic glycolysis with 2-deoxyglucose retards polycystic kidney disease progression in Han:SPRD rats

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Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disorder characterized by the development of multiple bilateral renal cysts. Using microarray analysis and qPCR, we identified altered glucose metabolism in the Han:SPRD rat model i.e. upregulation of genes involved in aerobic glycolysis (Hk1, Hk2, Ldha) and downregulation of genes involved in gluconeogenesis (G6pc, Lbp1), indicating a 'Warburg effect'.
We examined the effect of 2-deoxyglucose (2DG), a glycolytic inhibitor, on renal function loss and cyst progression in Han:SPRD rats, a PKD model with a phenotype closely resembling human ADPKD. Male heterozygous cystic (Cy/+) and wild-type (+/+) rats were administered 2DG (500 mg/kg/day) for 5 weeks (n = 10/group).
Treatment with 2DG significantly reduced kidney weights and 2-kidney/total-body-weight ratios and decreased renal cyst index in Cy/+-rats (27%, 21% and 48% reduction vs vehicle, respectively, $p < 0.05$).
Cy/+-rats treated with 2DG also showed improved creatinine clearance (1.98 ± 0.67 vs 1.41 ± 0.37, $p < 0.05$), BUN clearance (0.69 ± 0.26 vs 0.40 ± 0.10, $p < 0.01$) and uric acid clearance (0.38 ± 0.20 vs 0.21 ± 0.10, $p < 0.05$). Interestingly, administration of 2DG led to a sustained increase in urine volume output, suggesting renal resistance to vasopressin. Immunoblot analysis of kidney tissues harvested from 2DG-treated Cy/+-rats showed increased phosphorylation of AMPK, a negative regulator of mTOR, and decreased ERK signaling.
Moreover, in cultured primary epithelial cells from Cy/+-rats, 2DG dose-dependently inhibited cell growth (assessed by MTS assay), limited cellular proliferation (examined by BrdU assay), reduced lactate secretion and decreased ATP production.
Taken together, our results show that the cystic kidneys of Han:SPRD rats display enhanced aerobic glycolysis which may play an important role in the pathogenesis of PKD. Administration of 2DG markedly delayed the loss of renal function and retarded cyst development in Han:SPRD rats with PKD. Targeting the glycolytic pathway may therefore present a novel therapeutic strategy to control cyst growth in polycystic kidney disease.

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### 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 significatively 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 comparing 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 after 5 weeks of treatment. 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 ± 0.1ml/min) after 5 weeks when compared to controls. DAPA treatment during 5 weeks showed a 2 kidney weight/ body weight ratio (2KW/BW) 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% $p = 0.55$)
Inhibition of glucose reabsorption with the SGLT2-specific inhibitor dapagliflozin caused significant glycuresis in Han:SPRD rats. Unexpectedly, even when the kidney weight increased, cyst index seems to decrease slightly and clearances reflect an enhanced kidney function. This suggests that there is dissociation between kidney weight and cyst growth in this model of ADPKD.

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### Kappa Light Chains Associated with Fanconi Trigger Aberrations of Endolysosomal Compartment in Proximal Tubule Cells

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Generalized dysfunction of the proximal tubule (renal Fanconi syndrome) can occur when specific monoclonal immunoglobulin light chains (LCs) accumulate within the endolysosomal system of tubular cells and form intracellular crystals. The early molecular events involved in proximal tubule (PT) dysfunction remain poorly understood. We characterized transgenic mice expressing human kappa-LC associated Fanconi syndrome (k-CHEB) and analyzed endocytic uptake, lysosome function, and differentiation and proliferation markers using primary cultures of PT cells derived from these transgenic and control mice. Metabolic studies revealed that k-CHEB mice show progressive manifestations of renal Fanconi syndrome, before structural damage and renal failure. These changes are related to decreased expression of specific apical transporters and receptors (megalin/cubilin) and to increased dedifferentiation (ZONAB transcription factor) and proliferation (PCNA and CyclinD1) rates. Exposure of PT cells to low concentration (25 µg/mL) of k-CHEB-LC resulted in perinuclear positioning of enlarged and dysfunctional lysosomes with impaired clearance of autophagosomes containing ubiquitinated proteins and damaged mitochondria. These changes led to excessive production of reactive oxygen species (ROS) and increased tyrosine phosphorylation of ZO-1, disrupting the integrity of tight junctions and promoting the nuclear translocation of ZONAB, which is responsible for proliferation and dedifferentiation of the PT cells. These changes were dramatically reduced in PT cells exposed to LCs lacking crystal formation in lysosomes. These findings reveal that accumulation of specific LCs within PT cells impairs the autophagy-lysosome pathway and activates a chain of events promoting dedifferentiation and dysfunction of the cells. The characterization of these early events opens new perspectives to prevent the progression of LC-induced renal Fanconi syndrome.

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### Mediator of ErbB2 Induced Cell Motility in Mineral Homeostasis

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**Background:** The 33kDa mediator of ErbB2 induced cell motility (Memo) modulates fibroblast growth factor (FGF) receptor, insulin receptor, estrogen receptor and sphingosine1-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 hypercalcemia, elevated 1,25-OH D3 and suppressed parathyroid hormone (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 1), with 1.5% vs 0.8% vs 0.2% dietary phosphate 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 with 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.

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### 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 l expansion, and electron microscopy revealed thickened and folded glomerular basement membrane (GBM). The foot process and endothelial fenestrations were relatively intact. mRNA levels of laminina5, agrin and nidogen 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 and chemotaxis when Nrp1 knock down cells were stimulated with PDGFbb.
**Conclusions:** This study shows an unexpected role of Nrp1 in maintenance of GBM and suggests a critical involvement of mesangial Nrp1 in this process.

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### Oncostatin M receptor is a sensitive and early marker of kidney injury

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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 KIM1 and NGAL changed most significantly according to degree of functional impairment (corr. P <0.001). The transcriptome analysis further identified more than 60 other potential 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.

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### Pathophysiology of Chronic Kidney Disease in Methylmalonic Aciduria (MMA)

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**Background:** MMA is an inborn error of metabolism caused by mutations in the mitochondrial enzyme Methylmalonyl-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 control cells.
**Conclusion:** 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.

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### Proteomic Signature of Hypertension-induced Damage in the Two-Kidney, One-Clip (2K1C) Rat Model

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**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 high abundant plasma protein depletion strategy with an extended 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 PDGFR-β 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.

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### 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, URAT1, 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.

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### Renal sensitivity to orthostatic stress: a comparison of neurol-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 the pathogenesis of 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/m$^2$ in HC and 34.7 ± 4.6 kg/m$^2$ 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

| | HC | | OB | |
|---|---|---|---|---|
| | Baseline | LBNP | Baseline | LBNP |
| Systolic BP (mmHg) | 110±9 | 113±10* | 128±15¶ | 134±19* |
| Diastolic BP (mmHg) | 64±8 | 69±7* | 77±11¶ | 84±13* |
| Heart rate (bpm) | 63±8 | 61±8 | 65±7 | 68±9* |
| Glomerular filtration rate (ml/min) | 102.4±21 | 90.0±29* | 102.0±45 | 102.1±37 |
| Renal plasma flow (ml/min) | 576 (434-675) | 514 (349-605)* | 611 (284-715) | 562 (415-656) |
| Sodium excretion (µmol/min) | 236±78 | 213±192* | 234±113 | 214±149 |
| NE (nM) | 1.14 (0.92;1.37) | 1.46 (1.17-2.1)* | 1.03 (0.76-1.46) | 1.54 (1.07-1.82)* |
| PRA (ng/ml/min) | 0.35 (0.3;0.5) | 0.5 (0.25-0.8)* | 0.5 (0.08-0.6) | 0.5 (0.2-1.0)* |
| Aldosterone (pg/ml) | 28.5 (21.0;50.9) | 29.5 (20.8-56.1) | 39.8 (18.0-57.2) | 42.4 (27.3-51.8) |

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. Heart rate 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

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

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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/m$^2$ rituximab 4 weeks before the transplantation, tacrolimus, mycophenolate mofetil and prednisolone starting 1 week preoperatively, and basiliximab induction. Specific immunoadsorption 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.

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### 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. Limited data exist on the comparison of radiological pattern based on distinct immunological etiologies in well-characterized groups, such as RTR and HIV patients.
**Aim:** To compare CT patterns of PCP between HIV-positive patients and renal transplant recipients (RTR).
**Methods:** Retrospective analysis of 40 immunocompromised patients (16HIV, 24RTR) 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. 25 ± 9% RTR; p = 0.02). Multifocal pattern distribution, central lung parenchyma affection, lung peripheral involvement, cysts and subpleural spearing 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.

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### Non-invasive kidney fibrosis assessment using optimized diffusion MRI.

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**Background:** Renal interstitial fibrosis is predictive of kidney function loss but can only be assessed by renal biopsies, an invasive procedure associated with complications and focal sampling limiting its use as an assessment or predictive tool. Diffusion MRI is emerging as a new tool to evaluate non invasively kidney fibrosis. Low image resolution and interindividual variations limit its clinical use.
**Methods:** We developed an optimized MRI diffusion sequence "RESOLVE". We validated the new sequence in two rats models of fibrosis: unilateral urinary obstruction (UUO) and inflammatory nephritis (IN). Sequence optimization for human was performed in healthy volunteers. 36 kidney allograft patients undergoing kidney biopsy were examined using the RESOLVE sequence and apparent diffusion coefficient (ADC) was measured. The association between renal ADC values and histological fibrosis assessment was investigated using Pearson's correlation.
**Results:** In two rats models of kidney fibrosis (UUO and IN), ADC values obtained using RESOLVE correlated well to histological automatized fibrosis assessment (R2 = 0.54, p = 0.0005). We further optimized the RESOLVE sequence in healthy volunteers allowing better image resolution and differentiation between cortical and medullary ADC. Absolute ADC values showed interindividual variability. We therefore derived a new index as the difference between cortical and medullary ADC (delta ADC). In kidney allograft patients undergoing biopsy, delta ADC correlated well to histological fibrosis assessment (R2 = 0.52, P <0.001). Similar results were observed in a few CKD patients with native kidneys. In addition, we observed negativization of delta ADC values for patients harboring more than 40% interstitial fibrosis. Using delta ADC allowed a better correlation to fibrosis and minimized interindividual variation.
**Conclusion:** Optimized diffusion MRI and delta ADC index appear to be useful in assessing the severity of interstitial fibrosis in kidney allograft and CKD and shows promise as a non-invasive and effective technique to guide therapy and follow-up.

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### 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 in the bladder and 2 fold higher for renal/ureter TCC compared to the general population. The impact of TCC after renal transplantation on the patients and

grafts outcome is not well investigated. Therefore, we evaluated our renal transplant patients for TCC in terms of clinical outcome, course of the disease, allograft function and associated risk factors.
**Methods:** We retrospectively evaluated patients after renal transplantation at the University Hospital of Basel between February 1982 and May 2014 for preexisting or posttransplant TCC of the bladder or the upper urinary tract. Clinical, demographic, nephrological and oncological data were investigated.
**Results:** During the study period 1855 patients were transplanted of which 31 had a history of TCC (1.7%). Overall incidence of de novo TCC in renal transplant recipients was more than 500fold increased compared to a general population. There was a shift towards more aggressive disease compared to a general population. Recurrence and progression rate were increased 2fold for TCC naïve (TCCn) and for patients with pretransplant history of TCC (hTCC) 3fold and 2fold, respectively. TCC related death occurred in 52% of TCCn and in 16.7% of hTCC patients. Hematuria was the main symptom leading to detection of TCC. The major risk factors were smoking and analgetic abuse. TCC associated graft failure was seen in 13% of patients.
**Conclusions:** TCC in renal transplant patients is associated with an increased recurrence as well progression risk and with a high tumor related mortality. TCC in these patients therefore requires prudent treatment and a rigid surveillance. Dip stick analysis for hematuria as well as urine cytology should be incorporated in the regular follow-up exams.

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## 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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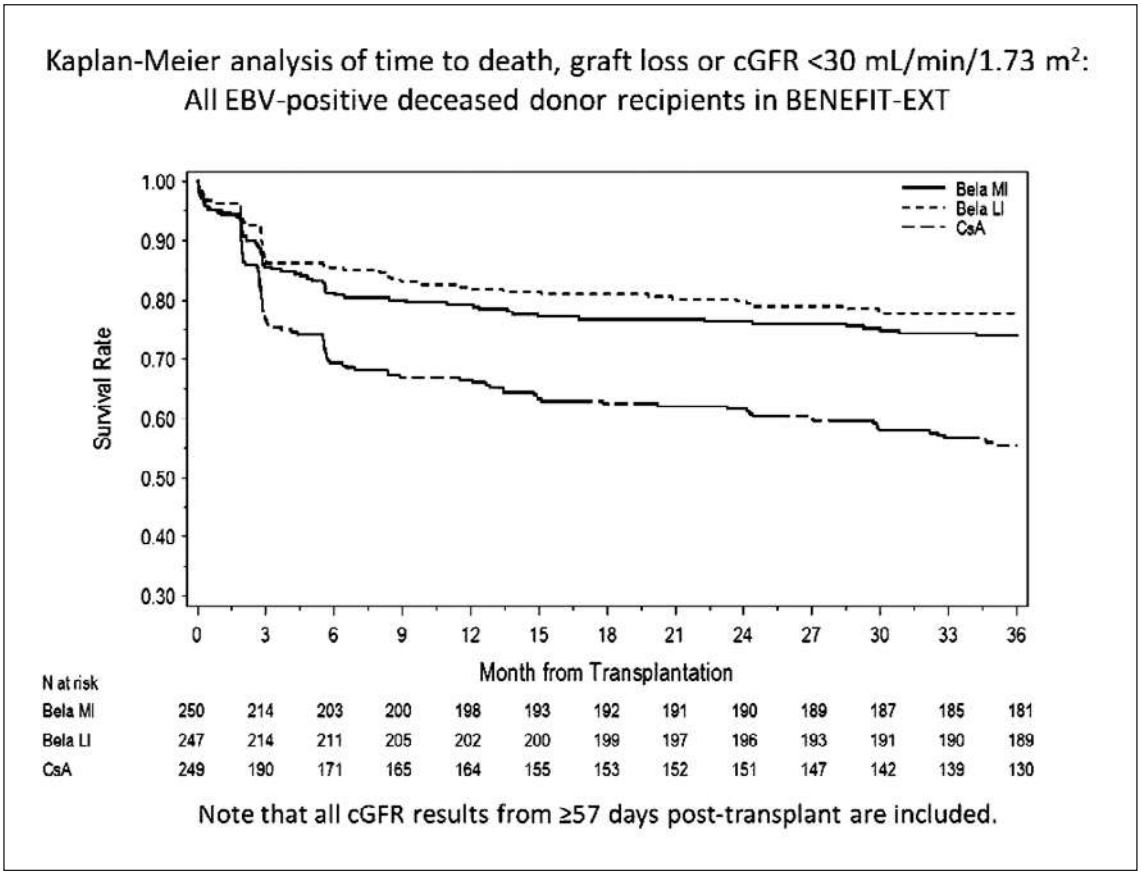
**Background:** Belatacept (bela; less intensive [LI] regimen) is approved to treat EBV+ adult kidney transplant patients (pts). Here we present post-hoc analyses of 3-year outcomes in EBV+ pts in the pooled populations of BENEFIT and BENEFIT-EXT who received a deceased donor kidney.
**Methods:** In 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 m$^2$ 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.



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### 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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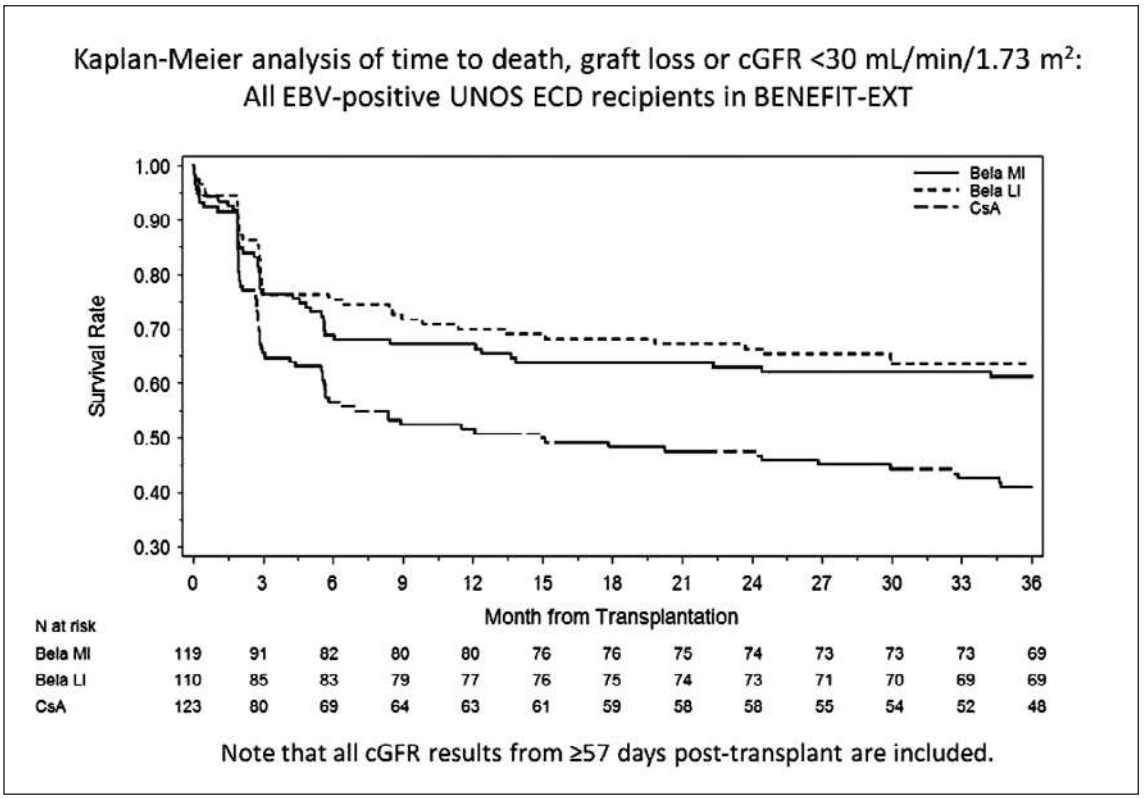
**Background:** Belatacept (bela; less intensive [LI] regimen) is approved to treat EBV+ adult kidney transplant patients (pts). Here we present post-hoc analyses of 3-year outcomes for EBV+ pts in BENEFIT-EXT who received deceased donor kidneys consistent with UNOS ECD criteria.
**Methods:** In BENEFIT-EXT, 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 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 m$^2$.
**Results:** 119 MI, 110 LI, and 123 CsA pts were EBV+ and received a UNOS criteria ECD kidney. At month (M) 36, survival with a functioning graft was similar across treatment arms: 95 (80%) MI, 90 (82%) LI, and 94 (76%) CsA. Mean (SD) MDRD cGFR at M36 was 40.0 (26) MI, 39.7 (24) LI, and 26.3 (21) mL/min/1.73 m$^2$ CsA. At M36, AR was 24 (20%) MI, 22 (20%) LI, 18 (15%) CsA. Fewer bela pts reached the composite EP compared with CsA (figure). Rates of serious adverse events were generally similar across treatment arms.
**Conclusions:** Results of this post-hoc analysis of EBV+ recipients of UNOS ECD kidneys in BENEFIT-EXT demonstrate similar pt and graft survival with both bela regimens vs CsA. Renal function was also improved with bela MI and LI despite numerically higher rates of AR, and the rates of the composite EP were lower with bela MI and LI vs CsA. The positive outcomes in this subset of EBV+ pts are consistent with those observed for bela in the overall BENEFIT-EXT population.

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### Prevention of bone mineral density (BMD) loss after kidney transplantation with the RANK ligand inhibitor denosumab (POSTOP study): baseline data, biomarker response and initial safety

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**Background:** Renal allograft recipients are at high risk for BMD loss after transplantation. 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 a controlled clinical trial (NCT01377467) we tested the efficacy and safety of denosumab to prevent bone loss in the first year after kidney transplantation. Between June 2011 and May 2014 we enrolled 108 patients of which 90 were randomized 1:1 within 28 days after transplantation to either denosumab (60 mg sc at baseline and 6 months) or no treatment. All patients were prescribed standard treatment with daily vitamin D (800 IE) and calcium (1000 mg), and were followed at defined visits in the first year post-transplant.
**Results:** Patients (n = 90; mean age 48 ± 13 years; 63% males) had a baseline eGFR of 52.7 ± 15.0 ml/min/1.73 m$^2$. 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 P1NP (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, P1NP and BSAP can be used to monitor the effect of denosumab treatment. Further analyses are needed to correlate the change of these biomarkers with the effect of denosumab on BMD.

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## 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 immunosuppression protocols. The approach was validated using internal data 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 transplant recipients (43.2% of all deaths). 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.

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## Role of lymphotoxins 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). Lymphotoxins (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 expresed 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 transplant glomerulopathy we observed two different patterns of LT activation: One cluster was categorized by strong upregulation of LTalpha, TNF, LIGHT, HVEM, BTLA, CXCL13, CCR7 and CCL21, whereas the second pattern was characterized by expression of LTbeta and its receptor, TNF receptors 1 and 2, MADCAM and TROY. Finally, activation of LT signaling was reproduced in a mouse model of renal transplantation indicating a species independent mechanism.
**Conclusion:** LTs and downstream target genes are upregulated in acute and chronic allograft injury in human and in mouse renal allografts. Whether LTs promote or ameliorate allograft rejection is unknown. The mouse renal allograft model will help to define the functional role of LTs in future studies.

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## Sarcopenic obesity in male renal transplant recipients

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**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/m$^2$.
**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, glucocorticosteroid 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 was significantly lower at any measured skeletal site in SO (mean ± SD lumbar spine: 1.030 ± 0.168 g/cm$^2$, femoral neck: 0.764 ± 0.125 g/cm$^2$ and proximal femur: 0.916 ± 162 g/cm$^2$) compared to non-sarcopenic RTR (lumbar spine: 0.930 ± 0.142 g/cm$^2$ p = 0.03, femoral neck: 0.645 ± 0.137 g/cm$^2$, p = 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.

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## Severe calciphylaxis in a renal transplant patient after denosumab administration: causal relationship or mere coincidence?

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A 49-year-old woman was admitted with a painful skin ulcer on the right thigh that developed 4 weeks ago. She had a history of ESRD due to extracapillary glomerulonephritis. She underwent for two years peritoneal dialysis until the first living-donor kidney transplantation (KTx) that lasted eight years. She returned to hemodialysis for one year. After a second living-donor KTx, 4 years ago, her current allograft function was severely reduced (eGFR about 27 ml/min/1.73 m$^2$ by CKD-EPI) because of recurrent humoral rejections. Her past medical history was also notable for subtotal parathyroidectomy due to secondary hyperparathyroidism. Medications included tacrolimus, mofetil mycophenolate, prednisone, ramipril, torasemide, amlodipine, pantoprazole. Four months before admission, the patient received denosumab (Prolia® 60 mg sc.) for treatment of osteoporosis. At admission, physical examination revealed an isolated 2x2 cm necrotic ulcer with irregular margins surrounded by violaceous skin. Biopsy of the ulcer revealed small vessel involvement and distal calcifications, consistent with calciphylaxis. Calcium and phosphorus serum concentrations were within normal values at admission and during the previous period. Parathyroid hormone (iPTH) was 68.9 pg/ml (10–73) and 25-(OH)-Vitamin D 64 nmol/l.
Sodium thiosulfate 12,5 g intravenously once daily and wound care with daily dressing changes and enzymatic ointments were started. Unfortunately, the ulcer size progressed and an additional ulcer developed on the contralateral limb. Surgical debridement and maggot therapy were performed. After 28 weeks of treatment, the ulcers improved with size reduction of ulcers and development of granulation tissue.
The timing of denosumab administration and calciphylaxis presentation, as long as the rare occurrence of calciphylaxis in predialysis CKD patients lead us to speculate about causal relationship. To our knowledge, this case is the first case of calciphylaxis after denosumab administration. One could hypothesize that denosumab increased calcification risk by decreasing bone buffer function through induction of adynamic bone disease by inhibition of osteoclasts.

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### 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 concentrations obtained at biopsy time-points was calculated and the arithmetic mean used for determing the "inflammatory burden". Evaluated 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 gn/mmol; 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, 1.06–1.21; p = 0.001)) and total HLA-mismatches (HR of 1.36 (95% CI, 1.04–1.79; p = 0.03)), while donor age/type, 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-years 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 and independent and strong predictor of long-term renal allograft outcome.

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### 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 among living 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 GG formulas)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.

## Poster presentations – Hypertension / Mineral / Electrolytes

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### A rare cause of kidney stones or just coincidence?

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**Case report:** A 42 year-old man was referred to our stone clinic for recurrent episodes of symptomatic nephrolithiasis. The last episode was treated by ureterorenoscopy and subsequent analysis of the calculi revealed 100% calcium oxalate monohydrate stones. Metabolic work-up demonstrated borderline hypercalcemia and mildly elevated PTH levels of 1–1.5 times the upper limit of normal. 24-h urinary calcium excretion was in the "normal" range (3.94 mmol/24 hrs). 25-hydroxy-Vitamin D level was decreased, whereas 1,25-dihydroxy-Vitamin D was normal. Family history was negative for nephrolithiasis or hypercalcemia. Ultrasound examination and nuclear imaging did not show any evidence of parathyroid adenoma. Nevertheless PHPT was suspected and surgical exploration and parathyroidectomy (PTX) were planned. However, taking a closer look at the calcium/creatinine clearance ratio (CCCR) confirmed hypocalciuria with a ratio <0.01 suggestive of familial hypocalciuric hypercalemia (FHH). Direct sequencing of the calcium sensing receptor (CaSR) gene (CASR) disclosed a heterozygous inactivating mutation (c.788C>T, p. Thr263Met) in the CASR gene confirming the diagnosis of FHH.
**Discussion:** FHH is characterized by a positive family history, mild hypercalcemia, inadequately normal PTH levels, a CCCR <0.01, and a benign clinical course. However there are atypical cases with slightly elevated PTH levels (as in our patient), negative family history or a CCCR >0.01. Renal stones are uncommon in FHH patients, yet a recent study has described kidney stones in up to 19%. The reasons for stone formation in patients with FHH are unknown. Impaired distal acidification of urine and reduced dilution capacity as a consequence of inactivating CaSR are conceivable mechanisms.
**Conclusion:** In kidney stone formers who present with hypercalcemia and mildly elevated PTH levels, CCCR serves as a useful tool to accurately differentiate between FHH and PHPT to avoid unnecessary parathyroidectomy. To further confirm the diagnosis of FHH genetic analysis has to be performed.

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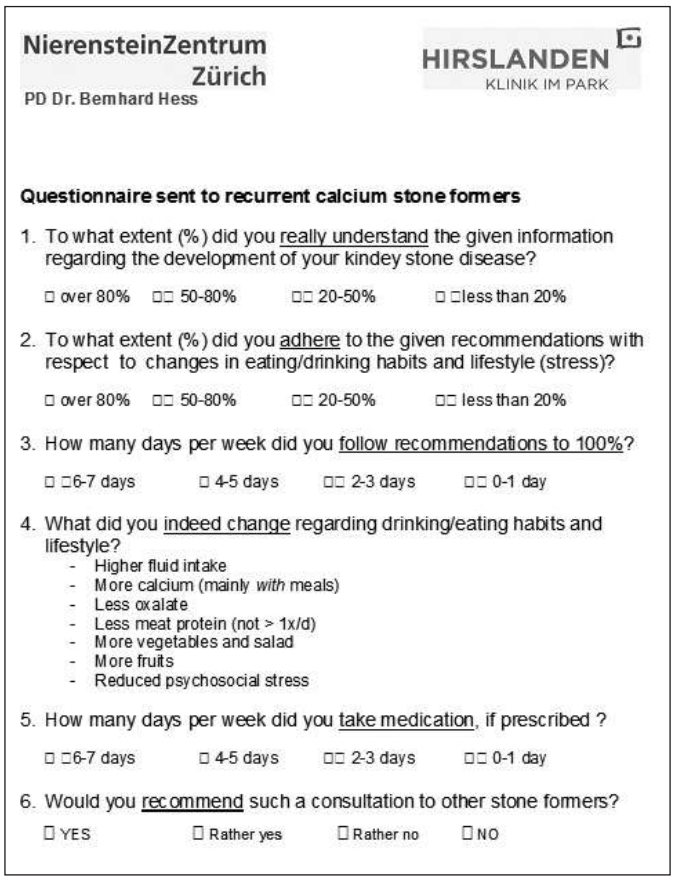
### Renal stone clinic – How do patients perceive our explanations and recommendations?

*Bernhard Hess*
*Renal Stone Center Zurich*

**Background:** Results of metabolic work-up have to be transferred into understandable explanations and individualized recommendations to stone formers. Not much is known about how well these prophylactic measures are perceived by stone formers.
**Methods:** Among 162 stone formers referred for evaluation, we selected 153 recurrent calcium SF (RCSF). Between 1–3 months after a 60-minute consultation explaining the disease pathophysiology and recommending therapeutic measures, RCSF received a questionnaire with 6 multiple choice questions regarding understanding of stone formation and adherence to therapeutic recommendations (fluid intake;



NierensteinZentrum Zürich
PD Dr. Bernhard Hess

HIRSLANDEN KLINIK IM PARK

**Questionnaire sent to recurrent calcium stone formers**

1. To what extent (%) did you really understand the given information regarding the development of your kindey stone disease?
   □ over 80% □□ 50-80% □□ 20-50% □ □less than 20%
2. To what extent (%) did you adhere to the given recommendations with respect to changes in eating/drinking habits and lifestyle (stress)?
   □ over 80% □□ 50-80% □□ 20-50% □□ less than 20%
3. How many days per week did you follow recommendations to 100%?
   □ □6-7 days □ 4-5 days □□ 2-3 days □□ 0-1 day
4. What did you indeed change regarding drinking/eating habits and lifestyle?
   - Higher fluid intake
   - More calcium (mainly *with* meals)
   - Less oxalate
   - Less meat protein (not > 1x/d)
   - More vegetables and salad
   - More fruits
   - Reduced psychosocial stress
5. How many days per week did you take medication, if prescribed ?
   □ □6-7 days □ 4-5 days □□ 2-3 days □□ 0-1 day
6. Would you recommend such a consultation to other stone formers?
   □ YES □ Rather yes □ Rather no □ NO

increased Ca intake; less oxalate-rich products, less meat protein; more vegetables, salad, fruits; reduced psychosocial stress; drugs). The 6 questions are listed on the table.
**Results:** Response rate was 61.4% (94 RCSF); 44 RCSF (47%) also had been prescribed medication (K-citrate). 63 RCSF (67%) had understood >80% of the information on stone disease, 27 RCSF (29%) 50–80%. Over 80% adherence to recommendations occurred in 25 (27%), adherence to 50-80% in 56 (60% of all RCSF). Only 23 (25%) of RCSF followed recommendations to 100% on 6–7 weekdays (perfect adherence), 52 (55%) on 4–5 weekdays. The most frequent change in dietary/lifestyle habits was higher Ca intake (93% RSCF), followed by more fluids (81%), more vegetables/salad (72%), less oxalate (59%), more fruit (52%), and reduced stress (23%). Perfect adherence was significantly more frequent for intake of medication than for following dietary/lyfestyle interventions (84% vs. 27%, p <0.001). Finally, 80% would certainly and 16% rather recommend the stone clinic to other RCSF.
**Conclusions:** 1) Pathophysiologic explanations of stone disease are understood to >80% by 2/3 of RCSF; 2) Perfect adherence to treatment is significantly more frequent with medication than with dietary/lifestyle measures; 3) Increasing calcium and fluid intake are the most popular dietary measures; 4) 96% certainly/rather would recommend the stone clinic consultation to other RCSF.

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**P 56**

### FGF23 and markers of phosphate and calcium homeostasis in subjects with preserved renal function

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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 98.1 RU/ml (SD 79.3 RU/ml). Log FGF23 levels were associated inversely with eGFR (β: –0.01, SE: 0.001; 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: 0.30, SE: 0.09; p = 6.99x10-4) 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 calcium excretion 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.
Measurements of PTH and 1,25-OH Vitamin D in this cohort will hopefully shed more light on this interesting novel aspects of FGF23 physiology.

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**P 57**

### Proton-pump inhibitor associated hypomagnesemia: a systematic review

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**Background:** First introduced in the 1980s, proton-pump inhibitors are widely prescribed. In 2006, hypomagnesemia was first described as a complication of these drugs.
**Methods:** To address this issue, we reviewed the literature using the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.
**Results:** 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 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.

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**P 58**

### 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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**Objectives:** Little is known about the circadian rhythm of fractional urinary Mg2+ excretion (FEMg2+) in humans as well as factors associated with FEMg2+ in the general population. Mice experiments suggest that estrogens play a key role in renal Mg2+ handling, but there are only scarce data in humans regarding the role of sex hormones on renal Mg2+ handling.
**Methods:** In 1053 participants to the family-based SKiPOGH (Swiss Kidney Project on Genes in Hypertension) study, serum electrolytes and urinary excretions (separately for day and night) of Mg2+ were assessed in nuclear families. We used a mixed linear model to explore the associations of FEMg2+ with sex, age, renal function, menopausal status and urinary 17β-Estradiol excretion.
Results: FEMg2+±SD was higher at night (3.1% ± 0.1) than during the day (2.7% ± 0.1), in men and women (P <0.001). Compared to creatinine clearance (119.2 ml/min during the day and 125.5 ml/min at night), day and night Mg2+-clearances±SD differed more proportionally (3.1 ml/min ± 1.3 and 3.8 ml/min ± 1.8). In multivariable models square-root transformed day and night FEMg2+ increased with declining renal function. Night, but not day FEMg2+ was associated positively with age. Night FEMg2+±SD was lower in pre-menopausal women (2.7% ± 0.1) than in post-menopausal women (3.6% ± 0.1) and in men (3.1% ± 0.1), whereas the three groups had similar day FEMg2+. This difference strongly attenuated upon adjustment for age. 17β-Estradiol was associated positively with total Mg2+ excretion, but not with FEMg2+.
**Conclusions:** FEMg2+ follows a circadian rhythm in the general adult population, with higher values at night, and night-time FEMg2+ varies with age, possibly explaining occurrence of muscle cramps during the night.
Estrogens had a major influence on total Mg2+ excretion in men and women, but not on FEMg2+. Estrogens may therefore play a role on Mg2+ absorption in the gut or the resorption from the bone. Further studies are needed to better understand the underlying molecular mechanisms.

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**P 59**

### Angiotensinergic innervation of the human right atrium, atrial angiotensins and implications for baroreceptor control of blood pressure

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**Background:** The autonomic innervation of the heart controls cardiac function and arterial blood pressure by autonomic baroreflexes originating in the right atrium and central vessels. Angiotensin II (Ang) is a neuropeptide co-transmitter of sympathetic fibers and may modulate intracardiac neurotransmission via its synaptic Ang receptors. The presence of angiotensinergic fibres in the human atria and their phenotype and potential function are not known.
**Methods:** Human right atrium specimens (n = 7, cardiac surgery) were immunohistologically stained for Ang (monoclonal antibody) and costained for tyrosine hydroxylase (TH) or synaptophysin (SYN) to identify a catecholaminergic phenotype using fluorescent light or laser scanning microsopy. Ang I-V concentrations were determined by tissue extraction, HPLC and radioimmunoassay.
**Results:** Atrial autonomic fibres and ganglionic cells stained either positive for TH or Ang or both. SYN and TH stainings suggested colocalization in catecholaminergic fibers. Ang-positive fibers were thicker than exclusively catecholaminergic fibers and, if varicose, showed fewer and larger varicosities. Epicardial Ang-positive fibers were grouped within bundles, mostly non-varicose and TH-positive. In the myocardium, Ang-positive fibers were infrequent, mainly non-varicose and TH-negative. These fibers were accompanied by numerous highly varicose, purely catecholaminergic fibers suggesting local neurotransmitter interaction. The perivascular plexus contained Ang-positive, mostly non-varicose, and numerous exclusively TH-positive and highly varicose fibers. Some fibers co-localized Ang and TH. Subendocardial Ang-positive fibers were mainly non-varicose and TH-negative except for clusters of (1) highly varicose tortuous or sprouting fibres, or (2) groupings of thin, palisade-forming fibers that ressembled afferent terminals. Tissue Ang I and Ang II concentrations were 6.2 ± 2.6 and 156.4 ± 174.1, and Ang III-V concentrations <2.9 fmol/g.
**Conclusions:** Angiotensinergic fibers innervate the human right atrium and are catecholaminergic or non-catecholaminergic (probably afferent or parasympathetic). Intracardiac neuronal Ang II-release may contribute to atrial Ang concentrations and may reset atrial autonomic baroreceptor reflexes via synaptic Ang receptors to control blood pressure.

**P 60**

### 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 could 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, comedication 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/m$^2$, respectively. Mean SBP/DBP was 119.3(17.2)/75.2(9.3) mm Hg for office, 120.8(12.7)/79.2(8.4) for daytime and –1.5(12.1)/–4.0(7.9) for the white-coat effects. 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 (GR) and PXR. Our findings are in line with a potential involvement of detoxification enzymes in blood pressure regulation, in particular when stress-induced.

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### 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, chlortalidon, hydrochlorothiazide, lercanidipine and lisinopril should be preferred to pulverized amlodipine, atenolol, bisoprolol, enalapril, irbesartan, 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 Pemzek®). For this purpose, a smiley-face scale depicting four degrees of pleasure was used.
**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

49 years. Pulverized brand-names and generics containing either amlodipine or candesartan did not differ with respect to their taste acceptability.
**Conclusions:** The taste of medicines is a crucial modulator of medication adherence in childhood, especially in asymptomatic conditions like hypertension. Future guidelines for the management of childhood hypertension should recognize the role of taste acceptability when deciding which medicine to prescribe to a child with hypertension.

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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. C57B/6 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 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 none of the 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 probably 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

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### 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) 20.8x$10^9$/l (norm: 0–0.1x$10^9$/l) confirming PD-associated peritonitis. Cultures of the peritoneal fluid were taken and empiric therapy with Amikacin 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 3.4x$10^9$/l. A CT-scan of the abdomen was performed without apparent pathologies. Due to further rise of the LCf to 15.3x$10^9$/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 inocoulum of E.coli and the very slow growth of itself.
**Conclusion:** In relapsing peritonitis despite treatment there should be thought of uncommon organism, primary resistant organism or catheter colonization. To our knowledge this is the first reported case of PD-associated peritonitis with Sphingomonas koreensis.

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### Histological and clinical findings in patients with post-transplantation and classical encapsulating peritoneal sclerosis: a European multicenter study

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**Background:** Encapsulating peritoneal sclerosis (EPS) commonly presents after peritoneal dialysis has been stopped, either post-transplantation (PT-EPS) or after switching to hemodialysis (classical EPS, cEPS). The aim of the present study was to investigate whether PT-EPS and cEPS differ in morphology and clinical course.
**Methods:** In this European multicenter study we included fifty-six EPS patients, retrospectively paired-matched for peritoneal dialysis (PD) duration. Twenty-eight patients developed EPS after renal transplantation, whereas the other twenty-eight patients were classical EPS patients. Demographic data, PD details, and course of disease were documented. Peritoneal biopsies of all patients were investigated using histological criteria.
**Results:** Eighteen patients from the Netherlands and thirty-eight patients from Germany were included. Time on PD was 78 (64-95) in the PT-EPS and 72 (50-89) months in the cEPS group ($p > 0.05$). There were no significant differences between the morphological findings of cEPS and PT-EPS. Podoplanin positive cells were a prominent feature in both groups, but with a similar distribution of the podoplanin patterns. Time between cessation of PD to the clinical diagnosis of EPS was significantly shorter in the PT-EPS group as compared to cEPS (4 (2-9) months versus 23 (7-24) months, $p < 0.001$). Peritonitis rate was significantly higher in cEPS.
**Conclusions:** In peritoneal biopsies PT-EPS and cEPS are not distinguishable by histomorphology and immunohistochemistry, which argues against different entities. The critical phase for PT-EPS is during the first year after transplantation and therefore earlier after PD cessation then in cEPS.

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## 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. PDGF receptor β (PDGFRβ) is a marker of pericytes and PDGFs 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.

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## Demographic characteristics of maintenance hemodialysis (HD) patients in Switzerland

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**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: 40–59 yrs, C: 60–79 yrs, D: ≥80 yrs). Comorbidity correlated clearly with age, with 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.

| | Range | Mean ± SD | Median |
|---|---|---|---|
| Age (yrs) | 21–91 | 68.3 ± 15.0 | 72.0 |
| Weight (kg) | 40–137.3 | 74.0 ± 16.1 | 72.5 |
| BMI | 14.9–47.3 | 26.3 ± 5.4 | 25.6 |
| Dialysis vintage (yrs) | 0.1–37.3 | 4.4 ± 4.7 | 3.0 |
| Charlson Comorbidity Index (CCI) | 2–13 | 4.3 ± 2.1 | 4.0 |
| ADL* | 10–100 | 90.0 ± 16.3 | 100.0 |
| * Questionnaire "Activities of Daily Living" | | | |

**Conclusions:** Compared to patients from the ERA-EDTA registry (2012), patients in our analysis from Switzerland have a lower mortality despite being older. Our data indicate an inverse correlation of patient survival with dialysis vintage independent of age. A more complete demographic picture will result from the Swiss dialysis registry collections.

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## Assessment of lean tissue mass (LTM) in maintenance hemodialysis (HD) patients

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**Background:** Physical capacity, and, therefore, muscle mass, is an important predictor for survival in maintenance HD patients. Bioelectrical impedance analysis (BIA) is a simple, noninvasive method to assess body composition. The aim of the present study was to analyze LTM and its longitudinal change in the Swiss HD population.
**Methods:** 427 patients were evaluated from the monitor! project, a prospective dynamic hemodialysis cohort assessing a wide range of medical data. LTM, which provides information on the patients muscle mass, was analyzed by BIA measurement once a year over 3 years.
**Results:** Mean score for LTM was 44.8%, indicating a very low portion of muscle mass. LTM was analyzed after stratification for age, dialysis vintage and Charlson Comobidity Index (CCI) (table).
Patients with high initial LTM tend to have a steep decline in follow-up measurements (>5%) regardless of age, sex, dialysis vintage and CCI. The majority of patients have stable LTM over the observation period.
**Conclusions:** Patients on maintenance HD present with severe reduction in LTM compared to healthy individuals, reflecting sarcopenia to be a serious problem in this population. However, LTM seems to be stable over time, especially in patients in the lower LTM range. As sarcopenia is associated with higher mortality and limited functional independency, efforts should be made towards improving muscle mass in HD patients.

**Table**

| | **Age (yrs)** | | | | **P** |
|---|---|---|---|---|---|
| | ≤39 yrs mean ± SD | 40–59 yrs mean ± SD | 60–79 yrs mean ± SD | ≥80 yrs mean ± SD | |
| LTM (%) | 59.8 ± 12.3 | 50.9 ± 14.6 | 42.0 ± 11.9 | 42.5 ± 9.1 | **0.000** |
| | **Dialysis vintage (yrs)** | | | | |
| | ≤1 year mean ± SD | 1.0–3.9 yrs mean ± SD | 4.0–6.9 yrs mean ± SD | ≥7 yrs mean ± SD | |
| LTM (%) | 47.1 ± 12.5 | 44.6 ± 13.8 | 43.2 ±12.0 | 42.8 ± 11.8 | **0.081** |
| | **CCI** | | | | |
| | **low** mean ± SD | **average** mean ± SD | **high** mean ± SD | | |
| LTM (%) | 47.4 ± 13.7 | 43.3 ± 12.0 | 41.0 ±10.8 | | **0.000** |

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## 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 22.3 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 strength 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.

| Handgrip strength (kg) | Age (years) | Weight (kg) | CCI• | Time on HD (years) | LTM (%) |
|---|---|---|---|---|---|
| Low (N = 126) | 71.6 ± 13.3 | 69.8 ± 15.6 | 4.0 ± 1.8 | 4.3 ± 5.5 | 41.7 ± 12.8 |
| Average (N = 101) | 70.0 ± 12.8 | 75.4 ± 15.4º | 4.4 ± 2.0 | 3.3 ± 4.6 | 42.0 ± 12.2 |
| High (N = 113) | 63.2 ± 16.4*/** | 80.0 ± 14.3* | 3.9 ± 2.0 | 3.2 ± 3.8 | 50.1 ± 12.7*/** |

*) P <0.001 vs. "low handgrip strength" **) P <0.001 vs. "average handgrip strength" º) P <0.001 vs. "low handgrip strength"
•) Charlson Comorbidity Index

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### 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, a prospective dynamic hemodialysis cohort assessing a wide range of clinical, laboratory and anthropometrical data. Nutritional risk was assessed by the NRS questionnaire. Lean tissue mass, serving as a proxy for muscle mass, was analyzed by bioelectrical impedance analysis (BIA) measurement. NRS scores were correlated with occurrence of LTM changes within 1 year.
**Results:** Mean LTM was 42.8%, indicating very low muscle mass. Stratification of the study population according to direction of LTM change (decline, none, increase) revealed no relevant association with comorbidity and age, but patients with an increase in LTM are significantly longer on HD.
The predictive power of an NRS score ≥2 for a substantial decline in muscle mass (≥10%) was calculated to have a sensitivity of 78%, and a specificity of 35%. In contrast, an NRS score of 1 has a negative predictive value (NPV) of 94% for severe muscle loss. An analog analysis was performed with hand grip strength instead of muscle mass, giving similar results.
**Conclusions:** Assessment of maintenance HD patients by NRS can be used as a straight forward 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.

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### 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 disorientated in a state of confusion, GCS 7, without signs of localization. Laboratory tests showed Hb 15 g/dl, leukocytes 8090/uL, platelets 154 000/Ul, 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 acute 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.

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### 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 [iNa] 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 [iNa].
**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 [iNa] 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 [iNa] 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 the dispersion of the individual [iNa] values is also different for the 3 monitors.
**Conclusions:** The present data show that for a same prescription not all the dialysis monitors deliver the same dialysate concentration of sodium, certainly due to difference in the algorythms 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.**

| Dialysis monitor | | Prescribed Na conductivity | Measured sodium concentration | Difference |
|---|---|---|---|---|
| | | mmol/l-equivalent | mmol/l | mmol/l |
| **Gambro AK 200** | n=49 | **139.49 ± 2.92** | **143.02 ± 3.98** | **3.53 ± 1.99** |
| **Nikkiso DBB-05/07** | n=62 | **139.81 ± 2.53** | **140.37 ± 2.73** | **0.56 ± 1.94** |
| **Fresenius 5008** | n=47 | **138.49 ± 3.39** | **139.13 ± 4.08** | **0.70 ± 1.84** |

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### The association between ultrafiltration volume and difference of the pre- and post-dialysis hemoglobin levels in maintenance hemodialysis patients

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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 examin 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 <1%).
T-test for paired samples: The differences between arithmetic means for pre- and postdialytic hemoglobin levels lies for total patients, diabetic and nondiabetic 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 addition illustrate patients and treatment.
**Conclusion:** Our results revealed correlations between ultrafiltration volume and changes in intradialytic hemoglobin levels. The results demonstrate a post-dialysis hemoconcentration effect.
The post-dialysis hemoconcentration 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 to be adapted on ultrafiltration volume.

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### 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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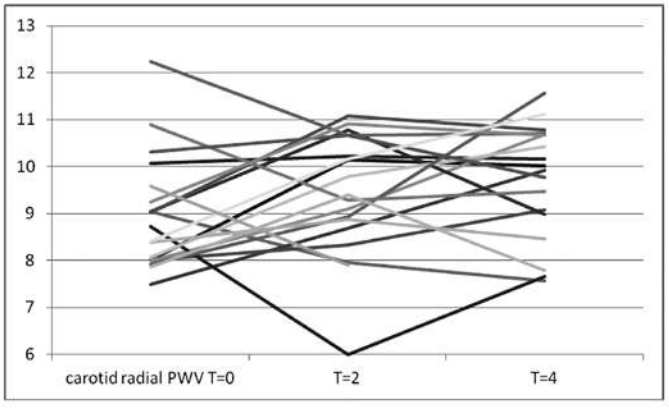
**Background:** Arteries of end-stage renal disease patients are characterized by accelerated atherosclerosis and chronically progressive arterial stiffening. The acute effects of hemodialysis sessions on arterial properties have been less intensively studied, with contradictory results, possibly due 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 (8.0–9.4) before to 9.8 m/sec (8.7–10.7) after hemodialysis, p = 0.09), cf-PWV did not (from 10.3 (8.8–13.1) to 10.1 m/sec (9.4–14.4), 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.

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### 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 30 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 pressures 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 (44hBPsys) was lower than pre- and postdialysis BPsys (127.6 ± 2.8 versus 131.5 ± 3.5 and 129.9 ± 3.2). In contrast, 44hBPdias was higher than pre- and postdialytic BPdias (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 BPsys), whereas 53% were nondippers and 37% reverse dippers. In-center pre-dialysis BPsys exceeded 44hBPsys by >20 mm Hg in 10 patients (24%), but was more than 20 mm lower than 44hBPsys in 16%. Discrepancies were less pronounced for post-dialysis BPsys(16% too high by >20 mm Hg, 8% too low by >20 mm Hg). There was no correlation of pre-dialysis BDsys with 44hBPsys (r = 0.17), and only a weak correlation with post-dialysis BDsys (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.

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### 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 or more often due to central venous 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 lower limb or placement of long-term catheters is required, associated to poor outcomes, especially in term of infection. However, the new HeRO® graft seems to be an satisfactory 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 radio-cephalic (group I) and 26 brachio-cephalic (group II) AVF. About one third of patients required a permanent tunnelled 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 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 fullfill 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 hemodialysis patients?

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**Background:** Deficiency of several water soluble vitamins has been reported in patients undergoing chronic hemodialysis (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 Dialvit® 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, VB-1 and VB-6 analyzed in 100 patients where 3182, 224 and 377 nmol/l respectively. In none 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 Dialvit® 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.