44th Annual Meeting of the Swiss Society of Nephrology

Zurich (Switzerland), December 5–7, 2012
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Frequency and Determinants of Pregnancy-Induced Child-Specific Sensitization

G. Hoenger1, I. Fornaro1, C. Granado1, J.-M. Tiery2, I. Hoessli1, S. Schaub1
1Basel, 2Geneva

Purpose: Pregnancies are a major cause of sensitization in females awaiting organ transplantation. The aim of this study was to define the frequency and determinants of pregnancy-induced child-specific sensitization shortly after delivery.

Methods: Three hundred and one pregnancies were analyzed using sensitive single HLA-antigen beads (SAB) and high resolution HLA-typing of the mothers and their children (n = 301). A positive child-specific SAB result was defined by a background normalized ratio >1 or a mean fluorescence intensity (MFI) >300, using ten negative control sera.

Results: The overall frequency of child-specific sensitization at the HLA-A/B/DR1 loci was 38% (ratio cut-off), 34% (MFI >300 cut-off), 31% (MFI >500 cut-off), and 28% (MFI >1000 cut-off), respectively. If sensitization had occurred, there were on average two child-specific HLA-antibodies. The number of live birth was associated with a higher frequency of sensitization, while miscarriages were not. There was a clear hierarchy of sensitization among the investigated loci (B-locus: 31%; A-locus: 26%; DRB1-locus: 20%; C-locus: 15%; p <0.0001). Some clear hierarchy of sensitization among the investigated loci (B-locus: 31%; A-locus: 26%; DRB1-locus: 20%; C-locus: 15%; p <0.0001).

Conclusion: This information can be useful to estimate the likelihood of occurred pregnancy-induced sensitization, even if no HLA-antibodies are detectable at the time of evaluation for transplantation.

Modulation of Lymphocyte Apoptosis to Induce Mixed Chimerism and Tolerance Without Myelosuppression

P. Cippà, J. Chen, A. K. Kraus, R. P. Wüthrich, T. Fehr

Purpose: Despite encouraging results of the first clinical studies, a broad application of tolerance induction strategies based on combined solid organ and hematopoietic stem cell transplantation to induce mixed chimerism is hampered by the toxicity of the conditioning therapy.

Methods: We investigated the role of the apoptosis pathway in a mixed chimerism induction protocol including costimulation blockade and fully MHC-mismatched bone marrow in mice.

Results: Using Bim-/mice we found that the pro-apoptotic factor Bim was critically required to induce mixed chimerism. Conversely, by blocking the role of RipK3 in small-molecule BH3-mimetic ABT-737 we were able to induce mixed chimerism with moderate doses of bone marrow cells and without any myelosuppressive conditioning. This protocol resulted in a complete deletion of peripheral donor-reactive CD8 T cells within one week after bone marrow transplantation. A stable myeloid-biased chimerism was detected over time in peripheral blood and in the thymus resulting in robust systemic donor-specific tolerance. Donor-type skin grafts were indefinitely accepted (observation time >200 days), donor-reactive antibodies and reactivity towards donor-cells in mixed lymphocyte reaction experiments were absent while transplantation of secondary donor-derived skin grafts confirmed the maintenance of robust tolerance.

Conclusion: In summary, we identified the apoptosis pathway as a new pharmacological target to induce mixed chimerism. Based on these findings we developed a new protocol that leads to tolerance across full MHC barriers in a manner that is completely independent of irradiation or myelosuppression. This approach represents a substantial advance towards a broader clinical application of tolerance as an ideal solution to prevent allograft rejection.

Outcome of Expanded Criteria Donor Kidney Transplants in an Immunological Low-Risk Population


Basel

Purpose: Outcome of standard and ECD kidney recipients with low immunological risk, defined by the absence of donor-specific HLA-antibodies (HLA-DSA).

Methods: We retrospectively analyzed death censored graft survival and graft function in a cohort of 265 recipients transplanted from 1/1999 to 12/2010.

Results: 112 (42%) kidneys derived from ECD and 153 (58%) from SCD. In multivariate Cox regression ECD status was the only significant risk factor for graft failure (HR 2.82 [CI 1.27–6.26], p = 0.01). Overall, the one-, three- and five-year graft survival rates for ECD kidneys (94%/92%/89%) were lower compared to standard criteria donors (SCD) (97%/94%/93%) (p = 0.004). Stratified by immunosuppression (IS) graft survival of ECD kidneys treated with tacrolimus-mycoportalone (Tac-MPA) was comparable to graft survival of SCD kidneys (p = 0.3), whereas survival rates of ECD kidneys treated without Tac-MPA were significantly lower (88%/83%/72%) (p <0.001). Overall, ECD kidneys had a lower median eGFR (37 [5–102] ml/min) than SCD kidneys (58 [5–137] ml/min) at three years (p <0.001). This difference remained constant after stratification for IS (p <0.001). Within the ECD group, recipients treated with Tac-MPA had a higher median eGFR at three years (43 [5–102] ml/min) and a preserved graft function from one to three years (median change −0.2 ml/min, p = 0.7) compared to those treated without Tac-MPA (34 [5–67] ml/min) (p = 0.002), who showed a significant decrease in eGFR (median change −2.2 ml/min) (p = 0.004).

Conclusion: In the absence of HLA-DSA, outcome of kidneys derived from ECD is favourable. Tac-MPA seems to improve graft survival and to preserve graft function.

**Method:** Patient 1 was the index case in whom the genetic defect was discovered. Detailed histological evaluation performed and the complex phenotype described. Subsequently, two other children with similar clinical features and ITGA3 mutations were identified. From all 3 patients and their parents genetic analysis for ITGA3 and other candidate genes was performed.

**Results:** Patient 1 revealed a homozygous mutation c.1173_1174del in exon 8 of ITGA3 gene, histologically leading to a loss of Integrin-α3 in the kidney, skin and lung accompanied by profound abnormalities of the basement membrane in all affected organs. Although skin fragility initially was mild, it provided clues to the diagnosis. Patients 2 and 3 were homozygous for the ITGA3 mutation in intron 11, and c.1883G>C;p.Arg628Pro in exon 14, respectively. The ITGA3 mutations in all patients were associated with congenital nephrotic syndrome accompanied by end stage renal failure, worsening epidermolysis bullosa and severe interstitial lung disease (NEP-Syndrome). Although skin fragility and interstitial lung disease, who were homozygous for mutations in the ITGA3-gene.

**Conclusion:** We identified 3 patients with homozygous mutations of ITGA3-gene associated with disrupted basement membrane structures clinically leading to NEP-syndrome. These new mutations reflect the impact and indispensability of Integrin-α3 concerning the organization of basement membrane and its clinical impact.

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**Purpose:** Tumor-associated FGF-23 Induced Hypophosphatemic Rickets in an Eight Year Old Boy M.-A. Burckhardt, A. Schifferli, A. Krieg, D. Baumhoer, M.-A. Burckhardt, C. Rudin Basel

**Method:** Tumor-associated fibroblast growth factor 23 (FGF-23) induced hypophosphatemic osteomalacia has primarily been described in adults. In recent occasions this entity may also cause renal phosphate wasting and rickets in children, resulting from local production of phosphatonin by various benign and malignant mesenchymal tumors.

**Results:** Biopsy of the iliac lesion suggested a primary solitary bone cyst over lain by a secondary and solid aneurysmal bone cyst. Laboratory findings, i.e. hypophosphatemia, renal tubular phosphate wasting, normal parathormone and normal calciotriol levels were not compatible with common forms of rickets in childhood. Tumor-associated rickets was therefore suspected and further investigated with various methods, including a PET-scan and measurement of FGF-23 plasma levels. A causal lesion other than the iliac tumor or use of oral cation-exchange resin and low K+-dialysate, serum K+ level remained high (6.1–7.9). Six months later, the bowel continuity was successfully restored and serum K+ decreased to the previous level (5.2–5.9). The measurement of fecal K+-level before and after restoration of bowel continuity revealed a remarkable difference between the values: 23 mmol/l and 60 mmol/l, respectively. We therefore assume that the severe hyperkalemia in our patient was caused by the failing colonic secretion of K+ due to the colonic diversion.

**Conclusion:** To our knowledge, this is first report on severe hyperkalemia following colonic diversion in patients with ESRD undergoing HD and demonstrates the importance of colonic K+-secretion for the maintenance of K+ homeostasis in these patients.

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**Purpose:** Severe Hyperkalemia in a Patient With Chronic Hemodialysis Following Colon Diversion Surgery N. Kononowa, M. Dickenmann, M. J. Kim Basel

**Method:** Potassium (K+) homeostasis in healthy subjects is maintained mainly by urinary excretion of K+, which is almost equal to the amount of dietary K+-ingestion. In patients with end-stage renal disease (ESRD), the capacity of the colon for K+-secretion increases to the extent that it makes a substantial contribution to K+-homeostasis.

**Results:** We report on a chronic hemodialysis (HD) patient developing severe hyperkalemia following colon diversion surgery.

**Conclusion:** A 56 year-old-woman with ESRD undergoing HD suffered from ischaemic colitis, leading to ileocaecal resection and temporary ileoanastomosis. She made a good recovery and her dietary intake was normalized in the following weeks. Three weeks later, a routinely measured pre-HD serum K+ was 7.2 mmol/l, which was much higher than her usual K+ level (range 4.9–6.1). There was no evidence of metabolic acidosis and any remarkable hyperkalemia-related symptoms or signs, including ECG. Despite a dietary restriction of K+ and use of oral cation-exchange resin and low K+-dialysate, serum K+ level remained high (6.1–7.9). Six months later, the bowel continuity was successfully restored and serum K+ decreased to the previous level (5.2–5.9). The measurement of fecal K+-level before and after restoration of bowel continuity revealed a remarkable difference between the values: 23 mmol/l and 60 mmol/l, respectively. We therefore assume that the severe hyperkalemia in our patient was caused by the failing colonic secretion of K+ due to the colonic diversion.

**Conclusion:** To our knowledge, this is first report on severe hyperkalemia following colonic diversion in patients with ESRD undergoing HD and demonstrates the importance of colonic K+-secretion for the maintenance of K+ homeostasis in these patients.

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**Purpose:** Dialysis for Two – The Zurich Dialysis Pregnancy Experience In 2012 M. Bonani, S. Wassmer, L. Schäffer, G. Andreisek, R. P. Wüthrich, S. Segerer Zurich

**Method:** Pregnancies in women on hemodialysis are rare and the outcome is hampered by a high number of pregnancy-related complications.

**Results:** A 29-year old woman was referred for the evaluation of renal failure in the 7th week of pregnancy. She presented without clinical symptoms, but with an eGFR of 17 ml/min, proteinuria of 3.5 g/day, bicarbonate of 15 mmol/l, and a hemoglobin of 8.0 g/dl. Renal ultrasonography demonstrated a shrunken kidney on the left side and a dilated pelvocalyceal system on the right side. A suspected pyeloureteral stenosis and a toxic injury by streptomyacin (in the childhood for tuberculosis) were the presumed causes of the renal insufficiency. She was treated with bicarbonate, iron, as well as erythropoietin and received a peripheral native AV fistula. Aspirin (100 mg per day) was given for preeclampsia prophylaxis. Once the urea levels exceeded 16 mmol/l and metabolic acidosis worsened, dialysis was started in the 17th week of pregnancy. With the advancement of the pregnancy, dialysis was intensified to 21 hours/week divided into six sessions per week. The median dose of erythropoietin to reach the target Hb level was 16700 U/week. From 22 weeks, a moderate polyhydramnion was present. In the last trimester, slight growth retardation was noted. At week 37 an elective cesarian section was performed with delivery of a healthy boy weighing 2080 grams.

**Conclusion:** Despite the improvements in hemodialysis therapy, only half of the dialysis pregnancies result in healthy children. Uncertainties remain in the decision when to start dialysis. Our case illustrates that intensive dialysis and a very close interdisciplinary monitoring can result in a successful pregnancy and delivery of a healthy child.
Hemodialysis Reduces the Calcification Propensity of Serum
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1Berne, 2Solothurn, 3Aachen/DE
Purpose: Vascular calcification is a major cause of death in hemodialysis (HD) patients. We have developed an in vitro test, which measures serum calcification propensity by detecting the spontaneous transformation of colloidal primary calciprotein particles (CPPs) to crystalline secondary CPPs. The effect of hemodialysis on serum calcification propensity has not been determined yet.

Methods: The intrinsic calcification propensity of pre- and post-HD sera obtained from 98 prevalent HD patients were analyzed with our novel test. Calcium, phosphate, magnesium, fetuin-A, albumin, and total protein concentrations were related to the test results and integrated into a multivariate model with stepwise selection.

Results: HD reduced serum calcification propensity by delaying transformation time (T50 pre-HD 244 ± 112 min., post-HD 340 ± 114 min., p = 0.0001) and reducing precipitation intensity (relative nephelometric units, RNU50 pre-HD 6892 ± 2404, post-HD 5234 ± 1789, p = 0.0001). A multivariate model showed, that the T50 of pre-HD sera depended mainly on magnesium (transformation delay, p = 0.0407), which was closely correlated to the albumin and fetuin-A concentrations. In contrast, the reduction of precipitation intensity RNU50 induced by HD depended only on the control serum precipitation intensity (p = 0.0047), which was closely related to the albumin and fetuin-A concentrations.

Conclusion: HD vastly improves the intrinsic calcification propensity of sera, with phosphate, magnesium and fetuin-A as major influencing factors. Monitoring serum-inherent calcification propensity may help improve morbidity and mortality of HD patients in the future.
A Common Variant in UMOD, Associated With The Risk Of Chronic Kidney Disease and Hypertension, Influences the Urinary Excretion Of Uromodulin

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Purpose: Uromodulin is exclusively produced in the thick ascending limb of the Henle’s loop and is the most abundant protein secreted in normal urine. Mutations in the UMOD gene that codes for uromodulin are responsible for autosomal-dominant kidney diseases characterized by hyperuricosuria and gout, interstitial fibrosis and progressive renal failure. Genome-wide association studies (GWAS) have shown that variants in UMOD are associated with the risk of developing hypertension and chronic kidney disease (CKD) in the general population. The biological mechanism of these associations remains unknown.

Methods: In these studies, we developed a specific ELISA to determine urinary uromodulin levels and characterized the optimal conditions of handling and storage for a stable uromodulin. We generated the first large database of uromodulin levels in more than 10,000 samples collected from 4 genetic isolates and a large urban population. We then performed a GWAS to find loci associated with urinary uromodulin. A common variant rs4293393 located in the promoter of UMOD appears to be the most important in regulating the level of uromodulin in urine. This variant acts as a potent regulator of the transcriptional activity of UMOD, as evidenced from luciferase reporter gene assays in renal epithelial cells. The major allele of rs4293393, which is consistently associated with the risk of CKD and hypertension in GWAS, is associated with a dose-dependent increase in urinary uromodulin levels in these cohorts.

Conclusion: These results give insights into the regulation of uromodulin excretion and the association between UMOD variants and the risk of CKD and hypertension.

Rapid Homeostatic Effects of Oral Potassium Loading on the Kidney

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1Zurich, 2Basel, 3Lausanne

Purpose: A large dietary potassium (K+) load is a homeostatic challenge for mammals. It is known to induce a rapid kaliuretic and natriuretic response. These renal effects are reported to occur even before plasma K+ and aldosterone levels increase. Here we elucidate the underlying molecular mechanisms of K+ induced kaliuretic and natriuretic response.

Methods: We analyzed in mice the time course (15’, 30’, 2h, and 6h) of the effect of a gastric K+ load on plasma ion concentrations, aldo and potassium levels, urinary Na+ and K+ excretion and expression and/or phosphorylation of renal ion transport proteins.

Results: Following a gastric gavage of 2% KCl, plasma K+ concentrations rose rapidly (at 15’), followed by a significant rise of plasma ald (at 30’). Enhanced urinary K+ and Na+ excretion was detectable as early as spot urines could be collected (~30’). The functional changes were accompanied by a rapid and sustained dephosphorylation of the NaCl cotransporter (NCC) (15’-6h) and a later up-regulation of proteolytic activated epithelial sodium channels (ENaC) (6h). The rapid effect on NCC and the late effects on ENaC were independent from the co-administered anion (same effect with KHCO3; no effect with NaCl). In contrast to the proteolytic ENaC regulation, NCC dephosphorylation was independent of plasma ald as indicated by experiments in aldol-deficient mice. The observed urinary Na+ loss was likely related to NCC, as it was not seen in NCC-deficient mice.

Conclusion: Rapid down-regulation of NCC contributes to the early kaliuresis and explains the natriuresis in response to an oral K+ load. Enhanced activation of ENaC occurs quite late and might be more important for the long-term control of K+ homeostasis.
Background: Medication non-adherence (NA) is common in renal transplant (RTx) recipients and is associated with negative clinical and economic outcomes. The aim of this study was to determine the prevalence and to assess a potential association between NA and daytime sleepiness (DS) in RTx.

Methods: Using a cross-sectional design, a convenience sample of 927 home dwelling RTx recipients who received their transplant at one of three Swiss transplant centers were enrolled in the study. Data on NA, DS and depression were collected by self-report. Non-adherence was assessed using the Basel Assessment of Adherence Scale for Immunosuppressives, DS using the Epworth Sleepiness Scale and depression with the Depression, Anxiety and Stress Scale. Binary logistic regression controlling for depression, co-morbidities, gender, age and years since Tx was used for the analysis.

Results: The prevalence of DS was 52%, taking NA 16%, timing NA 42% and overall NA 35%. Taking and timing NA were positively associated with DS and overall NA. The multivariate model showed that DS is a significant (p < 0.001) predictor for taking [1.06 (1.01–1.11)], timing [1.07 (1.03–1.11)] and overall NA [1.09 (1.05–1.13)]. Further, greater time since transplantation increased the odds of taking by 5%, timing 18% and overall NA by 18%.

Conclusion: There is an association between DS and immunosuppressive NA in transplantation. This novel finding that provides better understanding of NA, especially in view of non-compliance with chronic medication.
Soluble CD30 Correlates With Clinical but Not Subclinical Renal Allograft Rejection
P. Hirt-Minkowski, M. Roth, G. Hönger, P. Amico, H. Hopfer, S. Schaub
Basel
Purpose: Soluble CD30 (sCD30) has been proposed as a promising non-invasive biomarker for clinical renal allograft rejection, but its diagnostic characteristics have not been assessed in subclinical rejection.
Methods: We investigated sCD30 in 146 consecutive kidney allograft recipients under tacrolimus-based immunosuppression having 250 surveillance biopsies at 3 and 6 months as well as 52 indication biopsies within the first year post-transplant. Allograft histology results were classified as (i) acute Banff score zero or interstitial infiltrates only, (ii) tubulitis t1-3, (iii) tubulitis t1-2, and (iv) isolated vascular compartment inflammation.
Results: sCD30 correlated well with the extent of clinical (p < 0.001) but not subclinical tubulo-Interstitial rejection (p = 0.06). To determine diagnostic characteristics of sCD30, histological groups have been assigned to two categories: no relevant inflammation (i.e. acute Banff score zero and interstitial infiltrates only) versus all other pathologies (tubulitis t1-3 and isolated vascular compartment inflammation). For clinical allograft inflammation, AUC was 0.87 (sensitivity 89%, specificity 79%; p = 0.0006); however for subclinical inflammation, AUC was only 0.59 (sensitivity 50%, specificity 69%; p = 0.47).
Conclusion: In conclusion, sCD30 correlated with clinical but not subclinical renal allograft rejection limiting its clinical utility as a non-invasive rejection screening biomarker in patients with stable allograft function.

Lack of Contribution of Interferon Gamma Release Assays (Igras) to the Diagnosis of Latent Tuberculosis Infection after Renal Transplantation
Geneva
Purpose: Renal transplant recipients, as all immune-suppressed patients, are at increased risk of reactivating latent tuberculosis infection (LTBI). Detecting LTBI in this population is therefore important to prevent active tuberculosis. The tuberculin skin test has a poor sensitivity in this setting.
Methods: The aim of this prospective study was to compare the diagnostic performance of the tuberculin skin test with 2 interferon gamma release assays (IGRAs), T-SPOT.TB (OxfordImmunotec, UK) and QuantiFERON-Gold-In tube (QGIT, Collabtest, Australia), performed simultaneously, for the detection of patients with a probable LTBI or a definite history of tuberculosis, among renal transplant recipients under stable immune-suppression.
Results: 205 patients (aged 59 ± 13 years, tested 10.4 ± 7.1 years post transplant) were studied. Positive rate was 4.9% for tuberculin skin test, 20.2% for T-SPOT.TB and 23.8% for QGIT. Agreement between interferon gamma release assays was fair (κ = 0.71). Sensitivity of T-SPOT.TB and QGIT for detection of LTBI was 33.3% (95% CI: 19.6–49.5); specificity was 85.5% (78.9–90.7) and 80.1% (72.9–86.2), respectively. Combining interferon gamma release assays did not significantly improve either sensitivity or specificity.
Conclusion: Serum sCD10 and vascular lesions in surveillance biopsies
P. Hirt-Minkowski1, J. Ho2, A. Gao2, P. Amico1, H. Hopfer1, P. Nickerson1, S. Schaub1
1Basel, 2Winnipeg/CA
Purpose: Non-invasive biomarker correlating with subclinical allograft rejection would be very useful to identify patients who should be further investigated by surveillance biopsies. Previously, we have reported that urinary CXCL10 is a promising non-invasive biomarker for subclinical tubulointerstitial rejection, but it did not reflect vascular inflammation (i.e. glomerulitis, endothelialitis, peritubular capillaritis). The aim of this study was to investigate whether serum sCD10 correlates with subclinical vascular inflammation.
Methods: For this pilot study, 42 surveillance biopsies were selected and grouped according to histology: (i) Banff acute score zero (n = 10), (ii) tubulitis t1-3 without vascular inflammation (n = 16), (iii) vascular inflammation (n = 16). Serum sCD10 was measured by ELISA.
Results: There were no differences among the three histological groups regarding eGFR (49 vs 44 vs 44 ml/min; p = 0.76), urinary protein/creatinine ratio (13 vs 15 vs 12 mg/mmol; p = 0.42), urinary albumin/creatinine ratio (2.5 vs 3.6 vs 2.7 mg/mmol; p = 0.55), CRP (p = 0.32), and leucocyte count (p = 0.99). Urinary CXCL10 levels were significantly higher in the tubulitis t1-3 group than in the other two groups (p < 0.01). By contrast, serum sCD10 levels were significantly higher in the vascular inflammation group than in the tubulitis t1-3 and the Banff acute score zero group (96 vs 50 vs 41 pg/ml; p < 0.007). Ten of 42 patients had concomitant infections (i.e. urinary tract infection, CMV- and/or BKV-viremia). Serum CXCL10 levels were not different between patient with/without concomitant infections (69 vs 65 pg/ml; p = 0.67).
Conclusion: In this small pilot study, serum sCD10 levels correlated with subclinical vascular inflammation. These results require validation in a larger patient population.
A Randomized Open-Label Clinical Trial Examining The Effect Of Denosumab on the Prevention of First-Year Bone Mineral Density (BMD) Loss after Renal Transplantation (POSTOP Study; NCT01377467)
M. Bonani, A. Serra, T. Fehr, J. Brockmann, M. Schiesser, D. Frey, R. P. Wüthrich
Zurich
Purpose: Renal allograft recipients are at risk for bone loss after transplantation. Denosumab is a humanized monoclonal antibody targeting RANK ligand, which is effective in the treatment for postmenopausal osteoporosis. Whether Denosumab is effective to prevent BMD loss after renal transplantation has not been evaluated.
Methods: POSTOP is a randomized study testing the efficacy and safety of Denosumab to prevent bone loss in the first year after kidney transplantation and/or arterial hypertension at the time of conception, as described for the general population. Besides, pregnant transplant recipients are exposed to complications related to the immunosuppressive treatment as well as graft rejection and progression of RFL.
Results: Overall, we describe in detail 14 pregnancies in 11 kidney transplant recipients in our centre between 1994 and 2011. Our results suggest that pregnancy can be successful if carried out under tight nephrological and obstetrical surveillance, as well as in optimal circumstances including stable allograft function for at least one year after Tx, good control of blood pressure, no/low level proteinuria and appropriate adjustment of immunosuppression prior to conception.
Conclusion: Thus, pregnancy after Tx should be carefully planned to limit risks and insure best outcome for mother and fetus.

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Results: Overall, we describe in detail 14 pregnancies in 11 kidney transplant recipients in our centre between 1994 and 2011. Our results suggest that pregnancy can be successful if carried out under tight nephrological and obstetrical surveillance, as well as in optimal circumstances including stable allograft function for at least one year after Tx, good control of blood pressure, no/low level proteinuria and appropriate adjustment of immunosuppression prior to conception.
Conclusion: Thus, pregnancy after Tx should be carefully planned to limit risks and insure best outcome for mother and fetus.

Results: Case 1: A 63-year-old man was on dialysis for 9 years due to chronic GN, until he was first transplanted in 1984. After one year, a cellular rejection occurred, and a therapy with PDN, ATG and irradiation of the graft was initiated. Due to graft failure, a second transplantation followed in 1996. Sixteen years after the second transplantation, a CT scan showed a tumorous growth in both native kidneys. At this time eGFR was 65 ml/min. Immunosuppression consisted of CyA, Aza and PDN. Grossly the kidneys were shrunk, but massively increased perirenal fatty tissue with focal inflammation. Case 2: A 62-year-old man was first transplanted in 1983 because of a malignant transitional cell carcinoma. One year later, cellular rejection occurred and was treated with PDN, ATG and graft irradiation. Due to graft failure, the patient was on dialysis for 2 years, until a second transplant was realized in 1986. Twenty-eight years after the first transplantation, a tumor in the first graft was noticed by MRI. At the eGFR was 25 ml/min. Immunosuppression consisted of CyA and PDN. Grossly the kidney was shrunk and surrounded by predominantly myxoid tissue. Histology showed RFL with end-stage kidney and increased perirenal fatty tissue as well as rejection episodes. In immunosuppressed patients, the differential diagnosis between RFL and renal tumors or PTLD is crucial and can avoid unnecessary nephrectomies.

Conclusion: RFL is a rare condition described in renal grafts and native kidneys. RFL has been associated with kidney stones, recurring infections and rejection episodes. In immunosuppressed patients, the differential diagnosis between RFL and renal tumors or PTLD is crucial and can avoid unnecessary nephrectomies.

The Tolerogenic Effect Of Bcl-2 Inhibition in Allo-transplantation is Mediated by Enrichment of Regulatory T Cells
S. S. Gabriel, N. Bonl, A. K. Kraus, J. Cheni, P. Bardwell, A. Bushel, T. Fehr, P. Cippa
Purpose: Inhibition of anti-apoptotic Bcl-2 family members by the BH3-mimetic ABT-737 suppresses alloimmune immune responses and promotes the induction of immunological tolerance in combination with costimulation blockade. In this study, we investigated the contribution of classical CD4+CD25+FoxP3+ regulatory T cells (Tregs) to the tolerogenic effect of ABT-737.
Methods: FoxP3-GFP transgenic mice were used to assess the effect of ABT-737 on natural and induced Tregs in vitro and in vivo. Furthermore, we evaluated the contribution of Tregs to tolerance induction in a non-myelo-suppressive, mixed chimerism protocol based on Bcl-2 inhibition.
Results: Natural and induced Tregs were 10 to 100x more resistant to Bcl-2 inhibition compared to naïve T cells, leading to a relative Treg enrichment after exposure to ABT-737 in vitro and in vivo. This effect was not inhibited by cyclosporine A, indicating that this resistance was not mediated by the calcineurin-NFAT pathway as previously described in activated T cells. In vivo, Tregs enrichment by ABT-737 potentiated the effect of an established induction protocol which includes donor-specific transfusion and costimulation blockade, leading to long-term survival of fully MHC-mismatched skin grafts without maintenance of immunosuppression. Furthermore, we demonstrated that the favorable effect of ABT-737 to induce mixed chimerism and tolerance was mediated by Tregs, since tolerance was lost when either CD4−, CD25− or GITR- expressing cells were depleted during the induction phase. Conclusion: Tregs enrichment can easily be achieved in vivo by exploiting the relative resistance of Tregs to Bezo inhibition. In future, therapeutic protocols for immunosuppression or tolerance induction based on Tregs could take advantage of this fact.

Strength and Limitations of Regulatory T Cells for Immunotherapy in Transplantation
L. Goevender, J.-C. Wyss, M. Pascual, D. Golshayan
Lausanne
Purpose: In many experimental models, CD4+Foxp3+ regulatory T cells have been identified as key players in promoting peripheral T cell tolerance (Tx) at the cost of maintaining the graft. In clinical Tx, T cell tolerance is achieved by low numbers of cells in a normal individual. Moreover, although we previously described robust protocols to generate and expand antigen-specific nTreg in vitro, the process requires selection of highly pure nTreg and cumbersome ex vivo manipulations, rendering this strategy not easily applicable in clinical Tx.
Methods: In this study, we expanded Treg directly in vivo and determined their efficacy and stability in promoting donor-specific tolerance in a murine skin Tx model.
Results: Our data suggest that IL-2-based therapies lead to a significant increase of Treg in vivo. The expanded Treg suppressed
Teff proliferation and allowed prolonged survival of MHC-mismatched grafts in wild-type non-lymphopenic recipients. The expanded Treg alone were however not sufficient to induce tolerance in stringent conditions. The combination with rapamycin or costimulation blockade, given at the time of Tx, modified the alloreactive T cell pool by proportionally increasing Treg thus promoting long-term survival of grafts. In contrast, pro-inflammatory stimuli hindered the expansion of Treg and resulted in an increase in the frequency of Tfh and Th17 cells.

**Conclusion:** We propose an efficient method for expanding functional Treg in vivo, thereby favorably shifting the pool of alloreactive T cells towards regulation in response to an allograft. However, we also highlight potential limitations such as concomitant inflammatory events.

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**Luminex Prozone Effect Demonstrated in Vitro and in Vivo: Clinical Implications**

S.-R. Wassmer, M. Bonani, T. Fehr

**Purpose:** The prozone effect leads to false low antibody measurement. It occurs when excess of antibody is unable to bind to receptor sites. It can be unmasked by sample dilution. A prozone effect in solid phase anti-HLA antibody testing has rarely been described.

**Methods:** We present two cases, where a Donor Specific Antibody (DSA) was missed due to prozone effect and led to antibody-mediated rejection (AMR). We then reviewed our kidney waiting list for the frequency of prozone effect.

**Results:** A 59 y old patient with ADPKD received a 2nd kidney transplant. Because of DSA he received ATG induction and immunosuppression with TAC, MMF and PPN. After 13 days AMR occurred. Immunoadsorption (IADS) reduced all DSA, but a novel DSA to DQ7 paradoxically increased. Repeat biopsies showed persistent AMR and resolved only after bortezomib therapy. Because of paradoxical MFI increase of DSA DO7 after IADS, the prozone effect was considered and retrospectively confirmed by serum dilution. A 22 y old patient with primary FSGS required a 2nd kidney transplant. Because of low titer DSA, he received immunosuppression as above. After 8 months AMR occurred. Despite IADS, a novel DSA to DO5 appeared which increased from 2200 to 13000 MFI after treatment.

**Conclusion:** The prozone effect is common in highly sensitized patients tested by Luminex technology. Failure to detect it can result in severe AMR. We show for the first time the prozone effect in vivo.

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**Urinary Neutrophil Gelatinase-Associated Lipocalin Does not Predict the Occurrence of Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronary Artery Bypass Surgery**


**Purpose:** Diagnosis of contrast-induced acute kidney injury (CI-AKI) relies on a late marker, namely serum creatinine (SCr). Recently, urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) has been suspected to play a major role in the pathogenesis of CI-AKI. However, we also suspected that uNGAL correlates with the volume of CM used.

**Methods:** We enrolled 244 consecutive patients undergoing PCI with IABPprolomul at our institution. CI-AKI was defined as a ≥25% increase in SCr from baseline when measured 2 to 4 days after PCI. Urinary NGAL was measured at its peak (4–6 hours after PCI) with the Abbott ARCHITECT assay. Results are given as median [interquartile range].

**Results:** Among the 244 patients (age 66.6 [59.5–74.7] years, 70% male), 149 (61%) underwent a diagnostic PCP and 95 (39%) a therapeutic PCP with a median CM volume of 163 [88–168] ml per procedure. Twenty-five (10%) patients developed CI-AKI. In our cohort, there was no significant difference in uNGAL levels between patients with and without CI-AKI, and patients developing CI-AKI tended even to have comparatively lower uNGAL levels (8.4 [3.4–10.4] versus 8.2 [4.1–15.1] ng/ml; p = 0.20). Also, we found no significant correlation between CM volume used during the procedure and uNGAL levels.

**Conclusion:** In our large cohort of patients mainly at low-risk for contrast-induced nephropathy, the incidence of CI-AKI was 10%. Urinary NGAL measured 4–6 hours after the coronarography did not predict renal toxicity, and did not correlate with the volume of contrast medium used during the procedure.

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**Associations of Diuretic Medication and Electrolyte Disorders on Osteoporotic Fractures: A Cross-Sectional Analysis of Elderly Patients Admitted to the Emergency Department**

S. Arampatzis¹, G.-C. Funk², C. Schwarz², M. Mohaupt³, H. Zimmermann¹, A. K. Exadaktylos⁴, G. Lindner⁴

**Purpose:** Although hyponatremia is a well-recognized complication of treatment with diuretics and recently identified as a novel cause of osteoporosis, the impact of diuretic associated electrolyte disorders on osteoporotic fractures (OF) have rarely been studied in emergency department (ED) patients.

**Methods:** In this retrospective case series at Inselspital we identify 10823 adult outpatients (≥50 years) with a serum sodium measurement which were admitted between January 1, 2009 and December 31, 2010 at the ED.

**Results:** After exclusion of 573 patients with non-OF we identified 480 (5%) out of 10823 patients, with 547 OF. The OF group was characterized by higher mean age at presentation, smaller proportion of male patients, higher hospitalization rates and longer hospitalization stay compared to controls (N = 9.769). The use of any diuretic agent (p <0.0001) and in particular loop, potassium sparing and amilorid (p values 0.02, 0.02 and <0.01 respectively) was significantly more common among OF patients. The prevalence of hyponatremia increased with the number of diuretics taken by the patients (p <0.0001). The use of SSRI s and antiepileptic drugs between both
groups was similar. In the multivariable analysis, advanced age (OR 1.04, p = 0.0001), the presence of hyponatremia (OR 1.3, p = 0.011) higher serum creatinine (OR 1.53, p = 0.0001), furosemide use alone (OR 1.40, p = 0.01) or diuretic co-treatment with amloidin (OR 2.22, p = 0.02) were all associated with a higher risk for OF.

Conclusion: The use of loop diuretics or diuretic co-treatment with amilorid was associated with an increased risk for osteoporotic fractures in elderly ambulatory patients. Moreover this condition could possibly be prevented by simply serum sodium monitoring.

Acute Kidney Injury (AKI) in Cirrhotic Patients: Utility of New Biomarkers and Renal Resistive Indexes?
B. Ponte, L. Spahr, G. Berra, V. Pollet, N. Garin, P.-Y. Martin
Geneva

Purpose: AKI is frequent in cirrhotic patients. Pre-rerenal, acute tubular necrosis (ATN) or hepatorenal syndrome (HRS) are difficult to differentiate with plasma creatinine. We study new biomarkers and renal artery resistive indexes (RI) to evaluate their added value for better differentiate AKI etiologies.

Methods: We aim to include prospectively 100 adults with cirrhosis and ascites. Exclusions' criteria are multifocal hepatocellular carcinoma, acute gastro-intestinal hemorrhage, severe CKD (eGFR <15 ml/ min/1.73 m² or dialysis) and renal or hepatic transplant. AKI diagnosis is made according to AKIN criteria. Urine and blood samples are collected as soon as possible from the admission to analyze creatinine, cystatin C, NGAL and KIM1. A renal Doppler ultrasound is performed within the next days. We compare characteristics and biomarkers levels between AKI groups and use ROC curves to detect the best predictor.

Results: We include 77 patients in this intermediate analysis: 66.2% men, 58.3 ± 10.2 years old. AKI occurs in 50.6% cases: 78.6% have pre-renal injury, 15.4% ATN and 7.7% HRS. Height patients are CKD have higher rates of ATN (p = 0.01). In univariate analyses new biomarkers (NGAL, KIM1, cystatin C) and creatinine are useful to better differentiate AKI etiologies.

Conclusion: New biomarkers can help in differentiating ATN from pre-renal AKI but not from HRS in cirrhotic patients with ascites: RI has no added value in the differential diagnosis. Urinary NGAL seems to be the best predictor to diagnose ATN.

Determinants of Renal Artery Resistive Indexes in the Swiss Kidney Project on Genes in Hypertension (SKIPOGH)
B. Ponte1, M. Pruim2, D. Ackermann3, P. Vuistiner3, U. Eisenberger3, M. Mohaupt3, B. Vogt1, F. Paccaud1, M. Burnier1, P.-Y. Martin1, M. Bochud1
1Geneva, 2Lausanne, 3Berne

Purpose: Recent evidence suggests that the renal resistance index (RI), defined as the percentage reduction of arterial end-diastolic flow as compared with systolic flow, is correlated with arterial stiffness and predicts cardiovascular events. We analyzed the determinants of RI in the general adult population.

Methods: We randomly selected families from the general population in Bern, Geneva and Lausanne. We measured anthropometric parameters, cardiovascular risk factors, blood pressure, 24 hours urine and performed a renal Doppler ultrasound. RI was assessed in the segmental arteries of superior, middle and inferior poles of each kidney according to a standardized protocol. Generalized estimating equations were used to identify determinants of RI adjusting for pulse rate, center and other covariates, taking familial correlations into account.

Results: We analyzed 282 men and 307 women aged 46.8 ± 17.4 and 46.9 ± 16.6 years respectively. Mean RI value of both kidneys was 0.63 ± 0.06 for men and 0.65 ± 0.05 for women (p < 0.001). In multivariable regression analysis adjusted for confounders, age, diabetes, female sex, hypertension and SBP were significantly associated with higher RI. Urinary sodium excretion was also significantly associated with higher RI (coefficient per 100 mmol 0.01, SE 0.003; p <0.01) while urinary potassium (coefficient per 50 mmol –0.01, SE 0.005; p = 0.02) and urea excretion (coefficient per 100 mmol 0.006, SE 0.002; p = 0.01) were associated with lower RI.

Conclusion: The associations of RI with urinary sodium, potassium and urea excretion suggest that diet plays a role intra-renal arterial compliance and extrarenal resistance. These results are in line with previously described vasoconstrictive effects of salt intake and vasodilatory effects of potassium and protein intake on renal arteries.

No Correlation of Initial AntiPLA2R Positivity With Long Term Outcome Of Renal Function in Idiopathic Membranous Nephropathy
F. Burkhalter1, H. Hopfer1, E. Hoxha1, M. J. Mihatsch1
1Basel, 2Hamburg/DE

Purpose: Background: Recent findings in membranous nephropathy (MN) suggest that in most patients with idiopathic MN the underlying cause is a anti-phospholipase A2 receptor (antiPLA2R) antibody. In addition it was shown that antiPLA2R titer correlates with disease activity. Whether there is a correlation with initial antiPLA2R positivity and longterm outcome of renal function is unclear.

Objectives: Evaluation of the longterm outcome of patients with MN in correspondence to their initial antiPLA2R status.

Methods: This is a single centre retrospective observational study in patients with biopsy proven membranous glomerulonephritis from 1992 until 2007. Patient were selected by availability of serum sample from the day of renal biopsy (n = 38). In 19 patients with MN, follow up data were available. In 13 patients follow-up measurement of antiPLA2R were performed.

Results: biopsy proven MN n = 38

<table>
<thead>
<tr>
<th>AntiPLA2R</th>
<th>Positiv</th>
<th>Negativ</th>
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<tbody>
<tr>
<td>n = 18</td>
<td>n = 20</td>
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</table>

secondary cause of MN n = 12
idiopathic MN n = 18

(time of biopsy)
median GFR (mld/min) 88.3 (23–153)
median proteinuria (g/d) 6.5 (3.5–17)
Last follow-up n = 14 n = 5
Immunosuppressive therapy n = 6 n = 2
median follow up (years) 9.5 (5.2–19.4)
median GFR (mld/min) 91.7 (25.6–174)
median proteinuria (g/d) 1.2 (0.01–2.9)
ESRD n = 1 n = 2
anti-PLA2R follow up n = 10 n = 3
negativ 70% 100%
positiv 30% 0

Conclusion: There is no correlation of initial PLA2R positivity with the longterm renal function in this sample of patients with MN with an overall median follow up of 10.9 years.

Determinants and Heritability Of Kidney Length in a Family-Based Population Study
M. Pruim1, B. Ponte2, D. Ackermann3, P. Vuistiner4, G. Ehret2, I. Guessous1, U. Eisenberger3, P. Paccaud1, P.-Y. Martin2, M. Mohaupt1, F. J. Frey4, M. Burnier5, M. Bochud4
1Lausanne, 2Geneva, 3Berne

Purpose: Kidney length is an important parameter in renal clinical decision making, yet data from population-based studies are sparse, and the heritability of kidney size is unknown. We assessed the heritability and the determinants of kidney length in a family-based population study.

Methods: The SKIPOGH study (Swiss Kidney Project on Genes in Hypertension) is a cross-sectional survey exploring the role of kidney hemodynamics and genes in blood pressure regulation and hypertension. Anthropometric parameters and renal ultrasound measurements were obtained in subjects chosen at random from the general population and at least one first-degree relative of each selected subject. The ASSOC program in SAGE (Statistical Analysis in Genetic Epidemiology) was used to estimate the age, sex, weight and height, eGFR (CKD-EPI), and center-adjusted narrow sense heritability.

Results: In total, 739 participants from 205 nuclear families were included. Mean (±SD) kidney length was 11.4 ± 0.8 cm in men (n =
The reference values reported in this study are intended to help the physician determine whether kidneys are small, normal, or large for women with body height 159 (148–162), 165 (162–168), 171 (168–182) cm, versus 103 (100–109), 107 (102–110), 110 (106–115) mm in height of respectively 171 (157–174), 177 (174–180) and 183 (180–112 (108–118) and 118 (112–123) mm in men with median(range) body percentile) according to tertile of body height was 109 (106–116), 96 (15) mL/min/1.73 m², respectively. Median kidney length (25–75 percentile) was 52 ± 8%, p <0.001.

Conclusion: This study suggests that kidney length is an inherited trait, independent of other important determinants such as age, estimated kidney function, body height and weight.

Reference Values of Kidney Length According to Body Height in the Swiss Population

M. Pujiri1, B. Ponte2, D. Ackermann3, P. Vuistiner1, G. Ehret2, I. Gessous2, U. Eisenberger2, F. J. Frey2, M. Mohaupt1, F. Paccaud1, P.-Y. Martin1, M. Burnier1, M. Bochud1

Lausanne, *Geneva, *Bern

Purpose: In clinical practice nephrologists are often confronted with the question which kidney size is normal for a given body height, yet reference values from the general population are sparse. In this study, we assessed kidney length in healthy Swiss adults.

Methods: In the ongoing SKIPOGH study (Swiss Kidney Project on Genes in Hypertension), nuclear families were randomly selected from the general population in Lausanne, Geneva and Bern, and renal gray-scale ultrasounds were performed according to a standardized protocol. For the purpose of this analysis, participants with renal structural abnormalities, obesity (BMI ≥30 kg/m²), diabetes, chronic kidney disease (eGFRckd-epi <60 ml/min/1.73 m²) or insufficient ultrasound quality were excluded.

Results: Of the 854 participants, 570 were included in this analysis. In the 269 men and 301 women, mean(SD) age was 44(17) and 47(16) years, BMI 24.7(3) and 22.9(3) kg/m², eGFR 102 (16) and 96 (15) mL/min/1.73 m², respectively. Median kidney length (25–75 percentile) according to tertile of body height was 109 (106–116), 112 (108–118) and 118 (112–123) mm in men with median(range) body height of respectively 171 (157–174), 177 (174–180) and 183 (180–201) cm, versus 103 (100–108), 107 (102–110), 110 (106–115) mm in women with body height 159 (148–162), 165 (162–170), 171 (168–182) cm. In multilevel adjusted linear regression, body height was the strongest determinant of kidney length (adjusted regression coefficient [β per cm body height [95% CI]: 0.32 [0.23–0.41], p <0.001).

Conclusion: Kidney length correlates strongly with body height. The reference values reported in this study are intended to help the physician determine whether kidneys are small, normal, or large for a given body height.

Methadone and Glomerulonephritis

C. Jaeger, H. Heule

Albstädtlen

Purpose: Methadone is mainly used in substitution programs for intravenous heroin abusers. We remarked in our district an increase of glomerulonephritis (GN) in persons who use methadone. We studied its effect as we detected 8 patients with methadone, who were referred to our renal centre. All of them had a marked a membranoproliferative GN. Two of them were treated immuno-suppressive. One patient on prednisone monotherapy had a remission of these patients.

Results: Of these patients.

Conclusion: The cause of relationship between methadone and glomerulonephritis is not known, 5/6 of our patients admitted a contaminated intravenous abuse of methadone which is designed for orally use. Think of intravenous methadone use when finding an “idioticpathic” membranoproliferative GN.

Natriuretic Peptides for Early Prediction of Acute Kidney Injury in Community Acquired Pneumonia

A. Nowaki1, T. Breithardt2, S. Dejung1, M. Christ-Crain2, R. Bingisser1, B. Drexler1, C. Meuné1, D. Maron1, T. Mosimann1, B. Müller1, C. Mueller1

Zürich, *Basel, *Aarau

Purpose: Background: Community-acquired pneumonia (CAP) is common and associated with a considerable risk of acute kidney injury (AKI).

Methods: We prospectively enrolled 341 patients presenting to the emergency department with CAP (mean age 72, male 61%). Blinded measurements of three natriuretic peptides (NT-proBNP, MR-proANP and BNP) were performed upon presentation. The primary endpoint was the accuracy of the natriuretic peptides to predict AKI within 48 hours, the median follow-up 942 days.

Results: AKI occurred in 21 patients (7.6%) within the first 48 hours. NPs and creatinine was significantly higher in AKI compared with patients without AKI (NT-proBNP 9517 [2042–26792] vs 1177 [280–4167] pg/ml; MR-proANP 641 [196–1075] vs 182 [99–352] pmol/L; BNP 592 [230–1630] vs 160 [64–463] pg/ml; creatinine 166 [131–289] versus 100 [78–134] µmol/L. P <0.001 for each). Predictive accuracy, as quantified by the area under the receiver operating characteristics curve, was moderate to high: NT-proBNP 0.79 (95% CI 0.70–0.88), MR-proANP 0.78 (95% CI 0.67–0.88), BNP 0.74 (95% CI 0.63–0.85), creatinine 0.77 (95% CI 0.66–0.86). In multivariate logistic regression analysis, NPs remained the only independent AKI predictors: table 1. NPs and the Pneumonia Severity Index were more closely associated with short- and long-term mortality than traditional AKI predictors (serum creatinine, persisting chronic kidney disease), as assessed in multivariate cox regression analysis.

Conclusion: NP levels at presentation can be useful predictors for early AKI in patients with community acquired pneumonia and seem to be closely associated with mortality.

Prediction of acute kidney injury development.

Table 1

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Multivariate logistic regression OR</th>
<th>p-value</th>
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<tbody>
<tr>
<td>NT-proBNP</td>
<td>1.01 (1.00–1.01)</td>
<td>0.009</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.00 (1.00–1.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>CKD</td>
<td>1.92 (0.65–5.66)</td>
<td>0.24</td>
</tr>
<tr>
<td>PSI</td>
<td>1.00 (0.99–1.02)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
Evaluation of a Novel Diagnostic and Treatment Algorithm for Hyponatremia
A. Bock1, A. Huber1, C. Blum1, C. Nicke1, P. Schuetz1, M. Bally1, B. Anic2, I. Suter-Widmer1, B. Winzeler1, N. Nigro1, B. Müller1, M. Christ-Crain1
1Aarau, 2Basel
Purpose: Correctly diagnosing of the cause of hyponatremia is a frequent challenge in the emergency room setting, because appropriate therapy (water restriction; NaCl infusion) depends on the cause. Existing algorithms rely heavily on a correct assessment of extracellular fluid volume. The present new algorithm was designed with the idea to use the kidney as gauge for volemia and ADH state.

Methods: Patients presenting with severe hyponatremia (<125 mmol/l) to the emergency room of the two participating hospitals were prospectively attributed to diagnostic groups based on urine osmolarity, the fractional excretions of urea and uric acid as well as some evident signs of volume overload (Edema/Ascites/Orthopnea) as well as follows:

Algorithm based diagnoses were contrasted with final clinical diagnoses. The present data represent an interim analysis.

Results: Out of 37 evaluable patients of one hospital, the algorithm correctly identified 5/5 patients with polydipsia, 13/16 patients with general hyponatremia (3/16 erroneously as “SIADH”), 5/6 patients with intravascular hyponatremia and 8/8 patients with SIADH. The final diagnosis was unclear in 2.

Conclusion: The new algorithm performed well. “SIADH” was the diagnosis was unclear in 2. Conclusion: The new algorithm performed well. “SIADH” was the most common misclassification.

Renal Phosphate Handling in Gitelman Syndrome – The Results of a Case-Control Study
M. G. Bianchetti1, C. Viganò2, C. Amoruso2, S. A. G. Lava3, A. Bettinelli2, Bellinzona, 2Merate-Lecco/IT
Purpose: Patients with Gitelman syndrome, a hereditary salt-wasting tubulopathy, have loss-of-function mutations in the SLC12A3 gene coding for the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule. Since the bulk of filtered phosphate is reabsorbed in the proximal tubule, renal phosphate wasting is considered exceptional in Gitelman syndrome. We noticed a tendency towards low inorganic phosphate levels in some of our Gitelman patients which led us to investigate the renal handling of this ion in the context of a study.

Methods: We investigated the renal handling of inorganic phosphate in 12 unselected patients affected with Gitelman syndrome (5 females and 7 males, aged 6.0–18 years, median age 12 years) and in 12 healthy subjects matched for gender and age. The diagnosis of Gitelman syndrome among the patients had been made clinically and confirmed by molecular biology studies.

Results: The biochemical hallmarks of Gitelman syndrome, namely hypochloremia, hypokalemia, hypomagnesemia, increased urinary excretion of sodium, chloride, potassium and magnesium and reduced urinary excretion of calcium, were noted in the 12 patients. In addition, both the plasma inorganic phosphate concentration (1.28 [1.12–1.36] versus 1.61 [1.51–1.66] mmol/L; median and interquartile range) and the maximal tubular reabsorption of inorganic phosphate (1.08 [0.99–1.22] versus 1.41 [1.38–1.47] mmol/L) were significantly lower (P <0.001) in Gitelman patients than in control subjects. Circulating levels of 25-hydroxyvitamin D, intact parathyroid hormone and osteocalcin were similar in patients and controls.

Conclusion: The present case-control study discloses a hitherto unrecognized tendency towards renal phosphate wasting with mild to moderate hypophosphatemia in Gitelman syndrome.

Renal Cysts and Diabetes Syndrome due to Mutation of the Hepatocyte Nuclear Factor-1-Beta Gene
K. König, S. Kalbermatten, I. Grendelmeier, D. Kiss Liestal
Purpose: A 53-year old caucasian was referred to our outpatient clinic for the evaluation of chronic kidney failure. At the age of 18, the patient was diagnosed with diabetes and years later the diabetes became insulin dependent. Over the following years, function impaired, without relevant proteinuria.

Methods: n/a

Results: On presentation the patient complained about fatigue and weakness. Family history showed a brother with diabetes. Blood pressure was 142/73 mm Hg, pulse 114/min regular, BMI 19.4 kg/m2. Laboratory studies showed a creatinine of 443 μmol/l, with an estimated glomerular filtration rate of 13 ml/min/1.73 m2 and urea of 27.1 mmol/l. Urinalysis was significant for 2þ protein, 1+ glucose and a urine protein/creatinine ratio of 131 mg/mmol. Hemoglobin was 106 g/l. C-peptid <0.02 nmol/l with an HbA1c of 9.1%. i-PTH 251 pmol/l, calcium 2.55 mmol/l and phosphate 1.88 mmol/l. MRI was performed which revealed multiple cystic lesions in both kidneys with normal kidney size.

Conclusion: The combination of cystic kidney disease with early-onset diabetes best fits to the renal cyst and diabetes syndrome (RCAD) that was formerly called MODY type 5. The results of the genetic analysis confirmed mutation of the hepatocyte nuclear factor-1-beta gene (HNF1-beta). Affected patients develop a variety of manifestations. These includes pancreatic atrophy which leads to diabetes and abnormal renal development with slowly progressive renal failure. Mutations in the HNF1-beta gene inhibit the expression of Pkd1 which leads to cyst formation. Mutations of Pkd1 are responsible for the autosomal recessive form of polycystic kidney disease.

We thank Prof. T. Fehr for the helpful comments.

Varicella-Zoster-Virus Vasculopathy Presenting as a Stroke After Kidney Transplantation
I. Koneth, G. Kaegi, K. Boggian, I. Binet St. Gallen
Purpose: VZV cerebral vasculopathy is a rare disorder.

Methods: We report a case in a kidney transplant recipient presenting as a stroke.

Results: A 41-year old man received a preemptive deceased kidney transplantation. Induction consisted of antithymoglobulins, steroids, mycophenolate, tacrolimus and iv Ig. 3 weeks post-transplant the patient complained of fatigue and demonstrated a strange behaviour. Lab results were normal; ABPM showed no blood pressure dip, 24-hours-ECG and cerebral CT-scan were normal. 8 weeks after transplantation the patient was hospitalised because of headache, hemiparesis, dysarthria and complex oculomotor disorder. No fever,
null menstruation, normal blood analysis. MRI showed acute ischemic infarction in the pons and subacute ischemia in the pedunculus cerebri and corpus callosum. Because of the subacute aspect of most lesions, lysis was not performed. CSF showed mononuclear pleocytosis, high proteins and normal glucose. Intraocular VZV PCR and anti-VZV – Ab were positive. The patient was seropositive for VZV pretransplant but did not present herpes zoster at any time. Prednisone was shortly increased, mycophenolate mofetil paused for 2 weeks and restarted at halved 900 mg/day, then switched to oral valacyclovir 1 g bid. After 4 months neither VZV PCR in liquor nor new ischemia in MRI were detectable, prophylaxis with valacyclovir 500 mg bid was installed, 6 months after the acute illness a mild weakness of the left upper extremity and deficits in memory and attention persisted.

Conclusion: VZV vasculopathy should be suspected in immunocompromised patients with multiple acute and subacute cerebral ischemia even in the absence of a characteristic zoster rash. Diagnosis requires a liquor analysis for viral DNA and VZV antibodies.

**P30**

**PRES – A Diagnosis not Only for Neurologists: Two Case Reports in Renal Patients**

K. Günther, C. Bucher, G. Kaegi, I. Binet
St. Gallen

Purpose: Posterior reversible encephalopathy syndrome (PRES) is characterized by acute onset of headache, nausea, seizures, altered consciousness, visual disturbance and thinning of the glomerular basement membrane. Heterozygous defects in COL4A3 or COL4A4, including cases with familial clustering, are associated mainly with symmetric white matter defects in the parietal and occipital lobes. Nephrotic syndrome, chronic and acute kidney disease, HUS, organ transplantation, immunosuppressive therapy, autoimmune diseases and electrolytes disturbances are predisposing factors. We report two cases of PRES in young patients with ESRD.

Methods: First patient is a 34-year-old man on peritoneal dialysis due to diabetic nephropathy. He was hospitalized for chronic intermittent vomiting and chronically high blood pressure. After a blood pressure spike he developed an acute headache and sudden loss of vision with cortical blindness. The MRI showed bilateral symmetric cortical occipital defects. Hypokalemia (2.7 mmol/l), hypocalemia (Ica 1.05 mmol/l) and metabolic alkalosis were present. The second patient is a 21-year-old woman on chronic hemodialysis due to IgA-nephropathy and under immunosuppression with steroids and cyclophosphamide. She presented with a first dyscognitive seizures followed by a bilateral clonic-tonic seizure. The MRI showed multiple bilateral T2-weighted hyperintense signals, cortical and subcortical, temporoparietal and frontal. EEG demonstrated later on no seizure activity. CSF was unremarkable.

Results: After a closely monitored blood pressure lowering therapy and magnesium infusion in the ICU both patients experienced a complete recovery of their neurological symptoms.

Conclusion: Think about PRES in front of a renal patient with badly controlled hypertension and/or immunosuppressive therapy who presents with neurological findings such as severe headache, seizure or vision disturbances.

**P31**

**A Wolf In Sheep’s Clothing: The Course of Thin Basement Membrane Nephropathy (TBMN) on Basis of a Family Pedigree**

I. Grandelmeier1, H. Hopfer2, D. Kiss1
Liestal, 2Basel

Purpose: Thin basement membrane nephropathy (TBMN) is a common (up to 5–6% in gen. pop.) in general familial disorder (30–50% of cases with family history) with usual benign course and is therefore also called “benign familial hematuria.” The only finding on renal biopsy by focal segmental glomerulosclerosis (FSGS). The MRI showed bilateral symmetric cortical occipital defects. Hypokalemia (2.7 mmol/l), hypocalemia (Ica 1.05 mmol/l) and metabolic alkalosis were present. The second patient is a 21-year-old woman on chronic hemodialysis due to IgA-nephropathy and under immunosuppression with steroids and cyclophosphamide. She presented with a first dyscognitive seizures followed by a bilateral clonic-tonic seizure. The MRI showed multiple bilateral T2-weighted hyperintense signals, cortical and subcortical, temporoparietal and frontal. EEG demonstrated later on no seizure activity. CSF was unremarkable.

Results: After a closely monitored blood pressure lowering therapy and magnesium infusion in the ICU both patients experienced a complete recovery of their neurological symptoms.

Conclusion: Think about PRES in front of a renal patient with badly controlled hypertension and/or immunosuppressive therapy who presents with neurological findings such as severe headache, seizure or vision disturbances.

**P32**

**Flank Pain, Hypertension and Renal Infarcts in a Young Man: A Rare Manifestation of Sarcoïdosis**

L.-Y. Marn, B. Vogt, D. Golishayn
Lausanne

Purpose: A 34-year-old male was admitted to hospital with a few days history of abdominal and flank pain, headaches, malaise and visual blurring, without fewer or urinary symptoms. He had suffered weight loss, asthenia and exertional dyspnea over the last 2 months. Physical examination was normal except for severe hypertension. Laboratory tests revealed elevated serum creatinine at 127 µmol/l and moderate systemic inflammation, urinalysis was normal.

Methods: The CT scan showed multiple thoraco-abdominal adenopathies, lung micro-nodules and peripheral hypodense cortical lesions in both kidneys. A mediastinoscopy with node biopsies was performed, with the histological diagnosis of granulomas.

Results: Our patient thus presented with a systemic granulomatous disease. He underwent further laboratory investigations including infectious and immune serologies, Tb-spot and B2-microglobulin. Following on the CT aspect of the kidneys, a selective abdominal angiography was performed, confirming the presence of multiple renal infarcts as well as revealing coronary and cerebral aneurysms on renal as well as splenic arteries. Based on these findings, the diagnosis of sarcoïdosis was made. High dose steroids were started followed by azathoprine together with anti-hypertensive drugs.

Conclusion: Sarcoïdosis is a systemic inflammatory multiorgan disorder characterized by the presence of noncaseating granulomas. Virtually every organ can be affected, but about 90% of cases have lung involvement. Up to half of the patients are asymptomatic, identified upon incidental radiological findings. Clinically relevant renal disease seems to represent only an occasional problem in sarcoïdosis, the main finding being granulomatous interstitial nephritis. Granulomatous angitis and in particular renal vasculitis is a very rare manifestation of sarcoïdosis.

**P33**

**Caplan’s Syndrome: Rarely Presenting as “Pulmo-Renal” Syndrome**

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Zurich

Purpose: Presentation of a rare differential diagnosis of pulmo-renal syndrome.

Methods: History and admission findings. A 59-year-old man complained having dry cough for months and a recent sudden onset of asymptomatic arthritis, myalgia as well as loss of appetite and weight loss. He had an occupational history of 12-year exposure to anorganic dust as uranium miner in German Democratic Republic followed by 21 years as heavy construction worker in Germany and in Switzerland. Laboratory work-up positive for microhematuria and anti-neutrophil cytoplasmic antibodies (ANCA). Chest X-rays and CT scan showed bilaterally scattered nodules. Thorascopic wedge resection was performed, histopathological analysis revealed granuloma with central necrotic area containing black coal dust and silica deposition. The pulmonary opacities on X-ray and typical histology in the light of significant dust exposure allow the diagnosis of a Caplan’s syndrome.

Results: Treatment and course. Symptoms improved rapidly under steroid therapy. A clear renal cell carcinoma was diagnosed as a cause for the persistent microhematuria.

Conclusion: Rheumatoid arthritis, pulmonary nodules and history of prolonged dust exposure are classical findings that define Caplan’s syndrome. These patients present with different immunologic phenomena – in our case ANCA positivity without vasculitis. Interestingly, renal cell carcinoma, causing microhematuria and leading to the “pulmo-renal” syndrome, is another health problem overrepresented in uranium mine workers.

**P34**

**A Trial of Complement Inhibition in a Patient With Cryoglobulin-Induced Glomerulonephritis**

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Purpose: Cryoglobulinemia induces an immune complex-mediated glomerulonephritis that is characterized by the presence of large immune deposits, including complement C3 and C9, marked macrophage influx and mesangial cell proliferation. The precise role of complement in cryoglobulin-induced glomerulonephritis in humans
remains unclear, whereas in mice there has been evidence that complement activation might be a central factor favoring glomerular inflammation, particularly by the recruitment of neutrophils.

**Methods:** We report on an exceptional case of cytocoglobin-induced glomerulonephritis that resolved with a partial cytocoglobin type II. The clinical features included relapsing proteinuria and renal function impairment that were controlled by placemapheresis. Complement was low in plasma and two renal biopsies at one-year interval showed proteinuria, immunoglobulin deposits and complement deposits, with unusual high numbers of neutrophils. In a one-patient clinical trial we tested whether the monoclonal anti-CS antibody eculizumab would be sufficient to control renal function at the time of a relapse.

**Results:** Although the initial treatment was stabilized, slow increase in creatinine could not be controlled by this treatment, so that plasmapheresis was reinstituted.

**Conclusion:** This result suggests that despite evidence for a role of complement in enhancing renal damage in this patient, other inflammatory processes dominated.

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**Neonatal Hemolytic Uremic Syndrome Due to Shiga-Toxin-Producing Escherichia Coli**

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**Purpose:** Hemolytic uremic syndrome (HUS) is a leading cause of acute renal failure in children. The newborn was suspected to have Shiga-toxin-producing Escherichia coli STEC. Cobalamin C disorder, defective regulation of the alternative complement pathway and congenital ADAMTS13 deficiency are possible causes for atypical HUS in the neonatal period. STEC can also cause HUS in the neonatal period.

**Methods:** Description of a case.

**Results:** A newborn male, presenting with biliary vomiting two days after birth without diarrhea, showed on day six of life a sudden increase of total bilirubin. Laboratory findings showed hemolytic anemia with fragmented red blood cells. The newborn recovered quickly with normalization of all parameters within 24 hours and normal neurological condition, plasma exchange and the monoclonal antibody against terminal complement protein C5 were not considered for causes of atypical HUS remained negative. Fecal analysis of both the newborn and his mother disclosed STEC, indistinguishable by microarray analysis, and pulsed-field gel electrophoresis, and harboring stx2B. Shiga-toxin Stx2B is of low virulence, not normally causing HUS. We postulate that the mother is a healthy carrier, who transmitted the bacteria by fecal-oral route to the newborn during delivery. In a newborn's steril bowel this virulence might be insufficient to cause HUS.

**Conclusion:** Hemolytic uremic syndrome can be caused by Shiga-toxin producing Escherichia coli STEC.

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**Chicken Pox in a Varicella Vaccinated Hemodialysis Patient**

A. Kneubühl, T. Bregenzer

Lachen

**Purpose:** Varicella zoster Virus (VZV) primary infection may cause complications such as pneumonitis or encephalitis mainly in immunocompromised patients e.g. kidney transplant recipients. Varicella vaccination is recommended before kidney transplantation in seronegative patients.

**Methods:** We report the case of a 27 year old man vaccinated with two doses of VZV vaccine fifteen years ago. He had endstage kidney disease because of cystinosis and became kidney transplanted fourteen years ago. Immunosuppression consisted of Tacrolimus, Mycophenolate and Steroids. Tacrolimus was substituted by Ciclosporin when B-Cell Non Haemolytic Lymphoma was successfully treated 2003. Kidney transplant failure and start of dialysis followed 2010. In February 2012 his unvaccinated brother with no history of VZV infection became sick with chicken pox. Two weeks later our patient presented with primary VZV infection — Vesiculo papular rash, fever, head- and musclepain. VZV-IgG-level was <0.60. (IndexImmun >0.89). While on therapy with Valaciclovir 500 mg twice daily for one week and because of side effects 500 mg once daily for another week he fully recovered within three weeks.

**Results:** Chicken pox after kidney transplantation is rare because most of these patients are seropositive after primary infection in childhood or they are vaccinated. More often reactivation of VZV latent infection in sensory ganglia may result in shingles. The seroconversion rate after vaccination measured by immunofluorescence assay is 100% but results in only 88% protection rate.

**Conclusion:** Despite Varicella vaccination primary infection of VZV may occur. Immunosuppressive treatment and/or immunosuppression may be compromised status due to chronic renal failure may reduce vaccination efficacy. Monitoring of VZV-IgG levels and revaccination should be discussed.
Resetting of Kidney Renin-Angiotensin, Kallikrein-Kinin, and Cathecolalamine Systems After Unilateral Renal Denervation

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Purpose: Catheter-based renal denervation is an effective treatment for resistant hypertension. The resetting of renal hormone systems following denervation is still unclear and may include compensatory mechanisms.

Methods: Left kidneys of 8 WKY rats were surgically denervated and 8 rats sham-operated. After 6 days, renal concentrations of bradykinin (BK), kallikrein (K), renin (R), angiotensin (A) I and II, A(2-8), A(3-8), A(4-8), norepinephrine (NE), epinephrine (E), dopamine (D), and plasma R concentration (PRC) were determined by HPLC or biochemically. The renal innervation was studied immunohistochemically, mRNA expression by PCR.

Results: PRC gave no group difference (p = NS). Cathecolaminergic or sensory nerve fibers were absent in denervated kidneys. Left denervated kidneys showed lower AI (39.5%), All (35.1%, p = NS), R (30.2%), NE (99.2%), D (-30.4%) and BK (30.4%) concentrations (p <0.05) vs. sham left kidneys; K, A fragments, and E were comparable (p = NS). Right kidneys had lower BK (26.6%, p = NS), R (41.2%, p = NS), All (22.5%, p <0.05) and higher E (46.4%, p <0.05) levels vs. sham right kidneys without differences for K, R, A fragments, NE or DA. Intraindividually, left denervated kidneys had lower R (23.6%), A (2-8) (45.9%), D (28.6%), and NE (99.2%) levels vs. right kidneys (p<0.05). mRNA levels of D-decarboxylase (DDC), D-β-hydroxylase, eNO-synthase (eNOS) and transforming growth-factor β (TGFβ) were higher (22–59%) in denervated vs. right (p = NS) but not vs. sham kidneys.

Conclusion: Unilateral denervation suppresses ipsilateral kidney NE and bilateral All and BK levels by side-dependent mechanisms targeting the renal pressure-natriuresis relationship. This may include neuropeptide-mediated pathways.

Inhibitory Effects of Geldanamycin Analogues on Adipocyte Differentiation and Fat Mass Accumulation

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Purpose: The mineralocorticoid and the glucocorticoid receptors (MR and GR) are two steroid receptors expressed in adipocyte. Their activation either by aldosterone or glucocorticoids promotes the adipogenic transcriptional program and lipid droplets accumulation. The resetting of renal hormone systems following denervation may help preventing hypertension and hyperkalemia, respectively.

Nedd4-2 Ablation in Mice Leads to Upregulation of NCC

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Purpose: Control of renal Na and K transport by aldosteronism is crucial for maintaining Na/K balance and blood pressure (BP). Aldosterone acts in part by preventing ENaC degradation by the ubiquitin ligase Nedd4-2 (N-42). To determine the role of N-42 in mediating salt-sensitive hypertension observed in N-42 total knockout (KO) mice (Shi et al., 2008), inducible renal tubule-specific N-42 KO mice were generated using the TetOn/CreLoxP systems to delete exon 5-6 of the N-42 gene.

Methods: Pax8/LC1 mice, allowing tetracycline-inducible Cre-mediated recombination in renal tubules, were bred with N-42flfl/l mice to obtain mutants (N-42flfl/l/Pax8/LC1) and controls (N-42flfl/l/Pax8 or N-42flfl/l/LC1), all treated with doxycyclin.

Results: N-42 was completely lost in all renal tubular segments in diox-treated mutants. Under both standard and high-Na diets, mutants were able to maintain normal Na/K balance, whereas plasma aldosterone and urine volume were increased. Interestingly, mutants displayed hypertension and increased urine Ca excretion under high-Na diet that could be treated with thiazides, suggesting increased NCC activity. Consistently, mutants showed increased NCC protein abundance and phosphorylation, [3H]ENaC, [3H]EnaC, and ROMK protein expression increased (p <0.05). Unexpectedly, eNOS and eNOS mRNA were decreased, likely related to the lowered plasma aldosterone levels and compensating the increased NCC activity.

Conclusion: These in vivo data show: 1) N-42 effects on [3H]ENaC, but not [3H]EnaC; 2) importance of N-42 for controlling BP and Ca absorption via regulating NCC; 3) [3H]EnaC downregulation and ROMK upregulation that may help preventing hypertension and hyperkalemia, respectively.
Purpose: Myocardial stunning was assessed echocardiographically at baseline and 12 months. Nineteen patients were not available for the follow-up analysis. Diagnosis was performed using Hospal Integra monitors (Hospal, Mirandola, Italy). Diastolic composition was sodium, 138 mmol/L; potassium, 1 mmol/L; calcium, 1.25 mmol/L; magnesium, 0.5 mmol/L; bicarbonate, 32 mmol/L; glucose, 5.6 mmol/L; and acetate, 3 mmol/L. All treatments were for 4 hours’ duration. The extent to which predialysis troponin T was associated with the occurrence of HD-induced myocardial stunning was assessed as the primary endpoint.

Methods: Longitudinal prospective observational cohort study to analyze the renal abnormalities in the post-partum in 182 women having suffered from preeclampsia. Office and 24-hour ambulatory BP, renal function, ultra sensitive CRP, urine spot and 24-hour collection and genetics were obtained at 8 weeks and 8 months post partum, and then followed yearly.

Results: Mean (SD) age was 32.0 (5.8) years and BMI 29.5 (4.2) kg/m². Seventy percent were Caucasian and 21% were blacks. At 6 weeks, urine albumin/creatinine ratio was 10.8 (4.7) mg/mmol. The 24-hour urine excretion of albumin was 216.7 (97.1) mg/dl. GFR estimated with the Cockcroft formula was 149 ml/min [11.9]. Ultra sensitive C reactive protein was 12.7 [7.1]. The prevalence of hypertension or ongoing antihypertensive treatment was 36%. Ambulatory blood pressure daytime was (systolic/diastolic) 120.9 (15.6)/83.5 [10.8] and 112.3 [19.5]/75.1 [11.6] mm Hg. Thirty-nine % of women had an ambulatory blood pressure daytime ≥135/85 mm Hg, and 10% were non-dippers.

Conclusion: Preeclamptic women do not normalize their blood pressure daytime ≥135/85 mm Hg, and 10% were non-dippers.

Relationship of Aldosterone to Urinary Sodium and Potassium Excretion in the Swiss Kidney Project on Genes in Hypertension

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Purpose: Aldosterone plays a major role in the control of sodium and potassium balance by promoting renal sodium reabsorption and potassium secretion. Urinary excretion is mainly determined by diet which in turn should influence aldosterone production. We hypothesize this relationship to be maintained in a circadian pattern within an adult population.

Methods: Nuclear families were randomly selected from the adult population of Lausanne, Geneva and Bern. Sodium and potassium excretion were measured in discrete day and night urine samples according to a standardized protocol. Tetrahydroaldosterone, the major urinary aldosterone metabolite, was measured by gas chromatography-mass spectrometry and standardized for urinary creatinine.

Results: So far, 330 participants (150 women and 132 men) had data available for this analysis. Mean (SD) age and BMI were 47 (17) years and 25.3 (5) kg/m², respectively. Mean (SD) day and night excretions were 95.6 (49.2) and 43.1 (27.3) mmol/L for sodium, and 47.2 (18.4) and 18.4 (8.5) mmol/L for potassium. Daytime tetrahydroaldosterone excretion was higher than night time, even after considering duration (17.8 [24.9] versus 7.9 [13.6] µg/period, P = 0.01). In multivariable mixed linear models adjusted for age, sex, center, BMI and renal function, higher tetrahydroaldosterone excretion was associated with lower sodium excretion (coefficient [SE] = −0.067 [0.012] and −0.076 [0.022] per 10 mmol/L, P ≤0.001, for day and night, respectively) and higher potassium excretion (0.014 [0.003] and 0.048 [0.007] per mmol/L, P <0.001, respectively).

Conclusion: Circadian urinary sodium and potassium excretion is strongly associated to urinary tetrahydroaldosterone excretion in a population-based sample suggesting a timely adaptation to environmental demands.

The Role of Renal SGK1 in the Control of Potassium Homeostasis in Inducible Neprhen-Specific Sgk1-KO Mice

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Purpose: Dietary K+load results in increased kaliemia, leading to aldosterone (aldo) release in order to stimulate K+secretion in the ASDN. However, the regulatory mechanisms of this regulation are unclear. Here, we aim to identify new pathways involved in the regulation of K+secretion. More specifically, we have investigated the role of the aldosterone inducible Sgk1 kinase.

Methods: To avoid the compensatory mechanisms which may mask the role of Sgk1 during development, we employed the inducible nephron-specific specific Sgk1-KO mice which take advantage of the previously described TetOn/CreLoxP system, in which rtTA is under the control of the Pax8 promoter, allowing inducible inactivation of the floxed Sgk1 allele in the renal tubules (Sgk1fl/fl/Pax8/LC1 mice) (Faresse et al., AJP, 2012). Normal and mutant animals were challenged by different K+ diets. We are currently investigating accompanied changes in aldosterone, electrolyte levels and blood pressure. Moreover, blood pressure measurements will be undertaken.

Poster Presentations – Dialysis

Tropinon T for the Detection of Dialysis-Induced Myocardial Stunining in Hemodialysis Patients

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Purpose: Recently, recurrent episodes of myocardial ischemia and transient segmental left ventricular wall-motion abnormalities have been established to occur commonly during standard thrice-weekly HD. These repeated episodes of myocardial stunning can eventually lead to myocardial remodeling, scarring, and irreversible loss of contractile function and are becoming increasingly appreciated as a principal pathophysiological factor of excess cardiovascular mortality in HD patients. Cardiac troponins, structural proteins unique to the heart, are sensitive and specific biochemical markers of myocardial damage. In addition, cardiac troponin levels, as measured by fully automated standard assays, are superior to all other clinically available biomarkers for the diagnosis of acute myocardial ischemia. However, circulating levels of cardiac troponins are frequently elevated in long-term dialysis patients even in the absence of acute coronary syndromes. We therefore aimed to assess the association between the presence and extent of HD-induced myocardial ischemia and troponin T levels in unsedated patients undergoing maintenance HD.

Methods: In 70 prevalent hemodialysis (HD) patients, HD-induced myocardial stunning was assessed echocardiographically at baseline and after 12 months. Nineteen patients were not available for the follow-up analysis. Diagnosis was performed using Hospal Integra monitors (Hospal, Mirandola, Italy). Diastolic composition was sodium, 138 mmol/L; potassium, 1 mmol/L; calcium, 1.25 mmol/L; magnesium,
Conclusion: In conclusion, troponin T levels in patients undergoing long-term HD are associated with the presence and severity of HD-induced myocardial stunning. This mechanism provides a robust pathophysiologic basis for the prognostic importance of elevated troponin levels in the HD population.

Prevalence of Tunnelled Catheter Colonization in Longterm Hemodialysis Patients Using Different Catheter Lock Strategies

Basel

Purpose: Catheter related bloodstream infections (CRBSI) in longterm hemodialysis patients with permanent venous catheters have been attributed to adverse outcomes in terms of mortality, morbidity and excess costs. To minimize the danger of CRBSI by manipulation of dialysis catheters the needless luer-lock device TEGO®connector has been FDA-approved in 2006 as an alternative to standard catheter caps (SCC).

Methods: Our prospective, interventional study investigated the prevalence of asymptomatic catheter colonization as a risk factor for CRBSI in three different renal replacement therapy techniques in 39 patients with permanent venous dialysis catheters in the University Hospital of Basel, Switzerland: (i) TEGO®-system with saline locking solution, (ii) SCC with 46.7% citrate locking solution and (iii) SCC with 30% citrate locking solution plus intensive training of dialysis staff in aseptic catheter manipulation technique.

Results: We could demonstrate significantly higher rates of catheter colonization using the TEGO®connector with saline locking solution as compared to SCC with 46.7% citrate solution (OR 0.22, 95% CI 0.07–0.71, p = 0.011) or 30% citrate solution (OR 0.07, 95% CI 0.01–0.35, p = 0.001).

Conclusion: We recommend cautious use of needle-free connectors for dialysis venous accesses since they might bear the danger of increased rates of CRBSI.

Efficacy and Safety of Citrate-Based Anticoagulation in Patients With AKI in the Intensive Care Unit

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Geneva

Purpose: A systemic anticoagulation is often required to prevent clotting of filter and extracorporeal circulation in ICU patients undergoing continuous renal replacement therapy (CRRT). A regional citrate-based anticoagulation (RCA) does not induce a systemic anticoagulation and prolongs the filter lifespan. Nevertheless metabolic side-effects have been associated with this therapy. We are conducting a randomized controlled trial with patients requiring CRRT to determine whether a RCA is more effective than heparin in terms of renal replacement delivered dose.

Methods: Patients: included if ≥ 18 yrs old with AKI requiring CRRT in the intensive renal replacement therapies in 39 patients with permanent venous dialysis catheters in the University Hospital of Basel, Switzerland: (i) TEGO®system with saline locking solution, (ii) SCC with 46.7% citrate locking solution and (iii) SCC with 30% citrate locking solution plus intensive training of dialysis staff in aspecic catheter manipulation technique.

Results: We could demonstrate significantly higher rates of catheter colonization using the TEGO®connector with saline locking solution as compared to SCC with 46.7% citrate solution (OR 0.22, 95% CI 0.07–0.71, p = 0.011) or 30% citrate solution (OR 0.07, 95% CI 0.01–0.35, p = 0.001).

Conclusion: We recommend cautious use of needle-free connectors for dialysis venous accesses since they might bear the danger of increased rates of CRBSI.

Outcome of Patients on Renal Replacement Therapy (RRT) for Amyloid Nephropathy of Familial Mediterranean Fever (FMF)

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Purpose: Renal amyloidosis (RA) of FMF – although largely preventable – still is a major health problem in Armenia and an important cause of death.

Methods: From January 2002 till September 2012 279 patients were admitted to our centre for RRT, of whom 40 (14.3%) had RA of FMF. Their mean age was 31.4 ± 12.7 (range 12.6–52.9), 80% were males. Mean duration of hemodialysis (HD) was 1.6 ± 1.7 years (range 0.1–6.0).

Results: Hemodialysis: Of the 28 patients not undergoing renal transplantation (Tx) in Armenia, 9 died (systemic amyloidosis – 5, heart attack – 2, stroke – 2); 15 moved to another country and 4 remained on dialysis. Complications were severe erythropoietin resistance (7), intradialytic hypotension (4) and nephroptic syndrome (1). Living related donor Tx was done in our institution in 12 patients aged 38 ± 11.6 years, i.e. 12.5% of all Tx (96) done at the same period. In addition to standard immunosuppression all received low dose colchicine (0.6–1.2 mg/day). Main complications were rejection (8), delayed graft function and primary nonfunction (2), lymphocele (2), CMV disease (2) and tuberculosis (1). Additional problems included diarrhea (colchicine, MMF: generalized amyloidosis; 9) and severe neuropathy due to interaction of cyclosporin with colchicine (1). One patient died of generalized amyloidosis and 1 kidney was lost after reduction of immunosuppression due to tuberculosis. Ten patients have good renal function.

Conclusion: The number of patients with amyloidosis of FMF requiring RRT is alarming, and preventive measures must be strengthened. Outcome of HD was poor in contrast to renal Tx.

What Determines Beta 2 Microglobulin Levels in HD Patients in the 2010’s?

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Purpose: Beta2-microglobulin (B2M) is used as a marker for middle molecules uremic toxins and is associated with outcome on haemodialysis (HD). Our goal was to evaluate the determinants of B2M in a chronic haemodialysis population treated according to the current guidelines.

Methods: We retrospectively analysed B2M levels in all HD patients treated for at least 6 months at our center between 01.01.2010 and 01.08.2012. The B2M value from the last measurement was analysed. At the timepoint of B2M measurement we analysed dialysis modality, Kt/V, vascular access, urine output and residual renal function (RRF), diabetes, active neoplasia or autoimmune disease, current immunosuppression, CRP and current infection within 3 months.

Results: 136 patients (m = 86, f = 50) fulfilled the criteria, 62 on HDF, 37 on HD and 37 on Genius dialysis. B2M levels were 20.68 ± 7.6 mg/L after a mean dialysis time of 42.4 ± 49.6 months. Mean eKt/V was 1.5 ± 0.9, mean RRF 3.1 ± 4.1 ml/min. In an univariate analysis lower RRF emerged as the only significant predictor for B2M levels (p = 0.0003), which was also true for patients with B2M >30 mg/L.

Conclusion: In the era of high-flux membranes and for patients dialysed according to the current guidelines neither HD-modality nor vascular access were relevant for the B2M levels. This series the multivariate analysis revealed that residual renal function was the only determinant of B2M levels.

Accuracy of Five 25-Hydroxyvitamin D [25(OH)D] Assays as Compared to the Reference Method LC-Ms/Ms in Chronic Hemodialysis (HD) Patients

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Purpose: There are few data on the accuracy of 25(OH)D assays in HD patients. Thus, we wanted to assess the reliability of some currently used assays by comparing them to the reference method LC-MS/MS.

Methods: The 25(OH)D serum levels determined by liquid chromatography-tandem mass spectrometry (Thermoferisher, Quantum LC-MS/MS) were compared to those of the following assays:

Roche
Oral Post-Dialysis Cholecalciferol (VitD3)
Supplementation in Patients on Maintenance Hemodialysis (HD): One Size Does Not Fit All

Purpose: We studied in HD patients (pts) the post-HD dose of VitD3 (given as Dialvit with added 2000 IU of VitD3) needed to maintain the VitD levels in the optimal range of 75–150 nmol/l.

Methods: We included 26 pts (age 68 ± 9.8yr) with low VitD who gave their informed consent. 25(OH)D2-D3 was measured bimonthly (Jan 2011 to 2012) with the Roche vitD total assay. The first 2 months, 2000 IU of VitD3 were given after each HD by replacing 1 of the 2 tablets of Dialvit of 1 tablet of DialvitD (Bichsel AG). After month 2, the pts with vitD <75 nmol/l received 2 tablets/HD (= 12000 IU/wk). After month 4, the dose was adapted every 2 mo (by giving 1 to 6 of DialvitD). After month 6, 35% of the pts had vitD >150 nmol/l due to a higher amount needed to maintain these levels varied from 0 (n = 2) to 12000 IU/wk (n = 5).

Conclusion: a) The prevalence of VitD deficiency in Swiss HD pts varies according to the season, as in the general Swiss population; b) the amount of oral post-HD VitD3 needed to maintain the vitD levels within the optimal range varies widely among pts and may be influenced by seasonal changes.

References:

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Non-Pharmacological Interventions for Management of Anemia in Hemodialysis Patients: A Multicenter Study

Purpose: To assess whether non-pharmacological interventions alone could result in maintenance of Hb levels in a stable range for a target group of patients.

Methods: A prospective, multicenter, observational study was conducted at 33 centers in Italy involving 307 HD pts with Hb levels between 8.5 and 12.0 g/dL. Non-pharmacological measures were aimed at adjusting ESA dose, improving nutritional status, and controlling restless legs syndrome.

Results:

- Of the 307 pts, 242 met the inclusion criteria.
- The ESA dose was reduced in 54 pts (22%), and 179 pts (72%) had at least one non-pharmacological intervention.
- A significant decrease of Hb levels was observed in the group of pts with no changes in ESA dose (p < 0.001).

Conclusion: Non-pharmacological interventions alone may be effective in maintaining Hb levels in a stable range for a target group of patients.

New Generation of High-Flux Dialyzers: In-Vivo Quantification of Small and Large Size Solute Transport

B. von Albertini, C. Mathieu, A. Bösch, D. Huber, A. Cherpillo, Lausanne

Purpose: A 10% smaller inner diameter of hollow-fibers in newly available high-flux dialyzers is in greater resistance to blood flow and thereby increases hydrostatic pressure gradients across the membrane. This results in increased internal filtration with convection of solutes from blood to dialysate, with backfiltration of fresh dialysate to blood occurring simultaneously under volumetric control of the equipment. Aim was to quantify small and large solute transport with such dialyzers in vivo.

Methods:

At month six, 35% of the pts had vitD >150 nmol/l due to a higher mean dose of vitD associated to the seasonal increase of vitD. At month 12, 86% of the pts had vitD <75 nmol/l in the target but the amount needed to maintain these levels varied from 0 (n = 2) to 12000 IU/wk (n = 5).

Conclusion: a) The prevalence of VitD deficiency in Swiss HD pts varies according to the season, as in the general Swiss population; b) the amount of oral post-HD VitD3 needed to maintain the vitD levels within the optimal range varies widely among pts and may be influenced by seasonal changes.

Comparison of Hb Events (Decreases >1 g/dl) in a Hemodialysis Patient Population – An Analysis of the Swiss MOTION Survey


Purpose: Controversy exists regarding optimal Hb level and the upper limit of the desired range by ESA treatment. Current recommendations suggest an optimal target for Hb concentration between 10–12 g/dl. The survey’s objective is to analyze significant Hb events.

Methods: Multicenter, retrospective/prospective, observational, non-interventional survey in HD patients documenting Hb events defined by a drop <10 g/dl and by >1 g/dl from baseline along with associated factors. We present an analysis of 378 patients with a mean follow-up (SD) of 12 (0.2) months from 25 sites. Of all patients, 118 (31%) had 143 Hb events (group 1, n = 143). In order to analyze the impact of ESA dosing and Hb values prior to a drop below 10 g/dl the data was compared to decreases of >1 g/dl in the overall population remaining in the target range of 10–12 g/dl (group 2, n = 309).

Results: 378 patients (40% female), mean age and weight (SD) was 66 (14) years and 73 (16) kg, respectively.

Table: Comparison of Hb Events

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<thead>
<tr>
<th>Event</th>
<th>Group 1</th>
<th>Group 2</th>
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<tr>
<td>Hb</td>
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Conclusion: For Hb events remaining within target range (group 2) an intentional ESA dose reduction was documented prior to the observed Hb decrease. For Hb events below target range (group 1) this was less pronounced, suggesting interfering factors other than ESA dose adjustments as a trigger.

Survey supported by Amgen
Conclusion: High-flux HD, done with one of these highly permeable dialyzers, yields sizable diffusive small solute transport, which increases with higher Qb. The unprecedented high j2m clearance found suggests primarily convective transport by important internal filtration and simultaneous backfiltration under volumetric control and approximates in magnitude that of HDF.

Prevalence and Characteristics of Diabetic Subjects on Maintenance Dialysis in the Canton de Vaud in 2009


Purpose: The prevalence of ESRD in type1 and type2 diabetes is increasing around the world but data in Switzerland are lacking. Aims were to establish the prevalence and characteristics of diabetic subjects on maintenance dialysis in the Canton de Vaud as of December 31, 2009.

Methods: Diabetic subjects were identified in all 8 dialysis centres and data was collected from medical records.

Results: A total of 101 diabetic subjects (DM) on dialysis were identified with a sex ratio M/F of 2.15 and a DM2/DM1 ratio of 7.3. Mean HbA1c was 6.9 ± 1.8%. Diabetes duration to dialysis was 16.2 ± 11.4 y. Dialysis duration was 3.6 ± 5.2 y. In 13 cases, ESF had clearly another etiology than diabetes. 54% of patients experienced at least one macrovascular complication. 64% had diabetic retinopathy, 20% underwent amputation and 19% had chronic lower extremity wounds. Mean BP was 146/70 mm Hg at pre-dialysis. The mean Hb was 117.9 ± 11.0 g/l. DM1 subjects were younger, lighter, had a higher Hb1Ac and a longer DM duration at start of dialysis than DM2 subjects. The prevalence of diabetes among subjects on maintenance dialysis in the Canton de Vaud was 35.6%. Compared to the general population the prevalence of diabetes was lower in women and lower in patients with cardiovascular disease. The prevalence of diabetes among subjects on maintenance dialysis in the Canton de Vaud was 35.6%. Compared to the general population the prevalence of diabetes was lower in women and lower in patients with cardiovascular disease.

Conclusion: Prevalence and characteristics of diabetic subjects on maintenance dialysis in the Canton de Vaud as of December 31, 2009.

Prognostic Value of Circulating Klotho and FGF23 in Dialysis Patients

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Purpose: Klotho is known to activate the phosphatonin fibroblast growth factor (FGF23) which stimulates urinary phosphate excretion in an attempt to overcome the reduced phosphate excretion capacity in kidney disease. Thus, Klotho is assumed to have cardiovascular-protective and antiaging properties, but this hypothesis has not been proven. The present study therefore explored the effects of circulating Klotho levels on all-cause mortality in a large hemodialysis patient cohort.

Methods: We prospectively measured the baseline circulating Klotho and FGF23 levels of 239 prevalent hemodialysis patients from three dialysis facilities. The primary hypothesis of the study was that low circulating Klotho levels are not associated with mortality in hemodialysis patients. However, higher circulating Klotho levels seem to be protective against AF.

Results: Preliminary results considering 36 swiss nephrological centers (nearly 50% of all) showed: 244 individuals with the mean age of 67.1y (31–90), started renal replacement therapy in the first half of 2012. 79/244 (33%) patients contacted a renal specialist for the first time less than one month before initiation of RRT. Mean serum creatinine at that moment was 656µmol/l, eGFR (MDRD) 9 ml/min/1.73m². 244 patients initiated dialysis therapy with HDF and 32 patients with CAPD. In an adjusted analysis for age, gender, dialysis center, cardiovascular comorbidities and anuria, the relationship between Klotho and AF remained significant.

Conclusion: Low circulating Klotho levels are not associated with mortality in hemodialysis patients. However, higher circulating Klotho levels seem to be protective against AF.

Too Many Late Nephrology Referral in Pre-ESRD Patients in Switzerland

H. Elässer, D. Kiss

Liestal

Purpose: Multiple observational studies reported increased morbidity and mortality in pre-ESRD patients referred late to specialized renal services. Early detection and intervention to retard progression as well as prevention and treatment of uremic complications are the goals of pre-ESRD management. In addition patient information, choice and preparation for the individually adapted renal replacement modality needs an early referral to the specialist. Obtaining incident data of ESRD patients starting renal replacement therapy (RRT) in Switzerland was the aim of this survey.

Methods: For the timeframe of January 1st to June 30th 2012 all haemodialysis centers in Switzerland were asked for the number of incidents for ESRD leading to implementation of RRT. Patient age, serum creatinine and eGFR (MDRD), time after the first contact to the nephrologist, and time to initiation of RRT in days. The incidence data were evaluated in the pre-ESRD cohort.

Results: Thirty-seven patients (15%) died within the median follow-up time of 682 [657–761] days. Klotho levels were not significantly lower in patients with versus without AF. In an adjusted analysis for age, gender, dialysis center, cardiovascular comorbidities and anuria, the relationship between Klotho and AF remained significant.

Conclusion: Too many delays in nephrology referral in pre-ESRD patients in Switzerland.
Efficacy of PA21, a New Iron-based Phosphate Binder, as Compared to Lanthanum Carbonate and Sevelamer treated Cy/+ rats. Ki67 staining revealed a significantly lower number of positive nuclei in dilated tubules and cysts of Cy/+ rats treated with phlorizin, as well as a marked inhibition of the activated MAP kinase process is not known.

Methods: We tested the hypothesis that induction of glycosuria and osmotic diuresis with the SGLT inhibitor phlorizin could inhibit cyst growth and delay renal disease progression in a rat model of PKD. To that end we induced glycosuria by subcutaneous injection of phlorizin (400 mg/kg/d) in male heterozygous (Cy/+ ) and wild-type (+/+) Han:SPRD rats. As expected, phlorizin induced immediate and sustained increase in creatinine clearance, with a 12.6% lower 2 kidneys/body weight (2K/BW) ratio and a 28.4% lower renal cyst index, as well as a 63% reduction in urinary albumin excretion as compared with vehicle-treated Cy/+ rats. K67 staining revealed a significantly lower number of positive nuclei in dilated tubules and cysts of Cy/+ rats treated with phlorizin, as well as a marked inhibition of the activated MAP kinase pathway. In contrast, the mTOR pathway remained unaltered.

Conclusion: These data demonstrate that long-term treatment with phlorizin has a prominent inhibitory effect on cystic disease progression in a rat model of PKD, supporting the hypothesis that induction of glycosuria and osmotic diuresis (glycuresis) by renal SGLT inhibition could have a therapeutic effect in polycystic kidney disease.

Spleen Tyrosine Kinase Is Important in the Production of Proinflammatory Cytokines and Cell Proliferation in Human Mesangial Cells following Stimulation with IgA1 Isolated from IgA Nephropathy Patients

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Purpose: We previously reported that the inhibition of spleen tyrosine kinase (SYK) by a SYK inhibitor, R406 (fostamatinib), or SYK siRNA reduces the synthesis of various cytokines by human mesangial cells (HMC) following stimulation with IgA1 (pIgA1). We now examine whether SYK is involved in mesangial cell proliferation and production of extracellular matrix (fibronectin) following stimulation with pIgA1.

Methods: IgA1 was isolated from the serum of IgAN patients and aggregated at 63 °C for 150 min (alga1). HMC were incubated with alga1 for 24h and cell proliferation assay with BrdU was performed. We then incubated HMC with R406, 1h before stimulation with alga1 (200 µg/mL). HMC were stimulated with either Syk/IL2Rα siRNA for 72h or Syk/IL2Rα retrovirus or negative control siRNA, 72h before stimulation with alga1. In the next experiment, human fibronectin produced by HMC following stimulation with pIgA1 for 24h was examined in culture supernatants by ELISA.

Results: The proliferation of HMC was increased upon stimulation with alga1 and inhibited by R406 in a dose dependent manner. HMC transduced with Syk siRNA proliferated significantly less than the cells transfected with negative control siRNA. The concentration of human fibronectin in culture supernatants increased significantly following stimulation with pIgA1. The preincubation with R406 did not reduce the concentration of fibronectin.

Conclusion: Our previous and current data suggest the involvement of SYK in the production of various cytokines and mesangial cell proliferation, but not in the synthesis of fibronectin, upon stimulation with pIgA1. SYK may be considered as a potential target in the treatment of IgAN.

Functional Study of SLC2A9 (Glut9) Variants Associated With Plasma Uric Acid Level

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Lausanne

Purpose: Uric acid is the end product of purine metabolism in humans. GLUT9 has been identified as a new voltage-sensitive urate transporter expressed in the liver, the kidney and other tissues. In humans, GLUT9 loss-of-function mutations (L75R, T125R, R198C, R380W) have been associated with familial renal hypouricemia, a
condition associated with low plasma uric acid levels, uric acid kidney stones and exercise-induced acute renal failure. Moreover, a non-
synonymous single-nucleotide polymorphism (SNP) V253I, present 
with a frequency of 22.3% in the population, has been associated 
with low plasma uric acid levels. By contrast, a loss-of-function mutation 
identified in the Dalmatian dog strain (C210F) leads to hyperuricemia, 
kidney stone formation and renal insufficiency. Ongoing debates 
about functional studies of some GLUT9 variants and the absence 
of functional data of others have prompted us to study all of them.

Methods: Xenopus oocytes were injected with various GLUT9 
variants cRNAs and were subjected to 14-urea uptake (n = 30 
cytoples, 3 batches) and surface expression was assessed by immuno-
 staining.

Results: The uptake assay revealed a decrease of 14-urea flux for 
all the mutants compared to wildtype GLUT9 (69.8 ± 4.8% L75R; 85.6 ± 
8.0% T125R, 58.4 ± 21.1% R198C, 72.3 ± 13.8% R380W for human 
motors and 80.1 ± 5.1 C210F, p <0.01 compared to WT) with 
conserved expression at the cell surface. The SNP V253I showed a 
decreased14-urea uptake by 41.2 ± 22.2% (p <0.05) related to a 
decreased surface expression.

Conclusion: These results represent the first complete characteri-
 zation of known GLUT9 variants and pave the route toward a better 
understanding of the structure-function relationship for the urate 
transporter GLUT9.

Role of the Glucocorticoid Receptor in Podocyte Function?
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U. Ziegler, J. Loffing, C. D. Cohen
Zurich

Purpose: In proteinuric diseases glucocorticoids (GC) show a prompt 
anti-proteinuric effect in steroid sensitive patients. However, central 
aspects of the underlying mechanisms of GC’s action are still 
incompletely understood and both local effects on podocytes as well 
as systemic immune-modulating properties are discussed. Podocytes, 
which play an important role in nephritic syndrome, express the 
glucocorticoid receptor (GR). Hence we hypothesize that GC control 
expression of several reported GR-dependent gene transcripts than 
by GC in podocytes could be documented. Podocyte-specific-GR-
knockout mice exhibit protrusions of the glomerular basement 
membrane, collagen bundles, podocyte foot process effacements 
as well as changes of endothelial cells.

Methods: Datasets of the European Renal cDNA Bank allowed us 
to study the overall expression of GR-dependent gene transcripts in 
glomeruli of patients with minimal change disease, focal segmental 
glomerulosclerosis and membranous glomerulonephritis. Candidate 
genes were selected and further studied in an immortalized murine 
podocyte cell-line treated with dexamethasone. For further 
investigations a mouse model with a target deletion of the GR in 
podocytes was created.

Results: Glomeruli of patients with nephrotic syndrome showed lower 
expression of several reported GR-dependent genes than 
control tissue. A dose- and time-dependent up-regulation of 
FKBP5 and DUSP1, two of these GR-dependent glomerular transcripts, 
by GC in podocytes could be documented. Podocyte-specific-GR-
knockout mice exhibit protrusions of the glomerular basement 
membrane, collagen bundles, podocyte foot process effacements as 
well as changes of endothelial cells.

Conclusion: Collectively, these findings underline a link between the 
GR and glomerular function. Further studies are underway to 
understand the molecular function and the detailed phenotype of the 
podocyte-specific GR-knockout.

Quantification of Multiple Bile Acids Using Ultra-
Performance Liquid Chromatography tandem Mass 
Spectrometry: Impact of Uninephrectomy on Circulating 
Bile Acids in Rats
C. A. Pennoll, D. Arsenijevic, T. Da Cunha1, G. Kullak-Ublick2,
J.-P. Montani2, A. Odermatt1

Purpose: Bile acids (BAs) are end products of cholesterol catabolism 
and act as emulsifiers of lipophilic compounds. Besides, they were 
recently recognized as important signaling molecules. To understand 
the roles of individual BAs and due to limited blood sample volumes 
available from experimental animals, improved methods for the 
simultaneous quantification of multiple BAs are needed.

Methods: We developed and validated an ultra-performance liquid 
chromatography tandem mass spectrometry (UPLC-MS/MS) method 
for the quantification of 24 BAs, including 11 unconjugated, 6 glycine-
conjugated and 7 taurine-conjugated BAs, in 50 µL of rat serum or 
plasma. The application of UPLC-MS/MS allows a highly specific 
detection of BAs by using multiple-reaction monitoring (MRM) with 
specific fragmentation. The method showed acceptable intra- 
and inter-day accuracy, precision, extraction recovery and enhanced 
sensitivity compared with earlier approaches. We applied the 
established method to assess time-dependent changes of BAs in 
plasma from sham-operated and uninephrectomized male Sprague-
Dawley rats.

Results: The levels of several primary and secondary BAs were 
transiently elevated one week after uninephrectomy, followed by 
normalization after the second week. In contrast, several conjugated 
BAs showed increased levels at the second week post-surgery, 
followed by normalization thereafter.

Conclusion: The established UPLC-MS/MS method allows the 
simultaneous and specific quantification of multiple BAs in 50 µL 
serum or plasma samples. Application of the method revealed a 
transient increase of several primary and secondary BAs in 
uninephrectomized mice that was followed by a transient increase in 
conjugated BAs. The presented method can be used to assess BA 
profiles in various patho-physiological situations.

Roles of Claudins and Zonula Occludens 
in Epithelial Collecting Duct Cell Senescence
X. Qiao, E. Dizin, I. Roth, E. Feralille, U. Hasler 
Geneva

Purpose: Repair of kidney epithelia following acute injury depends 
on rapid cell proliferation, which is low under normal conditions. Since 
hypertonicity reduces cell division and promotes cell senescence, 
cell proliferation in the renal medulla is likely even lower. Recent evidence 
indicates that cell repopulation is achieved by differentiated tubular 
cells that retain an intrinsic ability to divide. This implies that loss of 
contact between neighboring cells might promote surviving cells to 
dedifferentiate and reenter the cell cycle. This led us to examine the 
roles of claudins and ZO as modulators of cell proliferation under both 
isotonic and hypertonic conditions.

Methods: Proliferation of principal collecting duct (CD) mCCDcl1 cells 
grown under isotonic and hypertonic (500 mOsm/kg) conditions was 
examined by microscopy analysis and FSC cell sorting. Claudin and 
ZO expression was examined by Real-Time PCR, Western blot and 
confocal analysis.

Results: mCCDcl1 cell proliferation under isotonic conditions 
decreased with cell confluency. This was accompanied by a reduced S 
phase and increased G0/G1 phase. While ZO-1 and ZO-2 abundance 
was unaffected by cell confluency, both ZO-3 and claudin-8 abundance 
increased while claudin-4 abundance decreased with cell confluency. 
All observed changes were accelerated in cells grown in hypertonic 
medium. Microscopy analysis further revealed increased ZO-1 
abundance by chronic hypertonic challenge and increased ZO-1 
expression in medullary CD.

Conclusion: Together, these results indicate that CD cell senescence 
is associated with increased claudin-8 and ZO expression. Modulated 
expression of TJ components will help establish their roles in cell 
proliferation and paracellular transport.

The Calcium Channel TRPC6, Known to Cause 
FSGS When Chronically Hyperactive, Protects 
Podocytes From Acute Complement-Mediated Injury
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Zurich, *New Delhi/IN, #Seattle/US, ~Miami/US

Purpose: Gain-of-function mutations in the calcium channel TRPC6 
lead to genetic FSGS. Podocyte expression of normal TRPC6 is 
increased in acquired human glomerular diseases, particularly in 
membranoproliferative glomerulonephritis (MPGN). We therefore 
speculated that overexpression of TRPC6 in cultured podocytes leads 
to cell damage.

Methods: We used standard methods, including podocyte culture, 
tenlivial gene transfer, Ca-imaging and cell surface biochemistry.

Results: Overexpression of TRPC6 in differentiated podocytes did 
not affect podocyte integrity despite correct membrane localization 
and activity of the channel. Unexpectedly, overexpression of TRPC6 
protected podocytes from complement-induced injury, an in vitro model 
of MN. In contrast, overexpression of dominant-negative TRPC6 
knock down of TRPC6 and the administration of a TRPC antagonist 
increased podocyte sensitivity to complement. This effect was 
mediated by CaMKII: complement attack activated CaMKII in 
podocytes and the degree of activation correlated with TRPC6 levels. 
Pre-treatment of podocytes with a CaMKII inhibitor phenocopied the 
effect of TRPC6 inhibition. Human MN biopsy samples, where induced 
TRPC6 expression has been previously shown, displayed increased 
activity of CaMKII. In the nephrotic syndrome model, where 
complement contributes to glomerular injury, podocyte-specific 
transgenic mice showed stronger CaMKII activation, reduced podocyte 
FP effacement and reduced levels of proteinuria, whereas TRPC6 
knock out mice exhibited reduced CaMKII activation and higher levels 
of proteinuria compared to wt controls.

Conclusion: These data suggest an unexpected dual role of TRPC6 
in podocytes: whereas chronic hyperactivity leads to FSGS, acute 
activation protects from complement-mediated damage in the short 
term.
Tight-Junctions in Response to Apical Sodium Entry

Coordinated Control Of Basolateral Na,K-ATPase and
Across Species!

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Purpose: We described a transcriptomic classifier of metzincins and related genes (MARGS) discriminating renal allografts and other solid-organs with or without fibrosis (AJT, 2009; Virchows Arch, 2011). Rats exposed to lithium are known to develop fibrosis (Nephrology, 2010).

In this study, we wanted to demonstrate, if our MARGS-based algorithm has diagnostic value in rat renal fibrosis. Male Wistar rats (n = 12) were divided into a control group (n = 6), and an experimental group (n = 6) that received 40 to 60 mmol lithium carbonate/kg dry food up to 24 weeks. After six months, animals were sacrificed to dissect cortex and medulla. We used 24 Affymetrix Rat Exon 1.0 ST arrays: healthy cortex (n = 6), healthy medulla (n = 6), lithium exposed cortex (n = 6) and lithium exposed medulla (n = 6). Three MARGS were examined by immunofluorescence.

Results: There were more differentially expressed genes in medulla-dataset than in cortex-dataset (ANOVA), MMP-2, CD44 and TGFβ2 were up-regulated in both lithium-treated cortex and medulla samples. In gene set analyses (GSEA), lithium-treated cortex and medulla samples showed enrichment of MARGS, TGFβ, ECM and fibrosis genes; lithium-treated medulla samples were also enriched in immune response pathways. The MARGS based IFASTA classifier was able to classify all samples correctly. Ingenuity pathway analysis of differentially regulated genes in medulla depicts relationship within MARGS and with respective mi-RNA. Immunofluorescence confirmed up-regulation of MMP-2, CD44 and TGFβ2.

Conclusion: Our MARGS classifier represents a cross-organ and cross-species classifier of fibrotic conditions irrespective of etiology and may help to design a low density array (LDA) to diagnose and to monitor fibrosis. These results provide evidence for a common pathway in the pathogenesis fibrosis.

EphA2 Receptors Contribute to the Renal Tubular Response to Hypoxic Injury

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Purpose: Acute Kidney Injury (AKI) is a major challenge to the nephrologist, and renal epithelial hypoxia is believed to play an important role irrespective of the underlying conditions. To identify novel mechanisms involved in the kidney response to hypoxic injury.

Methods: we performed segmental renal artery branch ligation in rats, a model which has been shown to induce an oxygen gradient vertical to the corticomedullary axis. Three distinct zones can be distinguished: (1) tubular necrosis, (2) infarction border zone, (3) preserved normal tissue.

Results: In previous work we showed that in the mouse skin, local oxygen deprivation triggered upregulation of Eph receptors, a family of receptor tyrosine kinases required for somitogenesis, vasculogenesis and axonal guidance in the embryo, and playing a central role for the homeostasis of many organs in the adult. In control kidneys, EphA2 receptor was expressed in tubular cells of Henle’s loop, and its ligand ephrinA1 in endothelial cells of the glomeruli and vessels. Hypoxia induced HIF-1α stabilization in the infarction border zone mainly. In this area, EphA2 receptor was upregulated in tubular cells, while ephrinA1 expression increased in neighboring interstitial cells. This coordinated upregulation in adjacent cells highly suggested that these processes would trigger juxtacrine signalling. We showed that in MDCK cells, endogenous EphA2 expression significantly increased following hypoxia. Stimulation of MDCK with ephrinA1/Fc enhanced cell adhesion and deposition of laminin, an important component of the tubular basement membrane.

Conclusion: Our findings present evidence that EphA2 receptors may contribute to fibrotic cellular response to hypoxic damage by influencing the extracellular matrix composition and increasing cell-matrix interactions at the sites of injury.

Effects of Renal Dysfunction on Bile Acid Homeostasis

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Purpose: Although the kidney is believed to play a minor role in bile acid (BA) excretion, chronic renal failure (CRF) has been reported to be associated with increased serum bile acid levels and alterations in the BA balance. This study was designed to examine the effects of naturally progressing CRF of longer duration on gene expressions of the key factors involved in hepatic bile acid synthesis and transport, i.e., Cyp7A1, Ntcp, Bsep.

Methods: Wistar rats were randomized to the CRF group (5/6 nephrectomy) and sham-operated, placebo-treated normal controls. They were allowed free access to regular rat chow and studied 8 weeks after surgery. Uninephrectomized (UNX) rats were also used to examine the impact of renal functions on bile acid metabolism. Liver mRNAs and protein mass or activities of the above factors were studied.

Results: The CRF group exhibited significantly increased plasma cholesterol concentration and bile acid levels. Hepatic Cyp7a1 mRNA, and Cyp7a1 protein mass measurements were virtually identical in the two groups. Examine on bile acid transporters showed elevated Mrp3, Ost-a and Ost-ι expressions at both mRNA and protein levels, indicating a shift of bile acid transport from apical canalicular to basolateral blood. Similar changes of plasma bile acid level and bile acid transporters were found in UNX rats.

Conclusion: In summary, chronic renal failure is associated with a strong increase in plasma bile acid levels, which is shown to be an early event before the time when kidney function is affected. Maintenance of bile acid synthesis and elevated basolateral Mrp3 and Ost-a/ι expressions may either be a desired response during chronic renal disease to release serum bile acid concentration or it may be a failing feedback regulation on bile acid formation and disposition.
Flow-Mediated Regulation of Sodium Transport in the Collecting Duct
T. Ermendz, A. Chassot, P.-Y. Martin, E. Feraul...Genova

Purpose: Na transport in renal tubules is tightly controlled and plays a central role in body fluid homeostasis. In addition to the classical neuro-endocrine inputs, local factors such as luminal flow may participate to Na homeostasis.

Methods: We designed an in vitro experimental setting to explore the effect of apical flow on a cellular model of collecting duct (CD) using the welldescribed mouse model of CDCCd principal cells grown on filters. Directional flow was generated using an orbital shaker delivering a shear-stress of 2 dyne/cm² mimicking physiological luminal flow.

Results: We observed a delayed and sustained decrease of the amiloride-sensitive Na current in cells subjected to flow reaching a plateau at 8h (40% decreased). This was correlated with a significantly decreased mRNA expression of ENaC subunits and SGK1. The flow-mediated Na transport decrease was not prevented by PKD1 or KIF3A genes silencing, excluding a role of the primary cilium in this response. This unique organelle protruding on the apical side of CD cells is indeed described as a putative mechanosensor. To obtain more insights on factors involved in ENaC flow-mediated regulation, we performed a transcriptomic analysis using RNAseq on control and flow-perturbed CDCCd principal cells subjected or not to flow. Significant down-regulation of genes involved in PKA and Rho GTPases pathways were identified. We speculate that these molecules may participate to Na homeostasis.

Conclusion: Flow-mediated regulation of Na transport might be of particular relevance in increased glomerular blood flow conditions such as in living kidney donors.

Hypoxia-Associated Gene Transcripts are Altered in Acquired Nephropathies
Zurich

Purpose: Most chronic kidney diseases (CKD) are initiated as glomerular diseases, with loss of glomerular architecture. The pathogenesis of the glomerular insult can be manifold. The best morphologic indicator of disease progression and development of end-stage renal disease, however, is interstitial fibrosis accompanied by a capillary rarefaction. As hypoxia – a potential consequence of the capillary rarefaction – has been associated with fibrosis, the question arises whether renal cells indeed face hypoxia in CKD and respond with a transcriptional program which could lead to disease progression.

Methods: Expression of hypoxia-associated genes was assessed in genomewide microarrays from more than 160 renal biopsies of patients with different CKD stages. Proximal tubular cells and podocytes with stable HIF1 and/or HIF2 suppression were generated. From a total of 84 established HIF-target genes 27 correlated with renal function (eGFR) in the cortical tubulointerstitium and 22 in the glomerular samples. Importantly, these correlations were both positive and negative and in part compartment-specific. The cell-type-specific response to hypoxia was tested by qPCR in the knock-downderivates and revealed in different cell types.

Conclusion: Our gene expression studies do not indicate an over-all hypoxia milieu in acquired kidney diseases. However, the data clearly point to compartment- and cell-type-specific dysregulation of hypoxia-associated genes in CKD. Elucidation of the mechanisms involved may help to understand the pathogenesis of anemia in CKD, intestinal fibrosis, and renal failure.

Impact of Chronic in Utero Hypoxia on Renal Glomerulogenesis and Tubulogenesis
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Berne

Purpose: Chronic kidney diseases (CKD) represent a growing public health problem, due to the aging population and higher prevalence of the metabolic syndrome. Recent studies have also suggested the role of early events in life. Intrauterine Growth Restriction (IUGR), resulting from an adaptation to inadequate supply of oxygen and/or nutrients during pregnancy, is thus thought to be responsible for adult hypertension, insulin resistance, cardiovascular and renal diseases. Studies of IUGR are still scarce and the molecular actors responsible for a deficient nephrogenesis remain to be better characterized. Our goal is thus to study the impact of chronic exposure to hypoxia on kidney development, using a mouse model of chronic hypoxia in uterus.

Methods: Pregnant mice were exposed to hypoxia (9.5% vs. 21% O₂) during renal development (E11.5 to D7) with quantification of food intake for caloric adjustment (control group). Kidneys from pups were collected at E18.5 and analyzed.

Results: First experiments (E14.5 to E18.5) showed a decreased food intake by hypoxic dams with no reduction in litter sizes. Pups from hypoxic dams showed a significantly lower birth weight compared to pups from normoxic dams (with or without adjusted caloric intake). Microarray and qPCR analyses of E18.5 kidneys showed a modified expression of genes mostly implicated in coagulation, lipid metabolism and vascular calcification. Morphometric and immunohistochemistry analyses are ongoing.

Conclusion: This study gives new insights into the mechanisms linking IUGR and abnormal kidney development and identifies potential molecular actors implicated in this process.

The Furosemide-Induced Increase of Plasma Parathyroid Hormone is Mediated by the Calcium-Sensing Receptor in Humans
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Lausanne

Purpose: Furosemide has been reported to increase intact plasma parathyroid hormone (iPTH) levels in humans, but the mechanisms of this interaction are still unclear. Experiments on rats suggested that acute administration of a calcimimetic blunts this effect. We designed a prospective randomized placebo-controlled crossover study addressing the role of the calcium sensing receptor in the IPTH response to furosemide.

Methods: 12 Caucasian, non-smoker healthy males were enrolled. After 3 days of a fixed salt diet, they received either a single dose of 60 mg cinacalcet or placebo with at least one week interval. Three hours after cinacalcet, 20 mg furosemide were given iv. Plasma levels of iPTH and plasma and urinary levels of calcium, sodium and potassium were measured at baseline (before cinacalcet), and before and at regular time intervals after the furosemide injection.

Results: Plasma iPTH levels were significantly lower in the cinacalcet group compared to placebo at 1.5-2 h after administration of cinacalcet. Under placebo, a sharp increase in plasma iPTH levels was seen as soon as 15 min after furosemide injection (from 20.9 ± 6.9 ng/l before to 33.2 ± 10.7 ng/l, mean ± SD) whereas under cinacalcet, iPTH response was blunted (from 2.4 ± 1.7 ng/l to 3.2 ± 2.9 ng/l, mean ± SD). Furosemide induced a significant decrease in plasma ionized calcium in cinacalcet-treated subjects, an effect which was absent under placebo. The changes in plasma Na and K after furosemide were comparable in both cinacalcet and placebo groups.

Conclusion: These data show in humans that furosemide acutely stimulates iPTH an effect which is blunted by cinacalcet and not by placebo, in agreement with the role of a calcimimetic despite a decrease in plasma ionized calcium. Changes in sodium and potassium levels do probably not play any role in the IPTH response to furosemide.

Oxygen-Regulated Expression of Erythropoietin in Cellular Models
F. Storti1, I. Abreu-Rodriguez2, S. Frede2, J. Fandrey2, R. Wenger2, D. Hoogewijs2
1Zurich, 2Essen/DE

Purpose: Erythropoietin (Epo), the key hormone regulating red blood cells homeostasis, is mainly produced in the adult kidney in response to hypoxia and anemia. Epo is regulated by the prolyl-hydroxylases (PHDs) via HIFs, but its tissue-specific induction remains largely obscure, mainly due to the lack of a kidney-derived cellular model capable of expressing Epo in a hypoxia-inducible manner. Recently, a new renal cell model (called Renal Epo Producing Cells, REPCs) became available and we started the characterization of this cell line. Moreover, Epo overexpression can be the cause of erythrocytosis, a disease in which the number of red blood cells is increased. Mutations in PHD2, VHL or HIF2A have been reported in patients with secondary congenital erythrocytosis. We aim to functionally characterize recently identified mutations found in the PHD2 gene of patients with erythrocytosis.

Methods: We are currently using REPCs, and the hepatoma cell lines HepG2 and Hep3B to explore the role of different players of the PHDs/VHL/HIF pathways in Epo transcriptional regulation, by a shRNA-mediated knockdown strategy. HIF transcriptional and stability assays, as well as mutant PHD2 overexpression in PHD2-silenced cells, are used to assess the functional effect of the novel PHD2 mutations.

Results: Besides HIF-2α, a novel transcription factor belonging to the
ETS family was found to have a strong effect on Epo transcriptional regulation in REPCs. Mutations in PHD2 lead to functional differences regarding HIF regulation.

**Conclusion:** The presented in vitro approach enabled us to identify a novel factor regulating oxygen-dependent Epo expression and functionally investigate erythropoietis-associated PHD2 mutations.

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**Poster Presentations – NCCR Kidney.CH**

**P78**

**Rapid Homeostatic Effects of Oral Potassium Loading on the Kidney**

S. Grossmann*, M. Sorensen†, M. Rösinger‡, D. Loffing-Cueni, G. Barmettler*, U. Ziegler*, O. Staub†, J. Loffing‡

**Zürich, Basel, Lausanne**

**Purpose:** A large dietary potassium (K+) load is a homeostatic challenge for mammals. It is known to induce a rapid kaliuretic and natriuretic response. These renal effects are reported to occur even before plasma K+ and aldosterone levels increase. Here we elucidate the underlying molecular mechanisms of K+ induced kaliuretic and natriuretic response.

**Methods:** We analyzed in mice the time course (15'; 30'; 2h; and 6h) of the effect of a gastric K+ load on plasma ion concentrations, aldosterone levels, urinary ion excretion, and expression and/or phosphorylation of renal ion transport proteins.

**Results:** Following a gastric gavage of 2% KCl, plasma K+ concentrations rose rapidly (at 15'), followed by a significant rise of plasma ald (at 30'). Enhanced urinary K+ and Na+ excretion was detectable at 30': two hours after gavines could be collected (~30'). The functional changes were accompanied by a rapid and sustained dephosphorylation of the NaCl cotransporter (NCC) (15'-6h) and a later up-regulation of proteolytic activated epithelial sodium channels (ENaC) (6h). The ENaC levels were regulated by a complex of ENaC and the late effects on ENaC were independent from the co-administered anion (same effect with KHCO3; no effect with NaCl). In contrast to the proteolytic ENaC regulation, NCC dephosphorylation was independent of plasma ald as indicated by experiments in aldosterone-deficient mice. The observed urinary Na+ loss was likely related to NCC, as it was not seen in aldosterone-deficient mice.

**Conclusion:** Rapid down-regulation of NCC contributes to the early kaliuresis and explains the natriuresis in response to an oral K+ load. Enhanced activity of ENaC occurs late and might be more important for the long-term control of K+ homeostasis.

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**P79**

**V-Atpase B1 Subunit Polymorphism P.E161K Affects Urinary Acidification in Vivo**

N. Dhayat, A. Pasch, D. Fuster

**Berne**

**Purpose:** The V-ATPase proton pump on the luminal membrane of α-intercalated cells is critical for urinary acidification. The V-ATPase consists of two multi-subunit domains, the V0 and V1 domain. The soluble cytosolic 640 kDa V1 domain is composed of subunits A-H in a A3B3C1D1E1F1G2H1 stoichiometry. In humans, there are two different isoforms of the B subunit in the V1 domain, of which B2 is enriched in lipid rafts, plays a crucial role in the regulation of V-Atpase B1 Subunit Polymorphism P.E161K Affects Urinary Acidification in Vivo.

**Methods:** We analyzed in mice the time course (15'; 30'; 2h; and 6h) of the effect of a gastric K+ load on plasma ion concentrations, aldosterone levels, urinary ion excretion, and expression and/or phosphorylation of renal ion transport proteins.

**Results:** Following a gastric gavage of 2% KCl, plasma K+ concentrations rose rapidly (at 15'), followed by a significant rise of plasma ald (at 30'). Enhanced urinary K+ and Na+ excretion was detectable at 30': two hours after gavines could be collected (~30'). The functional changes were accompanied by a rapid and sustained dephosphorylation of the NaCl cotransporter (NCC) (15'-6h) and a later up-regulation of proteolytic activated epithelial sodium channels (ENaC) (6h). The ENaC levels were regulated by a complex of ENaC and the late effects on ENaC were independent from the co-administered anion (same effect with KHCO3; no effect with NaCl). In contrast to the proteolytic ENaC regulation, NCC dephosphorylation was independent of plasma ald as indicated by experiments in aldosterone-deficient mice. The observed urinary Na+ loss was likely related to NCC, as it was not seen in aldosterone-deficient mice.

**Conclusion:** Rapid down-regulation of NCC contributes to the early kaliuresis and explains the natriuresis in response to an oral K+ load. Enhanced activity of ENaC occurs late and might be more important for the long-term control of K+ homeostasis.

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**P80**

**Role of Oxygen-Inducible PAG1 in Chronic Kidney Disease**

S. Santambrogio*, M. Lindenmeyer†, A. Schorg‡, J. Storti§, J. Schodeč, D. R. Mole*, C. D. Cohen†, R. Wenger‡, D. Hoogewijs‡

**Zürich, Oxford/UK**

**Purpose:** Accumulating evidence exists that hypoxia is an important modulator of chronic kidney disease (CKD) and the identification of novel hypoxically regulated genes will improve our understanding of the transcriptional mechanisms involved in CKD. Recently, we discovered PAG1(Phosphoprotein Associated with Glycosphingolipid enriched microdomains) as a novel hypoxia-inducible gene. PAG is exclusively localized in lipid rafts, plays a crucial role in the regulation of Src-kinase family and is involved in several signaling pathways.

**The aim of our work is to understand the role of PAG in kidney pathophysiology.**

**Methods:** RT-qPCR, immunoblotting and ChIP experiments were conducted to study hypoxia-dependent PAG regulation.

**Results:** PAG protein levels were robustly induced by hypoxia in non-malignant cells whereas 786-O showed high expression levels in normoxia and reconstitution of VHL as well as shRNA-mediated HIF-2α knock-down resulted in decreased PAG expression levels. Moreover, in vivo experiments confirmed hypoxically induced PAG mRNA levels in kidneys of mice exposed to 9% O2. Interestingly, ChIP-qPCR experiments specific for hypoxia-dependent HIF1 binding in 786-O and this putative enhancer site is localized 85 kb upstream of the PAG1 promoter, suggesting a novel mode of hypoxic gene regulation. A comprehensive screen of PAG expression in gene array data from glomerular and tubulointerstitial compartments of patients with progressive and non-progressive nephropathies revealed robust PAG induction in several glomerulopathies. The array data were confirmed by RT-qPCR in independent nephropathy samples.

**Conclusion:** Unraveling the role of hypoxic PAG regulation in a pathological context will add new insight in understanding CKD and will help to clarify its physiological role.

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**P81**

**Establishment of a Novel Genetically Modified Mouse Model Targeting the Renal Oxygen Sensing and EPO-Producing Cells**

I. Abreu Rodrigues*, P. Spielmann†, M.-L. Dénérâdz, E. Hummler‡, A. Hesse†, D. M. Katschinski‡, D. Hoogewijs‡, R. H. Wenger‡

**Zürich, Lausanne, Geneva**

**Purpose:** In CKD, renal oxygen consumption is decreased and the oxygen gradient decreased, leading to a drop in erythropoietin (EPO) synthesis and anemia. Although the mechanisms underlying inducible expression of Epo are generally understood, the mechanisms of constitutive tissue-specific and inducible hypoxic Epo gene regulation are largely unknown. EPO is synthesized by insufficiently cultured and novel models are hence urgently required to study the complexity of the renal oxygen signaling cascade and Epo regulation.

**Methods:** Transgenic Cre strains will be used to study the expression of EPO in a temporal and spatial manner, indirectly by reporter genes (egFP and LacZ) and directly (by Cre-mediated VHL deletion); and to generate specific knock-outs of recently discovered novel members of the oxygen signaling cascade to investigate their role in (patho) physiological EPO regulation. Renal hypoxia imaging will be complemented by using transgenic O2Dox-luc mice.

**Results:** Generation of novel BAC transgenic Cre vectors expressing the Cre recombinase under the control of the mouse Epo gene locus. Following pronuclear microinjections, two potential founder lines were obtained and they are currently being analyzed.

**Conclusion:** These mice model will be used for detailed characterisation of the Epo-producing renal cells, analysing the physiological relevance of novel factors involved in oxygen signaling for EPO expression regulation and imaging the number and distribution of EPO producing cells during development, hypoxic insults and CKD.

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**P82**

**The Impact of Reduced Kidney Mass on Adipose Tissue Metabolism and Whole-Body Glucose Homeostasis in Mice**

S. H. Chin, F. Item, S. Wueest, M. Wiedemann, E. J. Schoenle, D. Konrad

**Zürich**

**Purpose:** Reduced kidney function deteriorates insulin sensitivity in children and adults. However, the underlying mechanisms are poorly understood. Activation of the RAAS/angiotensin receptors (ATR) in adipose tissue impairs insulin signalling in adipose tissue, skeletal muscle and liver and its prevention by ATR blockade (pharmacologically or genetically) improves glucose homeostasis. We therefore hypothesise that reduced kidney mass impairs glucose metabolism via activation of the RAAS.

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Methods: Seven-week-old C57Bl/6J mice underwent uninephrectomy (UniNx) or sham operation. After operation, animals were fed either a chow (standard) or a high fat diet (HFD) and glucose homeostasis was assessed 2, 8, and 20 weeks after surgical intervention.

Results: No differences were observed in glucose tolerance in chow-fed animals. However, in HFD-fed animals, glucose tolerance was further impaired in UniNx mice after 8 and 20 weeks when compared to sham-operated mice. Moreover, skeletal muscle insulin resistance was significantly deteriorated and adiposity was increased in UniNx mice after 20 weeks of HFD. In contrast, hepatic steatosis was decreased and hepatic insulin sensitivity was improved in UniNx mice. Plasma angiotensin I concentration was elevated in UniNx compared to sham-operated mice under both chow and HFD 2, 8 and 20 weeks after surgical intervention. Moreover, expression of proinflammatory cytokines was decreased in both mesenteric and epididymal fat of UniNx compared to sham-operated mice after 20 weeks of HFD.

Conclusion: Uninephrectomy further impairs obesity-induced skeletal muscle insulin sensitivity but protects from obesity-induced adipose tissue inflammation as well as hepatic insulin resistance and steatosis.

Uninephrectomy May Alter Immune And Metabolic Regulation: A Role for the Brain?

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Purpose: Uninephrectomy (UniNX) induced a small decrease in fat pads and a chronic elevation in markers of lipolysis (plasma glycerol, hormone-sensitive lipase, adipocyte triglyceride lipase). Increase in lipolysis was significantly correlated to increased adrenalin and noradrenaline concentrations known to be involved in lipolysis and body fat regulation (interferon-γ, IFNg, granulocyte macrophage colony stimulating factor, GM-CSF) and acylation stimulating protein, ASP, rather than with changes in hormones such as T3, leptin, insulin or ghrelin. Does the brain play a role in lipolysis via these immune peptides?

Methods: To study the metabolic consequences of UniNX young male Sprague Dawley rats, fed on an isocaloric standard diet, were subjected to either sham-operation or UniNX, and sacrificed at selected time intervals (1, 2, 4 and 6 weeks) after surgery.

Results: In UniNX rats, receptors for the three immune peptides (IFNg, GM-CSF, ASP) were upregulated in the brain stem and hypothalamus at the mRNA level as early as 1 week after surgery and remained elevated throughout the study. Proteins for the IFNg and GM-CSF receptors were also present. mRNA levels of melanocortin 4 receptor (MC4R) were upregulated in the same brain areas. Other studies have shown that central MC4R activation can induce lipolysis in peripheral fat pads via an increase in fat pad phosphorylated hormone sensitive lipase (p-HSL), an increase we also observe in UniNX compared to sham-operated mice.

Conclusion: Our study shows a role of the brain in lipolysis and body fat regulation, in particular the hypothalamus at the mRNA level as early as 1 week after surgery. This might be of relevance for obesity and diabetes, where adrenal steroid-dependent and -independent mechanisms of sodium retention may be at work. Rats harboring a mutation of the glucocorticoid receptor that inhibits dimerization will bring insights to the role of monomer and dimer forms of the receptor in sodium retention mechanisms.

Impact of Uninephrectomy on Body L-Arginine Homeostasis, Enos Function and Blood Pressure Control in Mice

S. M. Pillai, F. Verney
Zurich

Purpose: The proximal tubule of the kidney is the primary site for L-arginine metabolism. In cases of uninephrectomy (UNX), the remnant kidney increases in size and compensates GFR to some degree. The aim of this study is to test the hypothesis that UNX impacts on the metabolism of L-arginine and its metabolite ADMA and thereby also on endothelial NO production and blood pressure control.

Methods: C57/B6 female and male mice were submitted to left UNX or sham operated. Blood pressure was measured using a tail-cuff system, plasma amino acids and other parameters analyzed and kidney mRNA levels of transporters and enzymes involved in L-arginine metabolism determined.

Results: In the first series of UNX conducted for 3 weeks on female mice, the remnant kidney displayed a weight increase of 30%. A higher blood pressure was observed 7 days after UNX compared to sham operated mice (120 ± 1.4 vs. 112 ± 1.9 mm Hg). In terms of transporter expression, no significant changes of transcript levels were observed whereas that of the metabolizing enzyme arginase II was decreased by 48% in remnant kidneys. The changes however appeared to be sex dependent, since UNX males displayed a tendency to stronger increase in remnant kidney weight (36%) and no difference in terms of blood pressure and relative mRNA levels. Determinations of amino acid and ADMA levels and of blood pressure by telemetry are currently under way.

Conclusion: Our observations suggest that UNX affects blood pressure and remnant kidney transcript expression in females, whereas these effects are less pronounced in males. It is suggested that this gender difference is related to the more important remnant kidney compensatory growth observed in males.

Role of the Renal Mineralocorticoid Receptor for Potassium Homeostasis

M. Roesinger1, D. Loffing-Cueni1, C. Ronzaud2, J. Canicola3, O. Staub3, E. Hummler3
1Zurich, 2Lausanne

Purpose: The mineralocorticoid hormone aldosterone (aldo) is released from the adrenal glands upon a dietary K+ load. Aldo enhances renin release via ROMK and stimulates apical epithelial Na+ channels (ENaC) to provide the electrochemical gradient for K+ secretion. Here we studied knockout mice (MRflox/foxg1; MR+/-, MR-/-) for a potential central role of aldosterone in the regulation of renal responses to dietary K+ via the role of the renin-angiotensin system (RAS).

Methods: To test the metabolic consequences of UniNX young male Sprague Dawley rats, fed on an isocaloric standard diet, were subjected to either sham-operation or UniNX, and sacrificed at selected time intervals (1, 2, 4 and 6 weeks) after surgery.

Results: In UniNX rats, receptors for the three immune peptides (IFNg, GM-CSF, ASP) were upregulated in the brain stem and hypothalamus at the mRNA level as early as 1 week after surgery and remained elevated throughout the study. Proteins for the IFNg and GM-CSF receptors were also present. mRNA levels of melanocortin 4 receptor (MC4R) were upregulated in the same brain areas. Other studies have shown that central MC4R activation can induce lipolysis in peripheral fat pads via an increase in fat pad phosphorylated hormone sensitive lipase (p-HSL), an increase we also observe in UniNX compared to sham-operated mice.

Conclusion: Our study shows a role of the brain in lipolysis and body fat regulation, in particular the hypothalamus at the mRNA level as early as 1 week after surgery. This might be of relevance for obesity and diabetes, where adrenal steroid-dependent and -independent mechanisms of sodium retention may be at work. Rats harboring a mutation of the glucocorticoid receptor that inhibits dimerization will bring insights to the role of monomer and dimer forms of the receptor in sodium retention mechanisms.

Methods: The techniques used for the generation of these rats are Zinc Finger Nucleases (ZFNs) and Transcription Activator-Like Effectors (TALENs). Both molecules bind to target DNA and cut it; generating double stranded breaks (DSB). DSBs increase the chances of homologous recombination of up to 1000 fold. A donor plasmid containing the mutated sequence and homology arms allows the insertion of the mutated sequence into the rat genome.

Results: A pair of Zinc Finger Nucleases and five pairs of TALENs were designed. Donor plasmids were constructed either by cloning or synthetization. Vectors expressing the ZFNs or TALENs along with the corresponding donor plasmids were transfected into rat C6 cells. Three TALEN pairs were transfected into rat C6 cells and TALENs showed cutting activity of 20%, which was confirmed by clone screening. First injections of TALEN mRNA into rat oocytes along with the donor plasmid will give F0 pups carrying the mutation. Due to low expression of the ZFN pair, no cutting activity was detected in the rat GR sequence.

Conclusion: TALENs designed and cloned using the REAL method allowed the engineering of TALENs that bind and cut the targeted sequence with up to 20% efficiency, as observed by Surveyor assay. ZFNs and TALENs are both powerful and complementary techniques to generate genetically engineered mice and rats for the study of salt homeostasis.
Minimal Role of Sodium-Calcium Exchanger 1 in Thiazide-Induced Hypocalciuria

W. Li, O. Bonny
Lausanne

Purpose: Thiazide-type diuretics are commonly used in the treatment of calcium-containing kidney stones for their abilities to decrease renal Ca2+ excretion. However, the mechanisms of thiazide-induced hypocalciuria remain debated over whether the enhanced Ca2+ reabsorption occurs in the proximal tubule, the thick ascending limb or the distal nephron. Here, we investigated the role of sodium-calcium exchanger 1 (NCX1), an antiporter for Ca2+ reabsorption in the distal tubule, in thiazide-induced hypocalciuria by using kidney-specific NCX1 knockout mice (NCX1fl/fl, Ksp:Cre+).

Methods: A single dose of 25 mg/kg hydrochlorothiazide (HCTZ) was injected intraperitoneally to NCX1 KO mice and their control littermates. Time-dependent responses to HCTZ were studied on spot urines collected 0, 2, 4, 6 and 12 h after injection.

Results: NCX1-KO and control mice exhibited similar diuretic responses to HCTZ as shown by similar increases in urinary Na+/creatinine ratio and more diluted urines by 2 hours of HCTZ administration compared to vehicle. Concomitantly, Ca2+/creatinine ratio in KO and control mice respectively reduced to 0.26 ± 0.06 (mean ± S.D., n = 5) and 0.45 ± 0.15 (n = 5) by 4 hours of HCTZ treatment, compared to 0.72 ± 0.25 (n = 6) and 0.57 ± 0.18 (n = 5), respectively, by vehicle treatment. The time-dependent changes in urinary Ca2+/Na+ ratio were more pronounced in NCX1-KO and control mice after HCTZ treatment, suggesting similar mechanisms of Ca2+excretion.

Conclusion: Thiazide-induced hypocalciuric effect was maintained in the kidney-specific NCX1-KO mice. The data suggest minimal role of NCX1-dependent pathway in thiazide-induced increase in Ca2+reabsorption.

Sex Differences in Dietary Patterns Associated With Salt Intake at The Population Level

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1Lausanne, 2Zurich, 3Basel, 4Lucerne, 5St. Gallen, 6Locarno, 7Bellinzona, Varese, 8Geneva, 9Rom, 10Freiburg

Purpose: Current recommendations to lower population salt intake are not sex-specific, despite known sex differences in dietary patterns and behaviors. We explored the associations of body mass index (BMI), dietary protein and potassium intakes with dietary salt intake specifically in men and women.

Methods: Cross-sectional population-based survey in 1310 people (51% women) aged 15 years and over from three linguistic regions of Switzerland. Twenty-four hour urine collection was used to estimate dietary salt, potassium and protein intakes. We used multiple linear and logistic regressions to take potential confounders and statistical interactions into account.

Results: Men had higher mean [SD] age (49.4 [18.2] vs 47.1 [18.1] years) and BMI (26.1 [4.2] vs 24.4 [4.8] kg/m²) than women. Men had higher urinary Na, K and urea excretions than women (18 [71] vs 133 [56], 74.5 [25.7] vs 59.0 [21.3] and 434 [143] vs 305 [101] mmol/L/24 h, respectively). Obesity was positively associated with high dietary salt intake (>10 g/24 h) in men (OR [95%CI] = 4.1 [1.92; 8.76], P = 0.001), but less so in women (1.81 [0.75; 4.66], P = 0.18, P interaction<0.05). BMI was associated positively with salt intake in post-, but not in pre-menopausal women. Estimated protein intake was more strongly associated with high salt intake in men than in women (1.84 [1.53; 2.21] vs 1.28 [1.13; 1.48] per 10 g/24h, P int <0.05), whereas the opposite was true for potassium intake.

Conclusion: High protein intake and overweight were associated with high dietary salt intake in Swiss adults, with sex differences. Overall, the results are compatible with a sex-related difference in salt intake, partly related to the role of sex hormones. This might have to be considered when developing a salt reduction strategy at the population level.
Physical Performance and Activity in Hemodialysis Patients Analyzed in a Large Prospective Swiss Dialysis Cohort

R. Winzeler1, L. Walther2, F. Barnert3, M. Vonwiller1, M. Stücheli-Morsinkhov4, B. Sam Aka5, D. Kiss6, P. Ambühl1
1Zurich, 2Baden, 3Lachen, 4Schaffhausen, 5Winterthur, 6Liestal

Purpose: Impaired physical performance and poor physical activity are common problems among hemodialysis (HD) patients. The aim of the present study was to quantify physical capacity and bodily activity in a Swiss HD population.

Methods: 375 patients were evaluated from the monitor! project, a prospective dynamic hemodialysis cohort assessing a wide range of clinical, laboratory and anthropometrical data. Submaximal levels of functional capacity were determined by three-minute walk test (3MWT) and upper body strength (UBS) by a handgrip dynamometer. 24-hour step count and calorie consumption were measured by an armband motion detector (sensewear®, Bodymedia).

Results:

<table>
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<th>Age, yr</th>
<th>CCI*</th>
<th>3MWT, m</th>
<th>UBS, kg</th>
<th>Steps/day, n</th>
<th>Calories/day, kcal</th>
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<td>Min ± SD</td>
<td>67.5 ± 14</td>
<td>3.9 ± 2</td>
<td>158 ± 63</td>
<td>23.4 ± 10</td>
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*) CCI: Charlson comorbidity index

In the study cohort, walking distance (3MWT), but not handgrip (UBS), was reduced by 40 and 50% in male and female patients, respectively, compared to an age matched non-dialysis population. By multivariate analysis 3MWT and 24-hour step count, but not UBS, were inversely and independently correlated with age and comorbidity, but not with time on dialysis.

Conclusion: Age and comorbidity, but not dialysis vintage, are major determinants of impaired physical performance and activity – as determined by walking distance and step count – in a Swiss HD population. In contrast, upper body strength is comparable to healthy individuals. Implications of these findings on functional dependence, quality of life and survival in HD patients need to be studied.

Experience in Recruiting Participants to the Swiss Kidney Project on Genes in Hypertension

S. Tremblay1, G. Gok-Sogut1, D. Siminski1, M.-O. Levy2, U. Schupbach3, S. Estoppey-Younes1, M. Bochud4, The Skipogh Study1
1Lausanne, 2Geneva, 3Berne

Purpose: Family-based studies are costly and difficult to conduct, in particular when they are population-based. We here report our experience in recruiting families from the population for a study including renal ultrasound, ambulatory blood pressure monitoring and 24-hour urine collection.

Methods and results: Nuclear families were randomly selected from the general population in Lausanne, Geneva and Berne. In Lausanne and Geneva, around 400 participants from 100 families were recruited in three years. Recruitment is still ongoing in Berne. The first phone call to explain the purpose of the study lasted from 10 to 40 minutes. Important aspects at first contact were to mention the public source of funding, to listen to participants, to be flexible with appointment visits and to give sufficient time for participants to make their decision. Main reasons for refusal were refusal from family members, familial conflicts, chronic diseases, plan to move away, having done health studies before. People were often difficult to reach during working hours and easier to reach after 6 pm. In Lausanne and Berne, the study included a home visit, which was sometimes difficult to organize for non-retired adults, in particular those with small children. Phenotypes most appreciated by participants were renal ultrasound, ECG and bioimpedance. The clinic visit lasted between 2 and 3 hours. The self-reported prevalence of hypertension and diabetes were 26% and 4.1%. The vast majority of participants (90.1%) considered being in good health.

Conclusions: It is feasible, but challenging and time-consuming, to conduct a family- and population-based study within the Swiss context. Contact strategies play a key role in convincing people to participate to a study with extensive phenotyping.
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