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. Tiercy2, I. Hoessli3, S. Schaumb1
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/C/DRB1 loci was 38% (ratio cut-off), 34% (MFI >300 cut-off), >1 or a mean fluorescence intensity (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: 8%; C locus: 15%; p <0.0001). Some mismatched parental HLA-antigens led to a significantly higher rate of sensitization than the average (e.g. HLA-A2, HLA-B49, HLA-B51, HLA-C15). Furthermore, the mother’s own HLA-phenotype – especially HLA-B homozygosity – was associated with a higher rate and broadness of sensitization.

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.

Complement-Fixation Is Strongly Related to High Mean Fluorescence Intensity Values Of HLA-Antibodies

P. M. L. Amico, G. Höninger, S. Schaub
Basel

Purpose: The aim was to investigate determinants of complement-fixation of HLA-antibodies in the single HLA-antigen bead assay.

Methods: In this analysis, pre-transplant sera of 73 patients were screened for HLA-antibodies by the regular single HLA-antigen (SA) bead assay, a modified SA bead assay detecting complement-fixation (C1q-assay) and IgG1-4 subclasses. Results of the C1q-assay were then correlated with mean fluorescence intensity (MFI) values of the regular SA bead assay and IgG subclass assay.

Results: Out of 8.535 bead results, 1.896 (22%) bead results were positive by regular SA beads (MFI >500). Of these, 407 (21%) bead results were also positive by the C1q-assay (MFI >500). C1q-positive HLA-antibodies had significantly higher SA bead MFI than C1q-negative HLA-antibodies (median MFI: 10,828 [r: 3,316–19,214] vs. 2,127 [r: 501–12,134]; p <0.0001). C1q results were then correlated with MFI values of the IgG1-4 subclasses and the SA bead assay (i.e. pan IgG). By multivariate logistic regression, higher MFI values of pan IgG (OR 20; p <0.0001), higher MFI values of the subclasses IgG1 (OR 20; p <0.0001) and IgG3 (OR 3; p <0.0001) were significantly associated with complement-fixture, whereas the subclasses IgG2 and IgG4 were not (p >0.2).

Conclusion: Complement-fixture is strongly associated with strength of HLA-antibodies (here defined by MFI value). This association is mainly driven by high level HLA-antibodies of the subclasses IgG1 and IgG3, which are known to be complement-activating. Thus, the C1q assay does not provide substantial value beyond the MFI assessed by the regular SA bead assay.

Pathology of Resolving Polyomavirus Nephropathy

Basel

Purpose: Polyomavirus nephropathy (PVN) is a common complication after renal transplantation. Virus control is achieved by a reduction of immunosuppression allowing an effective T cell-mediated antiviral immune response. The morphology of resolving PVN has not been investigated.

Methods: 99 protocol biopsies of 35 patients with BK viremia treated by reduction of immunosuppression only were included and scored according to Banff criteria. The extent of interstitial inflammation was estimated as % of cortex area. The number of tubular cross sections with SV40+ cells per mm of biopsy length was counted. Findings were grouped as pre-, increasing, decreasing, and post-viremia.

Results: During the phase of decreasing viremia, we found a significant increase in the tubulitis score, the extent of tubules with intraepithelial lymphocytes, and interstitial inflammation (p <0.001). These, to a lower extent, persisted after virus clearance. The number of SV40+ tubules correlated with the virus load in the serum, but SV40 immunohistochemistry was frequently negative (33/55 cases), especially if viremia was below log 6 copies/ml.

Conclusion: Resolving PVN is characterized by a self-limiting acute interstitial nephritis. Our findings are important because the diagnosis of interstitial rejection depends on the same morphological criteria. Therefore, acute interstitial rejection cannot be diagnosed with certainty during PV viremia.

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

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Zurich

Purpose: Despite encouraging results of the first clinical studies, a broad application of tolerance induction strategies based on combined solid organ and hematopoietic 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 boosting the role of Ripc3 with a small-molecule BH3-mimetic ABT-737 we were able to induce mixed chimerism with moderate doses of bone marrow cells and without 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.
NEP- Syndrome: A New Genetic Condition with Nephrotic Syndrome, Epidermolysis Bullosa and Pulmonary Disease Based on Integrin A3 Mutation

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Purpose: Integrin-α3 (ITGA3) is a transmembrane integrin receptor subunit mediating signals between cells and their microenvironment. Mutations in integrin genes are associated with different human disorders. We report 3 infants with congenital nephrotic syndrome, skin fragility and interstitial lung disease, who were homozygous for mutations in the ITGA3-gene.

Methods: 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, historically 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.1863G>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 were the presumed causes of the renal insufficiency. The ITGA3 mutations reflect the impact and indispensability of Integrin-α3 concerning the organization of basement membrane and its clinical impact.

Tumor-Associated FGF-23 Induced Hypophosphatemic Rickets in an Eight Year Old Boy

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Basel

Purpose: Tumor-associated Fibroblast Growth Factor 23 (FGF-23) induced hypophosphatemic osteomalacia has primarily been described in adults. In rare 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.

Methods: An eight year old boy was investigated for suspected unilateral painless impingement. Radiographic evaluation showed a large and polylobulated osteolysis in the left iliac bone and acetabulum. Further typical clinical signs of rickets and the respective radiographic and laboratory signs including severe renal phosphate wasting were detected.

Results: Biopsy of the iliac lesion suggested a primary solitary bone cyst overlain by a secondary and solid aneurysmal bone cyst. Laboratory findings, i.e. hypophosphatemia, renal tubular phosphate wasting, normal parathormone and normal calcitriol 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 clearly abnormal FGF-23 plasma levels could not be found. A complete curtailage and stabilization of the iliac lesion were therefore performed and local FGF-23 expression could finally be proven by immunohistochemistry in solid portions of the lesion. After surgery, tubular phosphate absorption normalized immediately and rickets quickly resolved without any further substitution of phosphate or other interventions.

Conclusion: Tumor-associated rickets have only rarely been described in children. Nevertheless this diagnosis has to be considered in pediatric patients with acquired hypophosphatemic rickets beyond infancy.

Severe Hyperkalemia in a Patient With Chronic Hemodialysis Following Colon Diversion Surgery

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Basel

Purpose: 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.

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

Results: A 56 year-old-woman with ESRD undergoing HD suffered from ischaemic colitis, leading to ileocaecal resection and temporary ileoascendostomy. 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, serum K+ level remained high (6.1–7.9). Six month 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.

Dialysis for Two – The Zurich Dialysis Pregnancy Experience In 2012

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Zurich

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

Methods: Case-report of a successful pregnancy in a hemodialysis patient.

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 pelvic system on the right side. A suspected pyeloureteral stenosis and a toxic injury by streptomycin (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 19000 IU/week. With the advancement of the pregnancy, dialysis was intensified to 21 hours/week divided into six sessions per week. With the advancement of the pregnancy, dialysis was intensified to 21 hours/week divided into six sessions per week. With the advancement of the pregnancy, dialysis was intensified to 21 hours/week divided into six sessions per week. With the advancement of the pregnancy, dialysis was intensified to 21 hours/week divided into six sessions per week. The patient made a good recovery and her dietary intake was maintained mainly by urinary excretion of K+, which is almost equal to the amount of dietary K+-ingestion.
OC10

**Stimulated Sweating as a Therapy To Reduce Interdiastolic Weight Gain and Improve Potassium Balance in Chronic Hemodialysis Patients: A Pilot Study**

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**Lausanne, *StVitN***

**Purpose:** Controlling the extracellular volume in hemodialysis patients is a difficult task. The aim of this study was to evaluate the capacity of different methods of stimulated sweating to reduce mean interdiastolic weight gain (IWG), to improve blood pressure regulation and potassium/urea balance.

**Methods:** Two center, cross over pilot study. In Lausanne, hemodialysis patients took four hot water baths a week of 30 minutes each, on non-diary-days during one month. In Sfax, patients visited four times a week the local hammam-center. Hemodynamic parameters were recorded, and weekly laboratory analysis performed.

Results were compared with a preceding one-month control period.

**Results:** In Lausanne, five patients (all men, median age 55y) participated. Bathing temperature was (mean ± SD) 41.2 ± 3 °C and sweating-induced weight loss 600 ± 500 g. Mean IWG (control versus intervention period) decreased from 2.3 ± 0.9 to 1.8 ± 1 kg (p = 0.004), SBP from 139 ± 21 to 136 ± 22 mm Hg (p = 0.4), and DBP form 79 ± 13 to 76 ± 17 mm Hg (p = 0.4). In Sfax (n = 9, median age 46y), weight loss per hamman session was 420 ± 100 g. No differences were found in IWG or BP, but pre-dialysis serum potassium level decreased from 5.9 ± 0.8 to 5.5 ± 0.9 mmol/l (p = 0.04) and urea from 26.9 ± 6 to 23.1 ± 6 mmol/l (p = 0.02).

**Conclusion:** Hot water baths appear to be a safe way to reduce interdiastolic weight gain in selected haemodialysis patients. More data in larger patient groups are necessary before definite conclusion can be drawn.

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**Klotho as a Prognostic Marker in Patients on Maintenance Hemodialysis**

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**Purpose:** Circulating Klotho has been identified as one of the key hormones regulating calcium-phosphate metabolism, and, potentially, as a protective factor against atherosclerotic vasculopathies. The aim of this study was to investigate the relationship of Klotho with survival on chronic maintenance hemodialysis (HD) therapy.

**Methods:** Baseline Klotho levels were measured in the year 2006 from 150 chronic maintenance HD patients, aged 67 ± 13 years with a dialysis vintage of 6.4 ± 3 years, enrolled in the *monitor!* study, a prospective cohort of HD patients. Klotho baseline levels were correlated with age, gender, medical and biological parameters.

**Results:** Sixty two (41%) patients died during follow-up of 855 ± 429 days. Survivors were younger, had a higher body weight, a higher number of comorbidities, and were more likely to be on vitamin D supplements. Klotho plasma levels were similar between survivors and non-survivors (404 ± 173 versus 380 ± 204 pg/ml, respectively; P = 0.439). Klotho was negatively correlated with age, number of comorbidities, and LDL-cholesterol, and positively correlated with serum alkaline phosphatase and PAPP-A. In a multivariable logistic regression model including Klotho along with the covariates mentioned before, only age, PAPP-A and vitamin D therapy were independently predictive for survival. The lowest tertile of Klotho levels was associated with a trend towards a higher vitamin D supplementation rate, whereas Klotho did not correlate with serum calcium, phosphate, PTH and cardiovascular risk biomarkers such as IL-6, BNP, and CRP.

**Conclusion:** Klotho does not predict survival in chronic HD patients. Klotho is inversely related to age, and may be modified by vitamin D treatment, but is unrelated to biomarkers of bone mineral metabolism, except for alkaline phosphatase.

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**The Spectrum of Podoplanin Expression in Encapsulating Peritoneal Sclerosis**

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**Purpose:** Podoplanin is a glycoprotein expressed by mesothelial cells, lymphatic endothelial cells, and myofibroblasts in peritoneal biopsies from patients with encapsulating peritoneal sclerosis (EPS). To further evaluate podoplanin as a marker of EPS we measured podoplanin mRNA levels and described the morphological patterns of podoplanin-positive cells in EPS.

**Methods:** Included were 20 peritoneal biopsies from patients on PD with the diagnosis of EPS (n = 5), patients on PD without signs of EPS (n = 5), and control patients (n = 10). In 24 peritoneal biopsies with EPS, podoplanin and smooth muscle actin (SMA) were localized by immunohistochemistry.

**Results:** Patients with EPS biopsies revealed a significantly elevated levels of podoplanin mRNA (p <0.05). The most common podoplanin pattern (8 of 24) consisted of organized, longitudinal layers of podoplanin-positive cells and vessels in the fibrotic zone (“organized” pattern). 7 of 24 biopsies demonstrated a diffuse distribution of podoplanin-positive cells. Five biopsies exhibited a “mixed” pattern. These contained cuboidal podoplanin-positive cells within SMA-negative epithelial structures embedded in extracellular matrix. Less frequently observed was the complete absence of, or only focal accumulations of podoplanin-positive fibroblasts outside of lymphatic vessels (podoplanin “low”; 4 of 24 biopsies). Patients in this “low” group exhibited a lower index of systemic inflammation and a longer symptomatic period than in EPS patients with biopsies of the “mixed” type (p <0.05).

**Conclusion:** In summary we describe a novel cell differentiation process involved in EPS, confirm the increased expression of podoplanin in EPS, and distinguish EPS biopsies according to different podoplanin expression patterns which are associated with clinical parameters.
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 hyperuricemia 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. Of the 15 loci that achieved genome-wide significance, one loci was close to a peak signal in the GWAS.

Results: 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.
Daytime Sleepiness Associated with Immunosuppressive Non-Adherence in Renal Transplant Recipients: A Cross-Sectional Multi-Center Study

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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 Ewpworth 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 DS. A 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 2%, timing 18% and overall NA by 18%.

Conclusion: There is an association between DS and immunosuppressive NA in transplantation. This a novel finding that provides better understanding of NA, especially in view of non-intentional NA where forgetfulness is a driving factor.

Factors associated with quality of ambulatory blood pressure monitoring in the population-based SKIPOGH study

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Purpose: Ambulatory blood pressure monitoring (ABPM) has limited success rates which impacts population-based studies. We hypothesized that certain participants’ characteristics can be identified, which are associated with quality of ABPM.

Methods and results: Families were randomly selected from the general adult population in Lausanne, Geneva, and Bern. Validated Diasys Integra devices were used for ABPM. We used generalized estimating equations with a logit link and binomial distribution to explore predictors of having less than 80% valid measurements. We included 320 men and 325 women. The mean (SD) age was 47.6 (17.8) / 49.8 (16.9) years respectively, the mean BMI was 26.2 (4.4) / 24.1 (4.5) kg/m² and the mean (SD) number of measurements over 24-hour was 69 (13). The prevalence of overweight and obesity were 33% and 13%, respectively. Twenty-five percent of participants had less than 80% valid ABPM measurements. Main predictors of having less than 80% valid measurements were age older than 60 years (OR [SE] = 1.69 [0.41], P = 0.03), being obese (OR [SE] = 1.97 [0.55], P = 0.03), and having low pulse pressure (OR [SE] = 0.96 [0.01] per mm Hg, P <0.001). The association with obesity became non-significant upon adjustment for arm circumference.

Conclusions: In conclusion, selected characteristics of participants were identifiable that limit the accomplishment of an integral ABPM. Specifically, this was older age, obesity, and low pulse pressure. The effect of obesity was largely explained by large arm circumference. These results can help guiding nurses when instructing participants before monitoring.

Functional dependence related to physical activity in hemodialysis patients analyzed in a large prospective Swiss dialysis cohort

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Purpose: Functional impairment in hemodialysis (HD) patients has been suggested to severely impact on survival and quality of live (QoL). The aim of the present study was to analyze physical capacity and bodily activity in relation to functional status 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. Functional status was determined by the indices for activity of daily living (ADL, “Barthel score”), the instrumental activity of daily living (IADL) and the social adaptability index (SAI). Physical capacity was measured by three-minute walk test (3MWT), upper body strength (UBS) by a handgrip dynamometer and 24-hour step count by an armband motion detector.

Results: Mean scores for ADL, IADL and SAI were 92 ± 14, 5.4 ± 2, and 6.7 ± 2, respectively, indicating relevant impairment in functional activities of daily live and social adaptability. All 3 scores are closely and significantly correlated to each other.

Conclusion: Functional dependence is high in this Swiss HD cohort and directly related to physical impairment and physical quality of life. Measures should be taken to improve physical capacity and activity in order to reduce functional impairment and, thereby, improve outcomes in quality of life and survival in HD patients.

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<th>ADL score, median</th>
<th>Age, yr</th>
<th>CC1*</th>
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<td>Low</td>
<td>70.5 ± 13</td>
<td>4.1 ± 2</td>
<td>130 ± 62</td>
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<td>High</td>
<td>66.3 ± 14**</td>
<td>3.6 ± 2**</td>
<td>179 ± 55**</td>
<td>27 ± 10**</td>
<td>3313 ± 3168**</td>
<td>41.6 ± 11**</td>
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*) Charlson comorbidity index; **) P <0.05 vs. “low ADL.”
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 undergoing non-invasive-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, and (iii) isolated vascular compartmental inflammation.

**Results:** sCD30 correlated well with the extent of clinical rejection 
(p < 0.0001) but not subclinical tubulo-interstitial rejection (p = 0.06). To determine diagnostic characteristics, ROC calculations indicated that sCD30 histological groups had 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 compartmental 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.

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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 (Oxford Immunotec, UK) and QuantiFERON-Gold-In tube (QGIT, Cellestis, 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. Positivity rate was 49% 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:** Since the sensitivity for detecting probable latent tuberculosis infection in renal transplant recipients is very low, IGRAs will not contribute to exclude such an infection. It remains therefore mandatory to diagnose and treat latent tuberculosis infection before transplantation.

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Feasibility of T-Track® CMV and T-Track® EBV to Assess the Functionality of Virus-Specific Cell-Mediated Immunity (Cmi)

1Regensburg/DE, 2Mannheim/DE, 3Schwandorf/DE

**Purpose:** Epstein-Barr virus (EBV) infections are effectively controlled by cell-mediated immunity (CMI). Inadequate impairment of CMI by immunosuppressive treatment after transplantation (tx) occasionally causes late EBV reactivation potential coincident with serious complications (PTLD). The prospective pilot study aimed to investigate the suitability of (u)BZLF1 to monitor functional EBV-reactive CMI in kidney transplant recipients in the course of immunosuppressive treatment.

**Methods:** We performed a 2-year prospective observational study in 83 patients, of whom 92.8% had a positive EBV serostatus. Blood was collected pre and post tx to measure functional (u)BZLF1-reactive effector cells with an IFN-γ ELISpot. EBV load was determined from serum by quantitative PCR.

**Results:** Prior to tx, a significant (u)BZLF1-reactive CMI was detected in 63.8% of EBV-seropositive patients followed by a substantial decrease within the first 3 weeks post tx. In some patients, EBV-specific CMI started to recover in month 6 to 18. Transparent and weak, clinically inapparent EBV-reactivations occurred in 53% of the patients. Individual patient courses revealed that reactivations appeared preferentially at time points with low numbers of (u)BZLF1-reactive leukocytes.

**Conclusion:** Monitoring of functional (u)BZLF1-reactive CMI may be an interesting novel strategy to assess the risk for EBV-reactivation in immunocompromised transplant recipients.

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Serum CXCL10 and Vascular Lesions in Surveillance Biopsies

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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 CXCL10 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 infiltration (n = 16), (iii) vascular infiltration (n = 16). Serum CXCL10 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 CXCL10 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 CXCL10 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 apoptosis of RNL.

Methods: In this single-centre study, we retrospectively analyzed the effects of pregnancy in our cohort of kidney transplant recipients. The variables studied were: type of nephropathy, living donors (LD) vs. deceased donors (DD), age, time between Tx and pregnancy, immunosuppressive treatments, creatinine/blood pressure/urinary protein/creatine at conception and at different time-points during and after pregnancy, complications including infectious events, anti-HL antibodies, rejection episodes, gestation time, type of delivery, baby birth weight.

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 insures best outcome for mother and fetus.

Poster Presentations – Transplantation
Teft 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 Th1 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.

Luminex Prozone Effect Demonstrated in Vitro and in Vivo: Clinical Implications
S.-R. Wassmer, M. Bonani, T. Fehr*Zurich
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 PDN. After 13 days AMR occurred. Immunosorsption (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 DQ7 after IADS, the prozone effect was considered and retrospectively confirmed by serum dilution.

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.

Urinary Neutrophil Gelatinase-Associated Lipocalin Does not Predict the Occurrence of Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronography
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 shown to be a marker of acute kidney injury and a potential marker for CI-AKI. We, therefore, tested whether there is a correlation between uNGAL and CI-AKI.

Methods: We enrolled 244 consecutive patients undergoing PCI with iomeproolum 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 coronary arteriography. 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 (6.4 [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 coronaryography did not predict renal toxicity, and did not correlate with the volume of contrast medium used during the procedure.

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. Mohaupt1, H. Zimmermann1, A. K. Exadaktylos1, G. Lindner*Bern, Vienna/AT, Graz/AT
Purpose: Although hyponatraemia 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 hospitalisation 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 diuretics (p values 0.02, 0.02 and <0.01 respectively) was significantly more common among OF patients. The prevalence of hyponatraemia increased with the number of diuretics taken by the patients (p <0.0001). The use of SSRI and antiepileptic drugs between both

Case Report: Plasma Exchange in Lupus-Like Syndrome With Very High MPO-ANCA
S. Kalibermatter1, T. Öttl1, K. König1, I. Heijnen2, D. Kiss1*Liestal, “Basel
Purpose: A 43-year-old woman with a history of fatigue and swollen lymph nodes for three months, developed anemia and underwent a biopsy of a lymph node which revealed only a reactive lymphadenopathy. Due to increased serum creatinine and proteinuria in the nephrotic range she was transferred to our hospital. Pulse rate was 68 bpm and RR 117/77. C-reactive protein (CRP) was not elevated, S-Cr 174 µmol/l, albumine 27 g/l, hemoglobin 102 g/l, erythrocyte sedimentation rate 81 mm/h.

Methods: Renal biopsy revealed a diffuse segmental accentuated proliferative immune complex glomerulonephritis with crescents in four of 19 glomerula. Electron microscopy showed tubuloreticular structures within the endothelial cells. Myeloperoxidase Antineutrophil Cytoplasmatic Antibodies (MPO-ANCA) were elevated to 3622U/ml (<5), anti-nuclear antibodies (ANA) titer 1:80, Anti-SS-A/Ro52 22U/ml (<10), Anti-SS-A/Ro60 >240 U/ml, complement C3c 0.2 g/L (0.8–1.8), C4 0.01 g/L (0.1-0.4); CH50 14U Eq/ml (70–180). The vasculitis was not to classify, because there was a typical clinical presentation and compatible histopathologic findings for a systemic lupus, but an atypical presentation of the antibodies. We started a treatment with pulses of intravenous cyclophosphamide and oral methylprednisolone (1 mg per kg) without any improvement of the kidney function or the proteinuria. To eliminate the MPO-ANCA suspected to play a major role in the pathogenesis we performed five high volume (5000 ml) plasma exchanges (PE). After the PE S-Cr decreased from 324 to 237 µmol/l and MPO-ANCA from 3622 to 114U/ml.

Results: To our knowledge this is the first case with a lupus like syndrome and extremely high MPO-ANCA.

Conclusion: PE may improve outcome of lupus like syndrome with very high levels of MPO-ANCA.
Determinants of Renal Artery Resistive Indexes in the Swiss Kidney Project on Genes in Hypertension (SKIPOGH)

B. Ponte1, M. Pruim2, D. Ackermann2, P. Vuistinier1, U. Eisenberger1, M. Mohaupt1, B. Vogt2, F. Paccoud1, M. Burnier1, P.-Y. Martin1, M. Bochud1

Purpose: Recent evidence suggests that the renal resistance index (RI), defined as the percentage reduction of arterial end-diastolic flow compared as 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 48.9 ± 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 a 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 vasoactive effects of potassium and protein intake on renal arteries.
374, age 47 ± 18 years, BMI 26.2 ± 4 kg/m², eGFR 98 ± 18 ml/min/1.73 m², and 10.7 ± 0.8 cm in women (age 48 ± 17 y, BMI 24.5 ± 5, eGFR 95 ± 17). There was no significant difference in length between the right and left kidney. In multilevel adjusted linear regression analysis, body height, weight, and eGFR were positively associated with kidney length, whereas gender, diabetes, and hypertension were not. There was a quadratic association between age and kidney length. The heritability (h²) of kidney length, adjusted for confounders, was 52 ± 8% (p = 0.01).

Conclusion: This study suggests that kidney length is an inherited trait, independently 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. Piskunowicz1, M.-E. Muller1, M. Stuber1, B. Vogt1, M. Burnier1, R. Bingisser2, B. Drexler2, C. Meune2, D. Marono2, T. Mosimann2, A. Nowak1, T. Breidthardt2, S. Dejung1, M. Christ-Crain2

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 95 ± 17). There was no significant difference in length between the right and left kidney. In multilevel adjusted linear regression analysis, body height, weight, and eGFR were positively associated with kidney length, whereas gender, diabetes, and hypertension were not. There was a quadratic association between age and kidney length. The heritability (h²) of kidney length, adjusted for confounders, was 52 ± 8% (p = 0.01).

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

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

A. Nowaki1, T. Breithardt2, S. Dejung3, M. Christ-Crain4, R. Bingisser5, B. Drexl6, C. Meune7, D. Marono8, T. Mosimann9, B. Müller9, C. Mueller9

Zurich, 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%) within the first 48 hours. NPs and creatinine were 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.

Table 1

<table>
<thead>
<tr>
<th>Predictor of acute kidney injury development.</th>
<th>Multivariate logistic regression</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Multivariate logistic regression</td>
<td>OR</td>
<td>p-value</td>
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<tr>
<td>NT-proBNP</td>
<td>1.01 (1.00–1.01)</td>
<td>0.009</td>
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<tr>
<td>Creatinine</td>
<td>1.00 (1.00–1.01)</td>
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<tr>
<td>CKD</td>
<td>1.92 (0.65–5.66)</td>
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<tr>
<td>PSI</td>
<td>1.00 (0.99–1.02)</td>
<td>0.72</td>
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</table>
Evaluation of a Novel Diagnostic and Treatment Algorithm for Hyponatraemia

A. Bock1, A. Huber2, C. Blum2, C. Nicken1, P. Schuetz1, M. Bally1, B. Anic2, I. Suter-Widmer2, B. Winzeler2, N. Nigro2, B. Müller1, M. Christ-Crain1

1Aarau; 2Basel

Purpose: Correctly diagnosing the cause of hyponatraemia is a frequent challenge in the emergency room setting, because appropriate therapy (water restriction; NaCl infusion) depends on the cause. Existing algorithms rely 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 hyponatraemia (<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 the ADH precursor peptide copeptin.

Results: Of 37 eligible patients, 9/16 presented with normal hypovolemia (3/16 erroneously as “SIADH”), 5/6 patients with some evident signs of volume overload (Edema/Ascites/Orthopnea) as well as evident volume overload were associated with accuracies far below the KDOQI targets of 90%, present poor Spearman correlations. For an accuracy of 10%, only 6, and 27% of the eGFRs are accurate when using the MDRD, CKD-EPI, and Cockcroft–Gault formulas, respectively, being accurate.

Conclusion: Based on our results, the performances of all these formulas are unreliable for eGFR in children across all CKD stages and are associated with accuracies far below the KDOQI targets of >90% needed for validation. These formulas cannot be applied in children, therefore confirming the NKF–KDOQI recommendations.

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, kidney 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 mmol/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 2+ protein, 1+ glucose and a urine protein/creatinine ratio of 131 mg/mmol. Hemoglobin was 106 g/L, C-peptide <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 include 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.

Renal Phosphate Handling in Gitelman Syndrome – The Results of a Case-Control Study

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1Bellinzona; 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.

Assessment of Adult Formulas for Glomerular Filtration Rate Estimation in Children

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1Lausanne; Geneva

Purpose: Estimated glomerular filtration rate (eGFR) is an important diagnostic instrument in clinical practice. The NKF–KDOQI guidelines do not recommend using formulae developed for adults to estimate GFR in children; however, studies confirming these recommendations are scarce. The aim of our study was to evaluate the accuracy of the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, the Modification of Diet in Renal Disease (MDRD) formula, and the Cockcroft–Gault formula in children with various stages of chronic kidney disease (CKD).

Methods: A total of 550 inulin clearance (iGFR) measurements for 391 children were analyzed. The cohort was divided into three groups: group 1, with iGFR >90 ml/min/1.73 m²; group 2, with iGFR between 60 and 90 ml/min/1.73 m²; group 3, with iGFR of <60 ml/min/1.73 m².

Results: All formulas overestimate iGFR with a significant bias (p <0.001), present poor accuracies, and have poor Spearman correlations. For an accuracy of 10%, only 11, 6, and 27% of the eGFRs are accurate when using the MDRD, CKD-EPI, and Cockcroft–Gault formulas, respectively, being accurate.

Conclusion: Based on our results, the performances of all of these formulas are unreliable for eGFR in children across all CKD stages and are associated with accuracies far below the KDOQI targets of ≥90% needed for validation. These formulas cannot be applied in children, therefore confirming the NKF–KDOQI recommendations.

Varicella-Zoster-Virus Vascularopathy Presenting as a Stroke After Kidney Transplantation

I. Koneth, G. Kaege, 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,
no meningism, normal blood analysis. MRI showed acute ischemic infarction in the pons and subacute ischemias in the pedunculus cerebelli and corpus callosum. Because of the subacute aspect of most lesions, lysis was not performed. CSF showed mononuclear pleocytosis, high proteins and normal glucose. Inhalation 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 halfdose IV acyclovir administered at a dose of 30 mg/kg 3 times a day until switched to oral valacyclovir 1 g bid. After 4 months neither VZV PCR in liquor nor new ischemias in MRI were detectable, prophylaxis with valacyclovir 500 bid was installed. 6 months after the acute illness a mild weakness of the left upper extremity and deficits in memory and attention persist.

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

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

K. Günther, C. Bucher, G. Kaege, I. Binet

**St. Gallen**

**Purpose:** Posterior reversible encephalopathy syndrome (PRES) is characterized by acute onset of headache, nausea, seizures, altered consciousness and retinal disturbances along with thickening of the glomerular basement membrane. Heterozygous defects in COL4A3 or COL4A4, mainly of symmetric white matter defects in the parietal and occipital lobes. Nephritic syndrome, chronic and acute kidney disease, HUS, organ transplantation, immunosuppressive therapy, autoimmune diseases and electrolyte 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), hypocalcemia (iCa 1.05 mmol/l) and metabolic alkalosis were present. The second patient is a 21 year old man on chronic hemodialysis due to IgA-nephropathy and under immunosuppression with steroids and cyclophosphamide. He presented with a first dyscognitive seizures followed by a bilateral clonic-tonic seizure. The MRI showed multiple bilateral T2-weighted hyperintense signal cortical and subcortical, tempoparietal 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. Grendelmeier1, 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 is thinning of the glomerular basement membrane. The prognosis is good with occasional patients presenting with slowly progressive renal impairment or even on dialysis. New data suggest that this may be more common than previously suggested.

**Methods:** We report of a family with hematuria and autosomal dominant inheritance.

**Results:** 3 younger individuals had biopsy proven TBMN and different degrees of FSGS. One of them with significant hematuria (>50% of those with family history) with usual benign course and therefore also called “benign familial hematuria.” The only finding on renal biopsy is thinning of the glomerular basement membrane. The prognosis is good with occasional patients presenting with slowly progressive renal impairment or even on dialysis. New data suggest that this may be more common than previously suggested.

**Conclusion:** In conclusion TBMN is a common cause of familial hematuria and is caused by diffuse thinning of the glomerular basement membrane. Heterozygous defects in COL4A3 or COL4A4, the genes that encode for the alpha-3 and alpha-4 chains of collagen type IV, are responsible for this disorder in 40–50% of affected families. Those can be considered as “carriers” of autosomal recessive Alport syndrome. In most patients prognosis is excellent, however, some patients develop proteinuria. In these cases we recommend renal biopsy, close follow-up and treatment of those individuals who obviously exhibit progressive renal disease course.

**P32**

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

L.-Y. Mani, B. Vogt, D. Golshayan

**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 umol/l and moderate systemic inflammation, urinalysis was normal.

**Methods:** The CT scan showed multiple thoraco-abdominal adenopathies, lung micronodules 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 radiologic signs of granulomas on renal as well as splenic arteries. Based on these findings, the diagnosis of sarcoidosis was made. High dose steroids were started followed by azathioprine together with anti-hypertensive drugs.

**Conclusion:** Sarcoidosis is an inflammatory multisystem 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 sarcoidosis, the main finding being granulomatous interstitial nephritis. Granulomatous angitis and in particular renal vasculitis is a very rare manifestation of sarcoidosis.

**P33**

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

A. Nowak, K. Göhner, C. D. Cohen

**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 asymmetric arthritis, myalgias as well as appetite 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-neutrophilic 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 deposits, 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 immunological 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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*Basel, 2Lucerne*

**Purpose:** Cryoglobulinemia induces an immune complex-mediated glomerulonephritis that is characterized by the presence of large immune deposits, including complement C3 and C5b-9, 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 in a patient with partial cytocoglobinemia type II. The clinical features included relapsing proteinuria and renal function impairment that were controlled by plasmapheresis. Complement was low in plasma and two renal biopsies at one-year interval showed prominent immunoglobulin deposition 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 renal function 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.

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

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**Berne, 2Zürich**

**Purpose:** Hemolytic uremic syndrome (HUS) is a leading cause of acute renal failure in children. STEC is an emerging pathogen in this community and is responsible for an increasing number of cases as detected by an episode of diarrhea mostly due to 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 be a primary cause of neonatal HUS.

**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. The child was rehydrated, the fever decreased, and she was discharged home. Two weeks later it occurred again. The blood tests showed a drop in platelet count, leukocytosis, an increase of creatinine, decreased hemoglobin, leukocytosis, and elecrophoresis, and harboring stx2B. Shiga-toxin Stx2B is of low affinity, STEC is indistinguishable by microarray analysis, and pulsed-field gel electrophoresis, and harboring stx2B. Shiga-toxin Stx2B is of low affinity. STEC can also be a primary cause of neonatal HUS.

**Conclusion:** STEC can also rarely lead to neonatal HUS.

**Chicken Pox in a Varicella Vaccinated Hemodialysis Patient With Isopropyl Alcohol Ingestion**

M. T. Tuftal Hanel, T. Klima, A. Bock

**Aarau**

**Purpose:** Isopropyl is a common source of clinical intoxication. Acute renal failure due to Isopropyl ingestion is rare. We describe a patient, who ingested Isopropyl and presented with renal failure.

**Methods:** A 39 year old female with a history of alcohol abuse was treated 2003. Kidney transplant failure and start of dialysis followed Ciclosporin when B-Cell Non Hodgkin Lymphoma was successfully treated 2003. Kidney transplant failure and start of dialysis followed. In February 2012 his unvaccinated brother with no history of VZV varicella zoster infection before, fell ill with chicken pox. Two weeks later our patient presented with primary VZV infection – Vesiculo papular rash, fever, head- and muscle pain. VZV-IgG-level was <0.60. (IndexImmun >0.89). While on therapy with Valaciclovir 500 mg twice daily for an other week he fully recovered within three weeks.

**Results:** Isopropyl Intoxication can elevate creatinin by:

- interference of acetone with the colorimetric assay
- Enzymatic assays and Cystatin C assays are not interfered by acetone

**Conclusion:** Isopropyl-poisoning, Cystatin C should be used to verify renal function.
Resetting of Kidney Renin-Angiotensin, Kallikrein-Kinin, and Catecholamine Systems After Unilateral Renal Denervation

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1Freiburg, 2Berne, *Lausanne

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(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). Catecholaminergic or sensory nerve fibers were absent in denervated kidneys. Left denervated kidneys showed lower AI (39.5%), AII (31.5% 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 (23.5% (56%), D (28.6%), and NE (90.2%) levels vs. sham right kidneys (p <0.05). mRNA levels of D-decarboxylase (DDC), D-β-hydroxylase, eNOS-synthe (ENO) and transforming growth-factor β (TGFβ) were higher (22–59%) in denervated vs. right (p = NS) or sham kidneys (ENO, p <0.05; DDC, TGFβ); A-substrate and converting enzyme were unchanged.

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

Pregnancy Outcome Following Exposure to Angiotensin- Converting Enzyme Inhibitors or Angiotensin Receptor Antagonists: A Systematic Review

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Purpose: The objective was to analyze the outcome following prenatal exposure to angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor antagonists (ARBs).

Methods: For this purpose, a systematic review of published cases reports and case series dealing with intrauterine exposure to ACE-Is or to ARBs using Medline as source of data was performed. The publications retained for analysis included patients who were described individually, revealing at minimum the gestational age, substance used, period of medication intake and the outcome.

Results: In total, 72 reports were included: 37 articles (118 well-documented cases) described the prenatal exposure to ACE-Is and 35 articles (68 cases) described the prenatal exposure to ARBs. Overall, 52% of the newborns exposed to ACE-Is and 13% of the newborns exposed to ARBs did not exhibit any complications (p <0.0001). Neonatal complications were more frequent following exposure to ARBs and included renal failure, oligohydramnios, death, arterial hypertension, intrauterine growth retardation, respiratory distress syndrome, pulmonary hypertension, necrotizing enterocolitis, limb defects, persistent patent ductus arteriosus or cerebral complications. The long-term outcome is described as positive in only 50% of the exposed children.

Conclusion: Fetalopathy caused by exposure to ACE-Is or ARBs has relevant neonatal and long-term complications. The outcome is poorer following exposure to ARBs. We propose the term “fetal renin-angiotensin system blockade syndrome” to describe the related clinical findings. Thirty years after the first description of ACE-I fetopathy, relevant complications are at present regularly described, indicating that the awareness of the deleterious effect of prenatal exposure to drugs inhibiting the renin-angiotensin system should be improved.

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 that leads to the conversion of preadipocyte to mature adipocyte. We and others have demonstrated that geldanamycin analogues have a potent inhibitory effect on MR and GR signaling. Geldanamycin analogues are anti-tumor antibiotics used in phase II clinical trials in cancer treatment. They bind to the chaperone protein Hsp90 and, by altering its function, render steroid receptors insensitive to their ligands.

Methods: Given that the expression and activity of MR and GR are crucial for adipogenesis, we investigated whether geldanamycin analogues have an effect on adipocyte differentiation in vitro and in vivo.

Results: We found that early exposure of preadipocyte cells to geldanamycin analogues inhibits their adipocyte conversion, by inhibiting the adipogenic transcriptional program and lipid droplets accumulation into the cell. In vivo, the weight gain of mice treated with geldanamycin analogue is significantly lower than control mice. This difference in body weight is explained by a reduction of fat mass and not in lean mass or water, as evidenced by evaluation of the body mass composition. Biochemical analysis revealed that anti-adipogenic effects of geldanamycin analogues are related to an inhibition of MR activity and a reduction of GR expression.

Conclusion: Taken together, our observations lead us to propose geldanamycin analogues as potent therapeutics not only in cancer treatment but also in the control of obesity and all its related metabolic complications.

Renal Alterations in the Post Partum After a Preeclampsia

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1Geneva, 2Lausanne

Purpose: Preeclampsia is a hypertensive disorder of the pregnancy defined by BP ≥140/90 mm Hg and proteinuria >0.3 g/24 h, or 2+ on dipstick, occurring after 20 weeks gestation. Epidemiological data underscore that preeclampsia is not just a disease of pregnancy that resolves with delivery, but may be considered a risk marker for later-life diseases, including cardiovascular and renal diseases and the metabolic syndrome.
Methods: Longitudinal prospective observational cohort study to analyze the renal abnormalities in the post-partum in 182 women having suffered from preeclampsia. Office and 24th ambulatory BP, renal function, ultrasonic CRP, urine spot and 24th collect and genetics were obtained at 28e and 3mo 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 we, urine albumin/creatinine ratio was 10.8 [4.7] mg/mmol. The 24th urine excretion of albumin was 216.7 [97.1] mg/dL. GFR estimated with the Cockcroft formula was 149 ml/min [11.9]. Ultrasensitive C reactive protein was 12.7 [7.1]. The prevalence of hypertention or ongoing antihypertensive treatment was 36%. Ambulatory blood pressure daytime was (ystolic/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 and renal function in the postpartum. The prevalence of both office and ambulatory hypertension seems to be very high together with an elevated excretion of microalbuminuria and some degree of renal infiltration. These women have to be identified and targeted in order to establish an efficient prevention and to impact throughout the postpartum course.

Poster Presentations – Dialysis

P46

Troponin T for the Detection of Dialysis-Induced Myocardial Staining in Hemodialysis Patients
T. Breidhardt1, J. O. Burton2, A. Odetu3, M. T. Edelstein4, H. J. Jefferyes1, C. W. McIntyre3
1Basel, 2Darby/UK

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 stunning and troponin T levels in unselected 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. Dialysis was performed using Hospal Integra monitors (Hospal, Mirandola, Italy). Dialysate 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 of 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.

Results: The median troponin T level in this hemodialysis cohort was 0.06 ng/ml (interquartile range, 0.02–0.10). At baseline, 64% of patients experienced myocardial stunning. These patients showed significantly higher troponin T levels than patients without stunning (0.08 ng/ml [0.05–0.12] versus 0.02 ng/ml [0.01–0.05]). Troponin T levels were significantly correlated to measures of myocardial stunning severity (number of affected segments: r = 0.26; change in ejection fraction from beginning of dialysis to end of dialysis: r = 0.20). In receiver operating characteristic analyses, predialytic troponin T achieved an area under the curve of 0.82 for the detection of myocardial stunning. In multivariable analysis, only ultrafiltration rate and potassium levels correlated inversely with troponin T levels.

Conclusion: Our results indicate that troponin T is a useful marker for the detection of myocardial stunning in HD patients. Further studies are needed to investigate the clinical implications of this finding.
Prevalence of Tunneled 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 their domiciliary renal replacement 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 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.

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

F. Stubber, J. Pugin, J. Tatwat, B. Ponte, L. Brochard, P-Y. Martin, P. Saudan
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 their domiciliary renal replacement 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 aspecic catheter manipulation technique.

Results: From 10.2010 until 04.2012, 52 out of 120 patients treated with CRRT were randomized (exclusion criteria were active hemorrhagic disorders or severe thrombocytopenia [21%], terminal liver failure [9%], chronic maintenance dialysis [25%] or others [45%]). Mean age was 60 ± 9 years. Etiology of AKIs were medical (77%), surgical (23%). Mean CRRT duration was 5 ± 5 days. Effective daily RRT dose was 96 ± 12% in the RCA group and 85 ± 15% in the heparin group (p = 0.057). 28-days mortality was 29% in the RCA group and 27% in the heparin group.

Conclusion: These preliminary results seem to show an advantage of RCA over heparin-based anticoagulation in terms of effective daily delivered RRT dose.
Oral Post-Dialysis Cholecalciferol (VitD3) Supplementation in Patients on Maintenance Hemodialysis (HD): One Size Does Not Fit All

E. Descombes1, B. Fellay1, O. M. Hemett1, G. Fellay2, J.-L. Magnin1

Freiburg, Villars-sur-Glâne

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: Were included 26 pts (age 68 ± 9.8 yr) with low vitD who gave their informed consent. 25(OH)2D3 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 with 1 of DialvitD (Bichsel AG). After month 2, the pts with vitD <75 nmol/l received 2 tablets/HD (= 12000 IU/wk). After tablets of Dialvit with 1 of 2000 IU of VitD3 were given after each HD by replacing 1 of the 2

Conclusion: 1) These results show that in HD patients significant different serum values of vitamin D could be obtained depending on the assay used. 2) These discrepancies seem to be much more important in HD patients than those reported in healthy subjects and vary depending on the considered assay. These points should be considered for the diagnosis and therapy of vitamin D deficiency, or when comparing the results of the studies dealing with vitamin 25(OH)D, in HD patients.

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

L. Gabbi1, P. Meier1, A.-K. Schwartzkopf2, J. Züruba1, P. Ambühl1, S. Lucarno, S. Berne, U. Urdorf, U. Zurich

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. Group 1: Reduction in Hb from 11.4 g/Dl to 9.2 g/Dl (19%), 5% dose reduction. Group 2: Hb reduction of 15% (12.4 g/Dl to 10.5 g/Dl), 20% dose reduction. Most frequent reasons for Hb drops <10 g/dl: illness 36%, bleeding 21%.

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

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 results 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, with backfiltration of fresh dialysate to blood occuring simultaneously under volumetric control of the equipment. Aim is to quantify small and large solute transport with such dialysis in-vivo.

Methods:

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<td>PS Hetsen® plus</td>
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<td>180 μm</td>
<td>35 μm</td>
<td>64 mH2O/mm Hg</td>
<td>1.5</td>
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<td>Gambro</td>
<td>Polyyarylessulone</td>
<td>1.8</td>
<td>190 μm</td>
<td>35 μm</td>
<td>60 mH2O/mm Hg</td>
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Poster Presentations – Dialysis

D3(Cobas 6000), Roche D2-D3(Cobas 6000), Abbott(Architect i1000SR), IDS(YSYS), Thermo scientific(Dionex HPLC Recipe), Blood samples were taken before HD. The results were evaluated by the Passing-Bablok test.

Results: The 25(OH)D measurements with the different assays showed significant deviations compared to those obtained with LC-MS/MS. Compared to the reference method, the Passing-Bablok regression equations were: 25(OH)D (y = –2.53±0.71x, n = 49); Roche D2-D3 (y = –1.1 ± 0.82x, n = 142); Abbott (y = 16.03 + 4.7x, n = 142); IDS (y = 7.86 + 0.61x, n = 49); Thermo HPLC (y = –2.18 + 1.18x, n = 49).

These results show a significant and, for the majority of the assays excepted the Roche D2-D3 and the Thermo HPLC, a very important deviation from the ideal linear intercept and slope of the curve (ideally close to 0.00 and 1.00, resp.). These deviations are much more important compared to the assays accuracy data of the manufacturers (derived from 25(OH)D measurements in healthy individuals mostly with low levels).

Conclusion: 1) These results show that in HD patients significant different serum values of vitamin D could be obtained depending on the assay used. 2) These discrepancies seem to be much more important in HD patients than those reported in healthy subjects and vary depending on the considered assay. These points should be considered for the diagnosis and therapy of vitamin D deficiency, or when comparing the results of the studies dealing with vitamin 25(OH)D, in HD patients.

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 >150 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.
Prevalence and Characteristics of Diabetic Subjects on Maintenance Dialysis in the Canton de Vaud in 2009

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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 age was 69.6 ± 10.6y (38–88 y) and mean BMI 27.2 ± 4.3 kg/m2. Mean Hb1Ac was 6.9 ± 1.8%. Diabetes duration to dialysis was 16.2 ± 11.4 y. Dialysis was 3.6 ± 5.2 years. Of cases, ESFR 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 with a study conducted by Sandoz and al. in 2001, the prevalence of DM2 in the dialysis population has increased from 18% to 31% in 8 years while the total number of subjects on dialysis increased from 182 to 284.

Conclusion: The number of diabetic subjects on dialysis has greatly increased in 8 years in the Canton de Vaud. This increase is mainly due to an increase in DM2 cases. Considering the costs, poor quality of life and mortality linked to dialysis therapy, diabetic subjects with diabetic nephropathy and/or a decline in renal function urgently need multidisciplinary and intensified care to delay ESRD.

Prognostic Value of Circulating Klotho and FGF23 in Dialysis Patients

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1Zurich, 2Tübingen/DE, 3Basel

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 cardiovasculo-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 may correlate with mortality in a long-term observation period. The exploratory hypothesis was that high circulating Klotho levels may protect from atrial fibrillation (AF).

Results: Thirty-seven patients (15%) died within the median follow-up time of 682 [657–761] days. Klotho levels were not significantly different in non-survivors and survivors (347 [260–456] vs. 339 [260–425] RU/ml, P = 0.59). Increasing FGF23 (HR 1.2, 95% CI 0.98–1.45, P = 0.04 per 1000 RU/ml increase) but not Klotho levels (HR 1.0; 95% CI 1.00–1.00, P = 0.46 per 100 pg/ml) were associated with mortality, as assessed by the multivariate adjusted analysis. Klotho (350 [262–447] vs. 307 [238–383], P = 0.03) and FGF23 (474 [209–1413] vs. 177 [73–618], P = 0.003) levels were significantly higher 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: 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 incident cases for ESRD leading to implementation of RRT. Patient age, serumcreatinine and eGFR (MDRD), time before the first contact to the nephrologist, civil status and attendance in terms of daily living at initiation of RRT were of further interest.

Results: Preliminary results considering 36 Swiss nephrological centers (nearly 50% of all) showed: 244 individuals with the mean age of 67.7y (31–90), started renal replacement therapy in the first half of 2012. 79/244 (32%) patients contacted a renal specialist for the first time less than one month before initiation of RRT. Mean serumcreatinine at that moment was 656umol/l, eGFR (MDRD) 9 ml/min/27.8% were older than 75y. However 165/244 (68%) presented with ESRD were met their nephrologist substantially earlier (33.5 [6–98] months).

Conclusion: Around one third of the new Swiss ESRD patients were unexpected, e.g. have seen the nephrologist less than one month before initiation of renal replacement therapy – too late for optimal pre-ESRD management.

Results from the Multicenter Observational READY Survey: Effective Treatment With Mircera in Patients on Peritonal Dialysis

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Purpose: C.E.R.A. (methoxy-polyethylene glycol-epoetin beta), with its once monthly dosing interval, allows outpatient anemia management in patients (pts) with chronic kidney disease and may be useful in peritoneal dialysis (PD).

Methods: The READY postmarketing survey (03.2010–12.2011) was performed in 12 Swiss nephrology centers on 54 PD pts treated with erythropoiesis stimulating agents (ESA) at least once monthly over 12 months. Demographics, hemoglobin (Hb), previous ESA dose and iron parameters were evaluated in 3 questionnaires at baseline (BL), months 6 and 12.

Results: Here we present interim data after 6 months of observation. 42 pts were treated with C.E.R.A. and had complete data sets. 11 pts did not complete the 6 months due to switch to hemodialysis (5), transplantation (3), change of medication (2) and death (1). Pts were on PD for 3.5 years (range 1–9 years). During the first 6 months mean Hb stayed stable, with 11.2 ± 1.1 g/dl at BL and 11.1 ± 1.0g/dl at month 6 (p = 1.0). Mean dose of C.E.R.A. remained stable (111 ± 65 µg/month at BL vs. 127 ± 65 µg/month at month 6, p = 0.38).

Mean iron parameters were sufficient at BL (ferritin 311 ± 204 µg/l, TSAT 29 ± 11%) and month 6 (ferritin 372 ± 207 µg/l, TSAT 34 ± 11%). After 6 months, of the 46% of PD pts below guideline levels (ferritin 600 µg/l, TSAT 25 ± 10%) starting dialysis therapy in the first half of 2012. 79/244 (32%) patients contacted a renal specialist for the first time less than one month before initiation of RRT. Mean serumcreatinine at that moment was 656umol/l, eGFR (MDRD) 9 ml/min/27.8% were older than 75y. However 165/244 (68%) presented with ESRD were met their nephrologist substantially earlier (33.5 [6–98] months).

Conclusion: Around one third of the new Swiss ESRD patients were unexpected, e.g. have seen the nephrologist less than one month before initiation of renal replacement therapy – too late for optimal pre-ESRD management.

Conclusion: Low circulating Klotho levels are not associated with mortality in hemodialysis patients. However, higher circulating Klotho levels seem to be protective against AF.
Inhibition Of Sodium-Glucose Cotransporters Prevents Disease Progression in Han:SPRD Rats With Polycystic Kidney Disease


Purpose: Transepithelial cyst fluid secretion is one of the key features involved in the progression of polycystic kidney disease (PKD). The role of the apical renal Na+-glucose co-transporters (SGLT) in that 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 glycosuria and osmotic diuresis in these rats.

Results: Cy/+ rats treated with phlorizin for 5 weeks showed a 56% 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 potent 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.

Efficacy of PA21, a New Iron-based Phosphate Binder, as Compared to Lanthanum Carbonate and Sevelamer Carbonate in Mice with Polycystic Kidney Disease and Vascular Calcifications in Uremic Rats

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Purpose: The present study compared the efficacy of PA21 with lanthanum carbonate (La) and sevelamer carbonate (Se) on hyperphosphatemia, secondary hyperparathyroidism and vascular calcification in rats with chronic renal failure (CRF).

Methods: CRF was induced by feeding a 0.75% adenine-enriched high phosphorus (P 1.3%) diet for 4 weeks. Rats were randomized to one of three binder treatment groups (PA21, La and Se) or to CRF and non-CRF controls for another 4 week period. The concentration of each binder (% of binder added to the diet) was chosen to deliver 1% iron, 1% lanthanum, 1.6% Se and 1.5% NaPO4 to each rat: PA21 5% (corresponding to 1% iron), La 2% (1% lanthanum), PA21 is as effective as La and Se to control calcifications.

Results: Each binder treated with phlorizin for 5 weeks showed a 56% 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.

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

M. J. Kim1, J. Barratt2, K. Molyneux2, C. D. Pusey3, F. W. K. Tam3
1Basel, 2Leicester/UK, 3London/UK

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 isolated from the serum of IgA nephropathy (IgAN) patients (plgA1). We now examine whether SYK is involved in mesangial cell proliferation and production of extracellular matrix (fibronectin) following stimulation with plgA1.

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 transfected with either Syk siRNA or negative control siRNA, 72h before stimulation with alga1.

Conclusion: Our previous and current data suggest the involvement of SYK in the production of various cytokines in human mesangial cells (HMC) following stimulation with IgA isolated from the serum of IgA nephropathy (IgAN) patients (plgA1). We now examine whether SYK is involved in mesangial cell proliferation and production of extracellular matrix (fibronectin) following stimulation with plgA1.

Results: The proliferation of HMC was increased upon stimulation with alga1 and inhibited by R406 in a dose dependent manner. HMC transfected 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 plgA1. 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 plgA1. SYK may be considered as a potential target in the treatment of IgAN.

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

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Results: The proliferation of HMC was increased upon stimulation with alga1 and inhibited by R406 in a dose dependent manner. HMC transfected 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 plgA1. 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 in human mesangial cells (HMC) following stimulation with IgA1 isolated from the serum of IgA nephropathy (IgAN) patients (plgA1). We now examine whether SYK is involved in mesangial cell proliferation and production of extracellular matrix (fibronectin) following stimulation with plgA1. The preincubation with R406 did not reduce the concentration of fibronectin.

Conclusion: These results indicate a protective effect of SCDs on polycystic acid-induced podocyte death. SCD-1 in podocytes of patients with DN may be part of a protective mechanism against SFAs.
Role of the Glucocorticoid Receptor in Podocyte Function?

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 nephrotic syndrome, express the glucocorticoid receptor (GR). Hence we hypothesize that GC control via the GR a transcripational program that is critical for glomerular development, survival and function.

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 (FSGS) 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
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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 quantification of multiple BAs are needed. Results: The uptake assay revealed a decrease of 14C-urate uptake (n = 30 oocytes, 3 batches) and surface expression was assessed by immunostaining.

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

The Calcium Channel TRPC6, Known to Cause FSGS When Chronically Hyperactivated, Acts as a Podocyte From Acute Complement-Mediated Injury
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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 membranous nephropathy (MN). We therefore speculated that overexpression of TRPC6 in cultured podocytes leads to cell damage.

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

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: whereas chronic hyperactivity leads to FSGS, acute increased podocyte CaMKII activation and higher levels of proteinuria compared to wild controls.

Conclusion: These results indicate that CD cell damage in MN 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.
Tight-Junctions in Response to Apical Sodium Entry

Berne, Kontiolahti/FI, Dunedin/NZ

Solid Organ Fibrosis: Evidence for a Common Pathway Across Species!

Y.-B. Wang, V. Leroy, T. Ernandez, A. Maunsbach, Across Species!

related genes (MARGS) discriminating renal allografts and other solid-organ with with 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.

Methods: 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 iTFa 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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Basel, Berlin/DE

Purpose: Acute Kidney Injury (AKI) is a major challenge to the nephrologist, and related to the 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 juxta-vascular 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 the tubular response to hypoxic damage by influencing the extracellular matrix composition and increasing cell-matrix interactions at the sites of injury.

Coordinated Control Of Basolateral Na,K-ATPase and Tight-Junctions in Response to Apical Sodium Entry in Collecting Duct Cells


Purpose: CD principal cells are exposed to large variations of Na transport. Na crosses the apical membrane via epithelial Na channels (ENaC) and is extruded into the interstitium by the Na,K-ATPase. Backflux of reabsorbed Na is prevented by tight-junctions. This study was designed to decipher the cross-talk between ENaC, Na,K-ATPase and intercellular junctions in CD cells.

Methods: Doxycyclin-inducible overexpression of γ-ENaC was performed in mCCD cells. Total and biotinylated cell surface proteins were detected by Western-blot. mRNA levels were measured by RT PCR.

Results: γ-ENaC overexpression increased transepithelial Na current and expression of both total and cell surface Na,K-ATPase. Pulse-chase experiments with [35S]-Methionine revealed that Na,K-ATPase synthesis was unchanged while its degradation was decreased. Pulse-chase labelling of cell surface proteins demonstrated that Na,K-ATPase endocytosis was decreased. γ-ENaC overexpression inhibited p38 kinase activity and endocytosis of Na,K-ATPase was decreased in response to p38 kinase inhibitors. Overexpression of γ-ENaC also increased transepithelial resistance in correlation with increased expression of claudin-8 mRNA and protein but did not alter expression of E-cadherin.

Conclusion: We found that increasing apical Na entry via ENaC increased activity and cell surface expression of Na,K-ATPase through inhibition of p38 kinase. This cross-talk between apical and basolateral Na transport may prevent variations of intracellular Na. Transepithelial resistance is increased via incorporation of newly synthesized claudin-8 in tight-junctions that is independent of p38 kinase. This remodeling of tight junctions may prevent backflux of reabsorbed Na. In contrast E-cadherin-dependent intercellular junctions are not altered in response to transepithelial flux.

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. Uninephrectomied (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-i€ expressions at both mRNA and protein levels, indicating a shift of bile acid transport from apical canaliculi 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-i€ expressions may either be a desired response during chronic renal disease to raise serum bile acid concentration or it may be a failing feedback regulation on bile acid formation and disposition.

Poster Presentations – Renal Pathology

Poster Presentations – NCCR Kidney CH
Flow-Mediated Regulation of Sodium Transport in the Collecting Duct

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Geneva

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

Methods: We designed an in vitro experimental setup to explore the effect of apical flow on a cellular model of collecting duct (CD) using the well-described mouse mCCDcl1 principal cell line grown on filters. Directional flow was generated using an orbital shaker delivering a shear-stress of 2 dyn/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 ciliary 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 whole-genome transcriptional analysis in mCCDcl1 cells subjected or not to flow. Significant down-regulation of genes involved in PKA and Rho GTPases pathways were identified. We speculate therefore that shear-stress alters cAMP pathway and cytoskeleton dynamics that are involved in Na transport regulation. Preliminary data using PKA inhibitor suggest a central role of PKA in the flow-mediated regulation of Na transport. We are currently investigating this avenue.

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 structures. 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 glomerule-wide biopsies from more than 160 renal biopsies from patients with different CKD stages. Proximal tubular cells and podocytes with stable HIF1 and/or HIF2 suppression were generated. Results: From a total of 84 established HIF-target genes 27 correlated with renal function (eGFR) in the cortical tubulointerstitium and 22 in 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-down derivatives and revealed a transcriptional rewiring in different cell lines. To validate the results on protein level we are currently establishing immunohistochemistry of HIF-target genes in human biopsies from patients with a wide range of renal function.

Conclusion: Our gene expression studies do not indicate an over-all hypoxic 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, interstitial fibrosis, and renal failure.

Impact of Chronic in Utero Hypoxia on Renal Glomerulogenesis and Tubulogenesis

M. Janot, P. Boissier, S. Rodriguez, U. Huynh-Do
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 utero.

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 significantly lower birth weight compared to normal weight 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

M.-E. Muller, V. L. Forini, C. Zweilacker, M. Maillard, O. Bonny, M. Burnier, Lausanne

Purpose: Furosemide has been reported to increase intact plasma parathyroid hormone (iPTH) and urinary calcium as a consequence of increased uric acid. However, the causal interaction is still unknown. 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), before and at regular time intervals after the furosemide injection.

Results: Plasma iPTH levels were suppressed (38.0 ± 12.0 ng/l vs 2.4 ± 1.7 ng/l, p <0.05), and calciuria was increased 3 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 ± 6.8 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, indicating that the calcimimetic is responsible for the iPTH increase. This is in contrast to the acute administration of a calcimimetic, where an increase in calcium levels is observed. The 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

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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)/von Hippel-Lindau protein (VHL)/hypoxia-inducible factors (HIFs) pathway, but its tissue-specific induction remains largely unknown, 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.

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/HIFs pathway 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-2, 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 erythrocytosis-associated PHD2 mutations.

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**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 V0 domain is composed of subunits A-H in a aB3B3C1D1E1F1G2H1 stoichiometry. In humans, there are two different isoforms of the B subunit in the V1 domain, of which B2 is ubiquitous whereas B1 is restricted to specialized epithelia of the inner ear, epididymis and the distal renal tubule. Mutations in the B1 subunit gene ATP6V1B1 cause autosomal-recessive distal renal tubular acidosis. We recently identified a polymorphism in the human V-ATPase B1 subunit (p.E161K) that greatly diminished pump function in vitro (Fuster, Moe et al., Kidney Int 2008).

**Methods:** To study the impact of the p.E161K polymorphism on acidification in humans in vivo, we conducted a retrospective analysis of renal stone patient registry. Exon 6 of the ATP6V1B1 gene was sequenced in all patients bi-directionally.

**Results:** Patients heterozygous for the p.E161K polymorphism (n = 19) had higher urinary pH and lower urinary citrate excretion in 24 hr urines than patients carrying two wild-type alleles (n = 547). Enhanced urinary pH and lower urinary citrate excretion in patients heterozygous for the p.E161K polymorphism carriers. Clearly, however, much more work is needed to clarify the role of this polymorphism in human physiology and pathophysiology.

**Conclusion:** Our preliminary data are compatible with the hypothesis that a novel factor regulating oxygen-dependent Epo expression and functionally investigated erythrocytosis-associated PHD2 mutations. Clearly, however, much more work is needed to clarify the role of this polymorphism in human physiology and pathophysiology. Thus, our preliminary data are compatible with the hypothesis that a novel factor regulating oxygen-dependent Epo expression and functionally investigated erythrocytosis-associated PHD2 mutations.

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


**Zurich, 2Oxford/UK**

**Purpose:** Accumulating evidence exists that hypoxia is an important modulator of chronic kidney disease (CKD) and the identification of novel hypoxia-activated 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 HIP-2a 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 and inducible for HIF 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 n nepathophrophies revealed robust PAG induction in several glomerulopathies. The array data were confirmed by RT-qPCR in independent nephropathy samples.

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

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


**Zurich, Lausanne, Geneva/DE**

**Purpose:** In CKD, renal oxygen consumption is decreased and the oxygen gradient disrupted, 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 oxygenated cells. Mutations in PHD2 lead to functional differences of the oxygen signaling cascade to investigate their role in (patho) physiological EPO regulation. Renal hypoxia imaging will be performed on transgenic ODD-luc mice.

**Methods:** Transgenic Cre strains will be used to study the expression of Epo in a temporal and spatial manner, indirectly by reporter gene (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 ODD-luc mice.

**Results:** 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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**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

**Zurich**

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

Freiburg, Quebec/CA

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 associated with increased and adipocytes cytokines 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 compared to sham-operated mice after 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 HDF. 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 HDF 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 HDF.

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 in Mice

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1Freiburg, 2Lausanne

Purpose: Seven-week-old C57B6/J mice underwent uninephrectomy (UniNX) or sham operation. After operation, animals were fed either a Chow (standard) or a high fat diet (HDF) 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 HDF-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 HDF. 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 HDF 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 HDF.

Conclusion: Nephrectomy induces chronic activation of brain pathways involving cytokine receptors along with MC4R, signifying to fat pads regulatory pathways associated with lipolysis. What other central pathways are modified by UniNX remains to be determined.
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 NCX1KO 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 was respectively reduced to 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 not different between 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.
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:

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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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<tr>
<td>Minimum</td>
<td>67.5 ± 14</td>
<td>3.9 ± 2</td>
<td>158 ± 63</td>
<td>23.4 ± 10</td>
<td>3830 ± 3265</td>
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<td>25th percentile</td>
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<td>75th percentile</td>
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<td>5.0</td>
<td>206</td>
<td>30.2</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 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. Siminski2, M.-O. Levy2, U. Schupbach3, S. Estoppey-Younes3, 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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