Free Communications

Transplantation 3

TO001 ★ MONITORING OF BKV LOAD IN URINE ALLOWS IDENTIFICATION OF PATIENTS WITH THE HIGH RISK FOR BKV-ASSOCIATED NEPHROPATHY SEVERAL WEEKS PRIOR TO DEVELOPMENT OF VIREMIA: ANALYSIS OF 4128 URINE AND SERUM SAMPLES

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Introduction and Aims: BKV reactivation plays the causative role in the development of BKV-associated nephropathy. The quantitative analysis of BKV load in serum and urine for monitoring of BKV infection is well established. However, the data on relation between BKV load in serum and urine is contradictory. Here we performed a large cross-sectional and prospective epidemiologic study on BKV load in urine and serum of renal transplant patients and analyzed the correlation between both tests and clinical course of infection.

Methods: Total of 4,128 urine and serum samples obtained from 433 renal transplant patients (female/male 178/258, mean age 50.5 years) were analyzed for BKV positivity by real-time PCR. The prospective analysis included 7 measurements during the first posttransplant year.

Results: Total of 23 (5.3%) and 63 (14.5%) patients were positive for BKV in serum and urine, respectively. There was a good correlation between the level of viremia and viruria (r = 0.01). Interestingly, the BKV load in urine was preceded by the elevation of BKV load in urine. The prospective analysis demonstrated that the peak of viral load and number of positive patients appeared during the 3rd and 5th posttransplant month for urine and serum, respectively. While 100% of patients with BK viremia were BKV positive in urine, only 36.5% of patients with BK viruria showed simultaneous BKV positivity in serum. However, gradual comparison between viremia and viruria revealed an association between the level of BK viruria and percentage of BKV positivity in serum: 91% of patients with high level viruria (more than 10^7 copies/ml) were BKV positive in serum. 22.2% of patient with persistent BK viremia and high level BK viruria developed histologically proven BKVAN within 5 and 11 weeks after BKV reactivation in urine and serum, respectively. 60% of patients with elevated viral load value in serum showed resolution of BK viremia within a mean of 33 weeks.

Conclusions: The data obtained from this large prospective study demonstrate a good correlation between BKV load in urine and serum. Since the peak of viral load in urine appears 8 weeks earlier than the reactivation in serum and shows a clear correlation with viremia, the analysis of BKV load in urine will allow identifying patients with a high risk for BKVAN development at a very early stage.

TO002 ★ CIRCULATING ENDOTHELIAL PROGENITOR CELLS AND GRAFT LOSS IN RENAL TRANSPLANT PATIENTS

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Introduction and Aims: There is growing evidence that endothelial progenitor cells (EPCs) are involved in repairing damaged endothelium. We have previously shown that the number of EPCs is reduced in renal transplant (RT) patients, particularly in those with reduced glomerular filtration rate (GFR). We studied the EPCs in RT patients and prospectively analyzed cardiovascular outcomes and kidney function during a follow-up period of 24 months.

Methods: EPCs were isolated from peripheral mononuclear cells (PMN) by flow cytometry in 94 RT. Moreover, EPCs isolated from a majority of these patients were also studied in vitro after 7 days in culture. After 24 months, we evaluated the association between baseline levels of endothelial progenitor cells and graft loss, cardiovascular death, the occurrence of a first major cardiovascular event, hospitalization and the hospitalization causes.

Results: Of these 94 RT patients, 3 patients diagnosed of malignant neoplasm during follow-up were excluded for further analysis. Mean age was 56±13 years. Mean time from transplantation was 123±62 months. In the univariate analyses, baseline EPCs (CD34+/CD133+/CD45+) were significantly reduced in the RT patients who lost their graft as compared with those with functioning graft (median [IQR], IQ75) EPCs/10^5 PMN: 22 [8, 46] vs 42 [22, 61], respectively; p<0.009). Moreover, EPCs were also reduced in RT patients hospitalized for cardiovascular causes as compared with RT patients hospitalized for other causes (median [P25, P75] EPCs/10^5 PMN: 9 [7, 19] vs 47 [24, 64], respectively; p<0.003).

TO003 SIROLIMUS VERSUS MYCOPHENOLATE MOFETIL IN TACROLIMUS BASED PRIMARY SIMULTANEOUS PANCREAS-KIDNEY (SPK) TRANSPLANTATION: 1 YEAR RESULTS OF A MULTICENTRE TRIAL

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Introduction and Aims: This open, prospective, randomized trial compares 2 parallel groups of patients who underwent simultaneous kidney and pancreas transplantation.

Methods: We present the 1 year analysis of the 241 primary SPK recipients from 13 centers throughout Europe and Israel enrolled from 2002 to 2005. Following induction with antithymocyte globulin, patients were either treated with tacrolimus and short-term steroids or concomitant with tacrolimus and short-term steroids. Results: Baseline data are equivalent in both groups with a pre-emptive transplantation rate of 24%, ischemic times for both organs between 12 hours and 100% enteric drainage of the pancreas. At 1 year, patient, kidney and pancreas graft survival rates were 97%, 95%, 86% in the MMF group and 96%, 94%, 76% in the Siro group. The 1-year rejection rate was 37% and 40%. Thirty-five % of the MMF patients and 46% of the Siro patients were withdrawn from study. The main reasons for study withdrawal were graft loss (35% vs 34%) followed by immunosuppression toxicity (42% vs 45%). Steroids were withdrawn successfully in 83% and 87% of the in-study patients. The most frequently reported adverse events were urinary tract infections (42%), CMV infections (27%), abdominal infections (14%) with no difference between the two groups. Wound problems and lymphoceles occurred more frequently but not significantly in the Siro group (21%) as compared to the MMF group (13%). Biochemistry results of the in-study patients at 1 year were for MMF and Siro group: serum creatinine: 1.3 and 1.4 mg/dl; fasting glucose: 92 and 91 mg/dl; HbA1C: 5 and 5%; total cholesterol: 171 and 188 mg/dl (p<0.05). From week 2 to year 1,
triglycerides were significantly lower in the MMF group with values at 1 year of 106 vs 135 mg/dl (p <0.01). Creatinine clearance (Cockcroft) was slightly higher in the MMF group at year 1 compared to the Siro group: 77 ml/min versus 70 (NS).

Conclusions: At 1 year, good kidney and pancreas function are achieved in both groups. Lymphocele and hyperlipidemia are more likely to occur in the Siro group.

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TO004 GENE EXPRESSION DIFFERENCES BETWEEN LIVING AND DECEASED DONOR KIDNEYS IN HUMAN TRANSPLANTATION

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Introduction and Aims: A better knowledge of the molecular mechanisms associated with the use of deceased donor kidneys for renal transplantation could pave the way for targeted therapy and modulation of specific pathways, in order to improve the outcome of deceased donor kidney transplantation and bridge the survival gap between deceased (DD) and living donor (LD) kidneys.

Methods: Whole genome expression profiles were assessed of 46 renal allograft biopsies using Affymetrix cDNA arrays: 18 training set (9 DD, 9 LD) and 10 test set biopsies (5 DD, 5 LD) obtained at implantation prior to revascularization, and 18 post-transplantation protocol biopsies (9 DD, 9 LD) 3-6 months after transplantation. No graft had delayed graft function. Data were validated using qRT-PCR and immunohistochemistry.

Results: Samples obtained at implantation segregated in 2 distinct groups according to donor origin, with 319 unique genes higher and 329 genes lower expressed in DD compared to LD kidneys. Prediction analysis of microarrays perfectly classified all test set samples, with 100% sensitivity and 100% specificity. Using Ingenuity pathway analysis software and the PANTHER classification system, we identified a significant overrepresentation in DD implantation biopsies of complement genes of both the classical and the alternative pathway (p<0.0001; fig.1), with higher expression of C1Q, C1R, C1S, C2, C3, C4, C6, CFB and downregulation of CR1, which is a complement cascade inhibitor. Local complement gene expression correlated positively with cold ischemia time in the 14 DD baseline biopsies (all p<0.05). In addition, there was a significant overexpression in DD biopsies of genes involved in epithelial-mesenchymal transition and the β-catenin signaling pathway (p<0.005), together with significant expression differences of collagen genes and genes involved in decreased degradation of extracellular matrix (all q<0.05). There was also a significant overrepresentation of the leukocyte extravasation signaling pathway (p<0.01). Finally, genes of the ER stress pathway and unfolded protein responses were significantly overrepresented (p<0.01). The gene expression differences in implantation biopsies were no longer present in posttransplant biopsies.

Conclusions: Our study provides an in-depth analysis of the gene expression differences between living and deceased donor kidneys prior to revascularization. These differences were only present in the biopsies at the time of transplantation and disappeared thereafter, which suggests that any targeted therapy interfering with these molecular pathways, intended to improve the outcome of deceased kidney allografts, should be introduced prior to organ recovery, during organ storage or in the immediate post-transplant period.

TO005 MYCOPHENOLATE MOFETIL VS. SIROLIMUS IN HIGH IMMUNOLOGIC RISK RENAL TRANSPLANT RECIPIENTS RECEIVING TACROLIMUS-BASED IMMUNOSPRESSIVE REGIMEN WITH ATG INDUCTION

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Introduction and Aims: Outcome of kidney transplantation in high immunologic risk is unsatisfactory. The aim of this multicenter, randomized study was to determine efficacious and safe immunosuppressive regimen in this group of patients (pts).

Methods: 62 (30 males) sensitized cadaveric renal transplant recipients, aged 15-55 years, were included in the study and followed-up for 36 months. High immunologic risk was defined as retransplantation (2nd [n=34] or 3rd [n=1] graft) in pts with history of immunologic complications or PRA >25%, PRA range was 0-24% (n=28), 25-36% (n=23), and >36% (n=11). HLA mismatches (MM) in class I (A+B) were 16, 21, 36, 55, 11,4, and 4.8%, for 4, 3, 2, 1 and 0 MM, respectively and in class II (DR) were 14, 5, and 26% for 2, 1 and 0 MM, respectively. Pts were randomized to receive ATG (3 mg/kg; 4 doses) + Steroids + Tacrolimus (Tac) and either mycophenolate mofetil (MMF) (n=40) or Sirolimus (Sir) (n=22).

1-year graft and patient survival were estimated with Kaplan-Meier method. Renal function (expressed as estimated GFR [eGFR calculated by MDRD formula]) was monitored for 24 months.

Results: Renal function was stable in both MMF and Sir groups, with eGFR slope significantly more positive in MMF group over 2 years after transplantation (p<0.045). Delayed graft function was observed in 35.5% pts. In 39% pts biopsy-proven acute rejection episodes were diagnosed (early [up to month 3] in 17%, late in 20%), in 32.5% pts on MMF and in 45.5% on Sir. Significantly higher cholesterol and triglyceride levels, and lower hemoglobin and hematocrit were observed in Sir group. 8 kidney grafts were lost during follow-up 5 and 3 in MMF and Sir groups, respectively. 4 patients were converted from Rapa to MMF due to thrombotic microangiopathy. 2 patients from MMF to Sir due to neoplasia. Serious complications were comparable in both groups (1 pts died [brain abscess], 1 nephrectomy [renal cell carcinoma], 1 pulmonary aspergillosis).

Graft function (GFR ml/min [CG formula]), 1-year graft and patient survival

| Group      | GFR at Month 1 | GFR at Month 3 | GFR at Month 24 | Patient survival |
|------------|----------------|----------------|-----------------|-----------------|
| MMF group  | 58.8±8.258     | 58.2±19        | 62.4±21         | 87.5%           | 95.5%           |
| Sir group  | 46.8±20.4      | 47.6±20.6      | 52.3±20.2       | 81.4%           | 90.9%           |

Conclusions: MMF-based immunosuppressive regimen proved more safe and efficacious than sirolimus-based therapy in high immunologic risk kidney transplantation, resulting in better graft function and lower incidence of adverse effects. Kaplan-Meier estimates of 1-year patient and graft survival showed a trend in benefit of MMF.

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Growth hormone (GH) treatment improves the catabolic state in HD patients and is associated with an improvement in body composition. In the present study we investigated whether the improvement in body composition during GH treatment is associated with changes in the parameters of the lipid profile and glucose metabolism.

Methods: Adult patients (mean±SD) (83 male; 56 female; age 59.5±13.6 years, mean duration on dialysis 39.9±46.2) with s-albumin levels ≤40 g/L on maintenance HD were randomised to 3 daily doses of GH (0.020, 0.035 or 0.050 mg/kg; Norditropin®, Novo Nordisk A/S, Copenhagen, Denmark) or placebo in a 26 week, randomised, placebo-controlled, dose-ranging study. Lean body mass (LBM) and fat mass (FM) were evaluated by dual energy X-ray absorptiometry (DXA) at baseline and after 13 and 26 weeks. Levels of glucose, insulin and the lipid profile (Total cholesterol [TC], triglycerides [TG], LDL-cholesterol [LDL-C] and HDL-cholesterol [HDL-C]) were evaluated at baseline and weeks 2, 6, 13 and 26. Change in LBM from baseline was evaluated by ANCOVA with treatment group and baseline values as covariates.

Results: Treatment with GH resulted in a statistically significant increase in LBM after 6 months compared with placebo (mean [95% CI]) (0.02 mg/kg, 1.91 kg [0.84-2.99], 0.035 mg/kg, 2.29 kg [1.01-3.58], 0.050 mg/kg, 3.06 kg [0.84-5.2]) with s-albumin levels ≥40 g/L. There were significant positive correlations between % truncal fat mass and fasting plasma triglyceride (r=0.260, p<0.0001) and HDL-cholesterol (r=0.681, p=0.0039), triglyceride (r=1.510, p<0.0001), after adjustment of age, hemodialysis duration, and gender. Further, in each multiple regression analysis, % truncal fat mass was significantly, independently associated with fasting serum total cholesterol (β=0.681, p=0.0039), triglyceride (β=1.510, p<0.0001), HDL-cholesterol (β=0.471, p<0.0001), and glucose (β = 0.191, p=0.0017), after adjustment of age, hemodialysis duration, and gender.

Conclusions: These results demonstrate that increase in truncal fat mass was an indicator of presence of metabolic syndrome, even in hemodialysis patients, even in whom increased total body fat mass represents a good nutritional status.

Introduction and Aims: In general population, obesity is characterized by chronic low-grade inflammation, with increased serum inflammatory adipocytokines. Truncal fat or visceral fat is strongly associated with these abnormalities. In hemodialysis (HD) patients, low grade inflammation, as represented by increased C-reactive protein (CRP), is strongly associated with mobility and mortality. However, little is known about the association between inflammation and body fat mass or its distribution in HD patients. In this study, we investigated the relationship between serum high-sensitivity CRP (hsCRP) and truncal or non-truncal fat mass in HD patients.

Methods: 452 patients on maintenance HD (age 64±11 years; HD duration 89±77 months; 37% diabetics) were examined. Fat mass and lean mass were measured by dual X-ray absorptiometry. Fat mass were divided into truncal and non-truncal fat mass, the latter of which was a sum of fat mass of four extremities. All patients were grouped into two according to their serum hsCRP levels: normal CRP group (n = 346) with hsCRP less than 0.3 mg/dl (i.e., normal levels of hsCRP) and high CRP group (n = 106) with those equal to or more than 0.3 mg/dl.

Results: There were no significant differences in age, gender, HD duration, body weight, or prevalence of diabetes between the two CRP groups. Serum
albumin and blood urea nitrogen was significantly lower in high CRP group than in normal CRP group (p = 0.01 and p < 0.05, respectively). Although there were no significant differences in lean mass between the two groups, fat mass of high CRP group was significantly higher than that of normal CRP group (14.8 ± 6.6 vs 13.4 ± 5.4 kg, p < 0.05). While there was no significant difference in non-truncal fat mass between the two groups, truncal fat mass of high CRP group was significantly greater than that of normal CRP group (7.7 ± 4.3 vs 6.7 ± 3.4 kg, p < 0.05). Percent truncal fat mass out of total fat mass was significantly greater in high CRP group than in normal CRP group (49.7 ± 8.0 vs 47.8 ± 8.7%, p < 0.05). In all patients, there were significant positive correlations between serum hsCRP levels and total fat mass, truncal fat mass, truncal fat mass, or non-truncal fat mass, although there was no significant correlation between serum hsCRP levels and lean mass. In a multiple regression analysis, truncal fat mass (β = 0.227, p < 0.01) was a variable significantly and independently associated with serum hsCRP levels, in addition to other significant and independent variables of age, gender, and serum albumin (R² = 0.137, p < 0.01), whereas non-truncal fat mass was not a significant variable.

Conclusions: These results demonstrate that fat mass, particularly truncal fat mass, but not lean body mass or non-truncal fat mass, was significantly associated with serum hsCRP levels. The results suggest that truncal fat mass exhibit a distinct effect on low grade inflammation in HD patients, possibly associated with morbidity and mortality.

**TO009**

**HAEMODIALYSIS ACUTELY REDUCES PLASMA ASYMMETRIC DIMETHYLARGININE WITHOUT REVERSING IMPAIRED NITRIC OXIDE DEPENDENT VASODILATION**

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**Introduction and Aims:** Patients treated by maintenance haemodialysis (HD) have endothelial dysfunction, consistent with a high cardiovascular risk. They also have high plasma levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide (NO)-synthase. However, the link between these abnormalities is controversial. This study was designed to test whether a single haemodialysis session may impact on NO-dependent vasodilation and on plasma ADMA levels.

**Methods:** Twenty-four patients undergoing maintenance haemodialysis (HD-group: 67.9 ± 11.3 years, mean ± SD, 18 men) and 24 healthy age and sex matched individuals (C-group: 68.7 ± 11.7 years, 17 men) were enrolled. NO-dependent vasodilatation was assessed from the plateau increase of skin blood flow (SKBF), measured with laser Doppler imaging caused by local heating to 41°C (SKBF41), a response known to depend on NO. SkBF41 induced by local heating to 43°C (known to be independent of NO). SkBF41, on two different days. Blood samples were drawn for the assay of ADMA (tandem mass spectrometry) concomitantly to both sessions in the HD-group, and only once in the C-group.

**Results:** In the HD group, SKBF41 was not influenced by HD (before: 82.2 ± 13.1%, after: 82.7 ± 12.4%, p NS), although it was significantly lower than in the C-group (session 1: 89.6 ± 5.9%, session 2: 89.2 ± 7.9%, p < 0.01 vs HD-group). In contrast, plasma ADMA was reduced by HD (0.51 ± 0.21 mmol/L vs. 0.12 ± 0.09 mmol/L, p < 0.01) in the HD group. Plasma ADMA before HD was greater than in the C-group (0.51 ± 0.21 mmol/L vs. 0.19 ± 0.09 mmol/L, p < 0.05). However, ADMA levels after HD did not differ from those in the C-group.

**Conclusions:** These data show that HD patients are characterised by impaired NO-dependent vasodilatation which is not reversible by acute haemodialysis. Moreover, the normalisation of ADMA plasma levels, with regard to the unchanged SKBF response, suggests that mechanisms other than accumulated ADMA must operate to explain endothelial dysfunction.

**Diabetes 2**

**TO011** PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) AS A CLINICAL PROGRESSION MARKER OF DIABETIC NEPHROPATHY IS SECRETED BY PROXIMAL TUBULAR CELLS

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**Introduction and Aims:** PAI-1, known as a thrombogenic factor, inhibits activation of matrix metalloproteinases and decreases degradation of type I and III collagens, which causes extra-cellular matrix accumulation leading to the progressive renal fibrosis. As potent inducers of PAI-1, TGFβ, angiotensin II, thrombin and TNFα are documented, however, the role of high glucose and chronic hypoxia has not been clarified. In this study, we examined whether urinary PAI-1 concentration may reflect tubulointerstitial damage in patients with diabetic nephropathy, and the mode of PAI-1...
production in vitro by various stimuli such as high glucose, chronic hypoxia and inflammation in human proximal tubular epithelial cells (PTECs).

**Methods:** Urine samples were obtained from 12 healthy controls, and 36 type 2 diabetic nephropathy patients with overt proteinuria. Total PAI-1 concentration in fresh urine sample was measured by a latex agglutination with polyclonal anti-PAI-1 antibodies, together with urinary N-acetyl-β-D-glucosaminidase (NAG) levels. Human PTECs were cultured in the growth medium containing normal glucose concentration (100 mg/dl) under 18% O₂. Confluent cells were growth-arrested and the effects of high glucose (450 mg/dl), chronic hypoxia (1% O₂) and an inflammatory cytokine, TNFα (10 ng/ml) were examined after 24 hr stimulation by the measurements of PAI-1 mRNA and supernatant PAI-1 protein levels.

**Results:** The patients showed significantly higher mean PAI-1 (300 ng/gCr, range:8.5-1070) than those in controls (15 ng/gCr, range: 4.8-49),(P<0.01). The patients PAI-1 level showed strong positive correlation with NAG (r=0.77, P<0.001). In PTECs experiments, high glucose did not induce PAI-1 production, exhibiting 255.9±4.5 ng/ml in high glucose, vs 257.2±4.5 ng/ml in normal glucose. On the other hand, hypoxia or TNFα alone induced significantly higher mean PAI-1 than that in controls, both in mRNA amount (3.6-fold and 3.3 fold, respectively) and in protein secretion (2.7 fold and 1.8 fold, respectively). In addition, simultaneous stimulation with hypoxia and TNFα showed synergistic increases both in mRNA and protein secretion (12.0-fold and 4.6-fold, respectively).

**Conclusions:** These findings suggest that urinary PAI-1 may substantially be derived from injured tubuli in diabetic nephropathy and that the production of PAI-1 is up-regulated in the proximal tubular cells by the stimulation of chronic hypoxia and inflammatory cytokines but not high glucose.

**TOO12 COMPLETE REVERSAL OF STZ INDUCED DIABETES USING A NOVEL HUMAN CELLULAR THERAPY**

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**Introduction and Aims:** Cellular therapies hold potential for the treatment of diabetes. Evidence that candidate cells, which might fulfill this role, reside in the pancreatic ducts, has been provided by rodent models of pancreatic regeneration. We have sought to isolate such cells and demonstrate that they can mitigate the effects of diabetes in vivo.

**Methods:** Novel candidate cells were isolated from adult rat and human pancreatic ducts and characterized by ICC, FACs and RT-PCR. The ability of these cells to mitigate the effects of diabetes was assessed in a xenogeneic model of streptozotocin-induced diabetes mellitus. Female C57Bl/6 mice were made diabetic by injection of streptozotocin (STZ) to give a dose of 250 mg/kg on day 0 of the experiment. 750,000 PDPCs were injected into the tail vein on day 3 after STZ injection. Control animals were given an injection of saline or the equivalent number of Albino Swiss rat bone marrow cells. Blood glucose was monitored every 3 days. Animals receiving immuno-suppression were subject to a dose of cyclosporine at 20 mg/kg for 7 days. All procedures were conducted under authority of the UK Home Office.

**Results:** We have isolated a novel cell type from adult rat and human pancreatic ducts, which we have termed Pancreatic Derived Pathfinder Cells (PDPCs), on the basis that they appear to navigate a path towards sites of damage in vivo. We present the first evidence that direct intravenous injection of PDPCs into STZ diabetic mice completely normalizes blood glucose levels for over 100 days post transplant, preventing the progressive hyperglycaemia seen in controls. Significantly, immunosuppression had no effect upon efficacy. Importantly, we demonstrate that, although they contain cells with progenitor cell properties, they work in vivo primarily by stimulating host tissue to regenerate. Crucially, the insulin produced by these treated animals is principally mouse in origin and is of both type I (embryonic) and II (adult).

**Conclusions:** These results demonstrate the feasibility of using intravenous administration of adult cells to regenerate damaged tissue, enhance our understanding of the mechanisms relating to such repair and suggest a means for novel therapeutic intervention in diabetes.

**TOO13 PREDICTING ABNORMAL ALBUMIN EXCRETION RATE BY FIBRINOGEN LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS**

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**Introduction and Aims:** Plasma fibrinogen is a strong cardiovascular risk factor. Hyperfibrinogenemia frequently occurs in type 2 diabetes (DM2) and appears to be correlated with albuminuria. The aim of this study was to test if fibrinogen levels can predict patients (pts) with elevated albuminuria.

**Methods:** In a cross-sectional study, 54 DM2 pts (22 males and 32 females, age 63±9 years) were evaluated. According to the median albumin excretion rate (AER), measured in urine samples obtained during a 24h collection we performed a ROC analysis to determine the best fibrinogen levels cutoff threshold to predict elevated albuminuria.

**Results:** Fibrinogen levels were positively correlated with AER (r=0.55, p<0.0001). The median AER was 34.5 mg/24h and the area under the ROC curve was 0.806±0.059, p<0.001.

We found a cutoff threshold of 335 mg/dl for fibrinogen (sensitivity=81.5%; specificity=70.3%). Pts were divided in two groups according the fibrinogen levels (Normal <335mg/dl, n=24 and High ≥335mg/dl, n=30). Female gender was predominant in the Normal fibrinogen group (18 pts vs 14 pts; p=0.019) and this group had lowest creatinine levels (1.0 mg/dl vs 1.8 mg/dl; p=0.015), higher creatinine clearance, measured by Cockroft-Gault equation (80.7±6.9 vs 58.4±6.7 ml/min; p=0.026). There were more patients taking statins in the Normal fibrinogen group (21 pts vs 18 pts; p=0.025). AER was higher in the High fibrinogen group (18.5 mg/24h vs 91.5 mg/24h, Normal vs High respectively; p<0.001). There were no other clinical or biochemical differences between the groups. The positive and negative predictive values of fibrinogen were respectively 73.3% and 79.2%.

**Conclusions:** We conclude that in our DM2 population, a fibrinogen level ≥335 mg/dl can predict with reasonable sensitivity and specificity the presence of elevated albuminuria.

**TOO14 THE ROLE OF PROTEIN KINASE-C-ALPHA (PKCα) IN TGF-β AND GLUCOSE INDUCED APOPTOSIS IN PODOCYTES**

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**Introduction and Aims:** The progressive depletion of podocytes is the hallmark of chronic, progressive kidney disease. Changes in the glomerular milieu, associated with the development of diabetic nephropathy, lead to cellular hypertrophy and activation of TGF-β. The enhanced activation of proapoptotic signaling cascades by Glucose and TGF-β leads ultimately to apoptosis in podocytes. The aim of this study is to analyze the role of PKCα on TGF-β and Glucose induced apoptosis in podocytes.

**Methods:** We generated PKCα proficient murine Podocytes. By time-course experiments we studied anti- and pro-apoptotic signaling after stimulation with TGF-β and under high-Glucose conditions in PKCα+/+ and PKCα−/− podocytes. Furthermore we analyzed activation of Caspase3/7 after stimulation with TGF-β and Glucose. By immunoprecipitation and immunofluorescence-assays we studied interaction of PKCα with the TGF-β type-I-receptor. Endocytosis of the TGF-β type-I-receptor and Nephrin was
studied by an Endocytosis-assay. Furthermore we analyzed Expression of PKCs on human kidney tissues with different glomerular diseases.

**Results:** We found that the sensitive balance of anti- and proapoptotic signaling cascades in podocytes is strongly influenced by the presence of PKCs. Treatment with TGF-β showed an earlier and prolonged activation of PI3K/AKT and ERK1/2 in PKCs+/− podocytes compared to PKCs−/− podocytes. Similar to this culturing under high-Glucose conditions leads to increased activation of PI3K/AKT in PKCs+/− podocytes. Activation of p38MAPK is decreased in PKCs+/− podocytes compared to PKCs−/− podocytes after stimulation with TGF-β and high-Glucose. Functional analysis of apoptosis showed a decreased activation of Caspase3/7 in PKCs+/− podocytes. Interestingly we can show an interaction of PKCs with the TGF-β-type-I-receptor. Endocytosis assays showed that the TGF-β-type-I-receptor and Nephlin is early internalised in PKCs+/− podocytes. Furthermore Expression of PKCs is upregulated in several human kidney tissues.

**Conclusions:** Our results indicate, that PKCs influences the signaling cascades in podocytes as part of the intracellular signaling-complex formed after activation of the TGF-β-receptor. Glucose may lead to activation of PKCs via independent pathways. Therefore PKCs might be an interesting target molecule for podocyte protective therapy in diabetic disease.

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**ACCELERATED SENESCENCE IN THE KIDNEYS OF PATIENTS WITH TYPE 2 DIABETIC NEPHROPATHY**

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**Introduction and Aims:** In this work we examined the hypothesis that acceleration of senescence represents a proximate mechanism by which the kidney is damaged in diabetic nephropathy (DN).

**Methods:** We studied whether the senescence-associated beta-galactosidase (SA-beta-gal) and the cell cycle inhibitor p16INK4A are induced in renal biopsies from patients with type 2 DN. Seventeen patients with DN (14M/3F, mean age 63±5 years) were studied.

**Results:** SA-β-Gal staining was ~4 fold higher (32.6±17% vs 7.3±5.8% in C, p<0.05) in the tubular compartment of diabetic kidneys with early disease (n=7) (proteinuria 1±0.2 g/day, eGFR 77±5 ml/min) than in C, in SA-β-Gal staining did not increase further in advanced DN (n=10) (proteinuria 3.5±0.8 g/day, eGFR 33±8 ml/min). The SA-β-Gal signal was predominantly confined to tubular cells, but it was also detected in vascular endothelial cells and in podocytes. The percentage of glomerular p16INK4A positive cells (19±0.5 to 13±0.2% in C, p<0.05), as well as the percent of glomerular p16INK4A positive nuclei (1.5±2.4% vs 0.9±1.3±% p<0.05), was similar in DN vs C. When analyzing nuclear p16INK4A expression in glomeruli by cell type, nuclear p16INK4A staining in podocytes was increased in DN when compared to C (p=0.04), while the p16INK4A signal in mesangial-endothelial cell nuclei and in the arterial vessels was similar to C. In tubuli (mainly proximal tubuli), p16INK4A expression was significantly increased in DN (DN=0.35±0.35%, C=0.04±0.03% p=0.0021). P16INK4A expression was associated with proteinuria (r= 0.72; P < 0.002) in glomerular cell nuclei while it was directly associated with BMI and HbA1C (r=0.82 and 0.89, respectively, p<0.05-0.02) in the tubuli. Similarly, SA-β-Gal staining in tubules was directly associated with BMI and blood glucose (p<0.05-0.03).

**Conclusions:** In conclusion, the results of the present study demonstrate that senescence is accelerated in the kidney of patients with type 2 DN, thus reinforcing the role of metabolic syndromes on biological aging of tissues. DN may act as an environmental stress inducing senescence in tubular cells and podocytes, which in turn may contribute the progression by arresting replication needed to sustain the nephron mass and increasing proteinuria.
hemodialysis, who had undergone twenty-four hour Holter electrocardiography during dialysis sessions (male/female, 105:70; mean age, 66±12 years; mean dialysis duration, 90.5 months). Patients who had a clinical history of myocardial infarction and/or coronary revascularization were excluded from the study. Time- and frequency-domain analyses of the heart rate variability were carried out. We calculated the percentage of differences between adjacent NN intervals more than 50 msec (pNN50) and high frequency component (HF, 0.15-0.40 Hz) as parameters of the cardiac parasympathetic activity, and the ratio of low frequency component (0.04-0.15 Hz)/HF (LF/HF) as a parameter of the sympathetic activity.

**Results:** During a 4.5±1.9-year follow-up, sudden cardiac death was recognized in 23 patients. In stepwise Cox hazard analysis, sudden cardiac death was associated positively with age or the LF/HF ratio, and tended to be inversely associated with pNN50 (Table). Kaplan-Meier analysis showed that the sudden cardiac death-free survival rates at 5 years were 29.4% and 98.1% in patients with the LF/HF ratio of 1.9 or more and below 1.9, respectively (Figure).

**Conclusions:** Cardiac sympathetic overactivity with impaired parasympathetic activity is likely to be involved in sudden cardiac death in patients on maintenance hemodialysis. Assessment of imbalance in the cardiac autonomic system using the heart rate variability may be useful for identifying the high-risk group of sudden cardiac death in hemodialysis patients.

**Patients** were followed from the start of dialysis until 5 years of follow-up. First, we calculated male/female odds ratios associated with the baseline presence of cardiovascular risk factors, using logistic regression analysis. Second, with Cox regression analysis we calculated hazard ratios (HR) for male sex and cardiovascular risk factors adjusted for age, dialysis modality, smoking, BMI, cholesterol, use of anti-hypertensive and lipid lowering drugs. Finally, we calculated the relative excess risk due to interaction (RERI) between sex and the cardiovascular risk factors, on the basis of departure from causal additivity of effects.

**Results:** In total, 1276 dialysis patients were included (61% men, age: 59±15 years, BMI: 24.7±4.1 kg/m²). At baseline, men had more cardiovascular comorbidity (41% vs 26% in women, male/female OR: 2.26 [95% CI: 1.71, 3.00]) but suffered less from diabetes mellitus (20% vs 26% in women, male/female OR: 0.76 [0.57, 1.01]) than women. During follow-up, 462 patients died. 323 from CVD. Both CVD (HR: 2.09 [1.72, 2.55]) and DM (HR: 2.37 [1.93, 2.91]) were associated with increased risks of mortality. Slightly more men died from CVD than expected, but the interaction effect between sex and CVD was non-significant (RERI: 0.43 [-0.20, 1.05]). Compared with women without DM, men with DM (HR: 2.30 [1.69, 3.11]) had a lower mortality risk than expected (HR in women with DM: 3.17 [2.33, 4.31]). This significant interaction effect between sex and DM (RERI: -1.05 [-1.98, -0.12]) may in part explain the equal survival in men and women (HR men: 0.94 [0.77, 1.14]).

**Conclusions:** The present study demonstrates that despite a more than two-fold lower prevalence of CVD at baseline, women starting chronic dialysis therapy have the same mortality risk as do men. This may partly be due to the presence of interaction between sex and diabetes, resulting in higher mortality in women with diabetes. To improve survival in the dialysis population, special attention needs to be paid to the treatment of female dialysis patients with diabetes.

**TO018 EXCESS MORTALITY IN WOMEN WITH DIABETES MAY BE DUE TO LOW RISK MYOCARDIAL INFARCTION, SUGGESTING RELUCTANCE TO TREATMENT IN WOMEN:**

**Patients** included 1276 dialysis patients (61% men, age: 59±15 years, BMI: 24.7±4.1 kg/m²), who had undergone twenty-four hour Holter electrocardiography during dialysis sessions (male/female, 105:70; mean age, 66±12 years; mean dialysis duration, 90.5 months). Patients were followed from the start of dialysis until 5 years of follow-up. First, we calculated male/female odds ratios associated with the baseline presence of cardiovascular risk factors, using logistic regression analysis. Second, with Cox regression analysis we calculated hazard ratios (HR) for male sex and cardiovascular risk factors adjusted for age, dialysis modality, smoking, BMI, cholesterol, use of anti-hypertensive and lipid lowering drugs. Finally, we calculated the relative excess risk due to interaction (RERI) between sex and the cardiovascular risk factors, on the basis of departure from causal additivity of effects.

**Results:** In total, 1276 dialysis patients were included (61% men, age: 59±15 years, BMI: 24.7±4.1 kg/m²). At baseline, men had more cardiovascular comorbidity (41% vs 26% in women, male/female OR: 2.26 [95% CI: 1.71, 3.00]) but suffered less from diabetes mellitus (20% vs 26% in women, male/female OR: 0.76 [0.57, 1.01]) than women. During follow-up, 462 patients died. 323 from CVD. Both CVD (HR: 2.09 [1.72, 2.55]) and DM (HR: 2.37 [1.93, 2.91]) were associated with increased risks of mortality. Slightly more men died from CVD than expected, but the interaction effect between sex and CVD was non-significant (RERI: 0.43 [-0.20, 1.05]). Compared with women without DM, men with DM (HR: 2.30 [1.69, 3.11]) had a lower mortality risk than expected (HR in women with DM: 3.17 [2.33, 4.31]). This significant interaction effect between sex and DM (RERI: -1.05 [-1.98, -0.12]) may in part explain the equal survival in men and women (HR men: 0.94 [0.77, 1.14]).

**Conclusions:** The present study demonstrates that despite a more than two-fold lower prevalence of CVD at baseline, women starting chronic dialysis therapy have the same mortality risk as do men. This may partly be due to the presence of interaction between sex and diabetes, resulting in higher mortality in women with diabetes. To improve survival in the dialysis population, special attention needs to be paid to the treatment of female dialysis patients with diabetes.
**TO020 ★ VARIATION BETWEEN DIALYSIS CENTRE ACHIEVEMENT OF AUDIT MEASURES FOR SERUM PHOSPHATE IN HD PATIENTS. DATA FROM 17,000 PATIENTS IN 55 CENTRES**

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**Introduction and Aims:** The UK Renal Registry collects audit measures relating to clinical practice guidelines for UK dialysis centres and ranks unit performance. This study illustrates additional statistical tests to enhance interpretation of performance data using phosphate as an example.

**Methods:** This study analysed the 2006 prevalent HD cohort. Data were audited against the current national (Renal Association) guideline i.e. % with PO₄<1.8mmol/L and were not adjusted for case mix. % of patients achieving the guideline for each unit for the last quarter (Q4) of 2006 was calculated and units ranked. Data were also plotted on funnel plots for comparison. The % of patients achieving PO₄<1.8mmol/L for each centre has statistical uncertainty. The distribution of this % for each centre is assumed normal with an individual centre mean and sd. A Monte Carlo procedure was used to sample from the distribution for each centre (10000 iterations). The median rank and 95% CIs were calculated and plotted to show the degree of uncertainty around the observed rank.

**Results:** The cohort was 17319 HD patients in 55 centres. Centre size varied from 23-1099 patients. Cross sectional analysis showed a mean of 65.5% (95% CI 64.7-66.3%, range 48.1-83.8%) with PO₄<1.8mmol/L but significant interunit variability ($\chi^2=158$ p<0.0001) (Figure 1). The funnel plot identified 30/55 centres within 2sd from the UK mean for % patients achieving PO₄<1.8mmol/L but also outlying centres, 7 units outside the 99.9% CIs and 18 centres between the 95%-99.9% CIs. The Monte Carlo analysis (Figure 2) showed marked uncertainty surrounding unit ranking e.g. Bristol, actual rank 20th (CI 10⁹-32⁹⁺) due to a large % of units lying within a relatively narrow range i.e. small change in % with PO₄<1.8mmol/L can cause a large change in rank. Certainty of ranking is improved at both extremes where differences in % with PO₄<1.8mmol/L are greater e.g. Reading, actual rank 4⁹ (CI 1⁹-10⁹) and is also a function of centre size due to characteristics of the underlying distribution.

**Conclusions:** These data highlight the limitations of simple rankings. Providing dialysis centres with the additional data shown in this study would aid in comparison of centre performance against audit measures for quality of care.

**TO021 TRENDS IN HEPATITIS C PREVALENCE (1997-2006) AND ASSOCIATIONS WITH FACILITY PRACTICE PATTERNS: THE DIALYSIS OUTCOMES AND PRACTICE PATTERNS STUDY (DOPPS)**

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**Introduction and Aims:** The prevalence of Hepatitis C (HCV) among hemodialysis (HD) patients varies greatly across countries. Recent studies
have suggested that the prevalence of HCV has decreased in recent years in HD patients but this claim was mostly based on relatively small sized, convenience samples or on the CDC yearly survey (USA) with a < 60% response rate. Our current work assesses changes in HCV prevalence over the past 9 years and re-examines relationships with facility practice patterns.

**Methods:** Data from 30,629 patients in DOPPS I, II, and III were analyzed. HCV prevalence was assessed in each phase from the initial cross-section of prevalent HD patients. Practice patterns were reported at the baseline of each study. Seroconversion rates were calculated from laboratory data received longitudinally throughout the study at 4 month intervals. Logistic models examined the associations of facility practices with HCV prevalence and Cox models were used to investigate associations with seroconversion; adjusted for age, sex, race, time on ESRD, 14 summary comorbid conditions, region and phase; and accounting for facility clustering.

**Results:** HCV prevalence has decreased since DOPPS I in all countries except Sweden and Germany (which already had very low HCV prevalence). Practices associated with lower HCV prevalence include an isolation policy for HCV patients and a policy of routine screening for HCV. Dialyzer reuse among HCV patients is associated with higher HCV prevalence. Facilities that isolate HCV patients had a trend toward lower seroconversion rates (RR=0.63, p=0.14), while facilities with higher HCV prevalence had higher rates of seroconversion (RR=1.01 per 1% higher, p=0.06).

**Conclusions:** This work confirms the findings of recent small studies that HCV prevalence in HD units appears to be decreasing. Our findings also support the possibility that certain facility practices may decrease nosocomial transmission, but further study is needed.

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**GAMMA-Glutamyltransferase is a strong risk factor for mortality in the ESRD population**

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**Introduction and Aims:** The enzyme γ-glutamyltransferase (GGT) is an established marker for liver function and represents the major factor responsible for the extracellular catabolism of the main antioxidant in mammalian cells, Glutathione. GGT is directly involved in atherosclerotic plaque formation and high GGT plasma levels are associated with death and increased cardiovascular (CV) risk in the general population. ESRD is a condition characterized by an exceedingly high risk of death and CV complications and with a high prevalence of liver disease but the link between GGT and clinical outcomes has never been studied in this population.

**Methods:** We therefore tested the predictive power of GGT for death in a large cohort of dialysis patients (n=584) representative (45%) of the dialysis population of a 2 million residents region.

**Results:** GGT (median 22 UI/L, inter-quartile range 16-36 UI/L) was above the upper limit of the normal range (75 UI/L) in 50 (9%) patients. As expected, GGT was higher (P<0.001) in patients with established liver disease. Furthermore GGT was slightly higher in males (P=0.03), in diabetics (P=0.04) and related directly with C-Reactive Protein (CRP) (r=0.15, P<0.001) and inversely with diastolic pressure (r= -0.10; P=0.02) and serum P (r= -0.16, P<0.001). Over a 4 years follow up 194 patients died.

GGT was higher in non-survivors (25 UI/L, 16-45 UI/L) than in survivors (22 UI/L, 15-33 UI/L) (P=0.006). On univariate Cox analysis GGT (hazard ratio (HR), 10 UI/L increase: 1.01, 95% CI: 1.01-1.06, P=0.006) as well as age, diabetes, background CV complications and plasma CRP were associated with the risk of death. In a multivariate Cox regression analysis the predictive power of GGT for death (HR: 1.06, 95% CI: 1.03-1.10, P<0.001) was largely independent of liver disease as well as of other potential confounders including age, sex, diabetes, diastolic pressure, CRP and CV complications. Remarkably, the predictive power of GGT for death was second only to age (Wald test P<0.001) and superior to that of Diabetes (P=0.06) and CRP (P<0.01).

**Conclusions:** In dialysis patients high GGT levels represent a strong risk factor for death. The association between high GGT and poor survival remained robust after adjustment for liver disease as well as for traditional and non traditional risk factors including CRP. These observations are in keeping with experimental studies indicating that a high level of this enzyme predicts a high risk of death also because it triggers a pro-oxidant action. GGT may be involved in the high risk of ESRD and may represent an useful risk marker in this population.

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