

## Chronic Allograft Nephropathy in Well Functioning Allografts: A Protocol Biopsy Study

M. Ertilav<sup>1</sup>, S. Sen<sup>2</sup>, H. Töz<sup>1</sup>,  
C. Hoscokun<sup>3</sup>, M. Sezis<sup>1</sup>,  
M. Özkahya<sup>1</sup>, E. Ok<sup>1</sup>

<sup>1</sup>Nephrology, Ege University, Izmir, Turkey; <sup>2</sup>Pathology, Ege University, Izmir, Turkey; <sup>3</sup>Surgery, Ege University, Izmir, Turkey

Chronic allograft nephropathy (CAN) is the most common cause of graft failure after the first year of posttransplantation. Once the diagnosis has been made, it is difficult to affect the outcome. Since protocol allograft biopsies (PBx) may be used as a surrogate end point to predict long-term graft function, we designed this study to investigate the early chronic histological changes and its determinants in well-functioning allografts.

One hundred twenty two living or cadaveric renal transplant (RT) patients (pts) (serum creatinin level below or equal to 2.0 mg/dL at 12<sup>th</sup> month) were included into this study. PBx at the time of transplantation (zero hour) and at the end of first year were performed in all pts. Calcineurin inhibitor based regimen (cyclosporine in 71, tacrolimus in 51 pts) was used as primary immunosuppressive treatment combined with azathioprin (28 pts) or mycophenolate mofetil (94 pts). ATG induction was used in all cadaveric RT. Specimens were blindly evaluated by the same pathologist according to Banff schema. CAN was classified as no CAN (ci+ct <2), mild CAN (ci+ct: 2-3) and moderate CAN (ci+ct: 4-5). Acute and chronic scarring were defined as sum of i, t, g, v and ci, ct, cg, cv, respectively.

CAN in mild and moderate form was detected in 66 (54 %) and 11 (9 %) pts, respectively. No case of severe CAN was seen. Pts sex, age, mode and duration of dialysis before RT, type of RT, donor age and sex, mean number of mismatch, distribution of haplotype, acute and chronic scarring at the time of RT were similar among three groups. Presence of delayed graft function, acute rejection and proteinuria were seen more frequently in pts with CAN. Different immunosuppressive protocols have no impact of the development of CAN. In multivariate analysis acute re-

Clinical and histological data			
	No CAN (n:45)	Mild CAN (n:66)	Moderate CAN (n:11)
Delayed graft function (%) a	8	15	36
CsA-based treatment (%) b	55	59	54
MMF-based treatment (%) b	82	62	81
Acute rejection (%) c	20	43	72
Creatinin at 12th month (mg/dL) b	1,32±0,3	1,42±0,3	1,60±0,3
Proteinuria >0,5 gm/day (%) a	11	18	63
Acute scarring at zero hour b	0,10±0,3	0,24±0,4	0,10±0,3
Acute scarring at 12th mo c	0,80±1,3	1,63±1,5	3,50±1,4
Chronic scarring at zero hour b	1,62±1,2	2,0±1,2	1,4±1,2
Chronic scarring at 12th mo	1,22±1,2	3,20±1,0	6,27±1,4

a: p=0,05, b: not significant, c: p<0,05

jection is the only factor that increases the risk of development of CAN (OR: 3,527, p=0,002).

In conclusion, subclinical CAN lesions are seen in 65 % of well functioning allografts. Acute rejection is the most important factor for the development of subclinical CAN. For early intervention, PBx may be useful tool to detect early lesions of CAN.

### Serum Creatinine during the Early Phase of Kidney Transplantation Predicts 10-Year Graft Survival

J. Pascual<sup>1</sup>, J. L. Merino<sup>1</sup>, R. Marcen<sup>1</sup>,  
J. Zamora<sup>2</sup>, M. C. Alarcon<sup>1</sup>,  
C. Galeano<sup>1</sup>, F. J. Burgos<sup>3</sup>,  
J. J. Villafruela<sup>1</sup>, J. Ortuno<sup>1</sup>

<sup>1</sup>Nephrology, Hospital Ramon y Cajal, Madrid, Spain; <sup>2</sup>Statistical, Hospital Ramon y Cajal, Madrid, Spain; <sup>3</sup>Urology, Hospital Ramon y Cajal, Madrid, Spain

New therapeutic strategies in kidney transplantation (KT) are difficult to evaluate because usual end-points are poor tools in the long run, and time-to-event of potentially useful end-points such as graft loss is too long. Consequently, short-term variables predicting long-term evolution of KT would be very useful for patient management. Early SCr may be a good marker of long-term survival, but published studies are based on registry data and 5-year survivals.

We have analyzed the value of SCr achieved during the first 12 months af-

ter KT in the prediction of long-term graft survival (over 10 years) in our 754 patients receiving a first cadaveric KT between November 1979 and August 2003 functioning more than 30 days. Univariate Kaplan-Meier analysis showed that SCr at 1, 3, 6 and 12 months stratified in three groups ( $\leq 1.5$ , 1.6-2 and  $> 2$  mg/dl) had an excellent predictive power of 10-year graft survival [SCr 3 mo: actual half-life of grafts with SCr  $< 1.5$  vs 1.6-2: 19.2 vs 14.3 yr (p=0.03);  $< 1.5$  vs  $> 2$ : 19.2 vs 10 yr (p=0.002)]. Early KT era, immunosuppression without tacrolimus or MMF, male sex and acute rejection during the first year, were also predictors of graft loss. Cox multivariate analysis always showed SCr as an independent predictor: SCr at 3 mo:  $< 1.5$  HR of 1 (reference); SCr 1.6-2 HR 1.47 (95%CI 1.09-1.98, p=0.013), SCr  $> 2$  HR 2.36 (95%CI 1.71-3.25, p=0.0000), SCr at 12 mo:  $< 1.5$  HR 1; SCr 1.6-2 HR 1.51 (95%CI 1.09-2.08, p=0.012), SCr  $> 2$  HR 3.12 (95%CI 2.24-4.34, p=0.0000). Graft function at 30 days post-KT predicts long term graft function (over 10 years). This predictive capacity improves with SCr at 3, 6 and 12 months. Mild differences in SCr such as between 1.5 and 1.6-2 are associated with highly significant impacts in long-term survival, longer than previously described.

## Impact of Sensitization to HLA Antigens on Receiving a Second Kidney Transplant after a Failed Graft

P. Eren<sup>1</sup>, S. Goral<sup>2</sup>, R. Bloom<sup>2</sup>,  
A. Doyle<sup>2</sup>, R. Grossman<sup>2</sup>, A. Israni<sup>2</sup>,  
A. Naji<sup>3</sup>, M. Sellers<sup>3</sup>, J. Markmann<sup>3</sup>,  
J. Kearns<sup>1</sup>, M. Kamoun<sup>1</sup>  
<sup>1</sup>Pathology and Laboratory Medicine;  
<sup>2</sup>Medicine; <sup>3</sup>Surgery, University of  
Pennsylvania, Philadelphia, PA, USA

Highly sensitized patients, determined by the presence of panel reactive antibodies (PRA), wait a long time for a kidney transplant. We retrospectively analyzed 154 patients who were re-listed and active for a second kidney transplant between 4/1995-7/2004 to determine the variables affecting their chances of receiving another transplant. In our center, in order to receive a second kidney, re-listed patients who have developed anti-HLA antibodies must have a compatible T and B cell cross-match by flow cytometry using current and historic serum samples. In addition, we avoid repeat HLA-A, B, and DR mismatches by assigning "unacceptable antigens" for these patients. In this study, all patients who waited  $\geq 4$  years had anti-HLA antibodies. Overall, 77% of all patients listed for a second transplant had anti-HLA antibodies: 62% had class I with or without class II; 15% had only class II antibodies. Of the 154 re-listed patients, 45 (29%) received a second kidney transplant. Thymoglobulin was used in all patients for induction. Baseline demographics are as follows: re-grafts (group 1, n=45): 62% male, 38% female, blood group: 44% O, 36% A, 13% B and 9% AB; and patients who remained on the waiting list (group 2, n=109): 57% male, 43% female, blood group: 52% O, 25% A, 21% B, and 2% AB. 59% of all patients in group 1 were transplanted within the first 3 years after being re-listed; the median waiting time was 793 days (range: 25 d-5.8 yrs). Patients with blood group O and B were less likely to be re-transplanted than patients with blood group AB and A ( $p=0.04$ ). 60% of patients who received a second transplant had anti-HLA antibodies detected by flow cytometry particle assay. 20% of re-grafted patients had PRA  $>20\%$  to HLA class I antigens, whereas 42% had PRA  $>20\%$  to HLA class II antigens.

Patients in group 2 had much higher PRA values than group 1. 67% of re-grafted patients received a 0 or 1 HLA-DR mismatched kidney, and 54% received a 0, 1 or 2 HLA-B/DR mismatched cadaveric kidney. This distribution of HLA-B and -DR matching in these re-grafted patients is very similar to that observed among all our transplant recipients, and it is consistent with what one would expect with the previous UNOS allocation policy, which gave priority for B and DR matching. Among re-grafted patients, 5 patients were treated for acute rejection (AR) (11%), four successfully. Two patients returned to dialysis. Median follow-up was 375 days (range: 18 d-5.8 yrs).

We conclude that, with current immunosuppressive regimens, in the setting of stringent HLA T and B cell cross-matching criteria, highly sensitized patients who were re-listed for a second transplant can have successful transplant outcomes with very low AR rates. Patients who remain on the list for 4 years or longer have significant amount of anti-HLA antibodies, which decreases their chance of receiving another transplant.

## Cytokine TNF- $\alpha$ , IL-10, IL-6, IFN- $\gamma$ Gene Polymorphisms and Long Transplanted Kidney Graft Survival

U. Siekiera<sup>3</sup>, J. Chudek<sup>1</sup>,  
H. Karkoszka<sup>1</sup>, L. Cierpka<sup>2</sup>, A. Wiecek<sup>1</sup>  
<sup>1</sup>Department of Nephrology Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice, Poland; <sup>2</sup>Department of General, Vascular and Transplantation Surgery, Medical University of Silesia, Katowice, Poland; <sup>3</sup>Tissue Typing Laboratory, Blood Center, Katowice, Poland

**Aims:** Proinflammatory cytokines are involved in the pathogenesis of chronic allograft nephropathy and influencing long-term graft function in patients after kidney transplantation. It was demonstrated that polymorphisms of TNF- $\alpha$ , IL-10, IL-6, and IFN- $\gamma$  modulate the synthesis of these cytokines. The aim of our study was to analyze relationship between genotypes, of above mentioned polymorphisms, and kidney function up

to 36 months after successful cadaveric kidney transplantation.

**Methods:** Genotyping was performed in 240 subsequent cadaveric kidney recipients transplanted in one center from 1998 to 2002. Genomic DNA was obtained from peripheral leukocytes. Identification of cytokine genotypes was based on PCR-SSP method for TNF- $\alpha$  at position (-308 A/G), IL-10 at positions (-1082 A/G, -819 T/C, -592 A/C), IL-6 at position (-174 G/C) and IFN- $\gamma$  at position (+874 T/A). Genotypes were grouped according to the strengths of expression of cytokines. Graft function was analyzed after 12, 24 and 36 months. In 18 out of 240 patients primary graft non-function (PGN) was observed. During the follow up period 33 patients underwent graftectomy due to chronic allograft nephropathy (CAN) and 12 patients died with functioning kidney allograft. Patients with PGN and those who died were excluded from survival analyses.

**Results:** A faster, significant decline of kidney graft function was observed in patients with genotypes: TT IFN- $\gamma$  (+874 T/A), GG and GC IL-6 (-174 G/C), and GG TNF- $\alpha$  (-308 A/G). Only in case of IL-6 polymorphism its influence on graft survival was confirmed. According to the Kaplan-Meier method the graft survival was in patients with GG and GC genotypes (determinating higher IL-6 production) significantly shorter worse (F-Cox test  $p=0.02$ ) than in patients with CC genotype (lower IL-6 synthesis). We did not observe any significant influence of IL-10 polymorphisms (-1082 A/G, -819 T/C, -592 A/C) on graft function or survival.

**Conclusions:** IL-6 promotor G174C genotype CC is associated with better kidney graft survival, and genotype TT of IFN- $\gamma$  intron 1 or genotype GG of TNF- $\alpha$  promotor with faster decline of graft function than any other genotypes of this cytokine.

## Complement C4d Deposition in Transplanted Kidneys and Long-Term Graft Survival

N. Kawamura<sup>1</sup>, M. Tomita<sup>1</sup>,  
M. Hasegawa<sup>1</sup>, K. Murakami<sup>1</sup>,  
K. Nabeshima<sup>1</sup>, H. Kushimoto<sup>1</sup>,  
K. Takahashi<sup>1</sup>, Y. Hiki<sup>1</sup>, N. Usuda<sup>2</sup>,  
T. Kinukawa<sup>3</sup>, S. Sugiyama<sup>1</sup>  
<sup>1</sup>Nephrology, Fujita Health University,  
Toyoake, Aichi, Japan; <sup>2</sup>Anatomy, Fu-  
jita Health University, Toyoake, Aichi,  
Japan; <sup>3</sup>Urology, Shakai Hoken Chukyo  
Hospital, Nagoya, Aichi, Japan

Antibody-mediated rejection has been considered to possibly coexist with acute cellular rejection and to contribute to graft injury. Circulating antidonor antibody and complement C4d deposition in peritubular capillaries are recognized as definite markers of antibody-mediated rejection. On some studies, antibody-mediated rejection is suspected to be responsible for chronic rejection. However, there have been few reports on the influence of antibody-mediated rejection on graft survival. The aim of this study is to clarify the influence of the C4d deposition in peritubular capillaries on long-term graft survival.

**Methods:** Inclusion criteria for the study were a graft biopsy performed during acute deterioration of graft function within the first two years after transplantation. Patients whose graft did not survive more than one year were excluded from the study. Recipients of donations from an HLA identical sibling or from an ABO incompatible donor were excluded. In 92 patients, one to four paraffin-embedded specimens in each patient were suitable for the study. C4d staining was performed on paraffin sections using a polyclonal rabbit anti-C4d antibody (Biomedica, Vienna, Austria). Peritubular capillary C4d staining was estimated positive if peritubular capillaries in at least a quarter of the cortical area were stained. When any C4d staining was present along glomerular capillary wall, positivity was estimated. In patients who had undergone two or more graft biopsies, C4d staining was scored positive even if only one of the specimens was stained positive.

**Results:** Among 92 patients, 22 patients (23.9%) had positive peritubular capillary C4d staining in at least one

graft biopsy specimen. In seven of 22 patients, glomerular capillary C4d staining was positive. Fifteen patients (16.3%) had glomerular capillary C4d deposition with/without peritubular capillary C4d staining. In eight patients, glomerular capillary C4d staining without peritubular capillary staining was evident. Concerning the impact of C4d deposition on long-term graft survival in recipients with peritubular capillary C4d deposition was significantly lower than that of C4d negative recipients ( $p=0.0419$ ). C4d staining in glomerular capillaries did not have any impact on long-term graft survival. Patients with both peritubular and glomerular capillary C4d staining had significantly lower rate of graft survival than those with negative staining of both peritubular and glomerular capillaries ( $p=0.0283$ ).

**Conclusion:** C4d deposition in peritubular capillaries has a substantial impact on long-term graft survival.

## Serum Advanced Glycation End Products and Matrix metalloproteinase-9 after Renal Transplantation

O. Mareckova<sup>1</sup>, V. Teplan<sup>1</sup>, O. Schuck<sup>1</sup>,  
J. Lacha<sup>1</sup>, S. Vitko<sup>1</sup>, M. Kalousova<sup>2</sup>,  
K. Sebekova<sup>3</sup>  
<sup>1</sup>Dept. Nephrol Transplant Centrum,  
Inst Clin Exp Medicine, Prague, Czech  
Republic; <sup>2</sup>1st Medical School, Charles  
Univ., Prague, Czech Republic; <sup>3</sup>IPCM,  
Bratislava, Slovakia

Increased serum levels of advanced glycation end products (AGEs) in chronic kidney disease (CKD) have been repeatedly demonstrated. The questions to be still clearly answered include whether or not the increase in serum AGEs is related to kidney function and whether or not the increasing graft function after renal transplantation (RTx) is associated with a decrease in serum AGEs. Matrix metalloproteinase-9 (MMP-9) play a role in renal tubule physiology and an increase in MMP-9 activity is associated with endothelial dysfunction.

**Methods:** Using fluorimetry FI(AU), serum AGEs were determined in a group of 22 healthy controls - 10 males,

12 females, age 51 (24-77) years and in 2 groups of patients: (1) 67 pts with CKD - 37 male, 31 female, age 48.8 (20-76) and (2) 59 pts after RTx - 39 male, 20 female, age 47.5 (22-76). Renal function was determined by inulin clearance. MMP-9 was determined in serum by ELISA in controls and RTx recipients.

**Results:** Serum AGEs were significantly increased in CKD and RTx pts versus controls ( $682 \pm 145$  and  $857 \pm 195$  versus  $443 \pm 130$  FI AU,  $p<0.01$ ). There was a significant inverse correlation between serum AGEs and inulin clearance in CKD ( $r=0.689$ ,  $p<0.001$ ) and after RTx ( $r=0.689$ ,  $p<0.01$ ). When comparing pts with the same renal function, serum AGEs after RTx were significantly higher than in CKD patients. MMP-9 was increased in pts after RTx - median 706 versus 355 ng/ml in controls,  $p<0.05$ . The increase in MMP-9 was related neither to inulin clearance nor to AGEs.

**Conclusion:** Serum AGEs were significantly related to kidney function. In patients after RTx, increasing graft function was associated with a decrease in serum AGEs. For a comparable level of kidney function, the increase in serum AGEs in patients after RTx was significantly higher than that in patients with CKD. MMP-9 was significantly increased in patients after RTx, but without any relation to inulin clearance.

## Venous Thromboembolism in Renal Transplant Recipients: High Rate of Recurrence

A. Rosati<sup>1</sup>, E. Berton<sup>1</sup>, A. Larti<sup>1</sup>,  
P. Becherelli<sup>1</sup>, D. Poli<sup>2</sup>, R. Marcucci<sup>2</sup>,  
D. Prisco<sup>2</sup>, R. Abbate<sup>2</sup>, M.o Salvadori<sup>1</sup>  
<sup>1</sup>Renal Transplantation, Careggi Uni-  
versity Hospital, Florence, Tuscany, It-  
aly; <sup>2</sup>Thrombosis Center, Careggi Uni-  
versity Hospital, Florence, Tuscany, It-  
aly

Renal transplant (RT) recipients have an increased risk of venous thromboembolism (VTE), possibly due to an impaired fibrinolysis and a persistent hypercoagulable state. A significant rate of recurrences after a first episode of VTE has been reported following the discontinuation of oral anticoagulant therapy (OAT).

The aim of this case-control study was to evaluate whether the rate of VTE recurrence after a first episode of VTE was higher in RT recipients in comparison to the other VTE patients.

During the follow-up 34 of 484 RT recipients developed a first episode of VTE and were accordingly treated. 28 patients stopped OAT after a median time of 6 months (group 1) and were enrolled in a prospective study to evaluate the incidence of recurrent VTE. For each of them, three patients with acute VTE without history of RT, matched for age, sex and type of thrombotic event (group 2) were also enrolled and followed-up. After OAT withdrawal all patients were studied both for thrombophilia markers as AT III, Protein C, Protein F, Factor V Leiden, Prothrombin gene G20210A, antiphospholipid antibodies, homocysteine and for clotting activation markers as prothrombin fragment 1+2 (F1+2) and D-dimers.

Group 1 patients (median age 58, 16 males and 12 females) were followed-up after discontinuation of AOT for a median time of 25.5 months. 2 group 1 patients during OAT had major bleeding complications (rate 9.5 per 100 patient-years). Group 2 patients (median age 59 years, 53 males and 31 females) had a median follow-up period of 21 months. During OAT, no major bleeding complication was recorded in this group. During follow-up period 14 out of 28 patients of group 1 (50%) experienced VTE recurrence with a median time of 18 months after OAT withdrawal. In group 2, 8 of 84 patients (9.5%) developed recurrence with a median time of 10.5 months after OAT withdrawal. The difference of event rate between the two groups was statistically significant ( $p < 0.0005$ ). A univariate analysis in relation to recurrent VTE events, showed that the recurrence were associated to RT history (OR 10; 95%CI 2.5-41.8;  $p < 0.005$ ). A multivariate analysis, adjusted for age and the presence of active cancer, confirmed the history of RT as an independent risk factor for VTE recurrence (OR 10.9; 95% CI 3.5-33.2;  $p < 0.0001$ ). Concerning the hypercoagulability condition, hyperhomocysteinemia was found in 24/28 group 1 patients and in 23/84 group 2 patients ( $p < 0.0001$ ). F1+2 and D-dimer levels were significantly higher in group 1 than in group 2 ( $p = 0.0001$ ).

The original finding of our study is the high incidence of recurrent VTE after OAT withdrawal in RT patients after a first episode of VTE. This fact implies the need of strategies for its prevention among which prolonged OAT should be considered with a careful risk/benefit evaluation, considering the high bleeding risk of transplant patients.

### Graft Dysfunction after Parathyroidectomy in Kidney transplanted Patients with Special Reference to Serum Calcium Level

*E. Toronyi, A. Rempert, K. Földes, J. Jansen, R. Chmel, S. Török, V. Weszeliits, J. Szabó, J. Járay*  
*Transplantation, Semmelweis University, Budapest, Hungary*

Renal hyperparathyroidism usually improves after successful kidney transplantation. In certain proportion of patients, hyperparathyroidism persists and they require parathyroidectomy.

Between 1996 and 2004, 50 kidney-transplanted patients were subjected to parathyroidectomy at our Department. (31 male, 19 female). The parameters of the kidney function were analysed in the postoperative period. The average time between kidney transplantation and parathyroidectomy was 39,92 months (4-140 months) The underlying kidney disease was chronic glomerulonephritis in 22; pyelonephritis in 11; polycystic kidney disease in 11, diabetic nephropathy in 2; Schönlein-Henoch in 1 case, hypertension in 3 cases. The indication to perform parathyroidectomy was based on laboratory values (elevated iPTH, alkaline phosphatase, serum calcium) and clinical symptoms. Ultrasound, isotope and CT investigation was performed in each case.

In two patients, this operation had been preformed for the recurrence of hyperparathyroidism.

In 7 patients, a reoperation had to be performed for insufficient removal of the parathyroid glands at the primary procedure. Reoperation was carried out within one week after the first operation.

Out of the 50 patients in 40 cases, the serum calcium concentration became normal immediately after parathyroidectomy and the kidney function remained unchanged. In 10 patients a progressive deterioration of kidney graft function occurred during the second postoperative week. (Histologically proven acute non-bacterial interstitial nephritis in 2 cases, and clinical signs of acute rejection without histological investigation in 8 cases) The graft function improved after Methylprednisolone pulse therapy.

All these patients had a significantly low calcium level (average:  $1,776 \text{ mmol/l} \pm 0,396$ ) at the onset of the graft dysfunction, in contrary to the average serum calcium level of the patients with a stable graft function  $2,503 \text{ mmol/l} \pm 0,233$  ( $p < 0,01$ ) at the same time. The basic immunosuppression remained unchanged in all cases during the postoperative period. (Cyclosporin based in 38 cases, Tacrolimus in 9 cases, Sirolimus in 1 and Imuran in 1 case, combined with prednisolone and MMF).

**Conclusion:** 20% (10/50) of the patients who underwent parathyroidectomy after kidney transplantation had deterioration of the graft function after surgery. We suppose that hypocalcaemia after parathyroidectomy predisposes to graft dysfunction and this might be due to the rapid changes in the calcium metabolism with effect on the mechanism of action of calcineurin inhibitors.

### Post-Transplant Macrophage Activation is Linked to Impaired Long-term Patient and Graft Survival

*S. O. Grebe<sup>1</sup>, U. Kuhlmann<sup>1</sup>, D. Fogl<sup>1</sup>, F. T. Mueller<sup>2</sup>*

*<sup>1</sup>Department of Internal Medicine, Renal Division, Philipps University Marburg, Marburg, Hessen, Germany; <sup>2</sup>Nephrology and Transplantation Immunology, University of Alberta, Edmonton, AB, Canada*

Post-transplant kidney function and inflammatory burden are the key determinants of chronic allograft nephropathy and cardiovascular disease, the limiting factors of long-term patient and

survival. Preliminary findings indicated that early macrophage activation is associated with poorer long-term survival rates. Therefore this subject was investigated in more detail and a larger patient group in the underlying study.

In 151 (99 male, 52 female) consecutive renal transplant patients the acute phase reactants serum amyloid A (S-AA, mg/dL) and serum C-reactive protein (S-CRP, mg/L), the macrophage activation product neopterin in serum and urine (S-/U-NEOP, umol/mol creatinine), and serum creatinine (S-CREA, mg/dL) were measured daily during the immediate postoperative course (mean period of measurements per patient  $x = 27.1 + 16.8$  days, total of  $S = 3436$  days). The association between the mean values of these parameters and the survival distribution function of the 151 patients was tested using log rank and Wilcoxon tests. In this analysis graft loss was defined as either return to continuous dialysis treatment or patient death with functioning graft. The 1- and 5- year graft survival rates were 95% and 82%, the patient survival rates were 98% and 90%, respectively. The markers showed the following mean post-transplant levels: S-CREA  $x = 5.1 + 2.7$  mg/dl, S-CRP  $x = 21.8 + 16.1$  mg/l, S-AA  $x = 12.8 + 8.5$  mg/l, U-NEOP  $x = 533 + 416$  and S-NEOP  $x = 220 + 142$  umol/mol creatinine. Both, the log rank test and the Wilcoxon test (p-values not shown here) indicate that graft survival is negatively related to the post-transplant levels of U-NEOP ( $p < 0.05$ ) and S-NEOP ( $p < 0.001$ ). S-AA, S-CRP, and S-CREA were not significantly increased. Post-transplant S- and U-NEOP also correlated inversely with patient survival ( $p < 0.001$  and  $p < 0.05$ , respectively), whereas all other markers did not show a significant correlation.

Macrophage activation, expressed by interferon gamma mediated increases in neopterin, is linked to poorer patient and graft survival. The activation of macrophages, induced by T cell mediated rejection, tissue injury or viral infections, and not the inflammatory burden per se seems to be of prognostic significance regarding long-term patient and graft outcome.

## Kidney Transplantation in the Elderly: Comparison of Results after Age-Matched as Compared to HLA-Matched Transplantation

A. Voiculescu<sup>1</sup>, K. Ivens<sup>1</sup>, F. Oeczan<sup>1</sup>,  
B. Mueller<sup>2</sup>, W. Sandmann<sup>2</sup>,  
B. Grabensee<sup>1</sup>

<sup>1</sup>Nephrology, University Clinic, Duesseldorf, Germany; <sup>2</sup>Vascular Surgery and Kidney Transplantation, University Clinic, Duesseldorf, Germany

**Background:** Since January 1999 the ET-Senior Program (ESP) was initiated. In this program allocation of kidney is performed according to age (donors  $\geq 65$  years, recipients  $\geq 65$  years) without taking the HLA match into consideration but a short cold ischemia time ( $< 12$  hours) being a prerequisite. We report about our experiences with ESP as compared to transplantation of elderly patients  $\geq 60$  years with regular (HLA-matched) allocation.

**Methods:** Between January 1999 and December 2004 a total of 69 patients were transplanted within the ESP and 60 patients  $\geq 60$  years were transplanted within the regular allocation. Patients within the regular allocation as well as ESP patients transplanted between 1999 and 2001 received a triple immunosuppression with steroids, Cyclosporine (CSA) (trough levels: 180 ng/ml) and mycophenolat (MMF). Since 2002 ESP patients receive a quadruple immunosuppression with additional Daclizumab at CSA trough levels of 150 ng/ml.

**Results:** Patients from the ESP were  $66.7 \pm 2.4$  years old (regular group  $63.3 \pm 2.7$  years) and their donors were  $69.3 \pm 3.8$  years old (regular group  $48.1 \pm 1.7$ ,  $p < 0.001$ ). ESP patients had spent a shorter time on dialysis ( $49 \pm 24$  months) as compared to the elderly in the HLA-matched group ( $73.8 \pm 35.5$ ,  $p < 0.001$ ).

Results are further shown in tab.1. After initiation of quadruple immunosuppression in the ESP patients we observed a trend towards fewer rejections and less infections.

**Conclusions:** Patients receiving an age-matched organ as a part of the ESP receive a graft earlier than similar patients during HLA-matched allocation. Despite an unfavourable HLA-match but with shorter cold ischemia times the rate of delayed graft function and the number of rejections were similar between the two groups. Graft function during short time follow up is worse in the age-matched group as compared to the HLA-matched group of elderly. Long term results remains to be elucidated in the future.

## The Impact of Early Diagnosed New-onset Posttransplantation Diabetes Mellitus on Long-Term Cardiovascular Mortality and Cardiac Events

J. Hjelmseth<sup>1,2</sup>, A. Hartmann<sup>1</sup>,  
T. Leivestad<sup>3</sup>, H. Holdaas<sup>1</sup>, S. Sagedal<sup>1</sup>,  
T. Jenssen<sup>1</sup>

<sup>1</sup>Nephrology, Rikshospitalet University Hospital, Oslo, Norway; <sup>2</sup>Department of Medicine, The Hospital in Vestfold, Tønsberg, Norway; <sup>3</sup>Institute of Immunology, Rikshospitalet University Hospital, Oslo, Norway

The literature on the potential association between new-onset diabetes mellitus after renal transplantation and cardiovascular (CV) disease is scarce. The objective of the present 8-years (range; 90-106 months) prospective single-centre observational study was to assess the long-term effects of early-diagnosed new-onset diabetes on cardiac events

	ESP (n=59)	Regular (n=60)	p
Cold ischemia time	13±4,8	20±7,1	<0,001
HLA-Mismatches	4,3±1,3	2,1±1,4	<0,001
Delayed graft function (DGF)	31 (46%)	24 (43%)	ns
Rejections	26 (38%)	25 (45%)	ns
Infections (including CMV)	40 (59%)	29 (51%)	ns
Creatinine at 1 years	2,2± 0,8	1,7± 0,6	0,001
Graft loss	14 (24%)	8 (13%)	ns

(sudden death or acute myocardial infarction), CV death and all-cause mortality.

Baseline glucose tolerance and CV risk factors were assessed 3 months after renal transplantation in 173 consecutive previously non-diabetic patients, during a period of 16 months (1995-96). A total of 167 recipients underwent an oral glucose tolerance test, and 35 patients (20%) were categorised to have new-onset PTDM. In addition, we collected retrospectively baseline data from patients with pretransplant type 1 or 2 diabetes transplanted in the same period (n=29). Follow up data were registered until the 31<sup>st</sup> of December, 2003.

The cumulative incidences of cardiac events, CV deaths and all-cause mortality in recipients with no diabetes, new-onset diabetes and pretransplant diabetes were; 7%, 20% and 24%; 8%, 20% and 41%; 20%, 37% and 72%, respectively. After adjustment for age, sex and pretransplant CV disease, new-onset diabetes was associated with an approximately 3-fold increased risk of cardiac events (RR=3.3, 95% CI=1.2-9.0, P=0.017) and CV death (RR=2.7, 95% CI=1.1-7.0, P=0.038). The corresponding figures for recipients with pretransplant diabetes were 3.1, 1.1-9.3, 0.040 and 4.9, 2.0-11.8, <0.001, respectively. Pretransplant diabetes, but not new-onset diabetes, remained associated with increased mortality after multivariate Cox regression analysis (RR=4.2, 95% CI =2.3-7.7, P<0.001).

We conclude that early new-onset diabetes mellitus after renal transplantation is associated with increased long-term risk of cardiac events and CV death.

### Prophylactic Perioperative Plasmapheresis does not Prevent Rebound of Permeability Factors in Patients with Focal Segmental Glomerulosclerosis (FSGS) who Undergo Kidney Transplant

M. Quaglia<sup>1</sup>, E. Turello<sup>1</sup>, V. Morellini<sup>1</sup>, E. Lazzarich<sup>1</sup>, D. Palmieri<sup>1</sup>, C. Canavese<sup>1</sup>, C. Gennaro<sup>2</sup>, M. Carraro<sup>2</sup>, P. Stratta<sup>1</sup>  
<sup>1</sup>Nephrology and Renal Transplant, Piemonte Orientale University, Maggiore della Carità Hospital, Novara, Piemonte, Italy; <sup>2</sup>Renal Pathophysiology Laboratory, Cattinara Hospital, Trieste, Friuli, Italy

Plasmapheresis (PE) has been used as a therapy for recurrent focal segmental glomerulosclerosis (FSGS) after kidney transplantation (Tx) with some promising results. As plasma from patients with recurrent FSGS contains factors that increase glomerular permeability and cause proteinuria after injection into rats, the rationale for plasmapheresis would lie in its ability to decrease permeability, as defined by measurement of albumin permeability (P(alb)). Some reports suggest that also prophylactic perioperative PE may be beneficial in reducing the incidence of recurrent FSGS, but its long-term effectiveness is debated.

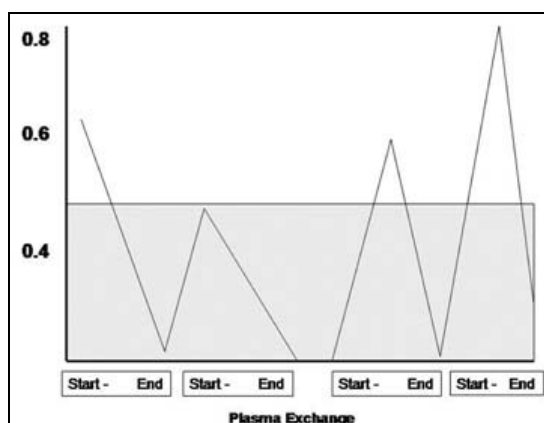
We describe our experience on 3 patients with biopsy-proven FSGS who underwent a prophylactic course of PE in the perioperative period. The first PE session was performed immediately before Tx (50 ml/kg of patient's plasma exchanged with 5% albumin) and 15

more sessions were performed afterwards (thrice weekly). Immunosuppressive therapy for all patients was based on induction with basiliximab, tacrolimus, MMF and steroid and maintenance with tacrolimus, MMF and steroid. Measurement of P(alb) was performed before and after each session to monitor PE effectiveness. 0.5 was considered a cut-off value for P(alb) positivity.

Levels of permeability factors showed a constant drop after PE sessions but in most cases a significant rebound occurred in the following 24-48 hours, with peak levels overcoming the threshold for P(alb) positivity. The kinetic of this rebound as detected in one of the patients is shown in the Figure. The gray area represents P(alb) negative values.

All of the patients have a satisfactory renal function after an average follow up of 7 months; proteinuria is 0,3-0,8 g/day in two patients and around 1 g/day in the third one.

Despite such encouraging clinical results, these data suggest that a prophylactic course of perioperative PE can only transiently reduce permeability factors levels because a rebound occurs in the interval between PE sessions. This preliminary observation suggests that prophylactic perioperative PE may provide a crucial protective effect only in the induction phase, without any apparent long-term impact on permeability factors levels. As an alternative, it is tempting to speculate that P(alb) may not be a reliable marker of PE effectiveness, which may in fact reflect removal of a wide range of different mediators. Further studies are needed to clarify the mechanisms of action of PE therapy in FSGS.



## Night-time Blood Pressure Load and Cardiovascular Risk in Renal Transplant Recipients

M. Balal<sup>1</sup>, S. Paydas<sup>1</sup>, M. Koc<sup>2</sup>,  
E. Demir<sup>3</sup>, Y. Sertdemir<sup>4</sup>, E. Acarturk<sup>2</sup>  
<sup>1</sup>Nephrology, Cukurova University, Adana, Turkey; <sup>2</sup>Cardiology, Cukurova University, Adana, Turkey; <sup>3</sup>Urology, Cukurova University, Adana, Turkey; <sup>4</sup>Biostatistics, Cukurova University, Adana, Turkey

Ambulatory blood pressure monitoring correlates better with than office blood pressure for cardiovascular damage. The aim of this study was to determine the influences of systolic and diastolic blood pressure load, insulin resistance, body mass index on right-left ventricular (RV-LV) M-mode, pulse wave Doppler and tissue Doppler (TDI) echocardiography measurements in renal transplant recipients, dialysis patients and healthy volunteers.

Thirty-two nondiabetic renal transplant recipients (RTx, GI) with functioning graft, 18 dialysis patients (GII) and 19 healthy volunteers (GIII) were included into the study. There were no differences among groups for age, gender, body mass index and insulin resistance (for all,  $p > 0.05$ ). The mean day-time systolic blood pressure (SBP) in GI, GII, and GIII were  $120.56 \pm 17.37$ ,  $127.29 \pm 27.02$  and  $112.63 \pm 1.49$  mmHg respectively, ( $p > 0.05$ ). The mean day-time diastolic blood pressure (DBP) in GI, GII, and GIII were  $80.05 \pm 12.56$ ,  $81.20 \pm 15.92$  and  $75.54 \pm 6.61$  mmHg respectively, ( $p > 0.05$ ). The mean night-time SBP in GI, GII, and GIII were  $119.77 \pm 17.41$ ,  $120.23 \pm 25.53$  and  $99.90 \pm 9.30$  mmHg respectively, ( $p$  I-II 1.0, PI-III 0.000, p II-III 0.013). The mean night-time DBP in GI, GII, and GIII were  $77.34 \pm 14.46$ ,  $76.17 \pm 18.77$  and  $64.35 \pm 8.77$  mmHg respectively, ( $p$  I-II 0.99, p I-III 0.001, p II-III 0.06). Although the mean day-time SBP, DBP and MBP were similar in three groups, the mean night-time SBP and DBP in GI and GII were higher than controls.

Also, while day-time SBP and DBP load were similar in three groups (for all,  $p > 0.05$ ), night-time SBP and DBP load in GI and GII were higher than controls ( $< 0.05$ ).

Pulse wave Doppler LV A wave (MVA), ratio of E/A, deceleration time (MVDT) and RV A wave (TVA), ratio of E/A in RTx were significantly different from GII and GIII and these parameters were between GII and GIII. But, there were no significance for TDI between GI and II.

In RTx, there were significantly correlations between night-time SBP load and septal wall thickness (IVS), LV end-diastolic diameter (LVd), posterior wall thickness (PWd), LV mass index (LVMI), MVA, LV E/A, TVA, RV systolic peak velocity (Sm) and also, between night-time DBP load and LVd, PWd, LVMI, TVA and LV early diastolic peak velocity (Em).

In RTx, there were also significant correlations between day-time SBP load and LV E wave (MVE), PWd and between day-time MAP and LVd, PWd, LVMI, TVA, LV Em, LV Em/Am. Consequently, in RTx even if renal functions, electrolyte imbalance, anemia and day-time blood pressure return to normal values, especially night-time SBP-DBP load are high and between dialysis patients and controls. Also, in RTx there were significant correlations between night-time SBP-DBP load and structural-functional cardiac damage. Even though, day-time blood pressures are normal in these patients, elevated night-time blood pressures load can cause cardiovascular complications and it should be considered to treat.

## Identification of Current Smokers Among Renal Transplant Recipients (RTR)

P. Nguyen<sup>1</sup>, L. Galanti<sup>2</sup>, Y. Pirson<sup>1</sup>,  
M. Jadoul<sup>1</sup>  
<sup>1</sup>Nephrology, Cliniques Universitaires St Luc, Brussels, Belgium; <sup>2</sup>Clinical Biology, Cliniques Universitaires de Mont-Godinne, Yvoir, Belgium

**Background:** The adverse health effects of smoking are well known, both in the general population and in RTR. In the latter group, smoking is associated with a higher burden of cardiovascular diseases and a higher risk of graft loss.

In contrast, little attention has been paid hitherto to the identification and description of the smoking group of RTR, a prerequisite for successful interventions aiming at reducing smoking in this high risk population.

**Methods:** We included (Feb 3<sup>rd</sup> - October 5<sup>th</sup> 2004) consecutive RTR residents in Belgium, with an isolated renal graft functioning for at least 1 year, returning for their periodic control. They were asked to fill out a validated questionnaire (Fagerström test for nicotine dependence). Standard demographic, physical, biochemical, urinary and comorbidity parameters were recorded. Cotinine, the main metabolite of nicotine, was measured in serum: in the absence of nicotine substitution therapy, its detection is a reliable marker of active smoking.

**Results:** We included 233 RTR (142 males), aged  $53 \pm 13$  years (y) (98% Caucasian, 13% diabetic), with a functioning graft (Cockcroft:  $61.6 \pm 24.8$  ml/min) for  $8 \pm 6.7$  y, after  $2.5 \pm 2.6$  y dialysis.

One hundred and six RTR (45%) reported to be lifetime and current non-smokers: cotinine was undetectable in all.

One hundred and twenty-seven RTR (55%) reported a lifetime history of smoking: 95 of them (75%) succeeded in stopping (cotinine -) whereas 32 (25%) are current smokers according to cotinine dosage. Twenty-one of the current smokers (66%) declared to the nephrologist they kept on smoking and 11 (34%) told they quit whereas cotinine was detected.

Most (80%) of the current declared smokers smoke cigarettes and the average number of cigarettes smoked per day is  $10 \pm 1$ . The first cigarette is smoked on average 1 hour after getting up in the morning.

Current smokers (cotinine +) and non-smokers are similar regarding gender, diabetes, time on dialysis, time after TP and Cockcroft whereas smokers are younger ( $47 \pm 13$  y) than non smokers ( $54 \pm 13$  y),  $p < 0.01$ .

**Conclusion:** The identification of current smokers should start with questioning about lifetime history of smoking and if positive, measurement of serum cotinine. Indeed up to 34% of RTR current smokers are reluctant to acknowledge they are active smokers. The younger age group has a high prevalence of smoking and thus appears as a

priority target for interventions aiming at encouraging stopping smoking.

## Changes in Left Ventricular Mass after Successful Renal Transplantation

D. Montanaro<sup>1</sup>, M. Gropuzzo<sup>1</sup>, P. Tulissi<sup>1</sup>, C. Vallone<sup>1</sup>, G. Boscutti<sup>1</sup>, A. Risaliti<sup>2</sup>, U. Baccarani<sup>2</sup>, G. L. Adani<sup>2</sup>, M. Sainz<sup>2</sup>, D. Lorenzin<sup>2</sup>, F. Bresadola<sup>2</sup>, G. Mioni<sup>1</sup>  
<sup>1</sup>Department of Nephrology, "S.Maria della Misericordia" Hospital, Udine, Udine, Italy; <sup>2</sup>Department of Surgery, University of Udine, Udine, Udine, Italy

Left ventricular hypertrophy(LVH) is an independent cardiovascular risk factor in the general population and in patients with chronic renal failure. Relatively little is known about the effects of renal transplantation(RTx) on LVH. The aim of this study was to determine the changes of left ventricular mass(LVM) after a successful RTx and to evaluate the importance of some clinical, laboratory and echocardiographic variables on the trend of LVH after RTx.

A total of twenty three adult renal transplant recipients were included in this study. Before and at two years after RTx we evaluated: serum level of creatinine (Creat), calcium (TCa), phosphorus (Pi), alkaline phosphatase (AP), parathyroid hormone (PTH), hematocrit (Htc), albumin (Alb), total cholesterol (Chol), triglycerides (Trigl), body mass index (BMI), casual blood pressure (BP), ambulatory 24-hr BP monitoring (ABPM), LVM and left ventricular mass index (LVMI) by echocardiography. LVH was defined as a LVMI value greater than 134 and 110 g/m<sup>2</sup> for men and women, respectively.

During follow - up there was a significant increase in Hct (29.8 ± 5.6 vs 40.3 ± 8.7 %, p<.001), Chol (187.7 ± 50 vs 238 ± 43.7 mg/dl, p<.01), Trigl (141 ± 45 vs 187 ± 34 mg/dl, p<.03), BMI (21.8 vs 23.6 ± 5, p<.001) and a significant decrease of Creat (11.5 ± 3.2 vs 1.5 ± 0.4 mg/dl, p<.001), Pi (5.7 ± 1.5 vs 3.6 ± 0.3 mg/dl, p<.001) and PTH (199.3 ± 98 vs 82.8 ± 42.2 pg/ml, p<.01). At two years after RTx all 23 patients showed a good renal function

(Creat <2mg/dl). During the study period there was a significant decrease of mean 24-hr systolic BP (148.2 ± 13.8 vs 139.2 ± 15.3 mmHg, p<.006), 24-hr diastolic BP (94.1 ± 12 vs 90.3 ± 11.3 mmHg, p<.01), 24-hr systolic BP load (66.2 ± 36.2 vs 43.6 ± 36.8 %, p<.02), LVM (246.2 ± 83.6 vs 202.7 ± 57.8 g, p<.01), LVMI (161.4 ± 48.2 vs 122.1 ± 27.7 g/m<sup>2</sup>, p<.007) and of the prevalence of LVH (76 vs 53 %, p<.03). Moreover we correlated the LVM and the LVMI with some supposedly associated variables such as age, sex, dialysis time, weight, BMI, Htc, AP, TCa, Pi, PTH, Creat, Alb, LVMI before transplantation, number of antihypertensive drugs, presence of hypertension, BP registries of ABPM, patent arteriovenous fistula, angiotensin-converting enzyme inhibitors and angiotensin II type-1 receptors blockers use. By analysis of multiple stepwise linear regression model the variables that independently predicted LVM and LVMI at two years following RTx were 24-hr systolic BP (p<.004 and .003, respectively) and 24-hr BP load (p<.006 and .007, respectively).

In conclusion a successful RTx causes a regression of LVH. This beneficial effect is dependent on a decrease in the systolic BP levels.

## Insulin Resistance is Related to an Early Reduced Function in Renal Transplant Patients

P. Messa<sup>1</sup>, B. Brezzi<sup>1</sup>, E. Bertoni<sup>2</sup>, A. Aroldi<sup>1</sup>, P. Passerini<sup>1</sup>, P. Beccherelli<sup>2</sup>, M. Salvadori<sup>2</sup>  
<sup>1</sup>Nephrology, Dialysis and Transplantation, Ospedale Maggiore -IRCCS, Milano, Italy; <sup>2</sup>Nephrology, Dialysis and Transplantation, Ospedale Careggi, Firenze, Italy

Insulin resistance (IR), a well-known causal factor of post-transplant diabetes mellitus (PTDM), might also play a causal role in the progression of transplant renal impairment. The aim of the present study was to investigate whether IR, assessed by both the short insulin test (SIT) and HOMA, is by any way related to either PTDM development and/or reduced graft function, in

the early post-transplant period. We studied 56 non diabetic renal transplant patients (RTx) (16 F, age 20-65 yrs) at the 6<sup>th</sup> month after RTx. All pts were treated with steroids, Cya or FK506, and MMF. Glucose, Insulin, Homa index were measured in fasting serum samples on two different days; SIT was performed by calculating the 1<sup>st</sup> order coefficient of glucose changes after i.v. insulin bolus (0.1/kg of b.w.). At the 6<sup>th</sup> month 44 patients had normal fasting glucose (NFG; glu < 110 mg/dl), 4 patients had impaired fasting glucose (IFG: glu 110-126 mg/dl), and 8 patients had developed PTDM (glu > 126 mg/dl, or hypoglycemic drug use). The SIT and Homa values in the 3 groups of RTx patients are shown in the Table 1. PTDM patients were characterized by significantly higher levels of both SIT and HOMA values, as compared with NFG patients.

The possible relationship between the levels of creatinine at the 6th month and IR, assessed by both SIT and HOMA, and PTDM was explored by a multiple stepwise regression analysis. Table 2 summarizes the main results of the analysis (overall model: F 3.03, p=0.044). SIT values, but not HOMA index, were predictive of higher creatinine levels, independently on the presence or otherwise of diabetes.

In conclusion, PTDM is associated with altered IR, evaluated either by SIT or HOMA index. IR, when evaluated with a more proper method such as SIT, seems to be also related to a worse renal outcome.

Table 1

	SIT 6th month	HOMA 6th month
NFG	44.4±20	2.9±1.11
IFG	28.8±3.6	5.27±5.32
PTDM	17.4±12.2 b	5.82±3.19 a

a= p<0.05 vs NFG; b=p<0.01 vs NFG

Table 2

	std coeff	t	p
SIT	-0.53	2.99	0.005
HOMA	-0.098	0.55	0.58
PTDM	-0.190	0.99	0.32

## The Presence of Recipient-derived Renal Cells in Damaged Allograft Kidneys

T. Mete<sup>1</sup>, A. Ensari<sup>2</sup>, S. Sengul<sup>1</sup>,  
K. Keven<sup>1</sup>, B. Erbay<sup>1</sup>, S. Erturk<sup>1</sup>  
<sup>1</sup>Nephrology, Ankara University School  
of Medicine, Ankara, Turkey; <sup>2</sup>Pathology,  
Ankara University School of Medicine,  
Ankara, Turkey

Both experimental and clinical studies have demonstrated that stem cells may be involved in the repair processes of the renal tissues during various renal disorders including experimental glomerular disease model, acute tubular necrosis, and chronic transplant rejection. We aimed to search the presence of recipient originated cells in renal tissues from patients with allograft dysfunction.

Eleven patients who had been performed a kidney allograft biopsy because of impairment of graft functions were included in the study. Seven patients who had received a kidney allograft from sex-mismatched donors were regarded as the study group and the remaining four patients were as the controls (recipient-donor gender: male-male, n=2, positive controls; female-female, n=2, negative controls). Histopathological evaluations in the study group revealed chronic rejection in four patients (together with calcineurin toxicity in three) and acute rejection, acute tubular necrosis, and cyclosporin toxicity in one patient each. Renal biopsy specimens were examined using chromogenic in situ hybridization (CISH) method for XY cocktail probe to search if any of the tubular, mesenchymal, or

endothelial cells in allograft kidneys were derived from the recipient.

Renal biopsy samples from the positive controls revealed that tubular epithelial, mesenchymal, and endothelial cells had XY chromosome, with a few cells (1-2%) showing a signal for X chromosome, and approximately 30% of the cells had no signal for either X or Y chromosome. Biopsy samples of the negative controls revealed that all renal cells had XX chromosome (i.e., no Y chromosome was observed). Evaluation of the renal biopsy samples from the study group showed variable ratios of recipient-derived tubular (2-76%), mesenchymal (5-83%), and endothelial cells (1-53%).

The presence of recipient-derived renal cells in allograft kidneys indicates that extra-renal (probably bone marrow-derived) cells may be involved in repair processes in the allograft. Stem cells may have a contributing role in kidney diseases, though further studies are needed to clarify the underlying mechanisms.

### Effect of Renal Transplantation on Sperm Quality and Sex Hormones Level

G. Pourmand, A. Mehrsai,  
M. T. Mahmoud, M. R. Nikoobakht  
*Urology, Sina Hospital, Tehran, Tehran, Iran*

**Objectives:** we examined the effect of successful renal transplantation on semen parameters, sexual function and sex hormones profile in a clinical trial.

**Material and Methods:** A total of 30 patients on hemodialysis underwent renal transplantation. Preoperative and postoperative sperm density, motility, and morphology were analyzed. Preoperative follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin and testosterone levels were measured and compared to six months postoperative results. Sexual function was measured before and after transplantation using an abbreviated version of the International Index of Erectile Function (IIEF), with a successful outcome defined as a level of satisfaction of 4 or 5 on a 5-point scale. The paired-samples T-test was used to measure level of statically significance in all analysis.

**Results:** We found that sperm motility improved significantly ( $p < 0.05$ ) without concomitant significant changes in morphology and density ( $p > 0.05$ ). Testosterone level increased and FSH, LH and prolactin decreased significantly ( $p < 0.05$ ) after renal transplantation. Of 30 patients 16 were impotent before operation and filled the questionnaire. There was a significant positive correlation between baseline sexual function and postoperative sexual function.

**Conclusion:** Although sperm morphology and density did not improve after renal transplantation, there was highly significant changes in motility of sperms. Hormonal changes in hemodialysis patients improve after transplantation and return to near normal. Sexual function is also significantly improved. Future studies need to confirm these data.

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