Indices of systemic atherosclerosis are superior to ultrasound resistance indices for prediction of allograft survival

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Abstract

Background. In renal allograft recipients, ultrasound resistance indices (RI) have been discussed as predictors of transplant survival. RI measurements are correlated with subclinical atherosclerosis. It is thus unclear whether RI measurements represent specific markers of allograft damage or merely reflect systemic vascular damage. We studied whether RI are superior outcome predictors compared to markers of subclinical atherosclerosis and global cardiovascular risk.

Methods. In 105 renal transplant patients, intrarenal RI and common carotid intima–media thickness (IMT) were measured. Risk for coronary heart disease was determined by Framingham risk scoring (FRS). Patients were followed up for 5.4 ± 0.4 years. The combined end point was a decrease of ≥50% in estimated glomerular filtration rate, need for dialysis or death.

Results. Both an increased IMT and a high FRS were predictors of the combined end point. In contrast, increased RI did not significantly predict the combined end point in the entire cohort. Only among low-risk patients with either normal IMT or FRS ≤20%, high RI measurements were associated with allograft loss.

Conclusions. Compared to markers of cardiovascular risk or systemic atherosclerosis, renal RI are inferior outcome predictors in unselected transplant recipients. Only in patients with mild or moderate cardiovascular risk may RI measurements allow additional risk stratification.

Keywords: allograft survival; renal transplantation; ultrasound

Introduction

Duplex ultrasound has become the dominant imaging technique in kidney allograft recipients. Ultrasound-derived resistance indices (RI) were initially measured for early diagnosis of acute allograft rejection [1,2]. However, subsequent studies cast doubt on the sensitivity and specificity of RI in discriminating different causes of acute allograft dysfunction [3].

Interest in measurements of RI re-emerged in 2003 when a large cohort study reported that RI measurements ≥80 were better independent predictors of renal allograft loss than all other classical and non-classical risk markers tested [4]. These findings were seemingly confirmed in two smaller retrospective cohort studies in which RI predicted long-term allograft functions in unadjusted analyses [5,6].

When measuring renal RI in order to predict long-term transplant survival, it was hypothesized that these indices will provide some specific information on allograft function, vascularization and/or histology, such as the extent of chronic morphological changes in chronic allograft nephropathy. Initially, it was suggested that high ultrasound indices directly reflect increased intrarenal vascular resistance resulting, e.g. from a reduction in intrarenal vessel area [7], which resulted in their denomination as ‘resistance indices’.

Unfortunately, few physiological or histological data support this hypothesis. Instead, ultrasound RI are a complex composite of vascular factors reflecting pulse pressure and compliance of the central arterial tree rather than renal vascular resistance alone [8].

In line with this, earlier cohort studies from Krumme and coworkers [9] and from our group [10] showed that recipient age is associated with RI, whereas donor age is not, again suggesting a major impact of systemic vascular changes on these ultrasound indices. Subsequently, we recently reported a significant correlation of elevated RI with cardiovascular risk factors and with markers of systemic atherosclerotic disease, but not with transplant function, in a cross-sectional cohort study comprising 105 allograft recipients [10]. These results were confirmed by Schwenger and coworkers [11] who reported an independent association of renal RI with pulse wave velocity, a marker of systemic vascular stiffening, but not with transplant function.

We now analyse the long-term outcome of those 105 allograft recipients who had been recruited for our initial study on RI, systemic atherosclerotic disease and cardiovascular risk factors [10].

We hypothesize that, if renal RI do not merely reflect systemic vascular damage, but provide at least some al-
lograft-specific information, they should be superior prognostic factors of transplant survival compared to established markers of systemic atherosclerotic burden.

Materials and methods

Between September 2003 and July 2004, 105 renal allograft recipients (60 male and 45 female) were included in a prospective cohort study. The baseline characteristics of the study cohort have been reported before [10].

Briefly, all patients had been transplanted for at least 6 months before study initiation (mean 83 ± 64 months). We excluded patients with rapid deterioration of renal function, with hydrenephrosis of grade 2 or higher or with angiographically proven, untreated renal artery stenosis resulting in a 50% reduction of the luminal diameter. Informed consent was obtained from all patients, and the study design was approved by the local ethics committee.

At study entry, all ultrasound measurements were performed by a single investigator who was blinded to the study hypothesis (M.K.G.). On the same day, plasma glucose, creatinine, total cholesterol and high-density lipoprotein (HDL cholesterol) were measured using standard techniques. Estimated glomerular filtration rate (eGFR) was calculated using the adjusted Modification of Diet in Renal Disease Study equation 3 [12]. Proteinuria was measured in morning specimens using the protein-to-creatinine ratio [12].

A standardized questionnaire was used to record a history of smoking, diabetes, current drug intake, cardiovascular comorbidity and a family history of premature onset of cardiovascular disease (defined as myocardial infarction or stroke before the age of 65 years in first-degree relatives). Additionally, comorbidity was assessed by chart review. Prevalent cardiovascular disease was defined as a history of myocardial infarction, coronary artery angioplasty/stenting/bypass surgery, major stroke, carotid endarterectomy/stenting, non-traumatic lower extremity amputation or lower limb artery bypass surgery/angioplasty/stenting.

Anthropomorphometric measurements and resting blood pressure were recorded. Body mass index (BMI) was calculated as the individual's body weight divided by the square of their height.

Patients with self-reported diabetes mellitus with a non-fasting blood sugar level of >200 mg/dl, with a fasting blood sugar level of >126 mg/dl or with current use of hypoglycaemic medication were categorized as diabetic. Patients were categorized as active smokers if they were current smokers or had stopped smoking <1 month before entry into the study.

Categories of risk for coronary heart disease (CHD) were determined by Framingham risk scoring (FRS). According to the Third Report of the National Cholesterol Education Program, patients were classified to have 'high coronary heart disease risk' if they had a risk score of >20%, including all patients with prevalent cardiovascular disease (as defined above) and/or with diabetes mellitus (‘FRS > 20’, corresponding to a 10-year CHD risk >20%) [13].

Renal resistance index

Colour Doppler examinations were performed with a phased-array transducer (Acuson Sequoia, Mountain View, CA, USA; B-mode frequency, 5 MHz; Doppler frequency, 2.5 MHz) in supine position.

Intrarenal Doppler spectra were obtained from the interlobar arteries along the border of medullary pyramids at five representative locations, and the resistance index was calculated according to the following formula:

$$RI = \left(1 - \frac{\text{maximum end diastolic velocity}}{\text{maximum systolic velocity}}\right) \times 100$$

Mean RI values were calculated as the average of these five RI measurements. We arbitrarily predefined RI measurements ≥80 as pathological, as suggested by Radermacher and coworkers [4].

Carotid ultrasound studies

The intima–media thickness (IMT) of the common carotid artery was measured from high-resolution ultrasound images obtained by a linear-array 8-MHz transducer (Acuson Sequoia). With the subject in a supine position and the head slightly extended and turned to the opposite direction, longitudinal B-mode images of the distal common carotid artery and the carotid bulb were acquired. IMT was defined as the distance between the leading edges of the lumen interface and the media–adventitia interface of the far wall. Three representative IMT measurements were performed in the far wall of both common carotid arteries at predefined positions (1.0, 1.5 and 2.0 cm proximal to the bifurcation), and these six IMT readings were averaged to give the mean common carotid IMT. IMT was not measured at the site of a plaque.

All participants were followed up from the baseline examination until death or until 30 June 2009. No patient was lost to follow-up. The prespecified combined end point was a reduction of 50% or more in eGFR from the value measured at the time of ultrasonography, development of end-stage renal failure requiring the reintroduction of dialysis or death with

Table 1. Baseline characteristics of the cohort

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (n = 105)</th>
<th>No event (n = 60)</th>
<th>Event (n = 45)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.5 ± 14.5</td>
<td>49.2 ± 12.8</td>
<td>56.8 ± 15.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Women (%)</td>
<td>45 (43%)</td>
<td>33 (47%)</td>
<td>12 (34%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>20 (19%)</td>
<td>15 (21%)</td>
<td>5 (14%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>109 ± 12</td>
<td>108 ± 10</td>
<td>111 ± 14</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>27 (26%)</td>
<td>10 (14%)</td>
<td>17 (49%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>207 ± 44</td>
<td>208 ± 47</td>
<td>205 ± 42</td>
<td>0.75</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>63 ± 18</td>
<td>64 ± 18</td>
<td>62 ± 19</td>
<td>0.47</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 ± 4.2</td>
<td>24.7 ± 4.4</td>
<td>24.6 ± 3.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.7 ± 0.7</td>
<td>1.5 ± 0.5</td>
<td>2.0 ± 0.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Estimated GFR (ml/min/1.73 m²)</td>
<td>47 ± 19</td>
<td>51 ± 18</td>
<td>43 ± 21</td>
<td>0.024</td>
</tr>
<tr>
<td>Proteinuria (g/g creatinine)</td>
<td>0.42 ± 1.05</td>
<td>0.19 ± 0.54</td>
<td>0.74 ± 1.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (%)</td>
<td>61 (58%)</td>
<td>36 (51%)</td>
<td>25 (71%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Tacrolimus (%)</td>
<td>40 (38%)</td>
<td>32 (46%)</td>
<td>8 (23%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Steroids (%)</td>
<td>86 (82%)</td>
<td>57 (81%)</td>
<td>29 (83%)</td>
<td>1.00</td>
</tr>
<tr>
<td>AZA (%)</td>
<td>31 (29%)</td>
<td>19 (27%)</td>
<td>12 (34%)</td>
<td>0.50</td>
</tr>
<tr>
<td>MMF (%)</td>
<td>7 (7%)</td>
<td>6 (9%)</td>
<td>1 (3%)</td>
<td>0.42</td>
</tr>
<tr>
<td>ACE inhibitor (%)</td>
<td>25 (24%)</td>
<td>17 (24%)</td>
<td>8 (23%)</td>
<td>1.00</td>
</tr>
<tr>
<td>AT-1 antagonist (%)</td>
<td>36 (34%)</td>
<td>24 (34%)</td>
<td>12 (34%)</td>
<td>1.00</td>
</tr>
<tr>
<td>β-blocker (%)</td>
<td>63 (60%)</td>
<td>42 (60%)</td>
<td>21 (60%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Total and HDL cholesterol in milligrammes per decilitre may be converted to millimoles per litre by multiplying by 0.02586; serum creatinine in milligrammes per decilitre may be converted to micromoles per litre by multiplying by 88.4.
a functioning graft. Death-censored transplant failure (eGFR reduction of ≥50% or reinstatement of dialysis, excluding patients suffering from acute allograft failure within 28 days before death) was assessed as secondary end point.

Serial measurements of RI

A subgroup of 34 patients had taken part in an ultrasound study performed 4 years earlier by us [14]. We analysed whether an increase in RI measurement between two elective ultrasound studies (from the initial examination in 2000 to the baseline examination of the present study in 2003/04) in stable transplant recipients would be a better predictor of subsequent allograft failure than a single ultrasound measurement. In addition, the increase in RI measurements between 2000 and 2003/04 was correlated with the following decrease in eGFR from 2003/04 to 2009.

Statistical analysis

Categorical variables are presented as percentage of patients and compared by Fisher's exact test. Continuous data are expressed as means ± standard deviation and compared by the Mann–Whitney test. Spearman’s correlation coefficients were calculated for measuring the relationship between continuous data.

For comparing the prognostic impact of high RI (predefined as RI ≥ 80), subclinical atherosclerosis (predefined as IMT > 0.8 mm) and high CHD risk by FRS (predefined as FRS > 20%), respectively, Kaplan–Meier survival curves were calculated and compared by the log-rank test.

Cox proportional hazards models were calculated to examine relationships of high RI, subclinical atherosclerosis and high CHD risk by FRS, respectively, with event-free survival after adjustment for those risk factors that were predictors of transplant loss in univariate analysis.

Finally, in the subgroup of 34 patients who had participated in our earlier ultrasound study in 2000 [14], event-free survival from 2003/04 until 30 June 2009 was compared between those patients who had had an increase in renal RI from the initial ultrasound study in 2000 to the baseline measurement of the present study in 2003/04 (n = 18) and those patients with stable or decreasing RI measurement between both measurements (n = 16; Kaplan–Meier analysis with subsequent log-rank test).

Data management and statistical analysis were performed with SPSS 13.0.1. The level of significance was set at P < 0.05.

Results

The combined end point occurred in 45 out of 105 transplant recipients. Twenty-six patients had a reduction of ≥50% in eGFR and/or need for dialysis (of whom eight patients died during further follow-up), while 19 patients died without prior allograft failure. The mean follow-up of the remaining 60 patients was 5.4 ± 0.4 years. No patient was lost to follow-up.

As expected, patients who suffered an event were older, had a higher degree of proteinuria, lower eGFR and a higher prevalence of diabetes mellitus (Table 1). Therefore, we adjusted for age, proteinuria, eGFR and presence of diabetes mellitus in all following Cox proportional hazard models.

Seventeen out of 105 transplant patients had high renal RI, predefined as RI ≥ 80. Compared to transplant recipients with RI < 80, patients with high RI measurements were older (59.0 ± 11.7 vs 51.2 ± 14.7 years; P = 0.024), had a higher prevalence of diabetes mellitus (47% vs 22%; P = 0.037) and had a higher level of proteinuria (0.72 ± 0.80 vs 0.36 ± 1.08 g/g creatinine; P = 0.021).

High RI measurements failed to significantly predict event-free transplant survival. Even though event-free allograft survival tended to be longer among patients with RI < 80 in the univariate Kaplan–Meier analysis (P = 0.293; Figure 1a), it no longer differed between both groups of patients after adjustment for age, transplant function, proteinuria and diabetes mellitus in a Cox proportional hazard model [hazard ratio for patients with RI < 80, 1.193 (95% confidence interval, 0.538–2.645); P = 0.663; Figure 1b]. Adjustment for heart rate does not affect the study results [hazard ratio for patients with RI < 80, 1.128 (95% confidence interval, 0.507–2.510)].

Similarly, those patients in whom renal RI increased between the first measurement in 2000 and the second measurement in 2003/04 did not show worse event-free allograft survival compared to those patients in whom RI measurements did not increase between both measurements (data not shown). In accordance, the increase in RI measurements between 2000 and 2003/04 was not significantly correlated with the following decrease in eGFR from 2003/04 until the end of follow-up in 2009 (Figure 2).
In contrast, increased IMT of common carotid arteries predicted event-free transplant survival both in univariate Kaplan–Meier analysis \((P < 0.001; \text{Figure 3})\) and in the multivariate Cox regression analysis [hazard ratio for IMT > 0.8 mm, 2.157 (95% confidence interval, 0.997–4.664); \(P = 0.051\)]. Similarly, patients with high CHD risk by FRS had shorter event-free transplant survival in univariate Kaplan–Meier analysis \((P = 0.007; \text{Figure 4})\), while in multivariate Cox regression analysis, event-free transplant survival tended to be lower [hazard ratio for high CHD, 1.836 (95% confidence interval, 0.745–4.523); \(P = 0.187\)].

When arbitrarily subdividing the study cohort into two subgroups (patients transplanted for 6–24 months before study initiation vs patients transplanted for >24 months), RI measurements \(\geq 80\) failed to significantly predict the combined end point in any subgroup, while pathological IMT were predictors in both subgroups (data not shown).

We then stratified patients by their RI and IMT measurements. Among those patients with normal IMT, allograft recipients with RI \(\geq 80\) were at similar risk for the combined end point as patients with pathological IMT measurements, whereas patients with RI < 80 and normal IMT measurements had an excellent prognosis \((P < 0.001; \text{Figure 5})\). Similarly, patients without high CHD risk, but high RI measurement, had substantially shorter event-free survival than patients without high CHD risk and RI < 80 \((P = 0.006; \text{Figure 6})\).

When defining death-censored transplant failure as secondary end point, RI measurements \(\geq 80\) again did not sig-
significantly predict allograft survival ($P = 0.234$ by log-rank test). Similarly, neither pathological IMT ($P = 0.212$) nor high CHD risk by FRS ($P = 0.104$) remained significant predictors of allograft survival after excluding death with intact allograft function from the combined end point. Again, the simultaneous assessment of both renal RI and systemic cardiovascular risk markers may allow better prediction of death-censored allograft survival than the measurement of a single parameter alone (Figure 7).

Discussion

We demonstrate for the first time that, in unselected kidney transplant recipients, ultrasound RI are inferior predictors of the combined end points of allograft failure and death compared to measurements of atherosclerotic disease burden, such as IMT, and compared to measurements of global cardiovascular risk, such as Framingham risk score.

Interest in RI as predictors of allograft loss emerged in 2003, when Radermacher and coworkers reported a prospective cohort study comprising 601 allograft recipients, of whom patients with RI of 80 or higher had a 9-fold increased risk of graft loss, even after correction for potential confounders [4]. Moreover, RI were better predictors of allograft loss than a wide range of established risk factors, such as blood pressure, proteinuria and age.

These results were seemingly confirmed by two smaller retrospective cohort studies: Saracino and coworkers stratified 76 allograft recipients by RI measurements performed within 4 weeks after transplantation [6]. Patients with RI measurements above the median ($\geq 63.5$) had worse allograft survival, defined as increase in serum creatinine of $\geq 50\%$, even though the survival curves diverged much less impressively than in the Radermacher trial. However, patients with higher RI were significantly older and had a higher level of proteinuria. As both higher age and proteinuria themselves predicted the study end point, we hypothesize that the small, albeit significant, impact of higher RI on allograft survival would have disappeared in a multivariate Cox regression analysis. Similarly, Kahraman and coworkers, who measured renal RI within 1 week after renal transplantation in 45 allograft recipients, found a modest decline in estimated creatinine clearance within the 1 year of follow-up in patients with high RI, arbitrarily defined as RI $\geq 70$ [5]. Again, the data were not adjusted for potential confounders.

Besides these statistical shortcomings, these two studies are limited by their retrospective design and the (presumably post hoc) exclusion of patients suffering from a wide variety of post-surgical complications with potential impact on resistance index measurements, leaving the generalization of the study results to a non-selected cohort very questionable.

Finally, stability of RI measurements within the first 4 weeks after renal transplantation is poor, and their predictive value for estimating long-term allograft function has been questioned by Trillaud and coworkers [15]: These authors performed duplex ultrasound in a heterogeneous cohort of 31 allograft recipients within the first 11 days after kidney transplantation. One-year allograft function did not differ when stratifying the patients by RI measurements above or below 80. In accordance with Radermacher and coworkers, we, therefore, deliberately chose to include patients who had been successfully transplanted for more than 6 months in the present study in order to exclude the confounding influence of any surgical or medical complication of the early post-transplant period.

Pape and coworkers reported an association between high RI measurements and a subsequent fall in estimated glomerular filtration in paediatric allograft recipients un-
undergoing diagnostic allograft biopsy because of the clinical suspicion of chronic allograft nephropathy [16]. Because of this highly preselected patient cohort, their results should not be transferred to adult allograft recipients with stable allograft function.

The prognostic impact of RI as predictors of allograft survival was questioned for the first time by a recent report from Vallejos and coworkers who reported a cohort of 87 allograft recipients in whom RI measurements performed 3–6 months after renal transplantation did not predict death-censored allograft survival after 60 ± 19 months of follow-up, whereas renal biopsy findings of chronic allograft nephropathy did [17].

Our study results are in line with these recent data from Vallejos and coworkers, but in contrast to the findings reported by Radermacher and coworkers. The sharp discrepancy between the latter study and our results remains enigmatic. Admittedly, Radermacher and coworkers recruited more patients than all other cohort studies on the prognostic impact of RI combined. In addition, the patients recruited in the present study were at higher risk for subsequent allograft failure and death, as they were older [mean age, 52.5 years (present study) vs 49.8 years (Radermacher and coworkers [4])], had a higher prevalence of diabetes mellitus (25.7% vs 17.9%), had worse renal function at baseline (eGFR 47 ml/min/1.73 m², corresponding to a creatinine clearance of 53 ± 21 ml/min in the present study vs 62 ml/min in the former study) and time since transplantation was longer (83 vs 60 months).

As a consequence, even though a similar percentage of patients reached the combined end point in both studies (31.6% vs 31.5%, respectively), this might partly explain why, in the present study, markers of systemic atherosclerotic disease were far better predictors of the combined end point than local ultrasound measurements within the allograft. In line with this, IMT measurements and Framingham risk scores lose predictive power when analysing death-censored allograft survival; still, they even then do not become inferior prognostic markers compared to RI measurements.

We deliberately predefined a combined end point comprises both loss of allograft function and death for two major reasons: Firstly, this definition allows direct comparison of our data to the seminal study presented by Radermacher and coworkers [4]. Secondly, given that half of all renal allograft recipients die before needing dialysis treatment, death with functioning transplant is a major contributor to allograft loss. Thus, any prognostic marker in transplant medicine should reliably predict the grimmest option of transplant loss, i.e. death.

Interestingly, we found that renal RI remained predictors of allograft failure in subgroups of patients with lower atherosclerotic burden, such as IMT measurement ≤0.8 mm and Framingham risk score ≤20%. Admittedly, these subgroup analyses are based on a rather small number of patients and will have to be confirmed by other investigators.

Our findings support the hypothesis raised by us [10,18] and by other groups [11,19] that ultrasound RI are not specific markers of organ-specific lesions, but reflect systemic atherosclerotic changes. They are in accordance with recent physiological, histological and clinical data:

Firstly, in an in vitro model, sonographic RI are dependent on both vascular compliance and resistance; they become less and less dependent on resistance as compliance decreases and they are independent of vascular resistance when compliance is zero [20]. In animal models of acute urinary obstructions, RI correlate well with ureteral pressure and with renal perfusion pressure, but poorly with vascular resistance [21]. Secondly, in an ex vivo perfusion system, RI of isolated rabbit kidneys rise only with marked, likely non-physiologic, increases in renal vascular resistance, whereas pulse pressure and RI are linearly correlated [22].

In addition, recent biopsy studies found no association between ultrasound RI and histological markers of chronic allograft nephropathy in patients undergoing protocol biopsy 3–6 months after renal transplantation [4,20] or at later time points [23]. Contrary findings by Pape and coworkers, who observed an association between RI measurements and histological changes in paediatric allograft recipients, may have resulted from the minor interference of aortic atherosclerotic changes in children [16].

Furthermore, in clinical cohort studies, RI are correlated with markers of subclinical atherosclerotic disease, such as IMT [10], and of vascular stiffness, such as pulse wave velocity [11]. In most cohort studies, they are neither correlated with donor age nor with allograft function in univariate [10,11,24] or multivariate [9] analysis.

Finally, even if ultrasound RI accurately measured intrarenal resistance, this information would anyway be of questionable use, as even the invasive measurement of intrarenal resistance turned out to be a poor prognostic marker in renal allograft recipients [25].

Conclusions

In summary, compared to markers of cardiovascular risk or systemic atherosclerosis, renal RI are inferior predictors of patient and allograft survival. We suggest that their use as prognostic markers should be restricted to patients at low cardiovascular risk in whom they might reflect organ damage more accurately. Alternatively, measurements of renal RI must be corrected for systemic atherosclerotic burden. In a future trial, we will test whether specificity of transplant renal RI might be increased by comparing allograft RI to indices measured in arteries of other organs, such as splenic arteries.

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Conflict of interest statement. None declared.

References

Increase in proteinuria >200 mg/g after late rejection is associated with poor graft survival

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Abstract

Background. There is no information on the effects of proteinuria on outcomes following rejection.

Methods. We addressed this question in a retrospective study of 925 kidney transplant recipients between January 2003 and December 2007. Selection criteria were based on (i) biopsy proven diagnosis of a first episode of acute rejection, and (ii) available data on urine protein to creatinine (UPC) ratios at baseline (lowest serum creatinine before biopsy), time of biopsy and 1 month after biopsy. We examined the effects of a change in UPC (ΔUPC = UPC 1 month after biopsy—baseline UPC) on outcomes.

Results. We identified 82 patients with both acute rejection and available data on proteinuria. Mean time (±SE) to acute rejection was 19 ± 2.3 months, and patients were followed up for 38.7 ± 2.6 months after transplant. Median ΔUPC was 200 mg/g (95% confidence interval 0.00 to 0.300). Forty-two patients had a ΔUPC ≥200 (high pro-