Proteinúria after kidney transplantation - prevalence and risk factors

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Abstract

Introduction: Proteinuria after kidney transplantation (Tx) has variable incidence and is associated with cardiovascular risk and graft survival. **Objective:** To evaluate the prevalence of proteinuria after kidney Tx and its associated factors. **Methods:** The prevalence of PTN was evaluated according to definition ≥ 500 mg/24 hours. Patients were divided into 3 groups: group A, < 500 mg, B, 500-1000 mg and C, > 1000 mg. We tested the association between PTN and: age/gender of the donor and recipient, type of donor, delayed graft function, acute rejection, hypertension and creatinine. The variables with a *p* value < 0.20 in the bivariate analysis were included in a multivariate logistic regression analysis. **Results:** 173 recipients were evaluated, mean age 39 years, 57.2% male and 60.7% deceased donor. The prevalence of PTN after kidney Tx was 24.3%. The distribution of patients according to PTN was 75.7% for group A, 15.6% for group B and 8.7% for group C. The following factors were associated with higher risk of PTN: male recipients, living donor and hypertension. Creatinine at month 12 moths post-Tx was higher among patients with proteinuria. 60% of patients with PTN ≥ 500 mg/24 hours were treated with ACEI/ARB. **Conclusion:** The prevalence of PTN after kidney Tx varied between 24.3%, according to the definition used. The male gender of the recipient, living donor and hypertension were associated with the occurrence of PTN after kidney Tx. Blockade of the renin-angiotensin system must be prescribed to more patients.

Keywords: kidney transplantation; prevalence; proteinúria; risk factors.

Introduction

Proteinuria (PTN) after kidney transplantation has been recognized as a risk factor for the progression of chronic allograft nephropathy and cardiovascular disease.[1]

Post-transplant proteinuria is usually defined as urinary protein excretion greater than 300-500 mg/24h for at least 3-6 meses.[2-4] Other authors consider this proteinuria value to be above 1000 mg/24h.[5] The incidence of post-Tx proteinuria in epidemiological studies have ranged between 10 and 45%.[2,4]

The etiology of post-transplant proteinuria is multifactorial,[6] and we can mention chronic allograft nephropathy, transplant glomerulopathy, repeated or recurrent glomerulonephritis, chronic pyelonephritis, nephrotoxicity by calcineurin inhibitors and diabetic nephropathy. High molecular weight Proteinuria is often seen after transplantation, but it tends to be brief and transient, reflecting the degree of preoperative ischemic damage to the graft. There may still be proteinuria from the native kidneys or even from the immunosuppressive therapy, especially related to the use of Sirolimus®.[7,8]

Microalbuminuria or high molecular weight proteinuria is associated with a higher incidence of hypertension, acute rejection, graft dysfunction and long-term mortality, being

reported in large studies as a single prognostic factor for both of the latter.[3,9,10]

In patients with post-transplant proteinuria, treatment with inhibitors of the renin-angiotensin-aldosterone system (RAAS) may reduce proteinuria, but there is no evidence from randomized studies that this strategy results in improved graft survival or better patient survival.[4]

The present study examined the prevalence and management of post-Tx PTN in recipients from a single center and the impact of proteinuria in renal function after 36 months of Tx, as well as the factors associated with it. Post-Tx PTN carries an increased mortality in the short and long term post-transplant period, the etiology and variable prevalence of this condition as well as the uncertainty in handling this proteinuria with the RAAS blockage in transplant patients, makes it mandatory to investigate the occurrence of post-renal Tx PTN and the factors associated with it.

Methods

The study population consisted of recipients submitted to renal Tx in a hospital in Fortaleza-Brazil, from January 2005 to December 2008, and included patients older than 18 years, with at least 12 months of follow-up post-Tx. The project was submitted to and approved by the Research Ethics Committee of the UniChristus University Center, under number 021/2011.

The study was a retrospective cohort. The evaluation was carried out by reviewing records of post-renal Tx outpatients.

The following variables were investigated: age and gender of donor and recipient; primary renal disease; type of donor (living or deceased); post-renal Tx hypertension (defined as the presence of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mm Hg and/or use of antihypertensive drugs post-Tx); delayed graft function (defined as the need for dialysis during the first week after transplantation) and acute rejection proven by renal biopsy.

Post-renal Tx PTN was defined as greater than or equal to 500 mg/24 hours. In order to assess the prevalence of PTN, the patients were divided into 3 groups. In group A, the patients had PTN less than 500 mg/24 hours, those in group B from 500 mg-1000 mg/24 hours, and Group C Patients with PTN greater than 1000 mg/24 hours.

Proteinuria was also evaluated at different times post-Tx: less than 12 months (period 1) between 12-36 weeks (period 2); between 36-60 months (period 3) and 60 weeks (period 4). Within these same intervals we recorded: serum creatinine, weight and the use of antihypertensive agents. Creatinine and weight in different periods were used to calculate creatinine clearance by the Crockroft-Gault formula.[11]

According to the protocol that guides recipient follow up after renal transplantation in the hospital under study, the 24-hour proteinuria should be evaluated annually.

The use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) was recorded.

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as a percentage. The variables with normal distribution were compared using the Student *t*-test and for those with abnormal distribution we used the Mann-Whitney test. The chi-square and Fisher's exact tests were used to test the difference between the proportion of variables in patients with and without proteinuria at different periods of study. The variables that reached a p-value < 0.20 in the bivariate analysis were included in a multivariate logistic regression model to identify factors associated with a higher chance of post-transplant PTN ≥ 500 mg/24 hours. A p value less than 5% was considered statistically significant.

Results

290 kidney transplants were performed during the study period, including 173 recipients (59.6%). The reasons for excluding 117 recipients were: younger than 18 years (n = 17), missing the

24-hour proteinuria during follow-up (n = 18) and incomplete or missing records (n = 82).

Demographic and laboratory characteristics of the patients studied are depicted on Table 1.

The primary renal disease was undetermined in 54 patients; hypertensive nephrosclerosis in 43; 34 for primary glomerular diseases, 14 with polycystic kidney disease; familiar nephritis in 8 and diabetic nephropathy in 6, among others.

The distribution of patients according to PTN range throughout the follow-up period was 75.7% for group A (< 500 mg/24 h), 15.6% for group B (500-1000 mg/24 h) and 8.7% for group C (> 1000 mg/24 h).

As defined in the study (PTN ≥ 500 mg/24 hours), high PTN prevalence was 24.3% (n = 42). If we considered PTN ≥ 300mg/24 hours over the whole study, we would find a prevalence of 37.6% (n = 65).

An important finding is that, despite the recommendation of performing an annual 24 hour-PTN analysis in the hospital under study, there was a significant percentage of patients who did not undergo PTN in all periods of the study. The best-rated period was between 12-36 months, when only 18.5% did not have a PTN measured. In the other periods, between 55-65% of patients did not undergo PTN assessment.

An association between the recipient's gender and the presence of PTN ≥ 500 mg/24 h was detected (males: 30.3% *versus* females 16.2% p = 0.033). In the group of recipients from living donors, 32.4% had post-Tx PTN ≥ 500 mg/24 hours, *versus* 19% in the group of deceased donors (p = 0.046). There was no association between PTN > 500 mg/24 hours and donor gender (p = 0.924) or the presence of delayed graft function (DGF) (p = 0.659). Among the patients who presented episodes of acute rejection, PTN ≥ 500 mg/24 hours was diagnosed in 31.9% of cases *versus* 21.4% among those without acute rejection (p = 0.152). In the group of patients who underwent thymoglobulin induction, 18.7% had post-Tx PTN ≥ 500 mg/24 hours, compared to 30.5% in the group that did not use thymoglobulin (p = 0.071). Post-Tx hypertension was associated with PTN ≥ 500 mg/24 hours (27% in the group with hypertension *versus* 4.8% in the group without hypertension; p = 0.028).

Creatinine at 12 months was higher in patients with PTN ≥ 500 mg/24 hours (1.53 ± 0.61 mg/dL *versus* 1.26 ± 0.62 mg/dl; p = 0.001). Creatinine clearance at 36 months was not statistically different in patients with and without PTN ≥ 500 mg/24 hours 62.97 ± 22.17 *versus* 66.85 ± 22.19; p = 0.345).

By assessing the groups according to proteinuria, we found that in groups A, B and C, 44.4%, 62% and 53.3% of the patients used ACEI/ARB, respectively (p = 0.23) (Figure 1).

We included in the multivariate logistic regression analysis the variables with a p significance < 0.20 in the bivariate analysis. The following variables were associated with higher likelihoods of having a PTN ≥ 500 mg/24 hours after transplantation: male recipient (OR = 2.25, CI 1.36 to 4.87; p = 0.004), living donor (OR = 2.21, CI 1.06 to 4.57; p = 0.034) and post-Tx hypertension (OR = 7.46, CI 1.02 to 58.4, p = 0.051) (Table 2).

Discussion

Proteinuria is an important marker for the risk of cardiovascular death and general death for the renal transplant recipient and it is associated with lower survival both for the graft and the recipient.[3,5] The incidence of proteinuria has increased in recent years, which may be due to choice of older donors and recipients, with more cardiovascular and metabolic risk than before.[12]

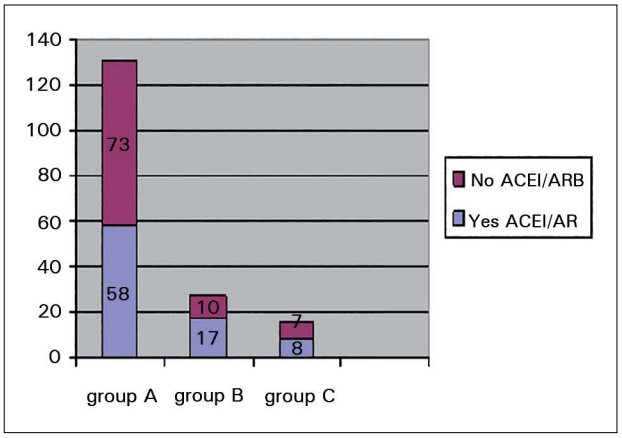
The prevalence of post-renal Tx PTN described in the literature has been variable, mainly because of different definitions used and different post-Tx periods evaluated. Sancho *et al*.,[3] evaluated 375 renal Tx recipients and reported a prevalence of 20.2%, with PTN greater than 500 mg/24 hours. Fernandez-Fresnedo *et al*.[5] found that at 12 months post-renal Tx in a cohort of 3,365 patients, 15.3% of the recipients had PTN greater than 500 mg/24 hours and 7.5% above 1,000 mg/24 hours.

Table 1 Demographics and laboratory characteristics of the study population

Variable		
Recipient age	39.3 ± 12.7 years	Variation: 18-73 years
Recipient gender	Male: 57%	Fem: 43%
Donor age	32.3 ± 12.1 years	Variation: 6-65 years
Donor gender	Male: 58%	Fem: 42%
Donor type	RLD: 29.5% NRLD: 9.8%	Deceased: 60.7%
DGF	35.3%	N: 61
Diabetes mellitus	22.5%	N: 39
Hypertension	87.8%	N: 152
Use of ACEI/ARB	50.3%	N: 87
	Median	Minimum-Maximum
PTN < 12 m	172 mg/24h	12-14240 mg/24h
PTN 12-36 m	210 mg/24h	3.6-6900 mg/24h
PTN 36-60 m	262.6 mg/24h	10.8-3625 mg/24h
PTN > 60 m	145.8 mg/24h	48.2-2300 mg/24h
	Mean ± Standard Deviation	Minimum-Maximum
Creatinine 12 m	1.33 ± 0.51 mg/dl	0.6-4.2 mg/dl
Creatinine 36 m	1.36 ± 0.49 mg/dl	0.6-3.5 mg/dl
Creatinine 60 m	1.38 ± 0.44 mg/dl	0.6-2.9 mg/dl
Weight 12 m	61.2 ± 10.5 Kg	36-109 kg
Weight 36 m	63.9 ± 11.5 Kg	35-115 kg
Weight 60 m	66.2 ± 10.2 Kg	43.6-85 kg
CrCl 12 m	64.8 ± 20.6 ml/min	12-139.6 ml/min
CrCl 36 m	65.9 ± 22.2 ml/min	12.1-137.1 ml/min
CrCl 60 m	63.8 ± 18.5 ml/min	28.5-111.4 ml/min

DGF: Delayed Graft Function PTN: proteinuria; CrCl: creatinine clearance.

Figure 1. Frequency of ACEI/ARB use in the study population, according to the proteinuria classification in groups A, B and C.



Amer *et al.*,[6] investigated 613 patients at 12 months post-Tx and considering a PTN greater than 150 mg/24 hours, found a prevalence of 45%. Changing the PTN cutoff point to 500 mg/24 hours, in the same study the prevalence was only 15.3%. Roodnat *et al.*,[9] when evaluating 722 patients for one year, found 31% with PTN above 200 mg/24 hours.

Table 2 Multivariate analysis of factors associated with post-transplant proteinura

	p	OR	95% C.I. for EXP (B)	
Male *vs.* Female recipient	0.04	2.256	1.036	4.869
Live donor *versus* Deceased	0.03	2.205	1.064	4.572
AH *versus* No AH	0.05	7.464	1.014	58.451

Ibis *et al.*,[13] in a study with 130 patients during 12 months of follow-up, found a prevalence of 34.3%, considering a PTN above 300 mg/24 hours. Halimi *et al.*[10] found that 20.4% of the subjects of a cohort of 484 patients had PTN

greater than 1000 mg/24 hours and 35.2% had PTN above 500 mg/24 hours.

In our study we used a PTN value greater than or equal to 500 mg/24 hours, we found a prevalence of 24.3% of PTN. When the proteinuria cut-off point used was greater than or equal to 300 mg/24 hours, the prevalence was 37.6% - data corroborated by the literature. In Brazil, we do not know of previously published studies that assessed the prevalence of proteinuria after renal Tx. The distribution of patients according to the degree of PTN was similar to the study by Souqiyyeh *et al*.,[14] with 340 patients, which identified 61.5% of patients with 24-hour PTN < 300 mg, 27.1% between 300-1,000 mg and 11.5% above 1,000 mg/24 hours.

The highest percentage of proteinuria not performed was observed in the first 12 months (period 1) and longer than 60 months (period 4), i.e. around 65% of patients. Between 12-36 months post-Tx, only 18.5% of patients did not have the results from the 24h PTN assessment. So in other periods (periods 1 and 4), the prevalence of proteinuria was probably underestimated. In all periods studied, patients with PTN above 1000 mg/24 hours, represented the lowest percentage of patients (between 7.5-10%).

The recipient being male was associated with a greater likelihood of PTN in this study. Amer *et al*.[6] also found that male recipients had higher levels of proteinuria. Conversely, Sancho *et al*.[3] found a higher likelihood of female recipients developing PTN in a bivariate analysis. However, in the multivariate analysis of the aforementioned study, being a female recipient was not significantly associated with PTN, suggesting that female patients had other risk factors that contributed to their poor outcome, probably for receiving kidneys from female donors and older donors compared to male recipients - two situations in which the nephron mass may have been reduced compared to the ideal donor and could contribute to the increased risk of proteinuria and graft loss.[15] Donor and recipient gender affect the long-term survival rates, especially for elderly donors.

Regarding delayed graft function, with a prevalence of 35% in this study, there was no association with increased risk of post-Tx PTN. Previous studies found DGF[3,5] and long warm and cold ischemia times associated with an increased risk of PTN.[5]

In the present study, patients with post-Tx hypertension had a higher prevalence of PTN compared to normotensive patients (p = 0.017), and we found post-Tx hypertension in 87.8% of patients. Hypertension affects more than 90% of renal Tx recipients.[16,17] The literature has pointed to an increased risk of hypertension in the early stages of renal Tx, in the group of patients with PTN > 0.5g/day.[3] Fernandez-Fresnedo *et al*.[5] also found high blood pressure as a condition associated with post-Tx proteinuria. In other studies, hypertension was an important predictor of PTN.[18,19] The reduction of renal mass caused by hypertension may contribute to proteinuria. Brenner *et al*.[20] proposed the hypothesis that a deficit in the number of glomeruli predisposes the recipient to proteinuria, hypertension and progressive kidney disease. In experimental models, it has been shown that the reduced nephron mass is a determinant of proteinuria and long term survival[21,22] and that hypertension was associated with more severe glomerular hypertension and proteinuria.[23]

In this study, acute rejection was associated with greater proteinuria level only in the bivariate analysis. In a collaborative study in Spain with 3,365 patients undergoing transplant until 1998, episodes of acute rejection were associated with higher proteinuria rates,[5] with similar results in other previous studies.[6,24,25] On the other hand, Sancho *et al*.[3] showed no association between acute rejection episodes and the presence of proteinuria, just like Shin *et al*.[26] in their series. The authors explain that they included patients receiving immunosuppression, including the use of mycophenolate mofetil and tacrolimus, as well as induction therapy for those deemed to be of greatest immunological risk, which might have prevented more severe rejection and reduced the risk of PTN. In this study, using more modern

and intense immunosuppression, acute rejection was not associated with higher likelihood of developing post-transplant PTN as well as the use of thymoglobulin in the multivariate analysis.

In our study, patients with proteinuria greater than or equal to 500 mg/24 hours showed a renal function at 12 months (measured by creatinine) significantly lower when compared to patients with proteinuria of less than 500 mg/24 hours. This comes to reinforce the importance of the need for measures to control proteinuria in these patients. Sancho *et al*.[3] reported a 5-year graft survival of 69% in patients with proteinuria *versus* 93% in those without proteinuria, with no difference in patient survival in both groups. Proteinuria is an indicator of renal injury and a risk factor for subsequent decline in renal function in most kidney diseases. Significant proteinuria or nephrotic proteinuria were risk factors for graft loss in the long term.[9,27,28] Massy *et al*.[29] found that proteinuria greater than 500 mg/day was associated with lower graft survival. According to Fernandez-Fresnedo *et al*.[5] proteinuria expressed as a continuous variable was a risk factor for graft failure. Djamali *et al*.[30] reported poor graft survival associated with PTN above 200 mg in 24 hours and according to Amer *et al*.[6] even a low level PTN (less than 500 mg) was related to poor graft survival.

There was no difference in the frequency of ACEI/ARB use in patients with and without PTN in this study. This treatment was instituted in only 60% of patients with PTN greater than or equal to 500 mg/24 hours. Blockade of the renin-angiotensin systems causes a decrease in systolic pressure, in intraglomerular capillary pressure, proteinuria and cardiovascular events.[31] Moreover, this blockage can reduce the development of interstitial fibrosis and tubular atrophy induced by calcineurin inhibitors,[32] cause or exacerbate reduction in glomerular filtration rate,[33] exacerbate hyperkalemia, which is a common finding in delayed graft function, and also an adverse event with calcineurin inhibitors, and lower the hematocrit in 5-10%.[34] Therefore, it is prudent to wait 3-6 months after the Tx to start an ACE inhibitor or an aldosterone receptor blocker when indicated.

The data is currently available in the literature for the general population suggesting that protein excretion in urine above 1000 mg/day identifies patients who may benefit from therapy with angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), while other authors suggest the limit of 500 mg/day.[35,36] These drugs can slow the progression of renal disease. According to US guidelines from the Kidney/Dialysis Outcome Quality Initiative (K/DOQI), physicians should aim for a reduction in proteinuria to less than 500-1000 mg/day, in order to slow the progression of CKD by its effects on glomerular hemodynamics (reducing intraglomerular pressure), and changes in podocyte behavior, in view of the toxic effects of proteinuria at a mesangial level, directly proximal tubular toxicity and inflammatory state induction at a tubule-interstitial level.[37]

Considering the literature recommendations above, we note that not all recipients with PTN above 500 mg/24 hours used RAAS inhibitors, which can potentially contribute to poor graft survival. It is possible that the use of ACEI/ARB in only 60% of patients with PTN above 500 mg/24 hours, is due to the fact that only 5.1 to 10% of patients had PTN above 1000 mg/24 hours in different periods of the study.

In a retrospective cohort study of 2,031 renal transplant recipients in Austria, the authors found a significant improvement in patient survival and overall graft survival in 10 years in recipients who used an ACE inhibitor or an ARB. However, they found no effect on graft survival censored at death ($p = 0.57$), suggesting that the benefit may be due to a reduction in mortality, instead of preserving graft function.[38] On the other hand, there was no significant effect of RAAS inhibitors in patient and graft survival in kidney Tx among 17,209 recipients evaluated by Opelz *et al*.[39] In this study, graft survival was more closely associated with the control of systolic blood pressure at 1 year, regardless of ACEI or ARB that was used. This finding suggests that

blood pressure to be achieved is more important than the antihypertensive agent used to reach the target BP. Therefore, RAAS blockade will reduce proteinuria, but the effects of long-term patient and graft survival remain unknown.[40,41]

Proteinuria reduction is the target to be achieved in patients with chronic kidney disease under conservative treatment, in kidney transplant patients and even in patients with microalbuminuria (incipient proteinuria), aimed at nephroprotection.[14,41,42] Therefore, antiproteinuria measures need to be adopted with greater promptness in renal Tx recipients, in order to obtain better results in terms of function and survival of renal grafts.

In general, renal transplant units recommend the use of annual 24-hour proteinuria assessments or the protein/creatinine ratio in a spot urine sample in the long-term monitoring of renal Tx recipients. Despite this recommendation, in this study we noticed that a considerable number of patients did not undergo this test in the different post-Tx time intervals, and 18 patients were excluded for not having any results of 24-hour PTN during the whole period of follow-up. This can be justified due to difficulties in collecting the 24-hour sample by patients residing in the countryside of the state, the fact that the 24-hour collection is a laborious examination, not well accepted by the patient, or the failure to request the test by the attending physician in transplant year dates.

The gold standard for quantifying proteinuria is the 24-hour urine sample, since protein excretion follows a circadian rhythm. However, the test is uncomfortable and errors in sample collection are frequent, which may negatively influence its interpretation. In cases of difficulty in collecting urine for 24 hours, the albumin/creatinine ratio or protein/creatinine ratio in an isolated urine sample is a good alternative to 24h proteinuria.[43]

Because this study was retrospective and the data collection was based on chart review, the biggest limitation and risk was to obtain incomplete data, especially regarding the extent of proteinuria, which may be certainly underestimated in its prevalence and association with the variables studied. Another limitation of this study is that it did not include in the analysis some immunological risk variables as the panel reactivity to anti-HLA antibodies (PRA) and the presence of antidonor antibodies (DSA). These factors indicate a greater immunological risk and it has been associated with chronic antibody-mediated rejection, worse graft function and proteinuria.[44]

Our study did no aim to evaluate the etiology of proteinuria by renal biopsies. Further studies with assessment of renal histology are needed to understand the causes and consequences of PTN as well as the evaluation of the immune factors mentioned above that have not been studied.

It is imperative to stress that the examination of 24-hour proteinuria should be systematically requested by nephrologists and be performed by patients annually. Guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) in the care of renal transplant recipients suggest the measurement of urinary protein excretion within 1 month of transplantation, then every three months in the first year and then anually.[45]

Conclusion

The prevalence of PTN after renal transplant varied according to the definitions used in the study population. The male recipient, transplantation from a living donor and the presence of post-Tx hypertension were associated with a higher likelihood of developing post-renal Tx PTN. Renal function at 12 months (measured by creatinine) was significantly lower in patients with post-transplant PTN.

There was no difference in the frequency of ACEI/ARB use in patients with and without PTN, and this treatment was instituted in 60% of patients with PTN greater than or equal to 500 mg/24 hours.

In conclusion, proteinuria should be assessed in all recipients after renal transplantation, since, in addition to being a marker of kidney disease, it has also been considered a risk factor for the

progression of chronic allograft nephropathy, and cardiovascular disease.

References

1. Hernández D, Sánchez-Fructuoso A, Séron D. Spanish consensus document on chronic allograft nephropathy. Nefrologia 2006;26:S1-38.
2. Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. J Am Soc Nephrol 2000;11:S1-86.
3. Sancho A, Gavela E, Avila A, Morales A, Fernández-Nájera JE, Crespo JF, et al. Risk factors and prognosis for proteinúria in renal transplant recipients. Transplant Proc 2007;39:2145-7. DOI: http://dx.doi.org/10.1016/j.transproceed.2007.07.005
4. Knoll GA. Proteinúria in kidney transplant recipients: prevalence, prognosis and evidence-based management. Am J Kidney Dis 2009;54:1131-44. PMID: 19726115 DOI: http://dx.doi.org/10.1053/j.ajkd.2009.06.031
5. Fernández-Fresnedo G, Plaza JJ, Sánchez-Plumed J, Sanz-Guajardo A, Palomar-Fontanet R, Arias M. Proteinúria: a new marker of long term graft and patient survival in kidney transplantation. Nephrol Dial Transplant 2004;19:iii47-51.
6. Amer H, Fidler ME, Myslak M, Morales P, Kremers WK, Larson TS, et al. Proteinúria after kidney transplantation, relationship to allograft histology and survival. Am J Transplant 2007;7:2748-56. DOI: http://dx.doi.org/10.1111/j.1600-6143.2007.02006.x
7. Straathof-Galema L, Wetzels JF, Dijkman HB, Steenbergen EJ, Hilbrands LB. Sirolimus-associated heavy proteinúria in a renal transplant recipient: evidence for a tubular mechanism. Am J Transplant 2006;6:429-33. DOI: http://dx.doi.org/10.1111/j.1600-6143.2005.01195.x
8. Letavernier E, Legendre C. mToR inhibitors-induced proteinúria: mechanisms, significance, and management. Transplant Rev (Orlando) 2008;22:125-30. DOI: http://dx.doi.org/10.1016/j.trre.2007.12.001
9. Roodnat JI, Mulder PG, Rischen-Vos J, van Riemsdijk IC, van Gelder T, Zietse R, et al. Proteinuria after renal transplantation affects not only graft survival but also patient survival. Transplantation 2001;72:438-44. DOI: http://dx.doi.org/10.1097/00007890-200108150-00014
10. Halimi JM, Buchler M, Al-Najjar A, Laouad I, Chatelet V, Marlière JF, et al. Urinary albumin excretion and the risk of graft loss and death in proteinuric and non-proteinuric renal transplant recipients. Am J Transplant 2007;7:618-25. DOI: http://dx.doi.org/10.1111/j.1600-6143.2007.01665.x
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41. PMID: 1244564 DOI:http://dx.doi.org/10.1159/000180580
12. Roland M, Gatault P, Al-Najjar A, Doute C, Barbet C, Chatelet V, et al. Early pulse pressure and low-grade proteinuria as independent long-term risk factors for new-onset *diabetes mellitus* after kidney transplantation. Am J Transplant 2008;8:1719-28. PMID: 18694475 DOI:http://dx.doi.org/10.1111/j.1600-6143.2008.02308.x
13. Ibis A, Altunoglu A, Akgül A, Usluogullari CA, Arat Z, Ozdemir FN, et al. Early onset proteinúria after renal transplantation: a marker for allograft dysfunction. Transplant Proc 2007;39:938-40. DOI: http://dx.doi.org/10.1016/j.transproceed.2007.02.027
14. Souqiyyeh MZ, Shaheen FA, Sheikh I, Al-Khader AA, Fedhail H, Al-Sulaiman M, et al. Post-renal transplant proteinúria: the saudi experience. Saudi J Kidney Dis Transpl 2005;16:556-61.
15. Kwon OJ, Kwak JY, Kang CM. The impact of gender and age matching for long-term graft survival in living donor renal transplantation. Transplant Proc 2005;37:726-8. PMID: 15848514 DOI: http://dx.doi.org/10.1016/j.transproceed.2004.12.137
16. Rossi AP, Vella JP. Hypertension, living kidney donors, and transplantation: where are we today? Adv Chronic Kidney Dis 2015;22:154-64.
17. Kasiske BL, Anjum S, Shah R, Skogen J, Kandaswamy C, Danielson B, et al. Hypertension after kidney transplantation. Am J Kidney Dis 2004;43:1071-81. DOI: http://dx.doi.org/10.1053/j.ajkd.2004.03.013
18. Bochicchio T, Sandoval G, Ron O, Pérez-Grovas H, Bordes J, Herrera-Acosta J. Fosinopril prevents hyperfiltration and decreases proteinúria in post-transplant hypertensives. Kidney Int 1990;38:873-9. DOI: http://dx.doi.org/10.1038/ki.1990.285
19. Calviño J, Lens XM, Romero R, Sánchez-Guisande D. Long-term anti-proteinuric effect of Losartan in renal transplant recipients treated for hypertension. Nephrol Dial Transplant 2000;15:82-6. DOI: http://dx.doi.org/10.1093/ndt/15.1.82
20. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens 1988;1:335-47. DOI:http://dx.doi.org/10.1093/ajh/1.4.335
21. Mackenzie HS, Tullius SG, Heemann UW, Azuma H, Rennke HG, Brenner BM, et al. Nephron supply is a major determinant of long-term renal allograft outcome in rats. J Clin Invest 1994;94:2148-52. DOI: http://dx.doi.org/10.1172/JCI117571
22. Azuma H, Nadeau K, Mackenzie HS, Brenner BM, Tilney NL. Nephron mass modulates the hemodynamic, cellular, and molecular response of the rat renal allograft. Transplantation 1997;63:519-28. PMID: 9047144 DOI: http://dx.doi.org/10.1097/00007890-199702270-00006
23. Schindler R, Tullius SG, Tanriver Y, Noack K, Qun Y, Jürgensen JS, et al. Hypertension increases expression of growth factors and MHC II in chronic allograft nephropathy. Kidney Int 2003;63:2302-8. PMID: 12753322 DOI: http://dx.doi.org/10.1046/j.1523-1755.2003.00034.x
24. Koay HC, Vathsala A, Woo KT. Impact of proteinúria in cyclosporine-treated cadaveric renal transplant recipients. Transplant Proc 2000;32:1921-3. PMID: 11120001 DOI: http://dx.doi.org/10.1016/S0041-1345(00)01493-7
25. Hamdy AF, Bakr MA, Ghoneim MA. Proteinúria among primarily sirolimus treated live-donor renal transplant recipients' long-term experience. Exp Clin Transplant 2010;8:283-91.
26. Shin M, Song SH, Kim JM, Kwon CH, Joh JW, Lee SK, et al. Clinical significance of proteinúria at posttransplant year 1 in kidney transplantation. Transplant Proc 2012;44:610-5. DOI: http://dx.doi.org/10.1016/j.transproceed.2011.11.060
27. Hohage H, Kleyer U, Brückner D, August C, Zidek W, Spieker C. Influence of proteinúria on long-term transplant survival in kidney transplant recipients. Nephron 1997;75:160-5. PMID: 9041535 DOI: http://dx.doi.org/10.1159/000189525
28. Yildiz A, Erkoç R, Sever MS, Türkmen A, Ecder ST, Türk S, et al. The prognosis importance of severity and type of proteinúria of post-transplant proteinúria. Clin Transplant 1999;13:241-4. PMID: 10383104 DOI: http://dx.doi.org/10.1034/j.1399-0012.1999.130304.x
29. Massy ZA, Guijarro C, Wiederkehr MR, Ma JZ, Kasiske BL. Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. Kidney Int 1996;49:518-24. PMID: 8821839 DOI: http://dx.doi.org/10.1038/ki.1996.74
30. Djamali A, Samaniego M, Torrealba J, Pirsch J, Muth BL. Increase in proteinúria > 200 mg/g after late rejection is associated with poor graft survival. Nephrol Dial Transplant 2010;25:1300-6. DOI: http://dx.doi.org/10.1093/ndt/gfp613
31. Thomas B, Taber DJ, Srinivas TR. Hypertension after kidney transplantation: a pathophysiologic approach. Curr Hypertens Rep 2013;15:458-69. DOI:http://dx.doi.org/10.1007/s11906-013-0381-0
32. Burdmann EA, Andoh TF, Nast CC, Evan A, Connors BA, Coffman TM, et al. Prevention of experimental cyclosporin-induced interstitial fibrosis by losartan and enalapril. Am J Physiol 1995;269:F491-9. PMID: 7485533

33. Curtis JJ, Laskow DA, Jones PA, Julian BA, Gaston RS, Luke RG. Captopril-induced fall in glomerular filtration rate in cyclosporine-treated hypertensive patients. J Am Soc Nephrol 1993;3:1570-4.
34. Gaston RS, Julian BA, Curtis JJ. Posttransplant erythrocytosis: an enigma revisited. Am J Kidney Dis 1994;24:1-11. PMID: 8023814 DOI:http://dx.doi.org/10.1016/S0272-6386(12)80153-3
35. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004;43:S1-290.
36. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinúria. Lancet 1999;354:359-65. DOI: http://dx.doi.org/10.1016/S0140-6736(98)10363-X
37. Ziyadeh FN, Wolf G. Pathogenesis of the podocytopathy and proteinúria in diabetic glomerulopathy. Curr Diabetes Rev 2008;4:39-45. DOI:http://dx.doi.org/10.2174/157339908783502370
38. Heinze G, Mitterbauer C, Regele H, Kramar R, Winkelmayer WC, Curhan GC, et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. J Am Soc Nephrol 2006;17:889-99. PMID:16481415 DOI: http://dx.doi.org/10.1681/ASN.2005090955
39. Opelz G, Zeier M, Laux G, Morath C, Döhler B. No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: a collaborative transplant study report. J Am Soc Nephrol 2006;17:3257-62. DOI:http://dx.doi.org/10.1681/ASN.2006050543
40. Shamseddin MK, Knoll GA. Posttransplantation proteinúria: an approach to diagnosis and management. Clin J Am Soc Nephrol 2011;6:1786-93. DOI:http://dx.doi.org/10.2215/CJN.01310211
41. Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. Am J Transplant 2007;7:2350-60. DOI: http://dx.doi.org/10.1111/j.1600-6143.2007.01928.x
42. Knoll GA, Cantarovitch M, Cole E, Gill J, Gourishankar S, Holland D, et al. The Canadian ACE-inhibitor trial to improve renal outcomes and patient survival in kidney transplantation--study design. Nephrol Dial Transplant 2008;23:354-8. DOI: http://dx.doi.org/10.1093/ndt/gfm574
43. Kashif W, Siddiqi N, Dincer AP, Dincer HE, Hirsch S. Proteinúria: how to evaluate an important finding. Cleve Clin J Med 2003;70:535-7.
44. Pallardó Mateu LM, Sancho Calabuig A, Capdevila Plaza L, Franco Esteve A. Acute rejection and late renal transplant failure: risk factors and prognosis. Nephrol Dial Transplant 2004;19:iii38-42.
45. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9:S1-155.