# Original article

# Prevalence and Causes of Proteinuria in Kidney Transplant Recipients: Data from a Single Center

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## Abstract

**Introduction.** Proteinuria after renal transplantation increases the risk of graft failure and mortality. The aim of the study was to determine the prevalence and causes of proteinuria in kidney transplant recipients.

Methods. All kidney transplant recipients followed up in our clinic were included in the study. As a center protocol 24-hour urine collections were used to quantify protein excretion with 3-month intervals posttransplantation during the first year, and yearly thereafter. The etiology of chronic kidney disease and demographic characteristics of the study group were obtained from outpatient records. Data regarding the immunosuppressive regimens used, 24-hour proteinuria levels and creatinine clearences, new-onset hypertension, new-onset diabetes mellitus, rejection episodes, infections like cytomegalovirus (CMV) and polyoma (BK), and biopsy findings were noted. Results. A total of 260 kidney transplant recipients (97 females, mean age 42.3±12.3 years) were evaluated. Median follow-up period was 36 months; 137 of all transplantations were from living donors. Mean age of donors was 42.7±15 years and 133 were female. Proteinuria with protein excretion  $\geq$  300 mg/d was present in 35.4% of patients. The most common cause of biopsy-proven proteinuria was transplant-specific conditions (acute rejection, and borderline changes).

**Conclusion.** The prevalence of proteinuria was 35.4%. The transplant-specific diagnoses were the most likely causes. Even in nonnephrotic ranges it was associated with decreased graft survival.

Keywords: renal transplantation, kidney graft survival, proteinuria

### Introduction

Proteinuria is a well documented independent risk factor for progression of kidney disease, cardiovascular events, and increased mortality in both transplant and nontransplant populations [1,2]. Although the threshold to determine abnormal proteinuria in kidney transplant population is not clearly specified and although the low levels of proteinuria have been related to poor graft and patient survival, the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the care of the kidney transplant recipients suggested using the same values established for general population [1-4]. The prevalence of proteinuria varies from 7.5 to 45% in renal transplant patients, based on the threshold level to define proteinuria [1-5]. Recent reports have shown that posttransplantation proteinuria increases the risk of allograft failure by 2-to5-fold [3,5,6]. The origin of proteinuria in transplant patients primarily includes original renal disease that is associated with proteinuria (e.g. diabetic nephropathy or glomerulonephritis), recurrent or de novo glomerulonephritis, transplant-specific disorders such as rejections or transplant glomerulopathy, and drugs, especially mammalian target of rapamycin (m-TOR) inhibitors [1,3,7].

In this retrospective study we aimed to report the prevalence and etiology of proteinuria and its influence on graft function in kidney transplantation recipients in our center.

# Materials and methods

In this retrospective study the records of 260 kidney transplant recipients were evaluated for the presence of proteinuria. Proteinuria was defined as  $\geq$ 300 mg/d excretion which persisted for >6 months, and measured by 24-hour urine collection. The data regarding donor and the recipient demographic characteristics as well as clinical and laboratory variables were collected. The estimated glomerular filtration rate (eGFR) was determined by the modification of diet in renal disease [8]. Statistical analysis was performed using the SPSS for Windows, version 11.0 (SPSS, Chicago, IL). Continuous variables were expressed as mean  $\pm$  standard deviation, and categorical variables were expressed as median (mini-

mum-maximum). Categorical variables were analyzed by the chi-square and Fisher's exact tests. Comparisons between groups were analyzed by the Student's t-test, ANOVA; Mann-Whitney U, and Kruskal-Wallis tests, depending on the sample sizes and distribution of variables. Differences between matched groups were tested by the paired samples t-test, and Wilcoxon test. Bonferroni test was used for post-hoc analysis.

# Results

Ninety-two (35.4%) kidney transplant recipients had proteinuria. The median value of proteinuria was 425 mg/d (300-1900). The median month of overt proteinuria was 24(3-204). The maintenance immunosuppressive protocol included calcineurin inhibitor (CNI) in majority of patients (82.6%). Sixteen out of 92 (17.4%) recipients used inhibitors of mammalian target of rapamycine (mTOR) in their immunosuppressive protocol. The demographic and clinical data of patients are given in Table 1.

Table	1.	Demographic	and	clinical
charact	eristi	cs of the study o	roun	

characteristics of the study group				
Gender (F/M)	42/50			
Recipient age (mean±SD)	43.5±12.1			
Donor age (mean±SD)	43.8±15.1			
Primary renal disease (%)				
Hypertension	26			
Glomerular disease	25			
Chronic pyelonephritis	12			
Polycystic kidney disease	8			
Other	29			
Creatinine clearence at the				
time of overt proteinuria	63±24.1			
$(\text{mean} \pm \text{SD}, \text{ml/min})$				
Immunosuppressive protocol				
CNI-based (%)	82.6			
mTOR-based (%)	17.4			

The distribution of causes of proteinuria on renal biopsies are shown in Figure 1.



Fig. 1. Distribution of biopsy-proven etiology of proteinuria

The frequency of proteinuria in those under m-TOR inhibitor-based protocol was 39.4%, whereas in those under CNI-based protocol was 33.8%. Although the rate of proteinuria in m-TOR group was high, the difference was not statistically significant (p=0.35).

BK nephropathy (detected by serum viral load >4 log copies per ml) was diagnosed in 5.43% of patients (5 patients). Mean e-GFR at the time of proteinuria was  $63\pm24$  ml/  $1.73m^2$ /min. Those without proteinuria had a significantly better mean e-GFR of  $70\pm28$  ml/ $1.73m^2$ /min (p=0.03). The frequencies of new onset hypertension and diabetes in proteinuric patients were 44.2% and 42.3%, respectively.

#### Discussion

Proteinuria was implemented as an indicator of progression of kidney disease by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guideline on chronic kidney disease (CKD) [1-3]. Similarly, it is associated with progressive decrease in graft function, graft loss, and mortality in renal transplant recipients [1,5].

The prevalence of proteinuria varies from 7.5 to 45.0% depending on the criteria used to describe proteinuria in renal transplant patients, with the highest prevalence rates seen in thresholds just above the normal limit [1]. The amount of >150 mg/d at 1 year posttransplantation is detected in approximately 40% of patients [4]. Amer *et al.* [7] demonstrated that even at low levels (<500 mg/d) are significant prognostic factor at 1 year, independent of graft biopsy findings. In our study we demonstrated that over one-third of renal transplant patients (35.4%) had proteinuria, and transplant-specific causes were more commonly found on biopsies. Therefore, it can be accepted as a frequent complication.

The pathological diagnoses varied between studies, depending primarily on the degree of proteinuria when biopsy was performed [1,3,9]. Overall, more common pathologies have been reported to be transplant-specific diseases, including transplant glomerulopathy, acute rejection, and borderline changes than glomerulonephritis (recurrent or *de novo*) [1-3,7]. However, in some studies but not in all, glomerular diseases have been shown to be more prevalent when the amount of proteinuria exceeds  $\geq 1500 \text{ mg/d}$  [7,10,11]. This finding has important implication when determining therapies to decrease proteinuria in kidney transplant recipients.

In our study glomerular diseases were found in 20% of biopsies. The most frequently detected type of glomerulonephritis was focal segmental glomerulosclerosis (62%). Graft survival is influenced by variable factors other than proteinuria, including donor type, donor and recipient age, and primary glomerular disease (e.g. hypertension, diabetes). Therefore, it is important to adjust such potential confounding variables before analyzing the association between graft survival and proteinuria. As a continuous variable proteinuria was proven to be associated with graft loss in several studies [3,5,7]. Amer et al. [7] showed that the risk of graft loss increased by 27% for each 1 g/d increase in protein excretion. The e-GFR values in the present study were found to be statistically lower in patients with proteinuria than in those without proteinuria. This finding was similar to the rates reported in other studies [1-3]. In a previous study from a different center in our country, Ibis et al. showed that patients with proteinuria had significantly lower graft survival rates than those without proteinuria (58.6% vs 80.4%, p=0.02), and proteinuria was significantly associated with cardiovascular diseases [5-7]. The use of mTOR inhibitors has been associated with proteinuria in kidney transplant patients. Although the prevalence rate was high in m-TOR group in our study population compared to CNI group, the difference was not significant (p=0.35). This can be attributed to the low number of patients in m-TOR group.

Major limitations to our study include: first, the study was a single-center design with a limited number of biopsyproven diagnosis of proteinuric renal transplant recipients, which may restrain generalization, second, the data regarding pretransplantation presence of proteinuria from native kidneys could not be obtained, and third, we could not analyze the outcomes such as graft loss and death.

In conclusion, we demonstrated that proteinuria is a marker of poor prognosis in renal transplant patients. The goal of reduction of proteinuria by means of salt reduction and blood pressure control, diabetes regulation, use of renin-angiotensin-aldosterone blockers, and diagnosis-oriented therapies should be seriously taken into account during posttranplantation follow-up.

Conflict of interest statement. None declared.

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