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REVIEW

# Proteinuria after kidney transplantation

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## Summary

The prevalence of proteinuria at 1 year after renal transplantation ranges between 11% and 45% and is even higher in patients treated with inhibitors of the mammalian target of rapamycin (mTOR). Two main mechanisms can lead to proteinuria: an inadequate reabsorption of small proteins from proximal tubular cells damaged by ischemia-reperfusion injury, rejection, or toxic agents (tubular proteinuria) or an increased passage of albumin and/or protein with higher molecular weight (MW) because of a disruption of glomerular barrier caused by recurrent or *de novo* glomerulonephritis, transplant glomerulopathy, chronic rejection, or CNI toxicity (glomerular proteinuria). Proteinuric patients have worse patient and graft survival rates in comparison to non proteinuric patients. The amount of proteinuria is a reliable predictor of the allograft outcome. However, even microalbuminuria may be associated with a poor outcome. Treatment of proteinuria mainly rests on the management of the etiologic cause. Inhibitors of renin-angiotensin system (RAS) are useful in reversing microalbuminuria and can reduce proteinuria, but their efficacy in interfering with patient or graft survival is not demonstrated.

The onset of proteinuria in renal allograft recipients is a frequent complication that may be associated with an increased risk of graft failure and mortality. In this article, we will review the main mechanisms leading to proteinuria, its prognostic significance, and the possible therapeutic options in renal transplant recipients.

## The glomerular barrier

The capillaries of the glomerular tuft have peculiar characteristics that can inhibit the passage of plasma proteins into the tubular lumen, based on the size, shape, and charge of the respective molecules [1]. This filtration barrier is composed of perforated endothelium, a glomerular basement membrane (GBM), and a visceral epithelium with filtration slits formed by interdigitating foot processes.

Small proteins may pass the glomerular filtration barrier but usually they are reabsorbed by the megalin-cubulin complex of the proximal tubular cells. It is likely that a certain amount of albumin (68 kDa) may be filtered by glomeruli, but again it is almost completely reabsorbed by proximal tubular cells [2]. After partial degradation, albumin and other small proteins become incorporated into lysosomes and completely degraded. The endocytosed proteins undergo transcytosis in large vesicles near basolateral membrane where the albumin is disgorged back to the peritubular blood supply [3]. There is controversy about the amount of albumin that may be filtered by the glomerular barrier. Using 2- photon microscopy, Russo *et al.* [4] found that a huge amount of albumin is normally filtered by glomeruli and reabsorbed by proximal tubules. However, other studies did not confirm those data [5,6]. Whatever the amount of filtered and reabsorbed albumin, the daily amount of urinary albumin in healthy subjects is less than 20 mg, and only a proteinuria exceeding 150–200 mg/day is considered pathological.

## Types of proteinuria

There are different types of proteinuria. Apart from postural proteinuria and post-exercise proteinuria which reflect a physiological response of the kidneys, proteinuria may be caused by a defective tubular reabsorption of small proteins or by abnormalities of the glomerular barrier (Table 1).

*Tubular proteinuria* may result from a huge excretion of low molecular weight proteins that pass through the glomerular barrier and exceed the reabsorption capacity of proximal tubular cells. A typical example is represented by multiple myeloma in which there is an overproduction of light chains. In other cases, tubular proteinuria may be caused by congenital tubular defects, as in the case of Fanconi's syndrome and renal tubular acidosis, or by specific tubular injuries, as in the case of ischemia-reperfusion injury, acute rejection, or use of nephrotoxic drugs.

*Glomerular* proteinuria is usually consequent to podocyte injury. In a few cases of congenital glomerular diseases the defective podocyte function is related to the mutation of genes that encode podocyte proteins involved in the regulation of the actin cytoskeleton of foot processes. More frequently, immunological, toxic, or microbial injuries may directly alter the actin cytoskeleton leading to foot processes effacement, slit diaphragm disruption, loss of selective permeability, and passage of proteins in the tubular lumen [7]. The severity and reversibility of proteinuria largely depends on the nature of the injury and the treatment. According to the size of proteins lost in the urine, proteinuria is considered to be *selective* if it is mainly composed of proteins with a relatively low MW such as albumin (68 kDa) or trasferrin (76 kDa), or *non selective* if it is also composed of immunoglobulins with elevated MW. Cameron [8] proposed a selectivity index (urine IgG/serum IgG × serum albumin/urine albumin) using IgG (150 kDa) as the high MW protein, but α2-macroglobulin (720 kDa) and IgM (900 kDa) seem to provide more reliable results [9]. According to the amount of proteins lost in the urine, proteinuria is defined as *nonnephrotic* if the daily amount of proteinuria is lower than 3.5 g/day or *nephrotic* if it exceeds this limit.

**Table 1.** Main physiopathological mechanisms responsible of tubular and glomerular proteinuria.

| Tubular proteinuria | Glomerular proteinuria |
|---|---|
| Definition | Definition |
| Urinary excretion >150 mg/24 h of low molecular weight (<60 kDa) proteins | Urinary loss of proteins with molecular weight exceeding 60 kDa |
| Etiopathogenesis | Etiopathogenesis |
| Excessive production of small proteins exceeding the reabsorption capacity of proximal tubular cells (multiple myeloma, tumor lysis, leukemia etc.) | Primary or secondary glomerular diseases that alter the morphology and function of the actin cytoskeleton of podocytes and foot processes eventually leading to a reduced permselectivity and increased passage of proteins into the tubular lumen. The size of filtered proteins may indicate the degree of permselectivity loss (albumin 68 kDa, immunoglobin G 150 kDa) |
| Congenital proximal tubular defects (Fanconi syndrome, renal tubular acidosis) | |
| Acquired proximal tubular defects (ischemia-reperfusion-injury, nephrotoxic drugs, acute kidney injury, interstitial nephritis etc.) | |

## Post-transplant proteinuria

Proteinuria is frequently seen immediately after transplantation. It may come from the native kidneys or from the allograft [10], probably as a consequence of the ischemia-reperfusion injury. Differential diagnosis may be difficult. However, in both cases proteinuria tends to fall after a successful kidney transplantation reaching almost normal levels within few weeks [10–12]. The persistence or a late appearance of proteinuria, on the other hand, represents a sign of graft injury [13].

The prevalence of proteinuria at 1 year after renal transplantation ranges between 11% and 45% [14–21]. This large variation mainly depends on the criteria used to define proteinuria. In some series only patients with a daily proteinuria exceeding 1 g/day were taken into account, while other investigators considered patients with proteinuria >500 mg/day or even patients with proteinuria >150 mg/24 h.

A number of factors can be involved in the pathogenesis of post-transplant proteinuria (Table 2). Roodnat *et al.* found that new onset proteinuria occurred more frequently in transplant recipients with glomerulonephritis, systemic disease, or arterial hypertension as original

**Table 2.** Main causes of proteinuria in kidney transplantation.

| Main causes of tubular proteinuria | Main causes of glomerular proteinuria |
|---|---|
| Ischemia-reperfusion injury | Recurrent glomerular diseases |
| Acute kidney injury | *De novo* glomerular or systemic diseases |
| Acute rejection | Transplant glomerulopathy |
| mTOR inhibitors | Chronic rejection |
| CNI | mTOR inhibitors |
| Aminoglycosides | CNI |
| Antiviral drugs | Obesity |
| | Arterial hypertension |
| | Hepatitis C or B |

disease [15]. However, in the series of Amer *et al.* [18] proteinuria in patients with the pretransplant diagnosis of glomerulonephritis was not significantly higher than in patients with nonimmune related kidney diseases; nor did the characteristics of the donor and the recipient influence the risk of proteinuria at 1 year. Other investigators [17,22] reported that proteinuria developed more frequently in patients who received the kidney from donors positive for hepatitis C virus. In the series of Sancho *et al.* [19] a delayed graft function and a body mass index >25 were significantly associated with post-transplant proteinuria at multivariate analysis. Again these discrepancies may be accounted for by the different definitions of proteinuria used in these studies. The impression coming from personal experience and a review of the literature is that acute rejection, ischemia-reperfusion injury, nephrotoxic agents, such as gentamycin or antiviral drugs, usually cause tubular proteinuria while high levels of proteinuria are usually associated with transplant glomerulopathy, recurrent or *de novo* glomerulonephritis, or *de novo* focal glomerulosclerosis caused by chronic calcineurin inhibitor (CNI) toxicity.

A particular problem is posed by proteinuria associated with the use of inhibitors of mammalian target of rapamyicin (mTOR inhibitors), sirolimus, and everolimus. A high rate of proteinuria has been reported in transplant patients switched from a CNI-based immunosuppressive regimen to mTOR inhibitors [23–28]. The mechanisms responsible for proteinuria are still under discussion. The appearance of proteinuria might be attributable to the fact that a pre-existing proteinuria was masked by cyclosporine which has a well-known anti-proteinuric effect [29]. In fact, proteinuria is significantly less frequent in sirolimus-treated transplant patients who also receive CNI [30]. Moreover, after conversion from cyclosporine to sirolimus there is an increase in intraglomerular pressure with a concomitant reduction of kidney reserve, suggesting that proteinuria may be caused at least partially by glomerular hyperfiltration [31]. However, mTOR inhibitors can also cause proteinuria by other mechanisms. Sirolimus can exert antiproliferative and apoptotic effects on epithelial tubular cells [32] and experimental studies showed that mTOR inhibitors may interfere with the protein endocytosis in the tubular epithelial cell [33]. An impaired tubular reabsorption of albumin has been demonstrated in a transplant patient treated with sirolimus [34]. A randomized controlled trial comparing cyclosporine with sirolimus reported increased proteinuria, increased urinary excretion of markers of tubular damage, and evidence of tubular injury on kidney biopsy in patients treated with sirolimus [35]. Taken together, these data would speak in favor of a tubular toxicity leading to poor reabsorption of albumin and small proteins. On the other hand, nephrotic proteinuria has also been observed in patients treated with mTOR inhibitors, suggesting that these agents may interfere with the glomerular filtration barrier. A number of observations support this hypothesis. In primary cultures of human podocytes sirolimus significantly reduced the expression of nephrin and other slit diaphragm proteins essential for podocyte integrity and lead to reduced podocyte adhesion and motility [36,37]. In puromycin intoxicated animals, rapamycin provoked significant increases in proteinuria, together with a significant fall in podocin immunofluorescence, as well as clear additional damage to podocyte foot processes [38]. In kidney transplant recipients the administration of high doses of sirolimus was associated with the development of *de novo* focal segmental glomerulosclerosis [39]. The expression of slit diaphragm proteins such – as nephrin, podocin, C2AP, and actin – was significantly reduced in sirolimus-treated patients and was correlated with the sirolimus blood levels [40,41]. To make matters even more complex, recent experimental studies surprisingly showed that mTOR inhibitors can inhibit proteinuria through a reduction in both mTORC1 and unfolded protein response activity and can preserve nephrin expression in the glomerular podocytes [42]. Moreover, studies in mice reported that an abnormal activation of mTORC1 in podocytes induces diabetic nephropathy, suggesting that reduction of podocyte mTORC1 activity is a potential therapeutic strategy to prevent diabetic nephropathy [43].

In summary, the available studies show that mTOR inhibitors may have a dual role on proteinuria. In some models they cause proteinuria while in other models may protect from proteinuria. The clinical impression is that mTOR inhibitors can increase proteinuria and even impair kidney function when administered to patients with an already established allograft dysfunction [24,44]. Conversely, the risk of *de novo* proteinuria is not different from that observed with regimens based on CNI when mTOR inhibitors are administered early after transplantation [45–47].

## Consequences of post-transplant proteinuria

In a kidney transplantation setting, proteinuria has been associated with poor graft and patient survival (Table 3). Roodnat *et al.* [15] found that proteinuria doubled the risk of graft failure in comparison with nonproteinuric transplant patients. The influence of proteinuria as a continuous variable showed interaction with original disease. In patients with glomerulonephritis, hypertension, or systemic diseases proteinuria at 1 year significantly increased the risk of graft failure. Fernadez-Fresnedo *et al.* [16] found that graft survival in proteinuric patients was

**Table 3.** Risk of death and graft failure in patients with proteinuria.

| | Hazard ratio for death | Hazard ratio for graft failure |
|---|---|---|
| Roodnat (15) | 1.98 | 2.03 |
| Fernandez-Fresnedo (16) | 2.05 for proteinuria 0.5–1 g/day<br>2.3 for proteinuria >1 g/day | 2.33 for proteinuria 0.5–1 g/day<br>3.46 for proteinuria >1 g/day |
| Amer (18) | – | 1.40 for proteinuria >0.2 g/day |
| Halimi (48) | 5.37 for presence of NAP<br>4.12 for presence of macroalbuminuria | 4.0 for every g/day of NAP 1.86 for every g/day of macroalbuminuria |
| Cherukun (49) | 2.6 if proteinuria >1 g/day | 7.1 if proteinuria 0.16–0.5 g/day<br>10.5 if proteinuria 0.51–1 g/day<br>16.0 if proteinuria >1 g/day |

NAP, non albuminuric proteinuria.

significantly lower as compared with patients without proteinuria. The relative risk of graft failure increased with increasing amounts of proteinuria, being 2.33 for proteinuria 0.5–1 g/day and 3.46 for proteinuria >1 g/day. Even low-grade proteinuria, whatever the cause, has been reported to be a potent predictor of graft loss [17]. Amer *et al.* [18] found that any increase of 1 g/day of proteinuria increased by 27% the risk of graft loss. Halimi *et al.* [48] found that non albumin proteins were risk factors for graft loss and remained significant after adjustment on urinary albumin. Finally, a multivariate analysis revealed that even low-level proteinuria at 3 months predicted death-censored graft failure [49].

Although the onset of proteinuria after transplantation may be considered as a mere sign of pathologic lesions that directly influence the outcome of the allograft, it is likely that the abnormal traffic of proteins can exert nephrotoxic effects *per se*, and have a direct impact on kidney allograft function. The uptake of urinary proteins from proximal tubular cells, already damaged by ischemia-reperfusion or other injury, can trigger a complex reaction with increased production of angiotensin II, endothelin, cytokines chemoattractans, and transcriptional factors. These agents promote lymphocyte and monocyte recruitment with transdifferentiation of epithelial cells into fibroblast, leading to interstitial inflammation and scarring [50–53]. Although, the potential nephrotoxic effects of proteinuria seem to be mainly related to the amount and type of proteinuria, mild proteinuria composed of small MW proteins may also predict a poor outcome of the allograft.

However, proteinuria is not only associated with graft failure but also with an increased risk of mortality. A meta-analysis of cohort studies in nontransplant population showed a strong and continuous association between proteinuria and subsequent risk of coronary heart disease, and suggested that proteinuria should be incorporated into the assessment of an individual's cardiovascular risk [54]. Similar evidence also emerged from studies in kidney transplant recipients. Roodnat *et al.* [15] reported that the risk for death was almost twice as high for patients with proteinuria at 1 year compared with patients without proteinuria. In a French report both urinary albumin and non albumin proteinuria were significant risk factors for death [48]. In a Spanish study 5- and 10-year patient survival rates were lower in patients with proteinuria. The main cause of death was cardiovascular disease [55]. Not only proteinuria but also microalbuminuria may predict cardiovascular events in diabetics, hypertensive patients, and in general population [56–58]. In fact, microalbuminuria is now considered as a marker of systemic endothelial dysfunction that can eventually result in coronary heart disease or accelerated atherosclerosis [59,60]. Moreover, microalbuminuria and mild increase of C-reactive protein in transplanted patients may indicate an underlying subtle systemic endothelial inflammatory damage, that could contribute to reduced graft and patient survival [61].

In summary, the transplant physician should be aware that even microalbuminuria can indicate an endothelial damage, which could lead to development of kidney allograft dysfunction and/or cardiovascular disease.

## Monitoring and treatment of post-transplant proteinuria

As development or worsening of proteinuria are important prognostic markers of the outcome, to regularly monitor the amount of proteinuria at all follow-up visits is of paramount importance. Urine dipstick testing is usually highly specific, although it can give false-positive or false-negative results in some situations. On the other hand, it is not as sensitive as quantitative methods. Twenty-four hour urine protein excretion is the gold standard for quantitative protein assessment. If the 24 h urine collection is problematic, the urinary protein/creatinine (mg/mg) ratio assessed in a 'spot' urine is an excellent surrogate, as it has proved to have an excellent correlation with the protein content of a 24-h urine collection [62]. Whenever a new onset proteinuria is detected, the finding should be confirmed, as non renal factors can influence the development of proteinuria, including the dietetic intake of proteins, physical effort, stress, fever, and acute infection. If proteinuria exceeds

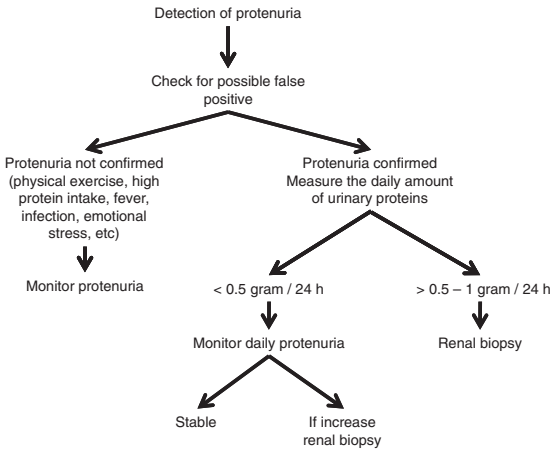


**Figure 1** A diagnostic approach to posttransplant proteinuria.

0.5–1 g/day a kidney biopsy should be performed to identify the possible cause and adopt adequate measures (Fig. 1).

It is out of the scope of this paper to discuss the possible therapeutic approaches for the different causes of post-transplant proteinuria. The reader may find reviews about rejection [63] recurrent renal diseases [64,65], CNI [66], mTOR inhibitors [67], and transplant glomerulopathy [68]. It should be noted, however, that in many cases, in particular for transplant glomerulopathy and chronic antibody-mediated rejection, no effective treatment is available. Thus, treatment of proteinuria is often symptomatic.

The first measure to be taken in proteinuric patients is to avoid glomerular hypertension that can favor protein leakage through the glomerular capillary wall. In view of the important role for renin-angiotensin system (RAS) and calcium signaling in the structural and functional integrity of podocytes [69,70], in proteinuric patients the agents interfering with RAS are usually preferred. The RAS inhibitors proved to be very effective in minimizing microalbuminuria not only in diabetic patients [71] but also in kidney transplant recipients [60]. A meta-analysis of comparative trials in nontransplant patients concluded that angiotensin-converting enzyme inhibitors (ACEIs) confer an antiproteinuric effect beyond that attributable to their blood-pressure-lowering effect. Calcium-channel blockers, beta-blockers, and other drug types showed a similar antiproteinuric response, although with a wide interstudy variation. Patient characteristics such as initial kidney function and blood pressure partly explained the variation in response, but most of it appeared dependent on the blood pressure reduction [72]. A systematic review in proteinuric patients with chronic renal disease reported that a combination of ACEi with angiotensin-receptor blockers (ARB) resulted in a small, but significant, increase in serum potassium levels (0.11 mEq/l) and a nonsignificant decrease in glomerular filtration rate (1.4 ml/min). In comparison with an ACE inhibitor alone the combination therapy further reduced proteinuria by 440 mg/day [73].

In a retrospective study on 2 031 kidney transplant recipients, the hazard ratio (HR) for mortality was 0.57 and the HR for graft failure was 0.55 for patients who received ACEi or ARB compared with nonuse [74]. A systematic review of randomized trials in kidney transplant recipients showed that after a median follow-up of 27 months, the use of ACEi or angiotensin-receptor blockers (ARB) was associated with a significant reduction in glomerular filtration rate (−5.8 ml/min), hematocrit (−3.5%), and proteinuria (−0.47 g/day). However, the data were insufficient to estimate the impact of RAS inhibitors on patient and graft survival [75]. Of concern, it is possible that RAS inhibitors may increase the risk of cancer. A retrospective analysis of Collaborative Transplant Study data reported that the standardized incidence ratio (SIR) for all nonskin malignancies was similar between the ACEi/ARB and no ACEi/ARB groups. However, multivariate Cox regression analysis showed that while ACEi/ARB treatment was not associated with an increased risk of respiratory tumors in nonsmokers, in patients with a history of smoking, the risk of respiratory/intrathoracic tumors was 2.77 in patients without ACEi/ARB treatment as compared to 7.10 in patients treated with ACEi/ARB [76].

In summary, blockade of the RAS with ACEi or ARB may reduce proteinuria, but the long-term effect of these medications on patient and graft survival remains unknown [77,78]. To better understand the role of long-term ACE inhibition in proteinuric kidney transplant patients a multi-center randomized trial has been initiated in Canada [79]. In prescribing RAS antagonists it should be taken into account that these drugs can increase the levels of serum creatinine and potassium and favor anemia probably by decreasing insulin growth factor-1 which can promote erythropoiesis [80]. Therefore, a strict monitoring of serum creatinine, potassium and hematocrit is recommended in kidney transplant recipients under treatment with RAS inhibitors. While awaiting further information about the potential oncogenicity of RAS inhibitors, it is safer to avoid the use of these agents in renal transplant patients who continue to smoke.

Other ancillary measures may also be of some benefit. Proteinuric patients should be encouraged to consume a diet with moderate protein intake and with low sodium content. Obesity may be associated with proteinuria and progressive renal damage [81], thus caloric intake should be just sufficient to maintain the ideal body weight. Apart from the atherosclerotic and oncogenic risks, smoking

may also increase urinary albumin excretion [82,83] and should be therefore avoided in proteinuric patients. Statins can not only reduce serum cholesterol levels but may also contribute to reduce proteinuria in patients with chronic kidney disease [84], although there is still controversy about their protective role on the kidney [85]. Vitamin D, a negative regulator of the RAS, may also contribute to reduce proteinuria [86,87]. Promising results have been obtained with direct renin inhibitors, pentoxifylline, endothelin receptor antagonists, and antifibrotic agents, but further studies are awaited to confirm these preliminary results [88].

In conclusion, persistent proteinuria is a frequent complication and an independent risk factor for patient and graft survival in kidney transplant recipients. Even mild proteinuria may have a prognostic significance but the higher the proteinuria, the higher its impact on clinical outcome. Efforts should be made to recognize the etiology of proteinuria and in this setting kidney biopsy is usually mandatory. Etiologic treatments are available for many, but not all, cases of proteinuria. Symptomatic treatment mainly rests on RAS inhibitors but their impact on the long-term outcome is still uncertain. The antiproteinuric efficacy of direct renin inhibitors, vitamin D analogs, pentoxifylline, endothelin receptor antagonists, and antifibrotic agents is under investigation. Hopes are also built on drugs that can interfere with the remodeling of actin cytoskeleton and restoration of the glomerular barrier.

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CP: had the original idea and prepared the manuscript, GG: participated in the preparation of the manuscript and review of the literature.

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