REVIEW ARTICLE

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Mechanisms and Management of Proteinuria in Kidney Transplant Patients

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Abstract

Proteinuria is a common complication occurring after kidney transplantation. It is associated with an increased risk of renal failure and patient death. Treatment with ACE inhibitors or angiotensin receptor antagonists (blockers) has been shown to reduce proteinuria after kidney transplantation, as well as improve both graft and patient survival. An increase in proteinuria has been observed in some patients after initiation of sirolimus therapy. Although the mechanism of this remains unclear, high proteinuria at baseline and poor renal function at baseline have been identified as potential risk factors for the development of proteinuria after conversion to sirolimus. Initiation of sirolimus therapy is not recommended in patients with early histological indicators of glomerular damage; however, in patients with healthy grafts, sirolimus may prevent future glomerulosclerosis. Early treatment with an ACE inhibitor and sirolimus, prior to the appearance of glomerular changes, may result in better outcomes.

1. Proteinuria in Kidney Transplantation

Increased glomerular permeability to large plasma proteins (proteinuria) is common in the early period after kidney transplantation, with a prevalence of somewhere between 15% and 30% at 1 year post-transplantation.[1,2] Proteinuria is a risk factor for subsequent renal function decline and has been found to be associated with decreases in patient and graft survival. In a retrospective study of 3365 kidney transplant patients, Fernandez-Fresnedo and colleagues[1] found that the relative risk of graft failure at 1 year for patients with proteinuria was about 2.3–3.5 times higher, depending on the degree of proteinuria, than that of patients without proteinuria. The relative risk of patient death at 1 year for patients with proteinuria was also twice that of patients without proteinuria. A study by Roodnat and colleagues[2] evaluated 722 kidney transplant recipients and found that the relative risk of graft failure (censored for death) at 1 year and the relative risk of death at 1 year was twice as high for patients with proteinuria as for patients without proteinuria. Another study by Fernandez-Fresnedo et al.[3] examined the effect of proteinuria on the risk of cardiovascular disease in 532 kidney transplant patients. Patients with persistent proteinuria, defined as >0.50 g/day over >6 months, had a higher risk of cardiovascular disease than patients without persistent proteinuria (relative risk [RR] 2.45), a >4 times higher risk of graft loss (RR 4.18) and twice the risk of patient death (RR 1.92).

Early, low-grade proteinuria has been shown to be correlated with donor age and cause of death, ischaemia time and acute rejection, suggesting that pretransplant renal lesions, ischaemia reperfusion

injury and immunological injury all may play a role in its aetiology.[4] Persistent proteinuria after kidney transplantation has been attributed to chronic rejection, recurrent or *de novo* glomerulopathy, glomerulonephritis, diabetes mellitus, and chronic and acute rejection.[5-8]

2. Sirolimus and Proteinuria

Sirolimus is a potent immunosuppressive agent with a mechanism of action different from that of calcineurin inhibitors (CNIs). A number of studies have demonstrated that converting to sirolimus from a CNI leads to improved renal function.[9-11] However, several reports have indicated that some patients develop a significant increase in proteinuria when switched to sirolimus therapy. Letavernier and colleagues[12] performed a retrospective study of 68 kidney transplant patients who had been switched from a CNI to sirolimus. The study showed that there was a significant increase in the mean 24-hour proteinuria level at 3 months after the switch (0.39 ± 0.69 vs 1.44 ± 1.90 g/day; $p < 0.0001$; n = 56), and that this increase was maintained at the 6-, 12-, and 24-month timepoints. Van den Akker et al.[13] performed a retrospective evaluation of 25 kidney transplant patients who had either continued treatment with azathioprine (n = 13) or switched to sirolimus (n = 12). After a mean follow-up of 360 days, proteinuria increased significantly from baseline values in the sirolimus group (0.37 ± 0.34 vs 1.81 ± 1.71 g/day; $p < 0.005$), whereas no change in proteinuria was observed in the azathioprine group (0.38 ± 0.63 vs 0.29 ± 0.35 g/day; p = not significant [NS]). Interestingly, in the sirolimus group a significant increase in proteinuria was observed only in the seven patients with pre-existing proteinuria before conversion. In five of these patients, sirolimus was discontinued and proteinuria levels returned to baseline values within 6 months.

Two studies by Ruiz et al.[14,15] have looked at the association between proteinuria levels before conversion in kidney transplant patients being switched from a CNI to sirolimus and the evolution of proteinuria after conversion. They performed a retrospective study of 94 kidney transplant patients converted from a CNI to sirolimus and analysed changes in proteinuria according to mean proteinuria values at baseline.[14] Patients were separated into three different subgroups: those with mean baseline proteinuria of <0.3 g/day (n = 18), those with 0.3–2 g/day (n = 51), and those with >2 g/day (n = 25). In the 6 months after conversion, a significant increase in proteinuria was observed; however, the increase was almost entirely due to a significant increase in proteinuria in patients with baseline proteinuria >2 g/day; in the other two subgroups, the change in proteinuria was not significant. However, a similar study by Ruiz et al.[15] showed different results. In this retrospective study of 149 kidney transplant patients, a significant increase in proteinuria after conversion was observed in patients with mean baseline proteinuria ≤0.3 g/day (n = 64; 0.14 ± 0.09 vs 0.67 ± 0.87 g/day; $p < 0.001$), and patients with mean baseline proteinuria 0.3–3.5 g/day (n = 79; 1.04 ± 0.80 vs 2.00 ± 2.02 g/day; $p < 0.001$), but not in patients with mean baseline proteinuria >3.5 g/day (n = 6; 6.20 ± 3.18 vs 4.86 ± 2.12 g/day; p = NS). Interestingly, an analysis of patients with a >0.5 g/day increase in proteinuria after conversion showed that they had a higher serum creatinine level at baseline (221 ± 70.72 vs 194.5 ± 61.9 μmol/L; $p = 0.002$) and higher baseline proteinuria than patients with a <0.5 g/day increase (0.96 ± 1.12 vs 0.79 ± 1.62 g/day). Thus, patients with high proteinuria combined with poor renal function at baseline appeared to be most at risk.

Diekmann et al.[16] performed a prospective study aimed at identifying predictors of successful conversion from a CNI to sirolimus in 59 kidney transplant patients with chronic allograft dysfunction. A multivariate analysis to identify independent outcome predictors demonstrated that low proteinuria (<0.8 g/day) at the time of conversion was the only significant independent factor ($p = 0.003$), with a positive predictive value for a positive outcome of 90%. Other variables tested included grade of chronic allograft nephropathy, creatinine at conversion, grade of vascular fibrous intimal thickening, and rejections prior to conversion.

A recent study by Saurina et al.[17] examined changes in glomerular haemodynamics following conversion to sirolimus in 14 kidney transplant patients with chronic allograft dysfunction. After conversion, a tendency toward an increase in renal pressure, calculated as intraglomerular pressure (Gomez's equation), was observed (42.7 vs 46.2 mmHg; p = 0.062), and renal function reserve decreased significantly (35% vs 13%; p = 0.019), both of which are considered to be haemodynamic glomerular changes characteristic of hyperfiltration. The authors concluded that these manifestations may explain, at least partially, the increase in proteinuria that can be observed with conversion to sirolimus in this cohort of patients. Thus, treatment of this condition with an ACE inhibitor or an angiotensin receptor antagonist (or blocker; ARB) may be warranted.

A prospective study by Sennesael et al.[18] evaluated the effect of sirolimus conversion on proteinuria in 40 stable kidney transplant patients without allograft dysfunction. At baseline, 34 patients had proteinuria <0.3 g/day, 5 had proteinuria 0.3–1 g/day and 1 had proteinuria 1–3 g/day. No significant change in the pattern of proteinuria was observed at 3 months; however, a gradual increase in the incidence and severity was observed at the 6- and 12-month timepoints; at 12 months, 9 of 34 (26%) patients developed *de novo* proteinuria. Renal function did not worsen in any of the patients with proteinuria. Multivariate analysis was performed to assess the relationship between proteinuria and the following independent variables: cause of end-stage renal disease, donor age, prior acute rejection, and delayed graft function. No predictors of proteinuria were identified.

Recently, a retrospective study was performed to compare proteinuria and graft function in live donor kidney transplant patients receiving CNI-based (n = 106) or sirolimus-based (n = 78) *de novo* therapy.[19] The proportion of patients with proteinuria >1 (dipstick proteinuria 100 mg/dL) was significantly higher in the sirolimus group than in the CNI group at 6 months (41% vs 21%; p = 0.006) and 12 months (38% vs 18%; p = 0.004). A multivariate analysis showed that proteinuria above 100 mg/dL at 12 months was significantly associated with delayed graft function (odds ratio [OR] 11.5; p = 0.02), a sirolimus-based regimen (OR 4.18; p = 0.002) and reduced glomerular filtration rate at 1 month (OR 0.62 per 10 mL/min/1.73 m^2; p < 0.001).

Most of the studies suggest that proteinuria occurs after conversion for declining kidney function with existing proteinuria and histological features of glomerulosclerosis. Therefore, sirolimus is less likely to help in patients with moderately severe renal insufficiency and should be avoided in the presence of proteinuria and focal segmental glomerulosclerosis.

3. Mechanisms of Sirolimus-Related Proteinuria

A study by Barama et al.,[20] presented at the 2006 World Transplant Congress, evaluated histological changes in the kidney following administration of sirolimus in the rat 5/6 nephrectomy model of chronic renal failure. Eighty-four rats underwent 5/6 nephrectomy or sham laparotomy (control). Animals received sirolimus at day 0 or day 21 or sirolimus plus lisinopril at day 0 or day 21. Rats were killed at week 8, and serum creatinine and proteinuria were monitored. Animals that received sirolimus or sirolimus plus lisinopril on day 21 had higher serum creatinine and more proteinuria than animals that received sirolimus or sirolimus plus lisinopril on day 0. Furthermore, rats that received sirolimus plus an ACE inhibitor on day 0 had better preserved histology than those receiving the same treatment on day 21. Rats treated with sirolimus alone on day 0 had podocyte hypertrophy and vacuolization in the podocytes, whereas, rats treated with sirolimus alone or sirolimus plus lisinopril on day 21 had pronounced focal segmental glomerulosclerosis (FSGS); in these groups, electron microscopy demonstrated effacement of foot process and detachment of the glomerular basement membrane.

In the study by Barama et al.,[20] the late introduction of sirolimus and simultaneous worsening of proteinuria appeared to be associated with an increase in vascular endothelial growth factor (VEGF)

expression. VEGF gene expression was upregulated in rats receiving sirolimus on day 21 and reduced in rats receiving sirolimus on day 0. Findings from a clinical study of a kidney transplant patient who developed proteinuria following conversion to sirolimus suggest that VEGF overexpression in podocytes may be associated with collapsing FSGS.[21]

A case-report by Straathof-Galema and colleagues[22] describes a patient who developed severe proteinuria within 10 days of receiving sirolimus as standard therapy after kidney transplantation, which disappeared completely after substituting tacrolimus for sirolimus. Renal biopsy showed normal glomeruli with no effacement of the podocytic foot processes. However, a complete absence of albumin was noted in the proximal tubules, whereas albumin was abundant in the tubules of a control patient with a similar level of proteinuria from the recurrence of FSGS after transplantation. These data, although only from one patient, suggest that reduced tubular protein reabsorption may be one of the mechanisms of sirolimus-induced proteinuria. In the retrospective study by Ruiz et al.,[15] results on urinary protein electrophoresis were able to be obtained in 16 patients. The mean albumin content of 93 ± 13% suggested that the protein excreted was mainly of glomerular origin.

4. Management of Post-Transplant Proteinuria

The effectiveness of ACE inhibitors and/or ARBs for decreasing proteinuria after kidney transplantation has been evaluated in a number of studies. A small, prospective 3-month study evaluated lisinopril in 12 renal transplant patients with proteinuria and found that mean daily proteinuria values decreased significantly with treatment from 2.98 ± 2.06 to 2.06 ± 2.29 g/day ($p < 0.01$).[23] Furthermore, when ACE inhibitor therapy was withdrawn at the end of the study, 24-hour proteinuria returned to baseline. Another retrospective study of transplant recipients examined the impact of ACE inhibitor therapy, initiated within 14 months of transplant, on proteinuria.[24] Patients treated with an ACE inhibitor (n = 20) had stable 24-hour proteinuria levels after 2 years of treatment (1.81 ± 0.21 g/day at baseline vs 1.39 ± 0.18 g/day at 2 years; p = NS), whereas proteinuria increased in patients (n = 24) who did not receive treatment with an ACE inhibitor (1.30 ± 0.20 g/day at baseline vs 6.60 ± 0.60 g/day at 2 years; $p < 0.001$). Lufft et al.[25] examined factors affecting interpatient variability in 28 kidney transplant patients treated with an ACE inhibitor (fosinopril). The study found that the effect of treatment on proteinuria was inversely correlated with the extent of pre-existing histological graft pathology. Thus, the degree of chronic morphological injury at drug initiation may be able to predict a patient's response to treatment.

In an animal model of passive Heymann nephritis, which is thought to mimic advanced renal disease, ACE inhibitor therapy alone failed to lower proteinuria.[26] This time-dependent protective effect of ACE inhibitors was also shown in an animal model of focal glomerular sclerosis, where only early onset of ACE inhibitor therapy was protective against development of renal damage and proteinuria; late introduction did not prevent further development of already established sclerosis.[27]

A small, prospective 12-month study evaluated the effect of the ARB losartan in 16 kidney transplant patients with severe proteinuria (≥3.6 g/day).[28] At the end of the study, a significant decrease in daily proteinuria was observed (5.68 ± 2.1 g/day at baseline vs 2.87 ± 2.53 g/day at 12 months; p = 0.003). Furthermore, at 2 (± 2.1) months, 24-hour proteinuria was significantly decreased (i.e. >50% reduction) in 10 of 16 patients.

A retrospective study compared patient and graft survival between kidney transplant recipients who had or had not received ACE inhibitor and/or ARB therapy.[29] Included in the study were 2031 kidney transplant recipients who had received a renal allograft between 1990 and 2003. In kidney transplant patients who had received ACE inhibitor and/or ARB therapy, the 10-year survival rate was 74% compared with 53% in nonusers ($p < 0.001$). The 10-year actual graft survival rate was 59% in the patients receiving ACE inhibitor and/or ARB ther-

apy, but only 41% in those not receiving similar therapy (p = 0.002). The study demonstrated that treatment with an ACE inhibitor and/or an ARB was associated with a 45% reduction in the risk of graft failure (hazard ratio [HR] 0.55; 95% CI 0.43, 0.70; p < 0.001) and a 43% reduction in the risk of patient death (HR 0.57; 95% CI 0.40, 0.81; p = 0.002).[29] Another smaller retrospective study of 72 kidney transplant patients also evaluated the effect of having received an ACE inhibitor or an ARB on graft survival.[30] Median follow-up time was 1.8 (0.1–13.6) years. The study found that patients who had received an ACE inhibitor or an ARB had a 75% lower risk of graft failure compared with those who had not received similar therapy (HR 0.25; 95% CI 0.11, 0.57; p = 0.001).

Recently, the results of a randomized, controlled trial evaluating different antihypertensive regimens in kidney transplant patients have been reported.[31] Patients were randomized to receive amlodipine-enalapril combination therapy (n = 32), amlodipine alone (n = 34) or enalapril alone (n = 33). The study found that the reduction in albuminuria after 6 months of amlodipine-enalapril treatment was similar to that seen with enalapril alone (−65% vs −60%), but significantly more than that observed with amlodipine alone (−65% vs −29%; p = 0.002). At 6 months, serum creatinine and creatinine clearance remained unchanged in the combination group as compared with baseline values. In the enalapril group, serum creatinine was significantly higher at 6 months (9 ± 12 μmol/L; p < 0.001) but creatinine clearance was unchanged, whereas, in the amlodipine group a significant increase in creatinine clearance was observed (15 ± 31 mL/min; p < 0.01) along with a significant decrease in serum creatinine (−5 ± 13 μmol/L; p < 0.05).

In addition to the randomized, controlled trial performed by Halimi and colleagues,[31] a randomized, double-blind, placebo-controlled trial evaluating ACE inhibitor therapy in kidney transplant patients is currently ongoing (NCT00270153). This study, which plans to include 110 patients, examines the use of ACE inhibitors in the early post-transplant period, with patients initiating treatment with enalapril (or placebo) 1–3 months post-transplant and continuing treatment for 6 months.

Data from the HOPE (Heart Outcomes Prevention Evaluation)[32] and LIFE (Losartan Intervention For Endpoint reduction in hypertension)[33] trials suggest that the ACE inhibitor ramipril also has benefits over the ARB losartan in reducing the composite endpoint of death, stroke and myocardial infarction. These benefits are believed to be a class effect of the ACE inhibitors; however, given the benefits of ramipril in the general population,[34] ramipril is our first choice of ACE inhibitor.

Limiting factors to the use of ACE inhibitors include cough, angioedema and hyperkalaemia, adverse effects which are less frequent with the ARBs. Early post-transplant anaemia can also be a limiting factor with the ACE inhibitors. We therefore recommend starting therapy within the first month, as soon as the anaemia is under control.

Although there are now several retrospective studies suggesting the benefits of ACE inhibitor therapy in reducing proteinuria, as well as improving graft and patient outcomes, results of prospective, well controlled trials, such as that conducted by Halimi and colleagues[31] (2007), are required to confirm these benefits.

5. Conclusions

Conversion to sirolimus in patients with pre-existing kidney damage is, in some cases, associated with an increase in proteinuria. Several studies have suggested that development of proteinuria is related to the level of pre-existing proteinuria, and a threshold baseline value from which proteinuria is more likely to develop has been suggested (e.g. >2 g/day). Treatment of proteinuria with an ACE inhibitor may be ineffective if there is pre-existing histological graft pathology. The introduction of sirolimus should be avoided in patients with early histological indicators of glomerular sclerosis, such as the presence of podocyte hypertrophy. However, introduction of sirolimus before this stage may be beneficial and prevent future glomerulosclerosis. In these cases, treatment with an ACE inhibitor prior to conversion to sirolimus may have a positive effect

on kidney function (decreasing serum creatinine and preventing the development of proteinuria), resulting in better outcomes with this treatment regimen.

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