Proteinuria in the transplanted patient

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Proteinuria and progressive renal disease—the unfortunate twins

The phenomenon of glomerular proteinuria has received considerable attention since it was suggested by Remuzzi and co-workers [1] that increased urinary protein concentrations might per se contribute to the progressive nature of renal disease. Findings of the Ramipril Efficacy in Nephropathy (REIN) studies are compatible with this assumption as the degree of nephroprotection obtained by angiotensin-converting enzyme (ACE) inhibitor therapy much better correlated with the reduction of urinary protein excretion than with systemic haemodynamic effects [2].

Although a definite pathophysiological link between proteinuria and progression of renal disease has yet to be established, it is generally accepted that proteinuria is at least a reliable prognostic marker. This is true for patients with secondary focal and segmental glomerulosclerosis, the structural correlate typically present in patients with a reduction of nephron mass [3], but also at least in some ‘immunologically’ mediated primary glomerulonephritides. In membranous glomerulonephritis for example the degree of persistent proteinuria predicts the renal prognosis of affected patients [4]. It is therefore not surprising that the impact of proteinuria in renal allograft recipients has also been studied by a variety of authors. The aetiology of proteinuria in these patients is diverse, including immunological injury during allograft rejection, de novo or recurrent glomerulonephritis, less clearly defined states like cyclosporin A nephrotoxicity and chronic allograft failure (reviewed in [5]), as well as ‘nephron underdosing’ as can be seen in recipients of paediatric kidneys.

In general, all studies concluded that, just as in native kidney disease, proteinuria is an excellent marker of poor long-term allograft prognosis, which is even independent of current allograft excretory function [6]. In a retrospective multivariate analysis performed in over 450 renal transplant recipients, the degree of proteinuria was the most powerful predictor of the decline of creatinine clearance [6]. Massy and
Is interstitial allograft disease after transplantation mediated by urinary proteins?

Remuzzi and colleagues proposed several mechanisms by which proteinuria might cause renal damage, one of the most appealing being a contribution to interstitial damage. In native kidney disease, interstitial pathology much more closely correlates with serum creatinine levels and renal prognosis than the extent of glomerular disease [9,10]. Similar findings can be obtained in transplant recipients. In a histomorphometry study we were able to correlate the expansion of the interstitial compartment with serum creatinine in patients with chronic renal allograft failure (see Figure 1). Additionally there was a close correlation between tubulointerstitial inflammation and atrophy and the degree of proteinuria. It is interesting to note that interstitial mononuclear cellular infiltrates can be found frequently in proteinuric native kidney diseases but are also common in renal allograft recipients [9]. Although these infiltrates are thought to be specific for patients with interstitial rejection, they have also been described in patients with proteinuria and apparently stable or slowly deteriorating excretory allograft function.

Several proposals have been put forward to explain how an increased concentration of proteins in the urinary space might exert chemotactic effects at the basolateral site. An increased reabsorption of proteins by tubular epithelial cells leads to lysosomal swelling and rupture, resulting in the contamination of the cytoplasm with injurious lysosomal enzymes. Some proteins such as transferrin might be especially toxic. Transferring delivers iron to the intracellular acidic environment, where these ions catalyse the formation of reactive oxygen species, causing peroxidative cell injury. Oxidative modification might also alter filtered and reabsorbed lipoproteins, which are specifically bound by membrane receptors and recycled within the cytoplasm. Overloading of proximal tubular cells in culture with albumin or transferrin–iron upregulates the gene of monocyte chemoattractant protein (MCP-1), an intercrine with chemoattractant properties for monocytes and T cells (reviewed in [1]). And very recently it was shown that activation of renal tubular cells by infiltrating T cells can amplify and perpetuate local inflammatory responses through chemokine production (mostly MCP-1) [11]. Additionally complement components, filtered during massive proteinuria, can be activated on the brush border of proximal tubular cells with a consequent insertion of the membrane attack complex onto the tubular cell membrane, followed by profound cytoskeletal alterations and cytolysis. Furthermore, a recent in vitro study showed that activation of complement on the surface of cultured human proximal cells triggers the generation of proinflammatory mediators such as tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) contributing to the tubulointerstitial injury [1]. Finally, it could be speculated that reabsorption of filtered TNF-α, as has been shown in membranous disease, could trigger the upregulation of adhesion molecules [12].

Another possible mechanisms of proteinuria associated recruitment of mononuclear cells to the interstitial compartment is a human leukocyte antigen (HLA)-dependent immune response. In contrast to normal renal tissue, renal tubular epithelial cells after transplantation commonly express HLA class II molecules [13] and Deckers et al. [14] were able to demonstrate that recipient T-cells are able to attack donor HLA class II expressing tubular epithelial cells. Expression of HLA class II molecules, however, is also typically found in antigen-presenting cells. Bohle et al. [10] suggested that glomerular basement membrane material shed into the urine may be reabsorbed by the tubules and presented as an antigen to T cells. This might be especially important in patients with transplant glomerulopathy, in whom marked alterations in the structure of the glomerular basement have been described [15]. Intracellular adhesion molecule (ICAM)-1 and HLA class II molecule expression has been especially noted during rejection episodes, providing a possible explanation for the often described association between acute rejection and chronic allograft failure. The importance of ICAM-1 in the induction of an interstitial nephritis has been shown by Cheng et al. very recently [16]. These authors used ICAM-1 antisense oligonucleotide treatment in mice with unilateral ureteral obstruction and were able to demonstrate that treated animals had markedly less...
infiltrates of inflammatory cells and accumulation of extracellular matrix in the tubulointerstitium [16]. Both pathways of immune reaction induced by uptake and processing of urinary proteins finally lead to cytokine production. As has been discussed recently by Paul [5], these excess cytokines might be of primary importance in the pathogenesis of chronic allograft damage.

Recent in vitro evidence also suggests a link between proteinuria and tubular metabolism of endothelin-1 (ET-1), a powerful vasoconstrictor peptide. Exposure of proximal tubular cells to a dose-dependent elevation in synthesis and release of ET-1. An excessive tubular release of ET-1 may cause an accumulation of this peptide in the interstitium, where it could increase the tone of afferent and efferent arterioles, thus reducing the blood supply to peritubular capillaries and leading to interstitial ischaemia and fibrosis. In addition, ET-1 accumulating in the renal interstitium could promote interstitial fibroblast proliferation, matrix deposition, and infiltration of active macrophages (reviewed in [1]). These mechanisms all could be augmented by administration of cyclosporin A [17].

**Will treatment of post-transplant proteinuria preserve renal allograft function?**

Based on the results of these intense in vitro and in vivo studies, it is not surprising that there is growing clinical interest to provide therapies that are able to reduce proteinuria in patients after renal transplantation. Several options, including protein restriction [18], ACE inhibitors [19], and calcium-channel blockers [20] are available, but until now no prospective study has been designed to evaluate the effects of antiproteinuric treatment on the course of chronic allograft nephropathy. This is surprising, given the fact that chronic allograft failure is one of the most common reasons for end-stage renal disease in the industrialized world. Until the results of such studies become available, however, it seems logical to focus on urinary protein excretion in renal transplant recipients to select a high-risk population in which therapy has to be intensified. Clearly, other mechanisms also are operative in chronic allograft failure and the significance of each contributor to this process has yet to be evaluated.

**References**


