Abstract

Introduction: Chronic allograft dysfunction (CAD) is the primary cause of chronic graft failure after kidney transplantation. The pathogenesis of CAD involves both antigen-dependent and antigen-independent mechanisms. Serum uric acid could have a role in both mechanisms.

Review: Hyperuricemia in subjects with renal transplantation is not usually viewed as clinically significant unless the subject develops gout. Drugs used in the treatment of hyperuricemia and gout are more likely to cause side effects in the kidney transplant recipient. However, there are recent studies that raise the possibility that uric acid could have a role in CAD. Soluble uric acid has been shown to stimulate the proliferation of vascular smooth muscle, to inhibit endothelial cell proliferation and to reduce bioactive levels of endothelial NO. Studies in experimental models have found that hyperuricemia can cause hypertension associated with renal injury characterized by microvascular disease, tubulointerstitial disease, glomerular hypertrophy and glomerulosclerosis. Hyperuricemia was also found to worsen preexistent renal disease, and to be associated with the development of severe vascular lesions that are reminiscent of those observed in CAD. Furthermore, chronic cyclosporine nephropathy is very similar to what is observed in normal rats simply by raising uric acid levels. In addition, raising uric acid levels in rats receiving cyclosporine accelerates the nephropathy whereas lowering uric acid ameliorates the renal lesions.

Conclusion: The pathogenic role of uric acid in CAD is still controversial. A controlled clinical trial would be the best approach to determine the effect of uric acid lowering treatment on the development of CAD and long term graft function.

Keywords: chronic allograft dysfunction, cyclosporine, uric acid, hyperuricemia, vascular disease

Introduction

Chronic allograft dysfunction (CAD) refers to progressive dysfunction of an allograft renal transplant, with biopsy findings of tubular atrophy, interstitial fibrosis, progressive glomerulosclerosis and variable degrees of arterial/fibrointimal thickening or arteriolar hyalinosis [1, 2]. CAD remains the primary cause of chronic graft failure after renal transplantation and increases the risk for cardiovascular mortality in this group of patients. Understanding the cause(s) of CAD and potential treatments remains a major goal in transplantation [1].

Most studies suggest that the pathogenesis of CAD involves both antigen-dependent and antigen-independent mechanisms [3]. Antigen-dependent (immune mediated) CAD, such as observed with chronic allograft rejection, is often associated with a previous history of acute or subclinical rejection, lower HLA matching, the presence of higher panel reactive antibodies (PRA), and in some instances the detection or development of donor specific antibodies (DSA). In contrast, antigen-independent CAD is often associated with the use of calcineurin inhibitors (CNI), a history of delayed graft function, the presence of classical cardiovascular risk factors (such as hypertension and dyslipidemia) and proteinuria. The differential diagnosis of antigen-independent CAD includes hypertension-associated vascular injury, viral infection, chronic obstruction, and chronic pyelonephritis [2].

One factor that could have a role in both antigen-dependent and antigen-independent CAD is serum uric acid. Uric acid is an end-product of purine metabolism that is excreted primarily by the kidney with a lesser excretion by the gastrointestinal tract. Serum uric acid levels are frequently elevated in subjects following renal transplantation [4, 5]. A variety of mechanisms may account for the presence of a higher uric acid in transplant recipients, including the effect of calcineurin inhibitors (especially cyclosporine) to reduce urinary net
uric acid has also been shown to have a variety of direct effects on tubular epithelial cells as well as on neutrophils and monocytes [23, 24].

Consistent with the in vitro studies, studies in experimental models have found that hyperuricemia can cause hypertension associated with renal injury characterized by microvascular disease, tubulointerstitial disease, and glomerular hypertrophy and glomerulosclerosis [17, 25, 26]. Hyperuricemia was also found to worsen preexistent renal disease, and to be associated with the development of severe vascular lesions that are reminiscent of those observed in chronic allograft nephropathy [27]. Other studies also suggest that uric acid may have a role in inducing features of the metabolic syndrome, including insulin resistance and dyslipidemia [28]. Fewer clinical studies are available, but there is also accruing evidence that uric acid may have a role in some forms of hypertension and chronic kidney disease [29, 30].

Experimental studies also suggest that uric acid could have a role in chronic calcineurin toxicity. Chronic cyclosporine use, and to a lesser extent, tacrolimus, are associated with the development of hyperuricemia, renal vasoconstriction, hypertension and a renal lesion characterized by afferent arteriolar hyalinosis and tubulointerstitial fibrosis. Interestingly, the administration of allopurinol (a xanthine-oxidase inhibitor which lowers uric acid) to rats can attenuate both the renal vasoconstriction and the decrease in glomerular filtration rate induced by cyclosporine [31, 32]. Furthermore, chronic cyclosporine nephropathy is very similar to what has been observed in normal rats simply by raising uric acid levels [26]. In addition, raising uric acid levels in rats receiving cyclosporine accelerates the nephropathy whereas lowering uric acid ameliorates the renal lesions [33]. Whether lowering uric acid can improve cyclosporine nephropathy in humans is unknown. However, a pilot study did report that lowering uric acid with allopurinol was associated with an improvement in renal function in hyperuricemic liver transplant recipients [34].

While these studies implicate uric acid as a potential risk factor for antigen-independent CAD, there may also be a potential role for uric acid in antigen-dependent CAD. Recently Shi et al found that uric acid has a critical role in the activation of dendritic cells to host antigens, particularly in conditions associated with chronic tissue injury [35]. The same group later showed that uric acid participates in the activation of CD8 T cells to transplanted cells [36]. More recent studies have shown that uric acid can directly activate T cells [37] and enhances the T cell responses to dendritic cell-based vaccines [38]. Uric acid also potentiates B cell immune responses [39], and can activate the IL-1 receptor on monocytes via a Toll
receptor pathway involving MyD88-dependent signaling [40]. Allopurinol has also been shown to reduce immune responses to antigens in normal mice [41]. Moreover, one clinical report suggested that the addition of allopurinol translated into less rejection in renal transplant recipients [42].

Studies in man suggest that uric acid may be a predictor for reduced renal function [12], cyclosporine nephrotoxicity [43], and CAD associated with renal transplantation [44]. Uric acid has also been associated with allograft vasculopathy in cardiac transplant recipients [45]. Nevertheless, there are also studies that have not been able to show a relationship between uric acid and long term renal outcomes [46]. However, it may be difficult to show the epidemiological association of uric acid with progressive renal insufficiency since uric acid itself is also altered by the degree of underlying renal function. Hence, the best approach to determining the effect of uric acid on CAD and long term renal outcome will require a controlled clinical trial in which uric acid levels are actively lowered. Given the potential toxicities with current uric acid-lowering therapies, this may not be an easy task. However, there are newer agents on the horizon that may be useful for this purpose, including the xanthine-oxidase inhibitor, febuxostat, in which dosing is not affected by renal function and in which serious allergic reactions are rare. Until then, the possibility that uric acid has a pathogenic role in CAD must remain conjectural.

Conclusion

The pathogenic role of uric acid in CAD is still controversial. However, there are several reports in the literature suggesting that hyperuricemia is a contributing factor to the development of CAD. A controlled clinical trial would be the best approach to determine the effect of uric acid lowering treatment on the development of CAD and long term graft function.

References


