SEMINARS IN
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Uric Acid and Transplantation

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Hyperuricemia is a common complication in organ transplant recipients, and frequently is associated with chronic cyclosporine immunosuppressive therapy. Kidney and heart transplant recipients are prone to develop posttransplant hyperuricemia. Risk factors for hyperuricemia include decreased glomerular filtration rate (GFR), diuretic use, and preexistent history of hyperuricemia. The influence of hyperuricemia in patient and graft survival is unclear because uric acid is not usually considered a common risk factor for cardiovascular disease that affects graft and patient survival. However, there have been small studies that have suggested that control of uric acid levels contributes to recovery of renal function (in heart and liver transplant recipients) and in an improvement in GFR in renal transplant recipients. Despite controversies in the need for hyperuricemia treatment in transplant patients, strategies to decrease uric acid levels includes a decrease or avoidance of cyclosporine treatment, adequacy of antihypertension treatment, avoidance of diuretics, nutritional management, and use of uric acid–decreasing agents. In this article we review the incidence and risk factors for the development of posttransplant hyperuricemia, discuss the influence of different immunosuppressive agents on uric acid metabolism, and suggest some alternative treatments for posttransplant hyperuricemia. We also consider that uric acid should be considered as a potential risk factor for renal allograft nephropathy or for renal dysfunction in nonrenal transplant recipients, as well as a comorbid factor for a decrease in patient and graft survival.
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The incidence of posttransplant hyperuricemia varies according to the organ transplanted and the immunosuppressive regimen, with the highest incidence in renal transplant recipients receiving cyclosporine therapy. In the precyclosporine era, hyperuricemia was found in approximately 25% of renal transplant patients, but the prevalence increased to over 80% after the widespread use of cyclosporine.[1-4] Uric acid levels in patients with cyclosporine-induced hyperuricemia ranges from 8 to 14 mg/dL, and approximately 10% of them develop gout.[1] In other solid-organ transplants, hyperuricemia also is frequent, ranging from 14% to 50% in liver transplant recipients[5,6] and about 30% in cardiac transplant patients.[7] Gout episodes are frequent in heart transplant recipients, but are rare in liver transplant patients.[5]

Hyperuricemia occurs early after transplantation and is associated with decreased glomerular filtration rate (GFR), diuretic use, cyclosporine therapy, and preexistent history of hyperuricemia and gout.

A previous history of hyperuricemia and gout are more frequent in heart and kidney transplant recipients, usually associated with diuretic use while on the waiting list.[8] The decreased incidence of hyperuricemia observed in some series of liver transplant recipients may relate to the avoidance of loop or thiazide diuretics in patients with cirrhosis waiting for transplantation in some groups.[5]

Diuretics also are associated with posttransplant hyperuricemia.[9] Renal transplant recipients often develop hypertension and edema, leading to the frequent prescription of thiazide and loop diuretics. It is well known that these classes of drugs cause hyperuricemia by interference in urate clearance and by inducing a certain degree of circulatory hypovolemia, which increases tubular urate reabsorption.[9]

However, the most common association of posttransplant hyperuricemia is with cyclosporine. There are a general lack of reports of increased uric acid levels in organ transplant patients in the precyclosporine era. Studies of uric acid handling by the transplanted kidney in the absence of cyclosporine use failed to show abnormalities in fractional uric acid reabsorption or excretion. These findings argue against an abnormal uric acid handling by the renal transplant itself.[10]

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After the introduction of cyclosporine as immunosuppressive therapy in solid-organ transplantation, the incidence of hyperuricemia and gout increased. Cyclosporine can cause hyperuricemia by 2 different mechanisms: (1) by increased proximal uric acid reabsorption, especially in the presence of volume depletion associated with diuretic use,[11] and (2) by a decrease in GFR secondary to afferent arteriolar vasoconstriction.[12] Both effects are not restricted to renal transplantation.

There are few studies evaluating uric acid handling with other immunosuppressive agents, and few studies analyzing the impact of hyperuricemia in patient and graft survival. As a complicating factor, we should consider that in the majority of clinical trials evaluating safety and efficacy of new immunosuppressive drugs, cyclosporine is often part of the maintenance therapy. Uric acid levels were evaluated in few clinical trials as it related to the use of these newer agents. Therefore, the association and importance of hyperuricemia and other immunosuppressive agents is based on case reports or small series.[1,4,7,13]

Immunosuppressive Therapy, Uric Acid Handling, and Incidence of Hyperuricemia

Steroids

Corticosteroids have been used in transplantation since the first days of solid-organ transplantation in the 1950s. Metabolic effects include hyperlipidemia, salt retention, and water retention, but no effects on uric acid metabolism have been described. However, this group of drugs increases appetite and can aggravate preexistent metabolic disorders.

Azathioprine

Azathioprine is a imidazoyl derivative of 6-mercaptopurine, which inhibits lymphocyte proliferation by inhibition of DNA and RNA synthesis. Azathioprine is distributed rapidly throughout all body fluids. Inside the cell it is broken down to 6-mercaptopurine, which can be oxidized by xanthine oxidase. Allopurinol, by inhibiting xanthine oxidase, may lead to inhibition of metabolism and increased azathioprine toxicity, with excessive bone marrow depletion leading to leukopenia.[14-16] No effects of azathioprine on uric acid metabolism have been described so far.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug that exerts a selective antiproliferative activity on activated lymphocytes by inhibition of inosine monophosphate dehydrogenase. Side effects include gastrointestinal intolerance and bone marrow toxicity. However, the inhibition of this pathway does not appear to influence uric acid metabolism, and as such no interaction of MMF with xanthine oxidase has been observed. As a consequence, no dose adjustment of MMF needs to be made in patients receiving allopurinol.[17,18]

Cyclosporine

Cyclosporine, a calcineurin inhibitor that inhibits interleukin-2 production, was introduced in the 1980s as an immunosuppressive agent, and quickly became a first-line treatment in organ transplantation and other immunologically mediated diseases.[19] Side effects of cyclosporine include nephrotoxicity, systemic hypertension, and hyperuricemia. Over 50% of patients taking cyclosporine become hyperuricemic, and approximately 10% develop gout.[1] The mechanism of cyclosporine-induced hyperuricemia includes increased net tubular urate reabsorption,[11,20] as well as decreased glomerular filtration[21] with a decrease in the filtered load of uric acid.[12] This effect is not restricted to renal transplant patients, and was observed in different groups of patients receiving cyclosporine, independent of the presence of impaired renal function before the initiation of the treatment.

Tacrolimus

Tacrolimus is a calcineurin inhibitor that has similar properties and adverse effects as cyclosporine, including nephrotoxicity and hypertension. The drug also can cause hyperuricemia, but there are no reports of gout with tacrolimus.[22,23] In liver transplant recipients, the incidence of hyperuricemia was similar when treatments with tacrolimus and cyclosporine were compared, with a positive correlation between serum uric acid level and creatinine levels. However, for similar levels of uric acid, the serum creatinine level was higher in the tacrolimus group.[5]

Sirolimus

Sirolimus is an immunosuppressive agent (macrocyclic lactone isolated from *Streptomyces hygroscopicus*) that inhibits lymphocyte activation at a later stage in the cell cycle, by inhibiting the interleukin-2–mediated signal transduction. Preclinical and clinical trials with sirolimus showed no deleterious effects on renal function, and common side effects include hyperlipidemia and bone marrow depression. The incidence of hyperuricemia in sirolimus-treated patients is difficult to ascertain because many regimens are based on sirolimus-cyclosporine association. However, recent studies comparing cyclosporine with non–calcineurin-based immunosuppression by using sirolimus (with azathioprine and steroids), showed both serum uric acid level and creatinine level were lower in the sirolimus group after 52 weeks, compared with cyclosporine-treated patients,[24,25] suggesting that sirolimus has substantially less effect on uric acid metabolism in patients undergoing renal transplantation.

Theoretically, sirolimus also could be beneficial in chronic allograft vasculopathy by inhibiting the proliferation of smooth muscle cells. Because uric acid activates smooth muscle cell proliferation and vascular remodeling in animal models,[26] further studies with this group of agents (sirolimus and everolimus) are needed.

Impact of Hyperuricemia in Transplant Follow-Up: Patient and Graft Survival

The influence of hyperuricemia in transplant survival is controversial.[21,27,28] There are few reports of the incidence of hyperuricemia and gout in organ transplant recipients and the majority are only small retrospective analyses. Although hypertension and diabetes, and in the latter years dyslipidemia, are considered important risk factors for patient and graft survival, most studies involving uric acid are restricted to reports of incidence and treatment of gouty arthritis and usually consider hyperuricemia strictly as a complication of decreased GFR or a side effect of cyclosporine treatment.

Controversy also exists about the levels of uric acid in transplants and the need for treatment. Gores et al,[13] studied a group of renal transplant recipients with normal renal function and blood cyclosporine levels between 100 and 200 ng/mL. Severe hyperuricemia (uric acid > 14 mg/dL) was observed in less than 10% of the patients, however, gout was infrequent. No differences were observed in serum creatinine level in patients in whom the serum uric acid level ranged from 8 to 14 mg/dL, suggesting that asymptomatic hyperuricemia does not adversely affect renal allograft function, and no specific therapy is required. The only recommendation was to avoid the use of diuretics in patients receiving cyclosporine.[13]

Recently, Gerhardt et al[29] analyzed the influence of uric acid levels on graft survival, and reported that hyperuricemia is associated with a lower graft survival after 5 years (68.8%) compared with normouricemic patients (83.3%).[29] The investigators concluded that hyperuricemia contributes to a significant decrease in renal graft survival. This finding can be explained by the aggravation of cyclosporine vasculopathy and interstitial injury by uric acid, as shown in animal models of hyperuricemia and cyclosporine nephrotoxicity.[30]

There are many similarities between renal dysfunction induced by hyperuricemia and cyclosporine nephrotoxicity. Both cause (1) renal vasoconstriction,[31,32] (2) depletion of nitric oxide and an increase in angiotensin II level,[33-35] (3) preglomerular arteriolopathy and hyalinosis,[26,36] and (4) interstitial disease.[33,36] However, these findings are not exclusive for these entities, and also are observed in the late phase of chronic allograft nephropathy and other forms of chronic renal disease, independent of transplantation. The occurrence of renal disease in nonrenal transplants mainly is associated with the chronic use of cyclosporine and recently with tacrolimus. However, other risk factors for renal diseases in these patients are poorly studied.[37]

A recent multivariate analysis of risk factors for development of chronic renal dysfunction in liver transplant recipients found hyperuricemia in the first month posttransplant as an independent risk factor. In addition, a risk for renal function deterioration was associated with recipients older than 45 years, pretransplant renal dysfunction, renal dysfunction within the first 6 months, and oil-based cyclosporine.[38]

Other cardiovascular complications associated with hyperuricemia also are poorly studied. Although in the normal population an increase in serum uric acid levels correlates with a higher risk for stroke, this is not true in renal transplant recipients[39] or in patients with chronic renal failure.

Hyperuricemia Posttransplant: To Treat or Not to Treat?

Although it is well established that gout attacks should be treated, the use of uric acid–decreasing agents in organ transplant patients remains controversial, and side effects of the usual medication (allopurinol, colchicine, and benzbromarone) must be considered.

Gerhardt et al[29] showed that patients with isolated posttransplant hyperuricemia had higher serum creatinine levels and lower graft survival. However, this group failed in proving if hyperuricemia was a risk factor for renal graft dysfunction or just a marker of decreased GFR. In the same study, treatment of hyperuricemic patients with allopurinol had no impact on graft or patient survival. On the other hand, in a set of liver transplant recipients with increased serum creatinine levels, treatment of hyperuricemia with allopurinol was associated with improvement in renal function, suggesting that hyperuricemia contributed to the increase in serum creatinine levels.[5]

An alternative to allopurinol outside the United States is the use of benzbromarone. Perez-Ruiz et al[40] analyzed a large group of renal transplant recipients who were treated with allopurinol or benziodarone in a long-term follow-up study. The patients had stable renal function (creatinine clearance > 20 mL/min), hyperuricemia lasting more than 12 months, and the investigators compared the efficacy of 2 different regimens: allopurinol and benzbromarone. Both drugs proved to be safe and well tolerated, however, a better serum uric acid level control was achieved with benzbromarone treatment. No differences in renal function were observed with serum uric acid level decrease, but the incidence of gout was lower than in other series.

Despite controversies about treatment of hyperuricemia in the absence of gout attacks in transplant recipients, there are some strategies that are useful to minimize cyclosporine nephrotoxicity or to decrease other cardiovascular risk factors that also can be applied in the management of posttransplant hyperuricemia. The major points are as follows: (1) nutritional management, (2) minimization of cyclosporine nephropathy, (3) blood pressure control, and (4) specific treatment for hyperuricemia.

Nutritional Management

One of the mechanisms underlying the development of hyperuricemia and gout is the excessive ingestion of purine-rich foods and alcohol. Studies showed that the risk for gout is increased with diets rich in meat, especially red meats and seafood, and diets poor in dairy, nonsaturated products, fruits, and vegetables.[41] The increase of obesity, hyperten-

sion, and dyslipidemia worldwide also affects transplant recipients and patients on the waiting list, especially those patients waiting for kidney transplants. After transplant, with the improvement in quality of life, steroid use, and recovery of appetite, patient nutritional habits should be reviewed and diets rich in fruits, vegetables, and low-fat dairy products may decrease the incidence of hyperuricemia and gout, as well as cardiovascular risk, in this setting of patients.

Minimization of Cyclosporine Nephrotoxicity

Because cyclosporine is the main drug associated with the development of nephrotoxicity, hyperuricemia, and gout after organ transplantation, many recent clinical trials have attempted to decrease or withdraw cyclosporine. However, because the effect in GFR is the most important end point for these trials, uric acid levels usually are considered a consequence of improvement in renal blood flow (RBF) and GFR after cessation of preglomerular vasoconstriction induced by cyclosporine.

Different regimens of cyclosporine minimization have been proposed in the past few years, and include cyclosporine withdrawal, conversion to less-nephrotoxic agents, cyclosporine dose decrease, and cyclosporine avoidance.

Cyclosporine withdrawal regimens usually are based on a short-term use of cyclosporine in association with sirolimus.[42] After cyclosporine withdrawal, an improvement in GFR is observed coupled with a decrease in serum uric acid level and blood pressure. Other trials with similar designs, but that use chronic maintenance therapy with MMF and steroids, have shown similar effects on renal function and blood pressure in different organ transplants. However, serum uric acid levels are not available in these reports.[43] Late cyclosporine withdrawal in stable renal transplant patients with chronic allograft nephropathy in the presence of MMF also was associated with GFR improvement and a decrease in uric acid levels and blood pressure.[44] These findings can be explained by the functional and structural reversibility of chronic cyclosporine vasculopathy after cyclosporine withdrawal, as suggested by experimental models.[45]

In some patients a decrease of the cyclosporine dose is enough to achieve better renal function and hyperuricemia control. In heart transplant recipients a decrease in serum uric acid levels was observed after cyclosporine decrease.[46]

Conversion from cyclosporine to less-nephrotoxic immunosuppressive agents, such as MMF or sirolimus, results in acute improvement in renal function with normalization of serum uric acid levels.[47] However, some groups suggest that conversion from cyclosporine to tacrolimus also is effective in patients with gout. Tacrolimus and cyclosporine are calcineurin inhibitors with comparable side effects, especially nephrotoxicity, hypertension, and hyperuricemia. However, small series suggest that hyperuricemia associated with cyclosporine occurs in early stages of renal dysfunction.[5] The absence of reports of severe gout attacks in transplant patients receiving tacrolimus also suggests that this drug can replace cyclosporine in patients with refractory gout or colchicine/allopurinol intolerance.[23] Analyses of serum uric acid profiles in larger series of patients receiving tacrolimus are needed to prove this hypothesis.

With the development of new immunosuppressive agents, new clinical trials avoiding calcineurin inhibitors have been proposed. One of these trials compares cyclosporine with sirolimus in association with MMF and steroids, and showed that, after 24 months, serum creatinine levels and serum uric acid levels are lower in the sirolimus arm,[25,48] with a low incidence of acute rejection episodes in both arms, suggesting that for some renal transplant patients, cyclosporine can be eliminated from the beginning. However, we need more trials and a longer follow-up period to confirm these findings.

Blood Pressure Control

The higher incidence of hypertension in renal transplant recipients, and the frequent association with increased serum uric acid levels, promoted small clinical trials comparing different antihypertensive drugs and the effect on serum uric acid level and renal function. The mechanism for decreasing uric acid level can be the direct uricosuric effect (eg, losartan) or improvement in renal blood flow and GFR (eg, amlodipine).

Losartan has a direct effect on the uric acid transport in the proximal tubule,[49] increasing the fractional urate excretion and decreasing serum uric acid levels in transplant patients.[50,51] Its beneficial uricosuric effect is higher in patients without diuretic treatment, but is independent of renal function.[51] This uricosuric property was not observed with other Angiotensin II (AII) antagonists, such as irbersartan, eprosartan, and other members of the angiotensin type I (AT1) antagonist family.[52]

Because cyclosporine activates the intrarenal renin-angiotensin system and promotes vasoconstriction,[19] the effects of blockade of the renin-angiotensin system on renal function, blood pressure control, and serum uric acid levels were analyzed by Schmidt et al,[53] who compared losartan and enalapril and noted that despite similar control in blood pressure and protein excretion, losartan decreased serum uric acid levels, whereas enalapril had the opposite effect. In this study, the uricosuric effect of losartan was mild, concordant with previous studies that suggested that the uricosuric effect is dose dependent in healthy volunteers.[54]

Calcium channel blockers are the antihypertensive treatment of choice in renal transplant patients, especially for the preglomerular vasodilating properties. Chanard et al[55] compared the effect of amlodipine and the ā-blocker tertatolol in hypertensive renal transplant recipients, and observed that amlodipine significantly decreased uric acid levels after 60 days of treatment, despite no changes in fractional urate excretion. However, this drug increased GFR, lithium, creatinine, and urate clearances, without changes in cyclosporine levels, suggesting a protective effect on the development of cyclosporine-induced hyperuricemia.

Common diuretics increase the net reabsorption of uric acid in the proximal tubule and decrease the urinary excretion, increasing the serum uric acid concentration. This hyperuricemic effect is observed with loop diuretics, thiazides,

amiloride, triamterene, and spironolactones. The increase in serum uric acid levels may be noted within a few days of the initiation of treatment, despite the use of low doses.[52] Avoidance of diuretics, especially thiazides, for treatment of hypertension in organ transplant patients with hyperuricemia is suggested in some series,[11] and its prescription should be based on the risk benefit of increasing serum uric acid levels.

These studies suggest that for renal transplant patients with systemic hypertension and hyperuricemia, calcium channel blockers or losartan are the treatment of choice whereas diuretics should be avoided.

Classic Treatments for Hyperuricemia and Gout: Allopurinol, Benziodarone and Colchicine

Allopurinol

Allopurinol is the most effective treatment for hyperuricemia. However, because its mechanism involves xanthine oxidase enzyme inactivation, the interaction with azathioprine is associated with severe bone marrow depletion,[16] requiring decreases in azathioprine dosage.[15] There are no reports of interaction of allopurinol and other immunosuppressive drugs. Recent studies showed that association with allopurinol and MMF is safe.[17,18]

Benzofurans

Benzofurans (such as benziodarone and benzbromarone) are uricosuric drugs that enhance renal excretion of uric acid, and are useful in the control of hyperuricemia in patients with normal or impaired renal function despite diuretic therapy.[56]

Colchicine

Colchicine exerts its anti-inflammatory action by binding tubulin, a subunit protein of microtubules, preventing their polymerization, and resulting in decreased leukocyte motility and impaired phagocytosis. Cyclosporine therapy increases the risk for colchicine toxicity. Cyclosporine blocks P-glycoprotein, which interferes in colchicine metabolism, increasing the risk for cytotoxicity, even at therapeutic doses. Adverse effects of colchicine treatment include gastrointestinal intolerance and myoneuropathy,[57,58] especially in the presence of impaired renal function.

Fenofibrate

Fenofibrate, but apparently not other fibrates,[52,59] decreases the net reabsorption of urate in the proximal tubule, promoting hyperuricosuria and decreasing serum uric acid levels. Its effect on decreasing uric acid levels in association with losartan in hypertensive patients with gout was shown by some reports.[52,60] However, in organ transplant patients receiving cyclosporine, fibrates should be used with caution because this association can cause myopathy and rhabdomyolisis.[61,62] We found no reports in the literature on the effects of fibrates in renal uric acid metabolism in organ transplant patients.

In summary, there are a lack of studies analyzing the incidence, impact, and need for treatment of hyperuricemia in renal transplant recipients. Although the majority of studies correlate posttransplant hyperuricemia and gout with cyclosporine treatment and decreased GFR, the impact of other immunosuppressive drugs are not known because uric acid usually is not considered in clinical or preclinical trials. The impact of hyperuricemia in graft and patient survival remains controversial. However, recent studies in other populations suggests that uric acid is an important risk factor for cardiovascular mortality and renal disease.[63,64] The histologic findings of chronic allograft nephropathy, characterized by tubular atrophy, interstitial fibrosis, glomerulosclerosis, and arteriolar hyalinosis also can be observed in animal models of chronic cyclosporine toxicity[45] and chronic hyperuricemia,[33,65] as well as in chronic rejection, long-term hypertension, and other forms of chronic renal disease, independent of the transplanted organ.

If we consider that in the past few years, with the development of more potent immunosuppressive agents, chronic allograft nephropathy and cardiovascular mortality have become the most frequent causes for graft and patient loss in solid-organ transplants,[66] we should consider uric acid as a potential risk factor and not as just a marker of renal dysfunction in both renal and nonrenal transplant patients.

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