

Hyperuricemia and gout following pediatric renal transplantation

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Abstract Hyperuricemia and gout are common complications in adult renal transplant recipients. In pediatric recipients, however, hyperuricemia seems to be rare, but data are scarce. Thirty-two children (21 males, 11 females) were investigated for a median time of 4.8 years (range: 0.4–11.2 years) following renal transplantation. The median age of this pediatric study group was 13.9 years (range: 5.7–20.3 years), and the calculated glomerular filtration rate (GFR) was 61 ml/min per 1.73 m² (range: 12–88 ml/min per 1.73 m²). All patients were given calcineurin inhibitors, with 22 and ten children receiving cyclosporine A (CSA) and tacrolimus (TAC), respectively. The median plasma uric acid was 385 µmol/l (range: 62–929 µmol/l); 15 children (47%) were above the age-related normal range. Only one patient experienced gouty arthritis. There was a significant correlation between plasma uric acid concentration and both time span after transplantation and plasma creatinine, and an inverse correlation to GFR ($p < 0.05$). No significant correlation was found between plasma uric acid and body mass index (BMI). Plasma uric acid concentrations were neither different among CSA- and TAC-treated children, nor did they correlate with drug exposure or blood trough levels of CSA or TAC. Plasma uric acid concentration was not different when compared to children with chronic renal failure (CRF) of a similar degree in native kidneys. We conclude that hyperuricemia is common among pediatric renal transplant recipients and rather a consequence of chronic renal transplant dysfunction than the use of calcineurin inhibitors. Gout, however, is rare.

Keywords Body mass index · Children · Cyclosporine A · Gout · Hyperuricemia · Kidney transplantation · Tacrolimus

Introduction

Hyperuricemia and gout are frequently observed among adult renal transplant recipients, with incidence rates of up to 80 and 10%, respectively [1, 2]. Post-transplant hyperuricemia in adults is often associated with the use of cyclosporine A (CSA) [1, 2]. Hyperuricemia is also frequent in non-renal organ transplant recipients, with the incidence rates ranging from 14 to 50% in liver transplant recipients [3] and up to 30% in heart transplant recipients [4].

Uric acid is the final product of the purine metabolic pathway originating either from endogenous or alimentary sources. As primates lack the hepatic enzyme uricase, uric acid in humans is mainly excreted via the renal pathway. The main handling of renal elimination of uric acid, either by reabsorption or secretion, takes place in the proximal tubule [5, 6]. During childhood, hyperuricemia is uncommon as children have an increased fractional excretion rate of uric acid [6]. Hyperuricemia is mostly associated with primary metabolic disorders of purine metabolism or tumor lysis syndrome. In addition, several reports have shown a correlation between plasma uric acid concentration and body mass index (BMI) in adolescents [7, 8].

Data on hyperuricemia and gout among pediatric kidney transplant recipients are rare. Hoyer et al. [9] described an increased net tubular absorption of uric acid in 28 CSA-treated pediatric renal transplant recipients. A retrospective study from Edvardsson et al. [5] revealed hyperuricemia in 23% of children on CSA 30 months following renal transplantation. There is only one report describing gout in five adolescent kidney transplant recipients [10]. To date,

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no study on Tacrolimus (TAC) and hyperuricemia among pediatric kidney transplant recipients has been published.

A case of hyperuricemia and gouty arthritis in an adolescent renal transplant recipient prompted this retrospective study. Our aim was to evaluate the prevalence and confounding clinical variables of hyperuricemia and gout in a group of 32 pediatric kidney transplant recipients. We hypothesized that baseline immunosuppression with either CSA or TAC had a differential effect on plasma uric acid levels.

Materials and methods

Thirty-two children and adolescents (21 males, 11 females) were evaluated in a retrospective single-center study. The median age of the children was 13.9 years (range: 5.7–20.3 years); only two patients were older than 18 years. The median time of the study after renal transplantation was 4.8 years (range: 0.4–11.2 years). All patients were given calcineurin inhibitors, with 22 and ten patients on CSA and TAC, respectively. In addition, 31 children were either on azathioprine ($n=16$) or mycophenolate mofetil ($n=15$); nine patients were on a steroid-free regimen, and 23 were on low-dose alternate-day prednisone. The following factors potentially predisposing to hyperuricemia and gout were studied: plasma creatinine and urea, glomerular filtration rate (GFR) as assessed by the Schwartz formula [11], dosing (mg/m^2 body surface area) and blood trough level of CSA and TAC, use of diuretics, time after renal transplantation, casual blood pressure measurement (BP) and BMI (based on Swiss reference data [12]). The measurement of uric acid plasma concentration by the uricase endpoint method is part of the routine laboratory assessment. Hyperuricemia was defined as a plasma uric acid concentration above the normal range for age and sex: for children between 2 and 15 years: 111–353 $\mu\text{mol}/\text{l}$; >15 years for girls: 143–339 $\mu\text{mol}/\text{l}$; >15 years for boys: 202–416 $\mu\text{mol}/\text{l}$. Plasma creatinine and CSA and TAC trough levels were measured by the Jaffé reaction, the fluorescence polarization immunoassay and the microbead enzyme immunoassay (MEIA), respectively.

All patients initially received triple immunosuppressive therapy: (1) CSA (aiming at a trough level of 180–250 $\mu\text{g}/\text{l}$ for the first 6 months and 80–120 $\mu\text{g}/\text{l}$ thereafter) or TAC (aiming at trough level of 6–10 $\mu\text{g}/\text{l}$ for the first 6 months and 4–7 $\mu\text{g}/\text{l}$ thereafter); (2) azathioprine (1 mg/kg per day) or mycophenolate mofetile (1200 and 800 mg/m^2 body surface area per day in combination with CSA or TAC, respectively); (3) prednisone (initially 1 mg/kg daily with rapid tapering and a switch to alternate days after 6 months). The antihypertensive drug of choice was a calcium-channel blocker (nifedipine). If additional antihypertensive treat-

ment were necessary, a beta-blocker (atenolol), angiotensin-converting enzyme (ACE)-inhibitor (enalapril) or diuretic (furosemide) was administered.

Beyond the first year after transplantation, patients were followed in the renal transplant clinic once every month. The statistical calculations (i.e. GFR and correlations) were based on a single measurement. The measured parameters, however, did not show any significant variation during three consecutive consultations (data not shown), with the exception of a single patient suffering from gout.

GFR and plasma uric acid concentration were also measured in a group of 23 patients (seven females, 16 males) with chronic renal failure (CRF) of their native kidneys (median age: 12.9 years; range: 4.8–19.7 years).

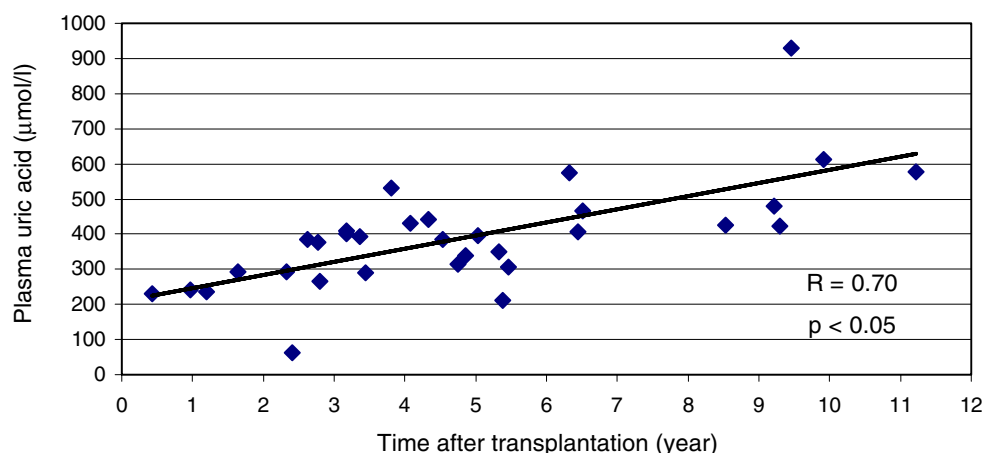
Statistical analysis was performed using a Pearson correlation coefficient and the Mann-Whitney-test for comparison of parametric variables between groups. Statistical significance was assigned to $p<0.05$.

Results

Median plasma uric acid concentration was 385 $\mu\text{mol}/\text{l}$ (range: 62–929 $\mu\text{mol}/\text{l}$). Fifteen children (47%) had hyperuricemia with uric acid concentrations above the age-related normal range; 12 (out of 22; 55%) were on CSA and three (out of 10; 30%) were on TAC. Median plasma creatinine was 102 $\mu\text{mol}/\text{l}$ (range: 53–482 $\mu\text{mol}/\text{l}$), with a median calculated GFR of 61 ml/min per 1.73 m^2 (range: 12–88 ml/min per 1.73 m^2). There was a significant correlation between plasma uric acid concentration and the time span after renal transplantation ($p<0.05$; Fig. 1). There was also a significant correlation between plasma uric acid concentration and plasma creatinine (data not shown) and an inverse correlation with GFR ($p<0.05$; Fig. 2). However, plasma uric acid concentrations did not differ among patients with CSA or TAC therapy (mean \pm SD: 402 \pm 114 vs. 332 \pm 114; $p=\text{n.s.}$). In addition, no significant correlation was found between plasma uric acid concentration and both CSA and TAC dose or blood trough level. The mean daily dose of TAC and CSA was 5.15 (\pm SD: 2.19) and 129 mg/m^2 (\pm 34.03), respectively, and the mean whole blood trough level was 6.9 (\pm 2.09) and 109 $\mu\text{g}/\text{l}$ (\pm 28.9 $\mu\text{g}/\text{l}$), respectively. All except two patients (SDS: -2.52 and $+3.61$) had a BMI within the normal age-related range [12]. There was no significant correlation between BMI (SDS) and plasma uric acid concentration. All patients had a casual blood pressure <95 percentile, with three adolescent boys on antihypertensive treatment: two were on atenolol and/or nifedipine, and one was also on furosemide.

The latter – a 15-year-old boy with sporadic steroid-resistant focal segmental sclerosis – was the only patient suffering from clinical gout. The first gouty episode

Fig. 1 Correlation between plasma uric acid concentration and the time span after renal transplantation ($p < 0.05$)



occurred 7.9 years after renal transplantation and manifested as arthritis of the metatarso-phalangeal joint of the left big toe. The maximal plasma uric acid concentration was 929 μmol/l, with moderate CRF (plasma creatinine: 214 μmol/l) due to chronic transplant nephropathy. Immunosuppression consisted of CSA (trough levels: 95–158 μg/l), azathioprine and alternate-day prednisone; this patient was the only one in this series on diuretics. Since receiving allopurinol over the long term, he has been free of gouty symptoms.

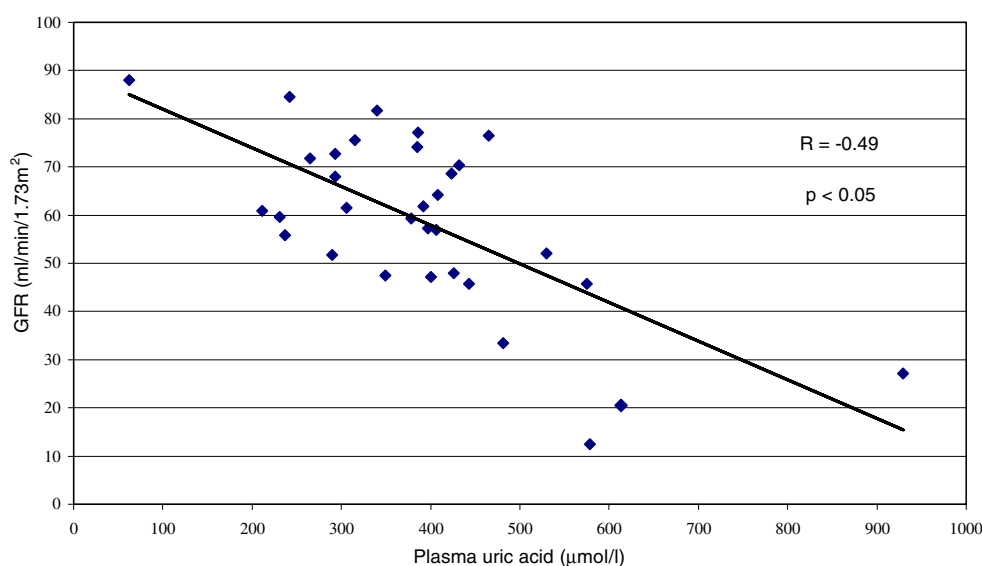
A control group of 23 patients with CRF of their native kidneys and a median GFR of 58 ml/min per 1.73 m² (range: 24–94 ml/min per 1.73 m²) had a median uric acid concentration of 368 μmol/l (range: 173–561 μmol/l). None of these patients received diuretics. The GFR and uric acid concentration were not significantly different from those of children who had received a kidney transplant.

Discussion

This report demonstrates that not only adult patients can suffer from hyperuricemia; among our study cohort also one-half of the pediatric renal transplant recipients were also found to have hyperuricemia. However, in contrast to adult patients, gout was rare. Interestingly, hyperuricemia in our series was not correlated to calcineurin inhibition, and the incidence rate was not different between CSA- or TAC-treated patients but, rather, it was correlated to chronic renal graft dysfunction. Consistent with the paucity of cases among pediatric renal transplant recipients [10], gout occurred in only one patient.

A previous pediatric study by Edvardsson showed a peak uric acid concentration in the patients at 6 months after transplantation, when 39% of the patients had hyperuricemia and 60% were receiving diuretics. At 30 months, significantly fewer patients had hyperuricemia (23%) or were on diuretics (17%) [5]. Our study differed from that of Edvardsson on a number of points: (1) our

Fig. 2 Inverse correlation between plasma uric acid concentration and calculated glomerular filtration rate (GFR; $p < 0.05$)



patients were studied after a median period of almost 5 years following the transplantation; (2) the calculated GFR was lower; (3) only one patient was on diuretics; (4) one-third of the patients were on TAC. Consistent with previous studies, impaired renal function – i.e. chronic transplant nephropathy – was the most important factor contributing to hyperuricemia [5, 9, 13, 14]. The fact that our control patients showed no difference in plasma uric acid concentration from our transplant patients when there was a similar degree of CRF in the native kidneys supports this notion.

CSA contributes to hyperuricemia and gout among adult renal transplant recipients [1, 2] and does this by two different mechanisms: (1) by increased proximal uric acid reabsorption, especially in the presence of volume depletion associated with diuretic use [9, 13]; (2) by a decrease in GFR secondary to afferent arteriolar vasoconstriction [15]. Both effects are not limited to renal transplantation as hyperuricemia and gout are also frequent in CSA-treated adults receiving non-renal solid organs, i.e. the liver [3] or heart [4]. On the other hand, Braun et al. reported a high incidence of gout among renal transplant patients treated solely with azathioprine and prednisone [16]. In pediatric renal transplantation, the hyperuricemic effect of CSA appears to be less significant. Our study did not find any correlation between calcineurin inhibition, measured as either a daily dosage or blood trough level, and plasma uric acid concentration. This result is consistent with that of a previous study [5]. The results of two different studies by Laine et al. [17] and Hoyer et al. [9], respectively, suggested that CSA may lead to hyperuricemia in pediatric renal recipients. These researchers based this proposal on the observation that the renal handling of uric acid demonstrated an increased net tubular reabsorption.

TAC is a calcineurin inhibitor with similar properties and adverse effects as CSA, including nephrotoxicity, hypertension and hyperuricemia; however, it may cause gout to a lesser extent than CSA [18–20]. Kanbay et al. recently reported on the influence of CSA- and TAC-based regimens on serum uric acid concentration: they observed that 155 adult renal kidney transplant recipients with both CSA and TAC increased their uric acid concentration in a similar manner [21]. In our series, three out of ten children on TAC had hyperuricemia; two were adolescents with a markedly reduced GFR of 12 and 33 ml/min/1.73 m², respectively.

Diuretics, i.e. loop diuretics, thiazides, amiloride, triamterene, and spironolactones, are also associated with post-transplant hyperuricemia, both in adult [1, 22, 23] and pediatric recipients [5]. The increase in plasma uric acid concentration may be noted within a few days of the initiation of treatment despite the use of low doses [24].

In our small series, we found no correlation between patients' BMI and plasma uric acid concentration. This is in

contrast with observations in healthy adolescents. However, only one patient had a BMI above the age-related normal range [12]. In addition, dietary excess (meat, seafood, alcohol), which is a frequent risk factor for hyperuricemia among adults, was not present [25].

Gout among pediatric renal transplant recipients is rare. Pela et al. reported five cases of adolescents developing gout 2–84 months after kidney transplantation; all were receiving CSA and two were on furosemide because of hypertension [10]. The contributing factors in the only patient of our series with gout were chronic transplant nephropathy and the combined use of CSA and diuretics. The uricostatic drug allopurinol is an effective prophylaxis for hyperuricemia and gout. However, because its mechanism involves xanthine oxidase enzyme inactivation, it interacts with azathioprine, and the dose of azathioprine has to be reduced by approximately 50% to prevent severe bone marrow depletion [23]. There are no reports of interactions of allopurinol and other immunosuppressive drugs. Acute antiphlogistic therapy with non-steroid-antiinflammatory drugs (NSAID) has to be considered carefully as this can lead to significant impairment of renal function in patients with chronic transplant nephropathy. A short course of steroids is an efficient and safe alternative.

Does hyperuricemia per se contribute to an aggravation of chronic transplant nephropathy? A single report suggested that hyperuricemia had a significantly negative impact on renal graft survival after 5 years in adult patients, with a survival rate of 68.8% in hyperuremic versus 83.3% in normoureimic recipients [26]. Animal models have shown that uric acid can induce aggravation of CSA-vasculopathy and interstitial injury [27].

In conclusion, hyperuricemia after pediatric renal transplantation is common. It is correlated with the time span after transplantation and is a consequence of chronic renal transplant dysfunction. Gout is rare.

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