Abstract

Objectives: We sought to evaluate the prevalence and confounding clinical variables of hyperuricemia in pediatric kidney transplant patients.

Materials and Methods: We retrospectively evaluated the medical records of 151 pediatric renal transplant recipients who received their grafts at Akdeniz University Medical Faculty in Antalya, Turkey, with a follow-up longer than 6 months. This retrospective, single-center study included 117 pediatric renal transplant recipients, after we had excluded the patients with changes in immunosuppressive treatment and graft loss, who were receiving therapy with allopurinol and furosemide. Patient information and laboratory data were obtained from patient charts and an electronic hospital database.

Results: Mean uric acid levels of patients were 311 ± 74 μmol/L, and 24 of all of the patients (20%) had high uric acid levels. Fifteen patients taking tacrolimus (16%), and 9 of patients taking cyclosporine (39%) had hyperuricemia. The hyperuricemia rate of patients taking cyclosporine was significantly higher than it was for those patients taking tacrolimus (P = .014). Mean levels of uric acid in patients taking cyclosporine were higher than those of patients taking tacrolimus (344 ± 62 μmol/L and 303 ± 75 μmol/L; P = .006). There was a significant positive correlation between mean uric acid concentrations, and both serum creatinine (P = .000; r=0.487) and cystatin C (P = .000; r=0.433). There was negative correlation between mean uric acid concentration and estimated glomerular filtration rate (P = .000; r=-0.417). Mean uric acid levels of patients with intact graft function (estimated glomerular filtration rate ≥ 60 mL/min/1.73 m²) was lower than the patients with a low estimated glomerular filtration rate (291 ± 67 μmol/L and 353 ± 71 μmol/L; P = .000). Mean uric acid level of patients with normal body mass index was significantly lower than that of patients who were obese-overweight (301 ± 64 μmol/L vs 343 ± 94 μmol/L; P = .045).

Conclusions: We found 20% of our patient group had high uric acid levels. We also found that lower glomerular filtration rate, higher serum creatinine, cystatin C, obesity, and being overweight were risk factors for hyperuricemia in pediatric renal transplant recipients.

Key words: Hyperuricemia, Tacrolimus, Cyclosporine

Introduction

In the general population, serum uric acid (UA) is associated with increased serum creatinine levels in both males and females. It also has been reported that hyperuricemia (defined as serum UA levels more than 356 μmol/L for females and 505 μmol/L for males) is an independent risk factor for end-stage renal disease in adults. Besides, hyperuricemia is a common complication in adult renal transplant recipients, especially those receiving cyclosporine (CsA). Also, diuretic therapy, graft dysfunction, and obesity may cause hyperuricemia in renal transplant recipients. In several studies with adult renal transplant recipients, it has been reported that hyperuricemia may contribute significantly to reduced kidney transplant
However, the data are scarce on hyperuricemia in pediatric kidney transplant recipients. Hoyer and associates have described fully increased tubular reabsorption of UA in pediatric renal transplant recipients receiving CsA. Edvardsson and associates have also described hyperuricemia in 23% of pediatric renal transplant recipients on CsA treatment 30 months after a renal transplant. Sparta and associates have described hyperuricemia in 47% of 32 pediatric renal transplant recipients.

In this study, we aimed to evaluate the prevalence and confounding clinical variables of hyperuricemia in pediatric kidney transplant recipients.

Materials and Methods

We retrospectively evaluated the medical records of 151 pediatric renal transplant recipients who received their kidney grafts at Akdeniz University Medical Faculty in Antalya, Turkey, between August 2000, and December 2011, with a follow-up that was longer than 6 months. This retrospective, single-center study included 117 pediatric renal transplant recipients, after we had excluded those patients with changes in immunosuppressive treatment and graft loss, who were receiving therapy with allopurinol and furosemide.

We obtained the patient information from patient charts and from an electronic hospital database. These data included age, sex, serum creatinine, cystatin C, blood urea nitrogen, serum calcium, phosphorus, magnesium, albumin, triglycerides, total cholesterol, blood glucose, and plasma calcineurin inhibitor levels. Body mass index, duration of transplant, donor source, hypertension, and posttransplant medications, which included immunosuppressive agents and antihypertensive drugs. Patient serum UA levels and blood chemistries were measured every 2 months during 6 to 12 months after the kidney transplants. The patients’ UA levels were obtained by averaging all UA measurements obtained during this follow-up, except those measured during the first 6 months after transplant. In total, 1292 blood samples were obtained. Also, serum creatinine and cystatin C measurements were taken at each follow-up visit with UA measurements.

Body mass index were calculated with the formula: weight/height m². Body mass index was evaluated according to age and sex of the patients and children were classified as normal weight, overweight, or obese according to International Obesity Task Force criteria.

Estimated glomerular filtration rate was calculated according to the Schwartz formula with cystatin C. The upper limits of serum UA levels were regarded as 352, 339, and 416 μmol/L in children aged 2 to 15 years in both sexes.

The blood pressure of each patient was measured at each follow-up visit. Hypertension was defined as the average systolic blood pressure or diastolic blood pressure ≥ 95th percentile for sex, age, and height on at least 3 separate occasions.

These laboratory parameters were recorded: serum creatinine, cystatin C, blood urea nitrogen, serum calcium, phosphorus, magnesium, albumin, triglycerides, total cholesterol, blood glucose, and plasma calcineurin inhibitor levels. We aimed for a tacrolimus trough level 6 months after the renal transplant as 4 to 8 nmol/L, a cyclosporine trough level of 83 to 124 nmol/L between 6 to 12 months, 41 to 83 nmol/L after 1 year, and cyclosporine second-hour blood levels of 457 to 582 nmol/L between 6 to 12 months, 208 to 291 nmol/L at 1 to 5 years, and 145 to 208 nmol/L after 5 years. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration.

Statistical analyses

Categoric variables are presented as frequencies and percentages, and we compared them using the chi-square test. Continuous variables are expressed as means ± SD, and we compared them with a t test, an analysis of variance, or a correlation analysis, as needed. P values < .05 were considered statistically significant. Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 16.0, IBM Corporation, Armonk, NY, USA).

Results

The study included 117 children (66 boys; 56%; mean age, 14.5 ± 3.2 y; age range, 4.5-18 y). The mean time after transplant was 33 ± 21 months (range, 7-120 mo). In total, 94 patients (80%) were using tacrolimus, and 23 patients (20%) were using cyclosporine. Additionally, 83 patients were receiving myco-phenolate mofetil and prednisolone, 32 patients were
receiving mycophenolate mofetil only, and 2 patients were receiving azathioprine along with prednisolone. The demographics of the patients are given in Table 1.

Mean UA levels of patients were 311 ± 74 μmol/L, and 24 of all of them (20%) had high UA levels. The characteristics of the patients with hyperuricemia and normal UA levels are presented in Table 2.

Eighty-nine patients (76%) had normal body mass index, 18 were overweight, and 10 were obese. In hyperuricemic patients, 12 had normal body mass index, 7 were overweight, and 5 were obese. Mean UA concentrations of patients with normal body mass indices was significantly lower with those of the patients who were obese and overweight (301 ± 64 μmol/L vs 343 ± 94 μmol/L; P = .006). The characteristics of patients receiving tacrolimus and cyclosporine are shown in Table 3.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hyperuricemic Patients (n=24)</th>
<th>Normouricemic Patients (n=93)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD, or n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>15.2 ± 2.8</td>
<td>14.4 ± 3.3</td>
<td>.289</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>9 / 15</td>
<td>42 / 51</td>
<td>.502</td>
</tr>
<tr>
<td>Time since transplant (mo)</td>
<td>48 ± 31</td>
<td>29 ± 16</td>
<td>.008*</td>
</tr>
<tr>
<td>Mean eGFR (mL/min/1.73 m²)</td>
<td>66 ± 16</td>
<td>74 ± 18</td>
<td>.073</td>
</tr>
<tr>
<td>Mean serum creatinine (μmol/L)</td>
<td>106 ± 42</td>
<td>79 ± 37</td>
<td>.030*</td>
</tr>
<tr>
<td>Mean creatinin (mg/L)</td>
<td>1.87 ± 0.73</td>
<td>1.37 ± 0.62</td>
<td>.000*</td>
</tr>
<tr>
<td>Mean UA (μmol/L)</td>
<td>416 ± 52</td>
<td>284 ± 51</td>
<td>.000*</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.5 ± 0.11</td>
<td>2.47 ± 0.14</td>
<td>.261</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/L)</td>
<td>1.49 ± 0.23</td>
<td>1.46 ± 0.26</td>
<td>.620</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>45 ± 2.7</td>
<td>46 ± 3.1</td>
<td>.336</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.61 ± 0.82</td>
<td>1.41 ± 0.77</td>
<td>.260</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.50 ± 0.88</td>
<td>4.09 ± 0.88</td>
<td>.052</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.66 ± 0.55</td>
<td>4.71 ± 0.44</td>
<td>.718</td>
</tr>
<tr>
<td>Serum magnesium (mmol/L)</td>
<td>0.73 ± 0.09</td>
<td>0.71 ± 0.09</td>
<td>.459</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of Patients With Normal Uric Acid Levels and Hyperuricemia

*P < .05 is significant
between serum UA and age, tacrolimus trough levels, cyclosporine trough levels, cyclosporine second-hour levels, 12-hour fasting blood glucose levels, serum calcium, phosphorus, albumin, magnesium, total cholesterol, and triglycerides \( P = .218, P = .832, P = .433, P = .767, P = .981, P = .500, P = .530, P = .866, P = .05, P = .048, \) and \( P = .238 \).

We categorized patients according to more-recent estimated glomerular filtration rates in 2 groups. Group 1 contained patients with estimated glomerular filtration rates < 60 mL/min/1.73 m², and group 2 contained those patients with an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m², which was determined as intact graft functioning. The mean UA concentrations of patients with intact graft function (group 2) were lower than those of group 1 (291 ± 67 μmol/L vs 353 ± 71 μmol/L; \( P = .000 \)). Eleven patients (13%) in the group with intact graft function (group 2), and 13 patients (34%) in group 1 had hyperuricemia (\( P = .011 \)) (Table 4). Among patients with an intact graft function, 71 were receiving tacrolimus, and 8 of these patients on tacrolimus with intact graft function (8/71; 11%) had hyperuricemia.

### Table 4. Characteristics of Patients Receiving Tacrolimus or Cyclosporine

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>14.6 ± 3.3</td>
<td>14.5 ± 2.9</td>
<td>.712</td>
</tr>
<tr>
<td>Duration of transplant (mo)</td>
<td>44 ± 25</td>
<td>27 ± 17</td>
<td>.000*</td>
</tr>
<tr>
<td>Calciuminhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(tacrolimus/cyclosporine)</td>
<td>23 /15</td>
<td>71/8</td>
<td>ND</td>
</tr>
<tr>
<td>Mean uric acid (μmol/L)</td>
<td>353 ± 71</td>
<td>291 ± 67</td>
<td>.000*</td>
</tr>
<tr>
<td>Number of hyperuricemic patients (%)</td>
<td>13 (34%)</td>
<td>11 (13%)</td>
<td>.011*</td>
</tr>
</tbody>
</table>

**Abbreviations:** ND, not determined

* \( P < .05 \) is significant.

Characteristics of patients in group 1 and group 2 (group 1: GFR < 60 mL/min/1.73 m², group 2: GFR ≥ 60 mL/min/1.73 m²).

Out of all the patients, 44 had hypertension (37%). The mean serum UA concentration also did not differ among patients with and without hypertension (306 ± 76 μmol/L and 314 ± 73 μmol/L; \( P = .527 \)). Thirty-five patients were receiving 1 antihypertensive medication, and 9 patients were receiving 2 medications. None of the hyperuricemic patients had gout-related symptoms.

### Discussion

In this study, we found that 20% of our pediatric renal transplant recipients had hyperuricemia. A longer transplant duration, a lower glomerular filtration rate, a higher serum creatinine concentration, and cystatin C were risk factors for higher UA levels. The rate of hyperuricemia in patients receiving cyclosporine was higher than it was for those patients receiving tacrolimus. Obese and overweight patients had higher UA levels. There was no difference between the UA levels of patients with and without hypertension.

In adults, the frequency of hyperuricemia was higher in renal transplant recipients than it was in healthy individuals. The influence of hyperuricemia on renal allograft functioning remains controversial. Akgül and associates⁴ reported that high UA levels do not have a role in developing chronic allograft nephropathy during the first 3 years after transplant. Gerhardt and associates¹² reported significantly reduced transplant survival rates among hyperuricemic patients compared with those who were normouricemic kidney transplant recipients. In 1 study, male sex, higher body mass index, longer term pretransplant dialysis, and hypertension were associated with the development of hyperuricemia.¹³ Kanbay and associates⁵ reported that cyclosporine and tacrolimus both may cause hyperuricemia in adult renal transplant recipients with stable graft function. In adult renal transplant recipients with intact graft function, it also has been reported that mean UA concentrations were higher in those patients receiving cyclosporine, than were those patients receiving tacrolimus.¹⁴ In another study, the prevalence of hyperuricemia was higher especially in renal transplant recipients with classic cardiovascular risk factors and lower glomerular filtration rates.¹⁵ In 1 study with 32 pediatric renal transplant recipients, the prevalence of hyperuricemia was reported as being 47%; the authors did not find any difference of hyperuricemia rate according to different calcineurin inhibitors.⁸

In this study, our group was larger, and we found that 39% of patients on cyclosporine and 16% of patients on tacrolimus had hyperuricemia. The rate of hyperuricemia was greater in those patients receiving cyclosporine; however, the patients on cyclosporine had lower estimated glomerular filtration rates and longer transplant durations compared with the patients receiving tacrolimus. Because there were only 8 patients receiving cyclosporine with glomerular filtration rates ≥ 60 mL/min/1.73 m², we could not compare the types of calcineurin inhibitors among patients with intact graft function. Most of our patients were...
receiving tacrolimus, 71 of them had intact graft function, and the rate of hyperuricemia in this group was 11%.

Hyperuricemia with renal disease may be a result of decreased glomerular filtration rate, or it may be a consequence of tissue hypoxia or increased cell breakdown. In experimental studies, it has been shown that UA potentiates the development and progression of kidney disease. Uric acid may cause preglomerular arteriopathy, tubulointerstitial inflammation, transition of epithelial cells to mesenchymal cells, which results in the production of the extracellular matrix. All of these events may lead to renal fibrosis. In this study, we found that lower glomerular filtration rates and higher serum creatinine concentrations, and cystatin C were associated with higher uric acid levels.

In the general population, hyperuricemia is reported in hypertensive patients because of an impaired tubular secretion of urate. In adult renal transplant recipients, UA has not been found to be related to blood pressure, but only the use of a diuretic has been correlated with higher UA levels. We found no difference in the mean UA levels between those patients with and without hypertension. In our study population, none of the patients were receiving a diuretic or allopurinol therapy, which may affect the UA levels.

Although our study was limited by its retrospective nature and small number of patients on cyclosporine, the data of this study may be more reliable owing to the higher number of pediatric allograft recipients: prevalence and predictors. We should now compare the effects of cyclosporine and tacrolimus on graft functioning using larger numbers of patients in prospective trials.

In conclusion, we found that 20% of our patient group had high UA concentrations. Lower glomerular filtration rates, higher serum creatinine levels, and cystatin C levels, as well as obesity and being overweight were risk factors for hyperuricemia in pediatric renal transplant recipients. Also, the rate of hyperuricemia was higher in patients receiving cyclosporine than it was for the patients receiving tacrolimus.

References