Original Article

# Hyperuricemia beyond 1 year after kidney transplantation in pediatric patients: Prevalence and risk factors

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## ABSTRACT

Hyperuricemia is frequent among adult renal transplant recipients; however, data among pediatric kidney recipients are scarce. This study is designed to estimate the prevalence and risk factors of late post-transplant hyperuricemia in pediatric recipients. A retrospective observational multicenter study on 179 pediatric renal recipients (5–18 years) was conducted between April 2008 and January 2011 from five kidney transplant centers of Tehran, Iran. All recipients were followed up for more than 1 year (5.9±3.3 years) after transplantation. A total of 17686 blood samples were obtained for serum uric acid (SUA). The normal range of SUA was defined as SUA 1.86–5.93 mg/dl for children between 2 and 15 years in both genders; 2.40–5.70 mg/dl for girls aged >15 years; 3.40–7.0 mg/dl for boys aged >15 and more than 6 and 7 mg/dl in boys and girls older than 15 years old. The median age of the children was 13 years. Male recipients were more popular than female (male/female 59/41%). Hyperuricemia was detected in 50.2% of patients. Mean SUA concentration was 5.9±1.7 mg/dl and mean SUA concentration in hyperuricemic patients was 7.7±1.2 mg/dl. While at multivariate logistic regression elevated serum creatinine concentration ($P$<0.001) and the time span after renal transplantation ($P$=0.02) had impact on late post-transplant hyperuricemia. High cyclosporine level (C0 and C2) was not risk factor for huperuricemia. Late post-transplant hyperuricemia was found in about half of pediatric renal recipients, and was associated with impaired renal allograft function.

**Key words:** Hyperuricemia, pediatric renal recipients, renal allograft impairment

## Introduction

Hyperuricemia is a frequent among adult renal transplant recipients[1,2] and it is also a frequent metabolic disorder after liver[3] and heart transplantations.[4] During puberty, there is increase in fractional excretion rate of uric acid, reducing the likelihood of development of this complication.[5] Moreover, several studies have shown a correlation between plasma uric acid concentration and body mass index in adolescents.[6,7] In pediatric recipients, however, published data in literature on hyperuricemia after transplantation are scarce.[8-10] In a retrospective study from Edvardsson *et al*.,[8] hyperuricemia was seen in 23% of children after renal transplantation. Hoyer *et al*.[11] described an increased net tubular absorption of uric acid in 28 cyclosporine (CsA) treated pediatric renal transplant recipients.

In the current study, our aim was to evaluate the prevalence and confounding variables of hyperuricemia in pediatric kidney transplant recipients.

## Materials and Methods

### Participants

A retrospective observational multicenter study on 179 children and adolescents renal recipients younger than 18 years old was performed between April 2008 and January 2011 from five Kidney Transplant Centers of Tehran, Iran to estimate the prevalence of late post-transplant hyperuricemia and its risk factors. They received kidney allograft for the first time and followed more than 1 year after transplantation (5.9±3.3 years). Both living and deceased kidney transplant recipients were included. All laboratory tests such as serum uric acid (SUA) were done in a single laboratory. In this period, a total of 17686 blood

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samples were obtained. This study was approved by the Local Ethics Committee of the Baqiyatallah University of Medical Sciences.

### Immunosuppression regimen

All patients treated with CsA (targeting trough level (C0) of 200 to 300 ng/ml for first 3 months, 100 to 250 ng/ml for 4 to 12 months, and 100 to 150 ng/ml thereafter; while we used 2 h post-dose (C2) target levels of 800 to 1000 ng/mL in the first 3 months after transplantation and C2 targets of 400 to 600 ng/mL for subsequent months); mycophenolate mofetil or azathioprine and prednisolone, except those who withdrew these drugs due to their side effects.

### Clinical and biochemical data collection

The clinical and biochemical parameters collected for all patients were age and sex of recipients and donors, donor source (living or deceased), serum creatinine (Cr) concentration, fasting blood sugar (FBS), CsA levels (C0 and C2), hemoglobin (Hb) value and lipid profile including triglycerides (TG), cholesterols (Chol), low-density lipoprotein (LDL), and high-density lipoprotein (HDL).

### Definition of hyperuricemia after renal transplantation

The normal range of SUA was defined according to age and sex: For children between 2 and 15 years in both genders: 1.86–5.93 mg/dl; for girls aged more than 15 years: 2.40–5.70 mg/dl; for boys aged more than 15 years: 3.40–7.0 mg/dl (9). Thus, we considered hyperuricemia if SUA concentration of ≥6 mg/dl in boys younger than 15 years old and all girls, as well as SUA level of ≥7 mg/dl in boys older than 15 years old on at least two successive determinations during follow up.

### Statistical analysis

Statistical analyses were performed using SPSS for Windows, versions 17.0. Quantitative variables were expressed as means±SD, while qualitative variables were shown by number and percentage. The Kolmogorov–Smirnov test showed that uric acid levels were distributed normally ($P$=0.5); therefore, parametric tests were used to comparisons of qualitative and qualitative data. Linear regression model and multivariate logistic regression analyses were used to examine the influence of the potential predisposing factors for hyperuricemia. All tests were two tailed, and $P$-values of less than 0.05 were considered statistically significant.

## Results

The patient demographic and laboratory information are shown in Table 1. The median age of the children was 13 years (range: 5–18 years) and the median time since of transplantation was 6 years (5.9±3.3 years). The majority of cases were male (59 *vs* 41%) and received the grafts from living donors (88.7% unrelated and 8.3% related), while 7.3% of them came from deceased donors. Mean SUA and serum Cr were 6.2±1.8 and 1.5±1 mg/dl, respectively.

Comparison between normouricemic and hyperuricemic groups is shown in Table 2. Low hemoglobin level as well as high serum Cr, high TG level and longer transplantation duration were significantly associated with post-transplant hyperuricemia ($P$=0.001, $P$=0.000, $P$=0.03, $P$=0.000) [Table 2].

Hyperuricemia was detected in 90 (50.2%) children 1 year after renal transplantation. Females were more likely to be hyperuricemic with no significant value (52% *vs* 45% in boys, $P$=0.08).

Univariate correlation analysis between SUA concentration and other possible affecting factors are demonstrated in Table 3. There were a negative and significant correlation between hyperuricemia and age of recipients, hemoglobin level, FBS, and HDL [Table 3]. Conversely, positive and significant correlation were seen between hyperuricemia and serum Cr, cyclosporine levels (through and 2 h postdoes), Chol, LDL, and TG [Table 3].

At linear regression analysis [Table 4], we found the renal allograft impairment and time since transplantation were only risk factors for late post-transplant hyperuricemia in pediatric renal recipients ($P$=0.000 and $P$=0.02, respectively). Anemia and hypertriglyceridemia were

**Table 1: Demographic and laboratory data of recipients and donors**

| Variables | Overall ($n$=179) |
|---|---|
| Sex of recipient, M/F, % | 59/41 |
| Sex of donor, M/F, % | 83/17 |
| Donor source, % | 8.3/88.7/3 |
| LRD/LURD/Deceased | |
| Age of recipient, yr | 13 ± 3 (5–18) |
| Age of donor, yr | 26 ± 5 (5–52) |
| Uric acid, mg/dl | 6.2 ± 1.8 |
| Last serum creatinine, mg/dl | 1.56 ± 1.03 |
| C0 level, ng/ml | 110 ± 58 |
| C2 level, ng/ml | 460 ± 139 |
| Hb, g/dl | 12.1 ± 1.9 |
| FBS, mg/dl | 89 ± 21 |
| LDL- Cholesterol, mg/dl | 93 ± 32 |
| HDL- Cholesterol, mg/dl | 48 ± 14 |
| TG, mg/dl | 148 ± 88 |
| Cholesterol, mg/dl | 174 ± 39 |
| Time since of transplantation, Yr | 5.9 ± 3.3 |

M = Male; F = Female; Yr = Year; SD = Standard deviation; Hb = Hemoglobin; FBS = Fasting blood sugar; LDL = Low density lipoprotein; HDL = High density lipoprotein, TG = Triglyceride

**Table 2: Comparison between normouricemic and hyperuricemic groups**

| Variables | Normouricemic patient (*n*=89) | Hyperuricemic patient (*n*=90) | *P* value |
|---|---|---|---|
| Sex of recipient,M/F, % | 57.3/42.7 | 50.5/49.5 | 0.08 |
| Sex of donor, M/F, % | 83.8/16.2 | 83.9/16.1 | 0.9 |
| Donor source, % LRD/ LURD/Deceased | 10.3/85.3/4.3 | 9.1/89.2/1.7 | 0.1 |
| Age of recipient, yr | 13.9 ± 3.8 | 13.6 ± 3.3 | 0.3 |
| Age of donor, yr | 26 ± 6 | 26 ± 5 | 0.2 |
| Last serum creatinine, mg/dl | 1.39 ± 0.80 | 1.74 ± 1.21 | 0.000 |
| C0 level, ng/ml | 113 ± 65 | 107 ± 50 | 0.3 |
| C2 level, ng/ml | 453 ± 149 | 469 ± 129 | 0.2 |
| Hb, g/dl | 12.4 ± 1.9 | 11.8 ± 2.0 | 0.001 |
| FBS, mg/dl | 91 ± 25 | 89 ± 14 | 0.2 |
| LDL- Cholesterol,mg/dl | 90 ± 33 | 97 ± 32 | 0.1 |
| HDL- Cholesterol,mg/dl | 49 ± 15 | 47 ± 13 | 0.3 |
| TG, mg/dl | 139 ± 64 | 156 ± 106 | 0.03 |
| Cholesterol, mg/dl | 173 ± 40 | 176 ± 38 | 0.3 |
| Time since of transplantation, Yr | 5.2 ± 3.1 | 6.5 ± 3.4 | 0.000 |

M = Male; F = Female; Yr = Year; SD = Standard deviation; Hb = Hemoglobin; FBS = Fasting blood sugar; LDL = Low density lipoprotein; HDL = High density lipoprotein, TG = Triglyceride; C0=Cyclosporine through level; C2 = Cyclosporine 2 h post dose

**Table 3: Univariate correlation between SUA and other parameters**

| Variables | Spearman's correlation | | Linear regression | |
|---|---|---|---|---|
| | r (Correlation Coefficient) | *P* value | *B* | *P* |
| Serum creatinine, mg/dl | 0.44 | 0.000 | 0.33 | 0.000 |
| Trough level of cyclosporine, ng/ml | 0.18 | 0.000 | –0.04 | 0.7 |
| 2 h postdose level of cyclosporine, ng/ml | 0.17 | 0.000 | 0.07 | 0.6 |
| Age of recipient year | –0.05 | 0.000 | – | – |
| Hemoglobin, g/dl | –0.07 | 0.000 | 0.1 | 0.1 |
| FBS, mg/d | –0.03 | 0.002 | – | – |
| Cholesterol, mg/dll | 0.02 | 0.04 | 0.03 | 0.7 |
| TG, mg/dl | 0.07 | 0.000 | 0.06 | 0.4 |
| LDL-Cholesterol, mg/dl | 0.07 | 0.000 | – | – |
| HDL-Cholesterol, mg/dl | –0.2 | 0.000 | – | – |
| Time from transplantation year | 0.01 | 0.000 | 0.2 | 0.02 |

SUA = Serum uric acid, FBS = Fasting blood sugar; LDL = Low density lipoprotein; HDL = High density lipoprotein, TG = Triglyceride

**Table 4: Multivariate correlation between SUA and other parameters**

| Variables | Linear regression | |
|---|---|---|
| | B | *P* |
| Serum creatinine, mg/dl | 0.33 | 0.000 |
| Trough level of cyclosporine, ng/ml | –0.04 | 0.7 |
| 2 h postdose level of cyclosporine, ng/ml | 0.07 | 0.6 |
| Hemoglobin, g/dl | 0.1 | 0.1 |
| Cholesterol, mg/dll | 0.03 | 0.7 |
| TG, mg/dl | 0.06 | 0.4 |
| Time from transplantation year | 0.2 | 0.02 |

SUA = Serum uric acid, TG = Triglyceride

not risk factors for elevated SUA concentration ($P$=0.1 and $P$=0.4, respectively). At multivariate logistic regression analysis after adjustment for categorical and continuous variables, elevated serum creatinine concentration ($P$=0.000) and the time span after renal transplantation ($P$=0.02) had only impact on late post-transplant hyperuricemia. High cyclosporine level (C0 and C2) was not risk factor for hyperuricemia ($P$=0.7, $P$=0.6).

## Discussion

This study demonstrates that as in adults, nearly one-half of pediatric kidney transplant recipients suffer from late post-transplant hyperuricemia.[12] This result is consistent with a previous report, which hyperuricemia occurred in 47% of 32 pediatric kidney recipients.[9] However, Edvardsson *et al*. in a retrospective study showed that the prevalence of hyperuricemia in pediatric kidney transplants was lower than our reports; it accounted for 23% of all patients at 30 months of transplantation.[8] This difference may be due to differences in race, age distribution, renal impairment, post-transplant duration, and other confounding factors. However, published data in the literature on post-transplant hyperuricemia especially late onset post-transplant hyperuricemia among these patients are scarce and a few studies have addressed the issue of hyperuricemia following pediatric kidney transplantation.[8-10] Moreover, our finding is consistent with reports in adult kidney transplantation.[1,13,14] Hyperuricemia is also a frequent complication after liver and cardiac transplantation.[4,15] Tumgor *et al*.[16] reported that hyperuricemia occurred in 29% of 70 pediatric liver transplant recipients. In adult kidney transplantation, males developing hyperuricemia than females,[14,17] which is opposite of our observation that the prevalence of hyperuricemia was higher in girls, but with no significant differences.

Consistent with previous studies, impaired renal allograft function was a major risk factor for post-transplant hyperuricemia.[8,11,13,18-20] One small study showed that post-transplant hyperuricemia had a significantly adverse effect on renal graft survival after 5 years in adult patients, with a lower survival rate (69%) in hyperuremic recipients compared to those with normouricemia (83%).[20] In addition, another report suggested that hyperuricemia was a risk factor for graft loss.[21] On the other hand, Meier-Kriesche *et al*. had results different from our findings, suggesting a lack of any significant association between SUA levels and deterioration of renal allograft function in the first three post-transplant years.[22] In addition, prospective and controlled clinical trials are required to determine if SUA lowering therapies may lead

to reducing the development of chronic allograft injury.

In this study, post-transplant hyperuricemia was a time-dependent variable and SUA was increasing over time, which matches with a previous report.[15] Conversely, Edvardsson *et al*. showed a peak SUA level in pediatric recipients at 6 months following kidney transplantation, with a hyperuricemia rate of 39% versus of 23% at 30 months after transplantation.[8]

CsA plays a key role in post-transplant hyperuricemia among adult kidney transplant recipients.[1,23] All of our pediatric patients received CsA as a major immunosuppression agent; however, the hyperuricemic effect of CsA appears to be less significant in terms of the drug doses and blood levels. Our study did not find any correlation between CsA blood levels and SUA concentration. This result is consistent with that of two previous studies.[8,9] Hyperuricemia is also a common complication among CsA-treated liver[15,16] and cardiac[4] recipients. There are several experimental[24,25] and clinical evidence[3,25] suggested that SUA may contribute to CsA nephrotoxicity. An animal study showed that SUA may have a role in aggravation of CsA vasculopathy and interstitial injury.[25] In a series of 53 children with steroid-dependent nephrotic syndrome, higher SUA concentration was associated with CsA-induced nephropathy.[26]

Although our study was clearly limited by its retrospective nature and uncontrolled of the study design, the data of this study may be more reliable because of the relatively higher number of our pediatric renal recipients compared to the previous studies. Additional prospective randomized trials with a larger cohort of renal transplant patients are required to determine the cause and effect correlation of SUA and graft dysfunction.

## Conclusion

We found that hyperuricemia is a frequent metabolic problem in pediatric kidney transplant recipients. It is correlated with the time since transplantation and is a consequence of renal allograft impairment.

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