A retrospective study of hyperurecemia in renal transplant recipients

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Abstract
Objective: This study was designed to estimate the prevalence, risk factors of post transplant hyperuricemia and to establish the serial changes in eGFR and uric acid in adult renal transplant recipients.

Methods: A retrospective observational study on 84 adult renal transplant recipients was conducted between January 2012 and January 2014 in PGIMER and Dr RML hospital, New Delhi, India. Clinical and laboratory data were obtained from hospital electronic database.

Results: Of 84 patients selected for this study 56 were males and 28 females. The median age was 31 yrs. Hyperuricemia was detected in 48.9% of the recipients at one month from transplantation. After 6 months there is a 15% increase in the number of hyperuricemic subjects. Mean eGFR decreased significantly along with an increase in the uric acid concentration during first year in the patients found hyperuricemic at 1 month of transplantation.

Conclusion: eGFR, serum phosphorus, serum cholesterol levels were risk factors for hyperuricemia in renal recipients. The risk is more in subjects who demonstrated increase uric acid level immediately post transplant.

Keywords: renal transplant recipients, hyperuricemia, eGFR

1. Introduction
Uric acid is the end product of purine metabolism which is excreted mainly by the kidneys and to some extent by the gastrointestinal tract. Uric acid plays a pivotal role in the onset of new renal disease, exacerbation of existing renal disease and it is also elevated frequently in patients of renal transplantation1-7. Uric acid also increases solid organ transplant recipients - liver (15-50%) and cardiac (30%) transplant patients1. A number of mechanisms may be responsible for these disease processes including stimulation of vascular smooth muscle cell proliferation, stimulation of profibrotic and inflammatory cytokines, impairment of endothelialcell function and promotion of T cell activation through macrophage/monocyte stimulation. Uric acid is also associated with ischemic stroke, myocardial infarction and cardiovascular events8-9. Various antigen dependent and antigen independent mechanisms are responsible for the nephropathy associated with uric acid. Studies have found the role of uric acid in activation of dendritic cells to host antigens, activation of CD8 T cells to transplanted cells and activation of T cell response to dendritic cell based vaccines10-11. Uric acid is also implicated in activation of B cells and IL-2 receptor on monocyte via MyD88 dependent signaling pathway12-13. Antigen independent mechanisms include interaction with cyclosporine 14-16, stimulation of smooth muscle cell and association with hypertension, insulin resistance and dyslipidemia 17-22. Hyperuricemia occurs early after transplantation and is associated with decreased GFR. Recent studies investigating the association between increased uric acid and graft dysfunction have suggested that hyperuricemia may contribute to the progressive deteriorative of graft function and ultimately to the graft loss.23,24,25 Cyclosporine and to some extent tacrolimus used in transplant recipients causes renal vasoconstriction, hypertension and hyperuricemia. A number of drugs are used in the treatment of hyperuricemia eg Allopurinol, NSAID, probenacid and colchicines. Allopurinol reduces renal vasoconstriction and decrease in GFR13-14 reduce immune response to antigen in normal mice26-27,28 and also slows progression of renal disease. However medications used in hyperuricemic patients have got many problems inherent to them. Colchicines precipitate myopathy in renal transplant patients, probenecid ineffective in patients with decrease renal function, allopurinol causes leucopenia and NSAIDs causes impairment of renal functions.

2. Methods and Material
A prospective observational study on 132 adults who have undergone renal transplant in Dr RML hospital, New Delhi was performed. Of these 48 were excluded. Exclusion criteria includes change of immunosuppression therapy during the follow up period ,treatment with allopurinol or other uric acid lowering drug or retransplantation during the follow up period. Patients received kidney allograft for the first time from living donor and followed for more than a year. Patient received n thymoglobulin, methyl prednisolone, basiliximab, cyclosporine, mycophenolate mofitil, azathioprin, tacrolimus or sirolimus. Patients also received trimethoprim / sulphamethoxazole and vancomycin for prophylaxis.

Patient information included age, gender, body weight, transplantation duration, donor source, donor age, post transplantation medications and anti hypertensive agents. The biochemical parameter collected for the patients are S creatinine, fasting blood sugar, lipid profile, S calcium and S phosphorus. All laboratory tests were done in a single laboratory using ORTHOCLINICAL VITROS 350 chemistry system. We examined the eGFR to see if change in uric acid is affected by the level of eGFR. To estimate GFR, Cockcroft Gault formula was used during the same day the uric acid was measured.
Hyperuricemia was defined as serum uric acid ≥ 6.0 mg/dl in women and uric acid ≥ 7.0 mg/dl for men. The ethical clearance for this study has been taken from the hospital administration.

2.1 Statistical analysis

Statistical analysis was performed using SPSS. Data was reported as mean ± SD. Quantitative variables were expressed as mean ± SD, while qualitative variables were shown by numbers and percentages. Comparison among variables was performed using Student T test. All reported P values were two sided and P value of ≤ 0.05 was considered to be statistically significant.

3. Results

For this study a total of 84 patients were selected. Out of these 56 were males and 28 females. The mean age of the patients is 31 yrs (15-45yrs).

The various characteristics of the patients selected for the study are depicted in Table 1. Comparison between normouricemic and hyperuricemic groups at 1 month after transplantation is shown in Table 2. The table clearly shows differences in serum creatinine, cholesterol, calcium, phosphate and hemoglobin between the hyperuricemic and normouricemic groups.

The patients who have increased uric acid at 1 month of transplantation are further followed and investigated at 6 months and 12 months. These patients who are at increased risk clearly shows increase in the serum creatinine and decrease in the mean eGFR. Also there is an increasing trend of serum phosphorus and cholesterol levels. Univariate correlation analysis between uric acid and other variables demonstrated positive correlation between hyperuricemia and serum creatinine (p value=0.003), serum cholesterol (p value= 0.03) and phosphorus (p value=0.05) while negative correlation is found between hyperuricemia and eGFR (p value <0.002).

### Table 1. Demographic and laboratory data of recipients

| Variables                  | Overall (n-84) |
|----------------------------|----------------|
| Age (years)                | 31 ± 10        |
| Male/ female (number)      | 56/28          |
| Diabetes mellitus (Y/N)    | 26 (30.9%)/58(69.1%) |
| Hypertension (Y/N)         | 53 (63%)/31(37%) |
| cyclosporin                | 64 (76%)       |
| Mycophenolate mofetil      | 48 (57%)       |
| Serum creatinine (mg/dl)   | 1.86 ± 1.0     |
| Uric acid (mg/dl)          | 6.98 ± 1.9     |
| Fasting blood sugar (mg/dl)| 96 ± 26        |
| Cholesterol (mg/dl)        | 167 ± 42       |
| Triglyceride (mg/dl)       | 154 ± 90       |
| HDL (mg/dl)                | 40 ± 11        |
| Calcium (mg/dl)            | 9.0 ± 0.9      |
| Phosphorus (mg/dl)         | 3.1 ± 0.9      |
| Hemoglobin (g/dl)          | 11.5 ± 1.5     |
| eGFR (mL/min/1.73 m²)      | 65.54 ± 11.6   |
| Diuretics                  | 4 (4.7%)       |
| ACEi                       | 58(70.2%)      |

### Table 2: Variables at 1 month between normouricemic and hyperuricemic patient

| Variables                  | Normouricemia | Hyperuricemia | P value |
|----------------------------|---------------|---------------|---------|
| Age (recipient)            | 31 ± 10       | 32.4 ± 8.2    | 0.4     |
| Age (donor)                | 39 ± 12       | 36 ± 6        | 0.6     |
| creatinine                 | 1.2 ± 0.7     | 1.9 ± 0.8     | 0.002   |
| hemoglobin                 | 12.0 ± 1.6    | 10.4 ± 2.2    | 0.07    |
| calcium                    | 8.6 ± 1.2     | 9.4 ± 0.6     | 0.09    |
| phosphorus                 | 3.1 ± 0.9     | 4.8 ± 0.6     | 0.006   |
| hypertension               | 88%           | 83%           | 0.4     |
| Fasting blood sugar        | 93 ± 32       | 90 ± 21       | 0.4     |
| cholesterol                | 154 ± 35      | 176 ± 29      | 0.02    |
| triglyceride               | 152 ± 78      | 189 ± 62      | 0.07    |
| HDL                        | 43 ± 12       | 34 ± 8        | 0.03    |
| Cyclosporine (Y/N)         | 31(74%)/12(24%) | 31(76%)/10(24%) | 0.42   |
| diuretics                  | 3(6.9%)/40(93.1%) | 1(2.43%)/40(97.57%) | 0.8    |
| ACE inhibitors             | 10(24%)/33(76%) | 11(26.8%)/30(73.2%) | 0.76   |
| eGFR                       | 70.7± 12.6    | 52.4± 16.4    | 0.004   |

### Table 3: Variables at different time on patients of hyperuricemia found at 1 month

| Variables                  | 1 Month       | 6 Months      | 12 Months     |
|----------------------------|---------------|---------------|---------------|
| eGFR                       | 52.4± 16.4    | 48.2 ± 22.1   | 40.8 ± 18.4   |
| Uric acid (mg/dl)          | 7.9 ± 0.9     | 8.2 ± 1.2     | 9.4 ± 1.5     |
| Fasting blood sugar (mg/dl)| 90 ± 21       | 92 ± 21       | 92 ± 18       |
| Calcium (mg/dl)            | 9.4 ± 0.6     | 8.6 ± 0.6     | 9.3 ± 0.8     |
| Phosphorus (mg/dl)         | 4.8± 0.6      | 5.2 ± 0.6     | 5.8 ± 1.0     |
| Cholesterol (mg/dl)        | 176 ± 29      | 185± 33       | 190 ± 53      |
| Triglyceride (mg/dl)       | 189 ± 62      | 156 ± 67      | 159 ± 78      |
| HDL (mg/dl)                | 43 ± 12       | 37 ± 6        | 30 ± 4        |
| Creatinine (mg/dl)         | 1.9 ± 0.8     | 2.3 ± 0.5     | 2.9 ± 0.3     |
4. Discussion

All the patients in this study received grafts from living donors. 85% of the renal grafts are from genetically related donors. Post operatively patients received cyclosporine, mycophenolate mofetil, azathioprin, sirolimus or tacrolimus. Cyclosporine and other calcinurin inhibitors are known causes of hyperuricemia.\(^{29,30}\) We found in this study that cyclosporine is associated with 76% of the patients with increase uric acid level. But this is in contraindication to another study by Kanby M who found that uric acid level didn’t differ significantly between renal transplant recipients receiving cyclosporine and non calcinurin inhibitors\(^6\). Also during the course of study 15% of normouricemic patients after 1 month of kidney transplant were converted at 6 months to patients having high uric acid level (data not shown). Our finding is consistent with adult kidney transplantation\(^{21,35,44}\) and other solid organ transplantation\(^{21,36,45}\).

This study does not show any relationship between high uric acid level and fasting blood sugar levels contrary to an epidemiological survey.\(^{42}\) However our study shows a clear relationship between hyperuricemia and derangements in the lipid profile. Progression of the cardiovascular disease with high uric acid levels has also been postulated by many researchers.\(^{43,44}\)

In this study we also evaluated the changes in uric acid with kidney function (eGFR). Our study clearly shows that increase in uric acid follows a decrease in eGFR along with an increase in creatinine levels. This is in accordance with Armstrong et al\(^{45}\), who found an inverse relationship between baseline uric acid and eGFR in 90 renal transplant recipients. However Gores et al studying 262 patients found severely hyperuricemic cases had a mean Creatinine similar to those with normal uric acid\(^{46}\). There are also several studies that shows that increase uric acid is a major risk factor for cardiovascular disease, kidney disease, pregnancy related complications and concomitant mortality\(^{47,48}\). Gerhardt et al found out that hyperuricemic patients have lower 5 year survival rate than normouricemic patients\(^{49}\).

The unique feature of this study is the measurement of serum uric acid at multiple time point’s. Although this study has a serious limitation of size and duration of follow up and because of its retrospective design residual confounding factors cannot be excluded. Despite these limitations our study has several strengths including selection of only those patients who are found to be hyperuricemic after transplantation and serial measurement of parameters. In conclusion in this retrospective study we found a significant association between serum uric acid levels with eGFR and SCr in patients who are found hyperuricemic post transplant.

Therapy should therefore be directed to these high risk groups to prevent morbidity and mortality.

References

1. Mazzali M. Uric acid and transplantation. Semin Nephrol. 2005; 25(1):50-5.

2. Perico N, Codreanu I, Caruso M, Remuzzi G. Hyperuricemia in kidney transplantation. Contrib Nephrol 2005;147:124-31.

3. Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. J Biol Chem 1991; 266(13):8604-8.

4. Gersch C, Paliis SP, Kim KM, Angerhofer A, Johnson RJ, Henderson GN. Inactivation of nitric oxide by uric acid. Nucleosides Nucleotides Nucleic Acids 2008; 27: 967-978.

5. Kato M, Hisatome I, Tomikura Y, et al. Status of endothelial dependent vasodilation in patients with hyperuricemia. Am J Cardiol 2005; 96: 1576–1578.

6. Khosla UM, Zharikov S, Finch JL, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int 2005; 67: 1739–1742.

7. Ansell J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 2003; 41: 1287–1293.

8. Kang DH, Han L, Ouyang X, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. Am J Nephrol 2005; 25: 425–433.

9. Shi Y, Evans JE, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. Nature 2003; 425: 516–521.

10. Shi Y, Galuska SA, Rock KL. Cutting edge: elimination of an adjuvant endogen reduces the activation of CD8 T lymphocytes to transplanted cells in an autoimmune diabetes model. J Immunol 2006; 176(7):3905-8.

11. Ma XJ, Tian DY, Xu D, Yang DF, Zhu HF, Liang ZH, Zhang ZG. Uric acid enhances T cell immune responses to hepatitis B surface antigen-pulsed dendritic cells in mice. World J Gastroenterol 2007; 13(7):1060-9.

12. Behrens MD, Wagner WM, Kroo CI, Erskine CL, Kalli KR, Kremerski J, Gad EA, Disis ML, Knutson KL. The endogenous danger signal, crystalline uric acid, signals for enhanced antibody immunity. Blood 2008; 111(3):1472-9.

13. Chen CJ, Shi Y, Hearns A, Fitzgerald K, Golenbock DT, Reed G, Akira S, Rock KL. MyD88-dependent IL-1 receptor signaling is essential for gutt inflammation stimulated by monosodium urate crystals. J Clin Invest 2006; 116(8):2262-71.

14. Mazzali M, Hughes J, Jin YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivilcim M, Johnson RJ. Elevated uric acid increases blood pressure in a rodent crystall independent mechanism by an increased blood pressure and vascular tone. Hypertension 2001; 38(5):1101-6.

15. Assis SM, Monteiro JL, Seguro AC. Low arginine and allopurinol protect against cyclosporine nephrotoxicity. Transplantation 1997; 63(8):1070-3.

16. Kobelt V, Hess T, Matziks F, Gerhardt U, Hillebrand U, Suwelack B, Sindermann J, Hohage H. Does allopurinol prevent side effects of cyclosporine-A treatment? Transplant Proc. 2002; 34(5):1452-7.

17. Mazzali M, Kim YG, Suga S, Gordon KL, Kang DH, Jefferson JA, Hughes J, Kivilcim M, Lan HY, Johnson RJ. Hyperuricemia exacerbates chronic cyclosporine nephropathy. Transplantation 2001; 71(7):900-5.

18. Neal DA, Tom BD, Gimson AE, Gibbs P, Alexander GJ. Hyperuricemia, gout, and renal function after liver transplantation. Transplantation 2001; 72(10):1689-91.

19. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI, Block ER, Herrera-Acosta J, Patel JM, Johnson RJ. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2006; 290(3):F625-31.

20. Mazzali M, Kanelis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, Lan HY, Johnson RJ. Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol. 2002; 282(6):F991-7.

21. Nakagawa T, Mazzali M, Kang DH, Kanelis J, Watanabe S, Sanchez-Lolaza LG, Rodriguez-Iturbe B, Herrera-Acosta J, Johnson RJ. Hyperuricemia causes glomerular hyperfiltration in the rat. Am J Physiol Renal Fluid 2003; 28:2(1):2-7.

22. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Trioung L, Harris RJ, Johnson RJ. A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002; 13(12):2888-97.

23. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006; 47(1):51-9.

24. Akalin E, Ganesan SVN, Winston J, et al: Hyperuricemia is associated with the development of the composite outcomes of new cardiovascular events and chronic allograft nephropathy. Transplantation 2008; 86:652.

25. Gerhardt U, Gross Hattmann M, Hohage H. Influence of hyperglycemia and hyperuricemia on long-term transplant survival in kidney transplant recipients. Clin Transplant 1999; 13:375-8.

26. Kato C, Sato K, Wakabayashi A, Eishi Y. The effects of allopurinol on immune function in normal BALB/c and SCID mice. Int J Immunopharmacol, 2000; 22(7):547-56.

27. Chocair P, Duley J, Simmonds HA, Cameron JS, Ianhez L, Arap S, Sabbaga E. Low-dose allopurinol plus azathioprine/cyclosporin/prednisolone, a novel immunosuppressive regimen. Lancet 1993; 342(8863):83-4.

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28. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, et al. Association between serum uric acid and development of type 2 diabetes. Diabetes care 2009; 32: 1737–1742.
29. Steidel K, Brandis M, Kramer M, Leititis JU, Zimmerhackl LB. Cyclosporine inhibits renal uric acid transport in renal transplants not in children treated for nephrotic syndrome. *Ren Failure* 1990; 12: 193–198.
30. Marce’n R, Gallego N, Orofino L, Gamez C, Estepa MR, Teruel JL, Ortun’o J. Impairment of tubular secretion of urate in renal transplant patients on cyclosporine. *Nephron* 1995; 70: 307–313.
31. Hoyer PF, Lee J, Omer BS, Krohn HF, Offner G, Brodahl J. Renal handling of uric acid under cyclosporin A treatment. *Pediatr Nephrol* 1988; 2: 18–21.
32. Marce’n R, Gallego N, Orofino L, Gamez C, Estepa MR, Teruel JL, Ortun’o J. Impairment of tubular secretion of urate in renal transplant patients on cyclosporine. *Nephron* 1995; 70: 307–313.
33. Hoyer PF, Lee J, Omer BS, Krohn HF, Offner G, Brodahl J. Renal handling of uric acid under cyclosporin A treatment. *Pediatr Nephrol* 1988; 2: 18–21.
34. Zawadzki J, Grenda R, Januszewicz P. Effect of nifedipine on tubular handling of uric acid in transplanted kidney on cyclosporine A treatment. *Nephron* 1995; 70: 77–82.
35. Laine J, Holmberg C. Tubular effects of cyclosporine in pediatric renal transplant recipients. *Transplant Proc* 1996; 28: 2104–2106.
36. Laine J, Holmberg C. Mechanisms of hyperuricemia in cyclosporine-treated renal transplanted children. *Nephron* 1996; 74: 318–323.
37. Armstrong KA, Johnson DW, Campbell SB, et al: Does uric acid have a pathogenetic role in graft dysfunction and hypertension in renal transplant recipients? *Transplantation* 2005; 80: 1565.
38. Kanbay M, Akcay A, Huddam B, et al: Influence of cyclosporine and tacrolimus on serum uric acid levels in stable kidney transplant recipients. *Transplant Proc* 2005; 37: 3119.
39. Clive DM. Renal transplant-associated hyperuricemia and gout. *J Am Soc Nephrol*. 2000; 11: 974–9. [PubMed: 10770978]
40. Min SI, Y Un IJ, Kang JM, Park Y J, Min SK, Ahn C, et al. Moderate-to-severe early-onset hyperuricaemia: A prognostic marker of long-term kidney transplant outcome. *Nephrol Dial Transplant*. 2009; 24: 2584–90. [PubMed: 19395726]
41. Burack DA, Griffith BP, Thompson ME, Kahl LE. Hyperuricemia and gout among heart transplant recipients receiving cyclosporine. *Am J Med*. 1992; 92: 141–6. [PubMed: 1541977]
42. Obermayr RP, Temml C, Gutjahr G, et al: Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol*. 2009; 19: 2407.
43. Dimeny EM. Cardiovascular disease after renal transplant. *Kidney Int* 2002; Suppl 80:S78–S84.
44. Gerhardt U, Grobe Huttman M, Hohage H. Influence of hyperglycemia and hyperuricemia on long-term transplant survival in kidney transplant patients, *Clin Transplant* 1999; 13: 375–379.
45. Armstrong KA, Johnson DW, Campbell SB, Isbel NM, Hawley CM. Does uric acid have a pathogenetic role in graft dysfunction and hypertension in renal transplant recipients? *Transplantation* 2005; 80: 1565–1571.
46. Gores PF, Fryd DS, Sutherland DE, et al. Hyperuricemia after renal transplantation. *Am J Surg* 1988; 156: 397–400.
47. Weiner DE, Tighiouart H, Elsayed EF, et al: Uric acid and incident kidney disease in the community. *J Am Soc Nephrol*. 2008; 19: 1204.
48. Kamath Rajalaxmi, Nayak, Radhakrishna; Shantharam Manjula. Serum uric acid levels in preeclampsia and its correlation to maternal and fetal outcome. *International Journal of Biomedical Research* 2014; 5 (1): 22-24.
49. Gerhardt U, Grobe Huttmann M, Hohage H. Influence of hyperglycemia and hyperuricemia on long-term transplant survival in kidney transplant recipients. *Clin Transplant* 1999; 13: 375.