Uric Acid Is Highly Associated With Kidney Allograft Survival in a Time-Varying Analysis

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ABSTRACT

Background. Hyperuricemia may be associated with the development of new cardiovascular events and graft loss in renal transplant recipients. This study was conducted to clarify whether hyperuricemia is a persistently independent predictor of long-term graft survival and patient outcome.

Methods. Renal allograft recipients ($n = 880$) who underwent transplantation from December 1999 to March 2013 were included. Participants were divided into 2 groups: a hyperuricemic group ($n = 389$) and a normouricemic group ($n = 491$). The mean serum uric acid (UA) level was obtained by averaging all measurements, once per month for 3 months, before the study began. Clinical and laboratory data were collected. We investigated the role of hyperuricemia in the primary endpoint of graft failure by using time-varying analysis and Kaplan-Meier plots. All-cause mortality in renal transplant recipients was also surveyed.

Results. During a mean follow-up of 43.3 ± 26.3 months, the major predisposing factors in the 389 patients with hyperuricemia were male predominance (62.98%), high entry serum UA (7.70; range 6.70–8.80 mg/dL), more hypertension (92.29%), previous hemodialysis mode (29.56%), hepatitis C infection (24.42%), more frequent use of UA-lowering agents (43.44%), and use of more drugs for inducing high serum UA (17.74%). After 12 months, the hyperuricemic group had persistently high serum UA (7.66 ± 2.00 vs 6.17 ± 1.60 mg/dL, $P < .001$) and poor renal function (serum creatinine 2.96 ± 3.20 vs 1.61 ± 1.96 mg/dL, $P < .001$) compared with the normouricemic group. Survival analysis showed the hyperuricemic group had poorer graft survival (60.47%) than the normouricemic group (75.82%, $P = .0069$) after 13-year follow-up. However, there was no difference in all-cause mortality between the 2 groups.

Conclusion. Persistently high serum UA seems to be implicated in elevation of serum creatinine, which could increase the risk for allograft dysfunction.

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BOTH OVERPRODUCTION AND UNDER-EXCRETION OF URATE can cause hyperuricemia and, in combination with possible risk factors, can affect long-term kidney allograft survival. Several well-known factors, such as male gender, racial difference (in Asia, the overall prevalence ranges from 0.1% in Vietnamese and Japanese populations to 11.7% in the Taiwanese aboriginal population), cyclosporine therapy, use of diuretics, and the high prevalence of metabolic syndrome were reported in renal transplant recipients [1,2]. Serum uric acid is commonly elevated in subjects with chronic kidney disease (CKD), and its effect contributes to renal and nonrenal disease [3]. Uric acid independently predicts progression in CKD, especially immunoglobulin A nephropathy and elderly CKD [4–7]. The proposed mechanisms include endothelial dysfunction, proliferation of smooth muscle cells, vasoconstriction, inflammation, up-regulation of renin-angiotensin system and cyclooxygenase-2 in progressive renal disease [4,8,9]. Increased uric acid levels may represent decreased transplant function and may even be observed in intact transplant function [10]. Several studies demonstrated that hyperuricemia is associated with new cardiovascular events [a 2 standard deviation difference in serum urate, 0.45 vs 0.27 mmol/L, was associated with a hazard ratio of 1.56 and 95% confidence interval (CI) = 1.32 to 1.84] [11], incidence of acute kidney injury [multivariate analysis, odds ratio (OR) = 4.739, 95% CI = 1.961–11.449, $P < .001$], and in-hospital mortality (unadjusted OR = 3.005, 95% CI = 1.186–7.867, $P = .021$) [12].

Despite recent evidence, the role of uric acid as a causal factor in the pathogenesis and progression of kidney disease in renal transplant recipients remains controversial, partly because of the inclusion in epidemiologic studies of patients with hypertension, diabetes, and/or proteinuria. The prevalence of post-transplant hyperuricemia is still high, particularly in patients with classical cardiovascular risk factors and lower estimated glomerular filtration rate [13]. We therefore conducted a prospective case-control study of renal transplant recipients to assess the association between serum uric acid (UA) levels and graft survival or all-cause mortality in an effort to clarify whether hyperuricemia is a persistently

Table 1. Baseline Characteristics of the Recruited Patients

	Normouricemia ($n = 491$)	Hyperuricemia ($n = 389$)	*P* Value
Age (y)	47.59 ± 12.57	50.03 ± 12.07	.004[c]
Male gender, *n* (%)	223 (45.42)	245 (62.98)	<.001[c]
Chronic diseases, *n* (%)			
Gouty arthritis	69 (14.05)	87 (22.37)	.002[c]
Hypertension	421 (85.74)	359 (92.29)	.003[c]
Diabetes mellitus	160 (32.59)	140 (35.99)	.324
Cardiovascular disease	51 (10.39)	56 (14.40)	.089
Congestive heart failure	44 (8.96)	51 (13.11)	.063
Hyperlipidemia	299 (60.90)	261 (67.10)	.068
Hepatitis B	66 (13.44)	63 (16.20)	.293
Hepatitis C	58 (11.81)	95 (24.42)	<.001[c]
Mycobacterium tuberculosis (previous)	23 (4.68)	31 (7.97)	.061
Cytomegalovirus infection (previous)	30 (6.11)	32 (8.23)	.278
Shingles[a]	4 (0.81)	2 (0.51)	.699
Dialysis mode—hemodialysis	101 (20.57)	115 (29.56)	.003[c]
Laboratory data			
UA (mg/dL, median [IQR])[b]	6.00 (5.30–6.80)	7.70 (6.70–8.80)	<.001[c]
Cr (mg/dL, median [IQR])[b]	1.10 (0.90–1.50)	1.60 (1.20–4.10)	<.001[c]
HbA1c (%, median [IQR])[b]	5.85 (5.50–6.63)	5.90 (5.50–6.80)	.823
Immunosuppressant therapy, *n* (%)			
CNI + MMF + prednisolone	445 (90.63)	357 (91.77)	.554
CNI + mTOR inhibitors	49 (9.98)	37 (9.51)	.816
mTOR inhibitors-based	106 (21.59)	69 (17.74)	.155
With CNI	439 (89.41)	352 (90.49)	.598
With Prednisolone	203 (41.34)	131 (33.68)	.020[d]
With Azathioprine (Imuran)	15 (3.05)	32 (8.23)	.001[c]
Allopurinol + Benzbromarone, *n* (%)	68 (13.85)	169 (43.44)	<.001[c]
Dithiazide + Aspirin, *n* (%)	49 (9.98)	69 (17.74)	.001[c]
Follow-up (mo; median [IQR])[b]	46.47 (18.97–67.80)	47.20 (22.43–68.10)	.496

Abbreviations: IQR, interquartile range; UA, uric acid; Cr, creatinine; HbA1c, hemoglobin A1c; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.
Calculated by Student *t* test, Pearson χ^2 test.
[a]Fisher exact test.
[b]Mann-Whitney test.
[c]$P < .01$.
[d]$P < .05$.