Risk Factors of Hyperuricemia After Renal Transplantation and Its Long-term Effects on Graft Functions

S. Eyupoglu[a,*], D. Eyupoglu[b], Z. Kendi-Celebi[c], S. Akturk[c], A. Tuzuner[d,e], K. Keven[c,e], and S. Sengul[c,e]

[a]Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey; [b]Department of Internal Medicine, Hacettepe University School of Medicine, Ankara, Turkey; [c]Department of Nephrology, Ankara University School of Medicine, Ankara, Turkey; [d]Department of General Surgery, Ankara University School of Medicine, Ankara, Turkey; and [e]Transplantation Center, Ankara University School of Medicine, Ankara, Turkey

ABSTRACT

Background. Hyperuricemia is a common complication in renal transplant recipients. Recent studies have suggested that hyperuricemia may contribute to the deterioration of graft function.

Methods. In this study, we aimed to investigate the risk factors related to hyperuricemia and the effects of hyperuricemia on graft dysfunction, graft survival, cardiovascular events, and mortality rates. Between the years 2005 and 2016, 141 renal transplantation patients with at least 5 years of follow-up were included in this retrospective cohort study. Multilinear regression analysis was used to determine the relationship between mean serum uric acid level and estimated glomerular filtration rate (eGFR).

Results. The average transplant age was 37.1 ± 12.1 years and the average follow-up time was 83.09 ± 20.30 months; the prevalence of patients with hyperuricemia was 39 (27.6%). The mean uric acid levels were higher in women ($P < .001$) in the condition of dyslipidemia ($P = .026$), β-blocker usage ($P = .002$), and thiazide diuretics ($P = .020$). Patients with hyperuricemia ($P < .001$), new-onset hypertension ($P = .027$), β-blocker usage ($P = .005$), and thiazide diuretics ($P = .040$) had statistically different eGFR levels than other recipients. Multivariant regression analyses showed that eGFR levels after transplantation were correlated with mean uric acid levels ($\beta = -0.46$, $P = .001$), donor age ($\beta = -0.18$, $P = .048$), recipient age ($\beta = -0.28$, $P = .0003$), and mean hemoglobin levels ($\beta = 0.31$, $P = .003$).

Conclusions. There was no difference in graft loss, general mortality, and cardiovascular events between normo-uricemic and hyperuricemic groups. Increased uric acid levels contribute to eGFR decline in patients with renal transplantation. On the other hand, effects of uric acid levels on graft survival, cardiovascular events, and general mortality are still controversial.

HYPERURICEMIA is a common complication in renal transplant recipients [1]. There is a strong correlation between hyperuricemia and renal function. The condition, therefore, may add the several other factors that contribute to progressive worsening of renal allograft function and eventual graft loss [2].

Hyperuricemia usually develops in the early post-transplantation period, and several factors appear to predispose patients to hyperuricemia [3], including male sex, obesity, diuretics, hypertension, and calcineurin inhibitors [4–6]. The incidence of hyperuricemia in renal transplant patients has increased from 25% to 80% with the widespread use of cyclosporine [5]. Time since

*Address correspondence to Sahin Eyupoglu, Ankara University Department of Internal Medicine, Sihhiye, Ankara 06100, Turkey. E-mail: eyupoglusahn@yahoo.com

230 Park Avenue, New York, NY 10169

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transplantation, male sex, estimated glomerular filtration (eGFR) level, diabetes mellitus, and serum calcium concentration were risk factors for hyperuricemia in kidney transplantation recipients with intact graft function [7].

Recent studies investigating the association between hyperuricemia and graft dysfunction have suggested that hyperuricemia may contribute to the progressive deterioration of graft function and ultimately to graft loss [8–10]. It is unclear, however, whether hyperuricemia plays a casual role in the development of graft dysfunction. First-year post-transplantation uric acid (UA) level >8 mg/dL was found to be a significant risk factor for chronic allograft nephropathy and poorer graft survival [11].

Asymptomatic hyperuricemia has been accepted as a risk factor for the development of major metabolic, renal, or cardiovascular diseases [12]. Wide epidemiological studies have shown that hyperuricemia has been related to the incidence of coronary heart diseases and increased mortality in these individuals [13–15].

In this study, we aimed to investigate the risk factors related to hyperuricemia and the effects of hyperuricemia on graft dysfunction, graft survival, cardiovascular events, and mortality rates.

METHODS

This was a retrospective cohort study of renal allograft recipients transplanted between September 2005 and February 2016 at Ankara University School of Medicine, Transplantation Center. One hundred forty-one patients who had a regular follow-up data of at least 5 years and were not on allopurinol treatment for any purpose were analyzed for the long-term effects of serum UA levels on graft functions.

Patient information was obtained retrospectively from the hospital electronic database. These data included general characteristics, donor features, post-transplantation medications, and laboratory data.

Corresponding serum creatinine (sCr) levels were used to estimate glomerular filtration rate (eGFR), with use of the Abbreviated Modification of Diet in Renal Diseases (MDRD) equation. Hyperuricemia was defined as mean serum UA (calculated from UA values accessed at multiple times after transplant to ensure UA exposure) level >7.0 mg/dL for men and >6.0 mg/dL for women.

Patients were followed up according to the recommended guidelines, which indicated that all organ recipients should return to the follow-up house for blood routine test, hepatic/renal function, metabolic status, and immunosuppression serum concentration.

Each patient's laboratory results had been recorded as every 3 months for the first year, then every 6 months after transplantation. Patients' laboratory data during the first 3 months after transplantation were not included in the study because retarded graft function in 3 months may affect measurements.

The primary outcome of this analysis was the attempt to testify the predictive value of UA level and the possible factors that might influence UA level. The secondary outcome of our study was graft survival and its correlation with hyperuricemia and UA level. Graft loss was defined as graft failure (re-start of dialysis) or death with functioning graft.

Categorical variables are presented as frequencies and percentages and were compared by use of the χ^2 test. Continuous variables are expressed as mean ± standard deviation (SD) and were compared with the use of the independent t test or Mann-Whitney U test. Correlation analysis and multiple linear regression analysis were used for two continuous variables in appropriate conditions. Values of $P \leq .05$ were considered to be statistically significant. All analyses were performed with the use of SPSS software (Statistical Package for the Social Sciences, version 20.0; SPSS, Evanston, Ill, United States).

RESULTS

The distribution of general characteristics of the patients based on the follow-up duration is summarized in Table 1. Before transplantation, 93 (66%) patients had been on the hemodialysis program and 19 (13.5%) patients had pre-emptive transplantation. Mean hemodialysis duration before transplantation was 41.95 33.47 months. The most common underlying kidney diseases caused renal failure can be listed as chronic glomerulonephritis (38 patients, 27%), hypertension (24 patients, 17%), urogenital anomalies (16 patients, 11.3%), and diabetes (14 patients, 9.9%).

The long-term effects of serum UA levels on graft functions and general features, depending on the first 60 months, are summarized on Table 2. The mean UA levels were higher in women ($P < .001$), in the condition of dyslipidemia ($P = .026$), β-blocker usage ($P = .002$), and thiazide diuretics ($P = .020$). Also, patients with hyperuricemia ($P < .001$), new-onset hypertension after transplantation ($P = .027$), usage of β-blocker agents ($P = .005$), or thiazide diuretics ($P = .040$) have statistically different eGFR levels from the other recipients. Pre-transplantation duration differs between normo-uricemic and hyperuricemic groups (36.5 ± 28.14 months and 51.69 ± 47.43 months, respectively, $P = .043$).

Correlation analyses to evaluate risk factors for serum UA level showed that the mean serum UA levels were positively correlated with blood urea nitrogen (BUN) levels ($\beta = 0.309$, $P = .039$) and mean serum low-density lipoprotein (LDL) level ($\beta = 0.183$, $P = .048$) and negatively correlated with eGFR level.

To evaluate long-term affecting factors on eGFR levels on the 60th month after transplantation, multivariant regression analyses were performed ($R^2 = 0.474$; $P < .001$). eGFR levels were correlated negatively with mean UA levels ($\beta = -0.46$, $P = .001$), donor age ($\beta = -0.18$, $P = .048$), and recipient age ($\beta = -0.28$, $P = .0003$) and were correlated positively with mean hemoglobin levels ($\beta = 0.31$, $P = .003$).

Although a clear relationship between eGFR and UA levels was observed, there was no statistical difference between normo-uricemic and hyperuricemic recipients in terms of graft loss ($P = .281$), general mortality ($P = .77$), or cardiovascular events ($P = .287$).

DISCUSSION

We observed that hyperuricemia prevalence was 27.6% over the mean 83 months of follow-up after renal transplantation