The Effect of Hyperuricemia and Allopurinol Treament Outcome of Graft in Kidney Transplant Recipients

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Abstract

Aim: Kidney transplant recipients (KTRs) may have high levels of serum uric acid (SUA) due to graft dysfunction and immunosuppressives. This study evaluated the effect of high SUA levels and allopurinol therapy on renal functions in KTRs.

Methods: 113 of 233 KTRs had elevated SUA levels (G1) others had normal SUA (G2) . Fifty seven of G1 received allopurinol treatment(G1A+), and 56 patients (G1A--) did not. 56 of 118 patients who were followed for five years(G5) were hyperuricemic (G5-1) and 26 of G5-1 treated with allopurinol (G5-1A+) and 30 of them did not(G5-1A-). 62 patients were normourisemic(G5-2). GFR<10 ml/min was considered as graft loss.

Results: Of the 233 patients the mean age was 42.8±11.6(17-76), 164 were male (70.0%). In 2.year graft loss developed in 9 (7.5 %) and 18 (15.9%) of G2 and G1 respectively (p=0.045). Graft losses occurred 10 in the G1A+ and 8 in the G1A-(p=0,330). In G5 graft loss occurred in 12 (21%) and 9 (14%) in G5-1 and G5-2 respectively(p=0.62). Graft loss occurred in 7 (23%) and 5 (19%) in G5-1A+ and G5-1A- respectively (p=0.71). Considering the first two years, graft loss in G5-1 was higher than in G5-2(p=0.023). Higher SUA levels increased the graft loss by 3.6 times compared to normal SUA levels (95% confidence interval: 1,2-12.70).

Conclusions: There was a significant relationship between high SUA levels and graft loss in KTRs in 2 years and 5 years. Treatment of high SUA with allopurinol therapy had a protective effect on renal functions. So, treatment of hyperuricemia, such as allopurinol, can be a good option to preserve kidney function in KTRs.

Keywords: *Uric acid, kidney transplant recipient, renal dysfunction, allopurinol*

1. Introduction

There are many risk factors for graft loss. In addition to immunological factors, hypertension, increased cardiovascular disease risk, recurrence of primary kidney disease, metabolic disorders such as hyperglycemia, lipid disorders, electrolyte disorders, and hyperuricemia are also important. Hyperuricemia associated with endothelial dysfunction, mitochondrial dysfunction, glomerular capillary injury, and tubular obstruction of urate crystal formation can cause structural kidney damage[1]. Elevated serum uric acid levels (SUA) appear to be associated with accelerated renal dysfunction in chronic kidney disease (CKD) patients[2 3]. There are also arguments that there may be an additional risk factor for graft loss in KTRs[4]. Studies show the effect of high serum levels of uric acid on the loss of function in renal allograft and chronic kidney disease [6].

Allopurinol is a xanthine oxidase inhibitor that increases urinary excretion of uric acid and is well tolerated. The literature has shown contrary results on this front. Some studies have shown that allopurinol can slow GFR loss in renal KTRs[7 8], while in another study, it was ineffective in KTRs[9]. In this retrospective observational cohort study, the effects of elevated serum uric acid and reduction of serum uric acid by allopurinol on renal function were evaluated in kidney transplant recipients.

2. Materials and methods

This retrospective study included 233 KTRs who underwent routine controls in the outpatient clinic within 12 months. The level of serum uric acid > 7 mg / dL for men and > 6 mg/dl for women were considered to be high SUA (G1) (n=113). The remaining 120 patients (G2) had normal SUA levels. Allopurinol (150 mg every other day) was given to reduce the high uric acid level. Fifty-seven KTRs (G1-A+) with high SUA levels received allopurinol treatment, and 56 patients (G1-A-) did not. The 118 patients (G5) followed for more than 5 years were evaluated separately. Of these, 56 (G5-1) had high SUA levels, and 62 (G5-2) were normal. Of the 56 patients with high SUA levels, 26 (G5-1-A+) received allopurinol treatment, and 30

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Received: 11.07.2023, Accepted: 24.12.2023, Available Online Date: 31.12.2023
Cite this article as: Paydas S, Yücel N, Nazlıcan E, Ünal İ. The Effect of Hyperuricemia and Allopurinol Treament Outcome of Graft in Kidney Transplant Recipients. J Cukurova Anesth Surg. 2023; 6(3): 483-7. doi:10.36516/jocass.1401282

(G5-1A-) did not (Table 1). Patients received triple immunosuppressive therapy (CNI+MMF or mTOR inhibitor and prednisolone) as standard therapy. In addition, patients continued antihypertensive drugs as needed.

Exclusion criteria: Patients with acute renal insufficiency, clinically overt heart failure, hepatic insufficiency, uncontrolled blood pressure (>140/90mm/Hg), and diuretic therapy were excluded from the study.

Age, sex, duration of post-transplant period, and laboratory measurements, including glucose serum uric acid, BUN, creatinine, sodium, potassium, chlorine, calcium, total protein, albumin, complete blood count, and drug levels were provided retrospectively from medical records. Control visits were recorded as 1 – Baseline, 2 – Six-month control, 3 – One-year control, 4 – Second-year control, and 5 – Fifth-year control. Glomerular filtration rate (GFR) was measured using CKD-EPI. Permanent reduction of GFR to 10 ml/min was considered graft loss.

The SPSS 20.0 Windows package program was used for the statistical analyses, and a p-value <0.05 was considered significant. Frequency analysis, chi-square test, t-test, and correlation analysis were also used. Repeated Measurements Analysis was applied to evaluate the change in the measurements obtained in the time interval.

This study was approved by Medical Faculty Clinical Research Ethics Council Meeting #91 on September 2019 Decision Number 21.

This article was previously posted to a pre-print server on April 27, 2020.

3. Results

Of the 233 patients included in the study, 164 were male (70.0%), and the mean age of all patients was 42.8±11.6 (17-76). The demographic characteristics of the patients are shown in Table 1. The serum uric acid levels and glomerular filtration rate of patients at each follow-up period are shown in Table 2. According to uric acid levels, there was graft loss in 9 patients (7.5%) from the G2 (n=120) and in 18 patients (15.9%) from the G1. In the first and second-year follow-ups, graft loss was significantly higher in G1 than in G2 (p=0.045). In G1, 10 graft losses occurred in the G1-A+ and 8 in the G1-A-; however, there was no difference between them (p=0.330).

Figure 1

According to serum uric acid levels, eGFR values of kidney transplant recipients during 2-year follow-up.

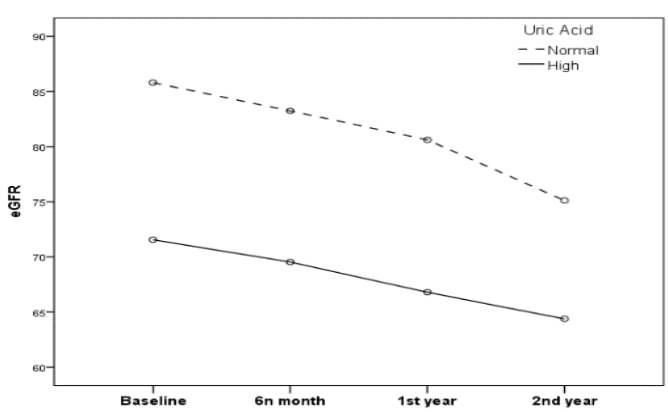


Figure 2

eGFR values according to allopurinol therapy during 2 years follow-up in kidney transplant recipients.

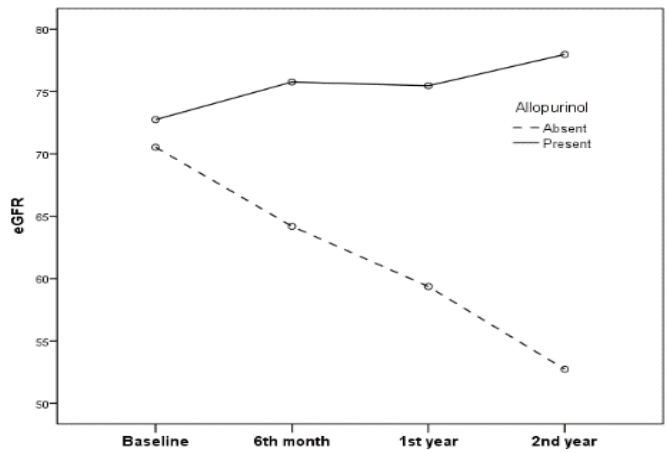


Figure 3

eGFR values during 5 years follow-up in patients

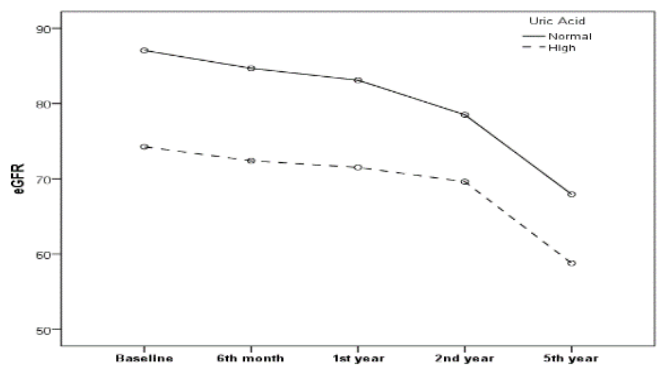
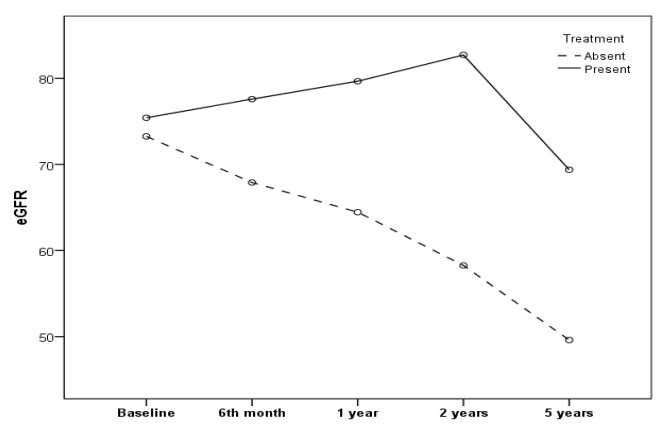


Figure 4

eGFR values according to allopurinol therapy during 5 years follow-up in kidney transplant recipients with high serum uric acid level



In the five-year follow-up group (G5, 118 patients), graft loss occurred in 12 (21%) patients from the G5-1 (n=56) and in 9 (14%) from the G5-2 (n=62). There was no statistical difference between these two groups (p=0.62). Graft loss occurred in 7 (23 %) patients from the G5-1-A+ group (30 patients) and in 5 (19%) patients from the G5-1A- group (26 patients). There was no significant difference between these two groups (p=0.71).

However, in the G5-1 (56 patients, n=118), 8 graft losses developed in the first two years, and 4 graft losses occurred between 2 and 5 years. Meanwhile, in the group with normal SUA (n=62), there were 2 graft losses in the first two years and 7 between 2 and 5 years (Table 3).

Considering the first two years in patients followed for five years, graft loss was significantly higher in G5-1 over the G5-2 (p=0.023), and higher SUA levels increased the incidence of graft loss by 3.6 times compared to normal SUA levels (95% confidence interval: 1.2-12.70).

Compared to baseline, GFR decreased in both the hyperuricemic group (G1) and normo-uricemic group (G2) followed for 2 years (p<0.001), and the decline was the same in both groups (p=0.691) (Figure 1). There was also a change in GFR in both the G1-A+ and G1-A- (p=0.043), and this change was significant in favor of allopurinol patients (p <0.001) (Figure 2).

In correlation analysis, it was found that GFR values significantly decreased in group with high uric acid (n=56) (G5-1) more than normal uric acid (n=62) (G5-2) during the 5-year follow-up (p<0.001). However, the decrease levels were similar in both groups (p=0.818) (Figure 3).

Compared to baseline, GFR values in G5-1-A+ during the 5-year follow-up decreased significantly (p=0.001). The levels of decrease of GFR were also significantly different depending on whether allopurinol treatment was provided (p=0.034). As seen in Figure 4, in patients treated with allopurinol, GFR increased in the first two years. In the second year, the reno-protective effect of allopurinol was still significant, and this effect continued into the fifth year. GFR was higher in those treated with allopurinol than those without allopurinol treatment at a difference of 20 mL/min (Figure 4).

Table 1

Groups of KTRs according to serum uric acid levels, follow-up period, and KTRs

Groups	Male	Mean age	N	Group Definition
G1	77 (%68,1)	43,2±11,6	113	Patients with high SUA levels followed for 2 years
G2	87 (%72,5)	42,6±11,7	120	Patients with normal SUA levels followed for 2 years
Total	164 (%70)	42,8±11,6	233	
G1-A+	45 (%78,9)	45,1±12,2	57	Patients with high SUA levels were treated with allopurinol and followed for 2 years.
G1-A-	32 (%57,1)	41,2±10,7	56	Patients with high SUA levels were not treated with allopurinol and followed for 2 years.
G5	85 (%72)	45,3±11,1	118	Patients followed for 5 years
G5-1	39 (%69,6)	45,2±11,5	56	Patients with high SUA levels followed for 5 years
G5-1A+	12 (%46,2)	43,7±9,6	26	Patients treated with allopurinol followed for 5 years
G5-1A-	21 (%70)	46,4±13,1	30	Patients with high SUA levels were not treated with allopurinol and followed for 5 years.
G5-2	46 (%74,2)	45,4±10,9	62	Patients with normal SUA levels followed for 5 years

Table 2

Serum uric acid levels and glomerular filtration rate of the groups at the follow-up period

		G1+G2 n=233	G1 n=113	G2 n=120	G1A+ n=57	G1A-n=56	G5 n=118	G5-2 n=62	G5-1 n=56	G5A+ n=30	G5A- n=26
1.	UA	6,6±1,8	7,94±1,2	5,16±1,0	8,2±1,5	7,5±0,9	6,6±1,9	5,3±1,1	8,2±1,5	8,6±1,6	7,6±1,1
	GFR	76,7±29,7	69,0±2,9	84,1±2,4	68,4±33,5	69,6±27,8	80,9±29,4	87,1±26,8	74,3±30,8	73,3±33,5	75,4±28,1
2.	UA	6,7±1,7	7,43±1,7	5,98±1,4	7,9±1,7	6,9±1,4	6,6±1,6	5,8±1,3	7,5±1,5	7,9±2,0	6,9±1,3
	GFR	72,9±29,2	64,0±2,8	81,2±2,3	61,5±30,6	66,6±29,7	78,8±27,1	84,7±24,6	72,4±28,4	67,9±25,6	77,6±31,0
3.	UA	6,6±1,7	7,28±1,8	5,87±1,3	7,6±2,0	6,9±1,2	6,6±1,6	5,9±1,4	7,4±1,6	7,9±1,6	6,7±1,3
	GFR	71,1±30,5	61,7±3,0	79,6±2,7	55,6±26,8	69,1±32,6	77,6±25,9	83,1±25,6	71,5±25,1	64,4±22,3	79,7±26,1
4.	UA	6,7±1,6	7,40±1,7	6,02±1,3	7,9±1,6	6,7±1,3	6,6±1,5	5,9±1,3	7,4±1,3	8,1±1,2	6,6±1,0
	GFR	70,2±31,6	64,4±3,8	75,1±3,0	52,7±30,3	78,0±31,9	74,3±28,6	78,5±24,9	69,6±31,7	58,3±28,5	82,7±30,5
5.	UA						6,9±1,6	6,6±1,7	7,4±1,4	7,5±1,2	7,3±1,5
	GFR						63,6±30,7	67,9±27,6	58,8±33,4	49,6±30,2	69,4±34,4

GFR: Glomerular filtration rate, UA: Uric acid, 1. Baseline, 2. 6. Month, 3. 1. Year, 4: 2. year, 5. 5. Year

Table 3
Graft loss of the groups at the follow-up period

Graft Loss	G2 120	G1 113	P	G1 A+	G1 A-	p	G5-2 62	G5-1 56	p	G5-1 A+ 30	G5-1 A- 26	p
2. year	9	18	0,045	10	8	0.33	2	8	0.018			
%	7.5%	15.9%	0.023									
5. year							9	12	0.062	7(23%)	5(19%)	0,71

4. Discussions

The prevalence of hyperuricemia in KTRs is 42.1 %[1º]. It can even be detected in 30-84% of patients treated with cyclosporine as a calcineurin inhibitor (CNI)[11]. Similarly, this study determined hyperuricemia to be 48.4% in KTRs. In the normal population, the prevalence is around 10-15%[11]. Factors that lead to increases in the tendency to hyperuricemia include advanced age, gender, low GFR, drugs such as diuretics, beta-blockers, CNIs (especially cyclosporine), as well as high body mass index and pre-transplant dialysis duration [7 11-13].

Uric acid is a potentially modifiable risk factor for the development and progression of CKD. Some reports suggest that hyperuricemia is related to the severity of CKD[2 3] or that it indicates progression to end-stage renal disease (ESRD)[14]. In a study, it was found that the treatment of hyperuricemia improves renal function[8]. Hyperuricemia is common in kidney transplant patients due to the use of calcineurin inhibitors and reduced kidney graft function. Allopurinol, which has been the first treatment option in patients with hyperuricemia, has considerable adverse effects, and its dosage adjustment is difficult. On renal graft survival, the effect of uric acid lowering therapy is still controversial, with some benefits, and may be the result of chronic allograft nephropathy and graft failure [15 17]. The KTRs with hyperuricemia had lower GFR, and progressive GFR loss was higher in our study. The SYMPHONY study suggests that hyperuricemia is not an independent risk factor for graft failure[18]. In addition, Kim et al. concluded that there is no risk factor for graft outcome according to the data obtained using the Marginal Structural Model[19]. According to the Korean-based meta-analysis of Miyeun et al. [4], hyperuricemia is an indicator of renal damage due to decreased excretion, and its association with normal renal function may indicate a negative endpoint, such as ESRD, similar to the present study. In a meta-analysis of Liu et al. [2º], high SUA lowering therapy with different drugs slows the development of CKD.

In the present study high SUA levels was determined as a possible risk factor for graft loss in the first two years. Treatment with allopurinol reduces the progression of kidney failure and even improves it initially. Allopurinol therapy prevented GFR loss in both the first, second, and fifth-year follow-up periods.

Uric acid itself is a source of oxidative stress and inflammation. In order to investigate the effect of elevated SUA levels on CKD progression in KTRs, multicenter studies that exclude the effect of rejection and graft dysfunction by biopsy can be used to explain the adverse effects of hyperuricemia further explain the adverse effects of hyperuricemia.

Similarly our study, it has been reported that febuxostat, another uric acid lowering drug, slowed GFR decline in 100 asymptomatic hyperuricemic chronic kidney disease patients in stages 3 and 4 over a 12-month follow-up period. Adverse events did not differ in the control group. They also titrated febuxostat dose for serum uric acid level <6 mg/dL[21]. Allopurinol therapy in KTRs with high SUA levels also positively affected renal function in our study. There are different reports about hyperuricemia and its available treatments. According to previous studies in KTRs, hyperuricemia has a negative effect on kidney function [13 2º 22], yet there is no relationship[7 9] or treatment of hyperuricemia preserves kidney function[21 23].

The limitations of our study are that it is single-centered and the number of patients is small.

In conclusion, we determined that hyperuricemia accompanied by loss of GFR and allopurinol therapy preserved renal function in kidney transplant recipients with high serum uric acid levels in follow-up 2 and 5-year periods. So, hyperuricemia should be treated, and low-dose allopurinol can be a good option, thus preventing the loss of kidney function in kidney transplant recipients.

Statement of ethics

This study was approved by Medical Faculty Clinical Research Ethics Council Meeting #91 on September 2019 Decision Number 21.

This article was previously posted to a pre-print server on April 27, 2020.
https://d197for5662m48.cloudfront.net/documents/publicationstatus/57503/preprint_pdf/a401c62a4073450c1cd79f7c4a433448.pdf

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

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