THE EFFECT OF HYPERURICEMIA AND ALLOPURINOL ON OUTCOME OF KIDNEY TRANSPLANT RECIPIENTS

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Abstract

OBJECTİVE: Kidney transplant recipients (KTRs) may have increased serum uric acid (SUA) level due to presence of existing greft dysfunction and used immunosuppressives. In this retrospective study, we evaluated effect of high SUA levels and allopurinol therapy in KTRs on renal functions. PATIENTS and METHODS: 113 KTRs of 233 KTRs included, had elevated SUA level (G1). Fiftyseven 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). RESULTS: Of the 233 patients included 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). According to allopurinol therapy 10 of the graft loss occurred in the G1A+ and 8 in the G1A- (p=0,330). 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 2 in G5; in G5-1 graft loss was higher than in the G5-2 (p = 0.023), and higher SUA levels increased the graft loss by 3.6 times compared to normal SUA levels (95% confidence interval: 1,2-12.70). CONCLUSION: There was a significant relationship between high SUA levels and graf loss in kidney transplant recipients in 2 years and 5 years. Treatment of high SUA with allopurinol therapy had protective effect on renal functions. So that hyperuricemia should be treated and low dose allopurinol can be option for treatment of hyperuricemia therefore prevention of loss of kidney function in kidney transplant recipients.

INTRODUCTION

Increased uric acid by endothelial dysfunction, mitochondrial dysfunction and glomerular arteriopathy, tubular obstruction of urate crystal formation can be cause of structural damage of the kidney[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 serious arguments that there may be an additional risk factor for graft loss in KTRs[4]. There are studies showing the loss of function in renal allograft as well as chronic kidney disease of hyperuricemia[5,6].

Xanthine oxidase inhibitor allopurinol increases urinary excretion of uric acid and is well tolerated. Allopurinol has been reported to slow GFR loss in renal KTRs[7,8]. However, another study was found to be ineffective in KTRs[8]. In this retrospective observational cohort study; effects of elevated serum uric acid and reduction of serum uric acid by allopurinolon renal function were evaluated.

METHODS

In this retrospective study, 233 KTRs were included in the study in our out-patient clinic for routine control within 12 months. KTRs according to uric acid level; uric acid> 7 mg / dL for men and> 6mg / dl for women

were considered to be high SUA (n: 113). Allopurinol treatment was started at post-transplant >3.Month-<12. month. The remaining 120 patients had normal SUA levels. Fiftyseven KTRs with high SUA levels received allopurinol treatment and 56 patients did not. There were 118 patients who were followed for more than 5 years and they were evaluated separately. Of these, 56 had high SUA levels and 62 were normal. Of the 56 patients with high SUA level, 26 received allopurinol treatment and 30 did not (Table 1). Allopurinol group received 150 mg allopurinol treatment every other day. Patients also received triple immunosuppressive therapy (CNI + MMF or mTOR inhibitor and prednisolone) as standard therapy. In addition, they continued to antihypertensive drugs as needed.

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

Age, sex, transplant date and laboratory results including serum uric acid, BUN, creatinine, sodium, potassium, chlorine, calcium, total protein, albumin, blood counts and drug levels were provided retrospectively from medical records. Visits were shown as 1. Baseline, 2. 6. Month, 3. 1. Year, 4: 2. year, 5. 5. year. Glomerular filtration rate (GFR) was measured using CKD-epi. Permanent reduction of GFR to 10 ml/min was considered as graft loss.

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

Ethical considerations

Written approval from the Ethics Board of Cukurova University Faculty of Medicine was obtained for the study.

RESULTS

Of the 233 patients included in the study, 164 were male (70.0%). The mean age was 42.8 ± 11.6 (17-76). Demographic features of the patients were shown in table 1. At follow up period, serum uric acid levels and glomerular filtration rate of patients were shown in table 2.

According to uric acid level at the end of the second year, there was graft loss in 9 patients (7.5 %) of G2 (n=120) and in 18 patients (15.9%) of G1. For first 2 year graft loss was found to be significantly higher in G1 than G2 (p = 0.045). According to allopurinol therapy 10 of the graft loss occurred in the G1-A+ and 8 in the G1 A-, and there was no difference between them (p = 0.330).

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

However, in 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 graft losses between 2 and 5 years. (Table 3)

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

Comparing to baseline GFR decreased in both hyperuricemic group (G1) and normouricemic group (G2) followed for 2 years (p<0.001), and the decline was the same in both groups (p = 0.691) (figure1). There was also a change in GFR in both G1A + and G1A + groups (p = 0.043) and this change was significant in favor of allopurinol patients (p <0.001) (figure 2).

In correlation analysis, eGFR values were decreased in both groups with high uric acid (n = 56) (G5-1) and normal uric acid (n: 62) (G5-2) during 5 years follow up (p: <0.001) However the decrements were found to be similar in both groups (p = 0.818) (Figure 3)

Comparing to baseline eGFR values according to allopurinol therapy during 5 year follow up in kidney transplant recipients decreased significantly (p: 0.001). The decrements of eGFR were also significantly different according to with or without allopurinol treatment (p: 0.034). As seen in figure 4 in patients treated with allopurinol GFR increased in the first two years. Although GFR begins to decrease after the second year, the protective effect of GFR was significant and 5 years of follow-up was still effective to cause for difference of 20 mL/min (figure 4).

DISCUSSION

The prevalence of hyperuricemia in KTRs is between 15-52%[6,9]. It can even be detected in 30-84% of those using cyclosporine as calcıneurin inhibitor (CNI)[10]. In the normal population, the prevalence is around 10-15%[11]. Older age, male gender, low GFR, drugs such as diuretic, beta blocker, CNI (especially cyclosporine), high body mass index, duration of dialysis treatment during pretransplant are the factors that increase the tendency to hyperuricemia[7,11-13].

Some data suggest that hyperuricemia is related to severity of CKD[2,3] or shows progression to end stage renal disaase (ESRD)[14]. In addition, there are studies on the treatment of hyperuricemia improves renal function[8]. Renal graft survival is still controversial, with some benefits, and may be the result of chronic allograft nephropathy and graft failure[15-17]. Meanwhile, 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, hyperuricemia is an indicator of renal damage due to decreased excretion, but its association with normal renal function may be indicative of a negative endpoint, such as ESRD[4]. According to the recent meta-analysis of Liu et al, high SUA treatment, albeit with different drugs, slows the development of CKD[20].

In our study, high SUA levels can be considered as a possible risk factor for graft loss in the first two years. Although treatment with allopurinol does not prevent graft loss, it decreases the progression of kidney function and even improves it initially. Also interesting allopurinol therapy prevented loss of GFR both first 2 and first 5. year follow up periods.

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 will further explain the adverse effects of hyperuricemia. Because uric acid itself is a source of oxidative stress and inflammation, although it is the result of renal failure. In our study, allopurinol therapy of high SUA had a positive effect on renal function. According to the results of studies in KTRs hyperuricemia is bad for kidney function[4,13,17,21], there is no relationship[7,9] or treatment of hyperuricemia preserves kidney function. or treatment of uric acid elevation preserves kidney function[20,22].

In conclusion we found that in kidney transplant recipients in 2 years and 5 years; hyperuricemia accompaning loss of GFR and alIopurinol therapy in hyperuricemic patients preserved the renal function. So that hyperuricemia should be treated and low dose allopurinol can be option for treatment of hyperuricemia thefore prevention of loss of kidney function in kidney transplant recipients.

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