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Allopurinol Treatment Reduces Proteinuria in Patients With Type II Diabetes Mellitus

KEYWORDS

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ABSTRACT *BACKGROUND - Diabetic patients go through several stages of renal disease, moving from normo- to micro- to macroalbuminuria. Diabetic nephropathy is the main reason leading to end-stage renal disease. Incidence of diabetic nephropathy is approximately 20% to 30% of diabetic patients are affected by nephropathy, 15 years after the beginning of DM.1 Besides factors such as angiotensin II, cytokines, and vascular endothelial growth factor, uric acid may play a role as the underlying cause of diabetic nephropathy. OBJECTIVE - We evaluated allopurinol effects on proteinuria in diabetic patients with nephropathy. MATERIAL AND METHODS - 80 patients with type 2 diabetes mellitus and diabetic nephropathy (proteinuria, at least 500 mg/24 h and a serum creatinine level less than 3 mg/dL) were recruiting. 40 patients were randomized to receive allopurinol (100 mg/d) and 40 were randomized to receive placebo. Administration of antihypertensive and renoprotective drugs (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers continued for both groups, without changes in dosage. Proteinuria was compared at baseline 2 and 4 months between the two groups. RESULTS - Each group consisted of 19 men and 21 women. Serum levels of uric acid (P = .02) and 24-hour urine protein (P = .049) were significantly lower in the patients on allopurinol treatment, after 4 months compared with the control group. CONCLUSIONS - Allopurinol (low dose) can reduce severity of proteinuria after 4 months of drug administration, which is probably due to decreasing the serum level of uric acid. Thus, allopurinol can be administered as an adjuvant cost-effective therapy for patients with diabetic nephropathy*

INTRODUCTION

Diabetic patients go through several stages of renal disease, moving from normo- to micro- to macroalbuminuria. Diabetic nephropathy is the main reason leading to end-stage renal disease and also an important risk factor for cardiovascular disease. 20% to 30% of diabetic patients are affected by nephropathy, 15 years after the beginning of DM. Hypertension and glomerular hyperfiltration contribute to the development of diabetic nephropathy.[1,2] In patients with type 2 DM, hyperuricemia may be accompanied by peripheral vascular disease, hypertension, hypertriglyceridemia, higher level of hemoglobin A1c, more severe albuminuria, lower glomerular filtration rate (GFR), and early start or rapid progression of diabetic nephropathy. Some study tells that prevalence of hyperuricemia is especially high in diabetic women.[3,4]Activation of cytokines, profibrotic factors, inflammation, and vascular endothelial growth factor (VEGF) may also play some roles in occurrence and progression of diabetic nephropathy.[5,6] Genetic susceptibility, age, poor glycemic control, some ethnic groups, obesity, and smoking are some other factors associated with diabetic nephropathy.[7,8] Many studies demonstrated that serum level of uric acid in these patients directly correlated with the level of urinary albumin excretion, and the serum uric acid level of patients was higher compared with healthy people.[9] The aim of our study was to evaluate allopurinol effects on proteinuria in diabetic patients with nephropathy.

MATERIAL AND METHODS

80 patients with type 2 diabetes mellitus and diabetic nephropathy (proteinuria, at least 500 mg/24 h and a serum creatinine level less than 3 mg/dL) were recruiting.The inclusion criteria were: age > 18 years old; proteinuria greater than 500 mg/24 h and absence of systemic diseases or other causes of proteinuria based on physical examination and history.This was a double-blinded randomized controlled trial on 80 patients with type 2 DM and nephropathy (at least 500 mg/24 h) at the nephrology clinics of Elbasan, from January 2013 to April 2013. 40 patients were randomized to receive allopurinol (100 mg/d) and 40 were randomized to receive placebo for 4 months. All of the patients who received antihypertensive drugs, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) continued them with the same schedule and dosage. All of the patients were using renoprotective drugs such as ACEIs and/or ARBs. Hyperglycemia treatment consisted of oral hypoglycemic agents (OHA) and/or insulin, which continued during the study with the same dose. After 2 and 4 months all patients were visited for evaluation of vital signs and results of laboratory tests. The following tests were performed for the patients: complete blood count, fasting blood glucose, blood urea nitrogen (BUN), serum creatinine, serum potassium, serum uric acid, urinalysis, and 24-hour urine volume, protein, and creatinine.

STATISTICAL ANALYSIS

The collected data were analyzed by descriptive indexes (mean ± standard deviation), the t test, the nonparametric Friedman test, and the Spearman correlation coefficient, using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS).

RESULTS

Table 1 demonstrates the demographic information of our patients. Each group consisted of 19 men and 21 women. The age of the patients was from 25 to 74 years with the mean of 55.6 ± 10.4 years.

Table 1. Demographic Characteristics of Patients on Allopurinol and Placebo

Variable	Study group	Control group
Number of pt	40	40
Gender	Type equation here.	
Male	19	19
Female	21	21
Age, y	55.3 ± 10.4	58.1 ± 10.4
Weight, kg	79.7 ± 10	72.1 ± 12.4
Body mass index, kg/m^2	28.9 ± 4.9	26.9 ± 4.4
Diabetes mellitus durations, y	11.7 ± 6.1	13.4 ± 7.4

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The weight of the patients ranged from 69 kg to 89.7 kg in study group and 60 kg to 84.5 kg in the control group. The mean weight was significantly higher in the study group than in the control group (P = .045). Duration of DM was between 2 and 29 years (mean, 12.4 ± 6.5 years). There were no differences between two groups regarding age, body mass index, duration of diabetes mellitus, systolic and diastolic blood pressure, fasting blood glucose, blood urea nitrogen, serum creatinine, serum potassium, and urine volume during the study period. The 24-hour urine creatinine level was significantly higher in the study group at baseline (P = .02), but there was no significant difference between the two groups at 2 and 4 months of the study.Based on repeated measure analysis of variance, regression analysis showed that the higher level of urine creatinine concentration in the study group was due to the higher weight of this group.The two groups were not significantly different regarding serum levels of uric acid (P = .35), but at 4 months, serum uric acid levels of the study group were significantly lower than those of the control group (P = .02). At baseline and 2 months of the study, 24-hour urine protein concentration was not significantly different between the two groups, but at 4 months, urine protein of the study group was significantly lower than that of the control group (P = .049)

DISCUSSION

Various agents have been used for treatment of diabetic nephropathy including ACEIs, ARBs, lipid-lowering agents, and protein intake restriction. Most studies have proved that ACEIs and ARBs are useful in the treatment of diabetic nephropathy.[10,11]Administration of these drugs in microalbuminuria stages resolve albuminuria, but when microalbuminuria develops, these drugs only slow down the progression of diabetic nephropathy and reduce the severity of proteinuria.[12,13] Concerning the side effects of these drugs, including cough and hyperkalemia, it is not possible to administer these drugs to all patients or at full doses. According to results of some studies, serum uric acid level of diabetic patients was higher than that of healthy people.[9,10] Moreover, some studies indicated that hyperuricemia in diabetic patients was accompanied by vascular complications, albuminuria, and decreased GFR. Thus, decrease in serum uric acid level can probably be effective in treatment of diabetic nephropathy. To the best of our knowledge, there is no report on the therapeutic effect of allopurinol in diabetic nephropathy. Consequently, results of the current study cannot be compared with findings of other similar studies. In the beginning of the study, the mean serum uric acid level was 5.8± 1.3 mg/dL and 6.4± 2.3 mg/dL in study and control groups, respectively.

Short-term treatment (after 2 months of administration of allopurinol), serum level of uric acid and severity of proteinuria in the study group did not significantly decrease, compared with the control group. Administration of allopurinol (100 mg/d) in our study group for 4 months resulted in significant decrease in serum uric acid level and also a significant decrease in proteinuria. It can be concluded that allopurinol, by lowering the serum uric acid, inhibited the effect of uric acid on glomeruli and kidney vasculatures, and consequently, reduced proteinuria. Thus, it can be concluded that low dose allopurinol (100 mg/d) can reduce severity of proteinuria, and possibly the progression of nephropathy, if administered for longer than 2 months.

CONCLUSIONS

In patients with diabetic nephropathy, allopurinol can be administered for treatment of diabetic nephropathy with no significant side effects. Allopurinol (low dose) can reduce severity of proteinuria after 4 months of drug administration, which is probably due to decreasing the serum level of uric acid. Thus, allopurinol can be administered as an adjuvant cost-effective therapy for patients with diabetic nephropathy.

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