Research Article

Efficacy of allopurinol in decreasing proteinuria and hyperuricemia in Indian patients with type 2 diabetes: prospective, placebo controlled, randomized double blind study

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Abstract

Introduction: Diabetic Nephropathy affects up to 30% of the population with ACE-I and ARB as mainstay of treatment but associated with side effect of hyperkalemia. Allopurinol has been studied to reduce the proteinuria in randomized double blind prospective trial for 1 month. Allopurinol has significantly reduced serum uric acid (P = 0.002) and urine protein (P = 0.0003) in study group as compare to control group.
Keywords: Allopurinol, Diabetic Nephropathy, Proteinuria, Indian.

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INTRODUCTION

Diabetic nephropathy affects 20% to 30% of diabetic patients after 15 years of the DM[1]. Hypertension, glomerular hyperfiltration[2,] Activation of cytokines, profibrotic factors, inflammation, and vascular endothelial growth factor (VEGF)[3], Genetic susceptibility, age, poor glycemic control, ethnicity, obesity, and smoking are factors associated with diabetic nephropathy[4]. ACEIs, ARBs, lipid-lowering agents, and protein intake restriction are useful in the treatment of diabetic nephropathy [5] and reduce the severity of proteinuria.[6] 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. In patients with Type 2 DM, serum level of uric acid was higher especially high in diabetic women.[7] compared with healthy people and directly correlated with the level of urinary albumin excretion[8]. Hyperuricemia consequently can lead to interstitial fibrosis[9], more severe albuminuria, and early start or rapid progression of diabetic nephropathy. Thus, decrease in serum uric acid level can probably be effective in treatment of diabetic nephropathy which has been demonstrated in studies from Taiwan[7] and Iran[10]. In India diabetes is in pandemic and emerging first line cause of mortality due to its complication. More and more people are on dialysis due to nephropathy. Any new intervention which is potential to prevent or retard the diabetic nephropathy must be welcomed in terms of quality of life. Regarding the higher level of serum uric acid in diabetic patients and also its role in causing vascular and glomerular injuries, thereby decreasing the GFR, to evaluate the role of allopurinol in patients with type 2 DM and nephropathy in Indian patients is of significant importance. In this study we evaluated the effect of allopurinol in proteinuria in type 2 diabetic patients with nephropathy and correlation between serum uric **a**cid **a**nd urine albumin excretion

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MATERIAL AND METHODS

Design of Study: double-blinded randomized placebo controlled trial was conducted after approval from institutional ethical committee

Duration of study: Study was conducted from April 2012 to September 2012

Place of study: D Y Patil Medical college, Kolhapur by Department of Pharmacology

Sample size

For a study with 1 control(s) per experimental subject, considering previous study[10] the response within each subject group was normally distributed with standard deviation 907.89, true difference in the experimental and control means 598, we will need to study 37 experimental subjects and 37 control subjects with probability (power) 0.8 with confidence limit of 0.05. Considering the loss in follow up we required to enroll 40 patients in each group. But because of less time being the student summer project funded by ICMR we could research on 12 patients in each group.

Patients: 12 patients in study group and 12 patients in control group

Randomization: simple random allocation

Inclusion Criteria

Patients with type 2 DM and nephropathy (proteinuria greater than 200 mg/24 h) with written informed consent, age over 18 years old, bilateral normal-size kidney on ultrasonography (9 cm to 12 cm), and absence of other causes of proteinuria based on physical examination and history.

The exclusion Criteria

administration of allopurinol for another reason, significant renal insufficiency (serum creatinine > 3 mg/dL or GFR < 25 mL/min), History of development of allopurinol side effects (elevated liver enzymes, cytopenia, and dermatitis), and uncooperativeness during the study.

Methods

The patients had received allopurinol tablet (100 mg) or placebo, twice per day, for 1 month. All patients were kept on angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) with the same schedule and dosage for renoprotection as well as for hypertension. If administration of new antihypertensive drugs was indicated, drugs without effects on proteinuria, such as beta blockers, was prescribed. Hyperglycemia treatment will be consisted of oral hypoglycemic agents (OHA) and/or insulin, which will be continued during the study to control the BSL. At baseline and at 1 month later, participants had visited for evaluation of vital signs and results of laboratory tests.

The following tests were performed for the patients

For inclusion: complete blood count, fasting and post prandial blood glucose, abdominal ultrasonography, 24-hour urine volume, protein, and creatinine.

For exclusion: serum creatinine, blood urea nitrogen (BUN)

For study parameters: serum uric acid, urinalysis

OBSERVATION AND RESULTS

Table 1: Demographic Characteristics of Patients on Allopurinol and Placebo

Variable	Study group	Control group
No. patients	12	12
Male	7	7
Female	5	5
Age(y)	57.2±9.36	59.3±7.48

Table 1 demonstrates the demographic information of the patients. Each group consisted of 7 men and 5 women. The age of the patients was from 42 to 75 years with the mean of 57.7 ± 9.36 year. Duration of DM was between 2 and 29 years (mean 12.6 ± 6.7 years). The variables between two group at base line were not different significantly.

Table 2: Clinical and Biochemical Parameters of Patients before starting the drug

	Baseline		
Variable	Study group	Control group	P
Serum uric acid (mg/dl)	4.83±1.05	4.75±1.12	0.85
Urine protein (mg)	52.45±32.26	63.33±18.25	0.32
Blood sugar level (f) mg/dl	160±89.2	127.08±19.91	0.21
Blood sugar level (pp) mg/dl	262.21±133.58	195±59.32	0.12
Serum creatinin(mg/dl)	1.34±0.26	1.35±0.28	0.87

Table 2 demonstrate that two groups at baseline (i.e. study and control group) were not significantly different regarding serum levels of uric acid, urine protein, blood sugar level and serum creatinine. Based on repeated measure analysis of variance, patients in the study and control groups were not significantly different in terms of systolic and diastolic blood pressure, fasting blood glucose, post prandial blood glucose serum creatinine, urine glucose, and urine volume levels during the study period (Table 2)

Table 3: Clinical and Biochemical Parameters of Patients after 1 month of giving drug

Variable	Study group	Control group	Unpaired
Serum uric acid (mg/dl)	3.58±0.55	4.87±1.14	0.002
Urine protein (mg)	31.19±19.38	64.5±18.99	0.0003
Blood sugar level (f) mg/dl	158.25±43.84	123.33±21.77	0.021
Blood sugar level (pp) mg/dl	245.45±107.15	162.25±35.15	0.081
Serum creatinin (mg/dl)	1.35±0.32	1.35±0.21	1

Table 3 demonstrate at 1 month, serum uric acid levels, Urine protein of the study group were significantly lower than those of the control group while serum creatinine and blood sugar level of both the group was not significantly different.

	Study group			Control group		
Variable	At baseline	At 1 month	Paired	At baseline	At 1 month	Paired
Serum uric acid (mg/dl)	4.83±1.05	3.58±0.55	0.0007	4.75±1.12	4.87±1.14	0.353
Urine protein (mg)	52.45±32.26	31.19±19.38	0.0028	63.33±18.25	64.5±18.99	0.1211
Blood sugar level (f) mg/dl	160±89.2	158.25±43.84	0.915	127.08±19.91	123.33±21.77	0.2313
Blood sugar level (pp) mg/dl	262.21±133.58	245.45±107.15	0.4751	195±59.32	162.25±35.15	0.0174
Serum creatinin(mg/dl)	1.34±0.26	1.35±0.32	0.8551	1.35±0.28	1.35±0.21	0.9603

At baseline and 1 months of the study, 24-hour urine protein concentration and serum uric acid concentration of the study group was significantly lower than that of the control group. Finally, no adverse effects were reported by our patients in the allopurinol group during the study.

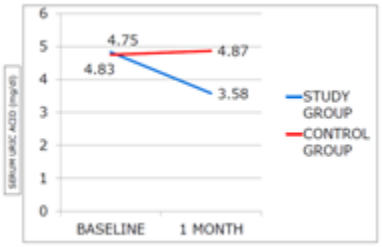

Figure 1: Mean serum levels of uric acid during the study in patients receiving allopurinol (study group) and placebo (control Group)

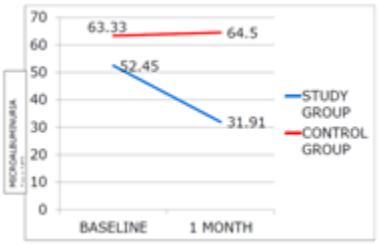

Figure 2: Mean 24-hour urine levels of protein during the study in patients receiving allopurinol (study group) and placebo (Control group)

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. To results of some studies, serum uric acid level of diabetic patients was higher than that of healthy people. 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 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. concerning the side effects of these drugs, including cough and hyperkalaemia, it is not possible to administer these drugs to all patients or at full doses. In the beginning of the study, the mean serum uric acid level was 4.83±1.05 mg/dL and 4.75±1.12 mg/dL in study and control groups, respectively. The mean serum uric acid level in another study carried out on Taiwanese patients with type 2 DM was 5.2 ± 1.6 mg/dL for patients with normalbuminuria, 5.6 ± 1.9 mg/dL for patients with microalbuminuria, and 6.7 ± 2.1 mg/dL for patients with macroalbuminuria. The mean serum level of uric acid in our patients was comparable with that of Taiwanese patients with macroalbuminuria. Administration of allopurinol (100 mg/d) in our study group for 1 month 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. Furthermore, allopurinol may have renoprotective effects via the mechanism of reducing the kidney microvasculature endothelial dysfunction. 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 1 months. Administering the drug at this dosage in the study did not bring about any adverse effects, and it seems that long-term treatment of patients with allopurinol is safe. As all of the patients of the current

study were receiving ACEIs or ARBs before and during, we can assume that the additional renoprotective effect (lowering the proteinuria severity) was not related to those drugs.

CONCLUSION

This study has analyzed the use of allopurinol in diabetic proteinuria. India is considered as diabetic capital of the world and we are more prone for its complication due to genetic susceptibility. At the same time treatment of proteinuria mainly relies on ACE-I and ARBs only. Allopurinol has been found effective in reducing the progression of proteinuria in management of diabetic nephropathy. Allopurinol reduce the serum uric acid as well as urine microalbumin excretion. Further studies are indicated to confirm the findings with more number of patients to strengthen the significance of findings as well as long term follow up is required considering the chronic pathophysiology of diabetic nephropathy.

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REFERENCES

1. Orchard TJ, Dorman JS, Maser RE, *et al*. Prevalence of Complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. Diabetes. 1990; 39:1116-24.
2. Pavkov ME, Knowler WC, Bennett PH, Looker HC, KrakoffJ, Nelson RG. Increasing incidence of proteinuria anddeclining incidence of end-stage renal disease in diabetic Pima Indians. Kidney Int. 2006; 70:1840-6.
3. Hilgers KF, Veelken R. Type 2 diabetic nephropathy: never too early to treat? J Am Soc Nephrol. 2005; 16:574-5.
4. Wolf G, Ziyadeh FN. Molecular mechanisms of diabetic renal hypertrophy. Kidney Int. 1999; 56:393-405.
5. Burns WC, Twigg SM, Forbes JM, *et al*. Connective tissue growth factor plays an important role in advanced glycation end product-induced tubular epithelial-tomesenchymal transition: implications for diabetic renal disease. J Am Soc Nephrol. 2006; 17:2484-94.
6. Adler S. Diabetic nephropathy: Linking histology, cell biology, and genetics. Kidney Int. 2004; 66:2095-106.
7. Tapp RJ, Shaw JE, Zimmet PZ, *et al*. Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Am J Kidney Dis. 2004; 44:792-8.
8. Nelson RG, Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetic kidney disease in Pima Indians. Diabetes Care. 1993; 16:335-41.
9. Gelber RP, Kurth T, Kausz AT, *et al*. Association between body mass index and CKD in apparently healthy men. Am J Kidney Dis. 2005; 46:871-80.
10. Tseng CH. Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. Kidney Int. 2005; 68:796-801.

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