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Impact of allopurinol on metabolic acidosis in patients with chronic kidney disease; a randomized controlled-trial

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is a disabling disease with multiple complications, like, increased serum levels of uric acid due to glomerular filtration rate (GFR) impairment.
Objectives: This study was designed to evaluate the effect of allopurinol on metabolic acidosis in patients with renal failure.
Patients and Methods: This is a randomized controlled-trial study on 50 patients with CKD stage II-IV, who referred to Qaem and Montaserieh hospitals in Mashhad. Patients were selected and randomly divided into two equal groups of 25 subjects. In addition to standard treatments, the intervention group received 100 mg allopurinol tablet for three months and the control group received placebo. Demographic data were obtained from each individual. Serum uric acid level, creatinine, blood pH and bicarbonate levels were assessed at the initiation of treatment and at the end of the third month.
Results: The mean age of patients was 54.04±12.62 years. Allopurinol administration resulted in a significant increase of serum bicarbonate levels and pH ($P<0.001$ for each) compared to the control group. A significant reduction in uric acid ($P<0.05$) and an increase in GFR ($P<0.05$) was observed in both groups.
Conclusion: Allopurinol could ameliorate metabolic acidosis, glomerular filtration and uric acid in patients with CKD.
Trial registration: This study was registered in Iranian Registry of Clinical Trial (identifier: IRCT2016122731604N1; https://irct.ir/trial/24831; registration date: 2017-08-05).

Original

Implication for health policy/practice/research/medical education:
In a randomized controlled-trial study on 50 patients with chronic kidney disease stage II-IV, we found, allopurinol could ameliorate metabolic acidosis and glomerular filtration by reducing serum uric acid levels.
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Introduction

Chronic kidney disease (CKD) is defined as chronic irreversible nephron damage either reduction in the number of nephrons or their function (1,2). CKD presents with reducing the renal function with or without azotaemia or kidney damage for more than three months (1,2). CKD is a global health issue which imposes high costs on nations (1). The prevalence of CKD was reported to be 13.4% for all five stages and 10.6% for stage II to V (1). CKD is associated with increased mortality mainly due to cardiovascular disease (CVD) and less importantly due to cancer (2).

Increased serum uric acid levels are commonly seen in CKD patients (3). For decades, increased serum uric acid was considered as a risk factor for CVD but recent epidemiological studies have shown that increased serum uric acid is associated with increased risk of hypertension, CKD, CVD and mortality (3,4). Hyperuricemia has been shown to be related to hypertension, proteinuria, renal function impairment and progressive nephropathy as well as CVD. Animal studies have shown that the mechanism of injury by hyperuricemia is through endothelial cell damage, activation of renin-angiotensin-aldosterone system and increased oxidative stress (5,6). Allopurinol is

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a xanthine oxidase inhibitor that inhibits the production of hypoxanthine from xanthine, a precursor of uric acid (7). Few studies assessing the effects of allopurinol on renal function and metabolic acidosis have shown that allopurinol prevents the progression of renal failure, its complications (3,8) and metabolic acidosis (9).

Objectives

The aim of this study was to evaluate the effect of allopurinol administration on metabolic acidosis in CKD patients in Mashhad, Iran.

Patients and Methods

Study design

This randomized controlled trial was conducted on patients with CKD who referred to Qaem and Montaserieh hospitals, Mashhad, Iran. Subjects were selected based on convenient sampling (Patients randomly selected with double blinded method). Patients were included in the study if they were within the age range of 18 to 80 years, with the diagnosis CKD (stage II to IV), hyperuricemia (serum uric acid between 6 and 10 mg/dL) and metabolic acidosis (serum bicarbonate between 15 and 20 mg/dL). Subjects were excluded if they had positive history of gout disease, myeloproliferative disease, or previous consumption of allopurinol or allergy to allopurinol. Patients were randomly allocated to either intervention group who received 100 mg/daily allopurinol or control group who received vitamin B1 as placebo in addition to conventional medications. The duration of intervention was three months. The Consort flow diagram of the study is presented in Figure 1.

The demographic information were obtained from all patients at baseline. Measurements included serum uric acid level, bicarbonate level, creatinine and pH. Measurements were performed at baseline and at the end of the third month. Glomerular filtration rate (GFR) was calculated by CKD-EPI (chronic kidney disease epidemiology collaboration) equation formula.

Ethical issues

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The study protocol was approved by the Ethical Committee of the Mashhad University of Medical Sciences (24/04/2016, Code: IR.MUMS.REC.1395.247). The purpose and procedure of the study was explained for patients. The informed consent was taken from the patients. This paper was extracted from the M.D thesis of Davod Gholami (# 950015) in The Mashhad University of Medical Sciences. This study was also registered in Iranian registry of clinical trial (#IRCT2016122731604N1; https://irct.ir/trial/24831; registration date: 2017-08-05). Mashhad University of Medical Sciences supported this study (Grant #950015).

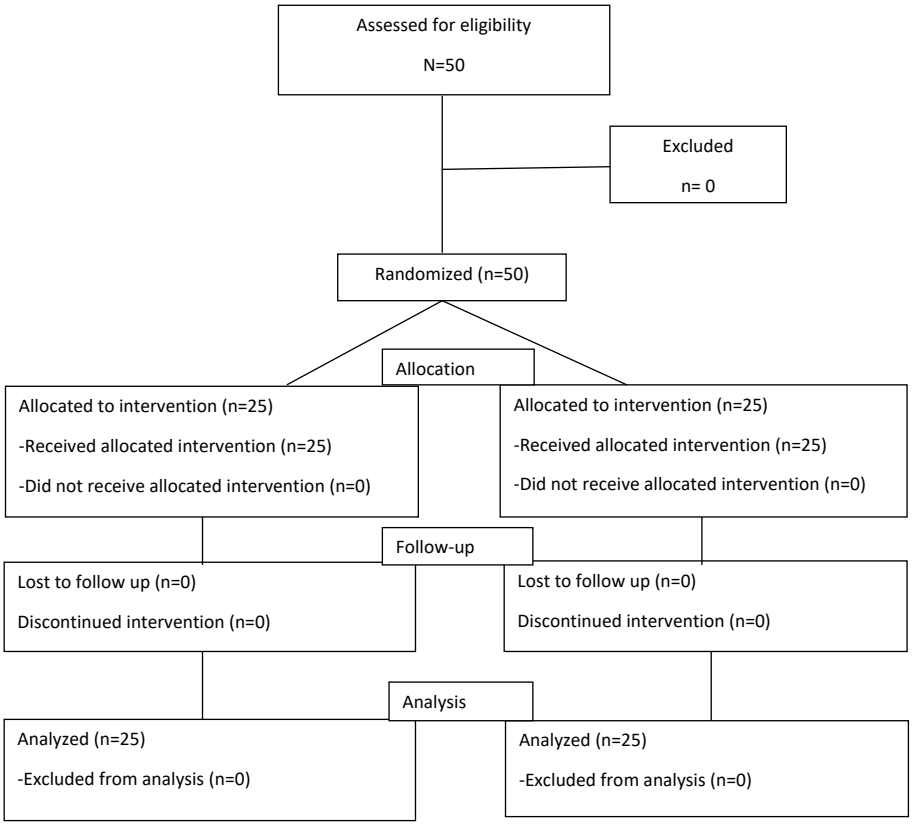

Figure 1. Consort flow diagram of the study.

Statistical analysis

Data were analyzed by the statistical package for social sciences (SPSS) version 22 (IBM Inc. Chicago, Il, USA). Continuous variables were checked for normality using the Shapiro-Wilk test and were presented as mean and standard deviation (SD). Categorical variables were presented as frequency and percentage. Comparison of continuous demographic variables between groups was performed by independent student *t* test while the chi-squared test was used to compare the distribution pattern of categorical variables. The repeated measures analysis of covariance (ANCOVA), with diastolic blood pressure as covariate, was used to assess the group, time and time× group effects of intervention and to compare changes in study variables between and within the groups.

Results

Totally 50 subjects (25 in the allopurinol group and 25 in the control group) participated in this study. Table 1 shows that the majority of the subjects in the current study were male. The most common etiology for CKD in the whole cohort was diabetes mellitus (36.0%) followed by unknown cause (20.0%) and GN (16.0%) (Table 1). The mean age of the subjects was 54.04±12.62 years. There was no significant difference in demographic characteristics between groups ($P>0.05$) except for diastolic blood pressure ($P=0.002$) (Tables 1 and 2).

There were no significant differences in outcome between the two groups at baseline ($P>0.05$) (Table 3). The ANCOVA revealed a significant effect ($P<0.05$) for all variables except uric acid ($P=0.96$) and significant time×group effect for all outcome ($P<0.05$) (Table 3). Intervention resulted in a significant reduction in serum uric acid ($P<0.001$), and a significant increase in serum bicarbonate, pH ($P<0.001$ for each variable) and GFR ($P=0.002$) in the allopurinol administered group. No significant difference was observed in serum creatinine between baseline and three months of intervention in allopurinol administered group ($P=0.10$). Among the subjects in control group a significant reduction was observed in serum uric acid ($P=0.01$) and GFR ($P=0.003$), and also a significant rise in serum creatinine at three months versus baseline ($P=0.01$) (Table 3).

Table 1. Comparison of demographic characteristics between study groups

Variable	Total (N=50)	Allopurinol (n=25)	Control (n=25)	χ^2	*P*
	No. (%)	No. (%)	No. (%)		
Gender					
Male	36 (72.0)	17 (68.0)	19 (76.0)	0.40	0.53
Female	14 (28.0)	8 (32.0)	6 (24.0)		
Smoking	11 (22.0)	5 (20.0)	6 (24.0)	0.12	0.73
Etiology					
DM	18 (36.0)	13 (52.0)	5 (20.0)		
Unknown	10 (20.0)	3 (12.0)	7 (28.0)		
GN	8 (16.0)	2 (8.0)	6 (24.0)	9.30	0.16
HTN	7 (14.0)	3 (12.0)	4 (16.0)		
Nephrolithiasis	4 (8.0)	3 (12.0)	1 (4.0)		
Reflux	1 (2.0)	0 (0.0)	1 (4.0)		

DM; diabetes mellitus, GN; glomerulonephritis, HTN; hypertension.

Discussion

This study showed that the mean age of CKD patients was 54.04 ± 12.62 years. This finding was in line with previous studies (10,11). On the other hand, the majority of the subjects in the current study were male which was in contrast to the higher reported prevalence of CKD among females. This difference might be due to small sample size of the current study, while our sample size was defined based on RCT design (10,12). Furthermore diabetes mellitus was the major underlying cause of CKD in the current study which was in line with the previous studies in the region (13,14).

The findings of this study revealed that inclusion of allopurinol in the treatment of CKD patients resulted in a significant increase in serum bicarbonate and PH. This effect was observed regardless of the increased GFR and reduced serum uric acid in both intervention and control group. This finding was similar to the findings of a previous study in which three months administration of allopurinol in 30 CKD patients in the stages II to IV resulted in improved endothelial function and acidosis (9,15,16). Although the mechanism of allopurinol action is yet unknown, animal studies have demonstrated that uric acid reduction might result in improvement of blood pressure and proteinuria and therefore reduce the progression of CKD by reducing the production of reactive oxygen species (17-20).

This study also showed a significant increase in GFR in

Table 2. Comparison of age and blood pressure between study groups

	Total	Allopurinol	Control	*t*	*P*
Age (y)	54.04±12.62	56.12±11.79	51.96±13.31	1.17	0.25
Systolic blood pressure (mm Hg)	135.60±15.99	132.80±19.90	138.40±10.48	-1.24	0.22
Diastolic blood pressure (mm Hg)	82.00±10.25	77.60±11.56	86.40±6.38	-3.33	0.002**

** Significant at α=0.01.

Table 3. Changes in study variables in allopurinol and control groups

Variable	Allopurinol			Control			Allopurinol versus control		Time effect	Group effect	Time*group effect
	Baseline	3 months	Baseline vs 3 months	Baseline	3 months	Baseline vs 3 months	Baseline	3 months			
Uric acid (mg/dL)	7.34±1.00	5.74±0.97	<0.001[b]	6.59±0.54	5.99±0.83	0.01[b]	0.08	0.32	0.77	0.96	0.005[b]
HCO_3 (mEq/L)	19.64±0.44	22.92±1.32	<0.001[b]	19.83±0.29	19.75±1.82	0.33	0.73	<0.001[b]	0.21	<0.001[b]	<0.001[b]
pH	7.31±0.03	7.37±0.32	<0.001[b]	7.31±0.04	7.30±0.43	0.13	0.75	<0.001[b]	0.54	0.001[b]	<0.001[b]
GFR (mL/min/1.73 m^2)	34.19±11.15	37.15±14.33	0.002[b]	36.75±8.45	34.01±6.94	0.003[b]	0.91	0.05	0.19	0.03[a]	<0.001[b]
Creatinine (mg/dL)	2.09±0.41	2.03±0.61	0.10	2.00±0.44	2.12±0.45	0.01[b]	0.90	0.12	0.12	0.02[a]	0.01[b]

HCO_3, bicarbonate; GFR, glomerular filtration rate.
[a] Significant at α=0.05.
[b] Significant at α=0.01.

the intervention group and a significant decline in GFR in the control group. However, at the end of three months there was only a trend in higher GFR in the allopurinol treated versus the controls ($P=0.05$). Although the difference was non-significant, however allopurinol administration was found to increase GFR more than placebo. This finding was in line with the findings of a previous study that reported a significant improvement in GFR and creatinine due to the administration of allopurinol (8).

Conclusion

The findings of the current study revealed that allopurinol administration might result in reduced metabolic acidosis and GFR in CKD patients by reducing serum uric acid levels

Study limitations

This study did not assess the mechanism of action of allopurinol on reducing metabolic acidosis in CKD patients. Further studies are recommended.
Another, limitation of this study was the assessment of few serum biomarkers of kidney function and other metabolic clues that might lead to the understanding the mechanism of allopurinol action in CKD.

Authors' contribution

MM and MH designed the study, observed accuracy and validity of the study. DG collected the data and follow the study. MM supervised the project. MM and BH wrote the paper. All authors edited and revised the final manuscript and accepted its publication.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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