Effect of allopurinol on diabetic nephropathy; a double-blind clinical trial study

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ABSTRACT

Introduction: Diabetic nephropathy (diabetic kidney disease) is the most common cause of renal failure.

Objectives: Regarding the role of allopurinol in the improvement of diabetic kidney disease, this study aimed to investigate the ameliorative effect of allopurinol in diabetic nephropathy patients.

Patients and Methods: This double-blind clinical trial study was performed on 60 patients with diabetic kidney disease referenced to nephrology clinic during 2019-2020. Patients were divided into case (treated with allopurinol 100 mg/d) and control (received placebo pill) groups. Three and six months of intervention, complete blood count (CBC), fasting blood sugar levels (FBS), serum blood urea nitrogen (BUN) levels, creatinine (Cr) and uric acid (UA) levels, 24 hours urinary protein, glomerular filtration rate (GFR), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were measured and compared between the two groups.

Results: After six months, reduction of UA and 24 hours urinary protein were not significant in the control group ($P > 0.05$) but it was significant in the allopurinol group ($P < 0.05$). In the allopurinol group, NLR and PLR levels decreased significantly during the six months ($P < 0.01$) however there was no significant change in the control group ($P > 0.05$).

Conclusion: Low dosage of allopurinol (100 mg/d) reduces UA, proteinuria, NLR and PLR in patients after six months. Therefore it can be used for diabetic nephropathy patients as a supplementary, inexpensive and safe treatment.

Trial registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20200117046158N1; https://irct.ir/trial/45533, ethical code; IR.SKUMS. REC.1397.303).

Implication for health policy/practice/research/medical education:
In this study, 60 patients with diabetic kidney disease divided into two groups. Patients in the intervention group were treated with allopurinol pill and patients in the control group received placebo pill. The results of this study showed that allopurinol can play a significant role in reducing uric acid and 24-hour urine protein levels without significant changes in the patients' blood factors.

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Introduction

In developing countries, diabetes mellitus is the leading cause of chronic renal failure and is considering the cause of more morbidity and mortality worldwide. Both types of diabetes, but principally type I, plays an important role in this problem due to its complications (1,2). Two types of diabetic patients experience same stages of clinical and pathogenic kidney damages such as kidney hypertrophy, primary nephropathy (micro-albuminuria, obvious nephropathy (macro-albuminuria) and finally ESRD (end-stage renal disease) which is detected by urinary

protein excretion, high blood pressure and reduction in kidney function up to 90% (1).

Diabetic nephropathy (diabetic kidney disease), among all these complications, has become the main cause of end-stage renal failure and cardiovascular mortality that would happen after many years of diabetes onset (1,3).

Some medicines are used to prevent the progression of diabetic nephropathy such as angiotensin-converting enzyme (ACE) and, angiotensin II receptor blockers (ARBs) (4).

Administration of these drugs in micro-albuminuria

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stage can reduce albuminuria, however in obvious albuminuria these drugs may slow the course of nephropathy and reduce proteinuria without complete improvement (1).

Previous studies on the role of uric acid in the development of renal failure have shown that uric acid levels are higher in patients with diabetes than in the general population (5,6). Additionally, the progression of diabetic nephropathy was faster in patients with higher serum uric acid levels (7).

Therefore, uric acid-lowering agents such as allopurinol may be effective in treating diabetic nephropathy (8,9). Animal studies have shown that allopurinol can reduce kidney damages due to inhibition of lipid peroxidation (10). In addition, by reducing serum uric acid levels, allopurinol ameliorates histological changes and improves renal function (11).

Recent clinical trials by evaluating the impact of allopurinol on reduction of proteinuria and improving renal function in diabetic nephropathy have shown that its low-dose (100 mg/daily) reduces proteinuria in the patients and is effective in increasing GFR (glomerular filtration rate) levels and also reducing serum uric acid levels (12,13). Therefore, they suggested that allopurinol may be useful as a supplementary drug in treatment of patients with diabetic nephropathy with fewer side effects, since it can play an effective role in improving kidney function by reduction of uric acid and proteinuria.

Objectives
This study evaluated the effect of allopurinol on the uric acid (UA) and 24-hour urine protein levels and inflammatory factors including neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in patients with diabetic kidney disease.

Patients and Methods
Study design
This double-blind clinical trial study was conducted on 60 diabetic nephropathy patients referred to university clinics of Shahrekord during 2019-2020. This sample was selected from eligible patients by convenience random sampling. Inclusion criteria were having more than 150 mg protein in 24 hours urine, serum uric acid levels between 6 to 15 mg/dL, bland urinary sediment and being satisfied to participate. Patients with significant kidney failure (serum creatinine >3 mg/dL) or glomerular filtration rate <25 cc/min (based on MDRD formula) or previously use of allopurinol, remarkable drug complications during the study such as nausea, vomiting, diarrhea, fever, sore throat, itching, blisters, swelling and hives, dermatitis, headache and shortness of breath, increased liver enzymes, cytopenia or unwillingness to continue the study were excluded.

At first demographic information such as age,

gender, height, weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated hemoglobin (HbA1c), level, diabetes duration, background disease (hypertension and ischemic heart disease), diabetes retinopathy, coronary artery bypass graft surgery, hypothyroidism and drugs (insulin or anti-diabetes oral medicines) were recorded.

At first, 60 patients were randomly allocated and divided into two groups through randomized block design (20 blocks of 3 to complete the two group of 30) (Figure 1).

Patients in both groups received anti-hypertensive, ACE inhibitors and ARBs according to the previous regimen which was continued unchanged during the study. However, if a new antihypertensive drug was needed we prescribed a drug with no effect on proteinuria in the patients.

The control group received placebo and intervention group received the allopurinol 100 mg/d (Darou Pakhsh Pharmaceutical Co., Isfahan, Iran).

For blinding before intervention; both drugs (allopurinol and placebo) were prepared with the same color and shape as the wheat flour and powdered allopurinol which were inserted in similar capsules respectively and labeled as A and B before giving to patients.

The tests of complete blood count (CBC), fasting blood sugar (FBS) levels, blood urea nitrogen (BUN) levels, serum creatinine (Cr) level, uric acid (UA) level and 24-hour urine protein level, NLR, PLR and GFR were assessed at the beginning of the study and three and six months after intervention again.

Ethical issues
The research was conducted in accordance with the Declaration of Helsinki as a statement of ethical principles for medical research. The ethics committee of Shahrekord University of Medical Sciences approved the study (#IR.SKUMS.REC.1397.303). Accordingly, written informed consent was taken from all participants before any intervention. This study was resulted from the residential thesis by Farzaneh Kadkhodaei-Elyaderani at department of internal medicine of this university. Additionally, the trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20200117046158N1; https://irct.ir/trial/45533).

Statistical analysis
The collected data was entered into SPSS software (version 23). Based on the Kolmogorov-Smirnov test results the distribution of variables such as age, weight, height, BMI, white blood cell (WBC), PLT, Hb, UA and FBS were normal therefore, parametric tests including independent t-test and for repeated measures the ANOVA test was used. However, according to the results of the Kolmogorov-Smirnov test on the abnormal distribution of 24-hour urine protein, the nonparametric tests including
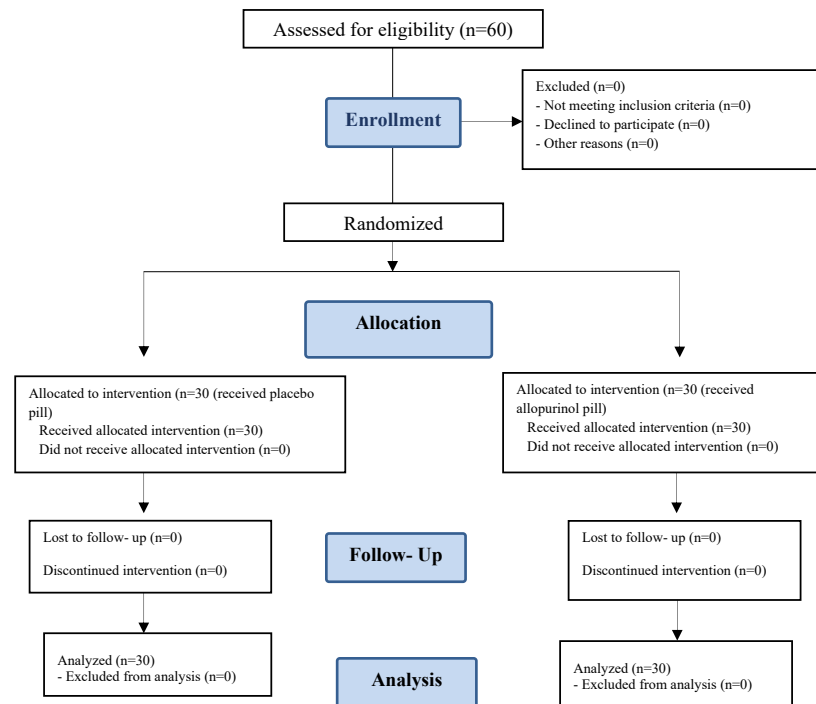
Figure 1. Consort flow chart.

the Mann-Whitney U and Friedman tests were used. In addition, the chi-square and the Fisher's exact test were used to compare the frequency distribution of qualitative data. In all statistical analyzes, the significance level was considered less than 0.05.

Results

In the present study, of 60 patients with diabetic nephropathy, 17 were male (56.7%) and 13 were females (43.3%) with the mean age of 65.3 ± 9.75 years in the control group and mean age of 65.63 ± 11.28 years in the allopurinol group. Allopurinol group consisted of 15 males (50%) and 15 females (50%). According to Table 1, no significant difference between the two groups was seen ($P > 0.05$; Table 1).

There was no significant difference in CBC, FBS, BUN and Cr between two groups at three investigated times ($P > 0.05$). In addition, 6 months after the start of the study, changes in these parameters over time were not significant in both groups ($P > 0.05$; Table 2).

Before intervention, there was no significant difference in UA level between the control group with the mean of 7.02 ± 1.16 mg/dL and allopurinol group with the mean of 7.14 ± 0.98 mg/dL ($P > 0.05$). Between groups comparison showed that after three and six months of intervention; UA levels were significantly different in allopurinol group with the mean of 5.87 ± 1.22 mg/dL and 4.99 ± 1.18 mg/dL and in the control group with the mean of 6.89 ± 0.89 mg/dL and 7.09 ± 1.39 mg/dL ($P < 0.05$). Within groups comparison showed that after six months of the study

onset, UA and 24-hour urine protein changes were not significant in the control group ($P > 0.05$), however, during this time, a significant decrease in the level of these two parameters was observed in the allopurinol group ($P < 0.05$; Table 3).

In addition, NLR and PLR levels were not significantly different between the two groups before the intervention ($P > 0.05$). However 6 months after intervention, the NLR level in the allopurinol group with the mean of 2.16 ± 0.41 was significantly lower than the control group with the mean of 2.48 ± 0.62 ($P = 0.017$). Additionally, in the control group no significant changes in NLR and PLR levels were seen after 6 months of intervention ($P > 0.05$); since in the allopurinol group, these two factors had a significant decrease ($P < 0.01$; Table 4).

Finally, it was indicated that the mean of GFR did not differ significantly between the two groups in any of the three times ($P > 0.05$). In addition, 6 months after the study, GFR changes were not significant in the two groups ($P > 0.05$; Table 5).

Discussion

The current study was conducted on 60 diabetic nephropathy patients assigned to the control and allopurinol groups with the aim of investigating the effect of allopurinol on uric acid. The two mentioned groups were similar in the basic factors such as age, gender, BMI, SBP, DBP and HbA1c levels ($P > 0.05$). In addition, the results of the preliminary blood tests, including CBC, FBS, BUN and Cr in none of the three trial times (before

Table 1. Patients basic factors in the two groups

Characteristics	Control group (n=30)	Allopurinol group (n=30)	P value
Gender			
Male	17 (56.7%)	15 (50%)	0.796
Female	13 (43.3%)	15 (50%)	
Age (year)	65.03±9.75	65.63±11.28	0.826
Weight (kg)	82.70±15.98	80.32±14.28	0.545
Height (cm)	176.47±55.34	165.33±9.37	0.282
BMI (kg/m^2)	28.89±7.01	29.47±5.50	0.723
SBP (mm Hg)	132.67±15.07	128.33±10.85	0.206
DBP (mm Hg)	80±0	80±0	1.00
HbA1c (%)	7.32±0.81	7.24±0.98	0.738
Underlying diseases			
Diabetes duration (year)	13.37±6.62	12.90±6.47	0.783
Hypertension	28 (93.3%)	28 (93.3%)	1.00
Hypertension duration (year)	12.17±7.36	11.07±6.04	0.529
Ischemic heart disease	4 (13.3%)	3 (10%)	0.688
Diabetic retinopathy	5 (16.7%)	5 (16.7%)	1.00
Coronary artery bypass surgery	1 (3.3%)	2 (6.7%)	1.00
Medications			
Insulin	18 (60%)	15 (50%)	0.604
Oral anti-diabetic medications	16 (53.3%)	17 (56.7%)	0.795
Both oral and insulin medications	4 (13.3%)	2 (6.7%)	0.389
Losartan	25 (83.3%)	24 (80%)	0.739
Thyroid medications	0 (0%)	3 (10%)	0.086

Abbreviation: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin.

Table 2. Comparison of patients' blood parameters during the 3 time period in the two groups

Variables	Time	Control group (n=30)	Allopurinol group (n=30)	P value[a]
WBC (×10^3/μL)	Before intervention	6.57±1.96	7.35±1.73	0.108
	3 months after intervention	7.08±1.62	7.99±1.06	0.335
	6 months after intervention	7.12±1.61	7.31±1.70	0.657
P value[b]		0.157	0.368	
Hb (g/dL)	Before intervention	14.03±2.16	14.23±1.88	0.708
	3 months after intervention	14.15±1.91	14.30±1.82	0.757
	6 months after intervention	13.91±1.87	14.47±1.96	0.259
P value[b]		0.336	0.182	
PLT count (×10^3/μL)	Before intervention	223.60±81.77	223.90±66.73	0.988
	3 months after intervention	215.37±80.36	224.13±63.56	0.641
	6 months after intervention	224.67±88.80	221.93±61.54	0.890
P value[b]		0.368	0.862	
FBS (mg/dL)	Before intervention	133.37±36.05	129.63±27.36	0.653
	3 months after intervention	136.67±30.08	127.93±25.32	0.229
	6 months after intervention	134.00±30.99	128.03±35.56	0.494
P value[b]		0.802	0.907	
BUN (mg/dL)	Before intervention	27.97±14.64	25.61±13.01	0.512
	3 months after intervention	26.13±10.51	25.57±15.83	0.873
	6 months after intervention	27.53±11.41	26.09±13.78	0.660
P value[b]		0.415	0.877	
Cr (mg/dL)	Before intervention	1.49±0.54	1.36±0.39	0.284
	3 months after intervention	1.49±0.49	1.41±0.42	0.468
	6 months after intervention	1.49±0.50	1.39±0.44	0.407
P value[b]		0.971	0.507	

Abbreviation: WBC, white blood cell; PLT, platelet; FBS, fasting blood sugar; BUN, serum urea nitrogen; Cr, Creatinine.
[a] The significance level obtained from the independent t-test in comparison of the mean of the variable between the two groups.
[b] Significant level of Repeated measure ANOVA to compare the mean variable over time in each of the two groups.

Table 3. Comparison of the mean level of uric acid (UA) and 24-hour urine protein levels in patients of the two groups at the three times

Variables	Time	Control group (n=30)	Allopurinol group (n=30)	P value
Uric Acid; mg/dL	Before intervention	7.02±1.16	7.14±0.98	0.690[a]
	3 months after intervention	7.09±1.39	5.87±1.22	0.001[a]
	6 months after intervention	6.89±0.89	4.99±1.18	<0.001[a]
P value[c]		0.488	<0.001	
24 hour urine protein; mg/d	Before intervention	504.98±556.16 221.50 (170-625)	687.40±743.04 330 (170-988.75)	0.286[b]
	3 months after intervention	558.63±607.93 229 (178.75-690)	605.09±727.79 258.50 (154.50-820.15)	0.789[b]
	6 months after intervention	517.80±525.39 252.50 (177-725)	494.10±576.81 258.50 (154.50-729.50)	0.868[b]
P value[c]		0.547	0.002	

Data are shown with mean ±SD or median (interquartile range, IQR).
[a] The significance level obtained from the independent t-test in comparison of the mean of the variable between the two groups.
[b] The significance level of the Mann-Whitney test in comparison of the mean of the variable between the two groups.
[c] Significant level obtained from repeated measure ANOVA in comparison of the mean of the variable over the time in each of the two groups.
[d] Significant level of Friedman test to compare the mean of the variable over time in each of the two groups.

Table 4. Comparison of mean NLR and PLR during the 3 time period in the two groups

Variables	Time	Control group (n=30)	Allopurinol group (n=30)	P value[a]
NLR	Before intervention	2.57±0.57	2.69±0.43	0.387
	3 months after intervention	2.59±0.54	2.38±0.46	0.128
	6 months after intervention	2.48±0.62	2.16±0.41	0.017
P value[b]		0.194	<0.001	
PLR	Before intervention	7.16±2.66	7.36±2.41	0.756
	3 months after intervention	7.08±3.13	6.97±2.11	0.866
	6 months after intervention	7.42±2.98	6.62±2.20	0.239
P value[b]		0.510	0.004	

Data are shown with mean ±SD.
PLR: platelet/lymphocyte ratio, NLR: neutrophil/lymphocyte ratio.
[a] The significance level obtained from the independent t-test in comparison of the mean of the variable between the two groups.
[a] Significant level obtained from repeated measure ANOVA in comparison of the mean of the variable over the time in each of the two groups.

Table 5. Determination and comparison of the mean GFR in patients of the two groups at the three times

Variables	Time	Control group (n=30)	Allopurinol group (n=30)	P value[a]
GFR (mL/min/1.73 m²⁾)	Before intervention	50.91±17.22	54.03±19.05	0.508
	3 months after intervention	49.75±17.57	51.97±18.56	0.636
	6 months after intervention	50.79±19.10	53.24±18.81	0.619
P value[b]		0.518	0.532	

GFR: glomerular filtration rate.
[a] The significance level obtained from the independent t test compared to the mean of the variable between the two groups.
[b] Significant level of repeated measure ANOVA to compare the mean variable over time in each of the two groups.

the intervention and at three and six months after the intervention) had no significant difference between the two groups ($P > 0.05$).

Therefore it seems that the biggest strength of the present study is the two study groups were matched in terms of confounding and possible factors affecting the impact of allopurinol on uric acid in diabetic nephropathy patients since they were not significantly different. Most of previous studies refer to factors such as patients' age

(14), obesity and over-weight (15), hypertension (16) diabetes duration (14) and hemoglobin levels (17) which are significant risk factors of diabetic nephropathy.

Evaluation of UA mean level showed that before intervention, UA level had no significant difference between the two groups ($P > 0.05$). After three and six months of intervention; UA level in the allopurinol group was significantly lower than the control group ($P < 0.05$). After 6 months of the study beginning; UA changes were

not significant in the control group; but in the allopurinol group it was seen a significant reduction in UA levels ($P < 0.05$).

Explaining this finding, UA levels are directly related to urinary albumin excretion, and in diabetic nephropathy patients, serum uric acid levels are higher than healthy individuals. Additionally, in patients with type 2 diabetes, hyperuricemia is associated with peripheral arterial disease, hypertension, higher glyceridemia, higher HbA1c, higher albuminuria, and lower GFR. It was shown a significant relationship between higher level of UA and diabetic nephropathy disease (18). Along this case, many studies were done to investigate the effect of allopurinol on UA reduction. Allopurinol as a safe drug can reduce UA level in diabetic nephropathy patients and resulted to lower risk of kidney diseases (13,19,20). Wei et al concluded that allopurinol consumption causes to UA concentration reach the proper level in 44.6% of patients that it was more common in males. They found a strong relationship between allopurinol dosage and desired UA concentration (21).

The results of our study showed that the mean of 24-hours urine protein was not significant in the three trial times between the two groups ($P > 0.05$). After six months of the study beginning, within group comparison revealed that this parameter had a significant decrease in the case group ($P < 0.05$) but a non-significant decrease was seen in the control group ($P > 0.05$). Similar studies have suggested that allopurinol may reduce the amount of 24-hours urine protein (12, 22-24). In fact, the earliest sign of diabetic nephropathy is the increase of urinary albumin excretion. Over time, protein excretion rises and even reaches more than a few grams per day. At this stage, due to high urine protein excretion, the concentration of protein decreases in blood and the possibility of ankle swelling (environmental edema) increases and body fluids balance would be disturbed. Thereby, proteinuria is the main characteristic of diabetic nephropathy and in diagnostic cases it is necessary to annual measurement. Allopurinol is one of the effective medicines to reduce urine protein. By lowering the level of UA, this drug inhibits the effect of uric acid on glomeruli and renal vessels and reduces proteinuria. Therefore, this drug can indirectly reduce the risk of kidney disease in diabetic nephropathy patients.

In addition, the results of the present study showed no significant difference between the two groups before and 3 months after the intervention, but 6 months after intervention, the mean of NLR in the allopurinol group was significantly lower than the control group. Generally, administration of allopurinol during the 6 months can significantly reduce the level of inflammatory parameters such as NLR and PLR.

It should be noted that the inflammation plays an important role in development of diabetic nephropathy, including the increased chemokine production, infiltration of inflammatory cells to the kidney, production of pro-inflammatory cytokine and tissue damage. Inflammatory process in the kidneys activates with several components of the diabetic milieu, as hyperglycemia, renin-angiotensin system and oxidative stress, which leads to infiltration of the organ by monocytes and lymphocytes, which secrete injurious molecules, such as proinflammatory cytokines and reactive oxygen species. This leukocyte activity increases the inflammatory response and improves cell injury and development of fibrosis. In diabetic kidneys better understanding of the inflammatory response is expected to identify the new anti-inflammatory strategies for the potential treatment of human diabetic nephropathy (25).

Therefore, the results of many previous studies have indicated a significant relationship between leukocytosis, lymphocyte count and diabetic nephropathy (26). In addition, Azab et al showed that higher NLR could be important in prognosis of worsening renal function in diabetic patients. They stated that NLR not only indicates the presence of nephropathy but also can be considered as a factor in the pathogenesis of the disease (27).

So, it seems that evaluating the role of allopurinol on inflammatory factors can be important. In this regard, Goicoechea et al (2010) showed that in patients with moderate CKD allopurinol treatment reduces inflammation and decelerates the progression of renal disease. Allopurinol also reduces cardiovascular and hospitalization risk. These results however have to be approved in larger prospective trials and are the basis for a hypothesis that still needs to be tested (28).

Although they evaluated C-reactive protein in their study and did not focus on NLR and PLR, it was consistent with our study because of the effect of allopurinol on reducing the inflammatory parameter. Due to few studies on evaluation of the effect of this drug on inflammatory factors in diabetic nephropathy; it is the strength of this study focused on these parameters, but further investigations are necessary.

Finally, GFR did not differ significantly between the two groups in any of the three times before the study and three and six months after the intervention ($P > 0.05$). After six months of study beginning; GFR changes were not significant in any group ($P > 0.05$).

Contrary to the present study, the results of another research suggest that allopurinol may be effective in increasing GFR levels (12). Another study showed that 12 months use of allopurinol could lead to higher GFR in patients without severe GFR, but in patients with very severe GFR, the drug had no effect (29). After a three years follow-up of diabetics nephropathy patients treated by allopurinol, Liu et al showed that the use of this drug was effective in increasing GFR, which is contrary to the present study (13). The reason for this discrepancy may be due to the follow up duration which is different in the

mentioned studies. Explaining this finding, GFR can be considered the most proper indicator of renal function, thus 24-hour albumin excretion of more than 300 mg and reduction of GFR is an indication of advanced stage of diabetic nephropathy. In fact, chronic kidney disease involves a range of different pathophysiological processes associated with abnormal renal function and progressive decline in GFR levels. Therefore, it is necessary to pay attention to this factor in order to diagnose kidney disease and its progress. It is recommended to do further studies to evaluate the effect of this drug on GFR levels in long-term follow-up. It has been suggested to consider the effectiveness of allopurinol rather than the other drugs such as beta-blockers, calcium channel blockers, diuretics, ACE and ARBs II in future studies.

Conclusion
According to the results of the present study, allopurinol can play a significant role in reducing UA, 24-hour urine protein, NLR and PLR levels without significant changes in the patients' blood factors. Additionally, 6 months after the start of the intervention, the GFR changes were not significant in two groups.

Limitations of the study
The limitation of the present study was comparatively small sample size. So it is suggested to do more investigations with larger sample size.

Authors' contribution
Conception and design; SM and FKE. Literature search and data acquisition; AM. Drafting the manuscript; MS. Analysis and interpretation of data, critical revision of the manuscript for important intellectual content; SM, FKE and AM. All authors read and approved the final paper.

Conflicts of interest
The authors declare that they have no competing interests.

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

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