Effect of allopurinol on the treatment of chronic kidney disease: a systematic review and meta-analysis

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is defined by glomerular filtration rates (GFR) of less than 60 mL/min per 1.73 m^2 or albumin to creatinine ratios of greater than 30 mg/g in urine for at least three months. Patients with CKD are at risk of developing the condition, leading to end-stage renal disease (ESRD). On the other hand, hyperuricemia can result in renal failure, increased blood pressure, fibrosis, and the progression of failure. In this study, using the meta-analysis method, we are looking to investigate the effect of allopurinol on the treatment of chronic renal failure.

Materials and Methods: In this meta-analysis, which was written based on PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol, International databases including Cochrane, Web of Science, Scopus, PubMed, and Google Scholar search engine were searched. The data were analyzed using STATA (version 14) software, and the significance level of tests was considered $P<0.05$.

Results: In 13 studies with a sample of 1172 people, allopurinol significantly reduced the serum level of uric acid (SMD: -1.28; 95% CI: -1.74, -0.82) more than the control group (SMD: -0.96; 95% CI: -2.09, 0.17). Additionally, allopurinol reduced the systolic blood pressure level by (SMD: -0.32; 95% CI: -0.54, -0.11) mm Hg and it was effective in reducing diastolic blood pressure level by (SMD: -0.39; 95% CI: -0.60, -0.17) mm Hg. However, the difference in scores GFR, proteinuria, cystatin C, before and after allopurinol were not statistically significant. In the control group, the difference in scores before and after the intervention was not significant in any of the above-mentioned cases.

Conclusion: In CKD, allopurinol is effective in reducing blood pressure and uric acid levels. However, due to the limited number of studies and the different type of treatment in the control group of the studied studies, it is suggested to conduct more studies in this field.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID=CRD42022371439, regional ethical code #IR.IAU. NAJAFABAD.REC.1399.140).

Implication for health policy/practice/research/medical education:
In this systematic review and meta-analysis, to find the effect of allopurinol on the treatment of chronic kidney disease, we found, allopurinol is effective in reducing blood pressure and uric acid levels.

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Introduction

Chronic kidney disease (CKD) is a long-term illness marked by a decline in kidney function. Diseases affect millions of people globally, including individuals with diabetes, high blood pressure, and genetic renal disease. According to earlier studies, CKD has affected around 10% of the world's population (1). In China, the overall prevalence of the disease is estimated to be 10.8%,

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implying that 119.5 million people have CKD (2). Other studied showed CKD has a prevalence of 10-13% among the population (3).

In both industrialized and developing countries, diabetes and hypertension are the leading causes of kidney failure (4,5). Glomerular nephritis and obsessive-compulsive disorder are the most common causes of CKD in Asian and Central African countries (6). In addition to the mentioned factors, autoimmune illnesses, systemic infections, urinary tract infections, kidney stones, lower-urinary tract blockage, family history of CKD, renal volume resection following neoplastic involvement, usage of specific medicines, and low birth weight are all clinical risk factors for chronic renal failure (5,7,8).

As mentioned, chronic renal failure is a disorder that leads to high mortality and can impose irreversible effects on patients by lowering their standard of living (9). Patients may present with numerous signs, including an increase in vascular volume, blood potassium, and phosphate, along with metabolic acidosis, hyperparathyroidism, anemia, or high blood pressure. Some of these consequences arise quickly following a loss in renal function (10).

In this study, an evaluation of studies conducted in this field was performed to better understand the association between uric acid concentration and disease progression in patients with renal impairment. The data were compared, and experiments were assessed through a systematic review (11) .The aim of this study was to investigate the effect of allopurinol on patients with chronic kidney failure using a meta-analysis method.

Materials and Methods
Study design
The present study is a meta-analysis examining the role of allopurinol on the treatment of chronic renal failure.

Search strategy
International databases including Cochrane, Web of Science, Scopus, PubMed, and Google Scholar search engine were explored without language and time limitation using standard keywords and MeSH of "Chronic kidney disease, Allopurinol, Chronic renal failure, CKD" and their Persian equivalents to retrieve relevant studies (September 2022). Combinations of the keywords were also searched on the mentioned databases using "AND" and "OR" operators. The initially retrieved studies were entered into EndNote 9 at this stage to detect duplicate studies quickly by referring to the software and have only one study remain from each group of duplicate studies. The list of the references mentioned in all initial studies remaining by the end of PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart was then used for a manual search. The following is an example of search strategy developed for PubMed: (Chronic kidney disease [Title/Abstract] OR chronic renal failure [Title/Abstract] OR CKD [Title/ Abstract]) AND (Allopurinol [Title/Abstract]).

PICO (Patient, Intervention, Comparison, Outcome) components
Patients: Chronic kidney disease, Intervention: Allopurinol, Comparison: A group of renal patients used not allopurinol, Outcome: Renal function.

Inclusion criteria
Studies examining the role of allopurinol on the treatment of chronic renal failure entered this meta-analysis. The intervention group received allopurinol while the comparison group received not allopurinol.

Exclusion criteria
Low-quality studies based on the quality assessment checklist, case report studies, full-text unavailability, and studies that had investigated the influence of allopurinol and other drugs on the treatment of chronic renal failure simultaneously were excluded from the study.

Qualitative assessment of studies
To assess the quality of RCT studies, two researchers used the Cochrane Collaboration's Checklist for Assessing Risk of Bias in Randomized Trials including seven different items each examining one important dimension or type of bias in clinical trials. Each item on the checklist had three options high risk of bias, low risk of bias, and non-applicable. STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist was also conducted for observational studies. The STROBE checklist has 22 sections that cover different sections of a report. In this checklist, the sum of the scores is decisive, therefore a score of 1-15 indicates low quality, 16- 30 indicates average quality and 31-44 indicates excellent quality. The cut-off point in this study was 15 points. After the risk of bias was assessed in all studies, the inconsistencies between the options of items were examined in each study, and all inconsistencies were resolved by reaching an agreement between the two assessors.

Data extraction
The two researchers extracted data from the studies separately to minimize the risk of bias in reports and errors in data collection. Researchers entered the data into a checklist including the name of the researcher, type of study, study title, year, country, mean age, sample size and third researchers examined the extracted data to resolve inconsistencies.

Statistical analysis
Since the primary outcome is quantitative, the effect size of the intervention was calculated. In addition, it was possible to calculate the intra-group mean difference (MD) in the treatment group. The standardized mean difference

(SMD), which is a classic measure of effect size, shows the strength of the relationship between the intervention and the target outcome. Usually, the closer this index (SMD) is to zero, the weaker the relationship. And the closer it is to one or above, the stronger the relationship. If the confidence interval for SMD includes zero, then that relationship is not statistically significant, and vice versa. The studies were merged based on the number of samples, mean, and standard deviation. Cochran's Q test and I^2 index evaluated the heterogeneity. There are three categories for the I^2 index; low heterogeneity (less than 25%), moderate heterogeneity (between 25% to 75%), and severe heterogeneity (over 75%). The fixed-effects model is used for low heterogeneity, and the stochastic-effects model is used for high heterogeneity. Hence, the stochastic-effects model was used in the present study. Data analysis was analyzed by STATA 14, and the significance level of the tests was considered $P < 0.05$.

Results

Selection of studies

In the first stage, 325 articles were found by searching the mentioned databases. By checking the title of the studies, 144 duplicate studies were excluded. The abstracts of the remaining 181 articles were reviewed and 168 articles were excluded based on the exclusion criteria. Finally, the remaining 13 articles entered the qualitative evaluation stage, all of which were of good quality and entered the meta-analysis process (Figure 1).

In 13 studies that were conducted on 1172 people, 593 people were in the control group and 579 people were in the case group, and the reviewed articles were published between 2005 and 2019. The average age of the case group varied from 34 to 72.9 years. On the other hand, in the control group, the average age of the participants varied from 40.1 to 71.4 years. The dose of allopurinol varied from 100 to 300 mg/d. The control group did not receive any drug in seven studies, febuxostat in five studies and placebo in another study. It should be noted that out of a total of 13 articles, four studies were conducted in China, two studies in Spain, two studies in Turkey, two studies in Japan, one study in England, one study in Thailand and one study in South Korea. The minimum follow-up period of the studies was 2 months and the maximum period was 55.9 months (Table 1).

In the group treated with allopurinol, the levels of systolic blood pressure, diastolic blood pressure, and serum uric acid were significantly reduced. However, the difference in glomerular filtration rate (GFR), proteinuria, cystatin C scores before and after allopurinol was not statistically significant. In the control group, we also saw that the difference in the scores before and after the intervention in none of the following cases; diastolic blood pressure, serum uric acid, systolic blood pressure, GFR, proteinuria and cystatin C, was not statistically significant, and in other words, there was no improvement in the failure of all patients in the control group (Table 2).

In the intervention (allopurinol) group, uric acid level was lower (SMD: -1.28; 95% CI: -1.74, -0.82) (Figure 2) than the control group (SMD: -0.96; 95% CI: -2.09, 0.17)
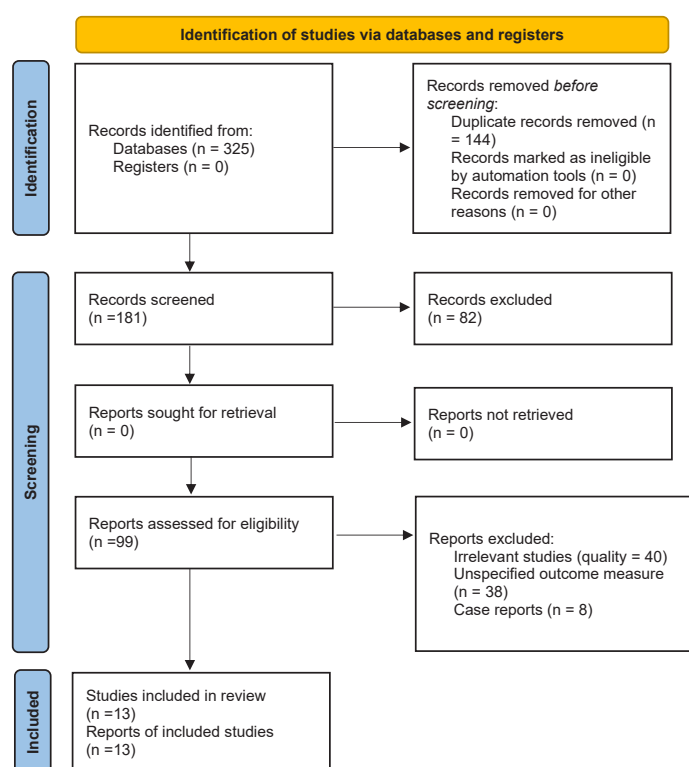

Figure 1. Process of inclusion of studies in systematic review and meta-analysis.

Table 1. Summary of the information available in the reviewed articles

Author, year of publication (ref)	Place	Sample size in case group	Sample size in control group	Dosage	Control group	Mean Age in case group (year)	Mean Age in control group (year)	Follow up (month)
Siu, 2005 (12)	Hong Kong	26	25	Allopurinol 100 or 200 mg daily	No study medication	47.7	48.8	12
Goicoechea, 2010 (13)	Spain	57	56	Allopurinol 100 mg daily	No study medication	72.1	71.4	24
Kao, 2011 (14)	UK	27	26	Allopurinol 300 mg daily	Placebo	70.6	73.7	9
Shi, 2012 (15)	China	21	19	Allopurinol 100-300 mg daily	No study medication	39.7	40.1	6
Sezai, 2015 (16)	Japan	44	43	Allopurinol 200 mg daily	Febuxostat	68.3	68.5	6
Goicoechea, 2015 (17)	Spain	57	56	Allopurinol 100 mg daily	No study medication	72.1	71.4	84
Satrapoj, 2015 (18)	Thailand	44	44	Allopurinol 50 mg daily	No study medication	70.14	-	2
Yelken, 2012 (19)	Turkey	19	19	Allopurinol 150 mg daily	No study medication	34	-	16
Tsuruta, 2014 (20)	Japan	22	51	Allopurinol 200 mg daily	Febuxostat	72.9	67.4	12
Liu, 2019 (21)	China	96	112	Allopurinol 100 mg daily	Febuxostat	53.4	51.79	6
Lee, 2019 (22)	South Korea	40	30	Allopurinol 100-300 mg daily	Febuxostat	62.3	64.3	55.9
Zhang, 2019 (23)	China	87	65	Allopurinol 100-200 mg daily	Febuxostat	61.1	62.6	6
Sezar, 2014 (24)	Turkey	39	47	Allopurinol 1.5 mg/kg/ daily	No study medication	65.9	66.2	12

Table 2. Comparison of scores before and after the intervention in each of the allopurinol and control groups

Group	Variable	SMD	Low limit	Up limit	P value	I² (%)
Intervention	SBP (mm Hg)	-0.32	-0.54	-0.11	0.478	0
	DBP (mm Hg)	-0.39	-0.60	-0.17	1	0
	SUA (mg/dL)	-1.28	-1.74	-0.82	<0.001	90.9
	GFR (mL/min/1.73 m²)	-0.13	-0.31	0.05	0.039	49.2
	Cystatin C (mg/L)	-0.41	-1.78	0.97	<0.001	95.6
	Proteinuria (g/dL)	-0.25	-0.78	0.28	0.001	84.7
Control	SBP (mm Hg)	-0.18	-0.45	0.09	0.733	0
	DBP (mm Hg)	-0.19	-0.46	0.08	0.586	0
	UA (mg/dL)	-0.96	-2.09	0.17	<0.001	98
	GFR (mL/min/1.73 m²)	-0.29	-0.72	0.14	<0.001	90.4
	Cystatin C (mg/L)	-0.09	-0.37	0.19	0.820	0
	Proteinuria (g/dL)	-0.38	-0.76	0	0.046	67.5

SBP; Systolic blood pressure, DBP; Diastolic blood pressure, GFR; Glomerular filtration rate, SUA; Serum uric acid; SMD, standardized mean difference.

(Figure 3). It means that allopurinol administration decreases the level of uric acid by -1.28 SMD and except a study by Tsuruta et al in 2014, others reported that allopurinol significantly decreases the level of uric acid.

In 13 studies with a sample of 1172 people, allopurinol significantly reduced the serum level of uric acid (SMD: -1.28; 95% CI: -1.74, -0.82). Furthermore, allopurinol reduced the systolic blood pressure level by (SMD: -0.32; 95% CI: -0.54, -0.11) mm Hg and it was effective in reducing diastolic blood pressure level by (SMD: -0.39; 95% CI: -0.60, -0.17) mm Hg. We discuss a number of systematic review and meta-analysis studies that have been published in the field of investigating the effect of allopurinol on blood pressure and hyperuricemia.

In a 2014 systematic review conducted by Fleeman et al in England, researchers investigated the effect of allopurinol on the treatment of CKD. The results of this study showed that there is very little evidence showing the effect of allopurinol on reducing the progression of CKD or cardiovascular events (25). In a 2022 meta-analysis by Wu et al three studies were investigated and

the results showed that allopurinol does not significantly improve kidney function and albuminuria in diabetic kidney patients. The results of these two studies are not consistent with the results of our research (25, 26). In a 2022 meta-analysis study, Luo et al investigated the effect of allopurinol on renal function in diabetic patients. They reviewed 10 clinical trial studies and concluded from a total of 866 subjects that allopurinol was more effective in reducing serum uric acid levels compared to standard treatment or placebo (26).

In 2012, Agarwal and colleagues conducted a meta-analysis study in which they investigated the effect of allopurinol on blood pressure levels. In this meta-analysis, 10 studies with a sample size of 738 people were examined and the researchers came to the conclusion that compared to the control group, the patients in the allopurinol group had a 3.3 mm Hg decrease in their systolic blood pressure and a 1.3 mm Hg in their diastolic blood pressure level. These changes were statistically significant which is completely consistent with the results of the current research (27). In 2020, in a systematic review study that
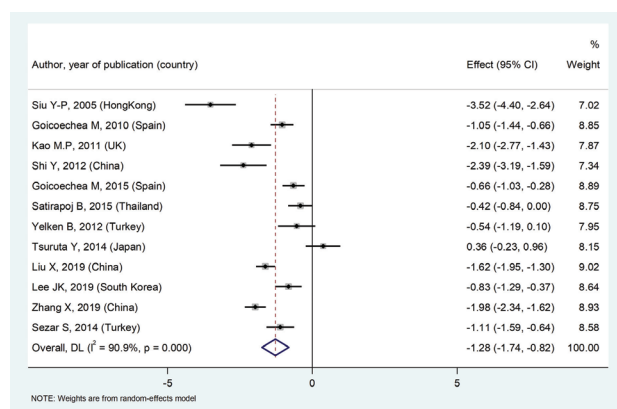

Figure 2. Forest plot showing effect of allopurinol on serum uric acid concentration.
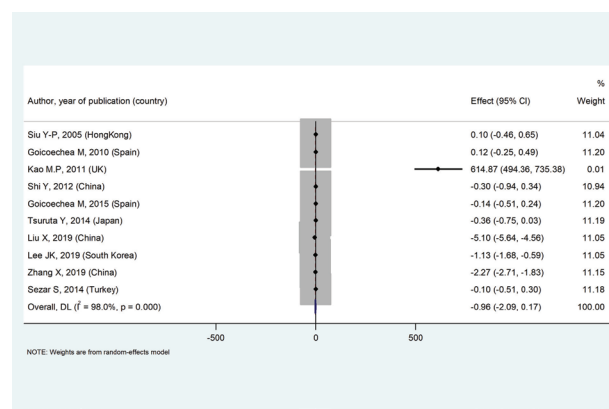

Figure 3. Forest plot showing serum uric acid levels changes in the control group.

was conducted on three articles, Hu et al compared the effect of allopurinol and febuxostat on hyperuricemia. In this study, articles whose follow-up period was more than 12 months were examined. According to the results of this research, patients in the febuxostat group compared to allopurinol group patients had higher GFR, decreased risk of kidney disease progression, and decreased serum uric acid levels(28). They discussed the effect of allopurinol and febuxostat on hyperuricemia and found in four studied studies that in the follow-up of one to three months, the change in serum uric acid level was significantly higher in the febuxostat group than in the allopurinol group (29). A 2013 meta-analysis study by Faruque et al compared the effects of allopurinol and febuxostat on chronic gout. The researchers in this research, by reviewing five studies, concluded that the probability of achieving serum uric acid less than 6 mg/dL was higher in patients receiving febuxostat than those receiving allopurinol (30). In the above three studies, febuxostat was more effective than allopurinol in reducing uric acid levels. While in the current meta-analysis, the opposite was true.

Conclusion

Based on the results of this study, we concluded that allopurinol was effective in reducing systolic and diastolic blood pressure levels as well as uric acid. In addition, we saw that allopurinol had the greatest effect in reducing the level of uric acid and the least effect in reducing the level of systolic blood pressure. Also, the effect of febuxostat in reducing uric acid level was lower than allopurinol. But in the control group, there was no improvement in any of the variables of diastolic blood pressure, serum uric acid, GFR, proteinuria, cystatin C, and systolic blood pressure. Due to the limited number of published studies in this field, it is suggested to conduct more studies in this regard in the future and to remove the limitations of the current study.

Limitations of the study

Due to the limited number of studied studies and the diversity of allopurinol dosage, average age and duration of follow-up in them, we could not have an analysis based on these variables. In addition, in some countries, no study had been conducted in this regard, so it is recommended that researchers pay attention to this issue in the implementation of future studies.

Authors' contribution

Conceptualization: HN; Methodology, data curation and project administration: SP, HN and AP; Validation, formal analysis, investigation, visualization, and supervision: HN and SP; Resources and funding Acquisition: SP and AP; Writing—original draft preparation: HN, SP, AP and SG; Writing—review and editing: NP, SJ, HN, AP and SG.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42022371439). The institutional ethical committee of Islamic Azad University, Najafabad Branch, Isfahan, Iran, approved all study protocols (ethical code#IR.IAU.NAJAFABAD. REC.1399.140). This study was extracted from M.D., thesis of Shabnam Pouladvand at this university. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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