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The effect of allopurinol on serum uric acid levels in patients with diabetic nephropathy; a systematic review and meta-analysis on randomized clinical trials

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Abstract

Introduction: The correlation between hyperuricemia and chronic kidney disease (CKD) is an approval issue; this study aimed to evaluate the effect of allopurinol on serum uric acid levels in patients with diabetic nephropathy, with the review of randomized clinical trials (RCTs).

Materials and Methods: This meta-analysis study was conducted on RCTs in diabetic nephropathy patients, which evaluated the effect of allopurinol on serum uric acid levels. Data were collected by searching international databases and Google Scholar search engines until May 2023. STATA 14 software and the random effects model were conducted to analyze the data. A P-value less than 0.05 was considered significant.

Results: In this study, five studies with a sample size of 942 patients were assessed. The effect of allopurinol on serum uric acid in comparison to the placebo group deduced that the standard mean difference between the allopurinol group and placebo group was -1.55 mg/dL, which was statistically significant (CI: -2.07 to -1.02).

Conclusion: Allopurinol through its uric acid lowering effect would be beneficial for patients with diabetic nephropathy in preventing the progression of CKD.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023412051).

Keywords: Allopurinol, Uric acid, Diabetic nephropathy, Diabetic kidney disease

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Introduction

The global prevalence of diabetes increased rapidly over the past three decades, and diabetic kidney disease is a common vascular complication in these patients (1). Clinical treatment of diabetic nephropathy is of great social importance due to its widespread use and enormous economic costs. Lifestyle and diet guidelines are two commonly recommended by the World Health Organization (WHO) to improve the clinical outcomes of these patients (2). A review of the literature demonstrated that these treatments have not achieved significant improvement in the treatment of diabetic nephropathy patients; and this issue has led scientists to explore promising drug treatments (3).

Hyperuricemia is defined as an increase in serum uric acid, and today it has taken a worldwide growing trend (4,5). Previous studies have reported that hyperuricemia is an independent risk factor for the progression of diabetic nephropathy (6), and its correlation with kidney dysfunction in patients with diabetes has been proven (7,8).

Allopurinol is a xanthine oxidase inhibitor and one of the first-line drugs in the treatment of hyperuricemia; which can inhibit purine synthesis and impact uric acid production (9,10). American College of Rheumatology (ACR) announced that allopurinol is one of the first-line drugs for patients with chronic kidney disease (CKD), especially in those with a stage of more than three (10).

Objectives

This meta-analysis study aimed to evaluate the effect of allopurinol on serum uric acid levels of patients with

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Implication for health policy/practice/research/ medical education

In a meta-analysis study, we found that allopurinol reduced the serum uric acid level, and regarding the approval of the correlation between hyperuricemia and chronic kidney disease in previous studies, it seems that allopurinol can prevent diabetic nephropathy by its urate-lowering effect. Therefore, it would be beneficial in preventing kidney disease in patients with diabetes mellitus.

diabetic nephropathy in a review of clinical trial studies.

Method and Materials

Study design

This study is a systematic review and meta-analysis on randomized clinical trials (RCTs), which aimed to evaluate the effect of allopurinol on serum uric acid levels in diabetic patients with kidney disease and nephropathy. All included article in this review research were RCTs. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline was conducted to search the literature (11). The study protocol was registered on the PROSPERO website (ID: CRD42023412051).

Search strategy

To make a complete search, international databases, including Embase, Cochrane library, Web of Science, Scopus, PubMed, and national databases such as SID, Magiran, Civilica, and Google scholar search engines were conducted with standard keywords and using Medical Subject Headings (MeSH). Allopurinol, Uribenz, serum uric acid, urate, trioxopurine, diabetic kidney disease, diabetic glomerulosclerosis, diabetic nephropathy, diabetic renal disease, diabetic renal injury, and clinical trials, were the most common keyword used in the search strategy. Search strategy was performed without any language and location limitations.

To make combination sentences, combination keywords, including AND and OR were used to make a better search in the noted databases. Search strategy was performed without language and location limitations and started from the initial to May, 2023.

The following string shows search strategy used in PubMed database: ((((((((((Allopurinol[Title/Abstract]) OR (Uribenz[Title/Abstract])) AND (Serum uric acid[Title/Abstract])) OR (Urate[Title/Abstract])) OR (Trioxopurine[Title/Abstract])) AND (Diabetic kidney disease[Title/Abstract])) OR (Diabetic Glomerulosclerosis[Title/Abstract])) OR (Diabetic nephropathies[Title/Abstract])) OR (Diabetic renal disease[Title/Abstract])) OR (Diabetic renal injury[Title/Abstract])) AND (Clinical trials[Title/Abstract])) OR (Randomized Clinical trials[Title/Abstract]).

PICO (population, intervention, comparison, outcome)

Population or patients: diabetic patients without considering diabetes type with kidney disease or nephropathy; intervention: allopurinol; comparison: placebo; outcome: serum uric acid.

Inclusion criteria

Randomized clinical trials assessed the effect of allopurinol on serum uric acid levels in diabetic nephropathy patients.

Exclusion criteria

Exclusion criteria included studies, which met lacking required data, duplicate, design except for clinical trials, unavailable full text, low-quality, and qualitative assessment studies. Additionally, studies evaluating the effect of drugs other than allopurinol on serum uric acid in diabetic nephropathy patients or studies evaluating the effect of allopurinol on serum uric acid in patients other than diabetic nephropathy patients were excluded.

Quality assessment

Two researchers separately assessed the initial articles based on Cochrane guidelines for RCTs; this checklist included seven items that rated a dimension or type of major bias in clinical trials. Each item has three categories, including low, high, and unclear risk. In cases of discrepancy, the discussion has been resolved by reaching a consensus on a single option. Studies in which four items or more met low-risk bias were considered high-quality and included in the study (12). All entered articles in this meta-analysis study had good quality.

Data extraction

To avoid data collection bias risk, two reviewers extracted the required data separately by a checklist, including the authors' names, study design, intervention period, mean age, mean diabetes duration, diabetes type, sample size, publication year, country, and standard mead difference between allopurinol and placebo group. In cases of inconsistencies, the third researcher reassessed the data.

Statistical analysis

Due to being quantitative nature of serum uric acid measurement in this study, the effect size was considered. The standardized mean difference (SMD) is a classic effect-size parameter that indicates the strength of the association. Extracted studies got pooled based on the sample size, mean, and standard deviation. After the heterogeneity assessment of the studies using the I2 index, a random-effect model was used. STATA 14 software and the random effects model were used to analyze the data. A *P* value less than 0.05 was considered significant.

Results

In this study, all RCTs studies which analyzed the effect of allopurinol on serum uric acid levels in patients with diabetic nephropathy were systematically reviewed and meta-analyzed based on the PRISMA guidelines. In

the initial search, 505 studies were identified. Then 247 duplicate studies articles were removed after reviewing the title. When we reviewed the abstract of 258 remaining articles, 104 were excluded, since they did not meet the inclusion criteria. Out of 154 resting articles assessed for eligibility, 145 were excluded based on exclusion criteria. Finally, we analyzed the five remaining studies (Figure 1).

In this review study, five RCTs articles from five countries and five continents were included. Total sample size was 915 (479 in the allopurinol group versus 446 in the placebo group) diabetic nephropathy patients. Regarding sample size, the study by Doria et al (13) in 2020 in the multi centers, including the United States, Canada, and Denmark was the biggest and included 502 patients. Also, the study by Momeni et al (14) in Iran was the smallest and evaluated 40 people. In terms of diabetes type, two studies were conducted on type 1, one study on type 2, and two other studies considered no diabetes type. Other studies information summarized in Table 1.

The effect of allopurinol on serum uric acid in comparison to the placebo group deduced that the standard mean difference (SMD) between the allopurinol group and placebo group was -1.55 mg/dL, which was statistically significant considering the confidence interval (CI) [-2.07 to -1.02] and *P* value less than 0.01 (Figure 2).

Figure 3 indicates the publication bias of the reviewed article in this study. According to this pyramid and the place of studies, no publication bias was found for this meta-analysis study. Studies that evaluate the positive direct effect of allopurinol on serum uric acid levels and those that assess the negative inverse effect of allopurinol on serum uric acid levels had a publication chance, and the literature review covered them.

Figure 4 demonstrates the effect plot of reviewed studies. Results showed that the study by Liu et al in 2015 (15) had the greatest impact on the results, and study by Doria et al in 2020 had the greatest impact on the heterogeneity (15).

Sensitivity plot of the entered studies showed that the greatest role in the reduction of serum uric acid compared to SMD was related to the available data in the study by Liu et al (15) and the greatest role in increasing was related to Doria et al study (13). Three other studies were approximately close to SMD (Figure 5).

The risk bias of the studied articles is shown in Table 2. For each included RCT study, we review the authors' judgment regarding the risk of bias position.

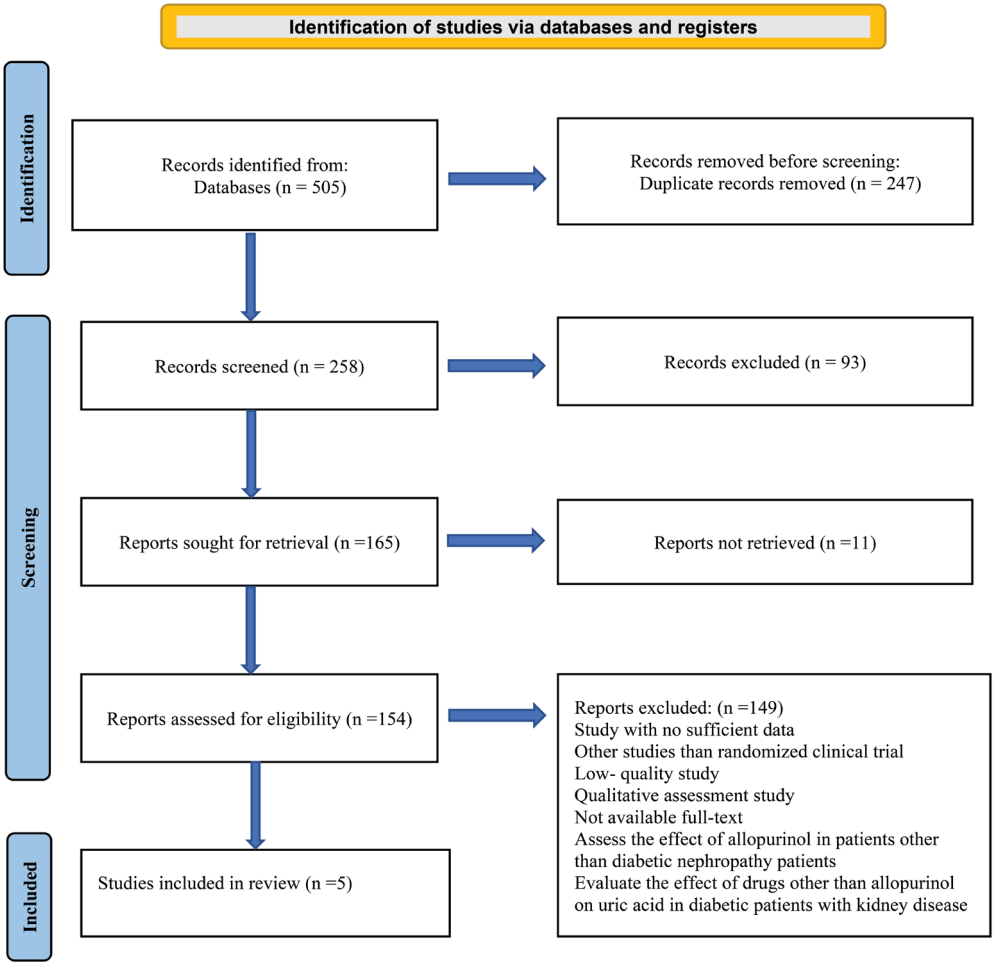

Figure 1. PRISMA flow diagram showing the number of studies identified, screened, eligibility, and included in this review.

Table 1. Baseline characteristic and summary of reviewed research in this systematic review and meta-analysis study

First author	Publication Year	Country	Age (y)[a]	Intervention period (mon)	Control group	Allopurinol dosage (mg)	Allopurinol group (N)	Placebo group (N)	Male percent No. (%)	Allopurinol SUA (mg/dL) Mean difference[a]	Placebo SUA (mg/dL) Mean difference[a]
Doria (13)	2020	USA Canada Denmark	51.1±10.9	36	Placebo	100-400 based on GFR	267	236	351 (66.2)	-2.2±0.21	0±0.23
Liu (15)	2015	China	50.5±10.7	36	Placebo	NA	82	70	70 (46)	-1.17±0.05	0.25±.04
Momeni (14)	2010	Iran	57.7±10.5	4	Placebo	100	20	20	18 (45)	-0.65±0.65	-0.06±1.33
Li (16)	2018	China	48.65±9.7	6	Placebo	300	80	80	91 (56.8)	-1.6±0.72	-0.33±1.41
Mardani (17)	2021	Iran	65.33±10.5	6	Placebo	100	30	30	32 (53.3)	-2.15±0.56	-0.13±0.53

SUA, Serum uric acid; N, Frequency; NA, Not available.

[a] Dara are expressed as mean ± standard deviation

Discussion

In this meta-analysis study, we reviewed five clinical trial studies on patients with diabetic nephropathy, and the results showed that the effect of allopurinol on serum uric acid compared to the placebo was statistically significant lowering. According to evidence from clinical trial studies, our study provided evidence of the efficacy and safety of allopurinol in patients with diabetic nephropathy. This study is in line with the meta-analysis study by Lou et al, they reported that allopurinol effectively reduced serum uric acid levels and protected renal function in diabetic nephropathy patients (18). Wu et al in a meta-analysis study consistent with our results stated that allopurinol significantly reduced serum uric acid (3). Previous studies showed that hyperuricemia is significantly associated with CKD (19); A study demonstrated that diabetic nephropathy prevalence in patients with hyperuricemia was higher than in patients with the normal uric acid level (20). Allopurinol as a first-line treatment for urate-lowering due to higher cardiovascular safety is recommended for CKD patients with hyperuricemia, especially in high-grade CKD (10). Furthermore, allopurinol was reported as a safe drug regarding side effects such as vomiting, rash, diarrhea, and changes in liver test function in previous clinical trial study (21). Several studies reported that the control of serum uric acid would be able to prevent early diabetic nephropathy and postpone the progress of kidney damage (4, 5, 19, 22). Our results, consistent with previous meta-analysis, showed that allopurinol reduced the uric acid level. Due to the approval of the correlation between

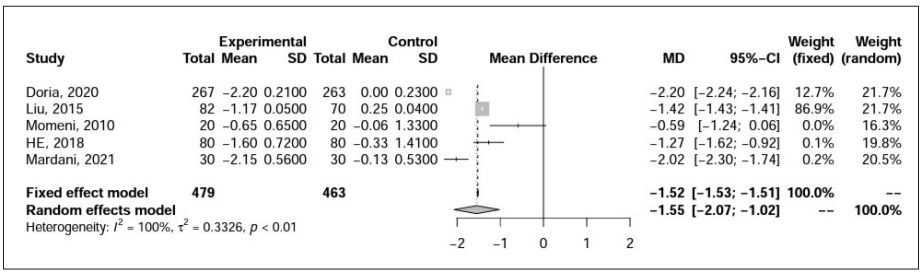

Figure 2. Forest plot indicating the effect of allopurinol on serum uric acid in comparison with the placebo group

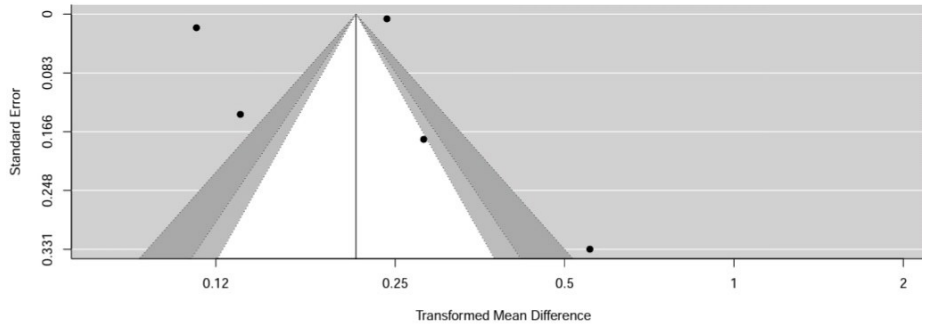

Figure 3. Publication bias plot of included study.

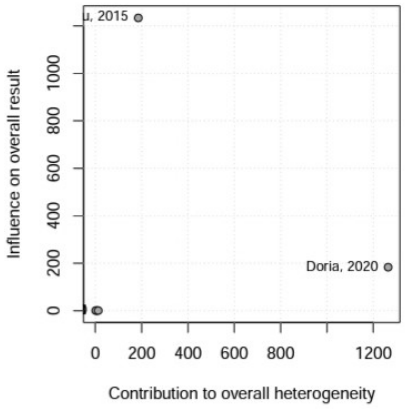

Figure 4. Effect plot of reviewed study.

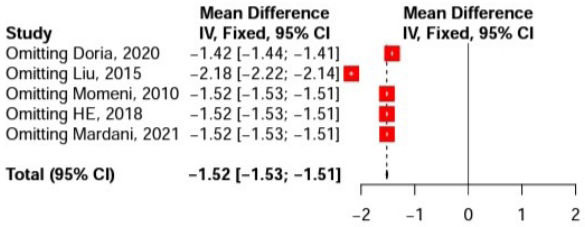

Figure 4. Sensitivity plot of the entered studies to this systematic review and meta-analysis.

hyperuricemia and CKD in previous studies, it seems that allopurinol can prevent diabetic nephropathy by urate-lowering, and it would be beneficial in preventing kidney disease in patients with diabetes.

Conclusion

Results showed that administration of allopurinol in patients with diabetic nephropathy is effective to lower serum uric acid; therefore, due to the approval of the correlation between hyperuricemia and CKD in previous studies, we concluded that allopurinol through serum uric acid lowering would be beneficial for patients with diabetic nephropathy in preventing progressing kidney disease.

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Authors' contribution

Conceptualization: JK, SA and SD.
Methodology: NA and FBA.
Validation: NP and MHT.
Formal analysis: RS and JK.
Investigation: HM and FBA.
Resources: SD and NA.
Data curation: MHT and SA.
Writing–original draft preparation: RS, JK, MHT, SA and NP.
Writing–reviewing and editing: HM, NA, FBA and SD.
Visualization: SD and FBA.
Supervision: JK.
Project Management: HM.

Conflicts of interest

There are 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 with (ID: CRD42023412051) https:// https://www.crd.york.ac.uk/prospero/#recordDetails). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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Table 2. Risk bias of the studied articles

First author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Sample size calculated bias
Doria (13)	Low	Low	Low	Low	Low	Low	Low
Liu (15)	Low	Unclear	High	Low	Low	Low	High
Momeni (14)	Low	Unclear	Low	Low	Low	Low	Low
Li (16)	Unclear	Low	Unclear	Low	Low	Low	Unclear
Mardani (17)	Low	Low	Low	Unclear	Low	Low	Low

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18. Luo Q, Cai Y, Zhao Q, Tian L, Liu Y, Liu WJ. Effects of allopurinol on renal function in patients with diabetes: a systematic review and meta-analysis. Ren Fail. 2022;44:806-14. doi: 10.1080/0886022x.2022.2068443.
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