JPPT | Systematic Review

Efficacy and Safety of Allopurinol on Chronic Kidney Disease Progression: A Systematic Review and Meta-Analysis

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OBJECTIVE Hyperuricemia is associated with the progression of chronic kidney disease (CKD). Whether urate-lowering treatment with allopurinol can delay disease progression remains controversial.

METHODS Relevant databases were searched. Randomized clinical trials comparing the efficacy and safety of allopurinol in patients with CKD were selected. The primary outcomes were changes in serum uric acid concentration and estimated glomerular filtration rate (eGFR). Random-effects modeling was used to calculate the standard mean difference (SMD) with 95% CIs.

RESULTS Four trials enrolling 698 participants were included. All were 2-arm parallel trials with a mean duration follow-up of 22.5 months. Congenital anomalies of the kidney and urinary tract were the most common cause of CKD in children, whereas diabetes was the leading cause of CKD in adults. Allopurinol significantly increased the eGFR compared with control groups (SMD, 2.04; 95% CI, 0.60–3.49; p = 0.005; I^2 = 98.23%). Allopurinol led to a significant decrease in serum uric acid concentration compared with the control group (SMD, −5.16; 95% CI, −8.31 to −2.01; p = 0.001; I^2 = 98.80%). No significant difference in adverse effects was identified between treatment and control groups.

CONCLUSIONS Allopurinol treatment in patients with CKD and hyperuricemia slows the decline in eGFR as compared with placebo, without risk of increased adverse effects.

ABBREVIATIONS AE, adverse event CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trial; SCr, serum creatinine concentration; SMD, standard mean difference.

KEYWORDS adverse events; allopurinol; chronic kidney disease; estimated glomerular filtration rate; uric acid

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Introduction

Hyperuricemia is associated with an increased risk for chronic kidney disease (CKD) progression.[1–4] Studies have also shown that high serum uric acid concentration is a strong and independent predictor of the decline in estimated glomerular filtration rate (eGFR) in patients with CKD.[5–7] Observational studies have also shown serum uric acid concentration increases linearly with decreasing eGFR because of reduced excretion.[8] More recent studies suggest that urate-lowering treatment with allopurinol could slow the progression of CKD over a short treatment follow-up period, beyond the effect on lowering blood pressure, especially in patients with mild to moderate CKD, stage 1 to 3.[9–12] However, other studies did not show that allopurinol treatment would attenuate the decline in eGFR over a longer follow-up in patients with stage 3 or 4 CKD.[13–16] Thus, it is unclear whether urate-lowering treatment with allopurinol plays a potential benefit in declining the progression of kidney disease. To our knowledge, 6 meta-analyses[7–12] have previously focused on the treatment of hyperuricemia in patients with CKD but none have included children with CKD.[17] The present systematic review and meta-analysis of randomized controlled trials (RCTs) was designed to test the hypothesis that allopurinol treatment would attenuate the decline in eGFR in patients with renal failure and to include children who are at risk of CKD disease progression. Confirming such a role for allopurinol would seem useful in the further management of CKD.

Methods

This systematic review and meta-analysis was conducted according to the recommendation of Cochrane Collaboration and written in accordance with the Preferred Reporting Items for Systematic Reviews

and Meta-Analysis (PRISMA) statement for reporting systematic reviews.[18] It was registered in PROSPERO (CRD42022371979).

Literature Search. We searched PubMed, Embase, and Scopus without language restrictions from inception to November 2022 for RCTs that compared the efficacy and safety of allopurinol versus placebo for the treatment of hyperuricemia in patients with CKD. The search terms were *uric acid*, *hyperuricemia*, *allopurinol*, *CKD*, *renal failure*, and *adverse events (AEs)*. In addition, the reference lists of eligible studies as well as review articles on allopurinol and CKD were also manually searched.

Data Extraction and Quality Assessment. The reviewers who screened the studies performed data extraction. The extracted data from each article included first author, publican year, participant age of patient, number of patients in each group, systolic and diastolic blood pressures, CKD stage, study design and level of blinding, serum uric acid concentrations, eGFR before and after intervention, allopurinol dose, treatment duration, and AEs. eGFR was calculated with the Schwartz formula that uses height (H), serum creatinine concentration (SCr; mg/dL), and an empirical constant (K) in children and adolescents as follows[19]:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = \text{KH/SCr.}$$

The value of K varies as a function of age and sex is 0.33 in preterm infants, 0.45 in full-term infants, 0.55 in children and adolescent girls, and 0.70 in adolescent boys.

Two authors (FGS, FA) independently reviewed the title and abstracts of all studies for eligibility. The third reviewer resolved any disagreements in the data extraction. Duplicate articles, articles with insufficient data, observational studies, and articles in abstract forms, letters, case reports, editorials, or comments were excluded. The risk of bias was assessed by using the Cochrane Collaboration risk of bias tool.[20,21] Random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other biases were evaluated for each study. Items were scored as "low," "unclear," or "high" risk of bias.

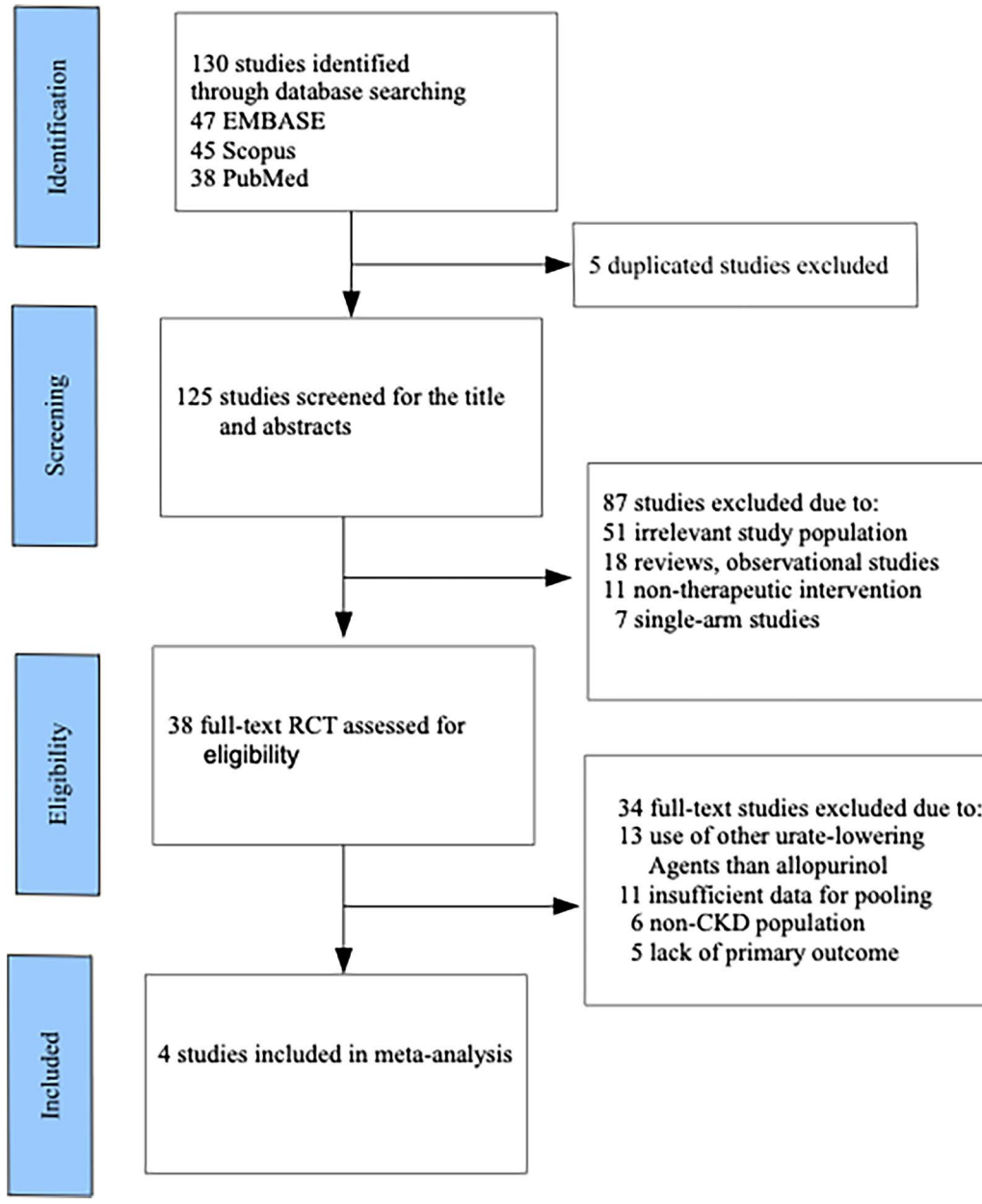
Inclusion and Exclusion Criteria. We included RCTs comparing allopurinol therapy with placebo or conventional treatment in patients with CKD without age restriction that reported any of the outcomes of interest including serum level of uric acid, eGFR, and any AEs considered to be related to the use of allopurinol. We excluded studies enrolling patients with gouty arthritis and tumor lysis syndrome. Also excluded were studies with insufficient data to calculate standard mean difference (SDM) and 95% CI.

Statistical Analysis. SMD and 95% CIs were used to determine the difference of serum uric acid concentration and eGFR between control and intervention groups. The Cochran Q statistic and inconsistency index (I2) were used to assess the heterogeneity of effect size among studies. If I2 was more than 50%, and the value was less than 0.05, heterogeneity was considered significant. When there was significant heterogeneity, the random-effects model was used. Sensitivity analysis was performed to assess the stability of the results by sequential omitting of individual studies in the meta-analysis. Publication bias was evaluated with Egger linear regression test. Statistical analysis was performed with the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ). Statistical significance was defined as p value less than 0.05.

Results

Literature Search. The search identified 130 studies, among which 5 were duplicates. Subsequently, 87 studies were excluded after screening for titles and abstracts, leaving 38 studies for full-text screening. Finally, 4 eligible full-text RCT articles with a total of 698 participants were included in the meta-analysis. Figure 1 shows the literature search and screening process. The 4 included trials[13,17,22,23] originated from 6 different countries including Australia, China, Spain, Turkey, Iran, and the United States. Three trials[13,22,23] were from a single center. The mean age was 47.7 years. All 4 eligible RCTs were 2-arm parallel trials. One of the 4 included trials exclusively reported on the effects of allopurinol in children with CKD.[17] All 4 trials had relatively small sample sizes ranging from 70 to 363 participants with a mean follow-up duration of 22.5 months ranging from 4 to 36 months. Congenital anomalies of the kidney and urinary tract were the most common causes of CKD stage 1 to 3 in children,[17] whereas diabetic kidney disease was the most dominant cause of CKD in adults. Three trials were reported on the CKD stage.[13,17,23] Two of these trials enrolled adults with CKD stage 3 or 4[13,23] and 1 trial included children with CKD stage 1 to 3.[17] All 4 trials reported on the primary outcomes of interest as defined by changes in eGFR and serum uric acid values from baseline and all reported on the incidence of AEs. Table 1 presents the demographic and clinical characteristics of the included studies at the baseline. The study by Liu et al[22] had a high risk of bias for blinding participants and personnel because of the open-label method in the design of the study. The studies by Goicoechea et al,[23] Liu et al,[22] and Ghane Sharbaf and Assadi[17] had an unclear risk of bias for allocation concealment. All included studies had a low risk of bias for sequence generation, incomplete outcome data, selective reports, and other biases. Table 2 presents the effect of allopurinol therapy on the study outcomes. The studies by Goicoechea et al,[23] Liu et al,[22] and Badve et al[13] were judged to be at low risk of bias and that of Ghane Sharbaf and Assadi[17] was

Figure 1. Flow diagram of study selection.



CKD, chronic kidney disease; RCT, randomized controlled trial.

judged to beat unclear bias for outcome assessor blinding as shown in Table 3.

Change in eGFR. All 4 trials compared eGFR between the allopurinol (n = 458) and the placebo (n = 340) groups. Random-effects modeling in meta-analysis confirmed that allopurinol significantly increased the eGFR compared with control groups (SMD, 2.04; 95% CI, 0.60–3.49; p = 0.005; I^2 = 98.23%). The Forrest plot is shown in Figure 2. In the study by Ghane Sharbaf and Assadi,[17] allopurinol treatment in children with CKD stage 1 to 3 for a period of 4 months led to an increase in eGFR by 16.3 mL/min/1.73 m^2 (21.4%, p < 0.001) (Table 2).[17]

Change in Serum Uric Acid Concentration. All 4 RCTs investigated the change in serum uric acid levels between the allopurinol treatment (n = 358) and the control (n = 340) groups. A meta-analysis, using random-effects modeling, suggested that allopurinol

Table 1. Demographic and Clinical Characteristics of Participants at Baseline. Plus-minus values are mean ± SD

Author	Badve[13]	Ghane Sharbaf[17]	Liu[21]	Goicoechea[22]
Country of origin	Australia	Iran/USA	China	Spain
Publication year	2020	2018	2015	2010
Age, mean, yr	62.4	6.3	50.5	71.8
CKD cause	Type-2 DM Non-DM	CAKUT, TID, GN	Type-2 DM	DM, TID, HTN, PKD
Sample size, N	363	70	176	113
Study design	2-arm parallel RCT	2-arm parallel RCT	2-arm parallel RCT	2-arm parallel RCT
Intervention/control, n	181/182	38/32	82/70	57/56
CKD stage	3–4	1–3	NR	3–4
Systolic BP, mm Hg	138.8 ± 18	115.9 ± 9.8	121 ± 8.0	NR
Diastolic BP, mm Hg	76.8 ± 11	62 ± 1.5	74 ± 6	NR
Allopurinol dose, mg	100–300	5 mg/kg	100	100
BP medication	ACEI or ARB	ACEI	No BP medication	NR
Treatment duration, mo	26	4.0	36	24
Serum UA, mg/dL	8.2 ± 1.8	6.7 ± 1.2	7.48 ± 0.2	7.80 ± 2.1
eGFR, mL/min/1.73 m^2	31.6 ± 11.7	76.2 ± 12.3	90.1 ± 17.5	40.7 ± 11.2

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; BP, blood pressure; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HTN, hypertension; NR, not reported; PCKD, polycystic kidney disease; RCT, randomized controlled trial; TID, tubulointerstitial nephritis; UA, uric acid

Table 2. Effect of Allopurinol on Primary and Secondary Outcomes

Author	Badve[13]	Ghane Sharbaf[15]	Liu[19]	Goicoechea[20]
Change in serum UA, SMD, mg/dL	−2.9*	−1.5*	−1.97†‡	−1.8§
Change in eGFR, SMD, mL/min/1.73 m^2	−3.33¶	16.3*	0.8†‡	1.4§
Change in systolic BP, SMD, mm Hg	Data NR¶	−8*	3.0†	NR
Change in diastolic BP, SMD, mm Hg	Data NR¶	−6*	1.04†	NR
Adverse events, n	Skin allergy, 6	No adverse events	GI symptoms, 3	GI symptoms, 7

BP, blood pressure; eGFR, estimated glomerular filtration rate; NR, not reported; SMD, standard mean difference; UA, uric acid

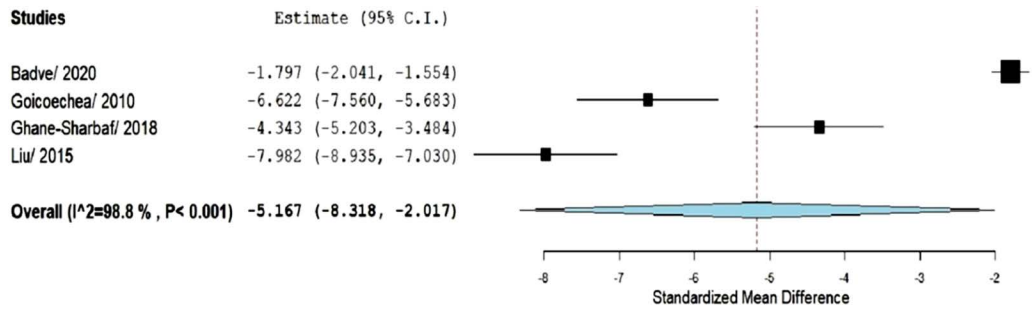
* $p < 0.01$.
† $p < 0.001$.
‡ Data converted from µmol/L to mg/dL for consistency.
§ $p = 0.016$.
¶ $p > 0.05$.
# Values converted from µmol/L to mg/dL for consistency.

therapy resulted in a significant decrease in serum uric acid concentration compared with the control group (SMD, −5.16; 95% CI, −8.31 to −2.01; $p = 0.00$; $I^2 = 98.80\%$). The Forest plot for serum uric acid concentration is shown in Figure 3. Treatment with allopurinol, over a 4-month period, also resulted in a significant increase in serum uric acid concentration by 1.5 mg/dL (−22.4%, $p < 0.001$) (Table 2).[17]

Table 3. Risk of Bias of the Included Study

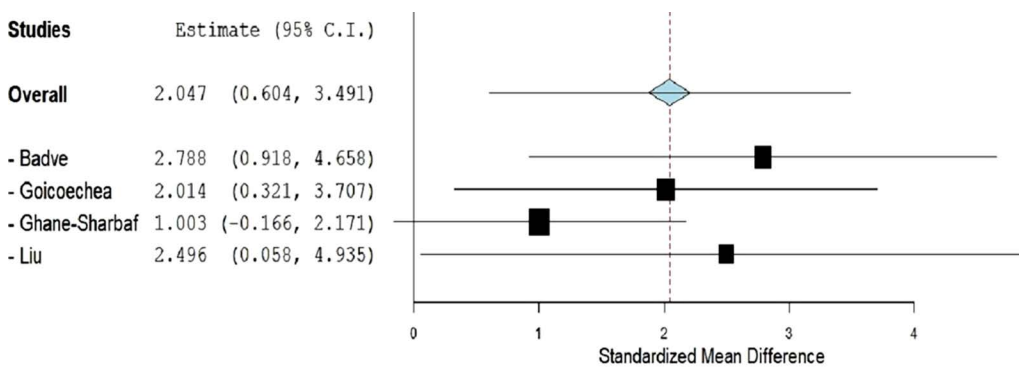
First Author (yr)	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Reporting/ Other Bias
Badve[13] (2020)	Low	Low	Low	Low	Low	Low
Goicoechea[23] (2015)	Low	Unclear	High	Low	Low	Low
Ghane Sharbaf[17] (2018)	Low	Unclear	Low	Unclear	Low	Low
Liu[40] (2015)	Low	Unclear	High	Low	Low	Low

Figure 2. Forest plot calculating the SMD for eGFR. Random-effects modeling in meta-analysis confirmed that allopurinol significantly increased the eGFR compared with control groups (SMD, 2.04; 95% CI, 0.60–3.49; p = 0.005; I^2 = 98.23%).



eGFR, estimated glomerular filtration rate; SMD, standardized mean difference.

Figure 3. Forest plot calculating the SMD for serum uric acid concentration. Treatment with allopurinol over a 4-month period also resulted in a significant increase in serum uric acid concentration by 1.5 mg/dL (−22.4%; p < 0.001).

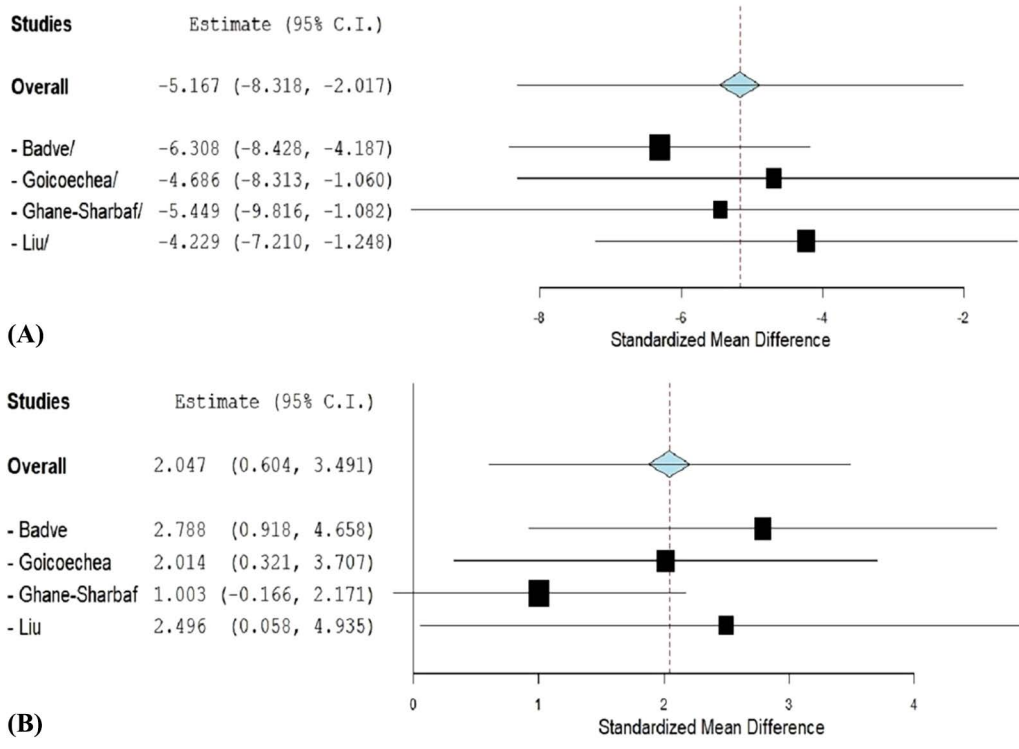


SMD, standardized mean difference.

Sensitivity Analysis. Sensitivity analysis was done to evaluate probable sources of heterogeneity. In our analysis, a significant change in the direction of pooled SMD for eGFR was observed after excluding the study of Ghane Sharbaf and Assadi[17] in the data analysis (SMD, 1.003; 95% CI, −0.16 to 2.17; p = 0.09) (Figure 4B).

However, in the sensitivity analysis for serum uric acid concentration, a significant change in the direction

Figure 4. (A) Sensitivity analysis of included studies for eGFR showing a significant change in the direction of pooled SMD for eGFR after excluding the study of Ghane Sharbaf and Assadi[17] from the data analysis. (B) Sensitivity analysis of included studies for serum uric acid demonstrating a significant change in the direction of pooled SMD for uric acid concentration after excluding the study of Ghane Sharbaf and Assadi[17] from the data analysis.



eGFR, estimated glomerular filtration rate; SMD, standardized mean difference.

of pooled SMD was not observed. Forrest plots are shown in Figure 4B.

Publication Bias. Begg funnel plot and Egger regression test were used to verify the publication bias of the included studies. The Egger test showed significant asymmetry for eGFR (p = 0.04) (Figure 5A) but not for serum uric acid (p = 0.06) (Figure 5B).

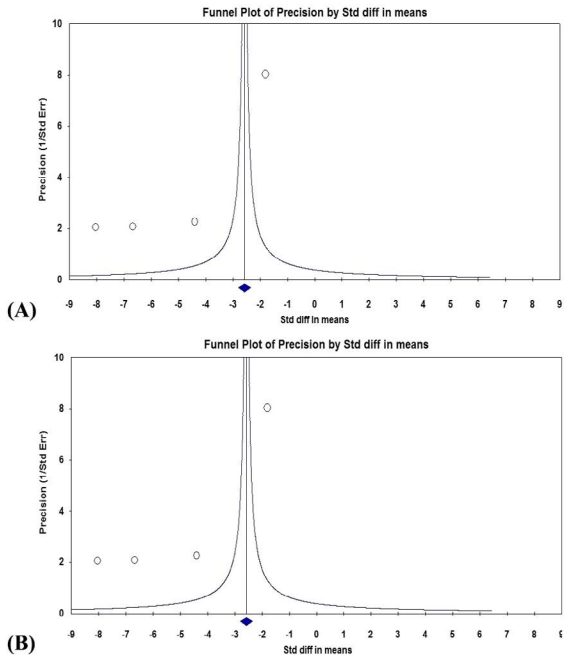
Adverse Events. All 4 trials assessed the safety of allopurinol. Safety was evaluated by monitoring serum concentrations of alanine aminotransferase and aspartate aminotransferase, the occurrence of agranulocytosis, skin allergic reactions, and gastrointestinal disorders. Vomiting and diarrhea were discovered in 7 cases,[22] an increase in alanine aminotransferase and aspartate aminotransferase in 3 cases,[23] and skin-related events in 6 cases.[13] Allopurinol therapy was not associated with any AEs in children with CKD.[17] Overall, no significant difference in AEs was identified between the treatment and control groups.

Discussion

Our systematic review and meta-analysis evaluating the effect of allopurinol in patients with CKD who are at risk for disease progression included 4 RCTs involving 698 participants. Allopurinol was compared with placebo in all trials, and there was no study medication in the control group. The results of this study showed that compared with the control group, the serum uric acid concentrations were significantly lower and the eGFR was significantly higher in the allopurinol group, without significant risk of AEs. The inclusion of children with stage 1 to 3 CKD in our trial is noteworthy because of their high risk of kidney disease progression and the effect of allopurinol treatment on the progression of CKD. To the best of our knowledge, this study is the first systematic review and meta-analysis of patients with CKD, which includes pediatric patients. Our results are consistent with those of Sampson et al,[2] Luo et al,[9] Kanji et al,[10] Spankaew et al,[11] and Kim et al,[12] but are in conflict with the findings of Badve et al,[13] Badve,[14] Doria,[15] and Ahola et al.[16] These authors did not find that allopurinol was more effective than placebo in slowing the decline in eGFR in patients with stage 3 or 4 CKD.

The discrepancy between the findings reported in our meta-analysis and in the study reported by other

Figure 5. (A) Funnel plot for publication bias in the pooled SMD analysis for eGFR. The Egger test showed significant asymmetry for eGFR (p = 0.04). (B) Funnel plot for publication bias in the pooled SMD analysis for serum uric acid. The Egger test did not show any asymmetry for serum uric acid concentration (p = 0.06).



eGFR, estimated glomerular filtration rate; SMD, standardized mean difference;

investigators can be explained by a number of reasons. Perhaps one of the most important discrepant findings in our study was that the enrollment of children with mild to moderate kidney disease (CKD stage 1 to 3) could have potentiated the ability of allopurinol to prevent decline in the eGFR. Further, other associated factors such as the variability in the study design, participants' ages, serum uric acid concentrations at baseline, primary CKD etiology (glomerular versus tubulointerstitial nephritis), diversity of the underlying disease, presence or absence of hypertension, and use of renin-angiotensin-aldosterone system inhibitors would affect the outcomes and make the data interpretation rather difficult.[24]

Our study analysis also showed that a higher uric acid concentration is associated with a significant rapid decline in eGFR and a higher risk of CKD progression. Patients with mean serum uric acid concentrations greater than 8.0 mg/dL had a higher prevalence of treatment failure than those with serum uric acid concentrations <6.0 mg/dL.

Hypertension is an important risk factor for the development of CKD. Several studies have also suggested that hyperuricemia independently predicts the development of hypertension,[25–28] and hypertensive patients with hyperuricemia have a 3- to 5-fold increased risk of CKD, cardiovascular disease, or cerebrovascular disease as compared with patients with normal serum uric acid levels.[29,30] Studies also suggest that uric acid lowering with allopurinol is associated with a small but significant reduction in blood pressure in hypertensive patients with hyperuricemia, which may also slow the progression of CKD.[30–33] The mechanism by which allopurinol is renoprotective and improves renal function is not clearly understood. Evidence from both clinical and experimental studies suggests that elevated hyperuricemia induces vasoconstriction by activation of renin-angiotensin system and reduction of circulating nitric oxide, leading to vascular endothelial dysfunction and development of hypertension, CKD, and cardiovascular disease,[34–38] which can be reversed by lowering uric acid.[39,40] Thus, the renoprotective effect of allopurinol, a xanthine oxidase inhibitor, may be explained by the reduction of reactive oxidative stress in this setting. However, the renoprotective effect of allopurinol in CKD remains controversial[13,15,24,41] despite some positive data.[42,43,44]

Our meta-analysis had several limitations. First, the number of included RCTs in this meta-analysis was small. We found 4 eligible RCTs of which 1 study involved children with an average of 80 participants per trial. Second, the follow-up duration was short with a median follow-up of 22.5 months. Third, some participants were taking a renin-angiotensin inhibitor before and after allopurinol treatment. Fourth, we did not adjust allopurinol doses against the study outcomes. The strengths of our study include a comprehensive search, accurate inclusion criteria, and careful consideration of study quality.

Conclusions

In the present systematic review and meta-analysis, we found that allopurinol was more effective than placebo in slowing the decline in eGFR in patients with CKD without risk of increased AEs. Our analysis of the limited available pediatric data suggests that maintaining a desirable serum uric acid concentration below 5.5 mg/dL might be associated with a lower decline in renal function and a lower risk of progressing to kidney failure in patients with CKD. Future research with larger sample sizes especially in children is needed to confirm the potential benefits of allopurinol for delaying the progression of CKD.

Article Information

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