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Original article

Colchicine use and the risk of CKD progression: a multicentre nested case-control study

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Abstract

Objectives. Despite the preclinical evidence on protective effects of colchicine against kidney fibrosis, whether colchicine could delay the progression of chronic kidney disease (CKD) in humans remains unknown. This study examined the association between long-term colchicine use and risk of adverse kidney outcome in patients with CKD who were treated for hyperuricaemia or chronic gout.

Methods. We conducted a multicentre, nested, case-control study in three Korean hospitals. Patients were aged ≥19 years; had CKD G3–G4; and used drugs including colchicine, allopurinol and febuxostat for hyperuricaemia or chronic gout during the period from April 2000 to October 2020. Patients with CKD progression, which was defined as ≥40% decrease from the baseline estimated glomerular filtration rate or the onset of kidney failure with replacement therapy, were matched to controls based on follow-up time, age and sex.

Results. Overall, 3085 patients with CKD progression were matched to 11 715 control patients. Multivariate conditional logistic regression analysis showed that patients with ≥90 cumulative daily colchicine doses were associated with a lower risk of CKD progression [adjusted odds ratio (AOR), 0.77; 95% CI: 0.61, 0.96] than non-users. In the sensitivity analysis with matched CKD stages, the AOR was 0.77 (95% CI: 0.62, 0.97). This association was more pronounced in patients without diabetes or hypertension, and in patients with CKD G3.

Conclusion. Colchicine use is associated with a lower risk of adverse kidney outcomes in CKD patients with hyperuricaemia, or chronic gout.

Key words: colchicine, hyperuricemia, gout, CKD

CLINICAL SCIENCE

Rheumatology key messages

- It is unknown whether colchicine could provide beneficial effects on adverse kidney outcomes.
- In this study, colchicine use was associated with lower risk of CKD progression.
- This finding calls for well-designed randomized controlled trials to investigate the benefit of colchicine.

Introduction

Uric acid is a byproduct of purine metabolism in humans. Purines are generally acquired from food such as red meat, bacon, alcohol, soft drinks and some sea foods, including anchovies, sardines, herring, codfish, mussels, scallops and trout. Increased serum uric acid levels have long been considered the main cause of gout, a painful inflammatory joint disease. In addition to gout, hyperuricaemia is linked to many other cardiometabolic diseases, such as hypertension, diabetes, coronary artery disease and stroke

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[1]. Moreover, hyperuricaemia is also associated with an increased risk of all-cause mortality [2, 3].

The kidney is a major organ that can regulate uric acid levels because ~70% of urate is excreted through urine. Thus, it is not surprising that hyperuricaemia inevitably occurs with kidney failure. Increased uric acid level is an independent risk factor for developing chronic kidney disease (CKD) [4–6] and is significantly associated with the risk of kidney failure in CKD patients [7]. Despite this strong association of hyperuricaemia and adverse kidney outcome, the use of uric acid-lowering drugs failed to show salutary effects regarding kidney protection. Several randomized controlled trials (RCTs) have shown that these drugs are not effective in delaying the progression of CKD. Notably, two RCTs did not demonstrate meaningful benefits of allopurinol in kidney outcomes in type 1 diabetes mellitus patients [8] and CKD G3–G4 patients [9]. Similar results were also observed in a recent RCT with febuxostat among Japanese patients with CKD [10]. Therefore, there is no solid evidence to support the use of uric acid-lowering drugs for kidney protection.

Concomitant anti-inflammatory prophylaxis therapy is recommended for gout management. The 2020 ACR Guidelines recommend anti-inflammatory prophylaxis for all patients when initiating uric acid-lowering agents as long as there is evidence of ongoing gout flare [11]. Colchicine is a plant-derived alkaloid that has a broad range of anti-inflammatory effects that interfere with neutrophil function [12]. It has long been used as an anti-inflammatory prophylactic for hyperuricaemia and chronic gout. Interestingly, two recent RCTs demonstrated that colchicine use significantly reduced adverse cardiovascular events in coronary artery disease patients [13, 14]. Preclinical animal studies with colchicine also showed promising results with respect to kidney inflammation and fibrosis [15–20]. However, the effect of colchicine has never been tested in human kidney diseases. Given its anti-inflammatory and anti-fibrotic properties, we hypothesized that colchicine might delay CKD progression. Therefore, we investigated the association between colchicine use and adverse kidney outcomes in patients with CKD and hyperuricaemia or chronic gout using a retrospective multicentre cohort study.

Materials and methods

Study design and population

We conducted a nested case-control study on CKD patients from three hospitals in Korea (Severance Hospital, Gangnam Severance Hospital and National Health Insurance Corporation Medical Center, Ilsan Hospital) between April 2000 and October 2020 (Severance Hospital, from January 2004; Gangnam Severance Hospital, from July 2006; Ilsan Hospital, from April 2000). All demographic, clinical and laboratory information were obtained from electronic medical records. We included patients who met the following criteria: (i) age $\geq$19 years; (ii) estimated glomerular filtration rate (eGFR) of 15–59 ml/min/1.73 m^2; (iii) diagnosis of hyperuricaemia or chronic gout; and (iv) use of allopurinol, febuxostat and colchicine. Patients were excluded if they had a follow-up duration of $<$3 months; had missing data for serum uric acid tests; and received kidney replacement therapy. CKD stage was categorized by eGFR according to the Kidney Disease: Improving Global Outcomes criteria [21], and the eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [22]. All patients were followed-up after the first eGFR measurement of $<$60 ml/min/1.73 m^2 and the last measured value. eGFR was measured at least twice to confirm decreased kidney function, the first of which was designated as the first visit date. All patient data were de-identified when retrieved from electronic medical records. This study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional review board (IRB) of Yonsei University Health System (IRB No. 4-2020-1437), Gangnam Severance Hospital (IRB No. 3-2020-0520), and National Health Insurance Corporation Medical Center, Ilsan Hospital (IRB No. 2021-02-004-001). The requirement for informed consent was waived because of the retrospective nature of the study.

Exposures and covariates

The main exposure of this study was the cumulative defined daily dose (cDDD) of colchicine during follow-up, as defined by the World Health Organization (https://www.who.int/tools/atc-ddd-toolkit). Demographic data included age, sex and comorbidities, which were defined according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), and the Charlson comorbidity index (CCI) scores were calculated. Prior history of hypertension and diabetes was rechecked by reviewing medication records and ICD-10 codes. Laboratory measurements included serum uric acid, serum creatinine, total cholesterol and albumin levels. Isotope dilution mass spectrometry (IDMS) has been used for measuring creatinine since April 2011. Thus, non-IDMS-tested creatinine level before this time point was converted to IDMS-tested creatinine level using the equation previously suggested [23]. Urinalysis was performed for random spot urine samples with a reagent strip using a semiautomatic urine analyser. Urine albumin levels were determined as absent, trace, 1+, 2+ or 3+, with albuminuria defined as $\geq$1+. We also included medications that could affect uric acid levels, such as diuretics (thiazide, loop diuretics and potassium sparing diuretics) and renin–angiotensin–aldosterone system (RAAS) blockers. We defined uric acid-lowering drug users as patients who received allopurinol or febuxostat for $>$30 days during the follow-up period.

Selection of case and control

To define case patients, we set primary outcome as the progression of CKD, which was defined by a first ≥40% decrease in eGFR or the onset of kidney failure with replacement therapy. We found 3168 patients who presented with the primary outcomes between April 2000 and October 2020. Each patient was matched to four controls by birth year, sex and follow-up time using incidence density sampling [24]. After excluding 83 cases that did not match the controls on 1:3 and 1:2 ratios, 3085 cases matched to 11 715 controls were included.

Statistical analysis

Continuous and categorical variables are presented as means (S.D.) and numbers with percentages, respectively. For primary analysis, conditional logistic regression was used to evaluate the association between colchicine use and the risk of CKD progression. In addition to the matching variables for the nested case-control study design, comorbidities (hypertension and diabetes), baseline eGFR, serum uric acid level, albuminuria, and medication use (allopurinol, febuxostat, diuretics and RAAS blockers) were adjusted. Adjusted odds ratios (AORs) and 95% CIs were used to estimate the risk of CKD progression. To confirm our findings, we performed an additional sensitivity analysis of 1:4 matched cases to controls according to CKD stage, sex, age and follow-up time to exclude the effects of differences in baseline kidney function. Additionally, matched subgroups were analysed based on the presence or absence of diabetes or hypertension, and baseline kidney function (eGFR <30 or ≥30 ml/min/1.73 m^2) to determine any differences caused by subgroup factors. All statistical analyses were performed using R (version 4.1.0; www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria) and Stata 17 (StataCorp, College Station, TX, USA), with a significance level of $P < 0.05$.

Results

Baseline characteristics

Among 7938 patients with baseline CKD G3–G4 who were prescribed medications for hyperuricaemia, 3085 were matched to 11 715 controls, and the median follow-up time was 2.4 (interquartile range, 1.0–4.6) years (Fig. 1). Table 1 presents the baseline characteristics of the case and control groups. The two groups had relatively even distributions of sex and age. However, there were some differences in other baseline characteristics between the two groups. Compared with the control group, the case group had relatively lower eGFR [37.8 (13.2) *vs* 42.4 (12.0) ml/min/1.73 m^2; odds ratio (OR), 0.97; 95% CI: 0.96, 0.97], higher uric acid levels [7.5 (2.5) *vs* 7.3 (2.3) mg/dl; OR, 1.04; 95% CI: 1.02, 1.06], higher likelihood of albuminuria (OR, 1.86; 95% CI: 1.63, 2.05), higher CCI (OR, 1.06; 95% CI: 1.04, 1.09), more frequent use of febuxostat (OR, 1.11; 95% CI: 1.02, 1.22) and diuretics (OR, 1.19; 95% CI: 1.07, 1.32) and less frequent use of RAAS blockers (OR, 0.80; 95% CI: 0.72, 0.90) (Table 1).

Colchicine use and the progression of CKD

During the follow-up period, the control group had a higher proportion of patients with ≥90 cDDD of colchicine (5.0%) than the case group (3.2%). In conditional logistic regression model analysis without adjustment, the crude OR in ≥90 cDDD colchicine users was 0.65 (95% CI: 0.52, 0.81) compared with non-users. After adjusting for comorbidities, baseline eGFR, serum uric

Fig. 1 Flow chart of this study

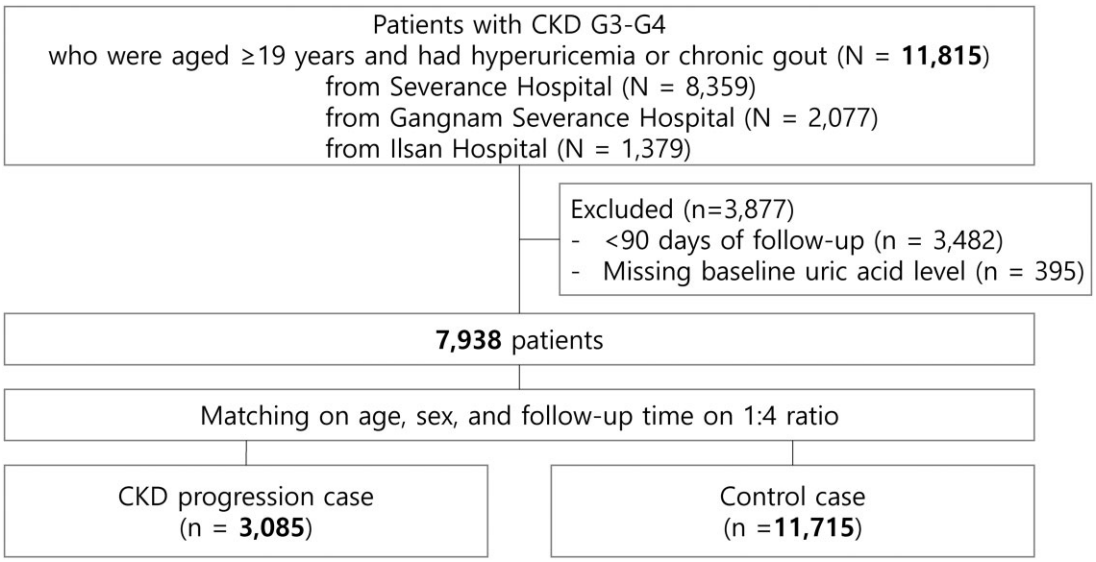

Table 1 Baseline characteristics of cases and matched controls

Characteristics	Cases *n* = 3085	Controls *n* = 11 715	Crude OR (95% CI)
Age[a], mean (S.D.), yrs	64.44 (14.2)	65.4 (13.2)	—
19–29, *n* (%)	32 (1.0)	28 (0.2)	—
30–39, *n* (%)	153 (5.0)	441 (3.8)	—
40–49, *n* (%)	350 (11.3)	1242 (10.6)	—
50–59, *n* (%)	465 (15.1)	1807 (15.4)	—
60–69, *n* (%)	802 (26.0)	3157 (26.9)	—
70–79, *n* (%)	859 (27.8)	3444 (29.4)	—
≥80, *n* (%)	424 (13.7)	1596 (13.6)	—
Male[a], *n* (%)	2161 (70.0)	8359 (71.4)	—
Diabetes mellitus, *n* (%)	899 (29.1)	2815 (24.0)	1.30 (1.19, 1.42)
Hypertension, *n* (%)	1782 (57.8)	7327 (62.5)	0.85 (0.79, 0.92)
CCI[b], mean (S.D.)	1.7 (1.7)	1.6 (1.6)	1.06 (1.04, 1.09)
0, *n* (%)	1036 (33.6)	4493 (38.4)	—
1, *n* (%)	278 (9.0)	1185 (10.1)	—
2, *n* (%)	1040 (33.7)	3514 (30.0)	—
≥3, *n* (%)	731 (23.7)	2523 (21.5)	—
Myocardial infarction, *n* (%)	76 (2.5)	344 (2.9)	—
Congestive heart failure, *n* (%)	271 (8.8)	893 (7.6)	—
Peripheral vascular disease, *n* (%)	200 (6.5)	811 (6.9)	—
Cerebrovascular disease, *n* (%)	307 (10.0)	1238 (10.6)	—
Baseline eGFR, mean (S.D.), ml/min/1.73m^2	37.88 (13.2)	42.44 (12.0)	0.97 (0.96, 0.97)
45–59, *n* (%)	1075 (34.8)	5478 (46.8)	—
30–44, *n* (%)	992 (32.2)	4107 (35.1)	—
15–29, *n* (%)	1018 (33.0)	2130 (18.2)	—
Uric acid, mean (S.D.), mg/dl	7.5 (2.5)	7.3 (2.3)	1.04 (1.02, 1.06)
Albuminuria[c], *n* (%)			1.83 (1.63, 2.05)
Negative	2454 (79.5)	10 030 (85.6)	—
Trace	119 (3.9)	535 (4.6)	—
≥1+	512 (16.6)	1150 (9.8)	—
Total cholesterol, mean (S.D.), mg/dl	164.4 (47.1)	165.4 (41.7)	0.99 (0.99, 1.00)
Allopurinol user[d], *n* (%)	1574 (51.0)	6113 (52.2)	0.95 (0.88, 1.03)
Febuxostat user[d], *n* (%)	875 (28.4)	3074 (26.2)	1.11 (1.02, 1.22)
RAAS blocker user, *n* (%)	1096 (35.5)	5719 (48.8)	0.80 (0.72, 0.90)
Diuretics user, *n* (%)	558 (18.1)	1836 (15.7)	1.19 (1.07, 1.32)
Loop diuretics, *n* (%)	351 (11.4)	965 (8.2)	—
Potassium sparing diuretics, *n* (%)	57 (1.8)	186 (1.6)	—
Thiazide, *n* (%)	229 (7.4)	890 (7.6)	—

[a]Matched for year of birth, sex, and follow-up time. [b]Calculated without DM. [c]Albuminuria was defined as >1+ on the dipstick test. [d]Use was defined as ≥30 days during follow-up. CCI: Charlson comorbidity index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; OR: odds ratio; RAAS: renin–angiotensin–aldosterone system.

acid levels, albuminuria, medication use and ≥90 cDDD of colchicine were significantly associated with a 23% lower risk of CKD progression (AOR, 0.77; 95% CI: 0.62, 0.96). However, <90 cDDD of colchicine was not significantly associated with CKD progression when compared with non-colchicine use in both crude and multivariable-adjusted models. Other urate-lowering agents, such as allopurinol and febuxostat, were also not significantly associated with CKD progression (Table 2). Additional analyses were performed with 90, 120 and 180 cumulative defined daily dose (cDDD) as reference. Colchicine use was associated with lower CKD progression risk even in patients with higher cDDD than 90 (Supplementary Table S1, available at *Rheumatology* online).

In the sensitivity analysis, we matched patients according to baseline CKD stage, in addition to age, sex and follow-up time. Therefore, 2967 patients were

matched to 10 387 controls (Supplementary Table S2, available at *Rheumatology* online). This sensitivity analysis also showed that the risk of CKD progression was significantly lower in patients with ≥90 cDDD of colchicine than in non-users (AOR, 0.77; 95% CI: 0.62, 0.97) (Supplementary Table S3, available at *Rheumatology* online).

Subgroup analyses

Baseline characteristics, including diagnosis of diabetes (Supplementary Tables S4 and S5, available at *Rheumatology* online) and hypertension (Supplementary Tables S6 and S7, available at *Rheumatology* online), and eGFR of 30 ml/min/1.73 m^2 (Supplementary Tables S8 and S9, available at *Rheumatology* online) are presented. Among patients without diabetes, 2152 were matched to 7937 controls. In this subgroup, ≥90 cDDD of colchicine was associated with a significantly lower risk of CKD progression (AOR, 0.76; 95% CI: 0.59, 0.98) than that in the control group (Table 3). In contrast, 861 patients with diabetes were matched to 3076 controls, and neither ≥90 cDDD nor <90 cDDD of colchicine was significantly associated with CKD progression (Table 3). Among matched non-hypertensive patients, ≥90 cDDD of colchicine was associated with a lower risk of the CKD progression (AOR, 0.51; 95% CI: 0.35, 0.75) than non-colchicine use (Table 4). However, this association was not observed among matched hypertensive patients. Among patients with eGFR ≥30 ml/min/1.73 m^2, ≥90 cDDD of colchicine was associated with a lower risk of CKD progression (AOR, 0.55; 95% CI: 0.38, 0.80) (Table 5).

Discussion

In this multicentre retrospective study, we investigated the association between colchicine use and adverse kidney outcome in CKD patients with hyperuricaemia, or chronic gout. Using nested case-control analysis, we matched 3085 cases of CKD progression with 11 715 control cases according to age, sex and follow-up time using a 1:4 ratio. We found that long-term colchicine use with a cDDD of ≥90 was associated with a lower risk of CKD progression than non-colchicine use. This finding was consistent after matching the patients according to CKD stage and was more pronounced in patients without diabetes or hypertension and in those with CKD G3.

Gout is a common crystal deposition disorder causing inflammatory arthritis. Its incidence and prevalence vary widely according to the population ranging from a prevalence of <1% to 6.8% and an incidence of 0.58–2.89 per 1000 person-years [25]. Nevertheless, the prevalence and incidence of gout are gradually increasing in many countries in parallel with the spread of a westernized lifestyle, medical care, more comorbidities and increased longevity [26, 27]. Interestingly, patients with gout are at higher risk of renal impairment [28, 29]. The prevalence of gout is also high in patients with pre-existing CKD [30]. Analysis with data from National Health and Nutrition Examination Survey in US showed that nearly a quarter of adults with CKD ≥ stage 3 reported having gout compared with 2.9% individuals with normal renal function [31]. Moreover, the incidence of gout was also higher in elderly patients with a lower level of eGFR [32].

As hyperuricaemia provides a condition for deposition of monosodium urate crystals and inflammatory response in joints, uric acid can play a key role in kidney damage. Its soluble form promotes inflammatory, proliferative, maladaptive glomerular and tubulointerstitial changes via various responses, including oxidative stress, endothelial dysfunction, arteriolopathy and apoptosis. Crystalline uric acid eventually leads to tubulointerstitial inflammation and fibrosis mediated through NLRP3 inflammasomes, NF-κB, IL-1 and NADPH oxidates and accumulates in the extracellular matrix [33]. Lowering the uric acid levels prevents or improves kidney injury in hyperuricaemic animals [34–40]. Considering this, clinical interventional trials on urate-lowering agents, including

Table 2 Relationship between colchicine use and CKD progression

Characteristics	Cases (*n* = 3085) *n* (%)	Controls (*n* = 11 715) *n* (%)	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Colchicine use				
Never use	2733 (88.6)	10 202 (87.1)	1.00	1.00
Ever use				
<90 cDDDs	252 (8.2)	929 (7.9)	1.03 (0.89, 1.19)	1.09 (0.94, 1.27)
≥90 cDDDs	100 (3.2)	584 (5.0)	0.65 (0.52, 0.81)	0.77 (0.61, 0.96)
Allopurinol use	1574 (51.0)	6113 (52.2)	0.99 (0.91, 1.07)	0.99 (0.91, 1.08)
Febuxostat use	875 (28.4)	3074 (26.2)	1.14 (1.03, 1.25)	1.01 (0.91, 1.11)

[a]Adjusted for comorbidities, baseline eGFR, baseline uric acid, baseline total cholesterol, baseline albuminuria and medication (allopurinol, febuxostat, diuretics and RAAS blocker). cDDD: cumulative defined daily dose; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; OR: odds ratio; RAAS: renin–angiotensin–aldosterone system.

Table 3 Relationship between colchicine use and CKD progression according to diabetes status

	Without diabetes				With diabetes			
	Case	Control	Crude	Adjusted[a]	Case	Control	Crude	Adjusted[a]
	n = 2152	*n* = 7937	OR (95% CI)	OR (95% CI)	*n* = 861	*n* = 3076	OR (95% CI)	OR (95% CI)
Colchicine use								
Never use	1903 (88.4)	6869 (86.5)	1.00	1.00	762 (88.5)	2727 (88.7)	1.00	1.00
Ever use								
<90 cDDDs	170 (7.9)	623 (7.8)	1.05 (0.88, 1.25)	1.10 (0.92, 1.33)	80 (9.3)	272 (8.8)	1.07 (0.82, 1.39)	1.14 (0.86, 1.50)
≥90 cDDDs	79 (3.7)	445 (5.6)	0.67 (0.52, 0.86)	0.76 (0.59, 0.98)	19 (2.2)	77 (2.5)	0.93 (0.56, 1.55)	1.12 (0.66, 1.89)

[a]Adjusted for comorbidities, baseline eGFR, baseline uric acid, baseline total cholesterol, baseline albuminuria and medication (allopurinol, febuxostat, diuretics and RAAS blocker). cDDD: cumulative defined daily dose; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; OR: odds ratio; RAAS: renin–angiotensin–aldosterone system.

Table 4 Relationship between colchicine use and CKD progression according to hypertension status

	Without hypertension				With Hypertension			
	Case	Control	Crude	Adjusted[a]	Case	Control	Crude	Adjusted[a]
	n = 1250	*n* = 4247	OR (95% CI)	OR (95% CI)	*n* = 1623	*n* = 6091	OR (95% CI)	OR (95% CI)
Colchicine use								
Never use	1144 (91.5)	3742 (88.1)	1.00	1.00	1392 (85.8)	5224 (85.8)	1.00	1.00
Ever use								
<90 cDDDs	72 (5.8)	249 (5.9)	1.01 (0.76, 1.33)	1.09 (0.82, 1.45)	169 (10.4)	611 (10.0)	1.07 (0.89, 1.29)	1.13 (0.93, 1.36)
≥90 cDDDs	34 (2.7)	256 (6.0)	0.39 (0.27, 0.57)	0.51 (0.35, 0.75)	62 (3.8)	256 (4.2)	0.94 (0.71, 1.25)	1.20 (0.90, 1.62)

[a]Adjusted for comorbidities, baseline eGFR, baseline uric acid, baseline total cholesterol, baseline albuminuria and medication (allopurinol, febuxostat and diuretics). cDDD: cumulative defined daily dose; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; OR: odds ratio.

TABLE 5 Relationship between colchicine use and CKD progression according to baseline kidney function

	eGFR of 30–59 ml/min/1.73 m^2				eGFR of 15–29 ml/min/1.73m^2			
	Case	Control	Crude	Adjusted[a]	Case	Control	Crude	Adjusted[a]
	n = 2048	*n* = 7628	OR (95% CI)	OR (95% CI)	*n* = 919	*n* = 2759	OR (95% CI)	OR (95% CI)
Colchicine use								
Never use	1801 (87.9)	6596 (86.5)	1.00	1.00	827 (90.0)	2484 (90.0)	1.00	1.00
Ever use								
<90 cDDDs	176 (8.6)	632 (8.3)	1.06 (0.89, 1.27)	1.09 (0.91, 1.30)	65 (7.1)	208 (7.5)	1.02 (0.75, 1.37)	1.04 (0.77, 1.42)
≥90 cDDDs	71 (3.5)	400 (5.2)	0.65 (0.50, 0.84)	0.75 (0.57, 0.97)	27 (2.9)	67 (2.4)	1.19 (0.74, 1.92)	1.28 (0.78, 2.10)

[a]Adjusted for comorbidities, baseline eGFR, baseline uric acid, baseline total cholesterol, baseline albuminuria and medication (allopurinol, febuxostat, diuretics and RAAS blocker). cDDD: cumulative defined daily dose; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; OR: odds ratio; RAAS: renin–angiotensin–aldosterone system.

allopurinol and febuxostat, have been conducted. However, three recent RCTs showed poor results. In the FEATHER (Febuxostat *vs* Placebo Randomized Controlled Trial Regarding Reduced Kidney Function in Patients with Hyperuricaemia Complicated by Chronic Kidney Disease Stage 3) trial, febuxostat therapy did not improve the slope of eGFR when compared with placebo in 443 patients with CKD G3 and asymptomatic hyperuricaemia [10]. The PERL (Preventing Early Renal Loss in Diabetes) trial failed to show clinically meaningful benefits of allopurinol in kidney outcomes among 530 patients with type 1 diabetes mellitus and early-to-moderate diabetic kidney disease [8]. Finally, in the CKD-FIX (Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase) trial, allopurinol did not slow the decline in eGFR when compared with placebo in 369 patients with CKD G3–G4 [9].

We included patients with an eGFR of 15–59 ml/min/1.73 m^2, which was similar to the inclusion criterion in the CKD-FIX trial. However, allopurinol or febuxostat use was not associated with improved kidney outcomes. These negative findings from RCTs raise the question of the causal link between high uric acid levels and kidney injury, despite a consistent and significant association between hyperuricaemia and adverse kidney outcomes. Interestingly, a Mendelian randomization study on a large European population by Jordan *et al.* [41] showed no causal effects of serum uric acid level on the eGFR level or the risk of CKD. Another Mendelian randomization study using data of 7979 patients of the Atherosclerosis Risk in Communities and Framingham Heart studies reported that the effect size associated with serum uric acid levels did not correlate with that associated with renal function, and that the activity of uric acid transporters appeared to be more protective of kidney function than uric acid level itself [42]. These findings may partly explain the lack of benefits of uric acid-lowering therapy in kidney protection.

Colchicine is recommended against gout attacks in patients beginning with uric acid-lowering therapy. Colchicine interferes with microtubule polymerization and neutrophil function [12] and has anti-inflammatory and anti-fibrotic effects. The anti-inflammatory properties of colchicine have recently been highlighted in cardiovascular research. In the Colchicine Cardiovascular Outcomes Trial (COLCOT), colchicine treatment resulted in a 23% reduction in composite adverse cardiovascular events when compared with placebo among 4745 patients within 30 days after acute myocardial infarction [13]. Such cardiovascular benefits were also demonstrated by the Low Dose Colchicine 2 (LoDoCo2) trial comprising 5522 patients with chronic coronary disease [14]. Given the success of canakinumab, a monoclonal antibody that binds to IL-1β [43], in reducing cardiovascular events, these findings shed light on colchicine as a promising anti-inflammatory therapy in cardiometabolic disease.

Whether the anti-inflammatory effects of colchicine may lead to kidney protection remains unknown. Notably, our group demonstrated these effects in an animal model of diabetic kidney disease [15]. Colchicine treatment significantly inhibited the expression of monocyte chemotactic protein-1 and intercellular adhesion molecule-1, and macrophage infiltration in the kidneys of diabetic rats, as well as significantly reduced albuminuria and fibrosis. In addition, there have been several experimental studies demonstrating the renoprotective effects of colchicine via various mechanisms in ciclosporin-induced kidney injury [16, 17], obstructive kidney [18], anti-glomerular basement membrane (anti-GBM) disease [19], and hypertensive CKD models [20]. Such experimental evidence may provide a rationale for the positive association of colchicine with lower risk of CKD progression. Nevertheless, we have insufficient clinical evidence and few studies dealt with this issue. In a previous study involving US veterans, Singh and colleagues reported that 31% (16/52) of colchicine users experienced episodes of kidney failure, which might be attributed to the inappropriate dose [44]. Interestingly, Wason and colleagues showed no significant accumulation of colchicine in patients with eGFR $\geq$30 ml/min/1.73 m^2, compared with a doubling of colchicine exposure in those with eGFR of 15–29 ml/min/1.73 m^2 [45], suggesting possible kidney toxicity in severe renal impairment. However, adverse effect on kidney was not reported during 40-h observation.

Given concern on toxicity of colchicine, the findings of the AGREE clinical trial were intriguing because low-dose colchicine was as efficacious as high-dose colchicine in gout flares with minimal side effects [46]. Our study could not analyse this issue, but we acknowledge its importance particularly in patients with CKD. Finding an optimal dose of colchicine for the purpose of kidney prevention should be further studied.

This study had some limitations. First, we cannot exclude the possibility of residual bias due to potential unmeasured confounders associated with observational studies. We used a nested case-control design matching case patients at a ratio of 1:4 based on sex, age and the follow-up time to avoid selection bias, despite its inevitability. Selection bias in observational studies could be minimized compared with that of conventional case-control studies by selecting cases and controls from the same source [47]. Nevertheless, this nested case-control method cannot determine the causality between exposure and outcome. Especially, there is a possibility that doctors prescribed colchicine less frequently in the case group with CKD progression because of potential renal toxicity. Although our study did not show a significant result in patients with eGFR $<$30 ml/min/1.73 m^2, colchicine use did not contribute to CKD progression in these patients at least. In addition, colchicine use was clearly associated with a lower risk of CKD progression among patients with eGFR $\geq$ 30 ml/min/1.73 m^2 in which no dose adjustment is required for colchicine.

Second, because colchicine use relied on prescription history from electronic medical records, frequency of intake and dosage may vary in the real world.

Third, the efficacy for prevention of gout flare and safety of colchicine in patients with gout and CKD are uncertain. In a literature review by Pisaniello *et al.* there were 20 studies of colchicine use with analyses stratified by renal function [48]. Among these studies, five studies reported efficacy outcome, but did not reach definite conclusion due to high heterogeneity of the studies and the low quality of the evidence. In addition, another 15 studies reported the safety outcome, which included various adverse events such as neuromyopathy, rhabdomyolysis, and toxicity secondary to drug–drug interaction. However, direct causality between colchicine use and adverse effects was unclear. Notably, according to the Food and Drug Administration report, adjustment of the recommended dose is not required for prophylaxis of gout flares in patients with mild-to-moderate kidney function impairment (estimated creatinine clearance, 30–80 ml/min) [49]. Even in a previous small sample-sized study involving patients receiving maintenance haemodialysis, there was no difference in colchicine-specific toxicities between colchicine users and non-users [50]. Nevertheless, given partial excretion of colchicine by the kidney, physicians should be cautious in using this drug in patients with CKD.

Fourth, we did not observe a significant association between colchicine use and a lower risk of CKD progression among patients with diabetes and hypertension. Notably, there were more comorbidities in these groups than in control groups, which may negate the benefits of colchicine. In addition, we narrowed the study population to patients with CKD G3–G4, hyperuricaemia or chronic gout. Thus, this issue should be further examined in various clinical settings.

In conclusion, we showed that colchicine use was associated with a lower risk of adverse kidney outcomes in patients with CKD category G3–G4 who were treated for hyperuricaemia or chronic gout. Our findings warrant well-designed RCTs in the future to test the potential renoprotective effects of colchicine in CKD patients.

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Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811–21.

2 Niskanen LK, Laaksonen DE, Nyyssonen K *et al.* Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med 2004;164:1546–51.

3 Liu WC, Hung CC, Chen SC *et al.* Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. Clin J Am Soc Nephrol 2012;7:541–8.

4 Krishnan E, Akhras KS, Sharma H *et al.* Serum urate and incidence of kidney disease among veterans with gout. J Rheumatol 2013;40:1166–72.

5 Weiner DE, Tighiouart H, Elsayed EF *et al.* Uric acid and incident kidney disease in the community. J Am Soc Nephrol 2008;19:1204–11.

6 De Cosmo S, Viazzi F, Pacilli A *et al.* Serum uric acid and risk of CKD in type 2 diabetes. Clin J Am Soc Nephrol 2015;10:1921–9.

7 Srivastava A, Kaze AD, McMullan CJ, Isakova T, Waikar SS. Uric acid and the risks of kidney failure and death in individuals with CKD. Am J Kidney Dis 2018;71:362–70.

8 Doria A, Galecki AT, Spino C *et al.* Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med 2020;382:2493–503.

9 Badve SV, Pascoe EM, Tiku A *et al.* Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med 2020;382:2504–13.

10 Kimura K, Hosoya T, Uchida S *et al.* Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. Am J Kidney Dis 2018;72:798–810.

11 FitzGerald JD, Dalbeth N, Mikuls T *et al.* 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res 2020;72:744–60.

12 Bhattacharyya B, Panda D, Gupta S, Banerjee M. Anti-mitotic activity of colchicine and the structural basis for its interaction with tubulin. Med Res Rev 2008;28:155–83.

13 Tardif JC, Kouz S, Waters DD *et al.* Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med 2019;381:2497–505.

14 Nidorf SM, Fiolet ATL, Mosterd A *et al.* Colchicine in patients with chronic coronary disease. N Engl J Med 2020;383:1838–47.

15 Li JJ, Lee SH, Kim DK *et al.* Colchicine attenuates inflammatory cell infiltration and extracellular matrix accumulation in diabetic nephropathy. Am J Physiol Renal Physiol 2009;297:F200–9.

16 Li C, Yang CW, Ahn HJ *et al.* Colchicine decreases apoptotic cell death in chronic cyclosporine nephrotoxicity. J Lab Clin Med 2002;139:364–71.

17 Disel U, Paydas S, Dogan A, Gulfiliz G, Yavuz S. Effect of colchicine on cyclosporine nephrotoxicity, reduction of TGF-beta overexpression, apoptosis, and oxidative damage: an experimental animal study. Transplant Proc 2004;36:1372–6.

18 Kim S, Jung ES, Lee J *et al.* Effects of colchicine on renal fibrosis and apoptosis in obstructed kidneys. Korean J Intern Med 2018;33:568–76.

19 McClurkin C Jr, Phan SH, Hsu CH *et al.* Moderate protection of renal function and reduction of fibrosis by colchicine in a model of anti-GBM disease in the rabbit. J Am Soc Nephrol 1990;1:257–65.

20 Guan T, Gao B, Chen G *et al.* Colchicine attenuates renal injury in a model of hypertensive chronic kidney disease. Am J Physiol Renal Physiol 2013;305:F1466–76.

21 Group KDIGO. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1–150.

22 Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

23 Levey AS, Coresh J, Greene T *et al.* Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;53:766–72.

24 Vandenbroucke JP, Pearce N. Case-control studies: basic concepts. Int J Epidemiol 2012;41:1480–9.

25 Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020;16:380–90.

26 Musacchio E, Perissinotto E, Sartori L *et al.* Hyperuricemia, cardiovascular profile, and comorbidity in older men and women: the Pro.V.A. Study. Rejuvenation Res 2017;20:42–9.

27 Lorenzin M, Ughi N, Ariani A *et al.* Impact of disease duration and gender on the sensitivity and specificity of 2015 ACR/EULAR classification criteria for gout. Cross-sectional results from an Italian multicentric study on the management of crystal-induced arthritis (ATTACk). Clin Exp Rheumatol 2021; https://doi.org/10.55563/clinexpheumatol/4rrgyt.

28 Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med 2017;15:123.

29 Vargas-Santos AB, Neogi T. Management of gout and hyperuricemia in CKD. Am J Kidney Dis 2017;70:422–39.

30 Abdellatif AA, Elkhalili N. Management of gouty arthritis in patients with chronic kidney disease. Am J Ther 2014;21:523–34.

31 Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009-10. PLoS One 2012;7:e50046.

32 Tan VS, Garg AX, McArthur E *et al.* The 3-year incidence of gout in elderly patients with CKD. Clin J Am Soc Nephrol 2017;12:577–84.

33 Johnson RJ, Bakris GL, Borghi C *et al.* Hyperuricemia, acute and chronic kidney disease, hypertension, and cardiovascular disease: report of a Scientific Workshop Organized by the National Kidney Foundation. Am J Kidney Dis 2018;71:851–65.

34 Omori H, Kawada N, Inoue K *et al.* Use of xanthine oxidase inhibitor febuxostat inhibits renal interstitial inflammation and fibrosis in unilateral ureteral obstructive nephropathy. Clin Exp Nephrol 2012;16:549–56.

35 Kim SM, Lee SH, Kim YG *et al.* Hyperuricemia-induced NLRP3 activation of macrophages contributes to the progression of diabetic nephropathy. Am J Physiol Renal Physiol 2015;308:F993–F1003.

36 Komers R, Xu B, Schneider J, Oyama TT. Effects of xanthine oxidase inhibition with febuxostat on the development of nephropathy in experimental type 2 diabetes. Br J Pharmacol 2016;173:2573–88.

37 Sanchez-Lozada LG, Tapia E, Soto V *et al.* Treatment with the xanthine oxidase inhibitor febuxostat lowers uric acid and alleviates systemic and glomerular hypertension in experimental hyperuricaemia. Nephrol Dial Transplant 2008;23:1179–85.

38 Mazzali M, Kanellis J, Han L *et al.* Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002;282:F991–7.

39 Mazzali M, Hughes J, Kim YG *et al.* Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001;38:1101–6.

40 Kang DH, Nakagawa T, Feng L *et al.* A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002;13:2888–97.

41 Jordan DM, Choi HK, Verbanck M *et al.* No causal effects of serum urate levels on the risk of chronic kidney disease: A Mendelian randomization study. PLoS Med 2019;16:e1002725.

42 Hughes K, Flynn T, de Zoysa J, Dalbeth N, Merriman TR. Mendelian randomization analysis associates increased serum urate, due to genetic variation in uric acid transporters, with improved renal function. Kidney Int 2014;85:344–51.

43 Ridker PM, Everett BM, Thuren T *et al.* Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.

44 Singh JA, Hodges JS, Asch SM. Opportunities for improving medication use and monitoring in gout. Ann Rheum Dis 2009;68:1265–70.

45 Wason S, Mount D, Faulkner R. Single-dose, open-label study of the differences in pharmacokinetics of colchicine in subjects with renal impairment, including end-stage renal disease. Clin Drug Investig 2014;34:845–55.

46 Terkeltaub RA, Furst DE, Bennett K *et al.* High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum 2010;62:1060–8.

47 Szklo M, Nieto FJ. Epidemiology: beyond the basics. Burlington, MA, USA: Jones & Bartlett Publishers, 2014.

48 Pisaniello HL, Fisher MC, Farquhar H *et al.* Efficacy and safety of gout flare prophylaxis and therapy use in people with chronic kidney disease: a Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN)-initiated literature review. Arthritis Res Ther 2021;23:130.

49 Food and Drug Adminitration. Colcrys full prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022352s022lbl.pdf (December 2015, date last accessed).

50 Solak Y, Atalay H, Biyik Z *et al.* Colchicine toxicity in end-stage renal disease patients: a case-control study. Am J Ther 2014;21:e189–95.