Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Effects of Citrate Mixture on Gout Flares During Urate-Lowering Therapy Initiation Among Chinese Male Underexcretion-Type Gout Patients: A Prospective Cohort Study

Lingfang Xu[1,*], Jidong Cheng[2,*], Lingling Cui[1,*], Kai Guo[1], Can Wang[1], Han Qi[2], Qian Zhang[2], Yuwei He[1], Xinde Li[1], Lin Han[1], Xuefeng Wang[1], Wenyan Sun[1], Xueyan Zhang[3], Mingshu Sun[4], Changgui Li[1,2,*], Zhen Liu[1,*]

[1]Shandong Provincial Clinical Research Center for Immune Diseases and Gout, Shandong Provincial Clinical Medical Center for Gout, the Affiliated Hospital of Qingdao University, Qingdao, People's Republic of China; [2]Department of Endocrinology, Xiang'an Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, People's Republic of China; [3]Jiangsu Medical College, Yancheng, Jiangsu, People's Republic of China; [4]Department of Rheumatology, Xiang'an Hospital of Xiamen University, Xiamen, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhen Liu, Shandong Provincial Clinical Research Center for Immune Diseases and Gout, Shandong Provincial Clinical Medical Center for Gout, the Affiliated Hospital of Qingdao University, Qingdao, 266001, People's Republic of China, Email liuzhen@qdu.edu.cn; Changgui Li, Xiang'an Hospital of Xiamen University, Xiamen, 361102, People's Republic of China, Email changguili@vip.163.com

Purpose: To evaluate the effect of urine alkalization with citrate mixture on reducing flare incidence during initial urate-lowering therapy period in male gout patients with renal underexcretion-type.

Patients and Methods: In this prospective cohort study, patients with renal underexcretion and urinary pH < 6.2 were enrolled. All participants received febuxostat 20 mg/day during weeks 0–4, later increased to 40 mg/day if serum urate (SU) levels > 360 μmol/L. According to group assignment, patients received either alkalization therapy (Alk group; citrate mixture, 3.5 g twice/day) or no alkalization (Control group). The primary outcome measure was gout flare incidence.

Results: In total, 240 patients (Alk 114, Control 126) completed the 12-week follow-up. The Alk group had a significantly lower flare incidence (35.1%) than the Control group (59.5%, $P < 0.001$) and a lower recurrence of flares (14.0% vs. 31.0%, $P = 0.002$). At week 4, the proportion of participants with SU < 360 μmol/L was significantly higher in the Alk than in the Control group ($P = 0.039$). The Alk group had lower triglycerides and higher high-density lipoprotein cholesterol levels than the Control group at weeks 4, 8, and 12 ($P < 0.05$). The urinary albumin-to-creatinine ratio (UACR) decreased from 1.65 (0.36–7.01) to 1.08 (0.62–2.99) at week 12 in the Alk group, significantly lower than that in the Control group ($P = 0.001$). No significant difference was noted in the incidence of adverse events between groups.

Conclusion: In patients with renal underexcretion gout, urine alkalization with febuxostat therapy prevented gout flares, improved lipid metabolism, and lowered UACR.

Study Registration: ChiCTR, https://www.chictr.org.cn, ChiCTR2100043573.

Keywords: gout, underexcretion subtype, urine alkalization, gout flares, inflammation

Introduction

Hyperuricemia is, based on the variables urinary urate excretion (UUE) and fractional excretion of uric acid (FEUA), clinically categorized into three subtypes: renal urate overload, renal urate underexcretion, and combined type.[1,2] The 2006 European League Against Rheumatism (EULAR) evidence-based recommendations for gout proposed a classification of hyperuricemia subtypes to guide urate-lowering therapy (ULT) management.[3] Growing clinical evidence supports a subtype-

https://doi.org/10.2147/JIR.S597592
Received: 30 January 2026
Accepted: 22 April 2026
Published: 22 May 2026

guided approach to ULT that may enable a more personalized and effective gout management. The sensitivity to different urate-lowering agents varies across clinical subtypes. A prospective cohort study involving 220 patients with primary gout demonstrated that fixed low-dose benzbromarone was more effective in patients with the renal urate underexcretion subtype than in those without subtype stratification.[4] Our previous prospective cohort study of 550 patients with primary gout showed that febuxostat resulted in a higher serum urate (SU) target attainment rate in patients with renal urate underexcretion than in those with the combined subtype.[2] Collectively, these findings support the utility of a pathogenicity-based approach in selecting patients for ULT.

The renal underexcretion type, clinically defined by FEUA < 5.5% and UUE ≤ 600 mg/day/1.73 m^2[1] accounts for approximately 60% of all patients of gout.[5,6] Previous data also demonstrated that compared with patients with the renal overload subtype, individuals with the underexcretion subtype were younger and had considerably higher SU levels.[2] As the predominant clinical subtype, renal underexcretion requires targeted ULT strategies to optimize SU control, prevent recurrent flares, and curb disease progression.[6] However, during the early phase of ULT, fluctuations in SU levels induce gout flares in 40–60% of patients, particularly those with baseline SU ≥ 600 μmol/L or rapid urate reduction.[7–10] Gout flares are linked to increased cardiovascular risk and deep vein thrombosis.[11–15] Furthermore, recurrent gout flares are associated with an increased incidence of chronic kidney disease and metabolic syndrome.[16,17]

Oral colchicine is commonly recommended during the first 3–6 months of ULT to prevent gout flares.[18,19] Although colchicine prophylaxis effectively reduces the incidence of gout flares to approximately 20–30% during ULT initiation,[20,21] its clinical use remains as low as 10–20%, primarily due to concerns over potential adverse effects and poor treatment adherence.[22,23] These findings highlight a significant gap between guideline recommendations and clinical practice, underscoring the need for improved adherence to prophylactic strategies during ULT.

In patients with the renal underexcretion subtype of gout, urine alkalization is particularly recommended in combination with uricosuric agents to reduce the risk of nephrolithiasis.[24,25] Beyond this well-established role in stone prevention, emerging evidence suggests that urine alkalization may confer additional anti-inflammatory benefits directly relevant to gout flare pathogenesis.[26] Mechanically, Pastor Arroyo et al demonstrated that increasing pH reduces the expression of CCL2 and CCL5 mRNA, which were the key chemokines responsible for recruiting inflammatory monocytes to sites of crystal deposition.[27] By attenuating this chemokine-driven inflammatory cell infiltration, urine alkalization may reduce both the frequency and severity of gout flares. However, whether urine alkalization provides consistent prophylactic benefits across the different clinical subtypes of gout remains unclear. Notably, its efficacy has not been sufficiently validated in patients with renal urate underexcretion, the most common pathogenic subtype.

Therefore, to provide a novel evidence-based urine alkalization strategy for gout management, this study evaluated the efficacy and safety of combining urine alkalization with xanthine oxidase inhibitors (XOIs) to prevent gout flares among patients with the renal underexcretion subtype.

Materials and Methods

Study Design and Participants

This prospective cohort study was conducted at the Gout Clinic of Qingdao University Affiliated Hospital between September 2021 and June 2023. The research protocol adhered to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Permit Number: QYFYWZLL26144). The study was prospectively registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn; ChiCTR2100043573). This study was conducted as an independent sub-cohort investigation within a larger prospective registry of hyperuricemia and primary gout patients (registered at ChiCTR2100043573). While participants were selected from the main registry based on specific eligibility criteria for this study, all enrolled patients were managed under the standardized follow-up protocol of the parent registry for systematic assessment of gout flares and clinical outcomes. All participants provided written informed consent. This cohort study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

This study evaluated the efficacy and safety profile of urine alkalization therapy in male patients diagnosed with the renal underexcretion subtype of gout who received 12-week ULT. Given established evidence for urine alkalinization benefits in

male gout patients,[28] the uncertain risk-benefit profile in women due to limited data, and statistical constraints imposed by the marked male predominance in gout epidemiology, enrollment was restricted to men. Inclusion criteria: (1) male sex; (2) age 18–70 years; (3) fulfillment of the 2015 ACR/EULAR classification criteria for gout; (4) SU concentration ≥ 420 μmol/L; and (5) confirmed renal urate underexcretion subtype, defined as FEUA < 5.5% and UUE ≤ 600 mg/1.73 m^2/day. Key exclusion criteria comprised: (1) acute gout flare within 14 days preceding enrollment, (2) hepatic dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels > 2 × their upper limit of normal [ULN]), (3) impaired renal function (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2), and (4) concurrent use of urate-modifying agents or medications influencing urinary pH.

Treatment and Procedures

Prior to baseline assessments, all enrolled patients completed a standardized 14-day washout period to discontinue medications with urate-lowering potential. All participants received standardized dietary counseling at enrollment based on established gout management guidelines, including recommendations to limit purine-rich foods, alcohol, and fructose-sweetened beverages. The participants were observed every 4 weeks over a 12-week period. The starting dose of febuxostat was 20 mg daily and escalated to 40 mg daily if SU levels remained ≥ 360 μmol/L.This study employed a non-randomized design following the grouping methodology established in our previous research.[26] The distinct taste of citrate preparations and the necessity of identifying participants who would tolerate this taste precluded both blinding and randomization. A citrate mixture (3.5 g twice daily) was administered to participants in the alkalization (Alk) group to promote urine alkalization. This mixture comprised 50% citric acid, 10% sodium citrate, 10% potassium citrate, and 20% sodium carbonate, with the remaining 10% consisting of excipients. Participants were considered withdrawn cases after 3 consecutive days without medication.[6] Colchicine, gout flare prophylaxis, and other urate-lowering agents were prohibited during the study. Transaminase elevation ≥ 2 × ULN triggered polyene phosphatidylcholine prescription, and acute gout flares were managed with etoricoxib 120 mg daily (3–5 days).

General information, including age, height, body weight, heart rate, age at onset of gout, duration of gout, presence of tophi, and coexisting conditions (obesity, fatty liver, hypertension, diabetes mellitus, kidney stones, and kidney cysts), was collected at the baseline visit. Blood pressure, body mass index (BMI), and all laboratory parameters, including fasting blood glucose (FBG), total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), ALT, AST, blood urea nitrogen, serum creatinine, eGFR, cystatin, and urine pH, were measured at every visit. Other parameters, including the urine albumin-to-creatinine ratio (UACR), FEUA, UUE, serum potassium (K^+), serum sodium (Na^+), serum chloride (Cl^-), and serum calcium (Ca^{2+}), were collected at baseline and week 12. Obesity was defined as a BMI ≥ 28 kg/m^2 using Asian-specific criteria.[29,30] Gout flares required both: (1) patient-reported pain with visual analogue scale (VAS) scores > 3 (0–10 scale) and (2) clinician-confirmed joint inflammation within 24 h.[31] The incidence of gout flares was defined as the proportion of patients who experienced at least one flare during the study period (%). Pain severity was defined using the VAS, and all subsequent analyses of severity were based on VAS scores. Gout flares were captured through continuous telephone monitoring, with all reported events verified against clinical records. A dedicated assessment team, blinded to treatment allocation, evaluated flare occurrence and severity to ensure objective outcome ascertainment.

Dual-energy computed tomography (DECT) and ultrasonography of the symptomatic joints and kidneys were performed at baseline and week 12. Ultrasonography was performed using an ALOKA 70 system (Hitachi) with a 9–13 MHz transducer, covering the first metatarsophalangeal, ankle, knee, elbow, wrist, and metacarpal joints. Longitudinal and transverse images of elementary lesions (including tophi size measurements) were collected according to the OMERACT guidelines. Concurrently, DECT scans (Siemens Somatom Definition Flash) employed dual-tube settings (140 kVp/55 mAs and 80 kVp/255 mAs), with urate volumes quantified automatically using syngo.via Gout software (Siemens). All imaging analyses were blinded to the group allocation.

Outcomes

The primary outcome was the cumulative incidence of gout flares during the 12-week follow-up period. Secondary efficacy outcomes included other gout-related outcomes (rate of patients with an SU level below the target of 360 μmol/L, FEUA,

UUE, maximum diameter of tophi, and pain levels) and other laboratory parameters (FBG, total cholesterol, TG, HDL-C, LDL-C, ALT, AST, blood urea nitrogen, serum creatinine, eGFR, cystatin, and urine pH). Safety outcomes assessed the incidence of treatment-emergent adverse events (AEs), with pre-specified monitoring for new-onset urolithiasis and changes in renal or liver function. Specifically, AEs included: (1) ALT or AST elevations ≥ 2 × ULN; (2) new-onset kidney stones or new-onset renal cysts confirmed by ultrasound; (3) new-onset eGFR < 60 mL/min/1.73 m^2 or 24 hour UACR ≥ 30 mg/g.

Sample Size

The sample size calculation was powered by the primary endpoint of cumulative gout flare incidence during the study. Our prior study[26] showed a differential flare incidence of 21.26% (40.88% vs. 62.14%) between the Alk and Control groups. The power analysis (two-sided $\alpha = 0.05$, $\beta = 0.15$) indicated that 85 participants per group (1:1 ratio) would result in 85% power to detect this effect size via Fisher' s exact test. Considering an attrition rate of 20%, 107 participants were required for each study arm. Ultimately, 114 participants in the Alk group and 126 participants in the Control group completed the protocol-mandated assessments.

Statistical Analysis

Statistical analyses were performed using SPSS v25.0 (IBM) and GraphPad Prism 9.0. Continuous variables were expressed as mean ± standard deviation (normally distributed, Shapiro–Wilk $P > 0.05$) or median [interquartile range, (IQR)] (nonparametric), with categorical variables reported as percentages. Between-group comparisons employed the independent Student's *t*-test or Mann–Whitney U (Hodges–Lehmann estimators) for continuous data and the chi-square test for categorical outcomes. Within-group longitudinal analysis utilized the paired *t*-test or Wilcoxon's signed-rank test. Kaplan–Meier curves with Log rank testing were used to compare flare-free survival between cohorts. All protocol-compliant participants were analyzed, with $P < 0.05$ considered significant. To explore the relationship between urine alkalization and the risk of gout flares, a backward stepwise logistic regression was performed. Results are expressed as odds ratio (OR) and 95% confidence interval (95% CI).

Results

Study Flow and Baseline Characteristics

As depicted in Figure 1, 497 screened candidates underwent rigorous biochemical and comorbidity evaluation, with 217 excluded due to protocol-defined contraindications. In the remaining 280 patients, ULT was initiated using febuxostat. Of these, 280 eligible patients were assigned to the citric acid mixture group (Alk group, n = 128) or the Control group (n = 152). The final analysis included 240 participants (114 Alk, 126 Control) who completed the 12-week endpoint assessments, representing 85.7% protocol adherence (Figure 1). Per-protocol dose escalation to febuxostat 40 mg/day was implemented in 62.9% of participants (n = 151) who had SU levels ≥ 360 μmol/L at week 4. The escalation rate was significantly lower in the Alk than in the Control group (56.1% vs. 69.0%, respectively, $P = 0.039$).

Baseline characteristics demonstrated a homogenous cohort allocation (Table 1). The all-male cohort (mean age 45.97 ± 12.87 years) exhibited median [IQR] SU levels of 538.2 [498.0, 585.6] μmol/L. Urinary pH profiles showed no significant difference at baseline (Control 5.52 ± 0.33 vs Alk 5.53 ± 0.33, $P = 0.753$). Coexisting conditions (obesity, fatty liver disease, hypertension, diabetes, kidney stones and kidney cysts), chemical parameters, and other urine parameters revealed no clinically meaningful intergroup differences (all $P > 0.05$). In univariable logistic regression analysis, BMI, disease duration, intra-articular tophus, and urine alkalization were significantly associated with the number of gout flares ($P < 0.05$; Table 2). In Model 1, urine alkalization was associated with lower odds of gout flares (adjusted OR 0.365; 95% CI 0.209–0.638). In Model 2, urine alkalization remained associated with lower odds of gout flares (adjusted OR 0.335; 95% CI 0.193–0.583).

Urine pH values, although increased in both Alk and Control groups, were higher in the Alk group at weeks 4, 8, and 12 (week 4: 5.99 [5.54, 6.43] vs. 5.66 [5.48, 6.04], $P < 0.001$; week 8: 5.90 [5.50, 6.40] vs. 5.69 [5.42, 6.02], $P = 0.004$; week 12: 5.98 [5.58, 6.49] vs. 5.61 [5.35, 6.12], $P < 0.001$) (Table 3).

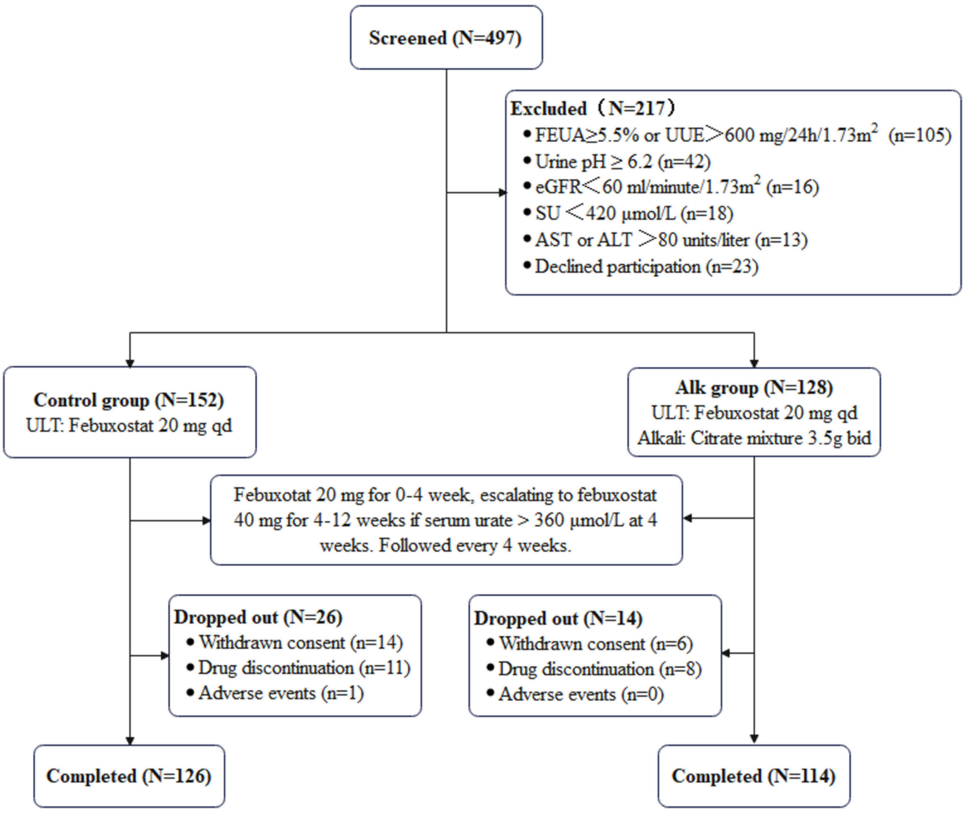

Figure 1 Flow chart.
Abbreviations: FEUA, fractional excretion of uric acid; UUE, 24-hour urinary uric acid excretion; eGFR, estimated Glomerular Filtration Rate; SU, serum urate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULT, urate-lowering therapy.

Primary Outcomes: Gout Flares

To compare the time-dependent distribution of gout flares between the two study groups, we assessed the flare frequency at each predefined study interval. During the 12-week follow-up, the overall cumulative incidence of gout flares was 47.9%,

Table 1 Baseline Demographics and Clinical Features of Gout Patients

	Total (n=240)	Control Group (n=126)	Alk Group (n=114)	P value
Demographic and clinical characteristics				
Age, mean ± SD years①	45.97±12.87	47.44 ± 12.86	44.34 ± 12.74	0.063
Male, no. (%) of patients②	240(100)	126(100)	114(100)	–
Height, mean ± SD cm①	174.66±6.16	174.37 ± 6.44	174.99 ± 5.85	0.442
Body weight, mean ± SD kg①	83.36±12.01	84.34 ± 12.05	82.46 ± 12.35	0.259
Body mass index, mean ± SD kg/m²①	27.27±3.12	27.63 ± 2.95	26.87 ± 3.27	0.078
Heart rate, mean ± SD bpm①	75.39±11.07	76.02 ± 10.20	74.70 ± 11.97	0.360
SBP, mean ± SD mmHg①	134.43±15.05	135.69 ± 16.50	133.04 ± 13.21	0.170
DBP, mean ± SD mmHg①	86.93±10.81	87.14 ± 10.90	86.69 ± 10.74	0.748
Gout features				
SU, median (IQR) μmol/L③	538.2 (498.0, 585.6)	537.0 (499.2, 582.0)	547.8 (498.0, 585.6)	0.703
Age at onset, median (IQR) years③	37 (30,45)	38 (31, 45)	35 (30, 45)	0.218
Duration of gout, median (IQR) years③	6 (2,10)	6.5 (2, 10)	6 (2, 11)	0.909
Intra-articular tophus, no. (%) of patients②	140 (58.33)	71 (56.35)	69 (60.53)	0.512

(*Continued*)

https://doi.org/10.2147/JIR.S597592

Table 1 (Continued).

	Total (n=240)	Control Group (n=126)	Alk Group (n=114)	P value
Coexisting conditions, no. (%) of patients				
Obesity②	90 (37.50)	54 (42.86)	36 (31.58)	0.072
Fatty liver②	70 (29.17)	39 (30.95)	31 (27.19)	0.522
Hypertension②	123 (51.25)	71 (56.35)	52 (45.61)	0.097
Diabetes②	4 (1.67)	3 (2.38)	1 (0.88)	0.624
Kidney stones②	12 (5.00)	9 (7.14)	3 (2.63)	0.109
Kidney cyst②	69 (28.75)	36 (28.57)	33 (28.95)	0.949
Blood chemistry parameters				
Fasting glucose, mean ± SD mmol/L①	5.81±0.56	5.80 ± 0.62	5.82 ± 0.48	0.827
Total cholesterol, mean ± SD mmol/L①	5.24±0.97	5.30 ± 1.02	5.16 ± 0.92	0.262
Triglyceride, median (IQR) mmol/L③	1.73 (1.25,2.58)	1.74 (1.31, 2.67)	1.73 (1.16, 2.57)	0.437
HDL-C, mean ± SD mmol/L①	1.20±0.27	1.17 ± 0.27	1.23 ± 0.27	0.086
LDL-C, mean ± SD mmol/L①	3.65±0.93	3.72 ± 0.97	3.58 ± 0.87	0.259
AST, median (IQR) U/L③	21 (18,26)	21 (19, 26)	21 (18, 25)	0.715
ALT, median (IQR) U/L③	24.5 (18,36)	25 (18, 36)	24 (18, 34)	0.975
BUN, mean ± SD mmol/L①	4.90±1.39	4.98 ± 1.46	4.81 ± 1.30	0.344
eGFR, mean ± SD mL/minute/1.73 $m^2$①	92.01±17.29	91.38 ± 18.44	92.71 ± 15.99	0.552
CREA, mean ± SD mmol/L①	85.98±14.56	86.21 ± 15.33	85.73 ± 13.74	0.800
Ccr, mean ± SD mL/min①	115.53±31.87	114.30 ± 32.31	116.88 ± 31.46	0.533
CYSc, mean ± SD mg/dL①	1.09±0.21	1.09 ± 0.23	1.10 ± 0.18	0.808
CA72-4, median (IQR) U/mL③	2.46 (1.36,6.42)	2.08 (1.15, 7.03)	2.9 (1.52, 6.41)	0.111
Urine parameters				
Urine volume, median (IQR) mL③	2750 (2150,3400)	2700 (2250, 3300)	2780 (2000, 3500)	0.507
Urine pH, mean ± SD①	5.53±0.33	5.52 ± 0.33	5.53 ± 0.33	0.753
UACR, median (IQR) g/mol③	1.30 (0.53,3.52)	1.19 (0.65, 1.88)	1.65 (0.36, 7.01)	0.640

Note: ①Independent Student's *t*-test, ②Chi-square test, ③Mann–Whitney *U*-test.
Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood. Pressure; SU:Serum urate; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BUN:Blood urea nitrogen; eGFR, estimated Glomerular Filtration Rate; CREA, serum Creatinine; Ccr:Creatinine Clearance Rate; CYSc:Cystatin; UACR, 24 hours Urinary Albumin Creatinine Ratio;

with the Alk group showing a significantly lower incidence (35.1%) than the Control group (59.5%, $P < 0.001$). A single gout flare was observed in 25.0% of the participants, with 21.1% in the Alk and 28.6% in the Control group ($P = 0.179$). Recurrent gout flares (≥ 2) occurred in 22.9% of participants. Importantly, the Alk group had a significantly lower rate of recurrent gout flares than the Control group (14% vs. 31% $P = 0.002$) (Figure 2A and B, Supplementary Table 1).

In the Alk group, the incidence of gout flares gradually decreased and was significantly lower at weeks 8 and 12 than in the Control group during the follow-up period (week 4: 23.7% vs. 33.3%, $P = 0.099$; week 8: 18.4% vs. 32.5%, $P = 0.013$; week 12: 13.2% vs. 34.1, $P < 0.001$). By contrast, the incidence of gout flares remained stable in the Control group (Figure 2C). The proportion of recurrent flares was lower in the Alk group at weeks 4 and 12 (week 4: 2.6% vs. 8.7%, $P = 0.044$; week 8: 3.5% vs. 7.9%, $P = 0.144$; week 12: 0.9% vs. 6.3%, $P = 0.026$) (Figure 2D). The proportion of patients with a single gout flare was also significantly lower in the Alk group at 12 weeks (week 4: 21.1% vs. 24.6%, $P = 0.513$; week 8: 14.9% vs. 24.6%, $P = 0.061$ week 12: 12.3% vs. 27.8%, $P = 0.003$) (Figure 2E).

During the 12 weeks, the 126 patients in the Control group experienced 171 flares (1.36 flares/patient), whereas the 114 patients in the Alk group reported 75 flares (0.66 flares/patient, $P < 0.001$). During the first 4 weeks, 61 flares were identified in the 126 patients (0.48 flares/patient) of the Control group and 30 flares in the 114 patients (0.26 flares/patient) of the Alk group. The two groups did not significantly differ ($P = 0.064$). In weeks 4–8, 56 flares occurred in the 126 patients (0.44 flares/patient) of the Control group, and 28 flares occurred in the 114 patients (0.25 flares/patient) of the Alk group ($P = 0.012$). In weeks 8–12, 54 flares were identified in the 126 patients (0.43 flares/patient) of the Control group, and 17 flares occurred in the 114 patients (0.15 flares/patient) of the Alk group ($P < 0.001$) (Figure 2F). Participants in the Alk group also reported lower pain levels during gout flares than those in the Control group ($P < 0.001$) (Table 3).

Table 2 Logistic Regression Model for Factors Associated with Gout Flare

	Univariate Analysis		Multivariate Analysis			
			Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, years	1.008 (0.988, 1.028)	0.458	1.004 (0.919, 1.096)	0.930		
Onset age, years	0.993 (0.970, 1.017)	0.573	0.991 (0.906,1.084)	0.841		
Body mass index, kg/m^2	1.142 (1.047, 1.247)	0.003	1.140 (1.025, 1.267)	0.015		
1 ≥ Comorbidities	1.415 (0.729, 2.746)	0.305	1.414 (0.615, 3.255)	0.415		
Disease duration, years	1.041 (1.000,1.085)	0.049	1.031 (0.940, 1.132)	0.515		
Intra-articular tophus	1.857 (1.103, 3.129)	0.020	1.725 (0.967, 3.076)	0.065		
Urine alkalization	0.368 (0.218, 0.621)	< 0.001	0.365 (0.209, 0.638)	< 0.001	0.335 (0.193, 0.583)	< 0.001
SU, μmol/L	1.001 (0.997, 1.005)	0.504			1.002 (0.997, 1.006)	0.486
Glucose, mmol/L	0.817 (0.516, 1.292)	0.387			0.850 (0.524, 1.380)	0.512
Total cholesterol, mmol/L	1.038 (0.800, 1.349)	0.777			0.232 (0.049, 1.106)	0.067
Triglyceride, mmol/L	1.057 (0.891, 1.254)	0.525			1.494 (0.953, 2.341)	0.080
HDL-C, mmol/L	0.518 (0.198, 1.359)	0.181			2.330 (0.420, 12.929)	0.333
LDL-C, mmol/L	1.083 (0.823, 1.425)	0.571			4.156 (0.928, 18.620)	0.063
eGFR, mL/minute/1.73 m^2	1.003 (0.989, 1.018)	0.644			1.005 (0.989, 1.022)	0.526
Urine pH	0.822 (0.377, 1.789)	0.621			0.853 (0.376, 1.935)	0.704

Notes: Model 1: fully adjusted by urine alkalization, age, onset age, body mass index, comorbidities, disease duration, and intra-articular tophus Model 1: fully adjusted by urine alkalization, serum urate, glucose, total cholesterol, triglyceride, High-Density Lipoprotein Cholesterol, Low-Density Lipoprotein Cholesterol, estimated Glomerular Filtration Rate, and urine pH.

Abbreviations: 95% CI, 95% confidence interval; SU, Serum urate; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; eGFR, estimated Glomerular Filtration Rate.

Table 3 Major Clinical Parameters During the Trial in Gout Participants

	Baseline	Week 4	Week 8	Week 12
Serum urate (SU), median (IQR), μmol/L①				
Control group	537.0 (499.2, 582.0)	404.4 (351.0, 468.0)$^{\#\#\#}$	349.8 (309.6, 411.6)$^{\#\#\#}$	339.6 (298.2, 404.4)$^{\#\#\#}$
Alk group	547.8 (498.0, 585.6)	370.2 (333.0, 411.6)$^{**\#\#\#}$	342.6 (316.8, 381.0)$^{\#\#\#}$	345.6 (311.4, 388.2)$^{\#\#\#}$
Urine pH, median (IQR)①				
Control group	5.53 (5.33, 5.73)	5.66 (5.48, 6.04)$^{\#\#\#}$	5.69 (5.42, 6.02)$^{\#\#\#}$	5.61 (5.35, 6.12)$^{\#\#\#}$
Alk group	5.47 (5.29, 5.80)	5.99 (5.54, 6.43)$^{***\#\#\#}$	5.90 (5.50, 6.40)$^{**\#\#\#}$	5.98 (5.58, 6.49)$^{***\#\#\#}$
Body mass index (BMI), mean ± SD, kg/m^{2}②				
Control group	27.63 ± 2.95	27.53±3.01	27.47±3.04	27.55±3.11
Alk group	26.87 ± 3.27	26.83±3.31	26.89±3.16	26.87±3.27
Systolic Blood Pressure (SBP), mean ± SD, mmHg②				
Control group	135.69 ± 16.50	134.44 ± 15.38	132.42 ± 15.71	131.44 ± 15.49
Alk group	133.04 ± 13.21	133.64 ± 13.63	134.47 ± 13.39	134.65 ± 14.27
Diastolic blood pressure (DBP), mean ± SD, mmHg②				
Control group	87.14 ± 10.90	87.89 ± 10.38	86.25 ± 10.70	86.57 ± 11.24
Alk group	86.69 ± 10.74	86.71 ± 10.45	87.25 ± 10.51	86.38 ± 9.81
Serum creatinine (CREA), mean ± SD, mmol/L②				
Control group	86.21 ± 15.33	87.36 ± 14.77	84.88 ± 14.95	85.54 ± 14.47
Alk group	85.73 ± 13.74	85.10 ± 11.65	83.39 ± 12.28	85.88 ± 11.66

(*Continued*)

Table 3 (Continued).

	Baseline	Week 4	Week 8	Week 12
Blood urea nitrogen (BUN), mean ± SD, mmol/L②				
Control group	4.98 ± 1.46	5.27 ± 1.59$^{\#\#}$	5.45 ± 1.56$^{\#\#\#}$	5.58 ± 1.36$^{\#\#\#}$
Alk group	4.81 ± 1.30	5.13 ± 1.26$^{\#\#}$	5.26 ± 1.17$^{\#\#\#}$	5.03 ± 1.15$^{**\#}$
Cystatin (Cys-c), mean ± SD, mg/dL②				
Control group	1.11 ± 0.24	–	–	1.10 ± 0.23
Alk group	1.10± 0.18	–	–	1.10 ± 0.15
Creatinine Clearance Rate (Ccr), mean ± SD, mL/min②				
Control group	114.30 ± 32.31	111.17 ± 32.28	114.20 ± 35.28	110.58 ± 34.87
Alk group	116.88 ± 31.46	115.83 ± 28.24	118.38 ± 28.67	114.69 ± 28.48
Estimated Glomerular filtration rate (eGFR), mean ± SD, mL/minute/1.73 m^{2}②				
Control group	91.38 ± 18.44	89.65 ± 16.75	93.59 ± 19.39$^{\#}$	92.57 ± 18.40
Alk group	92.71 ± 15.99	93.07 ± 15.65	95.46 ± 16.51$^{\#}$	91.92 ± 14.90
Urinary albumin creatinine ratio (UACR), median (IQR), g/mol①				
Control group	1.19 (0.65, 1.88)	–	–	3.66 (0.65, 8.46)$^{\#\#\#}$
Alk group	1.65 (0.36, 7.01)	–	–	1.08 (0.62, 2.99)**
Fractional excretion of uric acid (FEUA), median (IQR), %①				
Control group	3.76(3.29,4.30)	–	–	3.44(2.71,4.10)
Alk group	3.66(3.22,4.40)	–	–	3.34(2.95,4.07)
24 hours urinary uric acid excretion (UUE), median (IQR), mg/d/1.73 m^{2}①				
Control group	463.67(399.38,502.54)	–	–	332.99(241.09,428.89)$^{\#\#\#}$
Alk group	450.44(382.91,520.83)	–	–	355.32(269.90,466.19)$^{\#\#\#}$
Fasting blood glucose (FBG), mean ± SD, mmol/L②				
Control group	5.80 ± 0.62	5.73 ± 0.64	5.67 ± 0.62	5.61 ± 0.59
Alk group	5.82 ± 0.48	5.68 ± 0.52	5.60 ± 0.47	5.71 ± 0.54
Triglyceride (TG), median (IQR), mmol/L①				
Control group	1.74 (1.31, 2.67)	1.85 (1.40, 2.74)	1.74 (1.35, 2.80)	1.86 (1.32, 2.58)
Alk group	1.73 (1.16, 2.57)	1.67 (1.07, 2.26)*	1.53 (1.09, 2.37)*	1.44 (1.09, 2.26)$^{**\#\#}$
Total Cholesterol (TC), mean ± SD, mmol/L②				
Control group	5.30 ± 1.02	5.12 ± 1.05	5.10 ± 1.04	5.19 ± 1.07
Alk group	5.16 ± 0.92	5.09 ± 0.92	5.10 ± 0.95	5.14 ± 0.91
High-Density Lipoprotein Cholesterol (HDL), mean ± SD, mmol/L②				
Control group	1.17 ± 0.27	1.18 ± 0.26	1.18 ± 0.26	1.18 ± 0.25
Alk group	1.23 ± 0.27	1.26 ± 0.27$^{*\#}$	1.29 ± 0.28$^{**\#\#\#}$	1.31 ± 0.27$^{***\#\#\#}$
Low-Density Lipoprotein Cholesterol (LDL), mean ± SD, mmol/L②				
Control group	3.72 ± 0.97	3.51 ± 0.99	3.52 ± 1.02	3.60 ± 1.04
Alk group	3.58 ± 0.87	3.52 ± 0.90	3.57 ± 0.91	3.65 ± 0.90

(*Continued*)

Table 3 (Continued).

	Baseline	Week 4	Week 8	Week 12
Aspartate Aminotransferase (AST), median (IQR), U/L①				
Control group Alk group	21 (19, 26) 21 (18, 25)	22 (19, 27) 22(19, 29)	22 (18, 26) 22 (19, 27)	22 (18, 26) 22 (18, 26)
Alanine Aminotransferase (ALT), median (IQR), U/L①				
Control group Alk group	25 (18, 36) 24 (18, 34)	26 (18, 35) 25 (19, 42)	25 (17, 35) 28 (20, 40)	25 (18, 38) 24 (19, 34)
Visual analogue scale (VAS) scores of gout flares during the 12-week, median (IQR)②				
Control group Alk group	– –	– –	– –	0.67(0,2.0) 0(0,1)***

Notes: ①Wilcoxon's signed-rank test when compared to baseline or Mann–Whitney *U*-test when compared between groups; ②The paired *t*-test when compared to baseline or Independent Student's *t*-test when compared between groups. Compared to baseline,VAS scores represent average pain intensity per flare. # P<0.05, ## P<0.01, and #### P<0.0001.Compared between groups, * P<0.05, **P<0.01 and ***P<0.001.

Secondary Outcomes: Changes in Clinical Parameter

Both the Alk and Control groups showed reductions in SU levels compared with the baseline (Table 3). The proportion of participants with SU< 360 μmol/L was significantly higher in the Alk group than in the Control group at week 4.

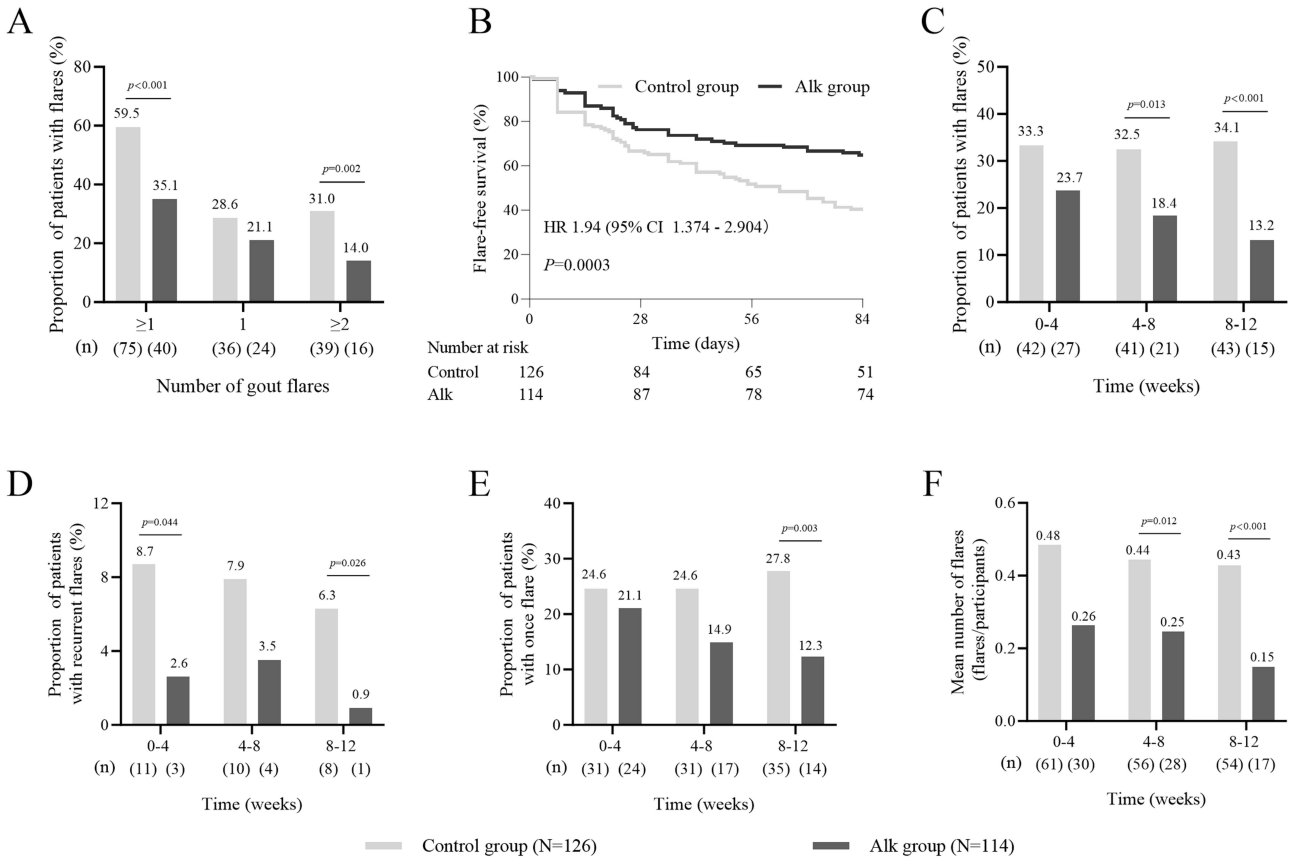

Figure 2 Incidence of gout flares during the 12-weeks follow-up. (**A**) Number of gout flares during the 12-weeks follow-up. (**B**) Kaplan-Meier analysis of the accumulated flare-free survival rates. (**C**) Proportion of patients with gout flares during every 4 weeks. (**D**) Proportion of patients with recurrent gout flares during every 4 weeks. (**E**) Proportion of patients with once gout flare during every 4 weeks. (**F**) Mean number of gout flares during every 4 weeks.

https://doi.org/10.2147/JIR.S597592

However, the proportions were similar in both groups at 12 weeks (Supplementary Figure 1A–D). At the study endpoint, no significant differences were observed in FEUA or UUE between the two groups (Table 3). The maximum diameter of the tophi detected by ultrasound and the volume of tophi evaluated through DECT were not significantly different between the two groups (Supplementary Figure 1E and F). However, the pain severity was lower in the Alk than in the Control group ($P < 0.001$). Triglyceride levels were lower and HDL-C levels were higher in the Alk than in the Control group at weeks 4, 8, and 12. The UACR increased in the Control group from 1.19 [0.65, 1.88] at baseline to 3.66 [0.65, 8.46] ($P = 0.091$), whereas the UACR decreased in the Alk group from 1.65 [0.36, 7.01] at baseline to 1.08 [0.62, 2.99] at week 12 and was significantly lower than that in the Control group ($P = 0.001$). Blood urea nitrogen was lower in the Alk than in the Control group at week 12 (5.03 ± 1.15 vs. 5.58 ± 1.36, $P = 0.001$); however, other renal function markers remained at equivalent levels. No differences between the two groups were observed in liver function parameters (ALT and AST), blood pressure, FBG, or BMI (Table 3).

Safety

As presented in Table 4, during the 12-week intervention period, the overall incidence of AEs did not differ significantly between the Alk and Control groups. Neither cohort experienced severe adverse reactions, including skin reactions, gastrointestinal events, fulminant hepatitis, or major adverse cardiac events (data not shown). No significant between-group differences were observed in hepatic safety outcomes, including the proportion of participants with ALT or AST elevations ≥ 2 × ULN. Additionally, no differential renal risk was identified, particularly regarding new-onset kidney stones ($P = 0.686$) and new-onset renal cysts ($P = 0.483$). Furthermore, no patients in either group developed new-onset eGFR < 60 mL/min/1.73 m^2 or 24h UACR ≥ 30 mg/g. The electrolyte profiles (serum potassium and chloride) remained similar in both groups, without significant group differences. Although serum sodium and calcium levels were higher in the Alk than in the Control group at week 12, both values remained within the normal ranges (Table 4).

Table 4 Adverse Events During the 12-Week Follow-Up

	Control Group (n=126)	Alk Group (n=114)	P value
New-onset AST level elevation, n(%)①			
1–2-times elevation	57 (45.2)	59 (51.7)	0.313
2–3-times elevation	2 (1.6)	2 (1.8)	1.000
>3 times elevation	0 (0)	1 (0.9)	–
New-onset ALT level elevation, n(%)①			
1–2-times elevation	51 (40.5)	59 (51.7)	0.080
2–3-times elevation	4 (3.2)	2 (1.8)	0.686
>3 times elevation	0 (0)	1 (0.9)	–
Serum electrolytes level at week 12, mean±SD			
Serum potassium (mmol/L)②	4.33±0.32	4.33±0.35	0.957
Serum sodium (mmol/L)②	141.29±1.97	142.30±1.50	<0.0001
Serum chlorine (mmol/L)②	102.33±3.72	101.89±2.27	0.266
Serum calcium (mmol/L)②	2.45±0.09	2.49±0.11	0.017
New-onset kidney stones, n(%)①	4 (3.2)	2 (1.8)	0.686
New-onset renal cyst, n(%)①	3 (2.4)	5 (4.4)	0.483
New-onset eGFR<60 mL/min/1.73 m2, n(%)①	0 (0)	0 (0)	–
New-onset 24h-UACR≥30mg/g, n(%)①	0 (0)	0 (0)	–

Notes: ①Chi-square test, ②Independent Student's *t*-test; Values are the number of patients.
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated Glomerular Filtration Rate; 24h-UACR, 24 hours Urinary Albumin Creatinine Ratio.

Discussion

This study demonstrated that a 12-week combined urine alkalization regimen significantly reduced the frequency of gout flares in patients with renal urate underexcretion and low urinary pH, supporting the potential role of urine alkalization as an adjunctive strategy in targeted gout management. Intriguingly, the observed reduction in gout flares occurred despite similar SU levels in the later stages of the study, suggesting that urine alkalization may exert therapeutic effects beyond the lowering of urate levels. Future studies incorporating specific inflammatory markers are warranted to clarify the potential anti-inflammatory effects of urine alkalization in gout management.

Renal underexcretion is the predominant cause of hyperuricemia, accounting for 60% of gout cases.[5,6] As urate excretion largely depends on glomerular filtration, patients with chronic kidney disease (CKD) stage 3 or higher were excluded to better isolate this phenotype.[32] In this study, urine alkalization combined with XOIs significantly reduced the cumulative flare incidence (35.1% vs. 59.5%) and recurrent flare rates (14.0% vs. 31.0%), accompanied by improved lipid profiles. Notably, 45% of patients in the renal underexcretion group exhibited acidic urine, which is similar to the percentages in general populations of patients with gout.[5,28] Our previous study demonstrated that low urinary pH is associated with an increased risk of gout flares, with a notably higher frequency observed when the pH falls below 6.9.[28] These findings suggest that persistent urinary acidification may contribute to inflammatory activity and crystal precipitation, particularly in the renal underexcretion subtype, highlighting the importance of urine alkalization as a targeted preventive strategy in this subgroup.

This study demonstrated that adjunctive urine alkalization in patients with the renal underexcretion subtype significantly reduced the frequency of gout flares with progressive improvement over 12 weeks. These findings align with accumulating evidence implicating urine pH as a modifiable factor in the pathophysiology of gout.[28,33] A low urinary pH is closely associated with chronic sub-clinical metabolic acidosis, particularly in patients with gout. Alkalization therapy can correct this acid load, improve the systemic acid-base balance, elevate urine pH, enhance uric acid solubility and excretion, and mitigate the inflammatory burden.[34,35] Mechanistically, low extracellular pH delays neutrophil apoptosis, promotes pro-angiogenic neutrophil phenotypes, and stimulates NLRP3 inflammasome activation in monocytes/macrophages, thereby enhancing interleukin (IL)-1β production.[36,37] In contrast, sodium bicarbonate supplementation promotes macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype.[38,39] Furthermore, alkalization therapy reduced renal chemokine expression (CCL2 and CCL5) and monocyte infiltration in a murine model,[27] suggesting a broader anti-inflammatory effect. Collectively, these findings support a pH-mediated immunoregulatory mechanism by which urine alkalization attenuates crystal-induced inflammation, offering a targeted anti-inflammatory strategy for patients with the renal underexcretion subtype of gout.

Citrate exerts complex immunomodulatory effects through two primary pathways. First, citrate serves as a precursor to itaconate, an anti-inflammatory metabolite generated by immune-responsive gene 1 (Irg1), which suppresses proinflammatory cytokine production (IL-1β, IL-12p70, and IL-6), inhibits the expression of inducible nitric oxide synthase, and reduces the generation of reactive oxygen species (ROS).[40,41] Irg1 deficiency enhances IL-1β secretion, underscoring the anti-inflammatory role of the citrate–Irg1–itaconate axis. Second, cytosolic citrate is cleaved by ATP-citrate lyase (ACLY) into acetyl-CoA and oxaloacetate (OAA), which contribute to inflammation via PGE2 synthesis and promote the production of ROS and NO.[42,43] Notably, citrate exhibits a concentration-dependent duality: while low levels may support cell proliferation, high concentrations inhibit ACLY, reduce acetyl-CoA and OAA levels, and exert anti-inflammatory effects.[44,45] Although exogenous citrate can also enhance NLRP3 and NF-κB signaling under certain conditions,[46] our study demonstrated that citrate supplementation significantly reduced the frequency of gout flares, suggesting a net anti-inflammatory effect. These findings highlight the therapeutic potential of citrate in gout management and warrant further mechanistic investigation, particularly regarding its modulation of monosodium urate crystal-induced inflammation.

After 12 weeks of treatment, the Alk group demonstrated significant improvements in TG and HDL-C levels. Previous studies have reported that combining citrate preparations with XOIs can improve the lipid profiles of patients with hyperuricemia.[47] Additionally, high concentrations of exogenous citrate have been shown to inhibit ACLY activity, thereby reducing fatty acid synthesis via a feedback mechanism.[44] Thus, both basic and clinical research support the idea that alkalization therapy can improve lipid metabolism.[26] TG and HDL-C are closely associated with inflammation, indicating the inflammatory condition and performing significant roles in the inflammatory process.[48,49] In this study, after urine alkalization

therapy, patients with the renal underexcretion type of gout showed improved lipid profiles, which may also indicate alleviated inflammation.

Our previous findings indicated that patients with the renal underexcretion subtype of gout exhibit heightened sensitivity to febuxostat, exceeding that observed in patients with the combined subtype.[2] In the present study, the Alk group of patients receiving febuxostat 20 mg daily had by week 4 significantly higher rates of patients not exceeding the target SU (360 μmol/L). However, at weeks 8 and 12, SU levels converged between the two study groups, which is consistent with earlier observations in the general gout population.[26] These results indicate that urine alkalization may potentiate the initial urate-lowering effect of febuxostat, even in patients with an underexcretion phenotype. UACR is a sensitive and reliable marker of glomerular injury and serves as a key criterion in CKD classification.[50] In this study, UACR was used to assess the renal effects of urine alkalization in patients with renal urate underexcretion gout. After 12 weeks of combination therapy, the UACR significantly improved, which is consistent with previous findings on the renoprotective effects of alkalization therapy.[26] Notably, this improvement occurred despite comparable serum urate levels between groups at week 12, suggesting a direct anti-inflammatory effect on the kidney rather than an indirect effect mediated solely by urate reduction. This is supported by experimental evidence that sodium bicarbonate alleviates renal inflammation via modulation of the NLRP3 inflammasome pathway,[51] as well as clinical data showing that urine alkalization reduces urinary inflammatory proteins in patients with nephrolithiasis.[52] This improvement in UACR underscores the potential of alkalization therapy to mitigate renal damage in patients with gout, particularly in those with underexcretion profiles.

Since the citrate mixture contains 50% citric acid, 10% sodium citrate, 10% potassium citrate, and 20% sodium carbonate, we observed statistically significant differences in serum sodium and calcium levels between the Alk and Control groups at week 12. The increase in serum sodium in the Alk group is biologically plausible given the sodium content of the intervention. However, both values remained well within normal laboratory reference ranges, and no patient developed clinically significant electrolyte abnormalities or required medical intervention. For serum calcium, there is no direct biological mechanism linking the intervention to these changes. Therefore, we consider both differences unlikely to be of clinical relevance.

This study has some limitations. Firstly, as a single-center and controlled study, potential selection bias and confounding factors may have existed. The open-label design for patients and treating physicians represents a limitation. However, blinded outcome assessment and statistical analysis were employed to minimize detection and ascertainment bias. Secondly, all participants were male with an eGFR $\geq$60 mL/min/1.73 m^2, limiting the generalizability of findings to female populations and patients with renal impairment. Thirdly, the 12-week intervention period was relatively short, making it difficult to assess the long-term efficacy and safety. Future multicenter studies with longer follow-up periods, broader patient populations (both sexes and varying renal function), and comparisons of different alkalizing agents are needed to further clarify the clinical value of alkalization therapy in all patients with gout, especially in those with the renal underexcretion type. The analysis of multiple secondary outcomes and time points was not adjusted for multiple comparisons. While the primary outcome was prespecified, the risk of type I error is increased for secondary findings. Therefore, these results should be interpreted as exploratory and warrant confirmation in future studies.

Conclusion

In patients with the common underexcretion-type gout and low urinary pH, adding a simple and safe alkalizing agent to standard XOI therapy represents an effective strategy to significantly reduce the burden of debilitating gout flares during the critical initial treatment phase.

Data Sharing Statement

The code and source data are available upon the requirement received by the corresponding author.

Ethics Approval

This study involves human participants and was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Participants gave written informed consent to participate in the study before taking part.

Acknowledgment

The authors gratefully acknowledge the assistance of Yazhou Luo with the statistical analysis.

Author Contributions

Lingfang Xu: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. Jidong Cheng: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. Lingling Cui: Conceptualization, Methodology, Data curation, Writing – review & editing. Kai Guo: Methodology, Data curation, Formal analysis, Writing – review & editing. Can Wang:Data curation, Investigation, Writing – review & editing. Han Qi: Data curation, Writing – review & editing. Qian Zhang: Data curation, Writing – review & editing. Yuwei He: Data curation, Writing – review & editing. Xinde Li: Data curation, Writing – review & editing. Lin Han: Data curation, Writing – review & editing. Xuefeng Wang: Data curation, Writing – review & editing. Wenyan Sun: Data curation, Writing – review & editing. Xueyan Zhang: Investigation, Funding acquisition, Writing – review & editing. Mingshu Sun: Data curation, Funding acquisition, Writing – review & editing. Changgui Li: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. Zhen Liu: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by National Key Research and Development Program of China (NO. 2022YFC2503300), the "Clinical Medicine + X" Research Project of the Affiliated Hospital of Qingdao University (NO. QYFY+X2024127), the Qingdao Science and Technology for Public Well-being Special Project (NO. 25-1-5-smjk-20-nsh), the National Natural Science Foundation of Shandong province (NO. ZR2024QH121) and the National Natural Science Foundation of China (NO. 82401032).

Disclosure

The authors have no other conflicts of interest to declare.

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