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Original article

The efficacy and safety of citrate mixture *vs* sodium bicarbonate on urine alkalization in Chinese primary gout patients with benzbromarone: a prospective, randomized controlled study

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Abstract

Objectives. To compare the efficacy and safety of citrate mixture and sodium bicarbonate on urine alkalization in gout patients under benzbromarone treatment.

Methods. A prospective, randomized, parallel controlled trial was conducted among 200 gout patients in the dedicated gout clinic of the Affiliated Hospital of Qingdao University. The participants were randomly divided into two groups (1:1), sodium bicarbonate group (3 g/day) and citrate mixture group (7 g/day). All patients were prescribed with 25 mg/day benzbromarone at initiation and maintained at a dose of 50 mg/day. Clinical and biochemical data were collected at each follow-up time point (baseline, weeks 2, 4, 8 and 12).

Results. A total of 182 patients completed the 12-week urine alkalization study. The urine pH value of both groups increased significantly from the baseline to the final follow-up time point (sodium bicarbonate group, 5.50–6.00, $P < 0.05$; citrate mixture group, 5.53–5.93, $P < 0.05$). While the comparisons regarding urine pH between treatment groups showed no significant differences for each time point. The estimated glomerular filtration rate (eGFR) dropped significantly after 12 weeks' trial in the sodium bicarbonate group ($P < 0.01$), while it was comparable between baseline and the last follow-up ($P > 0.05$) in the citrate mixture group. Results of urine analysis showed that the incident rate of occult blood in the sodium bicarbonate group was higher than that in the citrate mixture group (38 *vs* 24%, $P < 0.05$), accompanied by a similar occurrence of kidney stones. After 12-week follow-up, the frequency of twice gout flare in the citrate mixture group was significantly lower than that in sodium bicarbonate group (4 *vs* 12%, $P = 0.037$). No treatment-emergent adverse events occurred.

Conclusion. The efficacy of citrate mixture on urine alkalization is comparable to sodium bicarbonate under benzbromarone treatment without significant adverse events. Citrate mixture is superior to sodium bicarbonate in lowering the incidence of urine occult blood and the frequency of gout attacks.

Trial registration. Registered with ChiCTR (http://www.chictr.org.cn), No. ChiCTR1800018518.

Key words: gout, urine alkalization, citrate mixture, sodium bicarbonate

CLINICAL SCIENCE

Rheumatology key messages

- Citrate mixture shows similar efficacy to sodium bicarbonate in urine alkalization for gout patients.
- Citrate mixture is superior to sodium bicarbonate in lowering the incidence of urine occult blood and the frequency of gout attacks.
- A standardized method of urine pH determination should be instituted.

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Introduction

In recent years, the incidence of renal calculus in patients with gout has increased up to 33% [1]. Pure urate stones are found in ~50% of patients with gout [2]. Urate crystals are deposited in renal tubules and interstitium, causing substantial renal damage, such as inflammatory response and fibrosis. Low urine pH (≤5.5), low urine volume and high urine urate are considered as three main causes of urate renal calculus [3]. Although kidney damage in gout patients is mostly linked to hyperuricaemia-led vascular damage [4] and monosodium urate crystal deposition in the medulla [5], renal damage caused by hyperuricaemia and urate crystals is also closely related to urine pH as low urine pH decreases the solubility of urate in the kidney [6]. In the case of uricosurics, recent lesinurad trials support that the combination of xanthine oxidase inhibitors and uricosurics prevents the occurrence of stones [7]; however, the increased risk of adverse events should not be ignored [8]. Furthermore, Asplin and Goldfarb [9] demonstrated that the use of xanthine oxidase inhibitors such as allopurinol and febuxostat alone to prevent kidney stones is far less effective than alkalizing urine drugs. A lower urine pH determines the solubility of urate in urine and promotes the autophosphorylation of Pyk2, generation of reactive oxygen species and damage of the tubule interstitium, and causes proteinuria and kidney damage [10]. Although urine alkalization in the management gout patients has not been established, the urine pH in gout patients, especially for uricosurics users, needs appropriate attentions.

Thus far, there is still no standard treatment for alkalization and pH measurement of urine. The commonly used alkaline urine drugs are mainly sodium bicarbonate, potassium citrate and citrate mixture. Sodium bicarbonate mainly regulates acid-base disorders in the body by increasing serum bicarbonate ions. It is suitable for patients with chronic kidney disease (CKD) and metabolic acidosis [11]. Potassium citrate is the first choice to dissolve and prevent urinary acid kidney stones in the clinic [12]. Nevertheless, only 13% of patients who used potassium citrate to treat kidney stones can maintain long-term medication, because potassium citrate causes adverse effects such as abdominal pain and diarrhoea [13]. Citrate mixture has been reported to alkalize urine as well as to improve renal function [14], with its high water solubility and more acceptable taste. The methods used to monitor pH also seem to vary considerably, with some studies using pooled 24-h urine for pH determination [15–17] and others using periodic measurements [3, 18, 19]. Even if periodic measurements are used to measure the pH value of urine, they are inconsistent in measurement interval, collection conditions and analysis methods.

The indication of urine alkalinization in gout patients is still debatable [14, 20]. The British Society for Rheumatology Guideline for the Management of Gout and 2018 multidisciplinary consensus in Taiwan for gout suggest that gout patients, especially those using uricosuric agents and recurrent stone formers, should alkalize urine [21, 22]. However, the 2020 ACR Gout Clinical Practice Guidelines advise against alkalized urine for gout patients due to the lack of evidence [20].

In order to provide gout patients with a more reliable alkalized urine scheme and to provide evidence for the guidelines, this study was conducted to compare the efficacy and safety of the citric mixture (50% citric acid, 10% sodium citrate, 10% potassium citrate and 20% sodium carbonate) and sodium bicarbonate.

Methods

Study design and participants

The study was a prospective, randomized, parallel, controlled clinical trial. This trial was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University and registered at the China Clinical Trial Registration Center (No. ChiCTR1800018518). Patients with primary gout were recruited between July 2018 and April 2019 from the dedicated gout clinic of the Affiliated Hospital of Qingdao University. Written informed consent was obtained from all patients before the initiation of the trial.

Inclusion criteria were age between 18 and 70 years old, male, meeting the 2015 ACR/EULAR clinical diagnostic criteria for gout [23]. Exclusion criteria included glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, serum urate (SU) <420 μmol/l, transaminase >2-fold of the upper limit of normal, urine pH (morning urine) >6, combined with kidney stones or polycystic kidneys detected by US before the enrolment, taking other drugs affecting SU and/or urine pH (supplementary Table S1, available at *Rheumatology* online).

Treatment and procedures

All participants included in the study underwent a 14-day washout period with a low-purine diet and drug washout. If a gout flare occurred during this period, patients were given etoricoxib 120 mg per day for 3–5 days and restarted the period. Patients were randomly assigned to the sodium bicarbonate group or the citrate mixture group (1:1) according to a random number generator. Patients in both groups received urate-lowering treatment and urine alkalization treatment (sodium bicarbonate 1 g three times a day, citrate mixture 3.5 g twice a day) for 12 weeks. Benzbromarone was administrated at an initial dose of 25 mg/day and maintained at 50 mg/day with 2000–2500 ml water consumed daily. If the levels of transaminase were higher than twice of the upper limit of normal, polyene phosphatidylcholine would be given for liver protection. Colchicine (0.5 mg/day) was taken during the trial to prevent gout attacks that might be caused by SU dropping, and the regimen for the acute attack of

gout during treatment was 120 mg etoricoxib once a day for 3–5 days, while continuing to take urate-lowering therapy and urine alkalization.

General information including age, age of onset of gout, smoking history, drinking history, comorbidities and family history were collected. Laboratory indicators including SU, alanine aminotransferase, aspartate aminotransferase, triglyceride, total cholesterol, blood urea nitrogen, creatinine, glucose, and potassium (K^+), sodium (Na^+) and chloride (Cl^-) electrolytes in blood were measured using an automatic biochemical analyser (TBA-40FR, Toshiba Company, Tokyo, Japan). Urine protein, urine leucocyte and urine erythrocyte were measured using a urine automatic analyser (AX-4280, ARKRAY Company, Kyoto, Japan). The results were reported as positive when the concentration of protein was $\geq$0.3 g/l, blood cells or haemoglobin $\geq$0.6 mg/l and white blood cells $\geq$25/μl in the urine sample. Laboratory indicators were tested at baseline, weeks 2, 4, 8 and 12. The simplified Modification of Diet in Renal Disease formula [$186 \times (\text{serum creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203}$ for men] was used to calculate eGFR [24]. Patients were instructed to collect clean mid-course urine in the morning, and urine pH was directly measured using a pre-calibrated pH electrode (FE28-STANDARD, METTLER Toledo Company, Zurich, Switzerland). Urine pH was measured three times and the mean value was recorded.

Outcomes

The primary outcomes were change and distribution of urine pH. The comparison in urine pH distribution were mainly observed in percentage of acidic urine (pH <5.5) and normal pH urine (6.2 < pH < 6.9) in each group. For the categorization (pH <5.5, 5.5–6.2, >6.2) of urine pH, urine pH <5.5 referred as acidic urine [25], 6.2 < pH < 6.9 was considered to be beneficial for urine urate dissolution [26]. The secondary outcomes included change of SU, eGFR and blood electrolytes. The incidence of kidney stones, frequency of gout flare and treatment-related adverse events were recorded.

Statistical analysis

The study was powered to detect a 0.225 difference in urine pH between both alkalization strategies based on our preliminary study in which the urine pH of the patients taking sodium bicarbonate increased by 0.450 and (S.D.) was 0.420 while in the citrate mixture group the urine pH increased by 0.675 (S.D. 0.450). Therefore, to detect this 0.225 difference using a significance level of $\alpha = 0.05$ and a power of 90%, 100 patients were needed in each group with a 20% drop-out taken into account.

SPSS v25.0 (IBM SPSS, Chicago, IL, USA) was used for data analysis. Data were expressed as mean (S.D.), median (interquartile range) or number (percentage). Baseline comparisons were performed by independent sample *t*-test or Mann–Whitney rank-sum test. Comparison of categorical data was made by the χ^2 test. Follow-up data used the repeated measurement data model to analyse the change trend of the two groups of data. The calculation method of the model emphasized the comparison of the trends of eGFR, serum creatinine, blood urea nitrogen, triglyceride and other variables over time between the two groups. The comparison of distribution of urine pH between the two groups was calculated by χ^2 with three subgroups (pH > 6.2, 5.5–6.2, <5.5). $P < 0.05$ was regarded as statistically significant.

Results

Patients

A total of 538 gout patients was recruited from July 2018 to April 2019. Of these, 200 eligible patients were randomly assigned to the sodium bicarbonate ($n = 100$) or citric acid mixture group ($n = 100$). The other 338 patients were excluded because of the following reasons: SU <420 μmol/l ($n = 125$), eGFR <60 ml/min/1.73 m^2 ($n = 6$), kidney stones or polycystic kidney disease ($n = 19$), urine pH >6 ($n = 35$), transaminase >2-fold the upper limit of normal ($n = 8$), using other drugs affecting SU and/or urine pH ($n = 145$). Finally, 182 patients (sodium bicarbonate group, $n = 90$; citrate mixture group, $n = 92$) completed the 12-week follow-up study (Fig. 1).

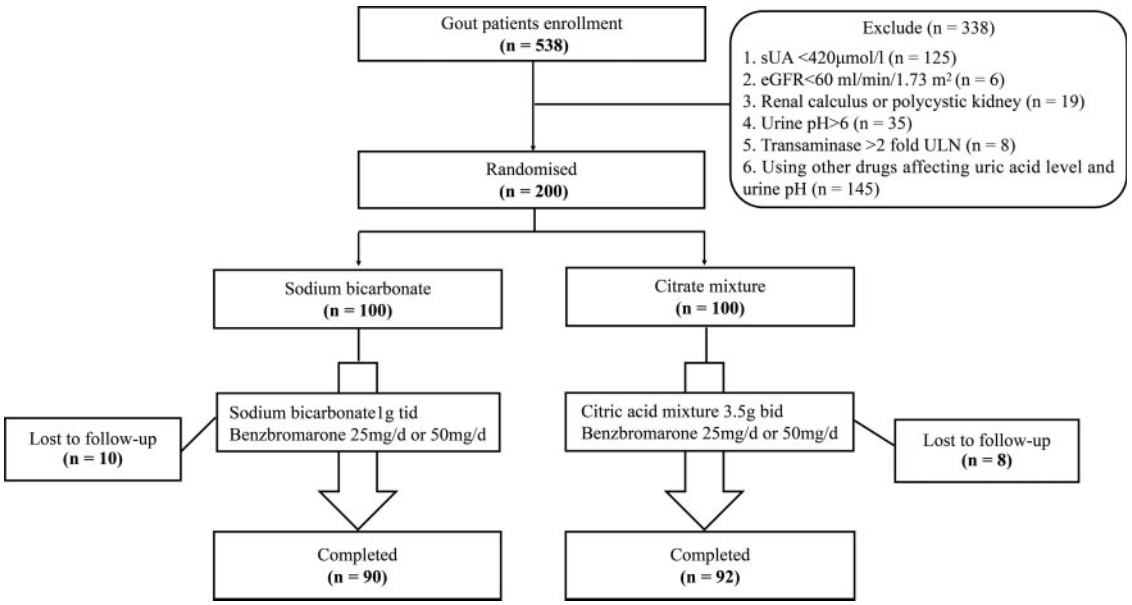
Baseline characteristics

As shown in Table 1, the demographic and general variables at the baseline were comparable between the sodium bicarbonate group and the citrate mixture group. The mean SU (S.D.) levels were 494.12 (51.26) μmol/l and 507.18 (68.12) μmol/l in the sodium bicarbonate group and the citrate mixture group ($P > 0.05$), respectively (Table 1). In the sodium bicarbonate group, the median (interquartile range) of urine pH was 5.50 (5.29, 5.75), similar to the citrate mixture group, pH 5.53 (5.26, 6.00) (Table 1). No significant differences of blood or urine parameters were detected between the groups (Table 1).

Primary outcomes

The urine pH value of both groups increased significantly from the baseline to the final follow-up time point ($P < 0.05$, Fig. 2). The median urine pH was elevated 9.1% in the sodium bicarbonate group [from 5.50 (95% CI 5.43, 5.57) to 6.00 (95% CI 5.81, 6.05)] and 7.2% in the citrate mixture group [from 5.53 (95% CI 5.48, 5.63) to 5.93 (95% CI 5.80, 6.01)] (Fig. 2A). Comparisons regarding urine pH between treatment groups for each time point showed no significant difference (Fig. 2A). We subgrouped the patients according to their pH values (>6.2, 5.5–6.2, <5.5) and found no significant difference of urine pH between the two groups either at baseline ($P > 0.05$, Fig. 2B) or at week 12 ($P > 0.05$, Fig. 2C).

FIG. 1 Flow chart of the study



Secondary outcomes—changes of clinical parameter

Patients in both of the groups underwent a 12-week urate-lowering and urine alkalization therapy. The mean SU of the sodium bicarbonate group decreased from 494.12 (51.26) to 363.24 (82.94) μmol/l (Table 2). In the citrate mixture group, the mean SU dropped from 507.18 (68.12) to 372.65 (95.05) μmol/l (Table 2). There was no significant difference between the two groups in SU at last visit ($P > 0.05$, Table 2). The mean eGFR value of the two groups fluctuated during the study. It was 94.72 (17.63) ml/min/1.73 m^2 at week 12, showing a 4.92 ml/min/1.73 m^2 decrease in the sodium bicarbonate group ($P < 0.01$, Table 2). However, the eGFR in the citrate mixture group was comparable between baseline and the last follow-up (99.15 ± 18.62 *vs* 96.40 ± 20.47 ml/min/1.73 m^2, $P > 0.05$), while it increased to 102.31 ± 19.03 ml/min/1.73 m^2 at week 2 ($P < 0.01$, Table 2). There was no significant difference between the two groups in eGFR at week 12 ($P > 0.05$, Table 2). During the trial, the average levels of hepatic- and other renal-related parameters of the two groups were both within the normal range (Table 2). No significant changes were detected in glucose and lipid metabolic indicators (Table 2).

Safety

Since sodium bicarbonate and citrate mixture may cause changes in serum electrolytes, we measured patients' serum K^+, Na^+ and Cl^- at the first and the last visit. When comparing the levels of serum electrolytes between the two groups, neither K^+ ($P > 0.05$, Fig. 3A), Na^+ ($P > 0.05$, Fig. 3B) nor Cl^- ($P > 0.05$, Fig. 3C) displayed significant differences. No significant changes of serum electrolytes were found between baseline and final in the sodium bicarbonate group ($P > 0.05$, Fig. 3). Although the mean (S.D.) Na^+ increased from 142.90 (2.58) to 144.02 (2.34) mmol/l ($P < 0.01$, Fig. 3B) and Cl^- increased from 102.87 (2.06) to 103.52 (2.36) mmol/l ($P < 0.05$, Fig. 3C) in the citrate mixture group, the absolute levels of Na^+ and Cl^- were within the reference range.

The incidence of kidney stones (7.0 *vs* 8.0%), urinary protein (2.0 *vs* 1.0%) and urine leukocytes (4.0 *vs* 1.0%) between the two groups of patients taking citrate mixture and sodium bicarbonate urine showed no significant differences ($P > 0.05$, Table 3). However, in terms of the incidence of urine occult blood, there was a significant difference between the two groups, with a lower rate in the citrate mixture group than in the sodium bicarbonate group (24.0 *vs* 38.0%, $P < 0.05$, Table 3).

The total frequency of gout flare was 32.0 and 28.0% in the sodium bicarbonate group and the citrate mixture group ($P > 0.05$, Table 3), while the frequency of patients with two attacks in the citrate mixture group was significantly lower than that in the sodium bicarbonate group (4 *vs* 12%, $P < 0.05$, Table 3). Given that benzbromarone may lead to severe liver damage [27, 28], we monitored transaminases in patients during the trial. The mean levels of transaminase in both groups were within the normal range, and the transaminase at week 12 was close to the baseline. Among the patients with elevated transaminases, only four patients' transaminases were >2-fold the upper normal limit. For these patients, we prescribed hepatic-protective drugs, such as polyene phosphatidylcholine. Although the eGFR of the sodium bicarbonate group decreased at week 12, there were no new-onset patients with CKD in either group. No obvious adverse reactions of digestion, respiration and cardiovascular function occurred in these two groups (Table 3).

TABLE 1 Baseline characteristics of the sodium bicarbonate and citrate mixture group

	Sodium bicarbonate ($n = 100$)	Citrate mixture ($n = 100$)	*P*-value
Demographic and general variables			
Age (years), mean (S.D.)	44.34 (12.64)	41.83 (13.53)	0.177
BMI (kg/m^2), mean (S.D.)	26.77 (2.98)	26.38 (4.08)	0.445
Systolic blood pressure (mmHg), mean (S.D.)	132.83 (13.04)	130.65 (14.98)	0.271
Diastolic blood pressure (mmHg), mean (S.D.)	82.87 (9.16)	81.01 (11.26)	0.199
Duration of gout (years), median (IQR)	3.00 (1.00, 7.75)	3.00 (0.73, 6.00)	0.764
Family history of gout, *n* (%)	20.00 (20.00)	16.00 (16.00)	0.462
Smoking, *n* (%)	35.00 (35.00)	35.00 (35.00)	1.000
Drinking, *n* (%)	50.00 (50.00)	54.00 (54.00)	0.571
Under regularly urate-lowering therapy	10.00 (10.00)	16.00 (16.00)	0.207
Comorbidities			
Hypertension, *n* (%)	23.00 (23.00)	19.00 (19.00)	0.487
Diabetes, *n* (%)	6.00 (6.00)	1.00 (1.00)	0.118
Fatty liver, *n* (%)	26.00 (26.00)	16.00 (16.00)	0.083
Tophi, *n* (%)	16.00 (16.00)	13.00 (13.00)	0.547
Blood chemistry parameters			
ALT (U/l), median (IQR)	25.00 (19.08, 36.15)	26.00 (19.00, 35.30)	0.970
AST (U/l), median (IQR)	19.80 (16.93 23.60)	21.00 (17.00, 24.05)	0.386
Fasting glucose (mmol/l), median (IQR)	5.45 (5.11, 5.77)	5.43 (5.02, 5.74)	0.400
Triglyceride (mmol/l), median (IQR)	1.90 (1.12, 2.69)	1.84 (1.33, 2.59)	0.763
Cholesterol (mmol/l), mean (S.D.)	4.86 (0.82)	4.79 (0.84)	0.582
Blood urea nitrogen (mmol/l), median (IQR)	4.30 (3.60, 5.20)	4.40 (3.60, 5.16)	0.824
Serum creatinine (μmol/l), mean (S.D.)	80.37 (12.18)	80.73 (12.67)	0.836
Serum urate (μmol/l), mean (S.D.)	494.12 (51.26)	507.18 (68.12)	0.125
eGFR (ml/min/1.73 m^2), mean (S.D.)	99.64 (19.51)	99.15 (18.62)	0.858
Serum sodium(mmol/l), mean (S.D.)	143.24 (2.18)	142.90 (2.58)	0.461
Serum potassium (mmol/l), mean (S.D.)	4.41 (0.31)	4.43 (0.27)	0.695
Blood chlorine (mmol/l), mean (S.D.)	103.19 (2.38)	102.87 (2.06)	0.455
Urine parameters			
pH, median (IQR)	5.50 (5.29, 5.75)	5.53 (5.26, 6.00)	0.294
Urine protein, *n* (%)	1.00 (1.00)	0 0	1.000
Haematuria, *n* (%)	5.00 (5.00)	9.00 (9.00)	0.268
Urine leucocyte, *n* (%)	0 0	2.00 (2.00)	0.497

Data are presented as the mean (S.D.), median (interquartile range) or number (proportion). ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; IQR: interquartile range; 1 mmHg = 0.133 kPa. *P*-values refer to comparison between the sodium bicarbonate group and the citrate mixture group.

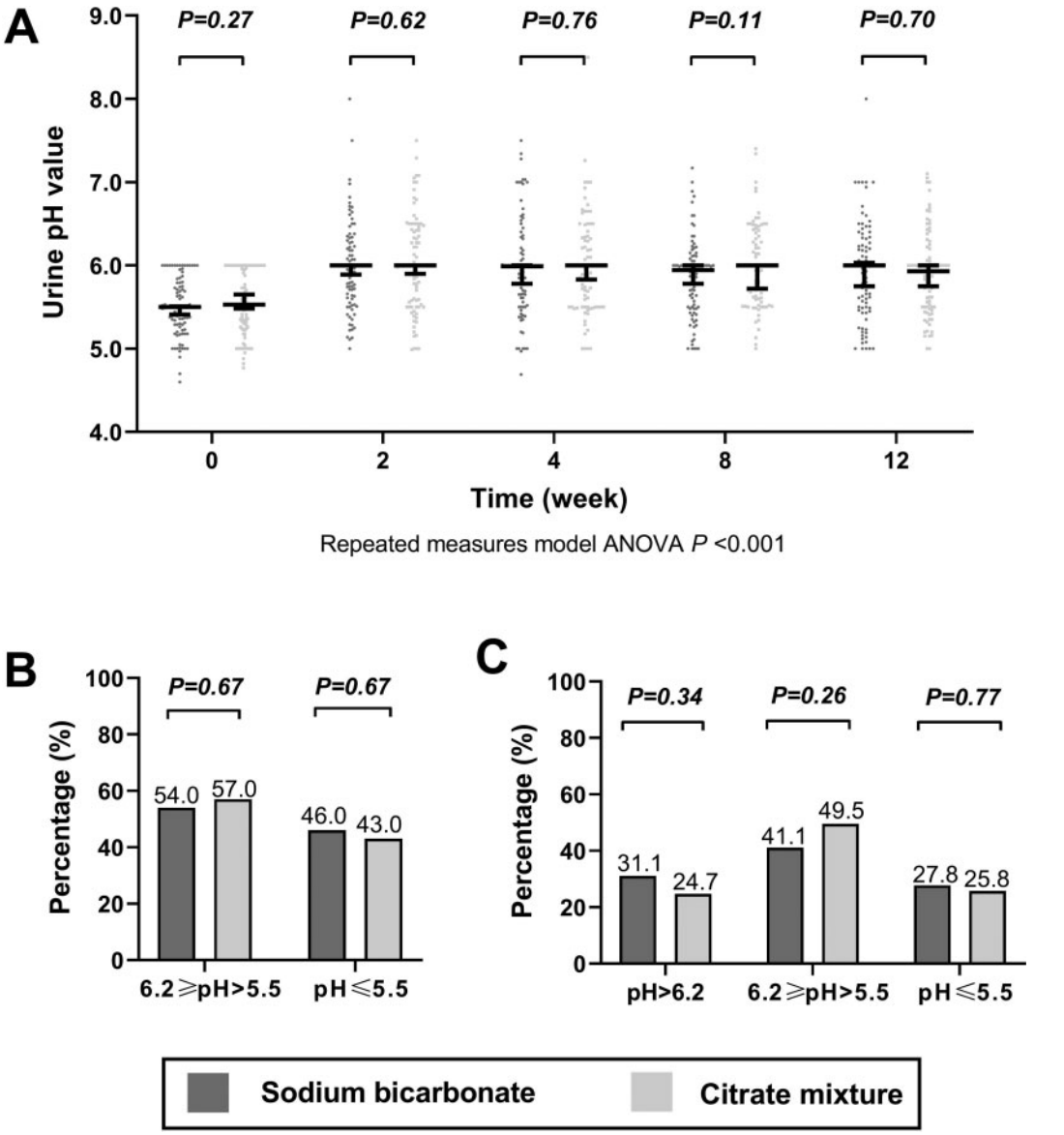
Discussion

In this study, the effects of a fixed oral dose of urine alkalization agents (citrate mixture and sodium bicarbonate) were investigated. After 12 weeks of treatment, the urinary pH increased with a similar scale in the citrate mixture group and sodium bicarbonate group. The results indicate that citrate mixture shows a similar efficacy to sodium bicarbonate in urine alkalization for gout patients.

The necessity of urine alkalization has been mentioned repeatedly in the gout and hyperuricaemia guidelines. The 2012 ACR gout guidelines considered urine alkalization with monitoring of urine pH as a risk management strategy for urolithiasis [29]. In addition, the 2018 Taiwan gout guidelines insisted on the institution of urine alkalization in gout treatment [22]. The 2017 British gout guidelines emphasized that alkalization of the urine with potassium citrate should be considered in recurrent stone formers [30]. However, the 2020 ACR Gout Clinical Practice Guidelines advise against alkalized urine for gout patients due to the lack of clinical evidence [15]. The unstandardized detection methods for urine pH and the underemphasis on the benefits of urine alkalization in gout patients hinder the clinical application of urine pH detection. Our evidence-based study supports the use of urine alkalization in gout patients and is expected to provide some evidence for the development of guidelines.

Gout increases the risk of CKD, which has become a major public health problem endangering human health [31, 32]. Gouty nephropathy is manifested by intermittent proteinuria, microscopic haematuria, impaired renal concentration function, increased nocturia and uremia [33]. The formation of urate crystals needs a specific pH and ionic environment. In the treatment of gout, it is reported that maintaining the pH of urine at 6.2–6.9 can dissolve urate crystals [26]. When the urine pH is >6.5 the nucleation of crystals will be inhibited and the excretion of urate will be promoted [34]. The mechanism of

Fig. 2 The trend and distribution of urine pH



Urine pH level (**A**), error bars indicate 95% CIs, each point represents urine pH of an individual patient. Urine pH distribution at baseline (**B**) and at the end of trial (**C**); data are expressed with proportions.

urine alkalization can be explained by reduction of the generation of oxygen free radicals, and thus reducing oxidative damage to the kidneys [10]. Gout guidelines indicate that alkalizing urine prevents the incidence of urinary stones in gout patients [21, 22], with a minimized incidence of CKD.

The primary outcome of this study showed that the effect of citrate mixture on alkalizing urine was similar to sodium bicarbonate. Our results were consistent with a previous trial of sodium bicarbonate and potassium citrate in homozygous cystinuria, showing citrate and sodium bicarbonate were equally effective in the alkalization of urine [35].

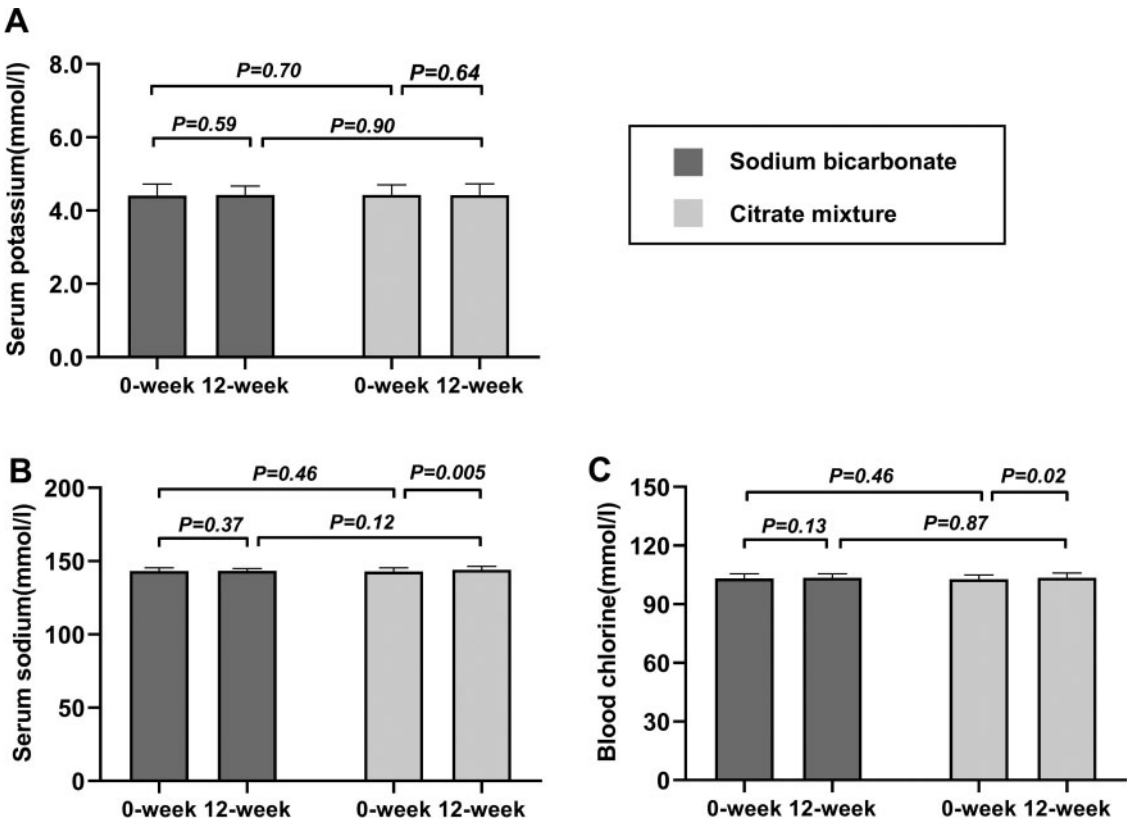
Compared with the sodium bicarbonate group, the incidence of urinary occult blood was lower in the citrate mixture group. It is well known that citrate ions can combine with calcium ions in the kidney to form soluble calcium citrate, which prevents the formation of urolithic calcium [36]. Also, potassium intake can also prevent the formation of kidney stones (odds ratio = 0.44, 95% CI 0.36, 0.53) [37]. The lower incidence of occult blood in the citrate group can reflect the role of potassium citrate in dissolving existing stones and preventing new stones. Citric acid can not only dissolve the stone to make it smaller, but can also weaken the edge angle of the stone, so as to avoid scratching the urethra and

Table 2 Main clinical parameters during the trial

Variable	Baseline	2 weeks	4 weeks	8 weeks	12 weeks
Systolic blood pressure (mmHg), mean (S.D.)					
Sodium bicarbonate	132.83 (13.04)	132.18 (13.04)	132.48 (14.38)	131.66 (13.31)	132.45 (13.04)
Citrate mixture	130.65 (14.98)	131.54 (14.34)	131.43 (14.36)	131.11 (13.77)	131.60 (12.77)
Diastolic blood pressure (mmHg), mean (S.D.)					
Sodium bicarbonate	82.87 (9.16)	80.33 (8.46)	80.81 (9.18)	80.95 (9.37)	81.31 (10.14)
Citrate mixture	81.01(11.26)	79.37 (9.80)	78.84 (10.68)	78.33 (9.66)	79.64 (8.77)
BMI (kg/m^2), mean (S.D.)					
Sodium bicarbonate	26.77 (2.98)	26.61 (2.98)	25.25 (6.55)	26.42 (4.20)	26.61 (3.07)
Citrate mixture	26.38 (4.08)	26.33 (4.12)	24.71 (7.37)	26.40 (3.31)	26.52 (3.29)
ALT (U/l), median (IQR)					
Sodium bicarbonate	25.00 (19.08, 36.15)	25.00 (18.00, 36.45)	24.00 (18.00, 33.00)	23.00 (18.50, 36.00)	22.80 (17.00, 37.00)
Citrate mixture	26.00 (19.00, 35.30)	23.00 (19.00, 33.20)	23.00 (18.00, 33.40)	24.00 (18.00, 33.10)	24.00 (18.00, 31.68)
AST (U/l), median (IQR)					
Sodium bicarbonate	19.80 (16.93 23.60)	19.00 (16.00, 22.85)	19.00 (15.25, 22.23)	19.00 (16.00, 24.80)	19.00 (16.00, 23.00)
Citrate mixture	21.00 (17.00, 24.05)	19.00 (16.00, 23.00)	19.00 (16.00, 22.38)	19.00 (16.70, 22.00)	19.30 (17.00, 23.00)
Fasting glucose (mmol/l), median (IQR)					
Sodium bicarbonate	5.45 (5.11, 5.77)	5.39 (4.99, 5.84)	5.34 (5.04, 5.79)**	5.41 (5.10, 5.77)	5.48 (5.12, 5.88)
Citrate mixture	5.43 (5.02, 5.74)	5.27 (4.98, 5.69)	5.21 (4.93, 5.62)*	5.21 (5.02, 5.65)*	5.33 (4.99, 5.70)
Triglyceride (mmol/l), median (IQR)					
Sodium bicarbonate	1.90 (1.12, 2.69)	1.69 (1.13, 2.94)	1.80 (1.23, 2.48)	1.71 (0.97, 2.79)	1.73 (1.14, 2.63)
Citrate mixture	1.84 (1.33, 2.59)	2.07 (1.22, 2.86)	1.76 (1.14, 2.67)	1.75 (1.17, 2.48)	1.86 (1.23, 2.74)
Cholesterol (mmol/l), mean (S.D.)					
Sodium bicarbonate	4.86 (0.82)	4.89 (1.00)	4.90 (0.96)	4.87 (0.92)	5.00 (1.03)
Citrate mixture	4.79 (0.84)	4.80 (0.86)	4.86 (0.91)	4.89 (0.83)	4.98 (0.88)
Blood urea nitrogen (mmol/l), median (IQR)					
Sodium bicarbonate	4.30 (3.60, 5.20)	4.90 (3.95, 5.50)	4.70 (4.05, 5.55)	4.50 (3.93, 5.50)	4.70 (4.18, 5.60)
Citrate mixture	4.40 (3.60, 5.16)	4.60 (4.00, 5.50)	4.90 (4.00, 5.61)	4.90 (4.00, 5.60)	4.90 (4.11, 5.80)
Serum creatinine (μmol/l), mean (S.D.)					
Sodium bicarbonate	80.37 (12.18)	80.86 (11.36)	80.77 (12.20)	81.57 (10.60)	84.69 (14.31)
Citrate mixture	80.73 (12.67)	79.13 (12.55)	80.74 (13.82)	79.49 (17.74)	83.90 (14.89)
Serum uric acid (μmol/l), mean (S.D.)					
Sodium bicarbonate	494.12 (51.26)	348.48 (84.22)***	340.34 (65.21)***	344.08 (63.64)***	363.24 (82.94)***
Citrate mixture	507.18 (68.12)	352.35 (91.14)***	359.16 (79.53)***	352.11 (86.40)***	372.65 (95.05)***
eGFR (ml/min/1.73 m^2), mean (S.D.)					
Sodium bicarbonate	99.64 (19.51)	98.91 (18.32)	99.49 (19.55)	97.76 (17.03)	94.72 (17.63)***
Citrate mixture	99.15 (18.62)	102.31 (19.03)***	100.32 (20.89)	99.89 (21.58)	96.40 (20.47)

Data were presented as the mean (S.D.), median (interquartile range) or number (proportion). ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; IQR: interquartile range; 1 mmHg = 0.133 kPa. Citrate mixture group *vs* sodium bicarbonate group, *$P < 0.05$; **$P < 0.05$, ***$P < 0.01$ refer to the comparison with baseline.

Fig. 3 Serum electrolyte changes in the two groups



Serum potassium (**A**), serum sodium (**B**) and serum chlorine (**C**) levels. Data are expressed as mean (S.D.).

Table 3 Adverse events

	Sodium bicarbonate ($n = 100$)	Citrate mixture ($n = 100$)	*P*-value
Renal calculus, *n* (%)	8 (8)	7 (7)	0.788
Urinary protein	1 (1)	2 (2)	1.000
Urine leukocytes	1 (1)	4 (4)	0.369
Urine occult blood, *n* (%)	38 (38)	24 (24)	0.032
Gout flare, *n* (%)	32 (32)	28 (28)	0.537
Once	20 (20)	24 (24)	0.495
Twice	12 (12)	4 (4)	0.037
Transaminase elevation from normal, *n* (%)	31 (31)	27 (27)	0.533
1–2 × ULN	28 (28)	26 (26)	0.750
2–3 × ULN	3 (3)	1 (1)	0.621
>3 × ULN	0 0	0 0	1.000
New-onset CKD based on eGFR, *n* (%)	0 0	1 (1)	1.000
eGFR <60 ml/min/1.73 m^2	0 0	1 (1)	1.000
eGFR <45 ml/min/1.73 m^2	0 0	0 0	1.000
Gastrointestinal disorders, *n* (%)	3 (3)	5 (5)	0.721
Cardiovascular events, *n* (%)	0 0	2 (2)	0.497
Skin and subcutaneous tissue disorders, *n* (%)	1 (1)	1 (1)	1.000
Respiratory, thoracic and mediastinal disorders, *n* (%)	3 (3)	1 (1)	0.621
Other adverse events, *n* (%)	0 0	0 0	1.000

ULN: upper limit of normal; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

causing haematuria when the stone is discharged. Furthermore, we also found that the eGFR of the sodium bicarbonate group was lower than before treatment, while the eGFR of the citrate mixture group did not change significantly. The reduction of eGFR in the sodium bicarbonate group may be related to the metabolic acidosis of the

kidneys, which produces more renal endothelin and in turn damages the renal tubules [38]. Our study suggested lower incidence of urine occult blood in the citrate mixture group, indicating a renal protection function.

To some extent, both citric mixture and sodium bicarbonate would cause the change of body electrolytes. Although the serum sodium and chloride increased in the citrate mixture group after 12 weeks of treatment, the levels of sodium and chloride ions were still within the normal range. No significant difference of serum potassium was found in the citrate mixture group.

Decreasing gout flare is the primary goal of urate-lowering treatment in patients with gout. Previous studies have shown that the frequency of gout flare of early urate-lowering treatment combined with colchicine was 20–30% [39], which is similar to the results of our trial. It is noted that the frequency of gout flare was lower in the citrate mixture group than in the sodium bicarbonate group. We suppose that the low proportion of patients with two gout flares in the citrate mixture group may be explained by the inhibition of monosodium urate crystal formation in joints by citrate.

Urine pH is affected by many factors, such as SU [40], components of metabolic syndrome [41] and the method of urine pH measurement. In this study, we adjusted the dosage of benzbromarone according to the SU to make comparable SU levels of the two groups. The components of the metabolic syndrome had no difference between the two groups. Although some studies used pooled 24-h urine for pH determination [16, 42], we measured urine pH directly after urinating in the morning given that 24-h urine could easily be polluted and prone to alkalization for bacterial growth and urea decomposition [43]. Our study used pH electrode rather than pH paper to determine urine pH, allowing for a greater accuracy [3].

Two limitations of the study should be acknowledged. First, the generalizability of the sample population is limited as this study was a single clinical centre trial. Second, there was a lack of detailed research on urine components, especially citrate ions.

In summary, our clinical trial emphasized the importance of urine alkalization in gout patients and that citrate mixture is superior to sodium bicarbonate for lowering the incidence of urine occult blood and the frequency of gout attacks, though with a similar role in urine alkalization. A standarized method of urine pH determination should be instituted in the monitoring procedure.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

Supplementary data

Supplementary data are available at *Rheumatology* online

References

1 Shimizu T, Hori H, Umeyama M, Shimizu K. Characteristics of gout patients according to the laterality of nephrolithiasis: a cross-sectional study using helical computed tomography. Int J Rheum Dis 2019;22:567–73.

2 Marchini GS, Sarkissian C, Tian D, Gebreselassie S, Monga M. Gout, stone composition and urinary stone risk: a matched case comparative study. J Urol 2013;189:1334–9.

3 Kamphuis GM, Wouter van Hattum J, de Bie P, Somani BK. Method of alkalization and monitoring of urinary pH for prevention of recurrent uric acid urolithiasis: a systematic review. Transl Androl Urol 2019;8:S448–56.

4 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.

5 Linnane JW, Burry AF, Emmerson BT. Urate deposits in the renal medulla. Prevalence and associations. Nephron 1981;29:216–22.

6 Marangella M. Uric acid elimination in the urine. Pathophysiological implications. Contrib Nephrol 2005;147:132–48.

7 Haber SL, Fente G, Fenton SN *et al.* Lesinurad: a novel agent for management of chronic gout. Ann Pharmacother 2018;52:690–6.

8 Fan M, Liu J, Zhao B *et al.* Comparison of efficacy and safety of urate-lowering therapies for hyperuricemic patients with gout: a meta-analysis of randomized,

controlled trials. Clin Rheumatol 2020. July 11. doi: 10.1007/s10067-020-05272-4. Online ahead of print.

9 Asplin JR, Goldfarb DS. Effect of thiazolidinedione therapy on the risk of uric acid stones. Kidney Int 2019; 95:1022–4.

10 Souma T, Abe M, Moriguchi T *et al.* Luminal alkalinization attenuates proteinuria-induced oxidative damage in proximal tubular cells. J Am Soc Nephrol 2011;22:635–48.

11 Melamed ML, Horwitz EJ, Dobre MA *et al.* Effects of sodium bicarbonate in CKD stages 3 and 4: a randomized, placebo-controlled, multicenter clinical trial. Am J Kidney Dis 2020;75:225–34.

12 Pearle MS, Goldfarb DS, Assimos DG *et al.* Medical management of kidney stones: AUA guideline. J Urol 2014;192:316–24.

13 Stern KL, Canvasser N, Borofsky M *et al.* Alkalinizing agents: a review of prescription, over-the-counter, and medical food supplements. J Endourol 2020; 34:1–6.

14 Saito J, Matsuzawa Y, Ito H *et al.* The alkalizer citrate reduces serum uric acid levels and improves renal function in hyperuricemic patients treated with the xanthine oxidase inhibitor allopurinol. Endocr Res 2010; 35:145–54.

15 Pak CY, Skurla C, Brinkley L, Sakhaee K. Augmentation of renal citrate excretion by oral potassium citrate administration: time course, dose frequency schedule, and dose-response relationship. J Clin Pharmacol 1984; 24:19–26.

16 Pak CY, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. Kidney Int 1986;30:422–8.

17 Spivacow FR, Negri AL, Polonsky A, Del Valle EE. Long-term treatment of renal lithiasis with potassium citrate. Urology 2010;76:1346–9.

18 Fabris A, Lupo A, Bernich P *et al.* Long-term treatment with potassium citrate and renal stones in medullary sponge kidney. Clin J Am Soc Nephrol 2010;5:1663–8.

19 Torrecilla C, Fernández-Concha J, Cansino JR *et al.* Reduction of ureteral stent encrustation by modulating the urine pH and inhibiting the crystal film with a new oral composition: a multicenter, placebo controlled, double blind, randomized clinical trial. BMC Urol 2020; 20:65.

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

21 Hui M, Carr A, Cameron S *et al.* The British Society for Rheumatology Guideline for the management of gout. Rheumatology (Oxford) 2017;56:e1–20.

22 Yu KH, Chen DY, Chen JH *et al.* Management of gout and hyperuricemia: multidisciplinary consensus in Taiwan. Int J Rheum Dis 2018;21:772–87.

23 Neogi T, Jansen TL, Dalbeth N *et al.* 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2015;74: 1789–98.

24 Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.

25 Park M, Jung SJ, Yoon S, Yun JM, Yoon HJ. Association between the markers of metabolic acid load and higher all-cause and cardiovascular mortality in a general population with preserved renal function. Hypertension Res 2015;38:433–8.

26 Trinchieri A, Esposito N, Castelnuovo C. Dissolution of radiolucent renal stones by oral alkalinization with potassium citrate/potassium bicarbonate. Arch Ital Urol Androl 2009;81:188–91.

27 Sun P, Zhu JJ, Wang T *et al.* Benzbromarone aggravates hepatic steatosis in obese individuals. Biochim Biophys Acta Mol Basis Dis 2018;1864: 2067–77.

28 Haring B, Kudlich T, Rauthe S, Melcher R, Geier A. Benzbromarone: a double-edged sword that cuts the liver? Eur J Gastroenterol Hepatol 2013;25: 119–21.

29 Khanna D, Fitzgerald JD, Khanna PP *et al.* 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431–46.

30 Hui M, Carr A, Cameron S *et al.* The British Society for Rheumatology Guideline for the management of gout. Rheumatology (Oxford) 2017;56:1246.

31 Stack AG, Johnson ME, Blak B *et al.* Gout and the risk of advanced chronic kidney disease in the UK health system: a national cohort study. BMJ Open 2019;9: e031550.

32 Singh JA, Cleveland JD. Gout is associated with a higher risk of chronic renal disease in older adults: a retrospective cohort study of U.S. Medicare population. BMC Nephrol 2019;20:93.

33 Mwasongwe SE, Fülöp T, Katz R *et al.* Relation of uric acid level to rapid kidney function decline and development of kidney disease: the Jackson Heart Study. J Clin Hypertension 2018;20:775–83.

34 Kanbara A, Miura Y, Hyogo H, Chayama K, Seyama I. Effect of urine pH changed by dietary intervention on uric acid clearance mechanism of pH-dependent excretion of urinary uric acid. Nutr J 2012;11:39.

35 Fjellstedt E, Denneberg T, Jeppsson JO, Tiselius HG. A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalinization of urine in homozygous cystinuria. Urol Res 2001;29:295–302.

36 Siener R, Glatz S, Nicolay C, Hesse A. Prospective study on the efficacy of a selective treatment and risk factors for relapse in recurrent calcium oxalate stone patients. Eur Urol 2003;44:467–74.

37 Ferraro PM, Mandel EI, Curhan GC, Gambaro G, Taylor EN. Dietary protein and potassium, diet-dependent net acid load, and risk of incident kidney stones. Clin J Am Soc Nephrol 2016;11:1834–44.

38 Wesson DE, Simoni J. Increased tissue acid mediates a progressive decline in the glomerular filtration rate of animals with reduced nephron mass. Kidney Int 2009;75: 929–35.

39 Feng X, Li Y, Gao W. Prophylaxis on gout flares after the initiation of urate-lowering therapy: a retrospective research. Int J Clin Exp Med 2015;8: 21460–5.

40 Dincer HE, Dincer AP, Levinson DJ. Asymptomatic hyperuricemia: to treat or not to treat. Cleve Clin J Med 2002;69:594, 597, 600–2 passim.

41 Lee J, Chang HK, Lee S. Association of low urine pH as a metabolic feature with abdominal obesity. J Int Med Res 2020;48:0300060519898615.

42 Boari B, Salmi R, Rizzioli E, Manfredini R. Circadian variation in urine pH and uric acid nephrolithiasis risk. Nephrol Dial Transplant 2007;23:411–2.

43 Cook JD, Strauss KA, Caplan YH, Lodico CP, Bush DM. Urine pH: the effects of time and temperature after collection. J Anal Toxicol 2007;31:486–96.