



Review

Urinary Alkalization Therapy in Primary Gout: A Narrative Review

Mingshu Sun ^{1,*} , Rui Wang ² , Chuantao Wu ², Xianghong Meng ³ and Changgui Li ⁴

¹ Department of Rheumatology, Xiang'an Hospital, Xiamen University Medical Center, Xiamen 361101, China

² R&D, Beijing Zhecheng Biotechnology Co., Ltd., Beijing 100012, China; berry.w@foxmail.com (R.W.)

³ College of Food Science and Engineering, Ocean University of China, Qingdao 266003, China; mengxh@ouc.edu.cn

⁴ Department of Metabolic Diseases, Xiang'an Hospital, Xiamen University Medical Center, Xiamen 361101, China; changguili@vip.163.com

* Correspondence: mingshu.sun@qdu.edu.cn; Tel.: +86-186-6180-8337

Abstract

Gout is a systemic metabolic inflammatory disease driven by hyperuricemia and monosodium urate crystal deposition, and is frequently accompanied by chronic kidney disease and uric acid nephrolithiasis. Current evidence indicates that acidic urine, hypocitraturia, and insufficient ammonium excretion are common in gout patients, and may be associated with insulin resistance, impaired renal ammoniogenesis, and abnormalities in tubular acid-base regulation. Persistent urinary acidification may contribute to the development and progression of uric acid stone formation and gout-related renal injury by reducing uric acid solubility, promoting crystal formation and intratubular deposition, and decreasing renal uric acid clearance. Urinary alkalization therapy can increase urine pH, thereby enhancing uric acid solubility and excretion, and has shown potential in some studies to improve serum urate levels, proteinuria, renal function parameters, and gout flare frequency, especially when using citrate-based alkali. However, the currently available evidence is mainly derived from observational studies and small prospective investigations, and recommendations across international guidelines remain inconsistent. High-quality evidence is still lacking regarding the optimal target population, urine pH range, choice of alkalizing agents, monitoring strategies, and long-term efficacy. Well-designed prospective studies are therefore needed to clarify the clinical role of urinary alkalization in renal protection among patients with gout.

Keywords: gout; aciduria; alkalization



Received: 19 April 2026

Revised: 17 June 2026

Accepted: 22 July 2026

Published: 28 July 2026

Copyright: © 2026 by the authors.

Published by MDPI on behalf of the Gout, Hyperuricemia and Crystal Associated Disease Network. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

Gout is now the most common form of inflammatory arthritis in adults, induced by hyperuricemia and the crystallization of monosodium urate (MSU). Cluster analyses from multiple countries have shown that approximately 80% of patients with gout have associated comorbidities, with metabolic syndrome being the most common (50–70%) and renal involvement representing the most severe complication [1–4]. A meta-analysis of 17 studies showed that gout was associated with chronic kidney disease (CKD) stage ≥ 3 (pooled OR = 2.41, 95%CI:1.86–3.11) and self-reported nephrolithiasis (OR = 1.77, 95%CI:1.43–2.19) [5]. In a recent large-scale, prospective study conducted in China, gout was independently associated with 5.6-fold higher incidence of CKD and 2.5-fold higher incidence of urolithiasis than in the general population [6].

Achieving well-controlled gout, defined as sustained target serum urate (SU) level and freedom from flares, is central to ameliorating renal disease in patients with gout [7].

Elevated SU, urinary urate (UU) and urinary uric acid (UUA) concentrations are considered major contributors to gouty nephropathy and UA nephrolithiasis, thereby orchestrating CKD deterioration. However, increasing attention has been directed toward urinary acid-base balance in primary gout [8–10]. Acidic urine has been identified as a prerequisite and one of the strongest predictors for UA stone formation [11,12]. Furthermore, in liver-specific Glut9 knockout mice, more acidic urine was associated with UU and UUA crystallization and renal injury [13]. An observational study on gout patients found that nearly 50% had aciduria ($\text{pH} < 5.5$), and low urinary pH was independently associated with renal damage indicated by hematuria, proteinuria, crystalluria, nephrolithiasis and eGFR decline, irrespective of SU levels [14].

Emerging studies suggest that urinary alkalization therapy in patients with gout may confer benefits with respect to renal outcomes, SU control, gout flares and metabolic condition [15–18]. However, the underlying mechanism and clinical rationale are incompletely understood. To date, international guidelines have either not addressed this issue or have provide inconsistent recommendations regarding urinary pH monitoring and alkalization in gout [19–21]. This review integrates evidence from relevant fields to clarify this unresolved question and to inform future research.

2. Results

2.1. Urinary pH Regulation in Primary Gout

The renal tubules, the site of HCO_3^- reabsorption and the secretion of H^+ and other organic anions, play a central role in systemic acid-base homeostasis. Under physiological conditions, tubule cells regulate urinary pH by adjusting excretions of citrate in the proximal tubule and ammonia in the distal tubule and collecting duct in response to intraluminal pH, thereby preventing the harmful consequences of extremely acidic or alkaline urine. Dietary components can cause transient fluctuations in urinary pH. A study in healthy volunteers who switched from their habitual diet to customized diets, either of protein-rich and less vegetable–fruit food for H^+ -load (acid diet), or less protein but vegetable–fruit-rich food (alkaline diet), showed that the acid generation was linearly related to renal net acid excretion, indicating that urinary H^+ is driven by the metabolic degradation of food substrates [22]. In addition to titratable acids, urinary NH_4^+ excretion spontaneously increased in those on acid diets. However, an acid diet was also associated with hypocitraturia [23]. Urinary concentration of citrate depends on the balance between glomerular filtration and tubular reabsorption. Citrate is primarily handled in the proximal convoluted tubule via a sodium-coupled dicarboxylate carrier. A proposed mechanism underlying the diet-induced hypocitraturia includes reduced diet alkali supply, altered filtrated citrate load, and a decrease in intracellular HCO_3^- in tubular cells, which promotes citrate reabsorption as a rapid buffer against diet acid load [24–26].

Primary gout may involve intrinsic defects that contribute to the acidic urine. As early as 1967, Yü and Gutman reported that fasting urine was acidic ($\text{pH} < 5.7$) more frequently in patients with primary gout than in healthy people (92% vs. 74%) [27]. More recently, a clinic population-based cross-sectional study enrolled 3565 Chinese patients with primary gout who had consumed a fixed metabolic diet for at least 3 days before fasting urine collection. The study showed that 46% of the participants had aciduria, and 76% had urinary $\text{pH} < 6.2$, proportions that were significantly higher than those observed in healthy people under the same dietary conditions [14]. Several studies have also reported relatively low urinary ammonium excretion despite acidic urine in patients with gout, suggesting an intrinsic defect in renal ammoniogenesis [28–30]. Renal citrate excretion has likewise been found to be significantly lower in patients with gout than in normal controls despite the presence of acidic urine [31].

Insulin resistance has been implicated in the regulation of urinary pH, although the underlying mechanisms remain incompletely understood (Figure 1) [32]. Insulin resistance and hyperinsulinemia are thought to impair the handling of glucose, triglyceride, and of the processing of amino acids, as well as cellular energy production and expenditure, thereby promoting free fatty acid accumulation, disturbing purine metabolism, and limiting glutamine utilization for ammonium generation [33]. These disturbances ultimately increase the production of acetate, ketones, and H^+ , while reducing ammonia output from renal tubular epithelial cells, leading to abnormal citrate and ammonia metabolism and excretion [25,26]. In a rat model of metabolic syndrome, dietary restriction and exercise-induced weight loss improved insulin resistance and were accompanied by increased urinary citrate excretion and urinary pH [34]. In a complementary experiment, Zucker diabetic fatty rats treated with insulin sensitizer thiazolidinediones showed reduced fat mass with normalization of urinary acidification and ammonium excretion [35]. A study by Moriwaki et al. showed that the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index was the only significant determinant of low urinary pH in patients with gout, and that improvement in insulin resistance by the PPAR α agonist fenofibrate significantly increased the 24 h urine pH [36]. Accumulating evidence suggests that persistent acidic urine combined with low urinary ammonium and citrate may represent characteristic renal features of the metabolic syndrome. Furthermore, studies have reported that insulin resistance might activate sodium–hydrogen exchanger 3 (NHE3) through the classic phosphatidylinositol 3-kinase and glucocorticoid-dependent kinase 1 (PI3K-SGK1) pathway, and electrogenic sodium-bicarbonate cotransporter 1 via the insulin receptor substrate 2/Akt pathway, thereby directly increasing urinary acidity [37,38].

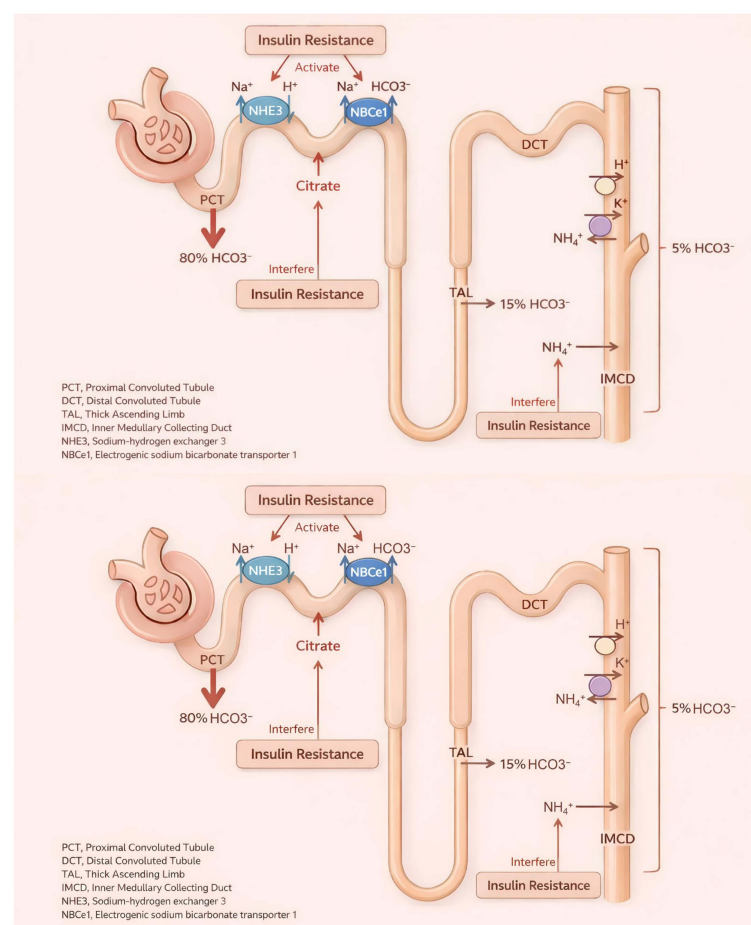


Figure 1. Urine acid-base regulation by the nephron and the impact of insulin resistance.

Genome-wide association studies (GWAS) have identified several genetic loci associated with SU levels and UA nephrolithiasis in patients with gout [32]. Recently, a GWAS focusing on individuals with central adiposity identified three specific loci, including GCKR, ABCG2 and SLC17A1, associated with UA nephrolithiasis [39]. Notably, GCKR is a shared risk loci for nephrolithiasis within gout populations and insulin resistance as well, suggesting a common genetic architecture underlying insulin resistance and its subsequent renal manifestations in gout.

2.2. Consequences of Excessive Aciduria in Primary Gout

Persistent acidic urine is the most important determinant of UA crystallization and nephrolithiasis [15]. The reported prevalence of urolithiasis in patients ranges from 14% to 39% across studies [5,40]. Kidney stones are now classified into mutually exclusive categories according to composition; therefore, any stone containing a UA component is classified as a UA stone [41]. Accordingly, dual-energy computed tomography (DECT) studies in patients with gout have shown that 77.8% of renal calculi contain either pure or mixed UA in renal calculus [42]. The principal mechanism proposed for UA-associated urolithiasis is the fixed-particle hypothesis, particularly the ‘plug’ pathway, in which crystal nuclei form within the nephron lumen and progressive stone growth leads to plugs that obstruct and markedly dilate the inner medullary collecting ducts (IMCDs) and ducts of Bellini, projecting into the kidney collecting system. Urinary pH determines both the urate-to-UA ratio and the solubility of UA [9]. The transportable fraction of UA is greater in alkaline urine than in acidic urine. At a urine pH below 5.5, poorly soluble protonated UA predominates. Large amounts of UA crystals may aggregate into pure UA stone or act as a nidus for CaOx stone formation, particularly when citrate levels are inadequate. In gout-associated UA urolithiasis, low urinary pH is considered the principal driver, whereas UUA load and CaOx may be secondary contributors.

In addition to urolithiasis, acidic urine promotes UA crystallization, thereby contributing to kidney injury and CKD progression. UA solubility depends on both pH and concentration. Hypertonic final urine is predisposed to a low pH, and favors crystallization in the distal tubule, collecting system, or outflow tract, as well as deposition within the interstitium, where UA crystals may induce inflammation, urinary tract injury and obstruction or plugging. Intratubular plugging is also associated with destruction of the epithelial lining and focal interstitial fibrosis. A diffuse hyperechoic medulla pattern has been observed in patients with severe gout [43], and low urinary pH has been independently associated with CKD, microhematuria, proteinuria and ultrasonographically detected renal cyst in this population [14,44].

Hypocitraturia is another key contributor to renal injury in primary gout. Citrate is an abundant urinary organic anion that plays an important role in both acid-base homeostasis and the prevention of nephrolithiasis. The pKa of the citrate-3/citrate-2 buffer system is approximately 6.4. The difference in pH between glomerular filtrate, which is essentially identical to systemic arterial pH, and final urine enables citrate to function as a titratable buffer in the regulation of urinary pH. When tubular citrate handling is disturbed, as described above, urinary pH declines. In addition, citrate readily complexes with calcium and thereby reduces ionized calcium activity, making it a major physicochemical determinant of calcium crystal nucleation, growth and dissolution [15,45].

Aciduria may increase SU levels by reducing UU excretion. In healthy individuals exposed to sequential dietary interventions, an acidic diet (protein-rich and less vegetable-fruit), compared with an alkaline diet (less protein and vegetable-fruit-rich), produced greater net acid excretion, lower urine pH and a lower UU excretion ratio, together with higher SU levels [22,24]. A positive linear correlation between urine pH and UU concen-

tration was observed in both dietary groups, regardless of differences in purine intake, suggesting that aciduria-related changes in SU are mediated by reduced renal urate clearance. Studies in primary gout have further shown that patients with acidic urine exhibited a higher HOMA-IR index and higher SU levels, together with lower UU clearance, and that PPAR α agonist fenofibrate improves HOMA-IR index and low urine pH while increasing UU clearance and lowering SU [36].

2.3. Urinary Alkalinization Therapy in Patients with Primary Gout: Pros and Cons

The optimization of urinary pH may protect the kidneys from gout-related renal injury. Urinary alkalization is an established treatment for UA stone, and effective urinary pH elevation through sodium bicarbonate supplementation has been shown to slow CKD progression significantly [46]. The rationale for the current stone classification is that UA crystal provides an excellent substrate for heterogeneous CaOx nucleation and that the management of these stones is distinct [15]. Urinary alkalization to a pH range of 6–7 is highly effective in preventing recurrence of UA stones [47]. These stones may be dissolved using urinary alkalization (chemolysis), obviating the need for surgical intervention. Xanthine oxidase inhibitors (XOIs), such as allopurinol or febuxostat, play a limited role in the management of UA stones, and are mainly reserved for patients who are intolerant of alkali therapy, those with severe hyperuricosuria (>1000 mg/24 h), or those with concurrent gout [48]. Accordingly, kidney stone guidelines recommend urinary alkalization as a first-line therapy for UA stones, and suggest achieving a urinary pH of approximately 7.0–7.2, with reported success rates exceeding 80% [23,49,50]. In addition, XOIs are recommended for patients with hyperuricosuria but not hyperuricemia, and as an alternative option for patients who do not have low urinary pH or for patients with calcium oxalate stones and hyperuricosuria.

For patients with gout without nephrolithiasis, recommendations regarding urine alkalization remain controversial [51]. The 2020 ACR guideline conditionally recommended against routine urine alkalization, even in patients receiving uricosurics, because of insufficient evidence for efficacy [20]. Nevertheless, studies published in recent years have provided supportive evidence for urinary alkalization in gout. A cross-sectional study showed that patients with a fasting urinary pH ≤ 6.2 were at higher risk of renal damage [14]. Aggregated evidence has suggested that hyperuricosuria and aciduria were causally associated with gout nephropathy in patients with hyperuricemia and gout, and that urinary alkalization may be important for renal protection [52]. Several clinical studies have reported improvement in markers of renal injury, together with enhanced renal urate excretion and modest SU-lowering effect, following urinary alkalization [17,18,53,54]. An earlier study also showed that citrate-based alkalization not only increased renal urate clearance and improved SU control but also attenuated CKD progression in patients with gout [22]. More recently, an observational study in patients with CKD found that those with hyperechoic crystal deposits in the renal medulla on ultrasonography were more likely to have a history of gout, higher SU levels, lower urinary pH, lower 24 h urinary citrate and lower 24 h UU [55]. A key point in interpreting these findings is the profound effect of urinary pH on UA solubility. Within the distal tubules and collecting ducts, where solute concentration is highest and pH is lowest, the milieu strongly favors intratubular UA crystal deposition, leading to subsequent renal injury. In that study, this process was reflected by hyperechoic medullary crystals and small cystic lesions on ultrasonography [55]. Based on these findings, the 2024 updated Chinese guidelines specifically recommend urinary alkalization therapy for patients with gout or hyperuricemia and fasting urinary pH < 6.0, with a target range of 6.2–6.9 [21]. However, more robust evidence is still needed to strengthen this recommendation, as acknowledged by the guideline itself.

The optimal alkalinizing agent for gout remains uncertain. Current urological recommendations list citrate preparations and sodium bicarbonate (SB) as standard alkalinizing agents for UA urolithiasis [15,50]. Citrate-based alkalization has been reported to reduce SU levels and improve renal function in patients with hyperuricemia treated with the XO inhibitor allopurinol [16]. However, the adherence to alkalinizing therapy may be poor, with one report showing a rate of only about 13%, largely because of frequent gastrointestinal side effects [56]. A wide range of prescription, over-the-counter agents, and medical food supplements are currently marketed for urine alkalization [57]. These combination formulations typically contain citrate or SB, together with vitamin B6 and magnesium, in an effort to improve tolerability and compliance. Traditional remedies used as alkali supplements include *Musa paradisiaca* (banana stem), stevia leaf extract, *Phyllanthus niruri* (Chanca Piedra). Given their low alkali content and the absence of robust peer-reviewed evidence, most of these products do not meet the basic requirements for a reliable alternative to potassium citrate or SB [58]. A head-to-head trial in 182 patients with gout and aciduria compared a citrate mixture (50% citric acid, 10% sodium citrate, 10% potassium citrate and 20% sodium carbonate, 3.5 g, twice a day) with SB, and found comparable alkalinizing efficacy, whereas the citrate mixture was associated with better preservation of eGFR and fewer episodes of occult hematuria and gout flares [54]. Another 12-week prospective study in 343 patients with gout and fasting urinary pH < 6.2 showed that the citrate mixture administration reduced the urine albumin/creatinine ratio, decreased gout flares and serum triglyceride, and increased HDL-C [18]. Furthermore, an open-label randomized trial in 282 men with gout and fasting urinary pH ≤ 6 found that a tart cherry-supplemented citrate mixture produced a greater reduction in urine albumin/creatinine ratio and a lower C-reactive protein level than either citrate mixture alone or SB [17]. More recently, a prospective cohort study in 234 gout patients with combined-type hyperuricemia and aciduria showed that this tart cherry-supplemented citrate mixture facilitated urate-lowering by increasing renal urate excretion and improved insulin resistance as assessed by HOMA-IR [53]. Because IR is mechanistically relevant to both UA production and renal urate excretion and has been shown to be a type-specific risk factor for combined-type hyperuricemia in gout, these serial clinical studies suggest that citrate mixture, particularly when supplemented with tart cherry, may provide renal protection together with additional anti-inflammation metabolic benefits in gout [59]. Additionally, potassium and sodium load should be considered where appropriate.

2.4. Biological Rationale for Urinary Alkalization in Primary Gout

Accumulating evidence indicates that approximately 70% of patients with gout or hyperuricemia have CKD stage 3 or worse [3,5]. Nevertheless, the 2013 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines neither supported nor refuted the use of urate-lowering agents in patients with CKD and symptomatic or asymptomatic hyperuricemia to delay CKD progression because the evidence was insufficient [60]. Subsequently, several landmark studies, including FEATHER, PERL, and CKD-FIX, failed to confirm the hypothesis that lowering SU slows CKD progression [61–63]. In contrast, the FREED study and a post hoc study of CARES suggested an association between ULT and attenuation of CKD progression in patients with cardio-cerebrovascular disease, implying that urate-lowering may protect the renal vasculature [64–66]. To date, KDIGO has not substantially updated its position on this issue.

A more appropriate question may be: what drives CKD in gout? Gout-related renal manifestations include nephrolithiasis and crystal-induced interstitial inflammation, which together comprise classic urate nephropathy and are further shaped by renal arteriopathy and glomerular hyperfiltration [52,67]. Urinary pH may be a critical pathophysiological contributor and a neglected therapeutic confounder. As discussed above, aciduria is

highly prevalent in gout, and is accompanied by low urinary citrate and ammonium, with antecedent insulin resistance presenting an intrinsic feature of hyperuricemia and gout. Evidence from urologic research has confirmed the central role of excessively acidic urine in UA crystallization and urolithiasis and has established alkalinization as a first-line therapy. Several studies have also summarized the effects of improving insulin resistance on urinary pH, kidney injury, and components of the metabolic syndrome. These relationships are illustrated in this review (Figure 2).

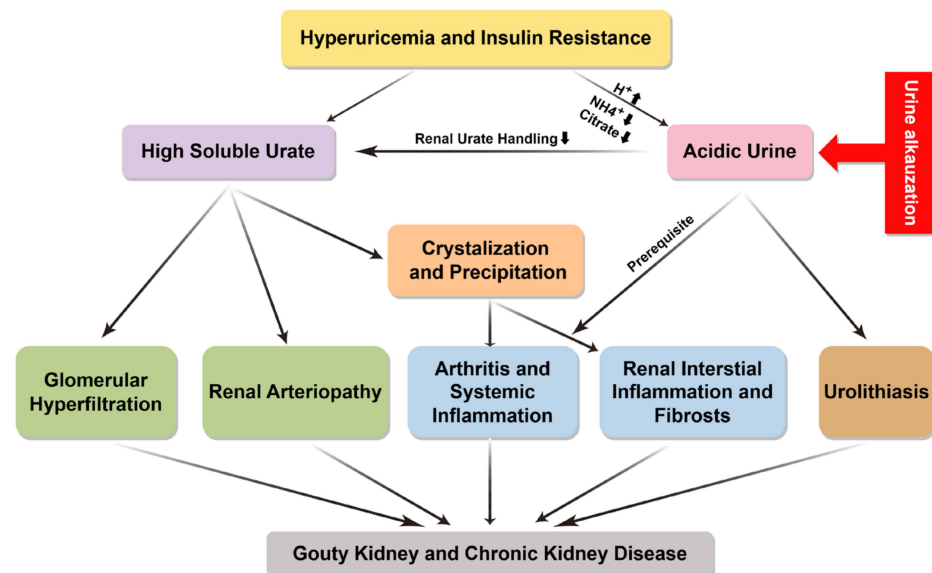


Figure 2. Biological rationale for urinary alkalization in patients with primary gout.

3. Conclusions

Persistent aciduria in combination with low urinary citrate may represent characteristic renal traits in a subset of patients with gout. Excessively acidic urine has emerged as both a key contributor to renal injury in gout and a potential therapeutic target. However, many questions in this field remain unresolved. At present, there is no Mendelian randomization study available to elucidate a causal relationship between acidic urine and CKD in patients with gout. Still, robust evidence regarding the optimal alkalinizing agent and the best method for urinary pH monitoring in patients with gout or hyperuricemia remains insufficient. Moreover, despite the clinical availability of alkalization therapy, long-term outcome data are lacking. The currently available studies are limited in number and carry notable risks of bias, which should be considered when interpreting their findings. Based on current knowledge, insulin resistance and its renal manifestations in gout seem to share a major genetic basis. Screening for and early intervention against metabolic dysfunction-associated traits in patients presenting with renal manifestations may therefore be warranted. Overall, more rigorous clinical trials are needed to inform guideline updates on gout-specific kidney protection and to optimize therapeutic strategies for gout.

Author Contributions: Conceptualization, writing-original draft, and funding acquisition, M.S.; Literature retrieval and interpretation, R.W. and C.W.; Writing-review and editing, X.M. and C.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Qingdao Science and Technology Bureau project (25-1-5-smjk-20-nsh).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors Rui Wang and Chuantao Wu are employees of Beijing Zhecheng Biotechnology Co., Ltd. The company did not provide funding for this study and had no role in the study design, data collection, analyses, data interpretation, or the preparation of this manuscript. The authors declare no conflicts of interest.

References

1. Richette, P.; Clerson, P.; Périssin, L.; Flipo, R.M.; Bardin, T. Revisiting comorbidities in gout: A cluster analysis. *Ann. Rheum. Dis.* **2015**, *74*, 142–147. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Bevis, M.; Blagojevic-Bucknall, M.; Mallen, C.; Hider, S.; Roddy, E. Comorbidity clusters in people with gout: An observational cohort study with linked medical record review. *Rheumatology* **2018**, *57*, 1358–1363. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Liu, S.; Sun, H.; Yang, S.; Liang, N.; Gao, Y.; Qu, S.; Chen, H. Clustering of gout-related comorbidities and their relationship with gout flares: A data-driven cluster analysis of eight comorbidities. *J. Endocrinol. Investig.* **2024**, *47*, 1119–1128. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Stern, L.; Johnson, R.J.; Shakouri, P.; Athavale, A.; Padnick-Silver, L.; LaMoreaux, B.; Marder, B.A.; Mandayam, S. Prevalence and Influence of Gout in Patients with Advanced Chronic Kidney Disease: Findings of a Large Retrospective Chart. *Review* **2024**, *2*, 77–85. [\[CrossRef\]](#)
5. Roughley, M.J.; Belcher, J.; Mallen, C.D.; Roddy, E. Gout and risk of chronic kidney disease and nephrolithiasis: Meta-analysis of observational studies. *Arthritis Res. Ther.* **2015**, *17*, 90. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Im, P.K.; Kartsonaki, C.; Kakkoura, M.G.; Mohamed-Ahmed, O.; Yang, L.; Chen, Y.; Du, H.; Yang, X.; Zhang, H.; Sun, D.; et al. Hyperuricemia, gout and the associated comorbidities in China: Findings from a prospective study of 0.5 million adults. *Lancet Reg. Health West. Pac.* **2025**, *58*, 101572. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Tabi-Amponsah, A.D.; Stewart, S.; Stamp, L.K.; Taylor, W.J.; Terkeltaub, R.; Dalbeth, N. The Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) definition of clinical remission in gout. *Ann. Rheum. Dis.* **2026**, *85*, 186–194. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Wagner, C.A.; Mohebbi, N. Urinary pH and stone formation. *J. Nephrol.* **2010**, *23*, S165–S169. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Maalouf, N.M.; Cameron, M.A.; Moe, O.W.; Sakhaee, K. Novel insights into the pathogenesis of uric acid nephrolithiasis. *Curr. Opin. Nephrol. Hypertens.* **2004**, *13*, 181–189. [\[CrossRef\]](#) [\[PubMed\]](#)
10. Kamphuis, G.M.; Wouter van Hattum, J.; de Bie, P.; Somani, B.K. Method of alkalization and monitoring of urinary pH for prevention of recurrent uric acid urolithiasis: A systematic review. *Transl. Androl. Urol.* **2019**, *8*, S448–S456. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Cicerello, E.; Merlo, F.; Maccatrozzo, L. Urinary alkalization for the treatment of uric acid nephrolithiasis. *Arch. Ital. Urol. Androl.* **2010**, *82*, 145–148. [\[PubMed\]](#)
12. Xu, L.H.R.; Adams-Huet, B.; Poindexter, J.R.; Maalouf, N.M.; Moe, O.W.; Sakhaee, K. Temporal Changes in Kidney Stone Composition and in Risk Factors Predisposing to Stone Formation. *J. Urol.* **2017**, *197*, 1465–1471. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Preitner, F.; Laverriere-Loss, A.; Metref, S.; Da Costa, A.; Moret, C.; Rotman, S.; Bazin, D.; Daudon, M.; Sandt, C.; Dessombz, A.; et al. Urate-induced acute renal failure and chronic inflammation in liver-specific Glut9 knockout mice. *Am. J. Physiol. Ren. Physiol.* **2013**, *305*, F786–F795. [\[CrossRef\]](#) [\[PubMed\]](#)
14. He, Y.; Xue, X.; Terkeltaub, R.; Dalbeth, N.; Merriman, T.R.; Mount, D.B.; Feng, Z.; Li, X.; Cui, L.; Liu, Z.; et al. Association of acidic urine pH with impaired renal function in primary gout patients: A Chinese population-based cross-sectional study. *Arthritis Res. Ther.* **2022**, *24*, 32. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Bargagli, M.; Scoglio, M.; Howles, S.A.; Fuster, D.G. Kidney stone disease: Risk factors, pathophysiology and management. *Nat. Rev. Nephrol.* **2025**, *21*, 794–808. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Saito, J.; Matsuzawa, Y.; Ito, H.; Omura, M.; Ito, Y.; Yoshimura, K.; Yajima, Y.; Kino, T.; Nishikawa, T. The alkaliizer citrate reduces serum uric Acid levels and improves renal function in hyperuricemic patients treated with the xanthine oxidase inhibitor allopurinol. *Endocr. Res.* **2010**, *35*, 145–154. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Wang, C.; Sun, W.; Dalbeth, N.; Wang, Z.; Wang, X.; Ji, X.; Xue, X.; Han, L.; Cui, L.; Li, X.; et al. Efficacy and safety of tart cherry supplementary citrate mixture on gout patients: A prospective, randomized, controlled study. *Arthritis Res. Ther.* **2023**, *25*, 164. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Wang, C.; Guo, K.; Dalbeth, N.; Sun, M.; Lu, J.; Chen, Y.; Zhang, H.; Wang, X.; Ji, X.; Li, X.; et al. Impact of adding urine alkalization therapy to xanthine oxidase inhibitor in gout management: A prospective cohort study. *Rheumatology* **2025**, *64*, 3509–3517. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Yip, R.M.; Cheung, T.T.; So, H.; Chan, J.P.; Ho, C.T.; Tsang, H.H.; Yu, C.K.; Wong, P.C. The Hong Kong Society of Rheumatology consensus recommendations for the management of gout. *Clin. Rheumatol.* **2023**, *42*, 2013–2027. [\[CrossRef\]](#) [\[PubMed\]](#)

20. FitzGerald, J.D.; Dalbeth, N.; Mikuls, T.; Brignardello-Petersen, R.; Guyatt, G.; Abeles, A.M.; Gelber, A.C.; Harrold, L.R.; Khanna, D.; King, C.; et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Rheumatol.* **2020**, *72*, 879–895. [[CrossRef](#)] [[PubMed](#)]
21. Sun, M.; Lyu, Z.; Wang, C.; Li, Y.; Zhao, D.; Ran, X.; Chen, H.; Su, B.; Chang, X.; Liu, P.; et al. 2024 Update of Chinese Guidelines for Diagnosis and Treatment of Hyperuricemia and Gout Part I: Recommendations for General Patients. *Int. J. Rheum. Dis.* **2025**, *28*, e70375. [[CrossRef](#)] [[PubMed](#)]
22. Kanbara, A.; Hakoda, M.; Seyama, I. Urine alkalization facilitates uric acid excretion. *Nutr. J.* **2010**, *9*, 45. [[CrossRef](#)] [[PubMed](#)]
23. Pearle, M.S.; Goldfarb, D.S.; Assimos, D.G.; Curhan, G.; Denu-Ciocca, C.J.; Matlaga, B.R.; Monga, M.; Penniston, K.L.; Preminger, G.M.; Turk, T.M.; et al. Medical management of kidney stones: AUA guideline. *J. Urol.* **2014**, *192*, 316–324. [[CrossRef](#)] [[PubMed](#)]
24. 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. [[CrossRef](#)] [[PubMed](#)]
25. Simpson, D.P. Citrate excretion: A window on renal metabolism. *Am. J. Physiol.* **1983**, *244*, F223–F234. [[CrossRef](#)] [[PubMed](#)]
26. Brennan, S.; Hering-Smith, K.; Hamm, L.L. Effect of pH on citrate reabsorption in the proximal convoluted tubule. *Am. J. Physiol.* **1988**, *255*, F301–F306. [[CrossRef](#)] [[PubMed](#)]
27. Yü, T.; Gutman, A.B. Uric acid nephrolithiasis in gout. Predisposing factors. *Ann. Intern. Med.* **1967**, *67*, 1133–1148. [[CrossRef](#)] [[PubMed](#)]
28. Falls, W.F., Jr. Comparison of urinary acidification and ammonium excretion in normal and gouty subjects. *Metabolism* **1972**, *21*, 433–445. [[CrossRef](#)] [[PubMed](#)]
29. Gibson, T.; Highton, J.; Potter, C.; Simmonds, H.A. Renal impairment and gout. *Ann. Rheum. Dis.* **1980**, *39*, 417–423. [[CrossRef](#)] [[PubMed](#)]
30. Sakhaee, K.; Adams-Huet, B.; Moe, O.W.; Pak, C.Y. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. *Kidney Int.* **2002**, *62*, 971–979. [[CrossRef](#)] [[PubMed](#)]
31. Marickar, Y.M. Calcium oxalate stone and gout. *Urol. Res.* **2009**, *37*, 345–347. [[CrossRef](#)] [[PubMed](#)]
32. Spatola, L.; Ferraro, P.M.; Gambaro, G.; Badalamenti, S.; Dauriz, M. Metabolic syndrome and uric acid nephrolithiasis: Insulin resistance in focus. *Metabolism* **2018**, *83*, 225–233. [[CrossRef](#)] [[PubMed](#)]
33. Bobulescu, I.A.; Dubree, M.; Zhang, J.; McLeroy, P.; Moe, O.W. Effect of renal lipid accumulation on proximal tubule Na⁺/H⁺ exchange and ammonium secretion. *Am. J. Physiol. Ren. Physiol.* **2008**, *294*, F1315–F1322. [[CrossRef](#)] [[PubMed](#)]
34. Sasaki, Y.; Kohjimato, Y.; Iba, A.; Matsumura, N.; Hara, I. Weight loss intervention reduces the risk of kidney stone formation in a rat model of metabolic syndrome. *Int. J. Urol.* **2015**, *22*, 404–409. [[CrossRef](#)] [[PubMed](#)]
35. Bobulescu, I.A.; Dubree, M.; Zhang, J.; McLeroy, P.; Moe, O.W. Reduction of renal triglyceride accumulation: Effects on proximal tubule Na⁺/H⁺ exchange and urinary acidification. *Am. J. Physiol. Ren. Physiol.* **2009**, *297*, F1419–F1426. [[CrossRef](#)] [[PubMed](#)]
36. Takahashi, S.; Inokuchi, T.; Kobayashi, T.; Ka, T.; Tsutsumi, Z.; Moriwaki, Y.; Yamamoto, T. Relationship between insulin resistance and low urinary pH in patients with gout, and effects of PPAR α agonists on urine pH. *Horm. Metab. Res.* **2007**, *39*, 511–514. [[CrossRef](#)] [[PubMed](#)]
37. Klisic, J.; Hu, M.C.; Nief, V.; Reyes, L.; Fuster, D.; Moe, O.W.; Ambühl, P.M. Insulin activates Na⁽⁺⁾/H⁽⁺⁾ exchanger 3: Biphasic response and glucocorticoid dependence. *Am. J. Physiol. Ren. Physiol.* **2002**, *283*, F532–F539. [[CrossRef](#)] [[PubMed](#)]
38. Hookham, M.B.; O'Donovan, H.C.; Church, R.H.; Mercier-Zuber, A.; Luzi, L.; Curran, S.P.; Carew, R.M.; Droguett, A.; Mezzano, S.; Schubert, M.; et al. Insulin receptor substrate-2 is expressed in kidney epithelium and up-regulated in diabetic nephropathy. *Febs J.* **2013**, *280*, 3232–3243. [[CrossRef](#)] [[PubMed](#)]
39. Lovegrove, C.E.; Besevic, J.; Wiberg, A.; Lacey, B.; Littlejohns, T.J.; Allen, N.E.; Goldsworthy, M.; Kim, J.; Hannan, F.M.; Curhan, G.C.; et al. Central Adiposity Increases Risk of Kidney Stone Disease through Effects on Serum Calcium Concentrations. *J. Am. Soc. Nephrol.* **2023**, *34*, 1991–2011. [[CrossRef](#)] [[PubMed](#)]
40. Alvarez-Nemegyei, J.; Medina-Escobedo, M.; Villanueva-Jorge, S.; Vazquez-Mellado, J. Prevalence and risk factors for urolithiasis in primary gout: Is a reappraisal needed? *J. Rheumatol.* **2005**, *32*, 2189–2191. [[PubMed](#)]
41. Thongprayoon, C.; Krambeck, A.E.; Rule, A.D. Determining the true burden of kidney stone disease. *Nat. Rev. Nephrol.* **2020**, *16*, 736–746. [[CrossRef](#)] [[PubMed](#)]
42. Li, Z.X.; Jiao, G.L.; Zhou, S.M.; Cheng, Z.Y.; Bashir, S.; Zhou, Y. Evaluation of the chemical composition of nephrolithiasis using dual-energy CT in Southern Chinese gout patients. *BMC Nephrol.* **2019**, *20*, 273. [[CrossRef](#)] [[PubMed](#)]
43. Bardin, T.; Nguyen, Q.D.; Tran, K.M.; Le, N.H.; Do, M.D.; Richette, P.; Letavernier, E.; Correas, J.M.; Resche-Rigon, M. A cross-sectional study of 502 patients found a diffuse hyperechoic kidney medulla pattern in patients with severe gout. *Kidney Int.* **2021**, *99*, 218–226. [[CrossRef](#)] [[PubMed](#)]
44. Nakanishi, N.; Fukui, M.; Tanaka, M.; Toda, H.; Imai, S.; Yamazaki, M.; Hasegawa, G.; Oda, Y.; Nakamura, N. Low urine pH is a predictor of chronic kidney disease. *Kidney Blood Press. Res.* **2012**, *35*, 77–81. [[CrossRef](#)] [[PubMed](#)]
45. Pak, C.Y. Citrate and renal calculi. *Miner. Electrolyte Metab.* **1987**, *13*, 257–266. [[PubMed](#)]

46. de Brito-Ashurst, I.; Varaganam, M.; Raftery, M.J.; Yaqoob, M.M. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J. Am. Soc. Nephrol.* **2009**, *20*, 2075–2084. [[CrossRef](#)] [[PubMed](#)]
47. Pak, C.Y.; Sakhaee, K.; Fuller, C. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int.* **1986**, *30*, 422–428. [[CrossRef](#)] [[PubMed](#)]
48. Tsaturyan, A.; Bokova, E.; Bosshard, P.; Bonny, O.; Fuster, D.G.; Roth, B. Oral chemolysis is an effective, non-invasive therapy for urinary stones suspected of uric acid content. *Urolithiasis* **2020**, *48*, 501–507. [[CrossRef](#)] [[PubMed](#)]
49. Taguchi, K.; Cho, S.Y.; Ng, A.C.; Usawachintachit, M.; Tan, Y.K.; Deng, Y.L.; Shen, C.H.; Gyawali, P.; Alenezi, H.; Basiri, A.; et al. The Urological Association of Asia clinical guideline for urinary stone disease. *Int. J. Urol.* **2019**, *26*, 688–709. [[CrossRef](#)] [[PubMed](#)]
50. Skolarikos, A.; Geraghty, R.; Somani, B.; Taily, T.; Jung, H.; Neisius, A.; Petřík, A.; Kamphuis, G.M.; Davis, N.; Bezuidenhout, C.; et al. European Association of Urology Guidelines on the Diagnosis and Treatment of Urolithiasis. *Eur. Urol.* **2025**, *88*, 64–75. [[CrossRef](#)] [[PubMed](#)]
51. Jiang, P.; Xie, L.; Arada, R.; Patel, R.M.; Landman, J.; Clayman, R.V. Qualitative Review of Clinical Guidelines for Medical and Surgical Management of Urolithiasis: Consensus and Controversy 2020. *J. Urol.* **2021**, *205*, 999–1008. [[CrossRef](#)]
52. Miake, J.; Hisatome, I.; Tomita, K.; Isoyama, T.; Sugihara, S.; Kuwabara, M.; Ogino, K.; Ninomiya, H. Impact of Hyper- and Hypo-Uricemia on Kidney Function. *Biomedicines* **2023**, *11*, 1258. [[CrossRef](#)] [[PubMed](#)]
53. Guo, K.; Li, C.; Terkeltaub, R.; Dalbeth, N.; Wang, X.; Ji, X.; Chen, Y.; Cui, L.; Liu, Z.; Li, X.; et al. Effects of adding urinary alkaliizer citrate mixture to febuxostat in gout patients with combined-type hyperuricemia and low urine pH: A prospective cohort study. *Arthritis Res. Ther.* **2026**, *28*, 76. [[CrossRef](#)] [[PubMed](#)]
54. Xue, X.; Liu, Z.; Li, X.; Lu, J.; Wang, C.; Wang, X.; Ren, W.; Sun, R.; Jia, Z.; Ji, X.; et al. 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. *Rheumatology* **2021**, *60*, 2661–2671. [[CrossRef](#)] [[PubMed](#)]
55. Bao, D.; Lv, N.; Duan, X.; Zhang, X.; Wang, J.; Wang, S.; Wang, Y.; Zhao, M.H. Prevalence and clinical association of hyperechoic crystal deposits on ultrasonography in patients with chronic kidney disease: A cross-sectional study from a single center. *J. Nephrol.* **2023**, *36*, 2467–2475. [[CrossRef](#)] [[PubMed](#)]
56. Dauw, C.A.; Yi, Y.; Bierlein, M.J.; Yan, P.; Alruwaily, A.F.; Ghani, K.R.; Wolf, J.S., Jr.; Hollenbeck, B.K.; Hollingsworth, J.M. Factors Associated With Preventive Pharmacological Therapy Adherence Among Patients with Kidney Stones. *Urology* **2016**, *93*, 45–49. [[CrossRef](#)] [[PubMed](#)]
57. Stern, K.L.; Canvasser, N.; Borofsky, M.; Gleason, V.M.; Kamphuis, G.; El Tayeb, M.M.; Hsi, R.; Scotland, K.B. Alkalinizing Agents: A Review of Prescription, Over-the-Counter, and Medical Food Supplements. *J. Endourol.* **2020**, *34*, 1–6. [[CrossRef](#)] [[PubMed](#)]
58. Canales, B.K. Editorial Comment on: “Alkalinizing Agents: A Review of Prescription, Over-the-Counter, and Medical Food Supplements” by Stern et al. (*J. Endourol* 2020;34(1):1-6; DOI: 10.1089/end.2019.0292). *J. Endourol.* **2020**, *34*, 639. [[CrossRef](#)] [[PubMed](#)]
59. Qi, H.; Sun, M.; Terkeltaub, R.; Merriman, T.R.; Chen, H.; Li, Z.; Ji, A.; Xue, X.; Sun, W.; Wang, C.; et al. Hyperuricemia Subtypes Classified According to Renal Uric Acid Handling Manifesting Distinct Phenotypic and Genetic Profiles in People with Gout. *Arthritis Rheumatol.* **2024**, *76*, 1130–1140. [[CrossRef](#)] [[PubMed](#)]
60. Group, K.W. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.* **2013**, *3*, 1. [[CrossRef](#)]
61. Doria, A.; Galecki, A.T.; Spino, C.; Pop-Busui, R.; Cherney, D.Z.; Lingvay, I.; Parsa, A.; Rossing, P.; Sigal, R.J.; Afkarian, M.; et al. Serum Urate Lowering with Allopurinol and Kidney Function in Type 1 Diabetes. *N. Engl. J. Med.* **2020**, *382*, 2493–2503. [[CrossRef](#)] [[PubMed](#)]
62. Badve, S.V.; Pascoe, E.M.; Tikun, A.; Boudville, N.; Brown, F.G.; Cass, A.; Clarke, P.; Dalbeth, N.; Day, R.O.; de Zoysa, J.R.; et al. Effects of Allopurinol on the Progression of Chronic Kidney Disease. *N. Engl. J. Med.* **2020**, *382*, 2504–2513. [[CrossRef](#)] [[PubMed](#)]
63. Kimura, K.; Hosoya, T.; Uchida, S.; Inaba, M.; Makino, H.; Maruyama, S.; Ito, S.; Yamamoto, T.; Tomino, Y.; Ohno, I.; et al. Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial. *Am. J. Kidney Dis.* **2018**, *72*, 798–810. [[CrossRef](#)] [[PubMed](#)]
64. Kojima, S.; Matsui, K.; Hiramitsu, S.; Hisatome, I.; Waki, M.; Uchiyama, K.; Yokota, N.; Tokutake, E.; Wakasa, Y.; Jinnouchi, H.; et al. Febuxostat for Cerebral and Cardiovascular Events Prevention Study. *Eur. Heart J.* **2019**, *40*, 1778–1786. [[CrossRef](#)] [[PubMed](#)]
65. Ghang, B.; Park, J.; Lee, J.S.; Lim, J.S.; Kim, H.; Liew, D.F.L.; Kim, J.; Kang, D.H.; Yoo, B. Post-hoc analysis of the CARES trial suggests delayed progression of chronic kidney disease in patients with gout during urate-lowering therapy. *Kidney Int.* **2025**, *107*, 521–529. [[CrossRef](#)] [[PubMed](#)]

66. Ramos, G.K.; Goldfarb, D.S. Update on Uric Acid and the Kidney. *Curr. Rheumatol. Rep.* **2022**, *24*, 132–138. [[CrossRef](#)] [[PubMed](#)]
67. Stamp, L.K.; Farquhar, H.; Pisaniello, H.L.; Vargas-Santos, A.B.; Fisher, M.; Mount, D.B.; Choi, H.K.; Terkeltaub, R.; Hill, C.L.; Gaffo, A.L. Management of gout in chronic kidney disease: A G-CAN Consensus Statement on the research priorities. *Nat. Rev. Rheumatol.* **2021**, *17*, 633–641. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.