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Editorial

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Editorial

Citrate in the management of gout, urate nephrolithiasis and kidney disease: an old therapy rediscovered?

This editorial refers to the article 'Impact of Adding Urine Alkalization Therapy to Xanthine Oxidase Inhibitor in Gout Management: A Prospective Cohort Study' by Can Wang *et al.* 2025; 64(6): 3509–3517. https://doi.org/10.1093/rheumatology/keaf091.

A study by Wang *et al.* in this issue [1] demonstrates the efficacy of an inexpensive and benign approach to lowering serum uric acid levels in gout patients. As a common form of inflammatory arthritis, gout is caused by the deposition of monosodium urate crystals in joints due to chronic hyperuricemia. Epidemiologically, gout is increasingly important due to its rising global prevalence. Gout goes hand in hand with poor metabolic health that also manifests as obesity, hypertension, type-2 diabetes and numerous other non-communicable diseases, highlighting its growing impact on public health.

Humans have higher serum urate levels than most other mammals due to mutations in uricase that resulted in its complete silencing in the mid-Miocene. This loss doubled serum urate to around 3–4 mg/dl (180–240 μM), potentially conferring a survival advantage at that time [2]. However, in modern societies, serum urate levels are much higher, in part due to the western diet (rich in alcohol, sugar and purines), resulting in hyperuricemia in up to 20% of the population (defined as >6 mg/dl in women and >7 mg/dl in men). These individuals are at increased risk for gout, kidney stones and chronic kidney disease (CKD).

The high uric acid burden in humans creates two challenges due to its poor solubility. First, the deprotonated form, urate, can precipitate as mono-sodium urate (MSO) crystals in the neutral pH milieu of interstitial fluids, including synovial fluid, where these crystals trigger the characteristic arthritis pain of gout. Second, the acidic form, uric acid, is even less soluble than urate, leading to crystal precipitation during renal excretion in low urinary pH conditions. This can cause significant damage to the kidneys, leading to 'gouty nephropathy', a form of CKD that can progress to kidney failure [3, 4]. Remarkably, 70% of individuals with gout have CKD at stage 2 or higher [5]—a striking prevalence that is often overlooked by rheumatologists focused primarily on the joint-related manifestations of the disease. The rules of physiology, and common sense, suggest that urine alkalization will prevent the precipitation of uric acid crystals in renal tubule lumens, thereby facilitating the safe excretion of uric acid via the kidneys. Indeed, several previous studies have already shown that urine alkalization with bicarbonate or citrate can enhance renal uric acid excretion thereby lowering serum uric acid levels [6–9]. However, perhaps because this inexpensive and safe non-pharmacological approach does not attract industry investment, larger studies have been lacking. Consequently, clinical guidelines for gout management do not include urine alkalization and only focus on urate-lowering therapy with drugs such as allopurinol and febuxostat.

The study by Wang *et al.* fills this gap. They performed a 12-week prospective study that sits on the spectrum between observational and interventional research, with 385 adult male participants with gout and low urinary pH (<6.2), initiating urate-lowering therapy with febuxostat. Participants self-selected into two groups: those who opted to add urine alkalization therapy using a citrate mixture, and those who did not [1].The outcomes were quite striking. As urine pH increased in the citrate-treated group, these participants experienced significantly fewer gout flares and lower pain levels. Furthermore, the dose of febuxostat could be significantly reduced in the citrate-treated group while maintaining the same serum uric acid goal. The possibility of dose reduction is important because febuxostat carries an FDA black box warning due to the risk of serious cardiovascular events and death.

Besides the rheumatological benefits of urine alkalization, the authors also found kidney and metabolic benefits. Patients in the citrate-treated group exhibited a significant decrease in the urinary albumin/creatinine ratio (although levels were within the normal range). Urine occult blood was also significantly lowered in the citrate group which may suggest improvement of micro-hematuria. These kidney benefits are consistent with the known benefits of alkalization in CKD patients, using citrate, bicarbonate or alkalizing diets.

Mechanistically, the effects of urine alkalization can be ascribed to the prevention of uric acid crystallization in the kidneys, augmenting uric acid excretion, mitigating kidney injury and lowering of serum uric acid levels. Interestingly, uric acid excretion did not differ between groups at study end point; however, this may reflect that all participants were titrated to achieve the same serum uric acid target, resulting in a steady state of production and excretion. It is plausible that absolute uric acid excretion was elevated at earlier timepoints with alkalizing therapy.

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A surprising, and not easily explainable, finding were improvements in dyslipidaemia in the citrate group. These patients exhibited a decrease in serum triglycerides and a rise in HDL cholesterol [1].

One major unacknowledged limitation of this study was the lack of a 'citrate-only' group, precluding determination of whether urine alkalization alone might exert an equivalent or superior urate-lowering effect compared with febuxostat. In future studies, a head-to-head comparison between the two could be highly informative.

Overall, this study suggests that the addition of citrate to gout therapy may not only lower serum uric acid levels and reduce gout flares—at lower drug doses—but also have beneficial effects on the risk for uric acid kidney stones and gout-associated kidney disease. Given the benign nature of citrate—certainly as compared with drugs like febuxostat—there seems to be no reasonable barrier to adopting citrate as a first-line approach to managing hyperuricemia. Citrate is commonly used for alkalization in various conditions and is usually well tolerated and safe with gastrointestinal discomfort being the most common complaint. The authors of this study appear to have used a custom-made citrate mixture containing sodium. Given the known benefits of sodium-reduction in CKD it may be advantageous to utilize sodium-free citrate products. For example, an available medical food for CKD contains citrate as a more kidney-friendly blend with potassium, calcium and magnesium [10]. The effect of urine alkalization with citrate can be easily monitored by patients using pH paper allowing dose adjustment. Combining citrate alkalization with sensible nutrition and lifestyle changes to lower uric acid production (lowering sugar/fructose and alcohol consumption) may be as effective, and safer, as plain pharmacotherapy with drugs like febuxostat. This should be considered as a first-line conservative approach by anyone treating patients with gout.

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