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REVIEW

Urine pH, citrate, and beyond: Challenges of pharmaceutical stone management in daily urological practice

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Summary *Kidney stone disease, or nephrolithiasis, is a prevalent urological condition with variable pathogenesis. Among various factors, urine pH is not only considered to be a more influential factor in stone formation, aiding in the early diagnosis and management of specific stone types such as uric acid, cystine, calcium phosphate and struvite stones, but the role of urine pH in calcium oxalate stones, which comprise most cases, is more complex. Hypocitraturia in routine evaluation is another recognizable factor in lithogenesis, and administration of citrate, a widely used agent in the conservative management of stones, corrects hypocitraturia. Citrate also alkalizes the urine and can therefore be used to dissolve and prevent uric acid stones. However, citrate can induce the formation of insoluble calcium phosphate salts, such as brushite and hydroxyapatite, which can lead to mixed stones and the development of nephrocalcinosis. To address this complexity, innovative treatments that focus on a broader inhibition of lithogenesis with pH-modifying strategies may allow for more comprehensive management. In addition, modern technological tools such as pH meters and pH-tracking mobile applications can offer personalized treatment plans, potentially improving patient outcomes. The current lack of consensus on the standard and optimal management of pH measurement and modification underscores the need for further research and greater collaboration among experts. The development of evidence-based strategies will be essential to improve the prevention and management of nephrolithiasis.*

KEY WORDS: *Kidney stones; Citrate; Phytate; Urine pH.*

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INTRODUCTION

Kidney stone disease or nephrolithiasis represents a significant global health burden due to the increasing prevalence of kidney stones worldwide, affecting approximately 10-15% of the population over a lifetime (1). Gender may be pivotal in the clinical presentation, as men are more frequently affected than women. This disparity is reflected in significant differences in the urinary excretion of potassium, oxalate, citrate, uric acid, sodium, magnesium, and phosphate, as well as lower urine volume and urine pH in men compared to women (2). Despite these physiological differences, common dietary habits may serve as a shared risk factor between genders. In both men and women, fluid and animal protein intake influence the risk of developing kidney stones (3). Given these influences, factors that mediate the relationship between diet, fluid intake, and lithogenesis must be considered. Studies advise that enhanced purine metabolism due to high consumption of meat and increased acid load can lead to uric acid kidney stones. The likely mechanism involves a reduction in urine pH and an increase in urinary excretion of uric acid, particularly in individuals with metabolic syndrome and diabetes (4). Conversely, alkalization of urine has been demonstrated as pivotal in the dissolution of existing and prevention of recurrent uric acid stones (5). In calcium stones, and particularly in calcium oxalate stones, which represent most kidney stones, the role of urine pH is controversial but still under investigation (6). Persistent urine pH less than 5.5 on at least two occasions daily has been noted in 14.6% of stone formers, following the most common abnormality of hypercalciuria (46%) (7). Moreover, low urine pH, as part of metabolic acidosis, has been associated with insulin resistance, implying that the body does not use insulin properly when urine becomes acidic. This inverse relationship has been noticed in healthy individuals and those forming uric acid stones, and therefore, urine pH could be considered a marker of overall metabolic health (8). Furthermore, the reduced ability to acidify urine can lead to recurrent nephrolithiasis, and refractory alkaline urine pH associated with *renal tubular acidosis* (RTA) is a key factor in the formation of calcium phosphate stones (9). Understanding the complex interplay between these factors is essential for developing more effective strategies for the prevention and manage-

ment of nephrolithiasis, highlighting the need for individualized approaches based on metabolic and dietary assessments. In this review, we discuss the role of pH in lithogenesis, explore strategies to measure and modify urinary pH, discuss the limitations of citrate as a treatment, and present novel molecules to improve patient outcomes.

Materials and methods

We performed a comprehensive PubMed review in June 2024, covering the period from 2000 to date. Our search string was ("*urine pH*"[MeSH Terms] OR "*urine pH*"[All Fields]) AND ("*lithiasis*"[MeSH Terms] OR "*lithiasis*"[All Fields] OR "*kidney stones*"[MeSH Terms] OR "*kidney stones*"[All Fields] OR "*nephrolithiasis*"[MeSH Terms] OR "*nephrolithiasis*"[All Fields] OR "*urolithiasis*"[MeSH Terms] OR "*urolithiasis*"[All Fields]). We selected studies examining the influence of pH on kidney stones, including mechanisms, pH level effects on various stone types, and pH modification for dissolution and prevention through dietary and pharmacological interventions, commercial products, and patient compliance. Additionally, we evaluated treatment recommendations from the *European Association of Urology* (EAU) and the *National Institute for Health and Care Excellence* (NICE) regarding urine pH.

Link of urine pH on kidney stones formation

Calcium oxalate and calcium phosphate stones constitute most kidney stones, accounting for up to 80% of all cases (10). Urine pH has an impact on the formation of various types of calcium-based kidney stones, influencing both the crystallization process and the metabolic environment within the urinary tract. Evidence highlights the role of urine pH modulation in the management of calcium oxalate stones, suggesting that raising urine pH with alkaline agents has a significant impact on reducing urinary calcium excretion and calcium oxalate saturation (11). However, the role of urine pH is also significant in the formation of idiopathic calcium phosphate stones, where elevated urine pH favours the precipitation of calcium phosphate crystals, leading to the formation of these stone – a process linked to defects in bicarbonate reabsorption in the kidneys (12). In patients with brushite stones, increased urine pH is a significant metabolic abnormality, observed in 61.5% of cases, along with a high prevalence of absorptive hypercalciuria and distal renal tubular acidosis (13). High urine pH is of particular interest, as it is linked to the transformation from calcium oxalate to calcium phosphate stones. One study suggests that high urine pH may be a key factor in predisposing certain individuals to this transformation, possibly due to dietary influences, hereditary factors, or the use of alkaline agents such as citrate. This underscores the importance of proactively monitoring urine pH to prevent the progression to calcium phosphate stones (14). Finally, higher urine pH has been positively associated with an increased calcium oxalate dihydrate to monohydrate crystal ratio, which possibly reflects underlying urinary metabolic risk factors, warranting further evaluation (15). Given the significant impact of urine pH on calcium stone formation, proactive management and monitoring of pH levels are essential components of effective prevention and treatment strategies for calcium-based nephrolithiasis.

While high urine pH is a risk factor for some types of calcium stones, it appears to have a protective effect against uric acid stones, highlighting the unique association between urine pH and the pathogenesis of different types of urinary stones (16). Uric acid stones account for approximately 10% of all kidney stones, making them the second most common type of urinary stone after calcium oxalate and calcium phosphate stones (17). The main defects leading to uric acid stones include hyperuricosuria, low urine pH – identified as the most common and significant factor – and low urine volume, with possible mechanisms involving insulin resistance, which can impair ammonia production in the renal proximal tubule (18). As a result, uric acid, a weak organic acid with low solubility and high pH dependence, can lead to kidney stone formation due to supersaturation when urine pH is less than 5.5. Within the pH range of 6.0 to 6.5, uric acid deprotonates to its more soluble form, urate, which is crucial for the effective dissolution of existing stones (19). Understanding uric lithiasis is essential for effective prevention and treatment, ultimately reducing the burden of this condition.

In addition to calcium and uric acid stones, there is a diverse group of non-calcium stones that present unique challenges, such as cystine and struvite stones. Cystinuria is the most common monogenic disorder leading to nephrolithiasis, characterized by the recurrent formation of cystine stones due to the poor solubility of cystine at urine pH levels below 7, and is often associated with a higher prevalence of chronic kidney disease (20). Mutations in genes encoding subunits of a transporter have been identified as responsible for cystinuria, and thus, diagnosis is usually made early in life, although late diagnosis is not uncommon. Management of cystinuria remains challenging, with patients often at risk of multiple surgical procedures due to recurrent cystine stone formation (21). On the other hand, infectious stones such as struvite, which account for less than 10% of kidney stone cases and are characterized by a female gender predominance, can lead to the development of large kidney stones such as staghorn calculi. Despite their infectious aetiology, metabolic abnormalities are highly prevalent in patients with staghorn stones, with conditions such as hypercalciuria and hypocitraturia observed in over 50% of cases (22). Bacteria that hydrolyse urea, such as Proteus mirabilis, raise urine pH levels above 7.2, creating an alkaline environment that promotes the crystallization of minerals, particularly magnesium ammonium phosphate, leading to the formation of large, capacious renal stones. These stones are associated with serious complications, including recurrent urinary tract infections, urinary obstruction, renal failure, and septicaemia (23). Understanding this pathogenic mechanism has driven experimental research efforts, such as the development of vaccines to prevent these infections and mitigate their severe consequences (24). Finally, it has been reported that certain populations, such as patients who have undergone bladder replacement or reservoir procedures, have significantly lower urinary citrate excretion and significantly higher urine pH (due to the altered

urine handling by the intestinal segment) compared to healthy controls, even in the absence of an active urinary infection. This leads to higher urinary supersaturation with respect to calcium phosphate, brushite, and magnesium ammonium phosphate, indicating that stone formation in these patients can be driven by altered urine pH and metabolic factors, rather than by infection alone (25).

Urinary pH modification strategies

Dietary interventions

Water intake is the most easily modifiable factor in urinary health, as both its volume and acidity can be adjusted, thus influencing urine pH and potentially altering the risk of lithogenesis. In a study of young athletes, low urine volume and low pH, together with increased uric acid and calcium concentrations, may increase the risk of lithogenesis. Therefore, preventing dehydration could be a strategy to balance urine pH and reduce the risk of kidney stones (26). Regarding the influence of the pH levels of drinking water on urine pH, a study involving Wistar Albino rats over a 13-day period, in which rats were given water with pH levels of 5.5, 7, and 8.2, showed statistically significant changes in urine pH on different days between groups. Specifically, the urine pH of the group given water with pH 7 was significantly lower on the first day and higher on the fourth day compared to the other groups. On the seventh day, the group given water with pH 8.2 had higher urine pH compared to the other groups. The authors concluded that the pH of drinking water is associated with fluctuations in urine pH over time (27). The mechanism may involve the buffer system, renal function, and other haemostasis procedures. Moreover, while the market for alkaline water is growing, the efficacy of water alone as a treatment to alter urine pH is questionable. A chemical analysis of various brands of alkaline water shows that, despite their high pH levels, they have negligible alkali content, calling into question the ability of these products to achieve therapeutic goals, and patients should consider adhering to established treatments such as potassium citrate (28). On the other hand, a study investigating the potential role of acidic sports drinks in lithogenesis did not show dramatic changes in pH, but a higher concentration of citrate in a sports drink may correlate with an increase in pH and increased citrate excretion, which may be a preventive strategy against some types of kidney stone formation (29). Therefore, effective prevention of kidney stones requires a multifaceted approach that focuses on adequate hydration and established treatments such as potassium citrate, rather than relying solely on the pH of drinking water.

Pharmacological interventions

Alkalizing agents

Urine alkalization with citrate is the most widely used approach for both the prevention and dissolution of uric and cystine stones (30). Potassium citrate is the most commonly used, although sodium bicarbonate, magnesium bicarbonate, or sodium-potassium citrate or magnesium-potassium salts have also been suggested (31, 32). Citrate is a tricarboxylic acid and an important intermediate in the Krebs cycle, which is filtered and partially reabsorbed in the kidney, where it prevents nephrolithiasis by binding to calcium to form soluble complexes, thereby inhibiting crystal formation. Additionally, citrate raises urine pH by being metabolized in the liver to bicarbonate, which is then excreted in the urine, creating a more alkaline environment that reduces the likelihood of stone formation (33).

Citrate therapy is reported to be highly effective for uric acid stones, with complete resolution in up to 70% of cases. Furthermore, in populations with suspected (radiolucent) ureteral uric acid stones, citrate therapy may result in a nearly 90% stone-free status (34). In terms of prevention, despite the lack of standardization in optimal administration, citrate-based alkalization can offer a stone-free status for several years, whether used frequently or on demand and with the option of troubleshooting dissolution therapy (31). As cystine stones also respond to alkalization, potassium or sodium bicarbonate, with or without penicillamine, is often used alongside surgical treatment. However, to be effective, the pH needs to be raised above 7.0-7.5, and this is very difficult to achieve in a sustained manner, so reoperation rates for recurrence or regrowth remain high (35). A recent systematic review highlighted that gastrointestinal disturbances, such as nausea and vomiting, were common side effects leading to discontinuation; non-compliance, failure, and non-adherence were also implicated (32). To avoid intolerance and discontinuation, dose reduction may be beneficial while still effective and can be achieved in combination with other agents such as theobromine, a novel inhibitor of uric acid crystallization. *Hernandez et al.* reported that the combination of citrate and theobromine (Lit-Control® pH Up) can reduce the risk of uric acid stone formation and may serve as an additional, more effective, more tolerable, and safer strategy in clinical practice (36).

Acidifying agents

L-methionine is a known acidifying agent recognized for its role in lowering urinary pH through the metabolic production of sulphuric acid during its breakdown. By creating an acidic environment, it can effectively counteract conditions that favour the crystallization of certain urinary stones, such as struvite and calcium phosphate stones, which thrive in alkaline urine. The use of a single dose of 1500 mg of L-methionine has been shown to reduce struvite supersaturation by 34% and brushite by 25%, while leaving calcium oxalate stone risk and urinary calcium excretion unaffected, emphasizing its use in stone cases associated with high urinary pH (37). In a 10-year study of former struvite stone formers treated with L-methionine to acidify the urine, a significant decrease in urinary pH from 7.5 to 5.5 was observed, along with an increase in the excretion of citrate, magnesium, potassium, and uric acid, with only 10% of patients developing new stones (38). Ammonium chloride, another urinary acidifier, effectively lowers urine pH by enhancing renal hydrogen ion excretion, creating a more acidic urinary environment. This mechanism disrupts the favourable conditions for the formation and growth of struvite stones. Therefore, L-methionine or ammonium chloride

in combination with antibiotics plays a crucial role not only in reducing stone formation but also in preventing recurrent infections, making it a key component in the comprehensive management of struvite nephrolithiasis (39). However, both L-methionine and ammonium chloride are still weak recommendations in the EAU guidelines as part of a broader strategy for the prevention and management of struvite stones, mainly due to the lack of randomized clinical trials (40).

Agents with no effect on pH

For calcium stones, the benefits of pH modification are less well established, but evidence in healthy volunteers suggests that potassium citrate can raise pH and reduce both urinary calcium excretion and calcium oxalate saturation. On the other hand, magnesium treatment may also be beneficial (11), by reducing oxalate absorption and forming soluble complexes with oxalate in the urine. In a prospective double-blind study, the administration of potassium-magnesium citrate for up to 3 years effectively prevented recurrent calcium oxalate stones, with a reduction in the risk of recurrence by 85% (41). *Zerwekh et al.* conducted a study in 20 normocalciuric subjects randomized to receive either placebo or potassium-magnesium citrate and reported that the latter significantly reduced the relative saturation of calcium oxalate (42). In patients with enteric hyperoxaluria due to previous bowel surgery, potassium citrate therapy may be beneficial against stone formation, as it binds urinary calcium and reduces the formation of insoluble calcium oxalate crystals, providing a valuable adjunct to the primary focus of dietary oxalate management (43). In these cases, the addition of magnesium may also provide additional benefit, as pairing magnesium with oxalate-containing meals can reduce oxalate absorption (44).

However, although potassium citrate effectively increases urinary citrate levels, the associated rise in urine pH, oxalate, and phosphate levels leads to increased calcium phosphate supersaturation, which may inadvertently contribute to calcium phosphate stone formation (45), or even to infection and struvite stones. As noted in the previous section, these stones should be treated with acidifying agents such as L-methionine. This challenge has been highlighted by researchers such as *Siener et al.* (46), who, after analysing 42,519 stones, concluded that new agents with no effect on urine pH are needed to treat calcium stones. *Grases* and *Costa-Bauzà* have been working for many years on the use of phytate, a safe natural ingredient approved by the US FDA, with strong inhibitory capacity on calcium oxalate and calcium phosphate crystallization and no effect on pH (47). Other authors have shown that phytate intake is associated with a lower risk of stone formation, can bind calcium, and reduce urinary calcium excretion in patients with hypercalciuria (48-50).

In a study conducted on 74 active calcium oxalate stone formers divided into three groups – no treatment, potassium citrate at a dose of 6,480 mg, and phytate at a dose of 120 mg – the risk of calcium stone formation was eliminated in both the potassium citrate and phytate groups. Moreover, the authors demonstrated for the first time that phytate could achieve similar efficacy at a significantly lower dose than citrate (51). Subsequently, other authors have shown that only 1.5 mg of phytate, *versus* 800 mg of citrate, is required to prevent calcium oxalate nucleation in synthetic urine (52). With this superior inhibitory capacity and no effect on pH, phytate appears to be a promising treatment for calcium stone patients. Finally, *Grases et al.* recently demonstrated a surprising and highly significant synergistic effect between phytate and magnesium in the inhibition of calcium oxalate crystallization (53). A combination of magnesium and phytates is currently used in clinical practice (Lit-Control pH® Balance).

Urine pH as a marker of early stone diagnosis

In addition to its established association with stone risk, urine pH plays a critical role in the assessment of possible nephrolithiasis at all levels of patient care and may be valuable in certain populations. An association between BMI and urine pH has been reported, suggesting that diet and lifestyle modifications may be beneficial in reducing the risk of stone formation and potentially improving overall kidney health. A decrease in urine pH with increasing BMI is associated with a higher prevalence of urate and calcium oxalate stones (54). Moreover, higher BMI and lower urine pH have been reported as significant predictors of asymptomatic renal stones ultimately requiring surgical treatment. Early detection by assessing urine pH may be crucial in identifying asymptomatic stones that may eventually require surgical intervention (55).

In diabetic patients, lower urine pH (OR 0.500, 95% CI 0.043-0.581) is associated with a higher likelihood of stone recurrence, particularly for calcium oxalate and uric acid stones. As urine pH is a modifiable factor, targeted therapy to modify it could potentially reduce the incidence of recurrent stones in type 2 diabetic patients (56). The pathophysiology in diabetic patients appears to be complex, as both lower urine pH and higher urine oxalate levels have been reported compared to non-diabetic individuals (57). This requires specific dietary advice, medical management, and tailored stone prevention strategies to effectively manage nephrolithiasis in this population.

Furthermore, sleep apnoea has been associated with lower urine pH even after adjustment for BMI, age, and gender, and the fact that this risk appears to be independent of obesity suggests that populations with sleep apnoea may be candidates for screening for pH alterations and potential stone risk (58).

Urine pH monitoring and adherence to treatment

Measurement of urinary pH is a critical aspect of monitoring alkalization therapy in the management of uric acid, cystine, and struvite stones, yet there is considerable variability in the methods (pH meter, reagent strips, or not disclosed), timing, and frequency used among researchers (31). The study by *De Coninck et al.* demonstrates that medical-grade portable electronic pH meters outperform reagent strips in terms of resolution, consistency, and reliability for urine pH measurement. Unlike strips, which rely on subjective colour interpretation prone to user error, the portable electronic pH meter provides precise numerical readings with the highest correlation to the gold standard, superior ability to classify pH

within target ranges, and better results in sensitivity, specificity, PPV, NPV, and accuracy (59). Other researchers have also suggested that the colorimetric method is not reliable for assessing urinary pH in patients receiving citrate treatment (60).

In addition, the timing and frequency of urine pH measurement is another area that lacks standardization, with studies varying between spot collection of freshly voided urine and 24-hour urine collection (31). Regarding the optimal time of collection, it is important to note that pH changes with increasing storage time and temperature. Therefore, prolonged storage or elevated temperatures should be avoided, as they may alter the results.

In terms of frequency, *Murayama et al.* found that uric acid stone formers have a consistently low urinary pH throughout the day, whereas calcium phosphate stone formers have a consistently high urine pH during the day, and calcium oxalate stone formers have a typical diurnal pattern, with low pH in the early morning, rising during the day, and falling again at night (61).

Overall, pH monitoring needs standardization, but in the meantime, it seems that the most efficient approach to urine pH measurement is to use a portable medical-grade electronic pH meter with freshly voided spot urine samples several times a day. This can be a challenge for adherence in stone patients; therefore, the development of new digital technologies such as the myLit-Control® App is needed to educate patients, change poor behaviours, and increase adherence.

Medical societies recommendations

To assess clinicians' access to guidance on the role of pH, we evaluated the guidelines from the *European Association of Urology* (EAU) and the National Institute for *Health and Care Excellence* (NICE), due to their prominence and influence in Europe and the UK, respectively.

The 2024 EAU guidelines recommend urine pH measurement as a basic laboratory test and as part of a specific metabolic assessment. A 24-hour urine collection is recommended to differentiate between renal tubular acidosis, infections, or acidic arrest, while dipstick or pH-meter measurements on freshly voided urine collected at different times of the day are suggested to monitor alkalization therapy. The guidelines also recognize the role of pH alkalization with agents such as citrate in the prevention and dissolution of uric acid stones (40).

In contrast, the NICE guideline on urolithiasis (NG118), published in 2019, provides limited information on urinary pH and makes no recommendations on stone dissolution therapy. Although the guideline mentions lemon juice as a lifestyle modification and the use of citrate for calcium oxalate stones, it does not emphasize the role of urine pH (62).

Although the exact role of urinary pH in the management of all kidney stones remains unclear, there are efficient strategies for uric acid, cystine, calcium phosphate, and struvite stones. Discrepancies between medical guidelines highlight the need for collaboration to improve the credibility of evidence and to consider cost-effectiveness. Cross-referencing between guidelines could improve clinical practice while awaiting further evidence.

Limitations

Our work has several limitations. This is not a systematic review, so relevant studies may have been omitted, while research into the influence of urine pH on lithogenesis is constantly evolving and new findings may alter current knowledge and recommendations.

Conclusions

Urine pH plays a crucial role in the management of kidney stone disease, particularly for uric acid, cystine, and struvite stones, although its influence on calcium stones is less clear and should be an area for future research. In addition, urine pH may mask underlying stone disease and could be used for early diagnosis in selected populations. In the treatment landscape, although effective pH modification should be an integral part of stone management, challenges remain in the standardization of measurement and monitoring. Advances in technology, such as pH meters and mobile apps, can provide valuable tools for patients and clinicians, improving adherence and promoting patient-centred, personalized care. Finally, discrepancies in clinical guidelines highlight the need for further research and collaboration to establish standardized pH management strategies in nephrolithiasis.

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