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Review

Medical management of urolithiasis: Great efforts and limited progress

Victoria Jahrreiss [a], Christian Seitz [a,*], Fahad Quhal [b]

[a] Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria
[b] Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia

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Abstract *Objective:* To provide a comprehensive review on the existing literature on medical management of urolithiasis.
Methods: A thorough literature review was performed using Medline, PubMed/PMC, Embase, and the Cochrane Database of Systematic Reviews up to December 2022 to identify publications on the medical management of urolithiasis. Studies that assessed dietary and pharmacologic management of urolithiasis were reviewed; studies on medical expulsive therapy were not included in this review.
Results: Medical management of urolithiasis ranges from the prophylactic management of kidney stone disease to dissolution therapies. While most treatment concepts have been long established, large randomized controlled trials are scarce. Dietary modification and increased fluid intake remain cornerstones in the conservative management of urolithiasis. A major limitation for medical management of urolithiasis is poor patient compliance.
Conclusion: Medical management of urolithiasis is more important in patients with recurrent urolithiasis and patients with metabolic abnormalities putting them at higher risk of developing stones. Although medical management can be effective in limiting stone recurrence, medical interventions often fail due to poor compliance.

1. Introduction

Kidney stone disease (urolithiasis) is a highly prevalent disease with a rising incidence worldwide [1]. Approximately 7%–13% of the adult population in North America, 5%–9% in Europe, and 1%–5% in Asia are affected by urolithiasis [1]. Moreover, urolithiasis is a highly recurrent disease with a relapse rate of 50% within 10 years [2,3]. The high prevalence and the recurrent nature of urolithiasis have resulted in an increased economic burden on healthcare systems [4].

The etiology of urolithiasis is multifactorial including environmental, hereditary, and dietary factors. Generally,

* Corresponding author.
E-mail address: christian.seitz@meduniwien.ac.at (C. Seitz).
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an imbalance of crystallization promoters (such as oxalate, calcium, phosphate, urate, and cysteine) and inhibitors (such as citrate, magnesium, uromodulin, and pyrophosphate) leads to the formation of urinary stones, subsequently resulting in supersaturation of the urine and therefore aggregation, nucleation, and stone formation [5,6]. Urinary metabolic imbalances are more often found in stone formers compared to the healthy population and patients with recurrent stone disease seem to have more significant metabolic imbalances than patients with a single stone episode [5—7].

Due to the low incidence of reversible metabolic causes of urolithiasis, first time stone formers do not routinely undergo a full metabolic workup consisting of stone analysis, and urine and blood evaluation. Nevertheless, in over 90% of recurrent stone formers, a reversible metabolic cause can be identified [8]. Therefore, a metabolic workup should be performed in high-risk stone formers in order to establish prophylactic medical therapies [9,10].

Although lifestyle change and dietary modifications are considered the cornerstone of urolithiasis prevention, patient adherence to these measures is generally poor [11]. Nevertheless, reports have shown better adherence to prescribed medication for stone prevention [11]. Therefore, it can be assumed that medical therapies are a more promising intervention in these patients. This review provides an overview of the current medical treatment options for urolithiasis.

2. Material and methods

A comprehensive literature review of publications was performed using Medline, PubMed/PMC, Embase, and the Cochrane Database of Systematic Reviews up to December 2022. To identify articles of interest, we used the following search terms: "nephrolithiasis", "urolithiasis", "kidney stone", "renal stone", and "urinary stone". The search was restricted to articles published in English that were published in peer-reviewed journals. No restriction was made based on the type of article. Studies that assessed dietary and pharmacologic management of urolithiasis were reviewed. We did not include in this review studies that reported on medical expulsive therapy.

3. General preventive measures and medical prophylaxis

Independent of individual risk factors, all stone formers should be advised to follow general preventive measures that can help reduce stone recurrence and new stone formation. High fluid intake and reduced salt and animal protein intake are considered the cornerstone of prevention for most forms of stones [12—16].

Pharmacological prophylaxis for high-risk patients is still not established. Until now, the evidence for prophylactic medical management is sparse due to the lack of randomized placebo-controlled trials. Moreover, conducting such trials has been proven to be difficult not only because of the low compliance, but also due to the long observational period that is needed [17].

4. Calcium stones

Calcium stones are the most common type of urolithiasis. In a review of almost 90 000 stone analyses, calcium-based stones were identified in 78% of stones (calcium oxalate 60%, calcium phosphate 15%, and brushite stones 3%) [18]. Metabolic abnormalities that are commonly associated with calcium stones are hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia.

4.1. Hypercalciuria

Hypercalciuria used to be classified as absorptive, renal, and idiopathic. However, this classification has fallen out of favor as it is not expected to change treatment [19]. However, modifiable causes of hypercalciuria such as hyperparathyroidism should be ruled out, especially in patients with high serum calcium level [20,21]. Medical management of hypercalciuria includes thiazide diuretics, urinary alkalization, and xanthine oxidase inhibitors.

4.1.1. Thiazide diuretics

In patients with hypercalciuria, thiazides are used as medical prevention therapy to reduce urinary calcium [22]. Thiazide diuretics decrease the urinary calcium excretion by stimulating calcium reabsorption in the distal renal tubules. A randomized placebo-controlled study showed lower recurrence rates in patients treated with thiazides compared to those receiving placebo [23] (Table 1). Moreover, a Cochrane review reported a 60% reduction in new stone formation in patients with idiopathic hypercalciuria receiving thiazides compared to those on placebo [24]. Long-term thiazide therapy may increase urinary excretion of potassium and can cause hypocitraturia [25]. Therefore, potassium supplementation in form of potassium citrate should be recommended [26].

The ongoing NOSTONE trial (NCT03057431), an investigator-initiated 3-year prospective, multicenter, double-blind, placebo-controlled trial, is currently assessing the efficacy of standard (50 mg or 25 mg) and low-dose (12.5 mg) hydrochlorothiazide treatment in the recurrence prevention of calcium-based urolithiasis [27] (Table 1).

4.1.2. Potassium citrate

Alkali citrates such as potassium citrate increase both urinary citrate and pH levels [28,29]. Citrates reduce urinary calcium excretion by binding to calcium in the urine and therefore inhibit calcium crystallization in patients with hypocitraturia [30]. Furthermore, potassium citrate can be used for urine alkalinization, through the increase in plasma bicarbonate concentration [28].

The high citrate excretion as well as urinary alkalinization leads to a prevention of crystallization in calcium oxalate as well as calcium phosphate stones [31]. A randomized trial demonstrated the efficacy of potassium citrate in preventing stone formation in hypocitraturic calcium stone formers compared to placebo [28]. Potassium citrate has also been

Table 1 Commonly used medications in the treatment or prevention of urolithiasis.

Medication	Dose	Indication	Side effect
Hydrochlorothiazide [23,27]	• 25–50 mg per day	• Calcium stones	• Gastrointestinal upset • Fatigue • Hypocitraturia
Potassium citrate [50]	• 10–20 g per day	• Calcium stones • Uric acid stones • Cystine stones	• Epigastric pain • Heartburn • Nausea
Allopurinol [37]	• 100–300 mg per day • 100 mg per day in isolated hyperuricosuria	• Calcium stones with hyperuricosuria • Uric acid with hyperuricosuria • Uric acid stones refractory to hydration and urine alkalization	• Skin rash • Muscle pain • Nausea • Diarrhea • Hypersensitivity reaction
Febuxostat [39]	• 80 mg per day	• Calcium stones with hyperuricosuria • Uric acid with hyperuricosuria • Uric acid stones refractory to hydration and urine alkalization	• Muscle pain • Constipation • Liver-function test abnormalities
Calcium supplements [42]	• Not available	• Enteric hyperoxaluria	• Not available
Tiopronin [48]	• Adults: dose starts at 600–900 mg per day, divided three times a day • Children of >20 kg: dose starts at 15 mg/kg per day	• Cystine stones refractory to hydration and urine alkalization	• Nausea • Vomiting • Diarrhea • Mouth ulcers • Rash • Proteinuria
D-Penicillamine [48]	• 500–1500 mg per day, divided two to three times a day	• Cystine stones refractory to hydration and urine alkalization	• Pancytopenia • Proteinuria • Nausea • Impaired taste • Rash
Captopril [55]	• 50–150 mg per day	• Cystine stones refractory to hydration and urine alkalization in patients intolerant to cystine-binding agents	• Rash • Hypotension
Pyridoxine [44]	• 5–10 mg/kg per day	• Primary hyperoxaluria type 1	• Diarrhea
Lumasiran [45]	• Loading dose: 3 mg/kg once monthly for 3 months • Maintenance dose: 3 mg/kg once every 3 months	• Primary hyperoxaluria type 1	• Injection-site reaction • Headache • Rhinitis • Upper respiratory infection

demonstrated to improve the stone-free rate and prevent new stone formation after shock wave lithotripsy or percutaneous nephrolithotomy [32,33]. Furthermore, a recent Cochrane review evaluated the use of citrate supplements (in the form of potassium citrate, sodium potassium citrate, or potassium-magnesium citrate) in patients with calcium-based stones [34]. Compared to placebo, citrate therapy significantly reduced new stone formation (relative risk 0.26, 95% confidence interval 0.10–0.68) and prevented additional stone size growth (relative risk 1.97, 95% confidence interval 1.19–3.26) [34].

In a recent prospective study, 80 patients with calcium oxalate stones were randomized to receive either hydrochlorothiazide (50 mg/day) or potassium citrate (13 g per day) after achieving a stone-free status following a stone-related procedure (percutaneous nephrolithotomy, retrograde intrarenal surgery, or ureteroscopy) or shock wave lithotripsy for urolithiasis [35]. The mean 24-h urine calcium levels decreased to 205 (standard derivation 54.5) mg/day and 220.6 (standard derivation 96.3) mg/day in the potassium citrate and hydrochlorothiazide groups, respectively ($p=0.93$). At 1 year, ultrasonography revealed stones in two patients in hydrochlorothiazide group and in one patient in the potassium citrate group. The authors concluded that potassium citrate provided comparable decrease in calcium excretion to hydrochlorothiazide treatment in patients with calcium oxalate stones with hypercalciuria [35].

Citrate therapy is generally well tolerated. The most common side effects are related to gastrointestinal upset (nausea and bloating). In the previously mentioned Cochrane

review, there were no statistically significant differences in the rates of adverse events or non-compliance to treatment between citrate therapy and placebo [34].

4.1.3. Xanthine oxidase inhibitors

Allopurinol, a xanthine oxidase inhibitor, is known to be used in the treatment and prevention of uric acid stones [36]. However, allopurinol is also used in the prevention of calcium oxalate stones formers who have hyperuricosuria [37]. Patients with hyperuricosuria are prone to develop calcium oxalate stones through heterogenous nucleation [38]. In a randomized double-blind trial, calcium oxalate stone formers with hyperuricosuria were assigned to receive allopurinol or placebo [37]. Stone growth or recurrence occurred in 31% of the patients with allopurinol compared to 58% with placebo. Moreover, patients with allopurinol had a longer time to first stone event [37] (Table 1).

Recently, febuxostat, a new xanthine oxidase inhibitor, has also been evaluated in the setting of hyperuricosuria. In a double-blind, randomized controlled trial, febuxostat showed a significantly greater reduction in 24-h urinary uric acid (−58.6%) compared to allopurinol (−36.4%; $p=0.003$) and placebo (−12.7%; $p<0.001$) [39]. There was no significant difference in the percent change from baseline in the size of the largest calcium stone [39]. However, due to the scarcity of data on the use of febuxostat in this setting, allopurinol remains the agent of choice for recurrent calcium oxalate stones in patients with hyperuricosuria (Table 1).

4.2. Hyperoxaluria

Increased oxalate in urine is an important factor in calcium oxalate crystallization and hence stone formation. Enteric hyperoxaluria is the most common form. Normally calcium binds oxalate in the intestinal lumen and limits its absorption. Factors that decrease intestinal free calcium can increase available oxalate for absorption and hence lead to hyperoxaluria [40]. These factors include decreased calcium intake or fat malabsorption, which can occur in patients who have undergone bowel resection. In these cases, the fat malabsorption can lead to calcium saponification and an increase in free intestinal oxalate [41].

There are no randomized trials on the optimal management of enteric hyperoxaluria. One of the commonly utilized treatment options is calcium supplements [42]. Calcium supplements bind oxalate in the intestine when administered during meals and promote its excretion in stool (Table 1). Several calcium supplements are available; however, calcium citrate offers the potential advantage of correcting hypocitraturia, which has been found to be commonly associated with enteric hyperoxaluria [42,43].

Primary hyperoxaluria (PH) is an extremely rare genetic disorder [21]. The disease usually manifests during childhood, and patients have very high levels of oxalate in urine. Because of its rarity, data are limited on medical treatments for PH [21]. Pyridoxine is an agent that has been studied in patients with PH type 1 (PH1); however, many patients eventually progress to end stage renal disease and require liver-kidney transplantation. Pyridoxine decreases the production of oxalate in the liver and therefore also the urinary excretion of oxalate [44].

Recently, lumasiran, an RNA interference therapeutic agent was approved by the United States Food and Drug Administration and the European Medicines Agency for patients with PH1 (Table 1). This agent targets the mRNA of glycolate oxidase and thereby inhibits the synthesis of oxalate [45,46]. In a double-blind, phase 3 trial, patients with PH1 aged 6 years or older were randomized to receive subcutaneous lumasiran or placebo for 6 months [45]. The lumasiran group showed a 65.4% reduction in the 24-h urinary oxalate excretion compared to the placebo group [45]. Lumasiran was well tolerated with mild injection site reaction and no adverse event leading to discontinuation of treatment [45]. Moreover, it was also found to be effective and safe for very young patients with PH1. In a single-arm, open-label, phase 3 study including 18 patients aged <6 years (median age 50 months), lumasiran achieved a rapid and sustained reduction in spot urinary oxalate to creatinine ratio with acceptable safety in younger children [47]. Based on these data, lumasiran shows great potential and provides hope for patients with this rare and deliberating disease.

5. Cystine stones

Cystinuria is an autosomal recessive disorder and it is the most common cause of inherited urolithiasis. Cystine stones account for 1%−2% of the overall incidence and up to 8% of pediatric urolithiasis [48,49]. Cystine is relatively insoluble at physiological urine pH levels leading to higher recurrence rates reaching 83% at 5 years [50]. The goal of medical management of cystinuria is to achieve solubility of cystine. Patients are encouraged to increase fluid intake to 3−5 L per day aiming to achieve urine output of more than 3 L per 24 h [9]. Additional dietary measures include avoiding diet with excessive protein and salt which can increase urinary cystine excretion [51,52]. Protein is a major dietary source of methionine, a precursor of cystine. Restricting dietary sodium intake has also been found to be effective in reducing urinary cystine excretion in patients with cystinuria [51]. Urinary cystine excretion is expected to decrease by up to 650 μmol if dietary sodium intake is reduced by 150 mmol per day [51,52]. As cystinuria is highly pH dependent, medical management should also aim to maintain urine pH of >7.5.

5.1. Urine alkalization

Pharmacological management of cystinuria aims at increasing cystine solubility through urine alkalinization and reducing free cystine by agents that bind free cystine [50]. Urinary alkalinization using potassium citrate with a pH target of >7.5 has been found to help prevent cystine stone formation [48,50] (Table 1).

5.2. Cystine binding agents

Cystine-binding thiol agents such as tiopronin and D-penicillamine are recommended for patients with cystine urine excretion of >3 mmol per day or patients refractory to previous measures [48]. These agents contain a sulfhydryl group that forms a disulfide bond with cystine which is

soluble in urine [50]. Side effects may include asthenia, gastrointestinal upset, rash, and joint aches. Severe hematological adverse events such as thrombocytopenia and neutropenia have also been reported [53]. Tiopronin is reported to be more effective than D-penicillamine with lower rate of adverse effects [54].

5.3. Captopril

Captopril is an angiotensin-converting enzyme inhibitor that contains a sulfhydryl group. Captopril has been shown to promote reduction in total urinary cystine excretion [55] (Table 1). However, due to the lack of high-quality data, captopril is not recommended as monotherapy and can only be used in patient intolerant to the cystine-binding agents (tiopronin and D-penicillamine) [9,54].

6. Uric acid stones

Uric acid stones account for approximately 6%—10% of urinary stones [56,57]. Risk factors for uric acid stone formation include low urinary pH levels, hyperuricosuria, and low urine volume [58]. One of the critical determinants of uric acid solubility is urine pH level. At low pH, the urine becomes supersaturated with uric acid and subsequently forms uric acid stones [59]. Dietary factors that are expected to lead to acidic urine and cause hyperuricosuria include high protein diet [60,61].

6.1. Urine alkalization

As uric acid stone formation is largely dependent on urinary pH and urine volume, urine alkalinization and increasing urine output can dissolve uric acid stones [62]. Uric acid stone formers are encouraged to increase fluid intake to achieve urine volume more than 2.5 L per day [9,63]. Urine alkalization in the management of uric acid stones mainly aims at increasing urine pH level between 6.0 and 6.5 [36,64]. Many agents have been used for urine alkalinization. Traditionally, this has been accomplished with sodium bicarbonate [36]. However, sodium alkalinization can be complicated by the development of calcium phosphate or calcium oxalate stones [36]. Nowadays, potassium citrate is considered the standard agent for uric acid dissolution [9,65—67]. Potassium citrate alkalinization has been shown to help in uric acid dissolution and reduce recurrence with lower risk of secondary calcium phosphate or calcium oxalate stones formation [36,66,67].

6.2. Xanthine oxidase inhibitors

In patients with hyperuricosuria and in patients who are refractory to urine alkalinization, the xanthine oxidase inhibitor (allopurinol) can be used [9,63]. Allopurinol decreases hyperuricemia and hyperuricosuria and should be used in addition to urine alkalinization [36]. Side effects associated with allopurinol include skin rash, nausea, and diarrhea. The new xanthine oxidase inhibitor febuxostat has been shown to produce greater reduction in hyperuricosuria [39]. However, febuxostat has only been compared to allopurinol in patients with gout and calcium oxalate stones and there are no data on its efficacy in uric acid urolithiasis.

7. Struvite stones

Struvite stones, "infection stones", are urinary stones that typically form in patients with recurrent urinary infections caused by urease-producing bacteria. Struvite stones can also be associated with metabolic abnormalities [68].

In patients with struvite stones, complete surgical removal of the stone burden is the main treatment [69]. In patients with recurrent stones, urinary acidification and/or short-term or long-term antibiotic prophylaxis can be used [70]. Acetohydroxamic acid, a urease inhibitor, has been used in the management of persistent struvite stones; however, the side effects are significant [70].

8. Conclusion

Despite the vast advances that have been achieved in the surgical management of urolithiasis in the past decade, the knowledge on medical management of stones has not matched this progress. Medical management of urolithiasis is more important in patients with recurrent urolithiasis and patients with metabolic abnormalities putting them at higher risk of developing stones. Although medical management can be effective in limiting stone recurrence, medical interventions often fail due to poor compliance.

Author contributions

Study concept and design: Christian Seitz.
Data acquisition: Victoria Jahrreiss, Fahad Quhal.
Data analysis: Victoria Jahrreiss, Fahad Quhal.
Drafting of manuscript: Victoria Jahrreiss, Fahad Quhal, Christian Seitz.
Critical revision of the manuscript: Christian Seitz.

Conflicts of interest

The authors declare no conflict of interest.

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