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REVIEW

Medical and alternative therapies in urinary tract stone disease

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Abstract

Nephrolithiasis is a serious problem for both patients and the health system. Recurrence stands out as a significant problem in urinary system stone disease, the prevalence of which is increasing gradually. If recurrence is not prevented, patients may go through recurrent operations due to nephrolithiasis. While classical therapeutic options are available for all stone types, the number of randomized controlled studies and extensive meta-analyses focusing on their efficiency are inadequate. Various alternative therapeutic options to these medical therapies also stand out in recent years. The etiology of urolithiasis is multifactorial and not always related to nutritional factors. Nutrition therapy seems to be useful, either along with pharmacological therapy or as a monotherapy. General nutrition guidelines are useful in promoting public health and developing nutrition plans that reduce the risk or attenuate the effects of diseases affected by nutrition. Nutrition therapy involves the evaluation of a patient's nutritional state and intake, the diagnosis of nutrition risk factors, and the organization and application of a nutrition program. The main target is the reduction or prevention of calculus formation and growth *via* decreasing lithogenic risk factors and increasing lithogenic inhibitors in urine. This review focuses briefly on classical medical therapy, along with alternative options, related diets, and medical expulsive therapy.

Key words: Urolithiasis; Prevention; Stone medical therapy; Nutrition therapy; Diet; Hypercalciuria; Hyperoxaluria; Hyperuricosuria; Hypocitraturia; Cysteine stones

Core tip: Nephrolithiasis is a serious problem for both patients and the health system. Recurrence stands out as a significant problem in urinary system stone disease, the prevalence of which is increasing gradually. While classical therapeutic options are available for all stone types, the number of randomized controlled studies and extensive meta-analyses focusing on their efficiency are inadequate. Various alternative therapeutic options to these medical therapies also stand out in recent years. This review focuses briefly on classical medical therapy,

along with alternative options, related diets, and medical expulsive therapy.

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INTRODUCTION

Nephrolithiasis is a widespread medical problem, with an increased incidence in the last 20 years[1-4]. Its prevalence is expected to rise in the upcoming decades, as has been the case for obesity, diabetes, and metabolic syndrome[2,3]. Another problem related to nephrolithiasis is recurrence. In patients who do not receive prophylaxis following the first attack, recurrence rates are reported as 10% in the first year, 35% in the next 5 years, and 50% in 10 years[5].

If recurrence is not prevented, patients may go through recurrent operations due to nephrolithiasis which, even if said operations are only minimally invasive, still results in hospitalization. This leads to higher monetary costs and loss of manpower, whereas preventing stone formation is far more economic.

Numerous reports have revealed that urinary stone disease recurrence rates can be reduced *via* the correction of environmental and metabolic factors, as well as by the use of certain drugs and diet treatments[6-9]. In a meta-analysis of randomized trials focusing on the effects of drugs and diet on stone recurrence, the risk was shown to be reduced by 26%[10].

Further investigation into the possible pathogenic effect of Randall's plaques and the role of renal tubular crystal retention as a precursor in calcium oxalate (CaOx) nephrolithiasis may allow for the development of new drugs for the prevention of plaque formation and crystal adhesion to kidney cells. Nevertheless, all future studies should aim to understand the molecular/genetic level and pathophysiological mechanism of nephrolithiasis for the development of a targeted therapy.

PHARMACOTHERAPY

Hypercalciuria

Thiazide diuretics are the main treatment for idiopathic hypercalciuria (IH)-related calcium stones. There have been at least 10 randomized controlled trials (RCTs) focusing on the efficacy of thiazide in the prevention of idiopathic calcium kidney stones recurrence. Of these, seven have reported a decline in recurrence rates in treated patients[11-17].

Potassium supplements should normally be applied alongside thiazide treatment in order to prevent hypokalemia and hypocitraturia secondary to thiazide, as well as any possible subsequent side effects[18]. A reduction in bone mineral intensity and an increase in osteoclasis accompanies IH, with some authors claiming that reducing urinary calcium excretion can improve bone histology[19]. Bisphosphonates are effective in the inhibition of bone resorption, and the lower urinary calcium secretion and higher bone mineral intensity provided *via* bisphosphonate treatment was reported in a few studies[20]. Heller *et al*[21] have reported that alendronate prevented the excretion of urinary calcium, decreased 24-h urine calcium, and adjusted calcium equilibrium in 9 calcium stone patients within a short time period. Since no RCTs have yet been conducted to evaluate the efficacy of bisphosphonates on recurrence, bisphosphonate treatment is not currently recommended.

Hyperoxaluria

Two pharmacological agents that can reduce urinary oxalate are magnesium and pyridoxine.

The effect of magnesium in CaOx stone and non-hypomagnesuria patients is explained by the complexes formed among magnesium and oxalate that can lead to a reduction in CaOx supersaturation and inhibit the development of CaOx crystals. Increased magnesium intake additionally leads to an increase in urinary citrate and pH levels. On the other hand, dietary magnesium can reduce intestinal oxalate absorption in a manner similar to that of dietary calcium[22].

Calcium supplements, such as calcium carbonate and calcium citrate, are another potential therapeutic to magnesium supplements, as the latter are relatively less studied in hyperoxaluria treatment and form complexes with oxalate anions by a similar mechanism.

The logic behind vitamin B_6 use, on the other hand, is that its deficiency may cause oxalate leakage in urine[13]. RCTs on the use of pyridoxine in the prevention of recurrent stone disease are lacking in the literature, yet studies without controls in CaOx stone patients suggest that vitamin B_6 decreases urinary oxalate and stone recurrence[14,15].

The discovery of the relationship of oxalate with bacterial flora in the gastrointestinal system has paved the way for research related to the function of probiotics in the management of repeated CaOx stones. Studies revealed that lacking *Oxalobacter formigenes* colonies, which use oxalate as their solitary source of nutrition, could lead to an increase in the incidence of CaOx stones. In multivariate analyses, stone recurrence risk is reduced by 70% in *O. formigenes* colonized individuals[23]. Batislam *et al*[24] investigated *O. formigenes* levels for the first time in stool samples of cases with hyperoxaluria and recurrent nephrolithiasis by real-time PCR, and eventually found reduced levels of *O. formigenes* in cases with hyperoxaluria and recurrent nephrolithiasis.

An increase in the intestinal colonization of oxalate-producing bacteria decreases oxalate absorption, which in turn causes a reduction in urinary oxalate. Use of *O. formigenes* enteric capsules in primary hyperoxaluric

patients decreases urinary oxalate levels substantially, which shows that oral intake is effective on the enteric metabolism of endogenously-produced oxalate[25]. Prospective trials are required to corroborate the efficacy of probiotics on reducing urinary oxalate levels, as well as the side effects. Although current uncontrolled studies show that use of lactic acid bacteria[26] decreases urinary oxalate levels, these are not prospective double-blind placebo-controlled studies[27].

The function of oxalate-reducing bacteria, such as *O. formigenes* in CaOx stone formation, is currently under investigation. A pilot study has shown that *O. formigenes* reduces blood oxalate levels and urinary oxalate excretion in many IH-related calcium stones cases[26], yet these results could not be reproduced completely in a recent multi-centered study. Furthermore, the results acquired from expending lactic acid bacteria as a probiotic for the reduction of urinary oxalate elimination are inconsistent[28]. Treatments involving increased anion transport activity or the upregulation of intestinal luminal oxalate secretion through the use of oxalate binders are among other potential treatment approaches[29].

As calcium binds diet oxalate in the intestinal lumen, calcium supplements may decrease oxalate absorption[30]. Consumption of 2-4 g cholestyramine with every meal is much more beneficial in binding oxalate, yet brings along such inconveniences as an unpleasant taste in the mouth and vitamin K insufficiency[31]. Although the phosphate binding agent sevelamer hydrochloride is thought to decrease oxalate absorption, the conclusions are discrepant[32,33].

Hyperuricosuria

Dietetic purine limitation should be the initial medicinal approach[34], with alternative approaches required for incompatible patients and actual non-responders.

The main strategy in the treatment of uric acid cases is alkalization of the urine, which is more important than uricosuria reduction[35,36]. Typical starting doses to preserve the urine pH between 6.5-7.46 are 40-60 mEq for potassium citrate (KCit) in divided doses, or 1300 mg 2 × 1/d for sodium bicarbonate[37].

Allopurinol addition should be considered for patients with persistent acidic urine that does not alkalize easily. Hyperuricosuric CaOx nephrolithiasis is traditionally a xanthine oxidase inhibitor that is treated with allopurinol, which decreases endogenous uric acid formation and urinary uric acid excretion. The typical daily dose of allopurinol is 100-300 mg[37].

Recent interesting research on uric acid metabolism suggests that novel therapeutic methods may be developed in the future for hyperuricosuric nephrolithiasis and uric acid nephrolithiasis. More specifically, recent studies have shown that novel xanthine oxidase inhibitor (febuxostat) and the recombinant form of uricase enzyme (rasburicase) had superior serum uric acid-reducing effects compared to allopurinol, and are more successful in reducing the periodicity of gout recurrences[38,39]. These drugs should be considered for potential therapeutic agents of stone disease, although they are not yet tested.

Hypocitraturia

While both potassium citrate (KCit)[40] and potassium-magnesium citrate[19] were demonstrated to remarkably reduce hypocitraturia and recurrent urolithiasis formation in randomized stone case studies, sodium-potassium citrate did not exert any beneficial effect[20]. Although KCit is available commercially in tablet, liquid, and powder forms, investigations are ongoing in terms of developing a drug form of potassium-magnesium citrate[37].

The standard initial dose of KCit is 40-60 mEq daily, in divided doses, until the desired citraturia level is achieved[37]. These patients should be closely followed due to the potential for hyperkalemia, which is a theoretical risk due to the use of potassium-containing preparations and the increased glomerular filtration rate of the patients. In addition, some patients speak of gastrointestinal complaints while using KCit. Due to the high monetary cost and low patient compatibility of KCit therapy, its substitution with a dietary treatment was investigated. Lemon juice is naturally rich in citrate, and while it was concluded that drinking lemonade for 21 d increased urinary citrate levels in an uncontrolled metabolic study[41], 2 other recently carried out controlled-metabolic studies have raised doubts concerning the effect of lemonade in reducing recurrence.

Koff *et al*[42] conducted a randomized comparative study where they compared lemonade and KCit therapy in a group of patients with recurrent stones. While no changes were detected in basic urinary citrate or pH levels following lemonade therapy, a notable increase in urine citrate was reported in cases who received KCit. In accordance with these findings, while the use of lemonade is unsuccessful in increasing urine citrate and pH levels, it provides a prominent advantage over KCit due to the increased urine volume.

Cystine stones

Dilution and alkalization of urine, as well as thiol-binding drug and claw (chelation) combination therapy, constitutes the main guidelines of the cystine stone treatment approach. Combinatory use of these drugs may be more effective compared to individual use, due to the relatively higher pKa (8.5) of cysteine[43].

Patients should wake up at least once every night to drink water, as well as drink additional water to prevent concentration of urine at night. Patients can take 10-20 mEq 3 × 1/d KCit to increase urinary pH if it is < 7. Cystine excretion can be mildly decreased with < 100 mmol/d per sodium and 0.8 g/kg per day/protein restriction diets.

If stone recurrence occurs in spite of appropriate fluid intake and base urinary pH, cystine-linking drugs should be added to the treatment. D-penicillamine and tiopronin are the most widely-used thiol-linking

pills. D-penicillamine and tiopronin therapy has been indicated to be beneficial in the reduction of urolithiasis formation in cases where there was no benefit from hydration and alkaline urine.

The frequently-used thiol group anti-hypertensive captopril is another theoretical pharmacological agent in cystinuria treatment. Nevertheless, it is reported that it was not adequately effective in the solubility of cystine in urine, and that it also gave speculative results in a number of small scale studies regarding its ability to decrease urine cystine levels[43].

Struvite stones

Early diagnosis and eradication is essential for struvite stones, due to their fast growth potential and significant morbidity[44].

Long-term, low dose culture-specific antibiotic treatment is significant in the prevention of post-operative new stone growth and progression. Furthermore, minimizing urease concentration may even provide post-operative eradication of small fragments. Treatment with antibiotics only is not a standard approach[45].

Even in the presence of hydroxyurea, acetohydroxamic acid (AHA) is the most frequently used medical agent. In three randomized double-blind studies where AHA was used, stone growth and formation was decreased[46-48]. AHA and antibiotic suppression regimes can typically be recommended in patients that may not be surgery candidates due to serious side effect profiles, and in which potential significant side effects of AHA can be considered as acceptable risks.

MEDICAL EXPULSIVE THERAPY

Medical expulsive therapy (MET) exerts its effects *via* relaxation of the ureter and augmentation of the hydrostatic physical force proximal to the calculus[30].

In a patient that admits with lumbar pain due to ureteric calculi, the most substantial elements predicting the unpremeditated transition of the calculi are the dimension and localization of the stone. Meta-analysis has given the unpremeditated transition ratio of ureteric calculus as 68% and 47% for < 5 mm and 5-10 mm dimensions, respectively[49]. The most widely-used drugs for premedication of ureteric stones are α-1 adrenergic receptor antagonists and calcium channel blockers (CCB). α-1D receptors are the most widely-localized α-adrenergic receptors in the ureter, and are most densely localized in the distal ureter[50]. α-1 adrenergic receptor antagonists reduce the frequency and strength of the urethral contractions[51]. The CCB nifedipine was demonstrated to soften urethral smooth muscles *in vitro*, and to exert its impact mainly in the distal urethra[52].

There are 2 meta-analyses examining the effects of CCB and α-1 adrenergic receptor antagonists. Hollingsworth *et al*[31] published a meta-analysis where described cases who received α-blockers or CCBs displayed 65% higher spontaneous calculi transition, compared to the unmedicated group. Guidelines show that cases with a urethral calculus of < 10 mm and well-controlled symptoms can be followed for a while with application of MET as an initial therapy, and recommends α-1 blockers alongside the drugs recommended for MET[49].

In spite of the useful effects of α-1 blockers that have been shown in many studies, there are also studies that report negative effects. Hermanns and Pedro did not find any superiority of α-blockers over placebo in stone expulsion time[53].

Use of corticosteroids in order to decrease edema and inflammation, and thereby ease calculi transition, are under testing. Dellabella *et al*[54], in a small scale study, compared the calculi transition ratio in cases that received tamsulosin with or without the addition of deflazacort. No change was observed in the calculi transition ratio, yet the corticosteroid + tamsulosin group passed their calculus 2 d earlier on average. Larger scale future studies are needed in order for corticosteroids to gain widespread use.

NSAIDs do not provide any benefit in calculi transition time or calculi transition in renal pain[55].

The development of and increasing experience in endoscopic approaches, such as r/f URS, have led to the questioning of whether MET application to urethral stone disease patients admitted with acute renal colic is a loss of time and money. However, recent studies comparing MET and early endoscopic stone removal report less direct and indirect costs with MET, while no difference was detected in hospitalization numbers[56,57].

NUTRITION THERAPY

The etiology of urolithiasis is multifactorial and not always related to nutritional factors. However, nutrition therapy still seems to be useful, either in combination with pharmacological therapy or as a monotherapy. Nutrition therapy involves evaluation of a patient's nutritional state and intake, diagnosis of nutrition risk factors, and the organization and application of a nutrition program[58]. The main target of nutrition therapy is the reduction or prevention of calculus formation and growth *via* decreasing lithogenic risk factors and increasing lithogenic inhibitors in urine.

There are two approaches for nutrition therapy. The first is the empirical approach that is applied to all patients. This approach is a general mixture of various nutrition strategies that target multiple risk factors and that can be applied to patients with no known specific urinary risk factors. The second is the planned/specific approach, and is an alteration aiming to decrease or eliminate specific risk factors of patients. In two studies that included calcium stone patients, the empirical diet side showed a greater decrease in stone recurrence compared to general nutrition, yet these were not compared to direct planned approaches[59,60]. On the other hand, in a study where the empirical and planned nutrition therapy approaches were compared, stone

recurrence rate was reported to decrease with planned therapy[9].

Evaluation of the patient's normal diet and the supplements they use is useful in detecting the effects of an excess, lack, or imbalance of the consumed food or non-food ingredients. A targeted evaluation should be performed in order to detect suitable nutritional factors from the list of foods consumed in the last 24 h provided by the patient in one-to-one conversation or the multi-day nutrition chart kept by the patient.

Hypercalciuria

If sodium intake is identified as a nutritional risk factor, high sodium foods, along with the other foods consumed alongside them, should be examined in preparation for nutritional therapy.

A scale has been developed for predicting the renal acid load capacity (RALC) of foods[61]. This scale calculates the anion/cation ratios of foods, and is accepted as a suitable model in calculating the effects of diet on renal net acid excretion. Foods that carry an acid load proportional to the sulfur amount in their amino acid structures are all meat-based foods (red or white), cheeses (all types), eggs (mostly egg yolks), and grains.

Milk, yoghurt, and fats naturally appear in the RALC scale. Alkaline content foods (those with negative numbers in the RALC scale) are almost all of the fruits and vegetables. A few fruits and vegetables, namely Cornelian cherries (*Cornus mas*) and lentils (*Lens culinaris*), have low acid loads. However, their restriction is not necessary, as their acid loads are far lower than other foods known to have high acid contents. Furthermore, increased fruit and vegetable consumption is usually recommended.

Fiber may reduce gastrointestinal absorption of calcium[62]. If high fiber food consumption is not at the desired levels (25-30 g/d for adult individuals), and calcium and bone statuses look normal, it may be appropriate to recommend higher dietary fiber intake or combination with fiber-reinforced supplements. Caffeine and alcohol may contribute to urinary calcium excretion and thus restriction of these may be useful[63,64].

Some reports show the efficiency of omega-3 fatty acids in reducing urinary calcium excretion[65-67], and supplementation is available *via* current commercial formulations in certain amounts.

Hyperoxaluria

Restriction of food-based oxalate is controversial. The majority of oxalate-containing foods are healthy, and, furthermore, contain special nutrients that frequently have general health benefits and contain fiber, potassium, magnesium, and antioxidants. Restriction or elimination of such foods from the diet will thus do greater harm than good. Reduction of dietary oxalate intake also requires a simultaneous reduction in dietary calcium, as it is essential to maintain the appropriate low calcium/oxalate ratio in the urine, and thus some authors question the low oxalate strategy for this reason.

Specific gastrointestinal microbiota profiles containing separate combinations of bacteria species have been recently identified, and these were observed to be regulated with diet habits[68]. For instance, individuals who consume diets with high fiber content have a different microbiota profile than those that do not[69]. In another study, individuals consuming diets with high meat content were shown to have different bacterial enterotypes than those that consume diets rich in carbohydrates[70]. As related research proceeds, it is possible that some diet patterns (such as oxalate-decreasing bacteria adjusting to suitable concentrations) will be shown to provide anti-lithogenic effects by leading to alterations in enteral microbes.

Hyperuricosuria

If a nutrition evaluation reveals a high content of purine-rich foods, a lack of foods with high purine concentration, and a reduction in the consumption foods with low purine, concentration should be recommended.

Another potential concern is blaming red meat as the only main culprit in uric acid synthesis. Recently, consumption of fish and chicken has also been shown to increase the concentration of serum and urine uric acid to at least the same extent as red meat[71]. As recommending that the patient decrease their red meat consumption will result in a higher consumption of chicken and fish instead, reducing the intake of all these foods is necessary in order to obtain suitable results. Reduction can be organized by decreasing portion sizes and the frequency of consumption during the week.

The quantity of alcohol and fructose consumptions should be evaluated in hyperuricosuria patients, and ways to reduce their intake should be discussed if they are believed to increase stone formation.

Hypocitraturia

When a diet with a high acid load that shows a hypocitraturic effect with its renal citrate reabsorption-improving effect is detected, small amounts of cheese, meat, and other meat products should be recommended in order to lower the acid load[61,72]. For instance, patients usually don't want to eliminate meat and other meat products from their diet, or are unable to apply such a change. Instead, special recommendations to restrict such foods to only small portions in one meal per day will have the same effect. If calorie load is not an issue for the patient, simply balancing the current high acid foods with low acid or alkaline foods (more fruits and vegetables) may be recommended.

Increased dietary intake of citric acid is useful and can increase urinary citrate excretion[40,73-75]. This can be partially achieved *via* the consumption of lemons (which contain concentrated citric acid) and lemonade. Recommendations on increasing consumption of citrus fruits will also provide benefit in terms of increased fiber, potassium, antioxidants, and prebiotics.

Recently, consumption of low sugar and calorie drinks sweetened with citrate and other organic acids has been recommended, as they have the capacity to increase urinary citrate[76]. On the grounds of presenting these drinks as therapeutics targeting the urinary citrate levels in a certain group of patients, liquid volumes provided by these drinks will also contribute to augmentation of overall liquid consumption.

If citrated fruit juices contain mainly citric acid, any bicarbonate obtained is neutralized by hydrogen ions. In that event, the net alkaline response will not take place and the eventual citraturic response will be at a minimum level. In contrast, if potassium accompanies citrate, the net alkaline response will take place, and urinary pH and citrate will rise. Ideal replacement therapy should be low in calories and oxalate, and rich in KCit. Yilmaz *et al*[77] have evaluated tomato, orange, lemon, and mandarin juices in terms of nutritional content. Interestingly, fresh tomato juice contains two times the amount of citrate compared to lemon juice or orange juice; however, the potassium concentration in fresh tomato juice is equal to orange juice and its oxalate content is 40% lower. In the light of these data, although fresh tomato juice seems to be suitable for preventing stone formation, its application is more difficult compared to lemon juice and orange juice. Ripe tomato juice, on the other hand, is rich in sodium.

Haleblian *et al*[78] evaluated 12 different commercial drinks that contained citrate, in an attempt to find natural treatment modalities that are more effective in preventing stone formation. Grapefruit juice was reported to have the highest citrate content, followed by lemon juice, orange juice, lemonade, and Cornelian cherry (*Cornus mas*) juice, respectively.

If frequent diarrhea is thought to contribute to hypocitraturia *via* increased renal citrate reabsorption as a result of excessive bicarbonate loss in the stool, nutrition strategies can be applied that target diarrhea treatment[79]. Probiotic supplements are recommended in the current literature for correction of diarrhea, and many probiotic formulations are commercially available for such use[80,81].

Low liquid consumption

All liquid types induce urinary output, and this is probably the most useful method that can spontaneously reduce the risk of stone formation on its own[8]. Low sugar- and low-calorie drinks are preferred.

Some patients may benefit more from a simple increase in liquid intake than far more specific recommendations. The liquid intake schedule is designed for these situations. The day may be separated into 3 equal parts (of 5 h blocks, for instance, depending on the lifestyle of the patient) and the individual may consume approximately 4 L of (120 oz) liquid by drinking 1200 mL in each part.

Hyperphosphaturia

Phosphate is widely present in all plant and animal-based foods, and so a reduction of dietary phosphate is not practically possible in calcium phosphate stone patients. Control of urinary citrate, calcium, pH, and volume is instead far more important in these patients.

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