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Effectiveness of Treatment Modalities on Kidney Stone Recurrence

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Abstract

Nephrolithiasis is highly prevalent across all demographic groups in the Western world and beyond, and its incidence rates are rising. In addition to the morbidity of the acute event, stone disease often becomes a lifelong problem that requires preventative therapy to diminish ongoing morbidity. Across the majority of stone types, increased fluid intake and targeted dietary modifications are mainstays of therapy. Specific dietary interventions associated with reduced calcium stone risk include adequate dietary calcium intake and restriction of sodium, protein, and oxalate intake, among others. Pharmaceutical therapy may be required if lifestyle changes are insufficient to minimize risk of stone recurrence, and must be targeted to the specific metabolic abnormalities portending risk for a given patient. Therapeutic options for idiopathic calcium stone disease include thiazides, citrate salts, and uric acid–lowering agents. Alkali salts are also the treatment of choice for uric acid stone disease. Management of struvite stone disease is largely surgical, but acetohydroxamic acid is a proven second line therapy. Cystinuria requires lifestyle modifications and may call for thiol-binding agents. Significant heterogeneity of the clinical population with stone disease has previously limited opportunities for large randomized controlled trials. However, as clinical phenotypes and genotypes are increasingly clarified, there are mounting opportunities for targeted randomized controlled trials in stone prevention. In the meantime, the currently available evidence for both lifestyle and pharmacologic interventions is reviewed herein.

Keywords: nephrolithiasis, thiazide, citrate, Cystinuria, Uric Acid, acetohydroxamic acid, Sodium, Salts, Calcium, Dietary, Struvite, Thiazides, Incidence, Kidney Calculi, Hydroxamic Acids, Sodium, Dietary, Life Style, Oxalates, Western World, Genotype, Phenotype, Sulfhydryl Compounds, Disease Management, Citrates, Alkalis

Introduction

Kidney stone disease is highly prevalent in the United States, affecting one in 11 individuals during their lifetime (1). Rates of nephrolithiasis in the United States population are increasing in adults and children, as well as across demographic groups, with National Health and Nutrition Examination Survey (NHANES) data reflecting a 70% increase in disease prevalence in the general population (from 5.2% in the 1988–1994 dataset to 8.4% in the NHANES 2007–2010 dataset) over the last 15 years (1). Nephrolithiasis is currently the most expensive urological condition, estimated to cost the health care system more than $10 billion per year (2), not accounting for time lost from work. Because of the concurrent epidemics of obesity, metabolic syndrome, and diabetes (all independently associated with increased risks of stone formation [3–5]) as well as anticipated population growth, current projections estimate costs due to stone disease to rise by $1.24 billion per year by 2030 (6). Emergency department (ED) visits for stones have increased by 91% between 1992 and 2009 (7). More than 10% of patients initially evaluated in the ED require a return visit in <30 days, further exacerbating costs and reflecting high patient morbidity (8). Quality of life measures are significantly lower in individuals suffering from nephrolithiasis than in the general population (9).

Nephrolithiasis is often a recurrent and lifelong disease, with recurrent stone episodes predicting even higher future recurrence rates and worse clinical outcomes (10). Precise estimates of recurrence rates are difficult to ascertain given clinical heterogeneity, but a recent retrospective cohort of more than 2200 first-time stone formers in Olmstead County noted that stone recurrence rates at 2, 5, 10, and 15 years were 11%, 20%, 31%, and 39%, respectively (11). Data from clinical trials of stone therapies that included recurrent stone formers suggest recurrence rates between 40% and 45% in untreated recurrent stone formers in the control groups in the thiazide trials (12–15), and up to 80% in the citrate trials at 3 years (16–18). Given the very high recurrence rates, treatment aimed at prevention of stone formation is critical to diminishing the morbidity and costs associated with the disease.

Treatment Options in Kidney Stone Prevention

The available treatment options for prevention of stone recurrence can be divided into lifestyle interventions and pharmaceutical therapies. In practice, a combination of therapies is most effective, but for the purposes of this discussion we will evaluate each independently. In this review we will also limit our focus to idiopathic stone disease, whether calcium or uric acid except as noted, and will not include commentary on secondary causes of stone disease such as primary hyperparathyroidism or bowel disease.

Lifestyle Interventions

Effect of Fluid Intake on Urinary Stone Recurrence

Regardless of the specific stone type, stone formation requires urine supersaturation (SS) with respect to stone-forming salts such as calcium oxalate or calcium phosphate (CaP), to allow crystal formation and stone growth. The most significant determinant of SS is urine volume, as concentrations of stone-forming salts vary with volume (19,20). Although multiple observational studies, including national cohorts (21–24) and individual kidney stone center experiences (25–27), have demonstrated the critical importance of increased urine volume in prevention of stone recurrence, there has been only one randomized controlled trial evaluating the role of increased fluid intake on prevention of recurrent

stones. Borghi *et al.* ([19](#)) randomized 199 Italian participants after their first idiopathic calcium stone episode to either increased water intake with a goal of 2.0 L of urine volume daily, which the patients were instructed to measure at home every 2–3 months, or to no therapy. After 5 years of follow-up, the group randomized to increased fluid intake had a significantly lower stone recurrence rate of 12%, compared with 27% in the control group. Notably, the mean attained urine volume in the group without a recurrence was 2.6 L, compared with 1 L in controls. On the basis of this limited literature, national guidelines ([20,28](#)) have adopted recommendations for encouraging increased fluid intake to facilitate at least 2.5 L of urine volume to prevent recurrence of stone disease. More recently, a large meta-analysis has confirmed a dose-dependent response to increased water intake, with every 500 ml of increased intake associated with a significant decrease in stone formation ([29](#)). It is important to note a key limitation of the literature, however, as Borghi *et al.* studied first-time stone formers with no residual disease burden on imaging obtained after the acute event. This is not representative of the stone-forming population in general, as recurrence is common, and residual stone burden after stone passage or postprocedure is known to predict a significantly higher rate of recurrence ([11,30,31](#)). There are thus no randomized controlled trial data in the population at highest risk of recurrence and in those with highest morbidity from the disease.

A few general points warrant attention, as patients are often counseled broadly to increase their fluid intake without regard for potential pitfalls. First, although it is clear that higher fluid intake increases urine volume and thereby decreases urine SS, generalized fluid intake targets do not account for the interindividual variability in the urinary excretion of other contributors to stone risk such as calcium, oxalate, and uric acid, or the presence of adequate quantities of crystallization inhibitors such as citrate. A more personalized approach using urine SS targets for a given stone type has never been prospectively tested, but this has been the approach in clinical practice at our institution for more than 40 years and has demonstrated durable prevention of stone recurrence ([26](#)). Second, a critical point that has never been studied in large trials is that for the majority of individuals, fluid intake is not evenly spaced throughout the course of the day because of work or school commitments, periods of exercise or sleep, and timing of meals. Data from studies of stone formers demonstrate that SS varies throughout the day and is highest overnight ([32](#)). Furthermore, 24-hour urine measurements are able to demonstrate overall 24-hour urine volume, but do not provide sufficient granularity to ascertain whether periods of low urine volume, and therefore high urinary SS, exist and correlate to risk of stone recurrence. It is our practice to highlight the importance of spaced fluid intake throughout the course of the day to our patients, which has met with clinical success ([26](#)), but this approach has not been prospectively studied nor directly compared with a generalized fluid target.

Recent data suggest the importance of not only absolute fluid intake, but also potentially the type of fluids consumed. Using data from three large prospective cohorts with nearly 200,000 participants, Ferraro *et al.* ([33](#)) demonstrated the heightened incidence of stone disease with increasing sugar-sweetened cola consumption, potentially because of the higher fructose content. Artificially sweetened beverages did not portend higher stone risk, whereas increasing quantities of punch consumption were also linked to higher incidence of nephrolithiasis. The authors also noted a protective effect with higher consumption of coffee (caffeinated and decaffeinated), tea, red and white wine, beer, and orange juice ([33](#)), confirming their previous reports ([34,35](#)). Although lemon juice and lemonade are commonly recommended in popular culture for stone prevention because of their potential to increase urinary

citrate, an inhibitor of calcium crystallization, prospective outcomes data for their use in stone prevention are lacking. Further, several studies ([36](#)–[38](#)) have noted increased urinary citrate when participants ingested 120 ml of lemon juice diluted in 2 L of water over the course of the day, the responses were either not durable or not associated with improvements in pH or urine SS. At this time, no data are available on stone event rates with this therapy.

Lastly, despite the published recommendations and evidence supporting its utility as an effective prevention mechanism for stone formers, achieving significant increases in hydration, and subsequently, urinary volumes remains a considerable clinical challenge ([39](#)). To date, adherence to increased fluid recommendations has generally been understudied, with little data assessing patient compliance specifically for fluid intake. However, noncompliance with metabolic treatment of nephrolithiasis is known to be as high as 30% ([40](#),[41](#)). Parks *et al.* ([42](#)) evaluated the increases in 24-hour urine volumes on follow-up urine collections in clinical practice from 14 clinical sites that included both private and academic institutions. Physicians at all sites were recommended to counsel their patients to increase their fluid intake to facilitate at least 2 L of urine volume, although whether this occurred could not be verified. In more than 2800 patients across the sites, the mean increase in urine volume was only 0.31 L every 24 hours. For the clinician, targeting behavioral strategies to maintain consistent fluid intake is critical for the durable prevention of stone recurrence.

Effect of Diet on Urinary Stone Events

Dietary risk factors are of critical importance in reducing the risk of stone formation. In the available studies, individual variables are often isolated to study risk and several will be reviewed independently below. However, it is important to remember that humans consume food, not individual nutrients, and their interplay is likely to be important as well. For example, Taylor *et al.* ([43](#)) studied the effect of the Dietary Approaches to Stop Hypertension (DASH)-style diet (high in fruits, vegetables, low fat dairy, and nuts/low in sodium and processed meats) in a prospective manner among more than 240,000 patients in three large cohorts. Over a combined 50 years of follow-up across the three cohorts and more than 5600 incident stone events, the highest DASH scores were associated with a 40%–45% decreased risk of stone events.

In the pivotal randomized controlled trial in the literature evaluating the effect of a diet on stone recurrence, Borghi *et al.* ([44](#)) randomized 120 men with recurrent calcium oxalate stones and hypercalciuria to either a normal calcium (30 mmol/d), low animal protein (52 g/d), and low salt diet (50 mmol sodium chloride) or to a low calcium diet (10 mmol/d) and prospectively followed the participants for stone recurrence events over the course of 5 years. Both groups were advised on adherence to a low oxalate diet. The relative risk of recurrence of stone disease was 0.49 (95% confidence interval 0.24 to 0.98; P=0.04) in the normal calcium, low animal protein, and low salt diet group. Importantly, although there is certainly a likely role of other nutrients in decreasing the risk of stone recurrence, the low sodium group had a significant decline in urinary calcium levels (while ingesting a higher calcium diet than the low calcium diet group), which was also reflected in the SS values for calcium oxalate. The ultimate dietary sodium intake achieved in the low sodium group (on the basis of 24-hour urine sodium measurements) was more than double the initial target of 50 mmol/d at 110–130 mmol/d, but significantly lower than the 200 mmol/d in the low calcium group. Although

the urine volumes were similar in the two groups, urinary oxalate excretion was significantly higher over the course of the 5 years in the low calcium diet group, significantly contributing to the noted higher SS. This is not unexpected, as the higher dietary calcium intake facilitates gut oxalate binding, with less oxalate available for distal absorption and, ultimately, urinary excretion ([45](#)).

Sodium. The positive relationship between dietary sodium intake and urinary calcium excretion was first recognized by Kleeman *et al.* ([46](#)). In a study with healthy volunteers, an 82% increase in urinary calcium excretion was noted when dietary sodium intake was increased from 19 to 419 mEq/d. Subsequent sodium chloride–loading studies in healthy volunteers demonstrated a ratio of approximately 0.8 mmol calcium per additional 100 mmol of sodium ingested per day (40 mg of calcium per 6 g of salt intake) ([47](#)). Epidemiologic data have corroborated the documented physiologic relationship. In a large prospective study involving more than 90,000 healthy women, a significant trend in relative risk of stone disease along increasing quintiles of self-reported dietary sodium intake was noted ([22](#)), although others have not shown the same correlation ([23](#),[24](#)).

Interestingly, experimental data suggest that idiopathic calcium stone formers are more sensitive to the effects of sodium intake on urinary calcium levels, suggesting that the effect of a decrement in dietary sodium would be more prominent in this group. For example, in a study of 14 hypercalciuric stone formers, increasing sodium intake from 213 to 276 mmol/d led to an increase of 11.1–13.3 mmol/d of calcium excretion (ratio of 3.5 mmol calcium per additional 100 mmol sodium ingested per day) ([48](#)). Two other studies also found increased calcium/sodium ratios in hypercalciuric stone formers of 1.9 ([49](#)) and 2.1 ([50](#)). In addition to the negative effect on calcium excretion, Sakhaee *et al.* ([51](#)) demonstrated a 20% decrement in urinary citrate, a crystallization inhibitor known to protect against stone disease, when dietary sodium was increased from 50 to 300 mmol/d (along with a 44% increase in urinary calcium). Lastly, in a study of 210 hypercalciuric calcium stone formers randomized to either a low sodium or an *ad libitum* diet (with a background of 2–3 L of fluid intake and an 800–1000 mg calcium intake in both groups), Nouvenne *et al.* ([52](#)) demonstrated a significant decrease of urine calcium (432±96–271±86 mg/d) in the low sodium diet group, where urinary sodium decreased from 228±57 to 68±43 mmol/d at 3 months.

The physiologic studies, epidemiologic data, and the single randomized controlled study reviewed above underscore the role of excessive dietary sodium intake in lithogenesis. It should be briefly noted that all observational data are limited by potential confounders such as age, sex, ethnicity, and weight (typically adjusted for in multivariate analysis), as well as other variables that may not be accounted for, including total caloric intake, dietary sodium intake as a marker for an overall poor diet (with regard to fruits or vegetable intake or processed food), or health habits such as lack of exercise, for example. However, given the lack of harm of a moderate sodium diet, along with potential cardiovascular benefits, moderation of dietary sodium intake should be recommended to all stone formers. Targeting a dietary sodium intake <100 mmol/d is a reasonable goal, on the basis of the data herein, and is supported by national guidelines ([20](#)).

Calcium. Historically, patients with calcium stone disease were advised to limit dietary calcium because it was thought to promote stone formation. The Borghi *et al.* ([44](#)) trial reviewed above convincingly demonstrated the increased risk of a low calcium diet, with the mechanism likely to be higher urinary oxalate when less dietary calcium is consumed. Additional support for the importance of dietary

calcium comes from prospective observational cohorts ([21]–[23]), where those in the highest quintile of calcium intake, compared with the lowest, were more than 30% less likely to develop a stone. Slightly variable across the cohorts, the highest quintiles were generally >1000 mg of daily calcium intake. Accordingly, guidelines recommend 1000–1200 mg of dietary calcium for calcium stone formers ([20]). Importantly, calcium supplements may not have the same benefits, as in one of the cohort studies, women taking supplements were 20% more likely to have a stone, although it is unclear whether supplement type (calcium carbonate versus calcium citrate) affects risk ([22]). The divergent effects may also be due to the timing of supplement ingestion, as when taken away from meal times the gut oxalate-binding effect may be negated.

Oxalate. The relative contribution of dietary oxalate to risk of stone formation remains controversial despite decades of study, due to multiple challenges such as difficulty in determining the precise content of oxalate in foods, the heterogeneity of patient populations studied, and the variability in gut oxalate absorption across populations and levels of dietary intake. High levels of urine oxalate have also been linked to increased risk of stone formation ([53],[54]), and in the general population of idiopathic calcium stone formers, up to 50% of patients have at least mild hyperoxaluria ([55]), defined as 24-hour urinary oxalate excretion >45 mg. In extreme form, patients with primary hyperoxalurias, the inborn errors of glyoxylate metabolism resulting in the overproduction of oxalate by the liver and profound hyperoxaluria, are well known to develop severe nephrolithiasis, nephrocalcinosis, and renal failure ([56]). Despite the frequency of hyperoxaluria in the stone-forming population, a large population-wide study has not documented a difference in intake of dietary oxalate between idiopathic calcium stone formers and the general population ([57]). Furthermore, in other large cohorts, dietary oxalate did not have a clinically significant effect on urinary oxalate excretion ([58]). In addition, multiple trials have failed to document a decrement in urinary oxalate excretion in response to a low dietary oxalate intake in stone formers ([59]–[61]), but others have suggested benefit ([62]–[65]). Although patients with calcium oxalate stone disease are often counseled to limit dietary oxalate intake, in the absence of hyperoxaluria, there is no evidence that this is helpful to prevent stone recurrence. In the presence of hyperoxaluria, it may be prudent to limit the intake of individual foods very high in oxalate, particularly in light of evidence that stone formers have a higher gut oxalate absorption ([59]). Notably, an adequate calcium intake of >1000 mg daily may mitigate the effect of dietary oxalate.

Animal Protein. In addition to the data from the Borghi et al. ([44]) trial indicating the benefit of a moderate protein diet for stone reduction, there are suggestions from prospective observational cohorts that, at least in men, there is a positive association between consumption of animal protein and new stone formation ([21]–[23]). Recent data have also linked the relative ratio of potassium intake to animal protein intake to lithogenic risk ([66]), presumably because potassium intake is associated with alkali loads. Protein intake is equivalent to an acid load, which lowers urine citrate excretion and increases urinary net acid excretion ([67]). As urinary net acid excretion is directly associated with urinary calcium excretion ([67]), it is not surprising that increasing dietary protein intake is associated with risk. However, in at least two randomized controlled trials comparing stone recurrence rates in participants advised on adherence a low animal protein diet, a high fiber diet, or a standard diet, the authors were unable to demonstrate a difference in stone recurrence rates at 3.4–4 years of follow-up ([68],[69]), although concerns have been raised that the control groups had a significantly higher fluid intake, which may explain the lack of effect.

Pharmacologic Therapy

Knowledge of the specific stone type and the metabolic risk factors in a given patient allows for a targeted treatment strategy aimed at those abnormalities.

Patients with Calcium Stones

Common abnormalities noted in calcium stone formers are hypercalciuria, hypocitraturia, and hyperuricosuria. Medical therapies aimed at each of these abnormalities are available. The randomized controlled trials are summarized in Table 1.

Table 1.

Major clinical trials in pharmacotherapy of calcium nephrolithiasis

Author	Study Design	Enrollment Criteria (n)	Treatment	Duration, yr	Treatment/Placebo, n	Recurrence Rate, %, Treated/Place
Thiazide						
Borghi et al. (12)	RCT, DB	CaOx SF (75)	Indapamide 2.5 mg daily	3	43/14	15/43
Brocks et al. (78)	RCT, DB	CaSF (62)	Bendroflumethiazide 2.5 mg three times a day	1.6	33/29	24/16
Ettinger et al. (13)	RCT, DB	CaOx (73)	Chlorthalidone 25 or 50 mg daily	3	19/23/31	14/46
Fernández-Rodríguez et al. (77)	RCT	CaSF (100)	Hydrochlorothiazide 50 mg daily	3	50/50	NR
Laerum (14)	RCT, DB	CaSF (50)	Hydrochlorothiazide 25 mg twice a day	3	25/25	20/48
Mortensen et al. (80)	RCT, DB	CaSF (22)	Bendroflumethiazide 2.5 mg three times a day	2	12/10	40/40
Ohkawa et al. (15)	RCT	CaSF (175)	Triclormethiazide 4 mg daily	2.1–2.2	82/93	NR

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95% CI, 95% confidence interval; RCT, randomized controlled trial; DB, double blind; CaOx, calcium oxalate; SF, stone former; CaSF, calcium stone former; HypoCit, hypocitraturic; NR, not reported.

Hypercalciuria/Thiazides

Thiazide diuretics are the mainstay of therapy for patients who require lowering of urine calcium levels. The mechanism of calcium lowering in the urine appears to be increased proximal tubule calcium reabsorption (70,71), with resultant increase in serum calcium and likely increased flux of

calcium into bone (72,73). There are at least ten randomized controlled trials in the literature assessing the efficacy of various thiazides on decreasing the rates of calcium stone recurrence in heterogeneous populations. Seven trials (12,13,15,74–77) have demonstrated a significant decrease in stone recurrence with thiazides over timeframes ranging from 2.1 to 5 years of use. Various agents were used including chlorthalidone (25–50 mg daily), bendroflumethiazide (2.5 mg three times a day), trichlormethiazide (4 mg daily), hydrochlorothiazide (25 mg twice a day, 50 mg daily, and 100 mg daily), and indapamide (2.5 mg daily), with the studies ranging in size from 22 to 175 participants. In all cases the participants were calcium stone formers, but only two of the studies focused specifically on calcium oxalate stone formers, whereas others allowed all calcium stone disease. The remaining three trials (78–80) that enrolled all calcium stone formers did not show evidence for decreased stone recurrence, but these studies were of significantly shorter duration (1–2 years). The proportion of patients with documented hypercalciuria in the ten studies ranged from 20% to 100%, somewhat complicating the interpretation of the results in the negative trials. Although no studies have specifically addressed the role of thiazides in patients with calcium stones without predefined hypercalciuria, given the continuous nature of risk with rising calcium excretion (53), one might predict that a risk-lowering benefit may manifest even in those without overt hypercalciuria as strictly defined.

If the clinician elects to use thiazides for their calcium-lowering effect, it is critical that they be dosed in a manner consistent with that used in the trial literature. According to at least one study, this is often not the case. Reviewing the use of thiazides for stone prevention at their institution, Vigen *et al.* (81) noted that of 107 patients in their cohort, 102 were treated with hydrochlorothiazide. However, only 35% were receiving dosages shown in the literature to be effective for stone prevention (at least 50 mg/d), with 52% receiving 25 mg daily and 13% receiving 12.5 mg daily. Four patients received indapamide and one received chlorthalidone at appropriate evidence-based dosing.

Hypocitraturia and Calcium Oxalate Stone Formers/Citrate and Alkali Therapy

Patients with low urine citrate are at an increased risk for stone formation because citrate acts as an inhibitor of crystal formation, growth, and aggregation. Therapeutic options to treat hypocitraturia (outside of correcting underlying issues such as hypokalemia or systemic acidosis) are limited to alkali supplementation. Furthermore, citrate supplementation has also been shown to be effective in stone prevention for calcium oxalate stone formers without hypocitraturia. To date, there are five studies in the literature focusing on supplementation with citrate salts, four of which showed a significant improvement in stone recurrence rates. In a double-blind placebo-controlled trial, Barcelo *et al.* (16) randomized 57 calcium stone formers with hypocitraturia (<643 mg/d) to either potassium citrate 30–60 mEq/d or placebo. At 3 years, stone growth or formation was documented in 14 out of 20 patients receiving the placebo and five out of 18 patients receiving citrate (*P*<0.001). Ettinger *et al.* (17) randomized 64 calcium oxalate stone formers with active stone disease to either placebo or potassium magnesium citrate (42 mEq citrate, three times a day). At 3 years, new stone formation or growth of old stones was noted in 64% of the placebo patients and 13% of the treated patients. Soygür *et al.* (82) studied the efficacy of potassium citrate (50 mEq/d) versus placebo in prevention of post-extracorporeal shock wave lithotripsy residual fragment growth or new stone formation in 90 patients with calcium oxalate stone disease. At 1 year, no patients receiving citrate supplementation formed

new stones or demonstrated evidence of residual fragment growth, whereas 14 out of 44 patients demonstrated new growth in the placebo group (P<0.05). In a more recent study evaluating new stone or residual fragment growth after urologic intervention, Lojanapiwat *et al.* ([83](#)) randomized 76 calcium stone formers 8 weeks postprocedure to potassium citrate 81 mEq daily versus placebo. Approximately 40% of the patients in both groups were hypocitraturic (24-hour urine citrate <325 mg daily). At 1 year, in the group that was initially stone free, 92% of the citrate group versus 58% of the placebo group remained stone free. Of the group with residual fragments, 31% of the treatment group and 9% of the placebo group were stone free at 1 year. In the only negative citrate trial, Hofbauer *et al.* ([18](#)) randomized 50 calcium oxalate stone formers to either placebo or potassium sodium citrate dosing sufficient to maintain a urinary pH of 7–7.2. Given the pH targeting requirement, the study could not be double blinded. At 3 years, 16 out of 22 patients in the placebo group and ten out of 16 patients in the citrate group developed new stone formation (P=0.65).

Classically, sodium salts are avoided in the treatment of stone disease because of concerns regarding increasing calcium excretion, as denoted previously, and there are no long-term prospective trials addressing long-term outcomes for stone recurrence. However, Pinheiro *et al.* ([84](#)) enrolled 16 adult hypocitraturic calcium stone formers in a randomized double-blind crossover trial comparing potassium citrate (60 mEq/d) and sodium bicarbonate (60 mEq/d) on a controlled diet, and evaluated 24-hour urinary parameters after 3 days on each drug. There were equivalent increases in urine citrate and pH with both agents, and despite an increase in urinary sodium with sodium bicarbonate, no increase in urinary calcium excretion was seen. However, therapy with potassium citrate resulted in a marked decrease in urinary calcium, as well as a more pronounced decrement in SS for calcium oxalate (CaOx). Although the efficacy data for alkali supplementation are highly encouraging, clinicians must assure regular monitoring of urine pH and SS for both CaOx and CaP in patients treated with alkalis, as the desired outcome of higher urine pH may lead to undesired increases in CaP (brushite) SS ([84](#),[85](#)), which may lead to CaP stone formation.

Hypocitraturia and CaP Stone Formers/Citrate and Alkali Therapy

In general, CaP stone formers are largely treated similarly to CaOx stone formers, with recommendations for increased fluid intake, dietary interventions as discussed above, and thiazides as necessary to modulate urinary calcium levels ([20](#)). As many of CaP stone formers have hypocitraturia and a higher urine pH at baseline, the role of alkali therapy is controversial and no prospective randomized controlled studies have specifically addressed the use of supplemental alkali therapy in this population. However, in at least two of the citrate trials ([Table 1](#)) the enrollment criteria did not specify the type of calcium stone and likely included participants with CaP nephrolithiasis ([16](#),[83](#)). A small observational trial in nine participants with renal tubular acidosis, who typically form CaP stones, noted decreased risk of CaP stone formation with potassium citrate therapy ([86](#)). Increasing urinary citrate should decrease both brushite and hydroxyapatite crystallization, urine calcium, and overall SS for CaP, the benefits of which may be offset by a higher urine pH and increases in CaP SS ([87](#)). As noted for the CaOx stone formers, clinicians must maintain vigilance to assure appropriate risk parameters are maintained with therapy.

Hyperuricosuria

Hyperuricosuria decreases the solubility of calcium oxalate *in vitro* and is felt to contribute to recurrence risk in calcium stone formers ([88](#)). However, recent epidemiologic data has questioned these assumptions, as a cross-sectional study of more than 3300 men and women across three large cohorts showed an inverse association between urine uric acid excretion and stone formation in men and younger women, but not in older women ([89](#)). Typically, dietary purine restriction is the initial therapeutic intervention in patients with hyperuricosuric calcium stone disease, as moderate protein restriction is warranted to decrease urinary calcium, but additional therapy may be required. In a randomized controlled trial of 60 hyperuricosuric calcium oxalate stone formers with normocalciuria, therapy with allopurinol demonstrated decreased risk for calcium stone recurrence and longer time to recurrence ($P<0.02$) ([90](#)). The authors of the aforementioned large epidemiologic study have suggested the possibility that the benefit of allopurinol is *via* an antioxidant effect, and not necessarily *via* lowering of uric acid excretion. More recently, Goldfarb *et al.* ([91](#)) demonstrated that at 6 months, febuxostat lowers urine uric acid levels more than allopurinol, but it should be noted that the comparison was between high-dose febuxostat and standard allopurinol dosing. Regardless, in this short timeframe, no difference was seen in stone growth rates and the overall contribution of hyperuricosuria to calcium stone formation remains nebulous.

Uric Acid Stone Disease

The three major risk factors for uric acid stone formation are low urine pH, low urine volume, and to a lesser degree, hyperuricosuria. Most often, it is the urine pH that is the key risk factor, as the urinary uric acid levels tend to be the same between normal patients and uric acid stone formers ([92](#)). The mainstay of therapy is increased fluid intake with urinary alkalinization with alkali salts to a target pH of 6.5–7. Notably, there are no randomized controlled trials addressing the efficacy of these maneuvers, but observational studies are highly convincing. Pak *et al.* ([93](#)) followed 18 patients with uric acid stones (six pure uric acid stones and 12 with mixed calcium and uric acid stones) for an average of 2.78 years receiving treatment with potassium citrate in dosages of 30–80 mEq/d. New stone formation decreased from 1.20±1.68 stones per year to 0.01±0.04 stones per year ($P<0.001$). A small study with eight participants suggested that complete uric acid stone dissolution with potassium alkali may also be possible ([94](#)), echoing older case series ([95](#),[96](#)), but larger trials are needed.

Struvite Stones

Struvite stones, also known as triple phosphate or calcium magnesium ammonium phosphate, require the presence of urea-splitting bacteria for stone formation, as an exceedingly high pH is a prerequisite. These stones are notoriously difficult to treat and generally require expert urological intervention, given their potential for rapid growth and staghorn formation. If complicating circumstances dictate that complete stone removal is not feasible, urease inhibitor therapy can be used to decrease rates of stone growth. Acetohydroxamic acid is the therapy of choice in this scenario, on the basis of three randomized controlled trials demonstrating decreases in stone growth ([97](#)–[99](#)). However, its clinical use is limited because of significant side effects including gastrointestinal upset, headaches, thrombophlebitis, and rash.

Cystine Stones

Cystinuria is a rare inherited disorder affecting renal tubular transport of cystine and dibasic amino acids, such as lysine, arginine, and ornithine. The cornerstone of therapy is adequate urine volume coupled with urinary alkalinization for a pH target >7, as this increases cystine solubility. If these maneuvers are insufficient to decrease risk of recurrent stone disease, treatment with a cysteine-binding drug may be necessary. Therapeutic options include D-penicillamine and tiopronin, although clinical effectiveness data are limited. The majority of the data comes from uncontrolled or observational trials with documented reductions in stone events of up to 75% (100). In one study (100), for example, 16 patients with cystinuria who failed treatment with fluids and alkalinization alone were started on either penicillamine (1–2 g/d) or tiopronin (800–1200 mg) in divided doses. Over an average of 78 months of follow-up, stone event rates were halved from 1.6 to 0.84 events per year. Generally D-penicillamine and tiopronin have similar efficacy (102–104), and both may be associated with significant side effects, including fever, rash, leukopenia, aplastic anemia, proteinuria, and hepatotoxicity. However, tiopronin appears to be better tolerated. If treatment with one of these agents is undertaken, it should always be in conjunction with hydration and urinary alkalinization, as the latter may also increase therapeutic effectiveness (105).

Summary and Conclusion

Prevention of recurrent stone disease requires a multifaceted approach involving both lifestyle and pharmacologic intervention. Decisions regarding therapy are made on the basis of specific metabolic abnormalities identified by stone type and metabolic evaluation, as well as potential comorbidities. Patients with calcium stone disease associated with hypertension and/or osteoporosis, for example, would have multiple potential benefits from either a low sodium diet or thiazide therapy. Although there is only one randomized controlled trial documenting the benefit of increased fluid intake, the necessity of SS for stone formation dictates that modulation of urine volumes will affect risk. Similarly, although there is also only one high-quality randomized controlled trial of a dietary intervention with a low sodium, low animal protein, and moderate calcium diet for diminishing stone recurrence, the physiologic data strongly supports the critical importance of these parameters to minimize calciuria and stone formation. The data for oxalate restriction is more nuanced, but in the setting of significant hyperoxaluria dietary restriction, is likely warranted as long as it does not come at the expense of overall fruit and vegetable intake, which would carry its own health risks. On the pharmaceutical front, there is strong evidence of the success of both thiazides and alkali salts for reduction of stone recurrence in idiopathic calcium stone disease. Patients with uric acid stone disease reap perhaps the most benefit from urinary alkalinization, but is must be noted that our literature is limited to observational data. Data are even more limited for therapy of cystine stone disease. Given the growing burden of stone disease in the population, it is imperative that we advance our understanding of the pathogenesis of stone disease while we continue to work to improve our therapeutic armamentarium.

Disclosures

A.L.Z. is a consultant for Retrophin.

Footnotes

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