Recurrent Renal Stones: Review on Medical Management

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Epidemiology of nephrolithiasis

One in every 11 people develops a renal stone at some point in their life.[1] Although nephrolithiasis may occur at any age, onset is more common in young and middle-aged adults. Lifetime prevalence is estimated at 13 percent for men and 7 percent for women.[2,3] Following an initial stone event, the spontaneous 5-year recurrence rate is 35 to 50 percent.[4]

Nephrolithiasis often is incidentally identified in asymptomatic patients who undergo plain radiographs or computed tomographic imaging for another indication.[5] Small stones generally pass through the urinary tract without symptoms. While larger stones may cause symptoms, more than 90 percent of stones less than 5 mm in diameter still pass through the urinary tract without intervention, as compared to spontaneous passage of approximately 50 percent of stones 5 to 10 mm in diameter.[6]

Basic screening evaluation of recurrent stone formers

Metabolic assessment of all kidney stone patients should be contemplated so as to rule out systemic disease that may be present with nephrolithiasis.This may be favorable for patients with:

- Multiple or bilateral stone disease
- Stones in pregnancy
- Stones in children (<18 years old)
- Non-calcium stones (e.g., cystine, uric acid)
- Recurrent stones
- Strong family history of stones (one or more first-degree relative)
- Stones in setting of a solitary kidney or an anatomical abnormality
- Stones in setting of renal insufficiency
- Systemic disease with increased risk of nephrolithiasis (e.g., gout, bowel disease, distal renal tubular acidosis)
- Critical occupations (airline pilots, sailors, military personnel, firemen).[7]

However, due to the low incidence of identified metabolic abnormalities; metabolic evaluation is not needed for pure infection stones (e.g., struvite). A close radiological and bacteriological review is, thus,advocated.[7]

A careful medical history along with thorough family history helps in revealingunderlying conditions that predispose patients to stone disease, including bowel disease, gout, diabetes and lithogenic medications. Dietary history should be studied properly to later assist in dietary counseling.

Metabolic evaluation can be limited to blood studies (sodium, potassium, chloride, bicarbonate, creatinine, calcium, albumin, uric acid and phosphorus), a urinalysis (including urinary pH) and a stone analysis. Furthermore, investigations should also consider evaluating parathyroid hormone (in association with calcium phosphate and/or calcium oxalate stones). Metabolic evaluation detailing will be done for kidney stone patients (in whom the stones are known or suspected tobe calcium-containing) and this includes the addition of ideally two 24-hour urine collections (with the patient following their usual diet), including minimum parameters of volume, creatinine, calcium, sodium, citrate, oxalate and uric acid. This should be done after discontinuation of stone preventing/promoting medications.[7]

The primary urinary abnormality in idiopathic uric acid stone formers is excessively acidic (pH <5.5) urine, not elevated urinary uric acid levels.A urinary screen for cystinuriaconsists of a single morning spot urine cystine concentration.[7]

Table 1: Dietary recommendations to prevent renal stone recurrence

Dietary component	Recommendation
Fluid	• Maintain fluid intake that achieves urine volume ≥ 2.5 L daily • Limit sugar-sweetened soft drinks • Orange juice with no added sugar to prevent calcium nephrolithiasis
Calcium	• Severe dietary calcium restriction is to be avoided • Maintain calcium intake of 1000-1200 mg/day
Oxalate	• Avoid oxalate rich foods (nuts, chocolate, brewed tea, spinach, rhubarb, beets, potatoes, peanut butter, wheat bran, beans) • Avoid juices with cranberry, grapefruit, starfruit • Maintain normal calcium intake
Protein	Modest restriction of animal protein (red meat, fish, poultry, pork, shellfish) to no more than 6-8 ounces daily
Carbohydrate	Refined carbohydrates restricted to <20 g/day
Sodium	Limit sodium intake to ≤ 100 mEq/day (2300 mg/day)
Citrate	Increase intake of fruits and vegetables; orange juice is beneficial
Calcium supplement	Consider for enteric hyperoxaluria but avoid for idiopathic calcium stone disease if dietary calcium intake is sufficient
Vitamin B6 supplement	Consider for primary hyperoxaluria type 1; not proven for idiopathic causes
Vitamin C supplement	Limit intake of vitamin C to <2 g/day
Vitamin D supplement	Do not withheld solely on basis of stone disease, if deficient and repletion indicated, monitor with 24 h urine analysis
Low carbohydrate/high protein diet (Atkins)	**Avoid** (increase in net acid; hypocitraturia; hypercalciuria, hyperuricosuria)
DASH diet; Mediterranean diet	Likely protective against stone disease

Abbreviation: DASH, dietary approaches to stop hypertension
Adapted from: Sorokin I, Pearle MS. Medical therapy for nephrolithiasis: State of the art. *Asian J Urol.* 2018;5(4):243–255.

Therapeutic approach: Dietary management

The therapeutic approach to preventing recurrent stones essentially revolves around correcting urinary abnormalities that predispose to stone formation as well as use of drugs and dietary measures.[1] Diet modification is an inexpensive, safe, and proven method to improve lithogenic risk factors.[8] The National Institute for Health and Care Excellence (NICE) guidelines recommend that recurrent stone formers maintain a healthy lifestyle to prevent weight gain, along with monitoring their fluid, salt and calcium intake.[9,10] An array of dietary factors can be targeted for modification to reduce stone formation, including increasing fluids, maintaining normal calcium intake, limiting foods rich in oxalate, consuming sodium and animal protein in moderation and enriching the diet in fruits and vegetables.[1,8] Table 1 enumerates the dietary recommendations that are likely to help prevent renal stone recurrence.[8]

Pharmacotherapy to prevent recurrence of renal stones: Leaving no stone unturned

Pharmacotherapy is indicated to reduce stone recurrence when dietary measures fail or are inappropriate in patients with particular metabolic backgrounds, or if the chronic kidney disease (CKD) and/or metabolic bone disorder (MBD) risks are considerable, or in certain groups of people (for example, flying airline personnel) and in those who have severe urine metabolic abnormalities.[8,11] A recently conducted systematic review and meta-analysis[12] of 21 randomized controlled trials (RCTs) comprising 2168 participants attested to drug therapy being more effective than dietary therapy in preventing stone recurrence among recurrent idiopathic calcium stone formers. The American College of Physicians (ACP) recommends pharmacologic monotherapy with a thiazide diuretic, citrate, or allopurinol to prevent recurrent nephrolithiasis in patients with active disease in which increased fluid intake fails to reduce the formation of stones.[13]

Specific prophylaxis based on stone composition

- **Recurrent calcium stones:** Thiazides diuretics have been demonstrated in clinical trials to decrease urinary calcium, thereby reducing rate of stone recurrence in calcium stone-forming patients.[1,14] Use of thiazides in recurrent hypercalciuric calcium oxalate (CaOx) and calcium phosphate stone formers is recommended by the American Urological Association (AUA) and European Association of Urology (EAU).[1] Concomitantly, alkali citrates are also effective in increasing urinary citrate and urinary pH.[14] Citrate therapy is indicated in recurrent CaOx stone formers with decreased urinary citrate excretion; in patients with complete or incomplete distal renal tubular acidosis, chronic diarrheal states, drug-induced or diet-induced hypocitraturia; and in patients with MBD who form stones.[11] In recurrent CaOx stone formers with hyperuricosuria and normocalciuria, allopurinol is effective in reducing stone recurrence[14]
- **Uric acid stones:** The primary intervention for preventing uric acid stones is alkali therapy to raise urine pH above solubility.[1] Herein, a target pH of 6-6.5 can effectively prevent and dissolve uric acid stones, which is readily achievable with bicarbonate or citrate salts (preferably potassium citrate) supplementation.[8,15] In patients with hyperuricemia or hyperuricosuria, allopurinol may be used as an adjunctive therapy.[14]
- **Cystine stones:** In patients with cystine stones, alkalinization of the urine targeting a urine pH of 7-7.5 is the initial therapy, achievable with administration of bicarbonate or citrate salts.[11,14] Thiolbinding agents should be considered second-line therapy, to be used in patients with severe cystinuria.[8,14] If cystinuria is >300 μmol per mmol of creatinine (>2,600 μmol per g of creatinine) or if the aforementioned therapies fail to prevent new stones, 6-mercaptopropionyl glycine can be administered, with d-penicillamine as an alternative treatment. However, close follow-up would be required in lieu of possible adverse effects of treatment[11]
- **Struvite stones:** Struvite stones occur as a consequence of urinary infection with urease-producing organisms.[14] Surgical removal of stone material is the standard therapy. New stone formation can however be avoided by prevention of urinary tract infections; foreign bodies such as urinary stents or catheters should thus be timely removed in high-risk patients.[14,15] The urease inhibitor acetohydroxamic acid (AHA) has been investigated for prevention of these stones, albeit with limited success[14]
- The pharmacotherapeutic regimens based on specific stone composition have been duly summarized in table 2.[1,8]

Potassium citrate: Place in therapy

Citrate salts reportedly prevent new stone formation, significantly reduce stone size, and result in stone size stability in patients with predominantly oxalate-containing stones. The need for retreatment for stone removal was also seen to be significantly less with citrate therapy.[16] Among alkali citrates, potassium citrate is the most commonly studied and used agent, with dosage ranging from 30-60 mEq in divided doses daily.[14] While alkalinising the urine, it offers the additional benefit of increasing urinary citrate which is an inhibitor of stone formation, thereby proving useful in patients with CaOx, cystine, and uric acid stones.[9]

Potassium citrate is preferred over sodium citrate for urinary alkalinisation due to several reasons. It attenuates calciuria and, therefore, is likely to be more effective in preventing calcium stones, while reducing urinary calcium excretion. Sodium citrate, on the other hand, tends to increase urinary calcium and the risk of calcium stones.[8,11,14] It enhances urinary cystine excretion as well.[8] The recent NICE recommendations on use of potassium citrate for preventing stone recurrence is enumerated in box 1.[10]

Calcium based stones

Potassium citrate corrects hypocitraturia, which occurs alone or in combination with other abnormalities in about 10-60% of calcium stone formers.[8] A recent study[17] conducted to this effect demonstrated patients receiving 40 mEq of oral potassium citrate daily for one year to have a significantly reduced stone recurrence rate of 1.72%, as compared to 25.86% seen in no-treatment subgroup. Both the groups were duly encouraged to high fluid intake with low salt, low oxalate diet. Furthermore, potassium citrate therapy was seen to have a good expulsive effect on residual stone fragments as well.[17]

In patients with enteric hyperoxaluria who inherently show a constellation of metabolic abnormalities, a liquid formulation of potassium citrate, such as a combination of citric acid and potassium citrate is recommended to treat the metabolic acidosis as the rapid intestinal transit in these patients precludes sufficient absorption of sustained release formulations.[1]

Non-calcium based stones

Potassium citrate, titrated to achieve the target pH, is first-line therapy for uric acid stone formers, with sodium bicarbonate reserved for those unable to tolerate potassium citrate or for whom renal dysfunction or hyperkalemia precludes its use.[10] For patients with cystinuria who continue to make stones despite dietary measures and high fluid intake, potassium citrate therapy provides an alkali load that increases urine pH, thus increasing cystine solubility.[1] A recent observational

Table 2: Pharmacotherapy based on specific stone composition			
Medication	**Rationale**	**Dose**	**Monitoring**
Calcium oxalate stones			
Thiazide	Hypercalciuria	Hydrochlorothiazide 25-50 mg BID; chlorthalidone 25-50 mg/day; indapamide 1.25-5 mg/day	BMP, uric acid, lipid profile
Potassium citrate (oral)	Hypocitraturia; low urine pH	10-30 mEq BID	Serum creatinine and potassium
Potassium citrate (liquid)	Enteric hyperoxaluria, chronic diarrhea	15-30 mEq TID-QID (titrate to reduce oxalate)	Serum creatinine and potassium
Allopurinol	Hyperuricosuria	100-300 mg/day	Liver enzymes
Uric acid stones			
FIRST–LINE THERAPY: Potassium citrate (oral)	Alkalinization	10-30 mEq BID (titrate dose to pH 6-6.5)	Serum creatinine and potassium
Sodium bicarbonate	Alkalinization	650 mg BID-QID	BMP
Allopurinol	When alkalinization unsuccessful	100-300 mg/day	Liver enzymes
Cystine stones			
Tiopronin (a-MPG)	Increase cystine solubility	Initial 400 mg/day; titrate to effect	CBC, BMP, urine protein
Potassium citrate (oral)	Alkalinization	10-30 mEq BID (titrate dose to pH 7-7.5	Serum creatinine and potassium
Struvite stones			
Acetohydroxamic acid	Urease-inhibitor	250 mg BID-TID	CBC

Abbreviations: BMP, basic metabolic profile; CBC, complete blood count; MPG, mercaptopropionyl glycine; BID, twice daily; TID, three times daily; QID, four times daily

Adapted from: 1. Morgan MS, Pearle MS. Medical management of renal stones. *BMJ.* 2016;352:i52. **2.** Sorokin I, Pearle MS. Medical therapy for nephrolithiasis: State of the art. *Asian J Urol.* 2018;5(4):243–255.

Box 1: Potassium citrate therapy for preventing stone recurrence: 2019 NICE recommendation

- Consider potassium citrate for adults with a recurrence of stones that are predominantly (more than 50%) calcium oxalate
- Consider potassium citrate for children and young people with a recurrence of stones that are predominantly (more than 50%) calcium oxalate, and with hypercalciuria or hypocitraturia

Recommendations on dietary and lifestyle advice are to be followed along with potassium citrate therapy.

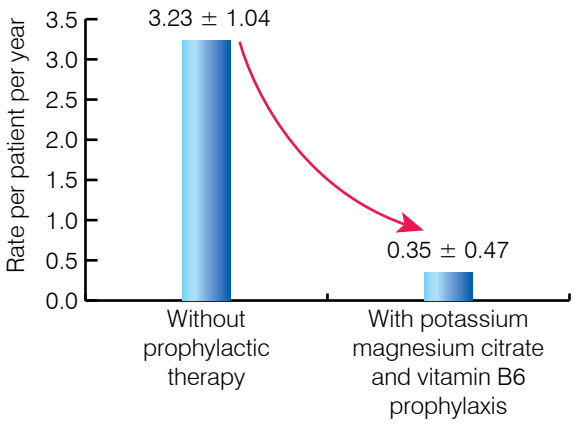
Adapted from: Renal and ureteric stones: Assessment and management. Available at: https://www.nice.org.uk/guidance/ng118/chapter/Recommendations#preventing-recurrence. Accessed on: 03/03/2020.

study[18] revealed that potassium citrate supplementation in recurrent renal stone formers beneficially altered the urinary risk profile by increasing anti-lithogenic factors. Importantly, fasting glucose, glycated hemoglobin, cholesterol levels and body mass index remained unaffected post 3 months of potassium citrate therapy, suggesting it to be safe and devoid of unfavourable metabolic adverse effects.[18]

Combining potassium citrate, magnesium citrate and vitamin B6: Therapeutic potential in recurrent stone formers

Provision of magnesium is likely to benefit stone formers as magnesium decreases urinary oxalate by binding oxalate in the intestinal tract as well as by complexing oxalate in urine that reduces its relative urinary saturation.[19] In fact, dietary magnesium deficiency has been suggested to increase risk of calcium calculi, with magnesium supplementation recommended as prophylaxis.[20] A potassium magnesium citrate combination is thus likely to be beneficial for stone formers. This was corroborated in a study[20] that demonstrated potassium-magnesium citrate to effectively prevent recurrent calcium oxalate stones. This therapeutic combination when given for up to 3 years in these patients, reduced their risk of stone recurrence by 85%.[20]

Figure 1: Reduction in stone recurrence rate with potassium magnesium citrate and vitamin B6 prophylaxis



Adapted from: Reddy SV, Shaik AB, Bokkisam S. Effect of potassium magnesium citrate and vitamin B-6 prophylaxis for recurrent and multiple calcium oxalate and phosphate urolithiasis. *Korean J Urol.* 2014;55(6):411–416.

Similarly, oxalate production and excretion has been seen to increase in the setting of vitamin B6 (pyridoxine) deficiency, while a high intake of vitamin B6 reportedly has an inverse association with risk of stone formation.[21] Evaluating the efficacy of potassium magnesium citrate and vitamin B6 prophylaxis in recurrent stone formers, a clinical trial[22] followed 247 Indian patients with hypocitraturia- and hyperuricosuria-induced recurrent CaOx and calcium phosphate stones for over 3 years. Potassium magnesium citrate prophylaxis was seen to produce a sustained increase in 24-hour urinary citrate excretion from initially low values (221.79 ± 13.39 mg/dL) to within normal to high limits (604.04 ± 5.00 mg/dL) at the 6-month follow-up, while urinary pH concomitantly rose significantly from 5.62 ± 0.2 to 6.87 ± 0.01, and remained maintained at 6.87 ± 0.01. Notably, the stone recurrence rate declined from 3.23 ± 1.04 per patient per year to 0.35 ± 0.47 per patient per year, as seen in figure 1. Clinical efficacy of the therapy after spontaneous passage or compelled procedural clearance of symptomatic stones was also seen to be better in treated patients as compared to controls who underwent similar procedures for their stones, thus lending credence to this therapeutic combination.[22]

Conclusion

A thorough evaluation that identifies the underlying cause of stone disease forms the foreground for directing medical therapy. While dietary approaches seem to be effective among single stone formers, pharmacotherapy often needs to be instituted, along with dietary changes, for recurrent stone formers. It is especially reserved for recurrent stone formers with demonstrable metabolic abnormalities. Follow-up remains the essential dogma to assess response to therapy as well as to monitor possible treatment adverse events.

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