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Clinical Practice Calcium Kidney Stones

Elaine M. Worcester, MD and **Fredric L. Coe, MD**
Nephrology Section, Department of Medicine, University of Chicago, Chicago, IL

A 43 year old man presents for evaluation of recurrent kidney stones. He passed his first stone nine years earlier, and has had two additional symptomatic stones. Analysis of the first and last stones showed that they contained 80% calcium oxalate and 20% calcium phosphate. A 24 hour urine collected off medications revealed a calcium level of 408 mg/day, oxalate 33 mg/day, and volume 1.54 liters/day; urine pH was 5.6. He had been treated with 20 to 40 meq of potassium citrate daily since he passed his first stone. How should this patient be further evaluated and treated?

The clinical problem

In the United States, the prevalence of kidney stones has risen over the past 30 years (1). Eleven percent of men, and 5.6% of women, will have a stone by 70 years of age; the risk is about three times higher in Caucasians than African Americans. About 80% of stones are composed of calcium oxalate with variable amounts of calcium phosphate. Diagnosis of a calcium stone requires analysis after passage or removal of the stone. After a first stone, the risk of recurrence is 40% by 5 years, and 75% by 20 years. Among recurrent calcium stone formers (e.g. those in the placebo arms of randomized controlled trials of interventions), 43 to 80% formed new stones within 3 years (2–9). Hospitalizations, surgery, and lost work time due to stones cost over $5 billion yearly in the United States (10). Stone formation is associated with increased rates of chronic kidney disease and hypertension (11;12), which are not completely explained by obesity, a risk factor for each of these conditions (13). Although many inherited and systemic diseases are associated with calcium kidney stones (14), most calcium stones are idiopathic. The majority of idiopathic stone formers have one or more metabolic abnormalities, identified by 24 hour urine testing. Prevention requires evaluation to identify systemic disease and modifiable factors.

PATHOGENESIS

Physicochemical factors

Supersaturation, often expressed as the ratio of urinary calcium oxalate or calcium phosphate concentration to their solubility, is the driving force for stone formation. At levels of supersaturation below 1, crystals dissolve, whereas at supersaturation levels above 1 crystals can nucleate and grow, promoting stone formation. Supersaturation is generally higher in stone formers than non-stone formers, and the type of stone formed correlates with urinary supersaturation. Calcium oxalate supersaturation is independent of urine pH, but calcium phosphate supersaturation increases rapidly as urine pH rises from 6 to 7. Since calcium oxalate stones form over an initial calcium phosphate layer (15), treatment optimally should lower the supersaturation of both species. Most 24-hour kidney stone risk panels from specialized labs include calculated supersaturation values.

Corresponding Author: Fredric L. Coe, MD Nephrology Section/ MC 5100 University of Chicago 5841 South Maryland Avenue Chicago, IL 60637 Phone: 773-702-1475 Fax: 773-702-5818 fcoe@uchicago.edu.

Urine also contains substances that can accelerate or retard urinary crystallization (16). The only such substance which can be modified in practice at this time is citrate, which can slow calcium crystal growth (17).

Anatomic abnormalities, in particular those that result in urinary stasis (such as ureteropelvic junction obstruction, horseshoe kidney, or polycystic kidney) may precipitate or worsen stone formation (18). Patients with a single functioning kidney are at particular risk, as stone passage with ureteral obstruction can result in acute kidney failure.

Metabolic Factors

Imbalances between excretions of calcium, oxalate, and water create supersaturation. Hypercalciuria, the commonest metabolic abnormality found in calcium stone formers, is most often familial and idiopathic (19), and is strongly influenced by diet. Gut calcium absorption is increased in individuals with idiopathic hypercalciuria, but serum calcium values remain unchanged, as absorbed calcium is promptly excreted (20). On a low calcium diet, such persons often excrete more calcium than they eat (21), and urine calcium excretion also rises markedly after the intake of calcium- free nutrients such as simple oral glucose; in such cases the only source possible is bone. Although hypercalciuria is sometimes divided into subtypes (absorptive, resorptive, renal leak), this classification is not helpful in guiding treatment. However, measurement of serum calcium is indicated to identify patients with primary hyperparathyroidism.

Calcium stone formers have modestly higher oxalate excretions than non stone formers, possibly due to increased gut oxalate absorption (22). Ascorbic acid and high protein intake may increase oxalate production (23). Because calcium binds with oxalate in the gut and hinders its absorption, oxalate is more readily absorbed when dietary calcium is low (24). This may be why a low calcium diet does not successfully prevent stone recurrences (25).

Citrate chelates calcium in the urine, decreasing supersaturation, and also reduces crystal growth (17); hypocitraturia is a risk factor for stones. Distal renal tubular acidosis, hypokalemia, and carbonic anhydrase inhibitors like topiramate lead to hypocitraturia, but its cause in most stone formers is unknown (26). Hyperuricosuria, often from high dietary intake of purines, is thought to promote calcium stones by reducing calcium oxalate solubility (27).

Histopathology of Calcium Stone Formers

Intra-operative papillary biopsies of stone formers show that the pattern of crystal deposition differs by stone type. Idiopathic calcium oxalate stones form over regions of interstitial calcium phosphate deposits (Randall's plaque) on the papillary surface (28), whereas idiopathic calcium phosphate stones are associated with inner medullary collecting duct crystal deposits containing mainly apatite (29;30) sometimes mixed with other crystals. (See Web appendix for details).

STRATEGIES AND EVIDENCE

Evaluation

Recurrent calcium stone formers should be evaluated to rule out systemic disease and guide preventive therapy. Evaluation includes a history directed at detecting potential causes of stones (Table 1). All stones should be analyzed to classify patients and detect conversion from one stone type to another; for example, to struvite in the presence of infection, or from calcium oxalate to calcium phosphate stones if urine pH rises in response to treatment (31).

A non-contrast CT provides information regarding the presence, size and location of stones, rules out anatomic abnormalities, and provides a baseline for assessing whether subsequent stones passed are old or new (the latter indicating a need for better preventive treatment). Given the expense and radiation exposure of CT, follow-up of known stones may utilize renal ultrasound or abdominal plain radiographs, although they are less sensitive than CT.

Metabolic testing should be done after the acute episode of stone passage resolves when patients have resumed their usual diet and activity. Evaluation includes a blood test to screen for hypercalcemia, chronic kidney disease, and renal tubular acidosis. 24 hour urine studies to detect metabolic abnormalities should preferably be done twice, as mineral excretions may vary day-to-day (32). Tables 2 and 3 provide a suggested framework for testing and interpretation. Whether to evaluate single stone formers is controversial; it seems prudent to rule out systemic disease, especially in those with a first stone prior to adulthood.

Treatment

Management of Symptomatic Stones—Stones in kidneys do not require removal or fragmentation unless causing obstruction, infection, serious bleeding or persistent pain. Ureteral stones less than 10 mm may be followed with conservative treatment in the absence of fever, infection, or renal failure, if pain is controlled. Opioid analgesics and nonsteroidal anti-inflammatory agents are both effective for pain control in acute colic. Medical therapy with an α-1 blocker or calcium channel blocker may facilitate passage of ureteral stones (33). In general, stones above 10 mm will not pass, those below 5 mm will, and those in between have variable outcomes; stones in the distal ureter are more likely to pass than those located more proximally.

If stones do not pass, there are several surgical options for removal (34); data for surgical recommendations come from meta-analyses of small trials. For ureteral stones, shock wave lithotripsy or ureteroscopy with laser lithotripsy are the treatments of choice; stone free rates are better with ureteroscopy, but complication rates are higher, including sepsis and ureteral injury. For stones lodged in the kidney, the size, location and presumed composition play a role in determining treatment. Not all stone types fragment equally well; for example calcium oxalate monohydrate and brushite stones are more resistant to fragmentation than calcium oxalate dihydrate or apatite stones. Shock wave lithotripsy and ureteroscopy are frequently used for smaller stones. Percutaneous nephrolithotomy may be used for single large stones (above 2 cm) or a large or obstructing stone burden; this requires general anesthesia and hospitalization, and carries a higher risk of complications, including bleeding and infection, than other techniques, but can result in a stone free kidney (35). Open or laparoscopic stone removal are occasionally used for challenging cases.

Prevention of Idiopathic Calcium Oxalate Stones—Prevention of recurrent stones requires decreasing urinary supersaturation, which is generally achieved by raising urine volume and lowering calcium and oxalate excretion. It should be recognized that urinary abnormalities are graded risk factors and thresholds for “normal” are not absolute cut points (36). Table 4 summarizes treatment strategies. (Web Appendix Table 1 summarizes details of treatment trials.)

A randomized trial of increased fluid intake (targeted to maintain urine volume greater than 2 liters daily) demonstrated a significant reduction in recurrent stone passage among first time calcium stone formers (37). A target urine volume of 2 to 2.5 liters is reasonable, achieved by increased intake of fluids, especially water, although most low sodium, low carbohydrate fluids are acceptable in moderation.

A diet low in animal protein (52 gm/day), sodium (50 mmol/day) and oxalate (200 mg/day) with normal calcium intake (1200 mg/day), reduced recurrences of stone formation by almost 50% over 5 years, compared with a low calcium (400 mg/day) and oxalate diet, in a randomized controlled trial in hypercalciuric Italian men (25). In contrast, in a US trial, a low protein diet did not reduce stone recurrence over 4.5 years, but compliance with the diet was poor and dietary sodium was not restricted (38). A low sodium diet can significantly decrease excretion of both calcium and oxalate (39), but studies are lacking of the effect of sodium-restricted diet alone on stone recurrence. Calcium restriction should be avoided in hypercalciuric individuals, as it may result in reductions in bone mineral density (40) and increased fracture rates (41).

Thiazide type diuretics decrease urine calcium excretion, and, in randomized controlled trials, these medications significantly reduced recurrence rates of calcium stones (by more than 50% over three years versus placebo) (2;4;6;9). Long acting agents like chlorthalidone and indapamide are effective with once daily dosing, whereas twice daily dosing is recommended for hydrochlorothiazide.

Hyperoxaluria may occur when dietary calcium is low or oxalate intake is unusually high, or (less commonly) when oxalate is overproduced. Dietary oxalate restriction to less than 100 mg/day and avoidance of ascorbic acid intake above 100 mg/day is prudent if hyperoxaluria is present. Foods that are very high in oxalate include spinach, rhubarb, wheat bran, chocolate, beets, miso, tahini, and most nuts. (A list of the oxalate content of various foods is available at: www.ohf.org under Resources.) Marked hyperoxaluria should prompt consideration of malabsorption or one of the primary hyperoxaluria syndromes (42).

Two randomized trials have shown substantial reductions in stone recurrence in hypocitraturic stone formers treated with potassium alkali, taken three times daily (3;7); one trial that used Na/K citrate was negative (8). Potassium alkali may be safely combined with thiazide (9;43) when indicated, but no trials have compared the combination against either agent alone for prevention of stone recurrence.

Hyperuricosuria can decrease solubility of calcium oxalate and increase the incidence of calcium oxalate stones. Allopurinol, 300 mg daily, decreased stone recurrence in a randomized trial of idiopathic calcium oxalate stone formers with hyperuricosuria (5). Reducing protein, and therefore purine, intake is also prudent, but has not been explicitly tested among patients with hyperuricosuria and recurrent kidney stones.

In long-term clinical follow-up, preventive treatment resulted in persistent reductions in stone recurrence with preventive treatment over at least two decades (44). However, compliance wanes over time, with non adherence rates approaching 20% per year (45).

Prevention of Calcium Phosphate Stones—Most calcium stones consist of more than 90% calcium oxalate with trace amounts of calcium phosphate, but the proportion of calcium phosphate in stones has increased over time (46;47). Idiopathic calcium phosphate stones (more than 50% calcium phosphate) are more common in women, and are associated with alkaline urine pH; the cause of the high urine pH is not well understood. Mild abnormalities of urine acidification may be present, although metabolic acidosis is uncommon (47;48). Some patients convert from forming calcium oxalate stones to forming calcium phosphate stones; in one study, these patients had a more alkaline urine pH (> 6.2) at baseline than those who continued to produce calcium oxalate stones (31). Calcium phosphate stones are associated with poorer stone free rates after percutaneous nephrolithotomy and with greater numbers of shock wave lithotripsy treatments than are calcium oxalate stones (47;49).

Treatment of calcium phosphate stones is the same as for calcium oxalate except that potassium alkali should be used cautiously because it raises urine pH, potentially worsening calcium phosphate supersaturation. Urine pH, citrate, and supersaturations should be assessed after starting therapy; if citrate does not rise and supersaturation worsens, the medication is unlikely to be of benefit.

Areas of Uncertainty

Treatment trials for calcium stones have not looked specifically at outcomes in calcium phosphate stone formers. Dietary recommendations to increase fluids, lower salt and protein, and maintain a normal intake of calcium are supported by an Italian randomized trial, but no women were included in this study, and it is unclear if many Americans can comply with the necessary dietary pattern sufficiently to successfully prevent stones. The DASH-Sodium diet (modified by the removal of high oxalate foods) replicates many of the features of the study diet, and may provide a model to follow, but its effects on stone recurrence have not been explicitly studied (50). Stone formation is associated with increased risks for bone disease, chronic kidney disease and hypertension, but it is not known whether effective stone prevention decreases these risks.

Guidelines

Guidelines of the American Urologic Association (www.auanet.org) recommend that patients who require surgery for ureteral stones should be informed about benefits and risks of all current treatment modalities. Shock wave lithotripsy and ureteroscopy with laser lithotripsy are both considered acceptable first line modalities, although ureteroscopy achieves greater stone free rates. Percutaneous access (and open or laparoscopic surgery) are used as needed for selected cases. The guidelines do not address evaluation or treatment to prevent recurrent stones.

Conclusions and Recommendations

Preventive treatment to decrease stone recurrence is indicated for patients with recurrent calcium stones, such as the patient in the vignette. If systemic disease is not present, treatment should focus on metabolic abnormalities uncovered during the workup, such as hypercalciuria, hypocitraturia, hyperuricosuria or hyperoxaluria. Although data are lacking comparing specific supersaturation targets, a logical strategy is to lower calcium oxalate and calcium phosphate supersaturation to the low end of the normal range.

Patients should be advised to increase fluid intake to at least 2 liters daily, and reduce sodium intake to 2300 mg (100 mEq) and protein intakes to 0.8 to 1 gm/kg/day, as these dietary interventions have reduced stone recurrence in randomized trials. Calcium intake should not be reduced below the recommended intakes for sex and age and should be supplied by food rather than by supplements, which may increase the risk of stone formation. In many patients, medication is also needed; the choice of medication is influenced by the metabolic abnormalities identified, the type of stone, and patient preference.

The stones of the patient in the vignette contain 20% phosphate, despite low urine pH off medications; the increased phosphate may reflect his prior treatment with citrate. Both hypocitraturia and hypercalciuria may contribute to his stone formation. In addition to the recommendations above, we would initiate therapy with a thiazide-type diuretic (for example, chlorthalidone 25 mg daily) to lower urine calcium; lowering sodium intake will also reduce thiazide – induced potassium losses.

A follow up 24 hour urine and serum chemistry panel should be done in 4 to 6 weeks to assess the efficacy of treatment and possible side effects, particularly hypokalemia, which can worsen hypocitraturia. If potassium supplementation is needed, it may be added as potassium alkali, but urine pH and calcium phosphate supersaturation should be monitored. If calcium phosphate supersaturation rises and is consistently above 1 potassium chloride should be substituted. Primary treatment with potassium alkali would be an alternative to a thiazide, but may not lower urine calcium phosphate supersaturation as effectively. Ongoing attention is warranted at follow-up visits to adherence to preventive recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Key Coexisting Medical Conditions, Medication Use, Diet, And Other Factors Associated With Calcium Kidney Stones

Variable	Features	Type of Kidney Stone	
		Calcium Oxalate	Calcium Phosphate
Medical or Surgical History			
Bowel disease	Chronic diarrhea, malabsorption	**X**	
Intestinal surgery	Small bowel resection, ileostomy	**X**	
Bariatric surgery	Duodenal switch, Roux-en-Y	**X**	
Sarcoidosis		**X**	**X**
Gout		**X**	
Renal tubular acidosis			**X**
Bone disease, fracture	PHPT, IH, myeloma	**X**	**X**
Immobilization	Trauma, prolonged illness	**X**	**X**
Hyperthyroidism	Untreated, iatrogenic	**X**	**X**
Renal anomaly	May lead to urinary stasis	**X**	**X**
Medications			
Topiramate	Seizures, migraine		**X**
Calcium supplements	Antacids, diet supplement	**X**	**X**
Carbonic anhydrase inhib	Glaucoma		**X**
Alkali	Bicarbonate, citrate		**X**
Vitamin D		**X**	**X**
Occupational, recreational			
Dehydration	Hot environment, unable to drink	**X**	**X**
Dietary factors			
Oxalate loads	Nuts, spinach, ascorbic acid	**X**	
Excess salt	Prepared foods, snack foods	**X**	**X**
Eating disorders	Vomiting, laxatives	**X**	**X**
Strange diets	Protein powder, sugar loads	**X**	**X**
Family History			
History of stones in a first degree relative	Idiopathic hypercalciuria, primary hyperoxaluria	**X**	**X**

CaOx, calcium oxalate; CaP, calcium phosphate; PHPT, primary hyperparathyroidism; IH, idiopathic hypercalciuria; PHO, primary hyperoxaluria

Table 2

DIAGNOSTIC TESTING FOR STONE FORMING PATIENTS*

MEASUREMENT	NORMAL RANGE (Adult Non Stone Formers)	PURPOSE
Blood screening tests for all calcium stone formers		
Calcium	8.8–10.3 mg/dl	Detection of primary hyperparathyroidism, excessive Vit D intake, sarcoidosis
Phosphate	2.5–5.0 mg/dl	Detection of primary hyperparathyroidism
Creatinine	0.6–1.2 mg/dl	Detection of chronic kidney disease
Bicarbonate	20–28 mmol/liter	Detection of renal tubular acidosis
Chloride	95–105 mmol/liter	Detection of renal tubular acidosis
Potassium	3.5–4.8 mmol/liter	Detection of renal tubular acidosis, eating disorders, gastrointestinal disease
24-Hour urine stone risk panel for calcium stone formers requiring medical prevention		
Volume (L/day)	> 1.5 L/day	Detection of low volume as cause of stones
Calcium (mg/day)	<300 (M), <250 (F), < 140mg/g creat	Detection of hypercalciuria
Oxalate (mg/day)	<40 (M or F)	Detection of hyperoxaluria
pH	5.8–6.2	Needed for CaP and uric acid SS; Diagnosis of RTA
Phosphate (mg/day)	500–1500	Needed for CaP SS
Citrate (mg/day)	>450 (M), > 550 (F)	Detection of low citrate, and diagnosis of RTA; needed for CaP SS
Uric acid (mg/day)	<800 (M), <750 (F)	Detection of hyperuricosuria as cause of stones; uric acid SS
Sodium (mmol/day)	50–150	Diet counseling; needed for SS calculations
Potassium (mmol/day)	20–100	Use of potassium salts; needed for SS calculations
Magnesium (mg/day)	50–150	Detection of malabsorption; needed for SS calculations
Sulfate (mmol/day)	20–80	Needed for SS calculations; gauges net acid production
Ammonium (mmol/day)	15–60	Needed for SS calculations
Creatinine	20–24 mg/kg (M), 15–19 mg/kg (F)	Needed to estimate completeness of collection
Protein catabolic rate†	0.8–1.0 gm/kg/day	Estimates protein intake
Calculated SS‡: CaOx	6–10	Guidance of treatment
CaP	0.5–2	
Other screening tests		
Urine cystine screen¶	Negative	Detection of cystinuria
Stone analysis		Basic classification of patients

*Blood testing for renal tubular acidosis, chronic kidney disease, and hypercalcemia, along with urinary cystine screening and kidney stone analysis, are appropriate for all patients with recurrent kidney stones. Collection of urine over a 24-hour period is appropriate if medical prevention of kidney stone formation is planned. To convert the values for calcium to millimoes per day, multiply by 0.025. To convert the values for phosphate to millimoles per day, multiply by 0.0323. To convert the values for creatinine to micromoles per day multiply by 0.00884. To convert the values for urinary oxalate to micromoles per day, multiply by 11.11. To convert the values for urinary citrate to mmol per day, multiply by 0.0052. To convert the values for urinary uric acid to millimoles per day,, multiply by 0.00595. To convert the values for urinary magnesium to mmol per day, multiply by 0.0411. To convert the values for urinary urea nitrogen to moles per day, multiply by 0.0357.

†The protein catabolic rate is calculated by multiplying the uriea nitrogen excretion in grams per day by 6.25 and dividing by body weight.

[‡] SS, supersaturation, is expressed as the ratio of urinary CaOx or CaP concentration in urine to its solubility. CaOx, calcium oxalate; CaP, calcium phosphate.

[¶] Urinary cysteine is tested with the use of the cyanide nitroprusside test. A negative test means that the cysteine concentration is less than 75 mg/liter.

Table 3

MAIN CAUSES OF CALCIUM STONES AND THEIR TREATMENTS

Disease	Key Abnormalities								SS			Tissue Changes		Treatment
	Sca	PTH	Uca	UpH	UCit	Uox	Uur	V	CaOx	CaP	UA	IP	CDP	
Idiopathic CaOx	N	N	↑ or N	N	↓ or N	↑ or N	↑ or N	↓ or N	H	N,H	N,H	↑↑	0	Thiazide for IH; potassium citrate for CaOx, perhaps CaP stones.Allopurinol for hyperuricosuria. Na restriction, possible protein or oxalate restriction. Increased fluids.
Idiopathic CaP	N	N	↑ or N	↑	↓or N	N	N	N	H	H	N	N	↑↑	
PHPT	↑	↑	↑	↑	N	N	N	N	H	H	L	↑↑	↑↑	Parathyroid surgery
Sarcoidosis	↑	↓	↑	N	N	N	N	N	H	H	N	?	?	Glucocorticoids, possible ketoconazole
Lithium use	↑	↑	↑	↑	N	N	N	N	H	H	N	?	?	Discontinue lithium
Oral supplements of calcium or vitamin D	N or ↑	N	↑	N	N	N	N	N	H	H	L	?	?	Discontinue supplements
Ileostomy	N or ↓	N	↓	↓	↓	N	N	↓	H	L	H	↑	↑↑	Fluids, alkali; supplements to reduce urine oxalate excretion for short bowel and bariatric surgery
Short bowel	N or ↓	N	↓	↓	↓	↑	N	↓	H	L	H	N	↑↑	
Bariatric surgery	N or ↓	N	↓	N	↓	↑	N	N	H	N	N	N	↑	
RTA	N	N	N or ↑	↑	↓	N	N	↑	N	H	L	N	↑↑	Alkali, possible thiazides

Abbreviations: SCa, serum calcium; PTH, parathyroid hormone; Uca, urine calcium excretion; UpH, urine pH; UCit, urine citrate excretion; UOx, urine oxalate excretion; Uur, urine uric acid excretion; V, urine volume; SS, supersaturation; CaOx, calcium oxalate; CaP, calcium phosphate; UA, uric acid; IP, interstitial apatite deposits (interstitial plaque); CDP, collecting duct (inner medullary and terminal ducts of Bellini) plugging with apatite deposits; IH, idiopathic hypercalciuria; PHPT, primary hyperparathyroidism; RTA, renal tubular acidosis; N, not different from normal; H, high; up and down arrows indicate change from normal people. ?, no available data; 0, not present.

Table 4

TREATMENT RECOMMENDATIONS FOR PREVENTION OF IDIOPATHIC CALCIUM STONES IN ADULTS

Treatment	Mechanism of action	Doses	Selection criteria	Potential complications
Fluids	Lowers supersturation by dilution of solutes	Adequate to maintain urine volume > 2 liters daily.	Useful for all SF. May be used as sole treatment for patients with a single stone episode.	Avoid fluids containing excess salt or carbohydrates
Diet	Lowers supersaturation by decreasing calcium and oxalate excretion	Na < 100 mmol/day Protein < 0.8–1 gm animal protein/ kg BW	Especially useful for hypercalciuric or hyperuricosuric SF.	May be hard to maintain
		Oxalate < 100 mg/day	Hyperoxaluric SF	May be hard to maintain
	Maintains bone mineral, prevents hyperoxaluria	Calcium 800–1000 mg/day	All calcium SF	Should obtain from dietary sources, avoid supplements
Thiazide-type diuretics	Lowers supersaturation by decreasing calcium excretion	Chlorthalidone 12.5–50 mg daily Indapamide 1.25–2.5 daily Hydrochlorothiazide 12.5–25 mg twice daily	Hypercalciuric SF, may be useful for some normocalciuric SF	Hypokalemia, lowers blood pressure (may be desirable), allergy and sun sensitivity
Potassium alkali	Lowers supersaturation by chelating calcium Inhibits calcium crystal growth	Potassium citrate 10–20 meq bid-tid	Hypocitraturic SF	Monitor urine pH and CaP SS, avoid SS > 1
Allopurinol	Lowers urine uric acid concentration, which may improve solubility of calcium salts	100–300 mg/day (may be taken once daily)	Hyperuricosuric calcium SF	Allergy, may be severe.