

A Woman with Recurrent Calcium Phosphate Kidney Stones

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Summary

Kidney stones composed predominantly (50% or more) of calcium phosphate constitute up to 10% of all stones and 15%–20% of calcium stones, 80% of which are composed of calcium oxalate. Calcium phosphate is a minor component of up to 30% of calcium oxalate stones as well. The cause of calcium phosphate stones is often obscure but most often related to a high urine pH. Some patients with calcium phosphate stones may have incomplete renal tubular acidosis. Others have distal renal tubular acidosis characterized by hyperchloremic acidosis, hypocitraturia, and high urine pH. The use of carbonic anhydrase inhibitors such as acetazolamide, topiramate, and zonisamide leads to a similar picture. Treatment options to specifically prevent calcium phosphate stone recurrence have not been tested in clinical trials. Increases in urine volume and restriction of sodium intake to limit calcium excretion are important. Citrate supplementation is probably effective, although the concomitant increase in urine pH may increase calcium phosphate supersaturation and partially offset the inhibition of crystallization resulting from the increased urine citrate excretion and the alkali-associated reduction in urine calcium excretion. Thiazides lower urine calcium excretion and may help ensure the safety of citrate supplementation.

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Introduction

A 22-year-old woman who had her first kidney stone at age 15 years was seen in the Kidney Stone Prevention Clinic because of recurrent calcium stones. In total, she has had five episodes of acute renal colic in 7 years. Each episode was associated with more than one stone causing at least temporary ureteral obstruction that required urologic intervention. She has had one unsuccessful shock-wave lithotripsy and five ureteroscopies. Stone composition has been variable: her first stone was 80% calcium oxalate and 20% calcium phosphate; 4 years later, 80% calcium phosphate and 20% calcium oxalate; 1 year later, a lab reported that one of her stones was composed of 50% brushite, 20% hydroxyapatite and 30% calcium oxalate; most recently a stone was reported to be 100% carbonate apatite. She had no history of urinary tract infections.

She is physically active and does aerobic exercises. She has not been on any weight loss diets, and eats “everything”, including milk with cereal, and some yogurt. She is not taking any medications but 1 year ago, had taken potassium citrate 15 meq two times per day for 5 months and then stopped it when she concluded that it had not been effective. She has no history of hypertension or diabetes. Both her father and paternal grandfather had stones of uncertain composition. On physical exam, she had a seated blood pressure of 114/78 mmHg. She is 165 cm tall and weighs 74.8 kg, with body mass index of 27.5 kg/m².

Laboratory Evaluation

Review of laboratory evaluations showed that serum creatinine was 0.8 mg/dl, uric acid was 5.2 mg/dl,

calcium was 9.4 mg/dl, potassium was 4.7 meq/L, HCO₃ was 24 meq/L, 25-OH-vitamin D was 32 ng/ml, and intact parathyroid hormone (PTH) was 23 pg/ml. She performed 24-hour urine collections (Table 1). All collections had similar creatinine excretion, indicating that the collections were comparable and consistent. At baseline, the results were notable for a very low volume less than 1 L and normal calcium, oxalate, phosphate, and uric acid excretion, with relatively low sodium excretion and very low citrate excretion. As expected in a calcium phosphate stone former, her urine pH was relatively high. The calculated supersaturation values indicated moderate risk of calcium oxalate and calcium phosphate crystallization.

Therapy

She was prescribed potassium citrate 15 meq two times per day and told to increase her fluid intake to at least 3 L (about 100 oz) per day. She was counseled to continue to limit her sodium and oxalate intake and have two to three servings of dairy products with meals per day, which she had been avoiding. A repeat urine collection several months later (Table 1, Treatment 1) showed increased potassium, citrate, sodium, and calcium excretion, with a significant increase in urine volume and pH. Despite the increased calcium excretion, the net effect was reduction in supersaturation of both calcium oxalate and calcium phosphate. Her increased sodium excretion was associated with an increase in calcium excretion and was probably more representative of her typical sodium intake. Although the resulting calciuria did not constitute hypercalciuria and because she was highly motivated to

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Table 1. 24-Hour urine chemistries

	Volume (L)	Sodium (meq)	Potassium (meq)	Calcium (mg)	Oxalate (mg)	Supersaturation Calcium Oxalate	Citrate (mg)	pH	Supersaturation Calcium Phosphate	Phosphorus (mg)	Uric Acid (mg)	Creatinine (mg)
Normal values	0.5–4.0	50–150	20–100	M<250; F<200	20–40	8–10	M>450; F>550	5.8–6.2	0.5–2.0	800–1200	M<800; F<750	M=18–24 mg/kg; F=15–20 mg/kg
Baseline	0.86	55	60	92	31	9.5	103	6.45	1.9	586	551	1379
Treatment 1	2.49	152	81	175	24	3.1	218	7.49	1.4	525	396	1412
Treatment 2	1.97	209	53	93	37	3.2	196	7.24	1.2	859	600	1352

Normal values apply to the general population but do not represent the optimal values to lower stone risk. Baseline represents the mean of two collections performed before the patient's first clinic visit. M, male; F, female.

avoid additional stones, I prescribed indapamide 2.5 mg one time each day and repeated the urine collection 1 month later (Table 1, Treatment 2). That collection showed a reduction in urine calcium excretion attributable to the indapamide, despite a further increase in urine sodium excretion; urine volume was slightly lower, and neither supersaturation of calcium oxalate nor calcium phosphate changed significantly. Her blood pressure and serum chemistry values were unchanged, including a serum potassium level of 3.9 meq/L (lower than her baseline value of 4.7 meq/L). She was again counseled regarding restriction of dietary sodium.

Case Discussion

Overview of Calcium Phosphate Stones

Kidney stones composed predominantly (50% or more) of calcium phosphate constitute up to 10% of all stones and 15%–20% of calcium stones, 80% of which are composed of calcium oxalate. Calcium phosphate is a minor component of up to 30% of calcium oxalate stones as well (1). The importance of calcium phosphate as an initiator of calcium stones has been highlighted by recent work showing that the vast majority of calcium oxalate stones form as overgrowths on Randall's plaque. Randall's plaque is an amorphous apatite that forms in the interstitium of the papillae, and it grows until it ruptures through the papillary urothelium and becomes exposed to urine; calcium oxalate crystals nucleate and grow into kidney stones (2). Some data suggest that calcium phosphate stones have increased in prevalence. If true, the reasons are uncertain and have been attributed to treatment with citrate supplements (see below) or adverse effects of extracorporeal shockwave lithotripsy (3,4). Lithotripsy has been hypothesized to lead to defective urinary acidification, but this effect is highly speculative.

There are several forms of calcium phosphate that appear in kidney stones, and these forms occurred in the patient presented here. The most common is hydroxyapatite, the same crystal form that composes bones; brushite (calcium hydrogen phosphate) is less common, probably because it is a less stable crystal structure that often transforms into hydroxyapatite. Why some calcium phosphate stones take the form of hydroxyapatite and others take the form of brushite is not known. Patients with carbonate apatite as a component of stones should have urinary tract infection ruled out, particularly if it exists combined with struvite, the ammonium–magnesium–calcium phosphate crystal associated with urease-producing organisms. However, carbonate apatite can be present in patients with idiopathic calcium phosphate stones not associated with infection, which is seen in the current patient (5). Recent data show that different laboratories analyzing the same calcium phosphate stones reported different results for these crystalline phases, leading to some question about the reliability of this determination (6). In recognition of this uncertainty, some labs simply report basic calcium phosphate to avoid inaccuracy.

Defective Renal Tubular Acidification

Calcium phosphate stone formers should be evaluated for distal renal tubular acidosis (dRTA). A low serum

bicarbonate concentration, hyperchloremic metabolic acidosis, and persistently alkaline urine pH of at least 5.5 is diagnostic. Hypokalemia is frequently present as well. Metabolic acidosis and hypokalemia both contribute to hypocitraturia. Hypercalciuria is frequent, and in the presence of a consistently elevated urine pH, these urinary characteristics lead to calcium phosphate precipitation. Nephrocalcinosis (calcification of the renal parenchyma) is often present and may lead to reduced GFR. Carbonic anhydrase inhibitors may lead to a similar picture, causing bicarbonaturia, hypokalemia, hypocitraturia, and calcium phosphate stones. The drugs most frequently associated with this presentation are acetazolamide when given orally to treat glaucoma and topiramate, which is in common use today for seizure disorders and migraines (7).

Calcium oxalate stones are more frequent than calcium phosphate stones in primary hyperparathyroidism, but some studies suggest an increased prevalence of calcium phosphate as at least a component of stones in this setting (8). As in this case, I usually check PTH levels in patients with calcium phosphate stones but only in calcium oxalate stone formers with high or high normal serum calcium concentration. Despite activation of 1- α -hydroxylase activity by PTH, urine phosphate excretion is not different between stone formers and nonstone formers with hyperparathyroidism, although stone formers have higher calcium excretion. The indications for measuring 25-OH-vitamin D in calcium oxalate or calcium phosphate stone formers, as I did in this patient, have not been clearly delineated. Hypervitaminosis D is a quite rare cause of hypercalcemia and calcium stones. Because of the low bone mineral density in patients with hypercalciuria, some of these patients may benefit from vitamin D supplementation if baseline levels are low. Admittedly, the yield in measuring 25-OH-vitamin D and PTH in such patients is relatively low.

The relatively high urine pH and low urine citrate with a normal serum bicarbonate concentration in the patient presented are quite typical of calcium phosphate stone formers, although many also have hypercalciuria. The cause of this constellation of features in calcium phosphate stone formers is not known. A higher urine pH distinguishes calcium phosphate stone formers from calcium oxalate stone formers, although there is overlap. At higher urine pH values, monobasic phosphate (H_2PO_4^-) gives up a proton and becomes dibasic phosphate (HPO_4^{2-}). This species is much more prone to combine with the divalent cation calcium. Compared with calcium oxalate stone formers, patients with mixed calcium oxalate/calcium phosphate stones have lower urine citrate and higher pH, whereas patients with predominantly calcium phosphate stones have even lower citrate and higher pH (9). Although males are about two times more likely to have stones, women are more likely to have calcium phosphate stones.

This patient's presentation may suggest incomplete RTA, in which a partial defect in urinary acidification may not be sufficient to lower serum bicarbonate below the normal range but can be revealed by the failure to lower urine pH to less than 5.3 after ammonium chloride loading. A recent study found a prevalence of incomplete RTA of 6.7% in patients with recurrent calcium-containing kidney stones; most had calcium phosphate stones (10). Patients with incomplete dRTA had significantly higher

fasting and 24-hour urine pH compared with calcium stone formers who did not have incomplete dRTA. In another study, an inability to lower the urine pH below 5.25 was present in calcium phosphate stone formers but not calcium oxalate stone formers (11). Because appropriate therapy addressing the specific urine chemistry abnormalities will be the same whether incomplete RTA is diagnosed or not, ammonium chloride loading is rarely done outside of a research setting.

Hypercalciuria

Although the patient presented here did not have hypercalciuria, many patients with calcium phosphate stones (with dRTA or on an idiopathic basis) do have increased urine calcium excretion. Although metabolic acidosis may contribute to causing hypercalciuria in patients with dRTA by activating osteoclasts and inhibiting renal tubular calcium absorption, the basis for hypercalciuria in most calcium stone formers, whether oxalate or phosphate, is not clear. Candidate genes for hypercalciuria have not explained the disorder in the general population with two possible exceptions. In people in Iceland and The Netherlands, mutations in claudin 14, expressed in the tight junctions of the proximal tubule, the thick ascending limb of the loop of Henle, and the distal convoluted tubule, were associated with hypercalciuria and reduced bone mineral density in different cohorts (12). This finding has not yet been confirmed in other populations. Polymorphisms in the calcium-sensing receptor gene may also contribute to increases in urine calcium (13).

No clear threshold of 24-hour urine calcium excretion separates stone formers from nonstone formers, and values of urine calcium seem to be a linear function; increases in urine calcium excretion within the range traditionally considered normal are associated with increased risk for stones. One might consider high urine calcium concentration (the combined effect of low urine volume and higher urine calcium excretion) to be a more important indicator of stone risk. For practical purposes, 24-hour urine calcium and other analytes are best measured on a patient's self-selected diet.

The usefulness of a widely known classification of hypercalciuria intended to explicate its pathophysiology and guide treatment has not been shown (14). At present, applying this classification to patients with hypercalciuria, regardless of stone composition, is not recommended. The published protocol used to characterize hypercalciuria is time-consuming, expensive, unwieldy, and not practical outside of a clinical research center. In addition, the findings are not always reproducible, and the vocabulary of the classification is misleading. The term absorptive hypercalciuria, said to be the most common phenotype accounting for calcium stones, would suggest that the primary abnormality in this disorder is increased intestinal absorption of calcium. Although hyperabsorption of calcium is indisputably present, it cannot be the sole cause of the widespread disorder of calcium metabolism evident in patients with hypercalciuria.

The inadequacy of the term absorptive hypercalciuria is best illustrated by the strong association of hypercalciuria with reduced bone mineral density (BMD) and increased fracture rates (15). An absorptive hypercalciuria not

accompanied by other disruptions in normal calcium metabolism would not be expected to lead to osteoporosis. Furthermore, many patients with hypercalciuria that partially remits on a low calcium diet continue to have negative calcium balance, suggesting that they are mobilizing bone calcium, which implies more than a disorder in intestinal absorption (16).

Therapeutic Options

As the result of a lack of trials specifically targeting calcium phosphate stones, the availability of high-grade evidence regarding their prevention remains negligible. Reviews often deal with these stones by suggesting a similar prescription of water, diet, and medications as used for calcium oxalate stones, but nuances regarding prescribed therapy for this subset of stones may be appropriate. Table 2 includes fluid, diet, and pharmacologic therapeutic options for calcium phosphate stone formers. The prescription of these options might occur sequentially,

intensify if stone activity persists, or occur all at one time. Patient preferences are important to explore; many patients will be reluctant to change diet or adhere to medical therapies, and motivation varies.

Fluid Therapy. The importance of increasing urine volume by increasing fluid intake cannot be overemphasized. Given uncertainty about the efficacy of diet and medications, a safe, inexpensive, and effective therapy like drinking more liquids cannot be rivaled. As the current patient shows, increasing urine volume from less than 1 L to more than 2 L per day dramatically reduces supersaturation for both calcium oxalate and calcium phosphate. Many patients can maintain a urine volume of at least 2.5 L per day. Recent evidence shows that urine calcium excretion is highest after dinner, and urine volume is lowest during sleep; this combination causes the highest urine calcium concentrations in the evening, and therefore, fluid should be taken at bedtime as sleep tolerates and on waking (17).

Table 2. Therapeutic approach to calcium phosphate stone formers

Steps 1–3 Might Be Instituted Sequentially or Simultaneously Depending on Stone Activity and Patient Preferences

1. Fluid therapy
 - increase fluid intake up to 3 L or more to ensure urine output ≥ 2.5 L/d
 - instruction: 3 L is approximately 100 oz or 12 \times 8-oz servings
 - measure 24-h urine output periodically (patient can do this measurement at home)
 - higher fluid intake should be consistent throughout the day
 - increase fluid intake with exercise
 - increase fluid intake with meals
 - increase fluid intake before bedtime but minimize disturbance of sleep
 - most fluid intake should be water
 - avoid grapefruit juice (associated with more stones)
 - limit cola (may have adverse effects on urine chemistry)
2. Dietary therapy
 - prescribe diet based on 24-h urine data but educate patient about general principles
 - limit sodium intake to 2 g (about 100 meq) per day
 - limit oxalate intake if calcium oxalate is an important stone component
 - reduce intake of high oxalate foods but avoid quantitative targets (<https://regepi.bwh.harvard.edu/health/oxalate/files>)
 - accompany ingested oxalate with ample fluids
 - accompany ingested oxalate with dairy products
 - moderate protein intake (e.g., 1.2 g/kg per day)
 - two to three servings of dairy per day may be desirable (if calcium oxalate is a stone component)
3. Pharmacologic therapy
 - judge efficacy based on results of 24-h urine collections
 - Potassium citrate 20–30 meq two times per day
 - one dose at bedtime to cover lower urine volume and higher calcium concentrations
 - benefit is uncertain if
 - urine volume does not increase
 - urine calcium does not fall
 - urine citrate does not rise
 - urine pH rises
 - Thiazides
 - may be useful even if hypercalciuria is not present
 - chlorthalidone 12.5–50 mg one time per day
 - hydrochlorothiazide 25–50 mg one or two times per day
 - indapamide 2.5–5.0 mg one time per day
 - maintain normal serum potassium concentration with potassium citrate if hypocitraturia is present or potassium chloride if hypocitraturia is not present
 - if necessary, consider amiloride 5–10 mg two times per day, spironolactone 25 mg two times per day, or eplerenone 25–50 mg one time per day
 - avoid poorly soluble triamterene

Dietary Therapy. The optimal diet for prevention of calcium stones, including calcium phosphate stones, has not been well defined (18). Reduction in sodium intake is often associated with reduced calcium excretion, whereas reduction in animal protein intake leads to increased urine citrate and reduced urate excretion. Compared with a more carnivorous diet, increased fruit and vegetable intake is associated with higher urine citrate and urine volume (19). A small trial of protein restriction did not lead to reduced stone incidence (20). The Dietary Approaches to Stop Hypertension diet was associated with reduced stone incidence in an epidemiologic study, but it has never been tested in a trial; whether it would prevent both calcium phosphate and calcium oxalate stones is unknown (21). Epidemiologic data generally show that higher calcium intake is associated with fewer stones; the basis for these data is thought to be related to the ability of calcium to complex oxalate in the intestine and prevent its absorption. In one small randomized controlled trial, a diet with reduced content of animal protein, salt, and oxalate and increased content of calcium was superior to a low calcium and oxalate diet in Italian men with hypercalciuria (22). It is not known whether this diet would be effective in women, calcium phosphate stone formers, or individuals with diets where limiting sodium intake is more difficult. Binding ingested phosphorus with aluminum salts was of unclear benefit for calcium stone formers in the past. Perhaps sevelamer carbonate or lanthanum would be more advantageous.

Pharmacologic Therapy.

Citrate. The question of whether citrate therapy is more useful or risky in the management of recurrent calcium phosphate stones with hypocitraturia, as in this case, is a vexing one. Citrate in the urine forms a soluble complex with calcium, serving as a competitive antagonist of precipitation of calcium salts. This inhibitory effect applies to the formation of both calcium oxalate and phosphate complexes and decreases the supersaturation of both poorly soluble calcium salts. Citrate also inhibits the growth of individual calcium salt crystals and the tendency for crystals to aggregate and form stones. These effects are independent of estimates of supersaturation.

The risk of citrate supplementation arises from the alkalinization of the urine that it produces. A portion of orally administered citrate appears in the urine as the result of glomerular filtration, and it complexes with calcium, inhibiting stone formation. However, some of the administered citrate is metabolized, like any organic anion, by the liver and kidney, consuming protons and generating bicarbonate. This bicarbonate, in turn, is filtered and appears in the urine, increasing urine pH and calcium phosphate supersaturation. In effect, the increase in urine pH is inevitable, and for calcium phosphate stone formers, it is an undesired side effect. (This effect, however, is both necessary and desirable to prevent uric acid and cystine stones). Alkalinization has an offsetting effect on supersaturation of calcium salts, because it also reduces urine calcium excretion through a direct effect on distal tubular calcium channels and reductions in bone turnover. Potassium citrate is preferable to sodium citrate, because the latter will tend to increase calcium excretion, negating the effects of the alkali. Urinary citrate excretion can also be augmented by drinking citrus juices; orange juice,

with a higher pH than lemon juice, has more potential base. Drinking more juice does not seem as effective as potassium citrate tablets in my clinical experience.

Alkali inhibits the proximal tubular sodium-dicarboxylate cotransporter. Its control by pH is suitable to its role of reclaiming filtered potential base; acid loads stimulate absorption, and alkali loads inhibit reabsorption. The net effect of citrate supplementation, even if the citrate is metabolized to bicarbonate, is enhancement of citrate excretion.

The therapeutic result of citrate supplementation may, therefore, be beneficial, neutral, or possibly harmful. Patients who do not increase urine volume and reduce urine calcium, have more bicarbonaturia, have increased urine pH, and have little rise in urine citrate excretion may be at increased risk of forming calcium phosphate stones instead of calcium oxalate stones. Whether they will form more stones or the same number of stones but of different composition has not been determined.

Given these competing risks and benefits, the net effect of citrate supplementation in calcium phosphate stone formers has not been established. Citrate was beneficial for prevention of calcium oxalate and mixed calcium oxalate/phosphate stones in one small trial (23). Other trials of citrate for calcium stones have not mentioned whether calcium phosphate stone formers were included. Anecdotal reports also claim benefit even for patients with dRTA, whose high urine pH and tendency to form calcium phosphate stones might make their response to citrate supplementation doubtful (24).

The patient presented here received potassium citrate; her urine potassium and citrate excretion as well as her urine pH rose. Her urine calcium failed to fall, possibly because of an increase in sodium excretion and the liberalization of her calcium intake. Because of a significant increase in urine volume, her supersaturation for both calcium oxalate and calcium phosphate fell.

Thiazides. Additional reduction in risk of stone recurrence can be achieved by the use of thiazides, which reduce urine calcium excretion. This effect is most likely caused by stimulation of proximal tubular calcium reabsorption through contraction of extracellular fluid volume, and it is also partly caused by a direct increase in calcium reabsorption in the distal tubule. The thiazide-induced reduction in urine calcium is associated with an increase in BMD (25). A number of randomized controlled trials have convincingly shown the ability of thiazides to reduce calcium stone recurrence (26). Although none of these studies specifically examined calcium phosphate stone formers, chlorthalidone, more potent and long-lasting than hydrochlorothiazide, did reduce brushite supersaturation in the genetic hypercalciuric stone-forming rat (27). The benefit of thiazides in patients who do not have hypercalciuria is not clear, and in that setting, they may yield a proportionately lower effect. However, they may still be very useful in calcium phosphate stone formers whose calcium phosphate supersaturation does not fall as the result of other therapies. One concern is the adverse metabolic effects of thiazides, such as hyperglycemia, hypokalemia, and hyperlipidemia. Although patients with hypertension seem to receive cardiovascular benefit from this class of drugs, the implications of these adverse effects in young, healthy people like the woman presented here might be different (28). Indapamide,

a thiazide-like drug, was effective in preventing recurrent calcium-containing kidney stones in a randomized clinical trial, and it seems to be associated with fewer of these adverse effects (29). It may, therefore, be ideal for younger normotensive people like this patient. Because urine calcium concentration is highest after dinner, prescribing thiazides after dinner or at bedtime might be most effective, but it has not been tested.

One last therapeutic option for calcium phosphate stones is sodium thiosulfate. The drug, approved only for treatment of cyanide poisoning and calcific uremic arteriolopathy, causes metabolic acidosis and reduces urine pH. It was effective in preventing calcium phosphate stones in the genetic hypercalciuric stone-forming rat (30). It has similar effects on urine chemistry in healthy controls and people with hypercalciuria in our own recent study (ClinicalTrials.gov identifier NCT01088555). The long-term effect of acidosis on BMD, however, would make this choice less than optimal.

I follow patients such as the one presented here with repeat 24-hour urine collections when changes in prescriptions are made or either I or the patient wants to see if dietary manipulations have led to improvement in stone risk. Calcium stones can be followed by plain abdominal radiographs or ultrasound. Although these methods have lower sensitivity and specificity than computed tomography, they are also less expensive and cause less radiation exposure. As lower dose stone protocols are more widely applied, reservations about computed tomography as a screening modality to judge stone activity may be relaxed. If asymptomatic stones are present or noted to grow, discussion with a urologist about the risks and benefits of urologic intervention may be recommended. Individual patient history and preferences and local urologic skills and modalities offered should be taken into consideration to select which urologic therapy, if any, is most appropriate.

Conclusion

The long-term course of this woman's kidney stones remains to be seen. Time will tell if she is able to adhere to a low-sodium intake in the working environment of New York City (rich in salt-laden, processed, and restaurant food), maintain a higher fluid intake, and adhere to the prescribed medications. Calcium phosphate stones are particularly challenging to prevent. Most studies of calcium stone prevention have concentrated on calcium stones in general or calcium oxalate stones in particular. Deficiencies in understanding the basis for the higher urine pH that leads to calcium phosphate stone formation contribute to the uncertainties about treatment. A diet addressing calcium phosphate stone prevention has not been developed. Questions about the relative risks and benefits of citrate supplementation persist, and a lack of data on the impact of this treatment on calcium phosphate stone formers may understandably inhibit prescription of this therapy.

Kidney stones affect a sizable proportion of both the American and the world's populations, with as many as 12% of American men and 7% of American women destined to have at least one stone in their lifetimes. About 1% of American working-age adults are treated each year

because of stone disease; about one-third of them will miss some work time, and about one-quarter of them will have a urologic intervention. The result is that, although stones may cause significantly less morbidity than kidney failure, there is a significant cost to the economy, with estimates of \$4.5 billion spent per year in the United States (31).

Stone prevention is also deemed valuable by many patients, whose recurrence rates lead them to state that they will do anything that they can to keep it from happening again. Whether kidney stone prevention is cost-effective or not is debated, but the avoidance of time-consuming and humiliating emergency room visits, difficulties obtaining adequate pain relief, and exposure to repeated doses of ionizing radiation are all highly worthy goals.

Dr. Jeffrey Berns. What guidelines could you suggest for deciding which patients with hypercalciuric nephrolithiasis and low bone density should be treated with vitamin D supplementation and how should such patients be monitored for the safety of vitamin D supplementation?

Dr. David Goldfarb. We recently addressed this important question in a small trial in which we supplemented hypercalciuric stone formers with 25-OH-vitamin D levels <30 ng/ml with 50,000 IU oral ergocalciferol weekly for 8 weeks (32). For the group of 29 participants, there was no change in mean 24-hour urine calcium excretion. However, there were some patients that didn't achieve 25-OH-vitamin D levels >30 ng/ml. Some patients had increases in urine calcium excretion, whereas others had decreases. Whether those variations were simply random changes, related to dietary changes, or individuals' responses to vitamin D was not clear. Because conversion of 25-OH-vitamin D to 1,25-OH-vitamin D by 1-hydroxylase is regulated, it isn't necessarily the case that vitamin D supplementation will lead to increases in urine calcium. Data regarding changes in urine calcium in response to seasonal sunlight exposure are quite equivocal in this regard. I favor supplementing such patients, emphasizing restriction of dietary sodium, and recommending measuring 24-hour urine calcium excretion for safety.

Dr. Alan Wasserstein. As you point out, potassium citrate could promote calcium phosphate stone formation by alkalinizing the urine and favoring conversion of monobasic to dibasic phosphate. What is the association constant (pK) of this reaction? Could appreciation of this association constant have clinical utility; *e.g.*, above what urine pH does this conversion become quantitatively less important?

Dr. Goldfarb. The pK of phosphate is 6.8, so it is reasonable to suggest that increases of urine pH to values higher than 6.5–7.5 will lead to greater conversion of monobasic to dibasic phosphate and increase risk of stones. Additional urine citrate excretion presumably helps prevent calcium phosphate and calcium oxalate stones, whereas urine alkalinization diminishes urinary calcium excretion. Therefore, it is certainly possible that citrate supplementation for prevention of recurrent calcium phosphate stones is effective and that its efficacy exceeds the risk. We are surprisingly short of good data about this question so uncertainty persists.

Dr. Gary Curhan. The presentation of this type of patient often raises the question of medullary sponge kidney. Is it important to make this diagnosis? If so, how

would you make the diagnosis? Would knowing that she had medullary sponge kidney affect your recommendations?

Dr. Goldfarb. The diagnosis requires administration of intravenous contrast, which occurs infrequently now in the management of renal colic. Although radiologists suggest the diagnosis based on the appearance of medullary calcification as seen on noncontrast computed tomography or even by ultrasound, I don't think these impressions have been validated. Since at present there is no specific stone-preventive therapy for the condition, appropriate treatment consists of responding to the urine chemistry, whether the dilated collecting ducts characteristic of medullary sponge kidney are present or not. I do not attempt to make the diagnosis in patients with a family history of medullary sponge kidney or for whom a radiologist has suggested the diagnosis.

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Disclosures

None.

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