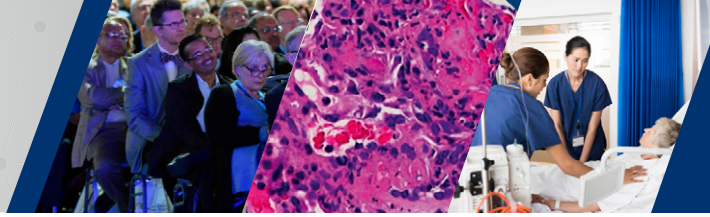

Recurrent Calcium Kidney Stones

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Patient 1

A 21-year-old man, a member of the track team, has his first kidney stone at college. Computed tomography showed a 4-mm obstructing distal ureteral stone and a nonobstructing 4-mm contralateral kidney stone. The stone passed: its composition was 100% calcium oxalate. Serum chemistry was normal with creatinine of 0.8 mg/dl.

Patient 2

A 27-year-old woman has spontaneously passed four hydroxyapatite (calcium phosphate) stones. Serum chemistries were normal. Two 24-hour urine collections were similar: urine volume was 1.7 L, calcium was 270 mg, oxalate was 37 mg, citrate was 390 mg, pH was 6.8, and sodium was 190 meq. Supersaturation of calcium oxalate was 8.87 and for calcium phosphate was 3.35.

Introduction

The prevalence of kidney stones is rising with a decreasing male-to-female ratio. Stones are associated with CKD, metabolic syndrome, hypertension, coronary artery disease, and reduced bone mineral density. Patients should understand stones as markers of metabolic imbalance, presaging other comorbidities. Therefore, prevention of stone recurrence offers an opportunity to avoid painful, expensive stone episodes, while improving overall health through dietary and pharmacologic interventions.

Most stones are composed of calcium oxalate and calcium phosphate. Both environmental and genetic factors contribute to their formation. Physicians should seek the phenotypes of rare, monogenic, autosomal recessive disorders. The presence of reduced GFR, abnormal serum electrolytes, hypercalcemia, and larger and more recurrent stone burdens should lead to more detailed evaluation and genotyping (1).

A history of diet, occupations, use of antibiotics, supplements, and athletic activities should be obtained. Females, especially younger individuals, have more calcium phosphate stones than males. Analysis of stone composition is inexpensive and rules out cystinuria, struvite, and uric acid stones, which require specific therapies.

Treatment

We engage in shared decision making with patients. They may regard kidney stones as an infrequent inconvenience or the worst sort of misery, affecting their choices to increase fluid intake, alter their diet, and take medications, potentially for the rest of their lives.

A useful tool to frame this discussion is the Recurrence of Kidney Stone Nomogram (2). Available as a mobile phone application, it identifies first-time stone formers at greatest risk for a second symptomatic episode.

Empirical Versus Targeted Therapy

Stone prevention prescriptions can consist of "empiric" recommendations or be on the basis of the results of 24-hour collections. Some believe that such collections are best utilized only for recurrent stone formers. The American Urological Association (AUA) recommends that: (*1*) "Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers," and (2) "Metabolic testing should consist of one or two 24 hours collections obtained on a random diet. . ." (3). Calculations of randomized controlled trial (RCT) saturation correlate with stone composition, and higher values are associated with more calcium stones (4). The results can focus patients on specific dietary manipulations and physicians on specific pharmacologic choices.

However, no RCT shows that managing patients based on 24-hour collections is superior to empirical therapy. The results may not reflect what patients usually drink or eat, and may differ during the week, as compared with weekends when they most commonly do the collections. Peaks of supersaturation that may occur after meals will be missed. The vast majority of stone formers do not have 24-hour collections performed, or prescribed, but the reasons for this omission are not clear (5).

Increasing fluid intake as empirical therapy is always appropriate. It is safe, inexpensive, effective, and proven by RCTs. We prescribe 96 ounces, or 3 L, per day. Most should be water, with limits on cola, but not coffee or alcohol. Many patients cannot achieve these intakes or have occupations, such as cab drivers and surgeons, that prevent high fluid intake or access

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to bathrooms. In such cases, more attention to dietary manipulation or medications is required.

Another empirical therapy is dietary manipulation following assessment of the patient's typical diet. Several choices exist, but the principles are similar. (*1*) The Borghi diet is the only one proven by RCT to prevent calcium stones in men (not women) with higher urinary calcium excretion: more dairy (more calcium), and less animal protein, sodium, and oxalate (6). Many patients are still told incorrectly, or intuit wrongly, that lower calcium intake is mandatory. (*2*) The Dietary Approaches to Stop Hypertension diet has not been tested in an RCT. However, people who adhered to the diet had fewer stones and lower urinary supersaturations (*7*). (*3*) As promoted by Dr. Fredric Coe (http://kidneystones.uchicago.edu/kidney-stone-book/), the US Dietary Guidelines for Americans 2015–2020 promotes health in general and, although not addressed specifically, would likely reduce stones (https://health.gov/dietaryguidelines/2015/guidelines/). These "healthier" diets will benefit metabolic syndrome, bone health, and stone disease.

We recommend: increasing dietary calcium intake to 3–4 portions a day; increasing fruits and vegetables, which contain citrate, potassium, and phytate; less dietary animal protein, sugar, and sodium; and elimination of supplemental calcium and vitamin C. Vegetarians may have calcium oxalate stones coinciding with higher spinach, soy, beans, and nut intake, without dairy intake to reduce intestinal absorption of oxalate. Urinary oxalate excretion may normalize if oxalate intake is reduced and concomitant dairy intake is encouraged. Water should also accompany higher oxalate-containing items.

Patient 1

This patient is a candidate for empirical therapy. His fluid intake is probably inadequate to his athletic pursuits and his diet likely contains higher sodium and animal protein content. By bringing water with him to activities, self-monitoring urine volume after exercise, and reducing excessive protein and sodium intake, his risk of stones might become negligible.

Pharmacologic Therapy

If diet fails, or is not chosen, thiazides and potassium citrate both prevent kidney stone recurrence. Thiazides reduce urinary calcium excretion by increasing both proximal and distal tubular reabsorption (8). Potassium citrate binds urinary calcium, inhibiting crystallization with oxalate and phosphate. Thiazides are effective even if urine calcium is not high, and citrate is effective if urinary citrate is not low. The relative benefit of these medications compared with dietary prescription is not known. Some patients are motivated to avoid medications and adhere to a strict diet, whereas for others it is impossible. A second, undecided issue is whether thiazides and potassium citrate have equipotent effects to prevent stones, or whether they are best prescribed concomitantly.

The choice between citrate and thiazides may be based on urine data, or on patient preferences. Both reduce calciuria, while increasing bone mineral density. Thiazides lower BP and reduce cardiovascular morbidity, particularly when prescribed with potassium supplements; amiloride and spironolactone can prevent hypokalemia and hypocitraturia. We usually use chlorthalidone 12.5 or 25 mg once per day, or indapamide 1.25 or 2.5 mg once per day; both are longer acting than hydrochlorothiazide. Indapamide may be less likely than chlorthalidone to lower BP (in normotensive people) and serum potassium. Potassium citrate is usually prescribed as 15–30 meq twice a day. We rarely prescribe allopurinol for calcium stone formers, except when other options are ineffective.

The Case for 24-Hour Collections

For patients with recurrent stones, and for those whose fluid intake and diet are not fixable or effective, 24-hour collections demonstrate specific metabolic abnormalities, whether urine chemistry has changed favorably, and whether patients are adherent to prescriptions. We repeat collections when prescriptions are changed, in combination with yearly (or more frequent) ultrasounds, to assess stone burdens. One compelling reason for doing 24-hour collections is to find cases of primary hyperoxaluria, which has a high incidence of kidney failure.

There is a continuous, not dichotomous, relationship between higher urinary calcium and oxalate and lower urinary citrate, and risk of stones. False threshold values for hypercalciuria, hyperoxaluria, and hypocitraturia may lead patients to be told their urine is "normal." Therefore the levels of calcium, oxalate, or citrate considered "abnormal" are arbitrary. If there is ongoing stone formation, the calcium supersaturation is too high and should be lowered. The AUA recommendation states: "Clinicians should offer thiazide diuretics and/or potassium citrate to patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists." (3).

Patient 2

This patient is typical of individuals with predominant calcium phosphate stones. They often have lower citrate excretion with higher urine pH, both of which promote calcium phosphate supersaturation. Normal serum bicarbonate concentration rules out renal tubular acidosis. The etiology of the higher urine pH is usually not identified. Copious fluid intake and sodium restriction are required. Increasing urine citrate by supplementation with potassium citrate may reduce the risk of calcium phosphate stones and outweigh the increased risk promoted by increased urinary pH (9). The net effect is no increase in supersaturation (10). There is a need for an RCT to evaluate this clinical conundrum. Treatment with concomitant thiazides regardless of calcium excretion may reduce any risk brought on by citrate supplementation.

Conclusions

Our approach to patients with recurrent calcium stones is to evaluate the risk of recurrence. Empirical prescription of fluids and diet may be highly effective. For motivated first-time stone formers, patients with more than one episode, or

higher risk, we recommend a 24-hour urine collection and more targeted dietary and pharmacologic stone prevention. We stress that a constructive conversation between the physician and patient leads to effective shared decision making.

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Disclosures

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