Metabolic Evaluation of First-time and Recurrent Stone Formers

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KEYWORDS

• Diagnosis • Calcium oxalate • Humans • Kidney calculi/urine • Nephrolithiasis • Uric acid • Urolithiasis

KEY POINTS

- Evaluation of stone formers should include careful attention to medications, past medical history, social history, family history, dietary evaluation, occupation, and laboratory evaluation.
- Kidney stones are associated with obesity, hypertension, and metabolic syndrome, and may be a harbinger of diabetes.
- Twenty-four–hour urine collections are most often appropriate for patients with recurrent stones or complex medical histories. They may be appropriate for some first-time stone formers, including those with comorbidities or large stones.
- Uric acid stones are usually associated with low urine pH, whereas calcium phosphate stones are most often associated with high urine pH. Very high urine pH suggests infection with urease-producing organisms.
- Young age and infrequent features, such as decreased glomerular filtration rate, proteinuria, or extremely high urine oxalate excretion, should lead to consideration of some rare genetic causes of stone disease, such as Dent disease and primary hyperoxaluria.

INTRODUCTION

Approximately 1 in 11 people in the United States will be affected by kidney stones at least once in their lifetime. The prevalence rate seems to continue to increase, as demonstrated by the National Health and Nutrition Examination Survey III cohort (1988–1994 and 2007–2010).[1] This increase in prevalence of kidney stones has also been seen globally. It may be attributable to changing dietary practices, increasing prevalence of diabetes and obesity, migration from cooler rural settings to warmer urban settings, and even global warming. These increasing prevalence rates are also associated with an increase in the cost of kidney stone management to an estimated $2.1 billion in 2000.[2,3]

The high cost of kidney stones and the associated social expenditures, such as missed work, play a role in medical decision making for both patients and physicians.[4] To decrease the cost and prevalence of kidney stones, it is important to provide patients with recommendations for

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prevention and control of kidney stone formation. Whether patients should receive a limited or a comprehensive metabolic evaluation regarding their kidney stone risk factors is a question frequently debated. With a relative lack of evidence-based guidelines for metabolic evaluation, it seems preferable to the authors to customize each patient's evaluation both to the individual patient's risk factors as well as other comorbidities. For instance, recent studies indicate that the prevalence of kidney stones is significantly associated with diabetes.[5] Recognizing the links between metabolic syndrome and stones allows the physician to highlight a stone as a harbinger of insulin resistance. To address these comorbidities, current recommendations include a change in diet, exercise, weight loss, and a shift toward more dietary calcium, fluids, and less sodium.[6,7] This article discusses the newest recommendations in the field for the metabolic evaluation of both first-time and recurrent kidney stone formers.

EVALUATION

The following discussion of evaluation applies both to first-time and recurrent stone formers. Much of these recommendations represent the practice of the authors and other lithologists and are not necessarily the result of high-grade evidence. Guidelines have been promulgated by the European Association of Urology[8] and by a consensus panel of the National Institutes of Health[9] and are not necessarily out of date.[10] Guidelines are likely to be formulated by the American Urological Association in collaboration with the American Society of Nephrology in the coming year.

HISTORY

The past medical history, family history, and social history are all essential to determine risk factors for each patient after a first stone is passed. These histories are predictors of future recurrent stones and can help to draw conclusions that will aid in behavior modification and metabolic evaluation.

Past Medical History

Stones can be associated with a variety of medical conditions. Gastrointestinal (GI) abnormalities, like chronic inflammatory bowel disease or chronic diarrhea, can cause low urine volume and acid urine pH, which are risk factors for uric acid stones, and hypocitraturia or hyperoxaluria, which are risk factors for calcium oxalate stone formation.[11] Ileal resection caused by GI tract abnormalities is a common cause of kidney stones and can be associated with chronic kidney disease; therefore, a comprehensive evaluation is necessary after the first stone. Other pertinent surgical history includes bariatric surgery. Patients with Roux-en-Y bypass are at risk for hyperoxaluria, metabolic bone disease, and nephrolithiasis.[12] A history of gallstone disease and high serum triglycerides is also associated with kidney stones, although the pathophysiology is uncertain.[5] Sarcoidosis leads to hypercalciuria and hypercalcemia.

Hypertension and diabetes are often associated with metabolic syndrome, whose features include abdominal obesity and insulin resistance. Metabolic syndrome is associated with an increased risk of uric acid stone formation caused by the associated unduly acid urine caused by insulin resistance.[12,13] These disorders might also be associated with more calcium oxalate stones because a greater body mass index is associated with greater urinary oxalate excretion.

Chronic kidney disease is probably associated with a reduction in stone risk because of the urinary concentration defects and the reduction in urine calcium excretion as the result of secondary hyperparathyroidism. However, some kidney diseases are associated with stone disease, such as polycystic kidney disease and medullary sponge kidney. Sjögren syndrome and other tubulointerstitial nephritides are associated with stones as the result of renal tubular acidosis (RTA).

A full list of current and past medications and supplements will be useful in the differential diagnosis of stone formation and will provide information about comorbidities. Certain medications can increase kidney stone recurrence risk. These medications include some protease inhibitors for human immunodeficiency virus (HIV), such as atazanavir; carbonic anhydrase inhibitors (acetazolamide, topiramate); triamterene; and felbamate an antiepileptic medication.[14] Supplements that may increase patients' risk include vitamin C and calcium supplements.[15–17] On the other hand, vitamin B6 and dietary calcium do not increase the risk for kidney stones and may help reduce the risk. Vitamin D does not seem to affect 24-hour urine calcium excretion and has not been shown to increase the risk of stones.[18]

Family History

A family history of kidney stones may suggest further evaluations. Twin studies demonstrate higher concordance for stones among monozygotic twin pairs compared with dizygotic twins, leading to an estimate that 56% of the stone phenotype is attributable to genetic factors.[19] However, the genetic basis for this strong genetic

influence remains uncertain, and genetic testing is almost never part of a clinical evaluation. The exception is genotyping for primary hyperoxaluria and Dent disease in appropriate circumstances (see later discussion). Because these disorders have autosomal recessive inheritance, family history will be negative. Infrequently, autosomal-dominant polycystic kidney disease can be associated with stones and be diagnosed via any renal imaging study. RTA may also be familial and may be associated and present with stones.

Social History

Social history, particularly occupational history, is another important component of the evaluation. Patients with professions that do not allow frequent hydration or use of toilet facilities have a decreased urine output and are susceptible to stone formation. Some examples of these occupations include professional drivers (cargo transporters, taxicab drivers, chauffeurs) and primary school teachers. People who live in climates with elevated temperatures, where patients are prone to water depletion, may also have difficulty maintaining a dilute urine. Examples include people with patients in construction, athletics, or other outdoor professions. Knowing a patient's occupation can provide insight into recommendations that will keep the patient hydrated and urine dilute with a high volume.

Diet History

Understanding a patient's diet will allow one to understand possible risk factors for stone formation and then to prescribe dietary modifications to prevent recurrent stone formation. A diet high in salt contributes to excessive calcium excretion. Young people particularly have less control of their diets and often ingest more processed and packaged foods high in sodium content. Often people are unaware of their high sodium intake until it is revealed by 24-hour urine collections. Animal protein (not just beef as many lay people think) can cause hypercalciuria, hyperoxaluria, and hyperuricosuria—all factors increasing the risk of calcium kidney stone formation and often contributing to stones in athletes and body builders. Protein also increases net acid excretion and contributes to the low urine pH of uric acid stone formers. The Atkins diet and other high-protein diets are not recommended as weight loss regimens for patients with kidney disease (unless, perhaps, potassium citrate is prescribed).[20]

More grapefruit juice consumption is associated with a higher risk for stones in both men and women for unclear reasons, and beverages high in fructose are also associated with stones.[21–23] Dietary oxalate content can be assessed by asking about the ingestion of nuts, dark greens (particularly spinach), concentrated and dried fruits, and chocolate. Low dietary calcium intake is consistently associated with more stones, perhaps because it allows more dietary oxalate to be absorbed by the intestine.[24,25] Although vegetarians may have higher urinary oxalate excretion, they have fewer stones because they have higher urine volume and urinary citrate excretion.[26]

The Dietary Approaches to Stop Hypertension (DASH) diet is high in fruits and vegetables, moderate in low-fat dairy, and low in animal protein.[27] The diet also contains sources of oxalate, such as nuts, legumes, and whole grains; but its variants include reduced intake of sodium, sweetened beverages, and red and processed meats.[28] A high DASH score is associated with a reduced risk of kidney stones.[28]

PHYSICAL EXAMINATION

Although kidney stones have no specific manifestations on physical examination, a full physical examination is important in patients with renal colic for ruling out other conditions. Because of the correlation between hypertension and stone formation, blood pressure (BP) should be measured during the physical examination.[29] High blood pressure is a significant predictor of kidney stone morbidity.[5] If treatment with thiazide-like drugs is contemplated, monitoring BP will be important.

LABORATORY EVALUATION

The most crucial component of a patient's evaluation is the laboratory evaluation of blood and urine. **Box 1** includes the relevant tests.

Blood Tests

A basic metabolic panel should be obtained for all stone formers. In addition to this routine chemistry test, measurement of serum phosphorus and uric acid may also be useful. Kidney function is assessed at baseline and over the years of the patient's history of stones. Correlations between decreases in estimated glomerular filtration rate and kidney stones have been demonstrated, although the nature of this relationship is not well established.[30] The decreased glomerular filtration rate associated with stones could be caused by the stone disease itself, for instance, caused by nephrocalcinosis; to recurrent episodes of ureteral obstruction; or to repeated urologic interventions.

Box 1
Laboratory evaluation of nephrolithiasis

Stone composition by x-ray crystallography or infrared spectroscopy

Serum chemistry

Calcium

Glucose

Sodium

Potassium

Chloride

Bicarbonate

Blood urea nitrogen

Creatinine

Phosphorus

Uric acid

Intact parathyroid hormone (if high normal to high serum calcium)

25-hydroxy-vitamin D (if low urine calcium or serum calcium)

Urinalysis

pH

Specific gravity

Protein

Microscopic

24-hour urine

For patients with recurrent stones

Some first-time stone formers

As glomerular filtration declines, risk may also decrease. Electrolytes are evaluated because hypokalemia and hypobicarbonatemia are features of RTA. Therapy with thiazides and potassium citrate will also require periodic monitoring of electrolytes.

If serum calcium levels are borderline or elevated (greater than 10.0 mg/dL, especially if hypercalciuria is present), measurement of the intact parathyroid hormone (PTHi) level is recommended to rule out primary hyperparathyroidism as a contributing cause for stone formation. Hypophosphatemia may also be present. Primary hyperparathyroidism may be present if both serum calcium and PTHi are at the high ends of their normal ranges, in which case ionized calcium may help confirm the diagnosis.[31] However, secondary hyperparathyroidism should be suspected if PTHi is high and serum calcium is at the low end of the normal range. This situation should be suspected if urine calcium is low or bone mineral density (BMD) decreased, in which case the measurement of 25-hydroxy-vitamin D may be indicated.

A uric acid measurement may be useful in managing associated gout; when prescribing xanthine dehydrogenase inhibitors, allopurinol or febuxostat; and in monitoring therapy with thiazides.[32,33]

Hypophosphatemia may suggest not only hyperparathyroidism but also phosphaturia related to mutations in proximal tubular phosphate reabsorption.[34] A measure of glucose and hemoglobin A1c can sometimes detect previously unrecognized diabetes, another risk factor for stone formation, which has health implications far beyond those of nephrolithiasis.[35]

Urine Tests

Urinary tests for all stone formers should begin with urinalysis. The specific gravity, urine pH, and presence of protein, blood cells, or bacteria will aid in the differential diagnosis of the causes of kidney disease and renal colic. A urine sediment may reveal crystals and may lead to the recognition of drug-induced crystalluria.[14] Uric acid crystals are seen in acidic urine, usually 5.5 or less, and calcium phosphate crystals in more alkaline urine, usually 6.5 to 7.0; identification can be aided if crystals are dissolved or precipitated by manipulating the urine pH *ex vivo*. Besides infection with urease-producing organisms, higher urine pH may be associated with distal RTA. Hexagonal crystals are pathognomonic for cystinuria. Struvite crystals are associated with organisms, such as *Proteus*, which produce urease and lead to high urine pH (7–9) and are a rectangular coffin-lid shape. Calcium oxalate dihydrate crystals are a tetrahedral envelope shape, whereas the monohydrate is often described as dumbbells. Urine culture should also be obtained to test for bacteria, pyuria, and infection.

Twenty-four–Hour Urine Collections

The difference in the evaluation of first-time versus recurrent stone formers has long centered on the appropriate application of 24-hour urine collections. Some reviews and consensus statements have suggested that the tests are appropriate and cost-effective only for recurrent stone formers.[9,36] The authors do not disagree with this recommendation. It is true that the frequency of recurrence and metabolic activity of stone formation cannot be judged in first-time stone formers who present with a solitary stone. It is also clear from the authors' clinical experience that most first-time stone formers, particularly younger people, are reluctant to adhere to recommendations regarding dietary manipulation or prescription of drugs. In such

cases, generic recommendations to increase fluid intake to 3 L/d may suffice if other comorbidities discussed earlier are absent.

However, there are other people with stones who might warrant the more thorough evaluation that includes 24-hour urine collections. Perhaps people presenting with larger stones, stones requiring a trip to the operating room, or older people with other comorbidities, such as heart disease or warfarin use, should have a more detailed evaluation. Such patients are among the ones most motivated to prevent stones and can best do so when presented with the results of their own risk assessments and corresponding prescriptions, not simply the generic advice proffered to most stone formers. The European Association of Urology prescribes 24-hour collections in complicated patients: those with multiple stones or other risk factors for recurrence.[8]

In any case, it is important to emphasize that today there remains a surprising dearth of data demonstrating that prescribing preventative regimens based on urine collections is superior to offering generic advice not specific to the individual. Despite that lack of evidence, it seems evident to the authors that 24-hour urine collections are a useful tool for understanding each patient's specific urine composition to access the risk factors for recurrence and make recommendations for prevention. Spot urine collections are not as accurate because of the daily variability of urine composition caused by dietary and other circadian variations throughout the day but may be useful when 24-hour collections are not possible.[37]

Urine collections are usually performed on the patients' self-selected diets. The analytes measured should include calcium; oxalate; phosphate; urate; urine volume; pH; and measures revealing dietary intake of sodium, potassium and protein. Based on the results, a laboratory specializing in the assessment of stone risk can calculate supersaturation of crystal-forming phases, so that changes in multiple urinary variables can be translated into a single number correlating with the stone risk. Stone composition usually correlates with urinary supersaturation.[38] For patients with hypercalciuria, protocols used in the past to classify the cause of the abnormality and then treat based on the results have not been shown to lead to a superior method of stone prevention, are costly and unwieldy, and are, therefore, not recommended.

At least two 24-hour urine collections should be completed before treatment is prescribed because of the additional diagnoses that multiple collections reveal.[39] Additional 24-hour urine collections should be performed 4 to 6 weeks after any prescribed intervention to judge efficacy and provide patients with feedback regarding achieved success in making modifications. Laboratories that specialize in evaluating patients with stones may perform a qualitative screen for cystine for all patients new to the laboratory.

In **Box 2**, the authors briefly explicate the results of these collections. For further discussion, the reader is referred to articles in this volume regarding corresponding dietary and pharmacologic therapy.

IMAGING

Every patient presenting with kidney stones should have, if not done previously in an emergency department, an imaging study to determine the stone burden present.[45] This counting will be useful in following stone disease and judging whether prevention regimens have been successful, in ensuring that other stones do not warrant urologic intervention, in demonstrating that hydronephrosis has resolved, and to rule out polycystic kidney disease or other anatomic variants. Most often, computed tomography is done during emergency department visits. Although ultrasound is less sensitive and specific for stones than computed tomography, it is less expensive and does not result in exposure to radiation; therefore, it often suffices for periodic follow-up. Plain radiography is very inexpensive and entails very-low-dose radiation and may be appropriate when a known calcium stone, large enough to appear on the film, is being followed. The authors usually repeat ultrasound or plain radiography at yearly intervals for a few years after an episode of symptomatic obstruction and continue indefinitely only if metabolic activity persists.

Medullary sponge kidney is not an uncommon cause of stones and nephrocalcinosis. However, as radiocontrast administration is now relatively infrequent in stone formers, the diagnosis is likely to be made much less often.[46] It can be suspected when family members are affected and nephrocalcinosis is demonstrated. Because the disorder has no specific therapy other than addressing urine chemistry, contrast administration to find it is not recommended.

STONE COMPOSITION

Composition of stones should always be determined by x-ray crystallography or infrared spectroscopy. Both tests are relatively inexpensive and can lead to important diagnoses, especially in detecting unusual causes of stones, such as

Box 2
Twenty-four–hour urine variables

Variables directly affecting supersaturation of stone-forming salts

Calcium: A clear demarcation of hypercalciuria cannot be clearly drawn. Risk of stones increases with increasing urine calcium excretion, even at values less than traditionally considered hypercalciuria.[40] Variations in urine calcium often correlate with urine sodium excretion and may correlate less with dietary calcium.

Oxalate: As with calcium, risk for stones increases with increasing oxalate excretion even at levels considered normal.[41] Dietary oxalate is only one determinant of urine oxalate excretion, with influences of body size, calcium intake, and colonization with *Oxalobacter formigenes*.

Volume: Low urine volume (<2 L) is often related to occupation, activities, and perceived thirst.

pH: Persistently low urine pH (<5.8) is commonly associated with uric acid stones and hypocitraturia.[42] Higher urine pH (>6.2) is commonly associated with calcium phosphate stones and RTA.[43] Values greater than 8.0 may suggest infection with urease-producing organisms.

Uric acid: Hyperuricosuria may be a risk factor for calcium stones, although contributes less strongly than pH to uric acid stones, and is usually the result of increased ingestion of animal protein.

Citrate: Hypocitraturia results from increased acid load, such as that resulting from increased animal protein intake or metabolic acidosis, but may also be hereditary.[44]

Dietary variables affecting relevant urine chemistries

Sodium: Increased salt intake is endemic in the Western world and often is far beyond what patients imagine they are eating. It is an important variable contributing to increased calcium excretion.

Urea, sulfate: These variables reflect animal protein intake. Urea can be used to calculate protein catabolic rate to estimate protein intake. Sulfate is a correlate of dietary acid ingestion and usually approximates urine ammonium, unless nondietary causes of metabolic acidosis, such as diarrhea, are present.

Phosphorus: Excretion of phosphorus is related to dietary animal protein as well as diary intake. Whether reduction of phosphorus intake is specifically useful for stone prevention is not known.

cystinuria or crystallization of drugs. Prescription of citrate for stone prevention can occasionally lead to increases in urine pH and might change calcium oxalate or cystine stone formers into calcium phosphate stone formers. This phenomenon is relatively infrequent because citrate prevents calcium phosphate precipitation and lowers urine calcium, but vigilance for this transformation should be maintained.[43]

EVALUATION OF BMD

For patients with hypercalciuria and calcium stones, measurement of BMD may be useful. The strong link between hypercalciuria, low BMD, and increased fracture rate leads to the consideration of performing dual-energy x-ray absorptiometry in such patients.[47,48] Highlighting this relationship may be of particular significance in postmenopausal women with stones who have not had BMD assessed previously. However, this relationship is also present in men. Calculation of bone fracture risk using the FRAX® tool (www.shef.ac.uk/FRAX) may also be useful. The FRAX score incorporates both the patient's risk factors and BMD to determine the 10-year probability of a fracture. Common risk factors that affect fracture risk are age, gender, history of fracture, alcohol use, smoking, and low body mass index. The authors find that describing these links often offers patients additional motivations to increase dairy intake or take thiazides. The latter drugs reduce urine calcium excretion and are associated with the prevention of recurrent stones as well as increased BMD and reduced fracture rates.[49] Bisphosphonates may also reduce urine calcium excretion and prevent stones, although the evidence of this effect is less clear.[50] However, the possibility of prescribing these drugs when osteoporosis is found constitutes an indication for measuring BMD in stone formers.

DETECTION OF UNUSUAL CAUSES OF STONE DISEASE

As the pathophysiology and genetics of kidney stone disease are uncovered, it has become clear that some cases of genetic nephrolithiasis are escaping detection because of a lack of familiarity of clinicians with their presentations. The Rare Kidney Stone Consortium (see www.rarekidneystones.org) has been highlighting this deficiency to improve

diagnosis of cystinuria, primary hyperoxaluria, Dent disease, claudin mutations, and adenine phosphoribosyltransferase deficiency (a cause of dihydroxyadenine stones).[51] Stone composition is always important, but young age, decreased glomerular filtration rate, proteinuria, and extremes of oxaluria are among the variables that should lead to more complete evaluation.

SUMMARY

Kidney stones are preventable. To maximize the efficacy of preventative regimens, the appropriate data need to be gathered. A thorough history should be directed toward assessing the past medical history, social history, occupation, activities, family history, and diet. Stone composition is always appropriate. Laboratory evaluation requires serum chemistries and urinalysis. Twenty-four–hour urine collections are most appropriate for recurrent stone formers; but some patients who are motivated to prevent recurrence and have large or complicated stones that required urologic intervention might also be appropriate candidates for complete metabolic assessment. The links between metabolic syndrome, hypertension, and obesity and stones suggest that stones may be a harbinger of important morbidity, particularly an increased risk of diabetes.

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