Evaluation of the Kidney Stone Patient

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Summary: Kidney stones are one of the most common chronic disorders in industrialized countries. In patients with kidney stones, the goal of medical therapy is to prevent the formation of new kidney stones and to reduce growth of existing stones. The evaluation of the patient with kidney stones should identify dietary, environmental, and genetic factors that contribute to stone risk. Radiologic studies are required to identify the stone burden at the time of the initial evaluation and to follow up the patient over time to monitor success of the treatment program. For patients with a single stone an abbreviated laboratory evaluation to identify systemic disorders usually is sufficient. For patients with multiple kidney stones 24-hour urine chemistries need to be measured to identify abnormalities that predispose to kidney stones, which guides dietary and pharmacologic therapy to prevent future stone events.

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Urolithiasis is one of the most common disorders of the urinary tract. Approximately 12% of men and 6% of women in the United States will have at least one kidney stone during their lifetime.[1] In fact, recent studies have shown that the prevalence of kidney stones in industrialized societies is increasing, likely because of dietary changes and the increasing rate of obesity. Once an initial stone has formed, more than 50% of patients will form additional stones over the next 10 years, with some patients forming multiple kidney stones.[2,3] The medical evaluation of the kidney stone patient is focused on identifying abnormalities of urine composition that cause stone formation. Urine composition can be affected by systemic disease, dietary habits, environmental factors, and genetic traits. Once urine risk factors have been identified, the clinician can formulate a selective therapeutic plan aimed at that patient's specific metabolic problem. This article reviews the evaluation of the kidney stone patient to prevent recurrent stone formation.

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HISTORY

When obtaining the medical history, it is helpful to quantify the number of stones and the duration of stone disease. Knowing the rate of stone formation (stones/year) will allow clinicians to gauge the success of their therapeutic interventions. In addition, the stone formation rate will guide the aggressiveness of the medical intervention; a patient who passes stones monthly likely will require more aggressive therapy than a patient who is forming stones once every few years.

The medical history also should identify other comorbid conditions such as urinary tract infection, bowel disease, and diseases that alter calcium homeostasis, all of which can affect stone risk. Urinary tract infection may be the result of stone disease, particularly from recurrent instrumentation of the urinary tract. However, recurrent infection also can be the cause of stones. If a patient has a urinary tract infection with *Proteus* or *Klebsiella* species, which likely possess the enzyme urease, then struvite (magnesium ammonium phosphate) kidney stones are likely.[4] This is a common problem in patients requiring chronic indwelling or inter-

mittent catheterization. Bowel disease is a common contributor to kidney stone formation as well. Chronic diarrhea leads to loss of fluid and alkali from the gastrointestinal (GI) tract, which results in low urine flow rates, hypocitraturia, and acidic urine; these factors enhance the risk of both calcium oxalate (CaOx) and uric acid stone formation.[5] Patients with an ileostomy are particularly prone to these problems. Patients who have extensive small-bowel disease or multiple small-bowel resections, leading to fat malabsorption, may develop hyperoxaluria and CaOx stones.[6] Bariatric surgery also has been shown to cause hyperoxaluria and nephrolithiasis[7] (see the article by Lieske et al in this issue, p. 163). Any disorder than can cause hypercalciuria may lead to nephrolithiasis. Certainly, primary hyperparathyroidism is well known to be a cause of kidney stone disease, accounting for 2% to 5% of stone formers referred to kidney stone centers.[8,9] Other mineral disorders that cause overproduction of calcitriol, such as sarcoid and other granulomatous diseases, can lead to hypercalciuria and stone formation.

Environmental Factors

The major environmental factors to be identified as stone risk factors include heat exposure, employment, and exercise. Heat exposure is a well-recognized risk factor for stone disease. Epidemiologic data from the United States show a greater incidence of nephrolithiasis in the Southern states, which of course have the highest mean temperatures.[10,11] The southeastern United States has the highest stone formation rate, and often is referred to as the "stone belt," although it is likely that other factors such as diet also play a role in stone risk because the stone rates are higher than equally hot areas in the southwest portion of the United States. The importance of environment is highlighted in a recent study of stone formation in US military personnel deployed to the hot, arid climate of southwest Asia.[12] The mean time to a symptomatic stone event, in 182 previously healthy soldiers who formed stones, was 93 days after arrival to the new environment. Stones may become symptomatic long after they formed. In addition to the patient's current area of residence, past habitats should be considered in assessing stone risk. A patient who had lived in a hot, dry environment may no longer have the same risk for recurrent stones after moving to a more temperate area.

A patient's employment can influence stone risk owing to effects on insensible water loss or alterations in fluid intake. If the employment environment is hot, then stone risk will be higher. Borghi et al[13] investigated the effect of work environment by determining the prevalence of nephrolithiasis for men employed in a glass factory in Italy. They found that men working in the area of the glass furnace were 3.5 times more likely to have stones than an age- and weight-matched group of men working for the same company in a climate-controlled environment. Employment also can influence stone risk by altering fluid intake. Some jobs limit the availability of water, but just as likely an occupation will limit the availability of toilet facilities, leading patients to reduce liquid intake to keep urine volume low. Leisure time activities also can play a significant role in stone risk. Patients who engage in vigorous exercise or any outdoor activity in the summer months may dehydrate themselves regularly, leading to highly concentrated urine.[14]

Diet

A patient's diet will greatly influence their urine chemistries and their risk of kidney stones. Although low-calcium diets once were commonplace in the treatment of kidney stones and high calcium intake was thought to be a risk factor, recent epidemiologic data have suggested otherwise. In 3 large prospective cohort trials, Curhan et al[15-17] found that subjects with the highest dietary calcium intake (>1,100 mg/d) had the lowest rate of forming an incident kidney stone. The mechanism for the reduction of kidney stone risk by high calcium intake has not been determined definitively. Calcium intake can be assessed quickly by quantifying intake of dairy products in the diet. Patients who are on a chronic low-calcium diet not only may increase their stone risk, but also the risk of osteopenia. Alternatively, excessive dietary calcium can increase kidney stone risk by increasing intestinal calcium absorption, leading to hypercalciuria. A calcium intake of

1,000 to 1,200 mg/d seems a reasonable compromise in kidney stone patients.

Oxalate in the urine is derived from endogenous production of oxalate and from absorption of oxalate from foodstuffs. Approximately 30% to 50% of urine oxalate is of dietary origin on a normal diet.[18] Because oxalate is an endproduct of human metabolism, the net oxalate absorbed from the intestine must be excreted via the kidney. Urine oxalate can increase significantly as diet oxalate content increases. A thorough history of a patient's intake of high-oxalate foods, both frequency and amount, may provide important insight into the cause of a patient's kidney stones. Food oxalate content is available from numerous sources.[19,20]

An estimate of fluid intake should be obtained from the patient as well as the types of fluids they consume. Epidemiologic studies have suggested that some beverages confer greater protection against kidney stones than others.[21,22] Regular ingestion of coffee, tea, beer, and wine were associated with a lower incidence of forming an incident stone. Whether specific beverages are beneficial in preventing recurrent stones is not known. Of interest, daily consumption of grapefruit juice was associated with an increased risk of stone formation. Although the mechanism of this association is not known,[23] it is prudent to discourage regular consumption of grapefruit juice in patients with kidney stones.

Excessive dietary intake of animal protein and sodium affects urinary stone risk factors. The increased metabolic acid load from protein lowers urine pH, increasing risk of uric acid stones, and also lowers urine citrate excretion, increasing CaOx stone risk.[24] Protein loads will increase urine calcium excretion, a further risk for CaOx stones.[25-27] In addition, purine intake tends to correlate with protein intake, so high-protein diets may lead to hyperuricosuria. A reasonable goal for protein intake is 1 to 1.2 grams of protein per kg body weight. The level of sodium intake plays a significant role in determining urine calcium excretion, and patients with hypercalciuria may be more sensitive to the calciuric effects of high sodium intake.[28-30] Diet sodium intake often is difficult to quantify from history. Patients who add salt to food after it is prepared invariably have excess sodium in their diet. Easily identified high-sodium foods include canned foods, prepared meats, and frequent consumption of restaurant meals. Urine chemistries also can be helpful in assessing dietary habits of patients, particularly sodium and protein intake, and should be used in conjunction with the history to estimate the impact of diet on stone disease.

Family History

Although diet and environment clearly play a role in stone formation, there is a strong genetic component as well. Stone formers are more likely to have first-degree relatives with kidney stones than are non–stone-forming patients.[31] Hypercalciuria is familial because it is found in 50% of first-degree relatives of patients with hypercalciuria.[32] Although the inheritance pattern has similarities to an autosomal-dominant pattern, it likely is inherited as a polygenic trait.[33] For other stone risk factors, such as citrate and oxalate, inheritance patterns are less clear. There are a number of uncommon monogenic disorders that include nephrolithiasis as part of the phenotype. Primary hyperoxaluria is inherited as an autosomal-recessive disorder and will show a horizontal inheritance pattern with siblings being affected but neither parent with disease (see the article by Bobrowski and Langman in this issue, p. 152). Cystinuria may be inherited as a recessive disorder but it also may present as autosomal dominant with incomplete penetrance (see the article by Mattoo and Goldfarb in this issue, p. 181). It usually presents within a generation but if it is the autosomal-dominant form, parents or children of a proband may have the stone phenotype. Distal renal tubular acidosis can be inherited as either autosomal dominant or recessive and includes nephrolithiasis as part of the phenotype.[34] Finally, a strong family history of kidney stones and renal failure in males within a family tree suggests Dent disease, a disorder characterized by hypercalciuria, low-molecular-weight proteinuria, and renal disease, which is inherited as an X-linked recessive trait in which the women in a family are asymptomatic carriers and the men have the disease.[35]

Table 1. Medications That Cause Nephrolithiasis

Drugs That Crystallize	Drugs That Cause Metabolic Stones
Triamterene	Calcium supplements
Protease inhibitors	Vitamin D supplements
Indinavir	Carbonic anhydrase inhibitor
Atazinir	Acetazolamide
Nelfinavir	Topiramate
Antimicrobials	Laxatives
Sulfonamides	Probenecid
Quinolones	Ascorbic acid
Guaifenesin	Alkali
Ephedrine	
Allopurinol (oxypurinol)	
Antacids	
Magnesium trisillicate	
Aluminum hydroxide	

Medications and Supplements

A thorough survey of current and past medications, vitamins, and supplements taken by the patient is critical to identify modifiable stone risks. Medications and supplements can increase stone risk by either altering urine chemistries to promote stones or by crystallizing in the urinary tract (Table 1). Medications that alter urine chemistries often affect renal tubular function. A prime example is carbonic anhydrase inhibitors, which cause abnormalities in renal acidification and increase the risk of calcium stones, particularly calcium phosphate stones. Carbonic anhydrase inhibitors will lower urine citrate, increase urine pH, and increase urine calcium excretion.[36] Topiramate, which is used to treat epilepsy and migraine headaches, has significant carbonic anhydrase activity and has been linked to stone formation in a number of studies.[37,38] Vitamin C can be metabolized to oxalate and therefore has been suspected to be a risk factor for stone formation. However, there are conflicting reports as to the extent of oxalate formation during vitamin C therapy.[39-41] In general, it is wise to limit ascorbic acid intake to no more than 500 mg/d in kidney stone patients. Calcium supplements will increase urine calcium and one epidemiologic study suggested that calcium supplements may increase stone risk.[16] In addition, a recent trial of vitamin D and calcium supplements to reduce bone loss and fractures in women showed that the women randomized to calcium supplements had higher rates of stone formation.[42] It has been postulated that risk will not be the same if calcium supplements are taken with meals to slow their absorption and to get the benefit of reduced oxalate absorption, but this theory has not been tested rigorously.

Some drugs have low solubility in urine and may form a pure stone composed only of the drug or its metabolites, or the drug may be incorporated as a component of more routine stones such as CaOx. Protease inhibitors used for human immunodeficiency virus (HIV) have been associated with stone formation.[43,44] Dehydration and volume depletion frequently seen in HIV patients as a result of chronic diarrhea and fever enhance the risk for crystallization of these drugs. However, Nadler et al[45] have shown that a significant number of stones from HIV patients on indinavir are not composed of the drug and likely are related to other metabolic causes.[45] It is important to determine the composition of stones in patients with HIV to prevent an unnecessary change in antiretroviral therapy. Over-the-counter preparations also may lead to stone formation. Both guaifenesin and ephedrine have been found to crystallize and cause kidney stones when taken chronically in high doses.[46,47] Finally, mention must be made of triamterene, a potassium-sparing diuretic that can crystallize in the urinary tract.[48,49] It often is used as a combination pill with hydrochlorothiazide (Dyazide, GlaxoSmithKline, Research Triangle Park, NC) and therefore it is easy to overlook in a patient's list of medications. It also is important to avoid prescribing Dyazide as a treatment for hypercalciuria because of the risk of triamterene crystallization. Other potassium-sparing drugs, such as amiloride, are preferred if needed to control potassium wasting from diuretic therapy in a kidney stone patient. A comprehensive review of drug-induced nephrolithiasis was published recently by Daudon and Jungers.[50]

RADIOLOGY

Most patients will have had a radiologic evaluation when presenting with their first episode of renal colic. A helical computerized tomography (CT) scan of the abdomen and pelvis is now the standard radiologic study for a patient suspected of having renal colic. The advantages of CT are that it does not require radiocontrast, it can identify stones smaller than often seen with an abdominal radiograph or ultrasound, all stones are radio-opaque, and it allows diagnosis of other causes of abdominal pain if stones are not present.[51,52] CT has been shown to have a higher sensitivity and specificity in detecting renal stones than abdominal radiograph and ultrasound.[53,54] CT scan is significantly better than ultrasound in the detection of stones in the ureter. Reduced-dose CT scans have been shown to be accurate in detecting nephrolithiasis, but with much lower radiation exposure for the patient.[54]

If a patient who has passed a stone presents for a medical evaluation without any radiographs having been performed, then some form of kidney imaging needs to be performed to determine the number of stones present in the urinary tract because the distinction of single versus multiple stones will determine the extent of metabolic evaluation the patient requires. CT is the gold standard for the detection of stones, but cost and radiation exposure may make radiographs and ultrasound reasonable alternatives in certain situations.[55] Ninety percent of stones will be radio-opaque on an abdominal radiograph, although small stones may be missed. Ultrasound can detect all types of stones, shown as echogenic images with back shadowing. An advantage of using ultrasound is that it does not expose the patient to radiation, which makes it the preferred test in pregnant women and may make it a useful study in patients who are expected to require frequent imaging.

In addition to differentiating single versus multiple stone formers, the radiologic evaluation is important in charting the success of therapeutic interventions to prevent new stones. Once dietary or pharmacologic therapy is initiated, the goal of therapy is to prevent new stones from forming and pre-existing stones from growing. Serial radiographs are required to determine if stones are growing, but, more importantly, any time a patient passes a stone it must be determined if the stone is new or if the patient is passing a pre-existing stone. If the stone is old, then there may be no reason to alter medical therapy. This knowledge also must be imparted to the patient, lest they become discouraged and give up on what may be an effective treatment regimen.

LABORATORY EVALUATION

In a patient with a single kidney stone, a limited work-up has been recommended by the last National Institutes of Health nephrolithiasis consensus conference.[56] The evaluation should include serum electrolyte levels to evaluate for RTA, creatinine level to assess renal function, and calcium level to screen for hyperparathyroidism. If a stone has been captured, crystallographic stone analysis should be performed. Optical microscopy, infrared spectroscopy, or radiograph crystallography all are acceptable methods for stone analysis. Although most stones are CaOx, crystallographic stone analysis allows identification of the less common stones such as cystine and struvite that require different evaluation. Also, stone analysis is the only way to diagnose stones composed of drugs (Table 1) and the very uncommon stones such as 2,8-dihydroxyadenine stones. A urinalysis should be obtained to screen for possible infection, and if pyuria or other findings indicative of infection are present then a urine culture should be performed. Urinalysis also provides an opportunity to evaluate crystalluria (Fig. 1). Although calcium crystals are more numerous and larger in stone formers than in normal subjects, the identification of CaOx and calcium phosphate crystals by itself has no diagnostic significance. Uric acid crystals also may be seen in normal subjects and stone formers, and usually form in acidic urine. However, the finding of cystine or struvite crystals is always abnormal and provides a diagnosis even in the absence of a stone analysis. If a stone analysis is not available, a qualitative screen for cystinuria should be performed to rule out this potentially devastating disease because treatment needs to be initiated after the initial stone

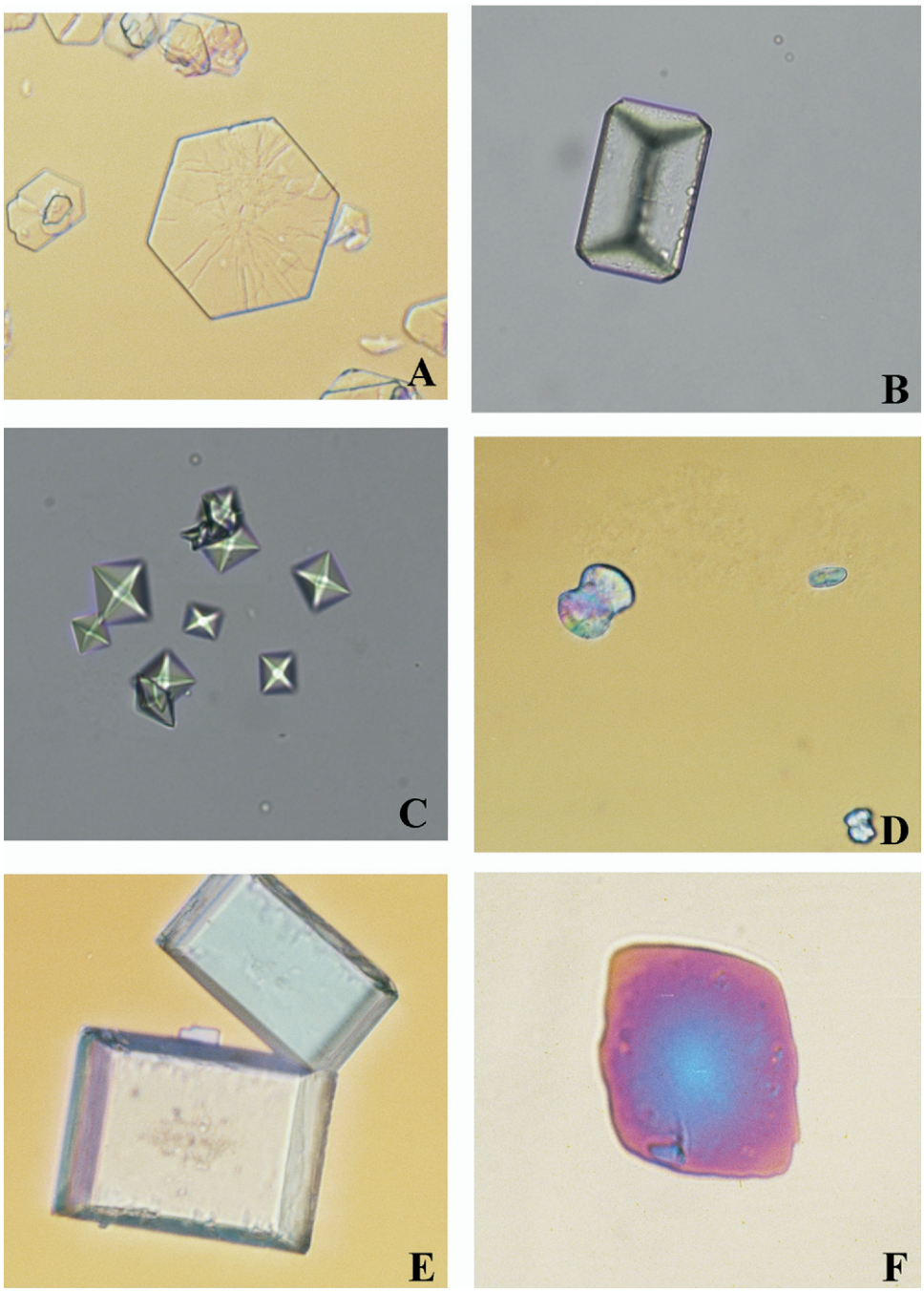

Figure 1. Light microscopy of urine crystals. (A) Hexagonal cystine crystals (200×); (B) coffin-lid–shaped struvite crystals (200×); (C) pyramid-shaped calcium oxalate dehydrate crystals (200×); (D) dumbbell-shaped calcium oxalate monohydrate crystal (400×); (E) rectangular uric acid crystals (400×); and (F) rhomboidal uric acid crystals (400×).

and not wait for a recurrence. Although the general recommendation is a limited evaluation for single stone formers, children should have a thorough evaluation after the initial stone event because they have a higher likelihood of inborn errors of metabolism, such as primary hyperoxaluria and cystinuria, as the cause of their stones. Some patients also require an evaluation based on their employment, such as airline pilots. If the limited evaluation of the kidney stone patient reveals no abnormalities, then the patient should receive standard dietary and lifestyle advice that would be beneficial for all stone patients, such as high fluid intake to keep

urine volume greater than 2.5 L/d, as well as a low-sodium, moderate-protein diet.[57,58] The patient also should be instructed to maintain normal dietary calcium levels because many patients will reduce calcium on their own.

A more extensive evaluation is needed for patients with recurrent nephrolithiasis. Twenty-four–hour urine chemistries should be measured to identify the abnormalities that contribute to stone formation and to identify dietary factors that may modulate excretion of lithogenic substances. The chemistries that should be included in a 24-hour urine analysis are listed in Table 2. The measurements listed in the left-hand column provide the minimal work-up needed for a stone-forming patient, allowing the clinician to assess the factors that relate most directly to stone risk. The measurements in the right-hand column provide additional information on stone risk itself, as well as the dietary factors that influence urine stone risk. Also, calculation of urine supersaturation (SS) of the common stone-forming salts can be a helpful guide in the treatment of patients.[59] All factors included in Table 2, except creatinine, would be included in the calculation of SS, the more chemistries included in the SS calculation, the more accurate it will be.

One issue that has not been resolved is the number of 24-hour urine collections that should be performed as part of the initial kidney stone work-up. Unlike serum tests, urine chemistries can change significantly from day to day based on changes in environment, activities, and diet. A number of investigators have suggested that multiple measurements are required to identify abnormalities in urine chemistries, although there is not universal agreement.[60-62] Table 3 shows the results of a comparison of 2 consecutive pretreatment 24-hour urine collections obtained from a database of a clinical laboratory specializing in kidney stone disease. Table 3 shows the percentage of paired urine samples that have deviations of at least 25% or 50% in any of the major urine chemistries. The chance that any of these critical chemistries will vary by 100% from one day to the next is 9%. I believe such variability is worth noting because without having a sound knowledge of the patient's baseline status it is impossible to judge the effectiveness of any given therapeutic intervention. It seems prudent to obtain 2 urine specimens when evaluating a patient, one during a weekday and one during the weekend. Such an evaluation will help uncover risk factors that may be unique to the work and/or home environment. Many patients will need to be told specifically to perform the collection during a workday because most prefer to perform collections during the weekend to avoid the embarrassment of collecting urine at the workplace.

A brief description of the clinical utility of each of the common measurements in a kidney stone evaluation is provided later. In considering urine chemistries it should be noted that all of these tests are continuous variables with a

Table 2. 24-Hour Urine Chemistries for Evaluation of Nephrolithiasis

Minimal Evaluation	Complete Evaluation
Calcium	Sodium
Oxalate	Potassium
Citrate	Chloride
Uric acid	Urea nitrogen
Volume	Phosphorous
pH	Magnesium
Creatinine	Ammonia
	Sulfate

Table 3. Variability of 24-Hour Urine Chemistries

	25% Variability Between 2 Consecutive 24-Hour Urines	50% Variability Between 2 Consecutive 24-Hour Urines
Volume	36%	15%
Calcium	20%	12%
Oxalate	20%	6%
Citrate	24%	10%
Uric acid	15%	3%
Any of the above	67%	36%

wide range of normal values.[63] An increase in stone risk can occur when values are still within the 95% confidence interval for a normal population. Strict cut-off values often are used in research studies of nephrolithiasis but clinicians caring for a patient need to recognize that some urine chemistries require treatment, even though the results are in the normal range.

Calcium

Most stones are composed of calcium and hypercalciuria is the most common metabolic abnormality found in calcium stone formers. Generally, hypercalciuria is defined as a urine calcium level greater than 300 mg/d in a man or 250 mg/d in a woman on their usual diet, compared with a mean urine calcium of 150 to 170 mg/d in non–stone formers. Urine calcium levels greater than the mean, although not in the hypercalciuric range, may contribute to stone disease and bringing high-normal values to the low-normal level may be of benefit. Low urine calcium levels can be found in stone formers, and although not a direct risk for kidney stones, hypocalciuria may indicate other pathology. Bowel disease may lead to malabsorption of calcium and yet still be associated with stones because of other abnormalities from chronic diarrhea such as low urine volume, low urine citrate, and low urine pH. Vitamin D deficiency also should be considered in any patient with low urine calcium levels.

Oxalate

Hyperoxaluria is found in 30% of kidney stone patients. In the vast majority of patients the hyperoxaluria is of mild to moderate level and is usually the result of dietary overindulgence of oxalate. It also may be related to other dietary issues such as a low-calcium diet, which allows a greater percentage of oxalate to be absorbed, or because of a high intake of oxalate metabolic precursors as might occur in some patients with a high protein intake. If very high levels of urine oxalate (>90 mg/d) are found, the patient should be evaluated for enteric hyperoxaluria or primary hyperoxaluria.

Citrate

Hypocitraturia generally is defined as less than 325 mg/d, although there is considerable overlap between normal subjects and patients with kidney stones.[64] Citrate reduces stone risk by complexing calcium in the urine, lowering the free calcium concentration.[65] In addition, citrate is a direct inhibitor of CaOx crystallization independent of its ability to complex calcium. Low urine citrate level may be caused by consumption of a high dietary acid load, metabolic acidosis, secondary to hypokalemia or idiopathic in origin.[66] Because hypokalemia causes hypocitraturia, it is particularly important to monitor the serum potassium level in patients whose hypercalciuria is being treated with thiazide.

Uric Acid

Hyperuricosuria may contribute to both uric acid and CaOx stone formation. It is present in 10% to 25% of stone formers. Hyperuricosuria may be caused by metabolic abnormalities that lead to overproduction, but most often is caused by excessive ingestion of purine in the diet.[67] Generally, purine in human diets comes from animal protein, and thus markers of protein intake also will guide the clinician as to the extent of purine intake. Hyperuricosuria promotes stone formation by salting out CaOx from the urine.[68] Lowering uric acid excretion with allopurinol has been shown to reduce CaOx stone formation in patients with hyperuricosuria.[69] Increased excretion obviously can contribute to uric acid stone formation, although uric acid excretion rate is not as important as urine pH or urine flow rate in determining the risk of uric acid stones. Some patients with severe metabolic derangements, such as Lesch-Nyhan syndrome, will have uric acid excretion rates so high that uric acid stones may form even with normal urine pH and urine flow.

Urine pH

Although CaOx stones are independent of urine pH, both uric acid and calcium phosphate stones are critically dependent on urine pH. With a pK of 5.4, uric acid becomes protonated

at low urine pH; protonated uric acid is poorly soluble, with a maximal solubility of approximately 100 mg/L in urine.[70] As urine pH increases above 6.0, uric acid risk decreases but calcium phosphate stone risk increases as H_2PO_4 is converted to HPO_4, increasing the SS of calcium monohydrogen phosphate. A urine pH of 6.0 is the double-minimum point for uric acid and calcium phosphate SS. Urine pH is useful in monitoring the effect of alkali therapy. If alkali is given to increase either urine pH or citrate, the urine pH should be measured to ensure an adequate response and prevent excessive alkalinization. Uric acid stone formers generally need a urine pH in the range of 6.0 to 6.5, higher urine pH does not lower uric acid saturation significantly but will increase the risk of calcium phosphate crystallization. Excessive alkalinization should be avoided for patients with hypocitraturia and hypercalciuria being treated with alkaline citrate because an increase in urine pH may lead to calcium phosphate stones.

Urine pH varies from 5 to 7.5 in normal subjects, so a single random urine pH is not a useful clinical guide in the evaluation of stone disease. The time averaging of 24-hour urine pH provides a much better indicator of stone risk because uric acid stone formers will have urine that persistently is acidic and those with calcium phosphate stones usually will have a persistently high urine pH.[71]

Volume

Urine volume is required in any timed urine specimen to allow calculation of excretion rates, and flow rate shows if the patient is drinking an adequate amount of fluid. Borghi et al[57] showed that high fluid intakes reduce stone recurrence in a prospective, randomized trial. Their work also provided a goal for urine volume: 2.5 L/d significantly reduced stone recurrence. Patients should be instructed to increase fluid intake so that this goal is reached. A goal of urine flow seems a more reasonable end point rather than a fixed fluid intake because every patient has different rates of extrarenal fluid loss via the GI tract and skin, which will affect their rate of urine flow independent of fluid intake. Certainly, higher urine flow rates should provide even greater therapeutic benefits, although few patients can keep urine volume above 3 L/d consistently.

Electrolytes

In patients without chronic diarrheal states, almost all dietary sodium is absorbed from the GI tract. To stay in balance, the absorbed sodium is excreted by the kidney, allowing the urine sodium excretion to act as an excellent marker of diet sodium intake. Because dietary salt load influences urine calcium excretion, and an estimate of diet sodium by patients is unreliable, measurement of sodium excretion is a practical way to confirm that the patient is complying with their diet therapy. Low potassium intake has been associated with an increased risk of stones and can be estimated from the urine potassium excretion. A diet rich in fruits and vegetables will increase the urine potassium excretion and seems to be associated with lower stone risk. Urine potassium is particularly useful in monitoring therapy with potassium citrate. If the patient is taking their potassium alkali, then urine potassium excretion should increase by approximately the amount of potassium that was prescribed. Changes in urine pH and urine citrate excretion during therapy may be variable, but the change in urine potassium will confirm the patient is compliant with medication.

Urea Nitrogen/Sulfate

Dietary protein intake may be assessed by urine urea and sulfate excretion. Urea is an end-product of amino acid metabolism and in the steady state protein intake can be estimated by the urea excretion rate.[72] Sulfate is the end-product of metabolism of sulfur-containing amino acids such as methionine. As such, sulfate may be monitored to estimate dietary intake of animal protein and provides insight into the acid load from a patient's diet.

Ammonium

Ammonium levels change with the amount of acid that the kidneys need to excrete to maintain acid-base equilibrium. As diet acid load increases, ammonium will increase, roughly

mirroring the changes in urine sulfate excretion. If ammonium greatly exceeds sulfate and urine pH is less than 6.5 it suggests an acidotic state such as a chronic diarrhea. In the setting of an alkali load, urine ammonium excretion will be suppressed as urine pH increases, the ammonium excretion can be monitored to determine the effectiveness of alkali therapy in titrating the dietary acid load. If urine pH is above 6.5 and urine ammonium excretion also is high, it is a state incompatible with normal human physiology. This situation suggests urinary tract infection with bacteria that possess urease activity. If this finding occurs, the patient will need to be treated for infection and the urine study will need to be repeated.

Magnesium

Hypomagnesuria has been suggested to contribute to stone risk.[73] Magnesium complexes oxalate in the urine and lowers urine saturation of calcium salts; diets low in magnesium may allow overabsorption of dietary oxalate. If urine magnesium is very low, it suggests magnesium deficiency, often seen in patients with small-bowel disease and malabsorption.

Phosphate

Urine phosphate provides a rough estimate of dietary phosphate intake because approximately 60% to 70% of dietary phosphate is absorbed. Although excess urine phosphate contributes to calcium phosphate stone risk, it is not as important a risk factor as urine pH, which determines how much of the phosphate will be in the form of HPO_4.

Creatinine

The creatinine excretion should be measured in all 24-hour urine specimens to ensure that the collection has been performed properly. Urine volume is not an adequate marker to determine if a urine collection was performed properly because urine flow may be as low as 500 mL/d to more than 3 L/d. Urine creatinine levels should be 18 to 25 mg/kg body weight in men and 15 to 22 mg/kg body weight in women, although it can vary with muscle mass and obesity.

Supersaturations

All the earlier-described urine chemistries can be used to calculate urine SS using a program such as EQUIL2.[59] SS is the ratio of the concentration of a salt in solution to the salt's solubility concentration, a value greater than 1 indicates SS, a value less than 1 is an undersaturated solution. In the absence of a crystallographic stone analysis, SS values can predict the type of stone the patient is most likely to form because SS values correlate with known stone types. SS is also a useful way to monitor therapy. At the University of Chicago Kidney Stone Clinic we have found that reducing CaOx SS by 50% from baseline led to a reduction of stone rates to 21% of the pretreatment rate.[74] For uric acid stones, the goal is to keep the urine undersaturated.

CONCLUSIONS

The evaluation of the kidney stone patient requires a careful history to determine dietary and environmental risk factors that can be modified as well as a thorough laboratory evaluation for patients with recurrent kidney stones to identify abnormalities that can be treated by dietary, lifestyle, and pharmacologic interventions. Medical intervention can reduce stone recurrence by up to 80%.

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