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Approach to the Adult Kidney Stone Former

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Abstract

Nephrolithiasis is a prevalent and costly condition with high recurrence rate. A medical evaluation to identify abnormalities responsible for nephrolithiasis and guide subsequent therapy has been advocated to reduce the risk of stone recurrence. The evaluation of kidney stone formers generally comprises an extensive medical history to identify metabolic, environmental, dietary and/or genetic factors contributing to stone formation. Imaging studies are utilized to evaluate and follow stone burden. Laboratory studies including stone composition analysis and serum and urinary chemistries are commonly obtained to further assess for any underlying systemic disorders, to detect environmental and metabolic processes contributing to stone disease, and to guide initial and follow-up dietary and pharmacological therapy. The nature and extent of such an evaluation is discussed in this review article.

Keywords

Nephrolithiasis; Urolithiasis; Kidney stones; Evaluation; Hypercalciuria; Hyperoxaluria; Hypocitraturia

Introduction

Nephrolithiasis is a costly and prevalent condition that afflicts 12% of men and 7% of women in the United States. [1] Following an initial presentation with renal colic, recurrent nephrolithiasis is quite common, with recurrence rates of 35%, 52% and 75% after 5, 10 and 20 years from the first stone episode, respectively.[2,3] Thus, recurrence is the rule rather than the exception. In view of the significant morbidity and cost associated with nephrolithiasis, [1] a medical evaluation to identify abnormalities responsible for stone formation has been advocated to guide therapy to reduce the risk of stone recurrence. The nature and extent of such an evaluation is discussed in this review article. The approach is also further illustrated by two typical cases described below.

Cases

Ms. Singlestone (Ms. S.) is a 34 year old woman who presented one month ago to the Emergency Department with renal colic. At the time, a computed tomography (CT) scan of the abdomen showed a single 4-mm left distal ureteral stone. She passed the stone spontaneously within hours of presentation. She would like to know whether she can prevent stone recurrence.

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Mr. Recurringstones (Mr. R.) is a 41 year old man with a history of recurrent nephrolithiasis since age 19. He has required ureteroscopy with laser lithotripsy on two different occasions in the past two years. On a recent follow-up CT scan of the abdomen, he was found to have two non-obstructive stones in each kidney, ranging between 2–6 mm in size. He denies any associated symptoms, but is interested in understanding why he keeps forming stones, and what can be done to prevent further stone formation.

History

The evaluation of the adult patient with nephrolithiasis begins with obtaining a detailed history focused history on identifying factors contributing to stone formation. Elements to be covered during the history portion include onset and rate of stone formation, past medical and surgical history, medication use, as well as family, environmental and dietary history.

Medical history

Ms. S. reported no history of kidney stones preceding the renal colic episode that occurred a month earlier. She had a single uncomplicated urinary tract infection diagnosed five years ago that resolved with oral antibiotics. She was otherwise healthy, denied any history of gout, chronic diarrhea, or any other systemic illnesses. She had never required any surgeries, and her review of systems was completely normal. Mr. R. reported spontaneous kidney stone passage at a rate of one stone every 4 years between ages 19–35 years, with a recent increase in size and frequency of stone formation and the recent need for urological intervention to help with passage of larger stones. Stone passage occurred from both right and left kidneys. His review of systems was notable for chronic fatigue, diffuse bone pain and depression. He denied any history of urinary tract infections, gout, or chronic diarrhea and he did not have any known systemic illnesses.

During the process of history gathering, it is vital to obtain details regarding the age of onset of nephrolithiasis, the frequency of stone formation and regarding the need for urological intervention. Earlier age of onset may suggest an inherited condition (see section on family history). The age of onset of nephrolithiasis in Ms. S. (4^{th} decade) is quite typical, while stone disease starting at age 19 years in Mr. R. may be more suggestive of an inherited and/or a systemic condition. Stone formation rate will help gauge the severity of stone disease and in turn the extent of evaluation and the need for treatment to prevent stone recurrence. Thus, the evaluation and treatment of Mr. R. will be more aggressive than that of Ms. S. in view of the higher frequency of stone passage. If stone formation occurs unilaterally, anatomical abnormalities predisposing to stone formation (such as stenosis in the urinary tract, horseshoe or ectopic kidney) should be considered.

History should also assess for medical conditions associated with metabolic abnormalities that lead to stone disease.[4] Some common conditions that the evaluator should keep in mind include primary hyperparathyroidism, granulomatous, diseases, recurrent urinary tract infections, chronic diarrhea, distal renal tubular acidosis, metabolic syndrome and HIV. As in the case of Mr. R., a detailed history may reveal the typical cluster of “stones, bones, moans and groans” (i.e. nephrolithiasis, fractures or osteoporosis, abdominal complaints and psychiatric or central nervous system symptoms respectively) which is suggestive of primary hyperparathyroidism.[5,6] However, nephrolithiasis may be the only presenting symptom in primary hyperparathyroidism.[5,6] Other diseases associated with hypercalcemia and hypercalciuric nephrolithiasis include sarcoidosis and other granulomatous disorders that lead to 1,25-dihydroxyvitamin D overproduction. Patients with obesity, type 2 diabetes, and/or the metabolic syndrome are at significantly higher risk for uric acid stones.[7] A history of recurrent urinary tract infections with urease producing organisms (such as *Proteus* and *Klebsiella*) may suggest struvite (or infection) stones,

although urinary tract infection may be a consequence of nephrolithiasis due to local stasis.[8] Patients with gout are at risk for both calcium oxalate and uric acid stones. Patients who are infected with human immunodeficiency virus (HIV) are at risk of nephrolithiasis because of some antiretroviral medications, but also because of chronic diarrhea and volume depletion.[9] A history of chronic diarrhea and/or inflammatory bowel disease predisposes to low urine volume, enteric hyperoxaluria and other metabolic abnormalities associated with stone disease.[10] A previous Roux-en-Y gastric bypass surgery similarly predisposes to nephrolithiasis.[11] Other surgical procedures that are associated with kidney stone formation include small bowel resection, ileostomy, and bladder diversion surgery.

Family history

Ms. S. reports that her mother had a history of nephrolithiasis. On further questioning, the mother developed kidney stones in her 60s and these were related to “excessive intake of calcium supplements” for the prevention of osteoporosis. Mr. R. denies a family history of nephrolithiasis.

Kidney stones develop in individuals with a family history of nephrolithiasis significantly more frequently than in those without a family history.[12] This higher risk is attributable to genetic, dietary, and other environmental factors. In patients with a family history of nephrolithiasis, stones tend to occur at a younger age and at higher frequency.[13] Several cohort studies have estimated the heritability (the index of the genetic contribution to a trait) of nephrolithiasis at around 50% [14] A similar degree of heritability was seen in a twin study,[15] which has the advantage of correcting for common environmental exposure by comparing the risk in monozygotic vs. dizygotic twins. Therefore obtaining a good family history at the time of initial evaluation of a nephrolithiasis patient is key. While a limited number of monogenic forms of nephrolithiasis have been identified, genetic susceptibility to nephrolithiasis is more likely inherited as a polygenic trait.[16]

In the case of Ms. S., the later onset of nephrolithiasis in her mother and the link of stone disease to intake of calcium supplements (an environmental factor) are less suggestive of an inherited condition.

The inheritance pattern of individual metabolic risk factors that lead to nephrolithiasis is quite variable. Hypercalciuria in most familial cases is polygenic.[17] Primary hyperoxaluria represents a group of rare disorders of glyoxylate metabolism inherited in an autosomal recessive fashion in which specific hepatic enzyme deficiencies result in overproduction of oxalate.[18] Citrate excretion and hypocitraturia are likely polygenic.[19] Cystinuria on the other hand can show an autosomal recessive or autosomal dominant inheritance.[20]

Social and environmental history

Both Ms. S. and Mr. R. held office clerical/office jobs with limited outdoor exposure at work. Ms. S. reported jogging outdoors for one hour daily, while Mr. R. was sedentary.

An occupational and environmental history can at times be helpful in identifying specific risk factors for nephrolithiasis. Several epidemiological studies have suggested a role of heat and climate as significant risk factors for lithogenesis.[21] In fact, global warming is predicted to lead to a significant rise in the incidence of nephrolithiasis in the U.S.[22] While the higher prevalence of nephrolithiasis in the Southeastern section of the United States (the “stone belt”) has been in part ascribed to a warmer climate, other factors (such as age, gender, race, dietary habits, and socioeconomic background) may potentially mitigate the effect of climate.[21]

In terms of occupational history, chronic dehydration in particular represents a definite lithogenic risk factor. Occupations that have been associated with nephrolithiasis due to excessive sweating include lifeguard[23], machine operators exposed to heat, [24] and outdoor work in a tropical environment.[25] In one study, machinists chronically exposed to a hot environment and massive sweating were found to be at increased risk for nephrolithiasis in general and uric acid stones in particular.[24] Other occupations limit the availability of water or of toilet facilities, leading patients to reduce fluid intake which increases nephrolithiasis risk. Examples include teachers [26] and chauffeurs.[27] Vigorous physical exercise may lead to nephrolithiasis[28] through several mechanisms including dehydration, hypocitraturia, and decline in urine pH.[29] Toxic exposures to industrial materials such as cadmium and oxalic acid have also been associated with kidney stone formation.[30,31]

Occupational history in Ms. S. and Mr. R. is thus non-contributory, but exercise history in Ms. S. may have contributed to stone disease.

Dietary history

Ms. S. reports she has been on a low-carbohydrate, high-protein diet for the past 4 months in an attempt to lose weight. Mr. R. reports that he has been restricting his dietary intake of calcium and dairy products ever since he was told his kidney stones were “made of calcium”.

Diet is a key determinant of nephrolithiasis risk. Excessive salt intake increases urinary calcium excretion and secondarily kidney stone formation.[32] High intake of animal protein (as in Ms. S.) enhances the risk of calcium oxalate stone formation by increasing urinary calcium excretion, lowering urine citrate and pH, and increasing urinary uric acid.[33] The latter two factors also account for the greater risk of uric acid nephrolithiasis with excessive animal protein intake. Epidemiologic studies have suggested an association of lower risk of kidney stones with higher dietary calcium intake,[34,35] although the contribution of dietary calcium to stone risk has not been directly explored in calcium stone formers. The protective effect of dietary calcium has been attributed to the complexation of intestinal luminal oxalate, thereby reducing urinary oxalate excretion. In the case of Mr. R., restriction of calcium intake may therefore be unwarranted. At the same time, excessive calcium intake (exceeding 2,000 mg/day) may lead to hypercalciuria and nephrolithiasis. Absorbed oxalate from dietary sources constitutes a substantial proportion of daily urinary oxalate excretion.[36] A dietary history should therefore assess the frequency and quantity of ingested oxalate sources. Fluid intake (both type and amount) and intake of fruits and vegetables (sources of alkali) are other important parameters to be assessed.[37]

Medications

Neither Ms. S. nor Mr. R. was taking any prescribed or over-the-counter medications or supplements.

Drugs and supplements account for around 1–2% of stones analyzed in specialized laboratories.[38] This proportion likely underestimates drug-induced nephrolithiasis due to under-reporting of medication use and because in some cases, drug-induced metabolic stones do not differ in appearance from typical metabolic stones. Therefore, a thorough review of past and current medications and supplements consumed is vital in the assessment of nephrolithiasis patients.

Drugs associated with stone formation can be divided into two groups based on the mechanism of stone formation (Table 2). The first group consists of drugs that are primarily excreted in urine but are poorly soluble in the urinary environment, favoring crystallization

and stone formation. In addition, patient-specific factors likely contribute to the process of stone formation since only a portion of patients exposed to these drugs develop stone disease. Such factors include pharmacogenetics of detoxifying enzymes, anatomical and other urinary tract anomalies (presence of prostatic hypertrophy, urinary tract infection or stasis) or low urine volume, abnormal urine pH, and other underlying metabolic abnormalities (such as hypercalciuria or hypocitraturia). Presence of the drug or its metabolites on stone analysis (by infrared spectroscopy or x-ray diffraction) identifies this mode of stone disease.[39] Historically, sulfonamides were the first drugs implicated in renal calculi soon after their introduction for clinical use.[40] In the 1970s, triamterene was the leading cause of drug-containing urinary calculi.[41] This potassium-sparing diuretic continues to be widely used in combination with hydrochlorothiazide, making it easy to overlook when reviewing a patient's medication list. In the last two decades, protease inhibitors used in the treatment of HIV-infected patients, including indinavir and nelfinavir, have become a more common cause of drug-containing stones.[42,43]

Calcium and vitamin D supplements are widely used for the prevention and treatment of osteoporosis in older individuals. Such supplements also significantly increase urinary calcium, thus predisposing to calcium nephrolithiasis. In the Women's Health Initiative randomized clinical trial of calcium and vitamin D supplements, the incidence of urinary tract stones was 17% more common in postmenopausal women treated with calcium carbonate and vitamin D supplements compared to the placebo group.[44] This may in part account for the history of nephrolithiasis in Ms. S.' mother. Furosemide, a commonly prescribed loop diuretic, also increases urinary calcium excretion potentially predisposing to calcium stones. Carbonic anhydrase inhibitors is another class of drugs that predisposes to metabolic stones. Among long-term users of topiramate, a neuromodulatory agent widely prescribed for the prevention of migraines and of seizures, the prevalence of nephrolithiasis may reach 20%.[45] The underlying mechanism is carbonic anhydrase inhibition which leads to a metabolic acidosis with urinary bicarbonate wasting, hypocitraturia and alkalinuria predisposing primarily to calcium phosphate but also to calcium oxalate stones.[46] Vitamin C (ascorbic acid) is metabolized to oxalate, and when taken in large doses (exceeding 500 mg/day), can lead to hyperoxaluria and potentially to calcium oxalate stones.[47] Allopurinol, widely used for the treatment of gout and occasionally among nephrolithiasis patients with hyperuricosuria, can itself potentially (though rarely) lead to stone formation through two separate mechanisms: Oxypurinol, a poorly soluble metabolite of allopurinol can precipitate in the urinary tract leading to oxypurinol stones.[48] On the other hand, allopurinol interferes with the conversion of xanthine to uric acid, and in cases of severe hyperuricemia, allopurinol therapy may lead to severe xanthinuria and secondarily to xanthine stones.[49] Other causes of drug-induced nephrolithiasis are summarized in Table 1 and a more extensive review has been recently published.[38]

Imaging Studies

Other than the 4-mm distal ureteral stone, no other kidney or ureteral stones were noted on Ms. S.' initial abdominal CT scan. Mr. R. had bilateral kidney stones on follow-up CT scan.

A number of imaging modalities are available for the initial and follow-up evaluation of patients with nephrolithiasis. These include plain radiography of the kidneys, ureters, and bladder (KUB), intravenous urography (IVU), Computed Tomography (CT) scan, ultrasound, and magnetic resonance urography.[50] Advantages and shortcomings of each modality are presented in Table 2.

Nowadays, a non-contrast helical CT scan of the abdomen and pelvis is considered the gold standard for detection of renal calculi. This was the imaging modality that was ordered in

the Emergency Department to evaluate the abdominal pain in Ms. S. Its major advantages include its high sensitivity and specificity for identification of stones,[51,52] as well as its ability to identify extra-urinary pathology in patients presenting with abdominal pain due to causes other than stones. A CT scan can detect stones of all types (including uric acid stones that are radiolucent on plain KUB), and in different locations (including those in the ureters, which can be missed by ultrasound). Additional advantages include the widespread availability of CT scanners and the fact that no contrast is needed for stone evaluation. Newer technology may even allow identification of stone composition by CT scan using attenuation values.[53] Some drawbacks of CT scan use include higher cost in comparison with KUB and ultrasound, and the significant radiation exposure. Newer reduced-dose CT scans which expose patients to lower radiation doses have been shown to be accurate in the diagnosis of nephrolithiasis.[54]

Plain radiography (KUB) is frequently used for the follow-up of stone burden in patients with known nephrolithiasis since 90% of stones are radio-opaque. Advantages include the low cost and lower radiation dose compared to CT scan. In the case of Mr. R., repeat CT scans may not be warranted for routine follow-up of stone burden, and KUB would be the imaging modality of choice for this purpose. However, stone visualization can be hampered by the presence of overlying bowel gas or extra-renal calcification. An additional limitation is the lack of anatomic detail of the kidney and surrounding structures.[55] Intravenous urography (IVU) identifies stones in the urinary tract as filling defects. Advantages include the ability to identify the degree of obstruction and anatomical abnormalities in the urinary tract as well as assessment of parameters such as infundibular width which has been postulated to correlate with future success of extracorporeal shock-wave lithotripsy.[56] However, IVU involves contrast administration and the concomitant risk of contrast nephropathy, and it has been largely replaced by CT scan.[57] In pregnant patients or those in the pediatric age group, ultrasound is the imaging modality of choice since it does not involve any ionizing radiation.[50] It can therefore be used in the follow up of all stone formers. It is also the modality of choice for the detection of hydronephrosis although one limitation is that it may not reveal the site of obstruction. Ultrasound can detect stones of all composition, although it has a poor sensitivity for detection of small (< 3 mm) or more distal stones.[50] Magnetic resonance urography (MRU) has been suggested as another imaging modality that does not involve radiation exposure. It may serve as an adjunct to ultrasound in pregnant women suspected of having a kidney stone.[58] However, the role of MRU in the diagnosis and management of urinary stone disease is limited by its significantly higher cost, the lesser availability of MR imaging instruments compared to CT scanner, and the fact that gadolinium contrast is relatively contraindicated in patients with chronic kidney disease.

Laboratory Studies

Laboratory evaluation of a patient with kidney stones is targeted at identifying factors underlying stone disease in order to guide therapy. Basic studies in all stone formers include serum chemistry profile, urinalysis and stone analysis whenever possible. In pediatric stone formers, adult patients with recurrent stones or those at high risk for recurrent nephrolithiasis, a more extensive evaluation including 24-hr urine chemistry profile is needed.

Serum chemistry profile

Ms. S. had the following serum electrolytes: Sodium: 139 mEq/L, Potassium: 3.9 mEq/L, Chloride: 104 mEq/L, Bicarbonate: 23 mEq/L, Blood Urea Nitrogen: 22 mg/dL, Creatinine: 0.9 mg/dL, Uric Acid: 6.0 mg/dL, Calcium: 9.8 mg/dL, Parathyroid Hormone: 42 pg/mL.

Serum electrolytes on Mr. R. were as follows: Sodium: 141 mEq/L, Potassium: 3.8 mEq/L, Chloride: 103 mEq/L, Bicarbonate: 26 mEq/L, Blood Urea Nitrogen: 23 mg/dL, Creatinine: 1.1 mg/dL, Uric Acid: 5.9 mg/dL, Calcium: 10.6 mg/dL (reference: 8.4–10.2), Parathyroid Hormone: 60 pg/mL (reference: 10–65).

Laboratory evaluation of all stone formers requires the determination of a serum chemistry profile consisting of fasting electrolytes and serum intact parathyroid hormone (PTH). Abnormalities in serum chemistries can provide clues of disorders associated with nephrolithiasis (Table 3). Serum creatinine provides an indication of renal function. Findings of hypercalcemia, hypophosphatemia and elevated serum PTH may lead to the diagnosis of primary hyperparathyroidism. In the case of Mr. R., hypercalcemia was accompanied by a non-suppressed ("inappropriately normal") serum PTH, which is also suggestive of primary hyperparathyroidism (i.e. serum PTH does not always need to be frankly elevated in this condition). Hypercalcemia with suppressed serum PTH suggest non-PTH mediated hypercalcemia (as in sarcoidosis, other granulomatous disorders and vitamin D toxicity). Hypophosphatemia in association with normal serum PTH is suggestive of a renal phosphorus leak. In this condition, hypophosphatemia leads to elevation in serum calcitriol, and consequently increased intestinal calcium absorption and hypercalciuria. The finding of low serum potassium and bicarbonate is suggestive of chronic diarrhea or of distal RTA. Hyperuricemia is suggestive of the diagnosis of gout, which can be associated with uric acid as well as calcium oxalate stones.

Urinalysis

Urinalysis on Ms. S. revealed a specific gravity of 1.020, pH of 5.5, 1+ ketones, some uric acid crystals, no protein, glucose, red blood cells (RBCs) or white blood cells (WBCs). On urinalysis, Mr. R. had a specific gravity of 1.010, pH of 6.5, 10–20 RBCs/high power field, calcium oxalate crystals, with no ketones, protein, glucose or WBCs.

A urinalysis with microscopy is obtained routinely in stone formers. Hematuria is relatively sensitive in the setting of acute renal colic, and its absence may suggest a search for an alternative diagnosis. The presence of pyuria or other indicators of urinary tract infection should lead to performance of a urine culture. Crystals are frequently identified on urine microscopy. The finding of calcium oxalate or uric acid crystals is non-specific and such crystals can be found in the urine of normal individuals (non-stone formers). On the other hand, benzene-shaped crystals are pathognomonic of cystinuria and should trigger a screen for this condition. Similarly, the presence of struvite crystals is always abnormal.

In the case of Ms. S., the urine is somewhat concentrated (specific gravity of 1.020), and the presence of ketonuria is compatible with her following a low-carbohydrate diet. The microscopic hematuria in Mr. R. may be related to the stones present in his kidneys. The findings of uric acid crystals (in Ms. S.) or calcium oxalate crystals (in Mr. R.) is not pathognomonic of any specific type of any condition, and may or may not be related to their stone disease.

Urine chemistry profile

Ms. S. had the following findings on 24-hr urine collection (reference ranges provided in Table 4): Urine creatinine: 1010 mg/day (20 mg/Kg body weight/day), total volume: 1.7 liters/day, pH: 5.70, calcium: 357 mg/day, citrate: 218 mg/day, oxalate: 30 mg/day, uric acid: 893 mg/day, phosphorus: 1,230 mg/day, sodium: 159 mEq/day, sulfate: 46 mmol/day, ammonium: 66 mmol/day.

24-hr urine electrolytes on Mr. R. were as follows: Urine creatinine: 1535 mg/day (22 mg/Kg body weight/day), total volume: 2.3 liters/day, pH: 6.70, calcium: 455 mg/day, citrate:

526 mg/day, oxalate: 42 mg/day, uric acid: 680 mg/day, phosphorus: 1,403 mg/day, sodium: 196 mEq/day, sulfate: 29 mmol/day.

Evaluation of urine chemistries on a 24-hr urine collection is recommended in the assessment of the recurrent stone former. It is also routinely obtained in pediatric stone formers, and in patients with a history of a single stone who are at high risk for recurrent stone formation or are required to undergo an evaluation because of employment. A typical urine chemistry profile for the evaluation of nephrolithiasis consists of the following parameters: creatinine, total volume, pH, calcium, oxalate, uric acid, citrate, sulfate, phosphorus, sodium, chloride, potassium, magnesium, sulfate, ammonium and cystine. Reference ranges and interpretation of abnormal tests are shown in Table 4. We will discuss some of the key parameters individually next.

Urine creatinine is measured with every 24-hr urine test to ensure the adequacy of the collection. Typical creatinine excretion ranges between 15–22 mg/Kg body weight/day in women and between 18–25 mg/Kg body weight/day in men. Creatinine excretion does vary depending on muscle mass and fat mass, but urinary creatinine values markedly below these ranges suggest urine undercollection while values above these ranges may suggest overcollection. Both Ms. S. and Mr. R. had adequate urine collection based on urine creatinine.

Urine volume is routinely reported with each 24-hr urine collection. It represents the integration between fluid intake and extra-renal fluid losses (such as fluid loss with stools or perspiration). Low urine volume leads to greater urinary saturation with respect to stone forming salts, and is therefore a risk factor for all stone types. Stone formers are recommended to maintain daily urine volume above 2 liters/day, a recommendation that was shown to significantly reduce the risk of recurrent nephrolithiasis in a randomized clinical trial.[59] Higher urine volume may be needed in some cases, particularly in patients with severe cystinuria.[60] However, in real life setting, urine volume increments accomplished by physicians treating nephrolithiasis patients are modest.[61]

Urine pH measurement by pH electrode (which is more accurate and reproducible than measurement by dipstick) is a key component of every stone risk profile. Low urine pH (< 5.5) increases urinary uric acid saturation and is the major risk factor identified in patients with uric acid stones.[62] It may result from gastrointestinal alkali losses (as in patients with chronic diarrhea) or from excessive intake of acidogenic diets (high protein diets). Diabetes, obesity, and the metabolic syndrome are other conditions that have been associated with low urine pH and uric acid stones.[63] On the other hand, a high urine pH (>6.5) increases urinary saturation with respect to calcium monohydrogen phosphate and is a risk factor for brushite and apatite stones.[64] High urine pH also increases urinary saturation with respect to ammonium magnesium phosphate and is associated with the formation of struvite (infection) stones.[65] High urine pH may be caused by distal renal tubular acidosis,[66] infection with urease splitting organisms,[65] primary hyperparathyroidism,[67] and alkali therapy.

Hypercalciuria is a major risk factor for calcium oxalate and calcium phosphate stones. It is generally defined as 24-hr urine calcium > 250 mg/day in women or > 300 mg/day in men. Alternative definitions are urine calcium > 4 mg/Kg body weight/day and urine calcium > 140 mg calcium/gram creatinine/day. Lower urine calcium levels may still contribute to calcium stone formation, and there may be benefit in reducing high-normal values to the low-normal range in some cases. Causes of hypercalciuria include excessive intestinal calcium absorption (absorptive hypercalciuria), excessive bone resorption (resorptive hypercalciuria), excessive salt and/or animal protein intake, hypercalcemia, and renal leak of

calcium. Besides lifestyle and dietary measures such as salt restriction and moderate reduction in animal protein intake, lower urinary calcium can be achieved by thiazide diuretics and to a smaller extent by alkali therapy (potassium citrate).

Oxalate is an end-product of metabolism in humans that is excreted in urine, and hyperoxaluria is a risk factor for calcium oxalate stones. It is typically defined as urine oxalate exceeding 45 mg/day (0.5 mmol/day). Hyperoxaluria may be caused by excessive intake of oxalate-rich foods such as various nuts, green leafy vegetables (including spinach), chocolate, and others. Ascorbic acid (vitamin C) is metabolized to oxalate, and when taken in doses exceeding 1000 mg/day, is associated with an increase in urine oxalate.[47] Enteric hyperoxaluria occurs in the setting of gastrointestinal disease or bowel surgery and is caused by an imbalance between intestinal calcium and oxalate content. In enteric hyperoxaluria, intestinal calcium is thought to be complexed by unabsorbed bile salts and/or fatty acids, leaving intestinal oxalate free to be absorbed into the bloodstream and secondarily excreted in urine.[10] When urine oxalate exceeds 100 mg/day, the possibility of primary hyperoxaluria should be considered. Depending on the clinical context, measurement of urinary glycolate and glyoxalate or genetic testing for mutations in the genes encoding for alanine-glyoxylate aminotransferase and glyoxylate reductase/hydroxypyruvate reductase may be indicated to ascertain the diagnosis of primary hyperoxaluria.

Citrate in urine acts as an inhibitor of calcium stones. It forms a calcium-citrate complex in urine that is significantly more soluble than calcium oxalate and calcium phosphate. Thus hypocitraturia, defined as urine citrate < 320 mg/day, is a major risk factor for calcium oxalate and calcium phosphate stones. It is encountered in 31% of calcium stone formers. Hypocitraturia is encountered in conditions of intracellular or extracellular acidosis, including metabolic acidosis from gastrointestinal alkali losses or distal renal tubular acidosis, hypokalemia, excessive animal protein intake, or use of carbonic anhydrase inhibitors, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

Hyperuricosuria is a risk factor for both uric acid and calcium oxalate stone formation. In the setting of low urine pH (<5.5), uric acid is poorly soluble and more likely to precipitate as uric acid stones. On the other hand, in the setting of normal urine pH hyperuricosuria produces urinary supersaturation of monosodium urate. In such a supersaturated environment, crystallization of calcium oxalate may occur by a “salting out” phenomenon. The most frequent cause for hyperuricosuria is the consumption of purine-rich foods (red meat, poultry and fish). In a minority of patients, hyperuricosuria results from urate overproduction (e.g. myeloproliferative disorders) or from uricosuric drugs. Recurrent stone formation can be ameliorated by dietary purine restriction or pharmacologically by allopurinol.

Urine cystine measurement is key in the initial and follow-up evaluation of patients with cystinuria. Urine sodium (and chloride) are indicative of dietary salt intake in a steady state. While not directly involved in the crystallization of stone-forming salts, urine potassium, magnesium, sulfate and ammonium provide an idea of overall protein intake, alkali intake and acid-base status (Table 4).

Prominent findings on 24-hr urine collection for Ms. S. were the low urine volume, hypercalciuria, hypocitraturia, slightly low urine pH, and elevated urine sulfate (a marker of animal protein intake). Ms. S. also exhibited elevated urine uric acid and phosphorus, but normal urine sodium and oxalate.

Review of urinary findings in Mr. R. is notable for significant hypercalciuria (urine calcium of 455 mg/day) that is unlikely to be related to excessive salt or animal protein intake

(normal urine sodium and urine sulfate). Urine was also notable for slightly high urine pH, but normal urine volume, citrate, oxalate and uric acid.

Stone analysis

Stone analysis in Ms. S. was 90% calcium oxalate/10% uric acid, while most recent stone analysis in Mr. R. was 75% calcium oxalate/25% calcium phosphate.

If a stone is retrieved, crystallographic stone analysis is valuable. Stone analysis allows identification of less common stone types including uric acid, cystine and struvite stones which may alter patient management. Stone analysis is also the only way to identify drug-induced stones.

The co-existence of more than one type of crystal in a single stone is quite common, as in the case of Ms. S. and Mr. R. Calcium oxalate is the most frequently encountered stone component.

Cases – Overview and Management

Ms. Singlestone presented for evaluation after a single episode of calcium oxalate nephrolithiasis at age 34. History was notable for strenuous physical activity (daily jogging for an hour) and for a diet high in animal protein intake, with no known systemic illnesses and no intake of stone-provoking medications. Serum electrolytes were essentially normal, and urine findings were notable for hypercalciuria and hypocitraturia likely related to high protein intake (suggested by high urine sulfate, uric acid and phosphorus) and for low urine volume (which may be related to insufficient fluid intake and excessive sweating during physical activity). Overall, she has a 50% of recurrent nephrolithiasis, although her risk can be reduced significantly by increasing her fluid intake and reducing her intake of animal proteins. One consideration would be to repeat a 24-hr urine collection after she makes the recommended lifestyle changes to document resolution of hypocitraturia and hypercalciuria, although this may not be entirely necessary if she does not develop recurrent stones.

Mr. Recurringstones presented for evaluation of recurrent calcium nephrolithiasis for the past 20 years. History was notable for bone pain, fatigue and depression (“stones, bones, moans, groans”), but no known systemic illnesses and no intake of stone-provoking medications. Serum electrolytes were notable for hypercalcemia with non-suppressed serum PTH, and urine findings were notable for significant hypercalciuria not likely to be caused by dietary aberrations (such as high protein or salt intake). His overall picture is compatible with nephrolithiasis related to primary hyperparathyroidism. This is most likely caused by a single parathyroid adenoma although the possibility of multi-gland hyperplasia (and even multiple endocrine neoplasia, MEN) should be considered in view of his young age. Parathyroidectomy is likely to correct his hypercalcemia/hypercalciuria and cure his stone disease (although he may pass the stones remaining in his kidneys).

Extent and cost-effectiveness of evaluation

While the cost of metabolic evaluation and of medical treatment of remediable causes can be substantial in kidney stone formers, such cost was shown to be balanced by the reductions in stone related events and medical encounters.[68,69] In one study, medical prevention of nephrolithiasis was estimated to result in cost savings of over $2,000/patient/year apart from its benefits to patients in terms of reduced morbidity and risk from procedures, obstruction, and infection.[68] This is particularly the case in recurrent stone formers in whom conservative therapy (dietary advice without metabolic testing) is unsatisfactory because of a high recurrence rate.[70] In first-time stone formers with uric acid, cystine or pure calcium

phosphate stones and those under 18 years of age, there is a significant likelihood that metabolic testing will identify underlying abnormalities and that specific medical prophylactic interventions will be of value.[71] In first-time calcium oxalate stone formers on the other hand, there are arguments for[72] and against[73] metabolic testing.

Another issue debated in the literature is the number of 24-hour urine collections that should be performed during the initial work-up of patients with nephrolithiasis.[74–76] Unlike serum tests, urine chemistries display significant variability from day to day based on dietary and environmental changes.[74] It therefore may be prudent to obtain two 24-hr urine specimens when evaluating a patient initially[77], although compliance with and cost-effectiveness of such strategy has not been evaluated.

Conclusions

The evaluation of kidney stone formers requires an extensive medical history to identify metabolic, environmental, dietary and/or genetic factors contributing to stone formation. Various imaging studies are available for follow-up of stone burden, but CT scan has become the gold standard modality for the initial assessment of patients with renal colic. Laboratory studies including urinalysis, stone composition analysis and serum and urinary chemistries are valuable for identifying environmental and metabolic processes contributing to stone disease, and in guiding initial and follow-up therapy.

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Table 1

Medications and Supplements Associated with Nephrolithiasis

Drug	Stone Type	Mechanism(s)
Drugs that Crystallize in Urine		
Protease Inhibitors (Indinavir, nelfinavir, atazanavir)	Drug itself	Poorly soluble drug with high renal excretion favoring crystallization in urine
Antibacterial Drugs (Sulfonamides, quinolones, others)		
Triamterene		
Other Drugs (Guaifenesin, ephedrine, etc…)		
Drugs Leading to Metabolic Stones		
Calcium and Vitamin D Supplements	Calcium Oxalate, Calcium Phosphate	Hypercalciuria
Carbonic Anhydrase Inhibitors (Topiramate, Acetazolamide, Zonisamide, Others)	Calcium Phosphate Calcium Oxalate	High urine pH, Hypocitraturia, Hypercalciuria
Ascorbic Acid (Vitamin C)	Calcium Oxalate	Hyperoxaluria
Uricosuric Agents (Probenecid, Benzbromarone, Others)	Uric Acid Calcium Oxalate	Hyperuricosuria
Allopurinol	• Xanthine • Oxypurinol	• Xanthinuria • Oxypurinol is a poorly soluble metabolite of allopurinol
Furosemide	Calcium Oxalate Calcium Phosphate	Hypercalciuria
Laxatives (chronic use, including laxative abuse)	Ammonium Urate	High urine pH and low urine cations (Na, K, Mg)

Table 2

Imaging Studies in Evaluation of Nephrolithiasis

Imaging Modality	Advantages	Limitations	Clinical Uses
Plain radiography of the kidneys, ureters, and bladder (KUB)	• Small radiation dose • Wide availability • Low cost	• Misses small and/or radiolucent stones • Can be limited by overlying bowel gas, body habitus, extra-renal calcification • Limited anatomical information	• Follow-up of known radiopaque calculi • Planning of fluoroscopically guided SWL
Intravenous Urography	• Wide availability • Estimation of renal function and of degree of obstruction • Detection of anatomical abnormalities	• Contrast use • Moderate radiation dose	• Occasional used in pre-operative planning • Largely replaced by CT scan
Computed Tomography (CT) scan	• Sensitive/specific • Fast • Widely available • No contrast needed • Detects extra-urinary pathology	• Expensive • High radiation dose	• Modality of choice in suspected renal colic patient • May be useful in identifying stone composition
Ultrasound	• No contrast • No radiation • Low cost • Wide availability	• Poor visualization of ureteral stones • Poor estimation of stone size	• Modality of choice in pediatric and pregnant patients
Magnetic Resonance Urography	• No radiation	• Limited availability • High cost • Contrast risk in CKD patients • Cannot distinguish stone from blood clot	• Rarely used, primarily in pregnant or pediatric patients

Table 3

Utility of Serum Chemistry Profile in the Evaluation of Kidney Stone Formers

Parameter	Clinical Utility
Creatinine	• Evaluation of kidney function (possible indication of obstruction and/or chronic kidney disease)
Calcium/Parathyroid Hormone (PTH)	• Hypercalcemia with concomitant hyperparathyroidism suggestive of primary hyperparathyroidism • Hypercalcemia with suppressed PTH suggestive of non-PTH mediated hypercalcemia (e.g. sarcoidosis, other conditions)
Phosphorus	• Hypophosphatemia may be a sign of hyperparathyroidism or of a renal phosphate leak
Bicarbonate (CO2)	• Low serum CO2 suggestive of renal tubular acidosis or chronic diarrhea
Potassium	• Hypokalemia suggestive of renal tubular acidosis or chronic diarrhea
Uric Acid	• Hyperuricemia suggestive of gout or metabolic syndrome

Table 4

Utility of 24-hour Urine Chemistry Profile in the Evaluation of Kidney Stone Formers

Urine Parameter	Reference Range	Risk factor for	Interpretation	Risk Modification
Volume	> 2 liters per d	All stones	Reflects fluid intake – extra-renal losses (stool, sweat)	Increase fluid intake to achieve desired urine volume
Creatinine	15–25 mg/Kg body weight/d	N/A	Reflects adequacy of urine collection	
pH	5.7–6.3	• Low pH: UA stones • High pH: struvite or CaP stones	• Low pH may be due to GI losses, excessive dietary proteins, or idiopathic • High pH may be due to infection or dRTA	• Low pH: reduce dietary acid sources, consider alkali Rx • High pH: address cause (medication, infection, dRTA, others…)
Calcium	<4 mg/Kg/d OR < 250 mg/d in women, < 300 mg/d in men	• CaOx stones • CaP stones	Hypercalciuria may be due to environmental (high salt or protein intake, drugs) or metabolic causes (hyperparathyroidism, genetic, idiopathic)	• Address underlying environmental or metabolic abnormality • Consider thiazides and/or alkali therapy
Oxalate	< 45 mg/d	CaOx stones	Hyperoxaluria may be 1ry (genetic) or 2ry (high dietary sources of oxalate or enteric hyperoxaluria)	• Evaluate dietary sources of oxalate, chronic diarrhea/other GI disease or surgery • Suspect 1ry hyperoxaluria in severe oxaluria (>100 mg/d)
Citrate	> 320 mg/d	CaOx stones CaP stones	Citrate is inhibits Ca stones Hypocitraturia reflects state of intracellular acidosis (dRTA, drugs, high dietary proteins, chronic diarrhea, …)	• Assess and treat causes of intracellular acidosis • Consider alkali therapy
Uric Acid	< 700 mg/d	UA stones CaOx stones	Hyperuricosuria reflects high purine intake and/or production	• Reduce dietary purine load • Consider use of allopurinol
Cystine	< 40 mg/d	Cystine stones	Solubility of cystine is < 250 mg/L in urine	• Raise urine pH • Lower urine cystine with medications, dietary changes
Phosphorus	< 1,100 mg/d	CaP stones	High urine Phos reflects high intake of proteins	Reduce protein intake
Sodium	< 200 mEq/d	CaOx stones CaP stones	High urine Na reflects salt intake, causes hypercalciuria	• Reduce salt intake
Chloride	< 200 mEq/d	CaOx stones CaP stones	High urine Cl reflects salt intake, parallels Na intake	• Reduce salt intake
Potassium	> 40 mEq/d	N/A	Low urine K suggests low dietary alkali or diarrhea	Recommend increasing dietary alkali or potassium alkali Rx
Magnesium	> 80 mg/d	Ca stones	Low urinary Mg suggests low intake or malabsorption; role as inhibitor is controversial	• Address underlying cause

Urine Parameter	Reference Range	Risk factor for	Interpretation	Risk Modification
				• Recommend increase in dietary alkali
Sulfate	< 40 mmol/d	Ca stones UA stones	Reflects dietary animal protein intake (excess raises urine Ca, lowers urine pH)	Recommend reduction of dietary animal proteins
Ammonium	< 40 mmol/d	N/A	Reflects high dietary (animal protein) or non-dietary acid load (e.g. diarrhea)	• Address underlying abnormality (e.g. reduction of dietary animal proteins)