Nephrolithiasis

Kelley Bishop, MD*, Tobe Momah, MD, Janet Ricks, DO

KEYWORDS

• Nephrolithiasis • Urolithiasis • Hematuria • Kidney stone • Calcium oxalate

KEY POINTS

- Kidney stones, which may asymptomatic or cause significant pain and other systemic symptoms, present both acutely and chronically and in various ureteral locations.
- Etiology of stones can arise from genetic or environmental factors, with diagnosis based on symptoms, laboratory work, and imaging.
- Treatment of nephrolithiasis is multifactorial and should address nutrition and hydration status as well as medical or surgical management.
- Complications should be identified and managed quickly to minimize permanent kidney damage.
- Referral to specialist care (nephrology or urology) should be considered when conservative measures have failed.

INTRODUCTION

Nephrolithiasis, otherwise referred to as kidney stones, is the most common chronic kidney condition, after hypertension.[1] The term originates from 2 Greek words: *nephros* (kidney) and *lithos* (stone)[2] and the condition is considered part of urolithiasis (stones in urine), alongside ureterolithiasis (stones in ureter) and cystolithiasis (stones in the urinary bladder).

The first case documented in the literature was reported between 3200 BCE and 1200 BCE.[3] Stones typically develop in the kidney and pass through the urine. Although some are asymptomatic, others may grow to the point that they obstruct the ureters, causing significant discomfort. Many people who have developed a kidney stone have another within a decade.[4]

INCIDENCE/PREVALENCE

The prevalence data from National Health and Nutrition Examination Survey has shown an increase in renal stones over the past few years. The most recent prevalence

Department of Family Medicine, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA
* Corresponding author.
E-mail address: kbishop2@umc.edu

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for 2007 to 2010 has been 8.8% nationally. There has been a similar increase internationally as well. The gender difference previously seen between men and women also is decreasing; the prevalence was 10.6% for men and 7.1% for women. According to these data, renal stones affect approximately 1 in 11 people in the United States.[5] The question arises of what is causing the increase: environmental changes or improved detection of asymptomatic stones due to improved or increased use of imaging studies.

Environmental factors, such as climate and occupation, may play a part in the development of renal stones. Heat exposure and dehydration may increase the risk, primarily in men. Evaluation of insurance claims data has found that stone-related claims peaked in the hotter summer months of July to September.

Another risk that is not as well defined is the association of obesity and metabolic syndrome and renal stones. Analysis of insurance claims data found that obesity and weight gain were independent risks independent of diet. The risk increases with increasing body mass index up to 30 kg/m^2, at which time it stabilizes. The pathophysiology of this increased risk is not completely understood.[6,7]

PATHOGENESIS/PATHOPHYSIOLOGY

Renal stones develop when urine becomes supersaturated with stone-forming salts, most commonly calcium oxalate (60% of all stones), although other crystals may precipitate. If urine becomes supersaturated and no inhibition is present, then the crystals begin to form on existing surfaces of epithelial cells, cell debris, or other crystals. Several molecules assist with inhibition, such as magnesium and citrate. Nephrocalcin inhibits calcium oxalate. Tamm-Horsfall mucoprotein inhibits aggregation; uropontin inhibits crystal growth. Bikunin inhibits crystal nucleation and aggregation. There are no known specific inhibitors of uric acid crystal formation.

Calcium Stones

Hypercalciuria is the most common abnormality leading to calcium-containing stones. Hypercalciuria may occur in up to 65% of patients with stones. Abnormalities in calcium metabolism by the kidney can be divided into 3 categories: absorptive hypercalciuria (increased absorption in the intestine), renal hypercalciuria (primary renal lead of calcium), and resorptive hypercalciuria (increased bone demineralization).

Several processes may lead to increased absorption of calcium in the intestine. Increased oral calcium load suppresses parathyroid hormone and increases renal filtration of calcium with the serum calcium being normal. There also are vitamin D–dependent processes—increased vitamin D production or intake and increased sensitivity to vitamin D. Renal phosphate wasting also increases the vitamin D level.

Renal hypercalciuria is caused by impaired renal tubular reabsorption of calcium, which causes elevated urinary calcium levels and secondary hyperparathyroidism. There are several genetic mutations and abnormalities that may lead to the calcium leak: Dent disease (X-linked recessive nephrolithiasis), familial hypomagnesemia with hypercalciuria and nephrocalcinosis (mutations in claudin-16 and claudin-19), Bartter syndrome (autosomal recessive involving the loop of Henle), and autosomal dominant form of hypocalcemia (mutations in the gene encoding CaSR). Resorptive hypercalciuria is infrequent and associated commonly with primary hyperparathyroidism. Other, more rare causes of resorptive

hypercalciuria are sarcoidosis, thyrotoxicosis, hypercalcemia of malignancy, and vitamin D toxicity.

Uric Acid Stones

Uric acid stones comprise 8% to 10% of all renal stones. The main determinants of uric acid stone formation are low urine pH, low urine volume, and hyperuricosuria. The most important of these is low pH. Congenital disorders involving renal tubular urate transport or uric acid metabolism lead to hyperuricosuria. Acquired causes are chronic diarrhea, volume depletion, myeloproliferative disorders, and uricosuric drugs. Uric acid stones also may develop with diets high in animal protein.

Struvite Stones

Struvite stones may be generated by urea-splitting bacteria, mycobacteria, or yeast creating urease. Urease normally is not present in human urine. The chemical cascade starts with urea (normally found in urine) and splits to urease, ultimately ending in struvite (magnesium ammonium phosphate), which can then form stones. Calcium also may adhere to struvite creating a mixed stone. The most common organisms that cause this type of stone are Proteus, Klebsiella, Pseudomonas, and Staphylococcus. Because these stones occur most commonly in people prone to frequent urinary tract infections (UTIs), women are affected more commonly than men, with a ratio of 2:1. Other comorbid states that may increase the risk are spinal cord injury, urinary tract malformation, diabetes, and urinary stasis.

Other

Other stones are rare but may include cysteine; infection stones consisting primarily of magnesium ammonium phosphate hexahydrate, xanthine, dihydroxyadenine, or ammonium acid urate; and protein matrix stones. Certain medications can precipitate in the urine and form stones; these are listed in **Table 1**. These stones generally form as crystals after taking excessive amounts of the drug.[6]

Table 1
Lithogenic drugs

Drug	Stone Formation
Atazanavir/ indinavir	Supersaturation
Acyclovir	Supersaturation
Sulfa drugs	Supersaturation
Methotrexate	Supersaturation
Triamterene	Supersaturation
Quinolones	Supersaturation
Ephedrine	Supersaturation
Magnesium trisilicate	Supersaturation
Loop diuretics	Calcium
Acetazolamide	Calcium
Zonisamide	Calcium

CLINICAL PRESENTATION

More than 40% of patients with kidney stones are asymptomatic.[5] Among the symptomatic patients, the most common presenting complaint is sudden-onset abdominal pain, cramping in nature, and associated with moderate to severe colic, also known as renal colic.[8] This pain is localized mostly to the flank or anterior upper abdomen[9] and usually occurs when the stone enters or obstructs the ureter. As the stone descends, however, it may present as pain in the ipsilateral testicle or labia.

Additional accompanying symptoms include urinary urgency, sweating, hematuria, and nausea and vomiting. Approximately 50% of nephrolithiasis patients who are symptomatic present with nausea and vomiting,[10] secondary to the shared splanchnic innervation of the renal capsule and intestines.[11] The abdominal pain, however, stops abruptly when the stone passes into the bladder, and it is not aggravated or alleviated by a change of position.

Hematuria is present in more than 90% of nephrolithiasis patients,[12] but its absence does not rule out nephrolithiasis. Individuals whose kidney stones are at the ureterovesical junction present with increased frequency of urination and dysuria[9] that could be mistaken for a UTI.

In order to differentiate nephrolithiasis from UTI, however, the patient must be evaluated for fever, chills, and cloudy foul-smelling urine. In patients with staghorn calculi, where large renal stones are impacted in the pelvis of the kidney, UTIs and obstructive symptoms that lead to permanent kidney damage and hydronephrosis could be the presenting signs and symptoms.[13]

Elderly patients with nephrolithiasis are more likely to have a subclinical presentation. They present with atypical or no pain, fever, gastrointestinal symptoms, pyuria, or UTI.[14] They also tend to have larger stone diameters and increased need for surgical intervention as they grow older. In children, on the other hand, nephrolithiasis symptoms are consistent with an adult's clinical presentation but may consist more of hematuria, generalized abdominal pain, or UTI.[1]

LABORATORY WORK-UP

Laboratory tests include urinalysis, complete blood cell count (CBC), and serum chemistry to evaluate creatinine clearance.[8] A woman of childbearing age should undergo a pregnancy test, and a CBC with differential level is indicated especially for patients with systemic signs of infection or an alternate abdominal etiology to nephrolithiasis. The most common urinalysis finding in nephrolithiasis patients is hematuria (more than 90%).[12] Other urinalysis findings seen in these patients include pyuria, leukocyte esterase, nitrites, or greater than 50 white blood cells per high-power field (if concomitant with UTI)[8] (**Box 1**).

IMAGING WORK-UP

Further radiologic testing may be necessary for establishing a diagnosis of kidney stones after initial clinical and laboratory assessment. The current gold standard for diagnosing the majority of kidney stones is the low-dose CT, with 95% sensitivity and 98% specificity. Another radiologic study that may be required in certain circumstances is the renal ultrasound, which is the usual choice in pregnant patients and in children. A drawback to renal ultrasound is that distal ureteric calculi that are less than 5 mm generally are not visible on ultrasound and the reliability is operator-dependent.[15] The intravenous pyelogram, which was the gold standard prior to the CT, in

Box 1
Laboratory work-up

Microscopic urinalysis
- Red blood cells, bacteria, leukocytes, urinary casts, crystals
- Urine culture and sensitivity

CBC
- Neutrophilia (can be suggestive of struvite stones)

Renal function panel/chemistry
- Hypercalcemia

Strain urine
- Stone analysis

24-Hour urine stone risk profile
- Determine dietary guidance/medicinal prevention

general lacks specificity and sensitivity but may be required in diagnosing radiolucent stones, such as those caused by protease inhibitors, such as indinavir.[16,17]

WORK-UP FOR RECURRENT STONES

The work-up should be considered based on a patient's risk factors and history. Taking a detailed personal and familial history can guide how extensive the initial work-up should be. Unless a patient has family or personal history of stones, a history of repetitive UTIs, a history of nephrocalcinosis, or a history of gastroenterologic disease, such as Crohn or ulcerative colitis, the diagnostic work-up assessment should consist of a urinalysis with microscopic, blood work including electrolytes and kidney function tests, serum calcium and phosphorus levels, and uric acid levels.[18]

While taking the history, a detailed dietary intake should be done as well as a complete medication intake history, focusing particularly on medications that can contribute to kidney stones[18] (see **Table 1**). Within the dietary history, a quantification of fluid intake should be documented. Other contributing diseases and conditions should be screened for in the history, such as hyperparathyroidism, renal tubular acidosis, and prior urologic surgeries.[16]

If available, collection of the stone by straining the urine can be helpful in directing prevention therapy and further diagnostic studies.[18] For patients found to have a uric acid or cystine stone, for those where a stone is unobtainable, and for patients with multiple calcium stones, studies including a 24-hour urine stone risk profile should be considered to help determine direction in dietary guidance or possible medicinal prevention[18,19] (see **Box 1**).

MANAGEMENT PRIOR TO REFERRAL

Management of acute renal calculi is determined by the presence of infection or obstruction. Larger stones, greater than 8 mm, rarely pass spontaneously and usually require urology referral. The American Urological Association recommends ureteroscopy and extracorporeal short-wave lithotripsy as first-line treatment of ureteral-placed stones and percutaneous nephrostomy if a stent is not possible.[20] Obstruction is less likely in stones less than 3 mm. Most of these calculi resolve with hydration as well as pain control.[16] Hydration should be attempted with the aim of maintaining a urine output of greater than 2 L per day.[15]

In the era of opioid crisis, effort should be made to attempt pain control without use of scheduled drugs.[21] Furthermore, nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be equivalent or superior to opioids and/or morphine. In a 2018 systematic review and meta-analysis published by Panthan and colleagues,[22] NSAIDs were shown to be equivalent to opioids or acetaminophen for the relief of acute renal colic at 30 minutes with less vomiting and fewer requirements for rescue analgesia. Of the NSAIDs available, diclofenac was shown to be superior in a 2017 review by Garcia-Perdomo and colleagues[23] and was superior to morphine for pain reduction.

Lifestyle Modifications for Prevention of Stone Recurrence

Management of patients with history of multiple kidney stones should be centered on prevention. In this realm, management through diet is one of the most cost-effective measures. Diets high in animal protein have been shown to increase acid load, thereby reducing the urine pH, which contributes to enhancing urinary calcium excretion. Avoidance of animal protein in a diet low in meat, fish, and poultry can help achieve an alkaline urine. In addition, a diet of increased intake of fruits and vegetables high in potassium has been shown beneficial.[24,25] Alkaline urine is preferable to prevent calcium, cystine, and uric acid stones.[25] Studies have shown that reducing soft drinks or colas acidified with phosphoric acid, as well as a diet high in calcium and low in protein and sodium, reduced stone recurrence.[20] Patients with calcium oxalate stones have been counseled in times past to limit oxalate dietary intake. This has shown to be ineffective unless the patient has hyperoxaluria. Furthermore, adequate calcium dietary intake (1000–1200 mg daily) could reduce the consequences of dietary oxalate.[26] For prevention of uric acid stones in particular, limiting purine-containing foods is recommended[15] (**Box 2**).

As in acute management, hydration to maintain an adequate urine output of greater than 2 L a day is a good step in prevention.[25] In that realm, recommendation of drinking 1 beer or so a day has had mixed results in that it has been shown to be somewhat helpful in the prevention of calcium stones but may be counterproductive in prevention of urate stones.[15] The importance of the type of hydration also has been seen in several large studies in that increased stone formation was seen with increased sugar-sweetened soda, postulated to be secondary to high fructose content. Artificial sweeteners did not convey the same risk, and increased intake of coffee, tea, red and white wine, beer, and orange juice had a protective effect[24] (see **Box 2**).

Iatrogenic Consideration for Prevention of Stone Recurrence

Consideration toward iatrogenic causes must be made in the prevention of stones. Some medications that are known to be lithogenic, prone to forming crystals in the urine, are atazanavir, indinavir, acyclovir, sulfadiazine, methotrexate, triamterene,

Box 2
Lifestyle modification for prevention of kidney stones

- Hydration to attain urine output greater than 2 L daily
- High-calcium, high-potassium, low-protein, low-sodium diet
- Limit soft drinks acidified with phosphoric acid
- Limit purine-containing food (prevention of uric acid stones
- Limit high-fructose corn syrup intake

quinolones, sulfa medications, guaifenesin/ephedrine, and magnesium trisilicate. In addition, loop diuretics, acetazolamide, topiramate, and zonisamide all have been seen to increase incidence of calcium stones (see **Table 1**). An effort to change from these medications in patients who have been diagnosed with a stone probably formed from drug deposition should be attempted. Also, limiting ammonium acid–based laxatives is prudent in uric acid stone formers because ammonium acid urate calculi can be seen with urine supersaturation with ammonia and uric acid.[15,27]

Pharmacologic Therapy for Prevention of Stone Recurrence

Pharmacologic therapy for prevention of calcium, uric acid, and cystine stones should be considered if hydration and dietary management have been ineffective. For those types of stones, affecting an alkaline urine is recommended. This can be achieved with supplementation of potassium citrate at doses of 20 mEq to 80 mEq divided 3 times to 4 times daily with a target urinary pH of not below 6.5. Special consideration should be given to avoiding increasing the pH too far to prevent calcium phosphate supersaturation, thereby contributing to stone formation.[15]

For calcium stones, addition of thiazides and/or allopurinol has been shown protective.[20] Thiazides help in resorption of calcium at the renal tubule, especially in combination with a low-salt diet. Doses used were at least 50 mg daily.[24] Reduction of dietary sodium can decrease renal tubular calcium reabsorption, encouraging urinary excretion of calcium.[25] Studies have shown that people following the Dietary Approaches to Stop Hypertension (DASH) diet with the highest DASH scores had a 40% to 50% reduced stone formation.[24]

For uric acid stone prevention, lowering serum uric acid by addition of allopurinol is recommended if diet is not sufficient.[15] Also, uricosuric medications, such as probenecid, should be avoided, because they contribute to urinary excretion of uric acid.[25] Furthermore, hyperuricosuria has been shown to increase formation of calcium oxalate crystals in vitro, leading to the supposition that it may increase incidence of calculi in calcium oxalate stone formers. Recommended dosing for prevention is 100 mg to 300 mg daily.[15,24]

If dietary management proves insufficient in preventing cystine stones, pharmacologic therapy with medications, such as D-penicillamine and tiopronin, which bind cystine, may be considered. Although robust studies are not available, decrease of calculi formation up to 75% has been seen in a few uncontrolled and observational trials. Dosages used were 1 g/d to 2 g/d of penicillamine or 800 mg/d to 1200 mg/d of tiopronin, both in divided doses. Unfortunately, both have drawbacks of possible leukopenia, aplastic anemia, proteinuria, and hepatotoxicity, with tiopronin tolerated slightly better.[24]

For infection or struvite stones, the key to treatment is retrieval of the stone because bacteria can live uninhibited by antibiotics in the interior of the stone. Urine culture and targeted antibiotics are key as well as referral to urology for percutaneous nephrolithotomy.[15] When retrieval is not possible, medical therapy with urease inhibitor acetohydroxamic acid is indicated. Three randomized controlled trials have shown proved decrease in growth of stones using this medication. Use of this drug is complicated by its high side-effect profile, including significant gastrointestinal upset[24] (**Table 2**).

POTENTIAL COMPLICATIONS

The main complications of renal stones are pyonephrosis (infected urine behind an obstructing stone) and hydronephrosis (complete blockage of the ureter with

Table 2
Dietary and Pharmacologic Intervention

Type of Stone	Target Urinary pH	Recommended Diet	Pharmaceuticals/Supplements to Consider	Drugs to Avoid
Calcium	Alkaline	Low in animal protein, high in potassium-rich fruits/vegetables; DASH diet	Thiazides, potassium citrate, allopurinol	Loop diuretics, acetazolamide, topiramate, zonisamide
Uric acid	Alkaline	Low in purine-containing foods	Allopurinol, potassium citrate	Probenecid, ammonium acid laxatives
Cystine	Alkaline	Low in animal protein, high in potassium-rich fruits/vegetables	Potassium citrate, D-penicillamine, tiopronin	—
Struvite	Alkaline	Low in animal protein, high in potassium-rich fruits/vegetables	Targeted antibiotics, Acetohydroxamic acid	—

Legent

subsequent urine collection). Both of these can cause significant morbidity. Pyonephrosis requires immediate drainage of the obstructed kidney, which can be accomplished either percutaneously or with a renal stent. Hydronephrosis also requires drainage in a similar manner. Hydronephrosis may be silent, however. The stone may become impacted in the ureter and then become covered with urothelium. This causes a more gradual collection of urine and the kidney eventually becomes atrophic and nonfunctioning. Surprisingly, this may cause little to no pain due to the gradual nature of the buildup.[28]

Another concerning complication may be increased risk of chronic kidney disease (CKD). One study found an increased risk in men with CKD: 15.21% had a history of renal stones versus 11.4% without. The difference was higher in women: 23.18% with versus 13.48% without renal stones.[29] The study did not state if there were other complications related to the treatment of the stone—just whether a history of stones was present.

NEPHROLOGY CONSULTATION/REFERRAL

Although urology is the mainstay in referral for acute surgical management of nephrolithiasis, referring to nephrology may be needed at times for the sequela and further management of recurrence of nephrolithiasis. There is an increased risk for CKD in patients with history of multiple symptomatic kidney stones shown in recent population studies. Stone formers have been seen, in a population-based historical cohort study, to be at increased risk of CKD, even when controlled for the usual causes of diabetes, hypertension, or obesity. The risk for clinical CKD was 50% to 65% greater in stone formers.[26] Although nephrolithiasis is an infrequent cause of kidney failure, struvite (infection) stones have been associated with an increased risk of acute kidney failure or CKD.[15]

Patients with recurrent nephrolithiasis should be referred to nephrology for a detailed evaluation of metabolic factors to determine preventable causes of the stones as well as aiming at promoting resolution of any existing stones. Also, consideration should be given to referral to a nephrologist when treating patients who have a family history of renal calculi along with inflammatory bowel disease, frequent UTIs, or a history of nephrocalcinosis, which is found most frequently incidentally while imaging in the quest for diagnosis of stones.[15,18]

SUMMARY

Nephrolithiasis or kidney stones is the second most common CKD, affecting 12% of all people. Early recognition and treatment of this condition are important to prevent complications that can occur with delayed treatment. Furthermore, increasing prevalence of this disease underlines the importance of correctly diagnosing the causative factors, thereby affecting prevention of recurrence.

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DISCLOSURE

The authors have nothing to disclose.

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