The Growing Prevalence of Kidney Stones and Opportunities for Prevention

KATHERINE RICHMAN, MD; JOHN O’BELL, MD; GYAN PAREEK, MD

ABSTRACT
The prevalence of kidney stones is climbing in the United States. Several investigators have demonstrated an association between metabolic syndrome and kidney stones and some have proposed a causal link. Risk factors for nephrolithiasis can be identified with a 24-hour urine collection and preventive measures can be customized to meet the needs of individual patients. Dietary and pharmacologic interventions are available to address urinary risk factors such as inadequate urine volume, hypercalcuria, hyperoxaluria, hyperuricosuria and hypocitraturia. Given that morbidity and healthcare costs associated with nephrolithiasis are on the rise, deterring stone formation is increasingly important. Multidisciplinary clinics that foster collaboration between urologists, nephrologists and dieticians offer patients effective prevention and treatment strategies.

KEYWORDS: kidney stones, nephrolithiasis, metabolic syndrome, risk factors

INTRODUCTION
The prevalence of nephrolithiasis in the United States is increasing [1, 2]. Patients with kidney stones often have a benign course, but life-threatening complications like acute kidney injury and infection can arise. Moreover, the financial burden from medical expenditures and lost productivity is substantial. By one estimate, more than 4 billion dollars were spent treating nephrolithiasis in the year 2000 and since that time costs have been steadily rising [3]. Healthcare providers practicing preventive care should be mindful of risk factors for nephrolithiasis and implement risk-reduction therapy when possible.

EPIDEMIOLOGY
In 1994, the National Health and Nutrition Examination Survey (NHANES) reported a kidney stone disease prevalence of 5.2%. More recent NHANES data, from 2007-2010, revealed an overall prevalence of 8.8%[1]. The prevalence of stones among men increased from 6.3% to 10.6% and from 4.1% to 7.1% among women. Nephrolithiasis continues to be most common in white individuals but the prevalence has increased by 150% (from 1.7% to 4.5%) in African Americans [1]. NHANES data also shows a 91% rise in emergency department (ED) visits for kidney stones since the 1990s. In 1992-1994, 178 per 100,000 ED visits were coded for nephrolithiasis. By 2004-2006 ED visits for stones had increased to 340 per 100,000[2]. ED visits for stones increased by 70% in men and by 128% in women, which is consistent with other observations that the gender gap in stone patients is narrowing [1, 2].

Data from Rhode Island Hospital (RIH) mirrors national data. In 2004, the RIH emergency department (ED) reported 111 cases of kidney stones. By 2013, ED visits coded for nephrolithiasis had grown to 695. As the prevalence of stones increases and medical expenditures mount, the need to focus on prevention intensifies.

Calcium oxalate and calcium phosphate calculi account for more than 80% of kidney stones. Less common stone types include uric acid, magnesium ammonium phosphate (struvite) and cysteine stones. Prevention and treatment strategies vary according to the stone composition. The remainder of this discussion will focus primarily on calcium stones.

RISK FACTORS
The growing prevalence of diabetes and metabolic syndrome and the rise in the number of patients with kidney stones may be more than a coincidence. Multiple studies have demonstrated a heightened risk of nephrolithiasis in patients with metabolic syndrome [4-6]. According to NHANES 3 data from 1988 to 1994, having just two metabolic syndrome traits (abdominal obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein, impaired glucose tolerance) was associated with a significant increase in self-reported kidney stone disease. Study participants with 4 or 5 traits were twice as likely to report kidney stones as those with no features of metabolic syndrome [5].

More recent data from Korea identified hypertension and metabolic syndrome as independent risk factors for radiographically-proven kidney stones. Patients with hypertension had an odds ratio of 1.47 for nephrolithiasis, while those with metabolic syndrome had an odds ratio of 1.25 [6]. Obesity, weight gain, fasting glucose ≥ 100, and glycosylated hemoglobin ≥ 6.5% have also been associated with an increased risk of stone formation [7, 8]. Although calcium oxalate stones remain the most common stone type in patients with metabolic syndrome, there has been a
substantial increase in the frequency of uric acid nephrolithiasis as well, which appears to be correlated with insulin resistance [9, 10].

While bariatric surgery is increasingly used to treat the morbidity associated with obesity, patients who have undergone Roux-en-Y gastric bypass are at higher risk for nephrolithiasis than obese controls [11]. Hyperoxaluria and hypocitraturia, two urinary risk factors for stone formation, have been observed in nearly half of patients post gastric bypass [12]. Malabsorption of fatty acids results in saponification of calcium which decreases calcium-oxalate complex formation in the gut. In turn, more oxalate is available for absorption from the intestine and is ultimately excreted in the urine [12].

Other medical conditions that confer an increased risk of kidney stones include hyperparathyroidism, renal tubular acidosis, recurrent urinary tract infections, inflammatory bowel disease and medullary sponge kidney [13].

**PREVENTION**

Patients presenting with nephrolithiasis for the first time have a 50% chance of recurrence by 10 years [13]. In order to prevent recurrence, a detailed medical history and basic metabolic evaluation should be completed in all patients with nephrolithiasis. Available calculi should be analyzed. Serum calcium, phosphorous, potassium, bicarbonate, blood urea nitrogen, creatinine, uric acid and a basic urinalysis should be checked. Abnormalities such as hypercalcemia suggestive of hyperparathyroidism, or low serum bicarbonate consistent with a metabolic acidosis should be thoroughly explored. Recurrent kidney stones, bilateral or multiple stones, age younger than 25, solitary kidney, diabetes or a strong family history of nephrolithiasis should prompt a 24-hour urine collection to identify specific urinary risk factors [13].

Kidney stone formation occurs when the urine is supersaturated with dietary minerals such as calcium, oxalate and phosphate. Crystals precipitate from solution and aggregate to form stones. A 24-hour urine collection that measures volume, sodium, calcium, phosphorous, oxalate, uric acid, pH and citrate identifies risk factors for supersaturation and stone formation [14]. Knowing the type of stone formed by a patient is important in determining preventive measures, but urinary risk factors may vary among patients with the same type of stone. An intervention that is effective in one patient with calcium oxalate stones may not be effective in another patient with the same stone type. For example, not all patients with calcium oxalate stones have hyperoxaluria and prescribing a low oxalate diet is not always necessary.

At least two 24-hour urine collections should be done to confirm risk factors. Collections should not be done within three months of passing a stone. Testing should be done on an outpatient basis when the patient is free to maintain a typical self-selected diet. Using the results of the 24-hour urine collection, the clinician can customize preventive strategies to meet the needs of the individual patient [14]. Once interventions are made, the urine collection should be repeated to make sure that the prescribed therapy is effective in attenuating risk factors.

**URINARY RISK FACTORS AND PREVENTIVE STRATEGIES**

**Inadequate Urine Volume**

The cornerstone of preventing stone formation is avoiding supersaturation of the urine with a stone-forming substance. Thus all stone formers are advised to maintain dilute urine. Drinking enough to maintain urine output of at least 2 to 2.5 liters per day could cut the risk of stone recurrence in half [15].

Although increasing fluid intake is a relatively low-cost intervention and has few adverse effects, barriers to utilization do exist. Some patients report not liking the taste of water and forgetting to drink. Other patients are highly motivated to prevent stone recurrence but are unable to void frequently because of occupational demands and workplace restrictions [16].

Increasing intake of any low-calorie fluid is generally recommended. A recent prospective study of 194,095 health professionals found that participants who consumed one or more servings of sugar-sweetened cola per day were 23% more likely to develop stones than those who consumed less than one serving per week. Consuming sugar-sweetened non-cola carried a 33% higher risk of nephrolithiasis. Conversely, daily decaffeinated coffee intake appeared to decrease the risk of stones by 26%. Decaffeinated coffee, tea, wine, beer and orange juice were also associated with a lower risk of nephrolithiasis [17].

**Hypercalcuria**

Hypercalcuria is usually idiopathic but can be the result of hyperparathyroidism. Parathyroid hormone levels should be checked in patients with electrolyte abnormalities like hypercalcemia and hypophosphatemia. Dietary calcium restriction is unnecessary and may, in fact, increase the risk of calcium stone formation [18]. In a prospective study of more than 78,000 women, the average daily dietary calcium intake was 39 mg lower in women who developed kidney stones than in those who did not. On the other hand, average sodium intake was 60 mg higher in stone formers [19]. Italian men, with recurrent calcium oxalate stones and hypercalcuria, randomized to a normal-calcium, low-salt and low-animal-protein diet had a relative risk of stone recurrence of 0.49 compared to men placed on a low-calcium diet [18].

Limiting sodium intake to 2300 mg per day is recommended to decrease urinary calcium and stone risk [20]. Thiazide diuretics also reduce urinary calcium and a recent systematic review of six randomized controlled trials found moderate-strength evidence that thiazide diuretics are...
effective in lowering the likelihood of stone recurrence. Hydrochlorothiazide, chlorothalidone and indapamide seemed to be equally effective [15]. Dosing has not been well studied, but quantification of urinary calcium with repeat 24-hour collections can be used to titrate therapy.

Hyperoxaluria
A low calcium diet might augment the risk of nephrolithiasis by increasing free oxalate in the gut. Enhanced oxalate absorption could ultimately lead to hyperoxaluria, thereby increasing stone risk. Although evidence is lacking for the efficacy of a low oxalate diet in stone prevention, restricting oxalate-rich foods like spinach, nuts and chocolate in patients with hyperoxaluria is generally recommended [20]. High doses of vitamin C amplify oxalate excretion and should be avoided [22]. As previously noted, bariatric surgery or small bowel disorders like Crohn’s disease can result in fatty acid malabsorption and hyperoxaluria. Restriction of dietary fat and oxalate and increasing calcium intake with meals may attenuate the risk of calcium oxalate stones in patients with malabsorption [20].

Hypocitraturia
Citrates chelates calcium in the urine and inhibits formation of calculi. Chronic diarrhea, renal tubular acidosis and diets high in animal-protein may all be accompanied by a decrease in urinary citrate and a higher risk of stone formation [23]. Urinary citrate can be increased via pharmacologic or dietary intervention. A number of investigations, including four small randomized controlled trials, have shown a decrease in stone recurrence with citrate supplementation, usually given in the form of potassium citrate [15]. For patients who are unable to tolerate pharmacologic therapy or prefer dietary intervention, consuming 4 ounces of lemon juice diluted in water or 32 oz of sugar-free lemonade daily results in a significant increase in urinary citrate [24].

When citrate is used in patients with a history of calcium phosphate stones the urine pH should be monitored closely. Citrate alkalinizes the urine which can be advantageous in preventing uric acid and cysteine stones but promotes the formation of calcium phosphate stones.

Hyperuricosuria
Hyperuricosuria is associated with both uric acid stones and calcium stones. Uric acid decreases calcium oxalate solubility and encourages stone formation. A high purine diet often underlies hyperuricosuria but myeloproliferative disorders and uricosuric drugs are other possible etiologies [20]. Decreasing intake of animal protein may be of benefit and a few randomized controlled trials suggest that allopurinol decreases the risk of calcium oxalate stones [15].

TREATMENT
When prevention fails and calculi form, urologic intervention may be required. Approximately 10–20% of symptomatic stones do not pass spontaneously [20]. Most stones smaller than 5 mm will pass freely while calculi >10 mm usually require intervention [13]. According to the American Urological Association’s treatment guidelines, shock-wave lithotripsy and ureteroscopy are first-line procedures for stone removal. For larger stones (>1.5 cm) minimally invasive percutaneous surgery may be required through a 1 cm incision in the flank. Uncommonly, open surgical methods may be necessary to render a patient stone-free.

Multi-disciplinary clinics that combine the services of urologists, nephrologists and dieticians provide an effective approach to prevention and management. Hosking coined the term, “stone clinic effect” after demonstrating a significant decrease in stone recurrence in patients who had visited a clinic and received basic instruction on dietary modification and fluid intake [25]. When calculi form despite preventive efforts, regular surveillance in a stone clinic fosters timely intervention and can minimize morbidity.

CONCLUSION
The incidence of kidney stones is on the rise but preventive measures can be deployed. A 24-hour urine collection can determine risk factors for stone formation and be used to customize preventive strategies for individual patients. Maintaining dilute urine is an important prophylactic measure for any stone type. Hypercalcuria, hyperoxaluria, hypocitraturia, and hyperuricosuria are urinary risk factors for calcium-containing calculi, the most common type of stone. Dietary and pharmacologic measures can be taken to address these risk factors. Primary care providers and specialists have an opportunity to decrease morbidity and health care costs by working with patients to design individualized prevention strategies.

References