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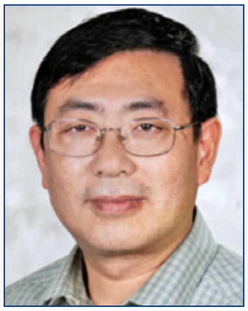

Jie Tang, MD, MPH

Gyan Pareek, MD

SPECIAL SECTION

Kidney Stone Disease

JIE TANG, MD, MPH
GYAN PAREEK, MD
GUEST EDITORS

Kidney Stone Disease – Clinical Perspectives

JIE TANG, MD, MPH
GYAN PAREEK, MD
GUEST EDITORS

Kidney stone disease poses a growing public health challenge worldwide. In the United States, its prevalence has been steadily rising from 3.8% in the 1970s to 8.8% in the late 2000s,[1] and up to 13% of men and 7% of women will develop a kidney stone in their lifetime.[2,3] More concerning is that kidney stone formers have a recurrence rate up to 50% by five years.[4] Kidney stone disease is now considered a complex systemic illness strongly associated with metabolic syndrome, hypertension, diabetes, cardiovascular disease, chronic kidney disease, and bone loss, leading to significant morbidity.[5] Although the disease by itself does not appear to portend a higher mortality compared to the general non-stone forming population with similar comorbidity,[5] disability-adjusted life years and deaths attributed to kidney stone have increased globally over the last two decades.[6] Equally, the economic impact associated with kidney stones has been huge. In the United States alone, it has been estimated to cost upwards of 5 billion US dollars annually.[7]

Most kidney stones are composed of calcium and oxalate, which account for about 80% of all kidney stones identified.[8,9] As a result, both hypercalciuria and hyperoxaluria are key risk factors for recurrent kidney stone. Hypercalciuria can be idiopathic or secondary to a variety of medical conditions including hyperparathyroidism, sarcoidosis, and inappropriate use of medications or dietary supplements. Hyperoxaluria is also common among kidney stone formers, and can result from genetic disorders such as primary hyperoxaluria or can be secondary to conditions associated with toxic ingestion or enhanced oxalate absorption from the gut. Additionally, obesity, metabolic syndrome and diet also have strong independent associations with the risk of kidney stone disease,[10,11] and appear to be the driving force for the rising global kidney stone disease burden.

For patients suspected of kidney stone disease, early diagnosis is essential. The classic presentation is flank pain and gross or microscopic hematuria. Imaging is critical to make the diagnosis and the gold standard modality utilized is a non-contrast computed tomography scan. Pregnancy must be ruled out with a urinary test in the female patient. Other imaging studies utilized during the work-up for suspected stone disease include kidney, ureter bladder X-ray, and ultrasound. It is imperative to act quickly to make the diagnosis. A urinalysis must be done at presentation, as any signs of an infection with the possibility of an obstruction is a medical emergency and should prompt the provider to send the patient to the emergency department.

In order to prevent serious health consequences, prompt identification and control of kidney stone risk factors are key in its clinical management. For patients with calcium oxalate kidney stones, the goal is to reduce the supersaturation of calcium oxalate in urine. Supersaturation is the gold standard for assessing crystallization potential, and represents thermodynamic driving force for the process of nucleation, growth, and aggregation, ultimately the stone formation. It is defined as the ratio of the concentration of the material of interest divided by its concentration at saturation. Supersaturations of calcium oxalate, calcium phosphorus and uric acid have direct predictive values for the risks of corresponding stone formation. In addition to various medications used to reduce the crystallization potential of stone-forming minerals, dietary modification is now becoming a key component of kidney stone management for prevention. In general, an alkaline diet rich in citrate and potassium, but limiting salt and purine is highly recommended. Maintaining adequate dietary calcium intake and oral hydration are also important.

Emergent surgical interventions are often indicated in cases of obstructing ureteral stones with urinary tract infection or acute kidney injury, especially in patients with a solitary functioning kidney. Elective surgery may be indicated in patients who are passing large ureteral stones (>5 mm), or in those who have difficulty passing ureteral stones less than 5 mm after four to six weeks of medical expulsive therapy, or in those who have uncontrolled pain or recurrent UTI related to stones. The urologist's armamentarium for surgical management of stones includes shockwave lithotripsy (SWL), retrograde ureteroscopy (URS), percutaneous nephrolithotomy (PCNL) and rarely, open or robotic surgery.

The most common procedure in the United States currently is URS. The procedure is an outpatient procedure performed under general anesthesia where a small endoscope is passed through the urethra and into the ureter or kidney depending on the location of the stone. A laser fiber is passed through the endoscope to fragment and "dust" the stone. A ureteral stent is left in the majority of cases at completion and removed one week post-operatively in the office. SWL is a non-invasive technique that breaks up stones with ultrasound waves and is most commonly done with sedation in the out-patient setting and is reserved for non-acute treatment. PCNL is indicated for stones larger than 2cm and involves access to the kidney from the flank, creation of track through which large stones are pulverized with lithotrites and suctioned out through an intricate system. Robotic and open surgery are indicated in situations where the minimally invasive methods mentioned above would not be possible (complex anatomy).

This issue of the *Rhode Island Medical Journal* features a series of articles on calcium kidney stone disease. Authors will review pathophysiology, and discuss diagnostic and therapeutic approaches.

Author Contributions

Idiopathic hypercalciuria, written by **OLIVE W. TANG, MD, PhD**, and **JIE TANG, MD, MPH**, will review current literature on the topic, and discuss diagnostic and therapeutic approaches.

Hyperoxaluria – a major metabolic risk for kidney stone disease, written by **CHRISTOPHER OWINO, MD**; **ANN MUTUGI, MD**, and **JIE TANG, MD, MPH**, will review current literature on the topic and discuss pathophysiology of hyperoxaluria as well as diagnostic and therapeutic approaches.

Dietary control of calcium kidney stone disease, written by **SAIRAH SHARIF, MD**; **JIE TANG, MD, MPH**, and **MATTHEW LYNCH, MD**, will review current literature on the topic and discuss the rationale of various dietary interventions for stone prevention.

Dietary magnesium intake and the risk of kidney stone disease, written by **SANDIPAN SHRINGI, MD**; **CHRISTINA RAKER, ScD**, and **JIE TANG, MD, MPH,** will present the findings of our analyses of the National Health and Nutrition Examination Survey 2011-2018, a large US population survey.

Diagnostic imaging for kidney stone, written by **SARAH MOORE, MD**, et al, will review all the current imaging modalities available in the work-up of stone disease and the clinical scenarios where each should be ordered.

Surgical interventions for kidney stones, written by **REBECCA WALES**, et al, will review all the surgical management procedures available to treat kidney stones and the clinical scenarios where they are indicated.

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Guest Editors

Jie Tang, MD, MPH, FASN, is an academic nephrologist from Brown Physicians, Inc. He is affiliated with Lifespan Hospitals and the Veteran's Administration Medical Center of Providence. He is an associate professor of medicine at the Alpert Medical School of Brown University. His primary research interest is in chronic kidney and kidney stone diseases.

Gyan Pareek, MD, FACS, is an academic urologist from Brown Physicians, Inc. He is affiliated with Lifespan Hospitals, and is the Krishnamurthi Family Professor at the Alpert Medical School of Brown University and Chief of Urology. His primary research interest is in prostate and kidney stone diseases.

Correspondence

Jie Tang, MD
jie.tang@brownphysicians.org

Idiopathic Hypercalciuria – A Major Metabolic Risk for Calcium Kidney Stone Disease

OLIVE W. TANG, MD, PhD; JIE TANG, MD, MPH

ABSTRACT

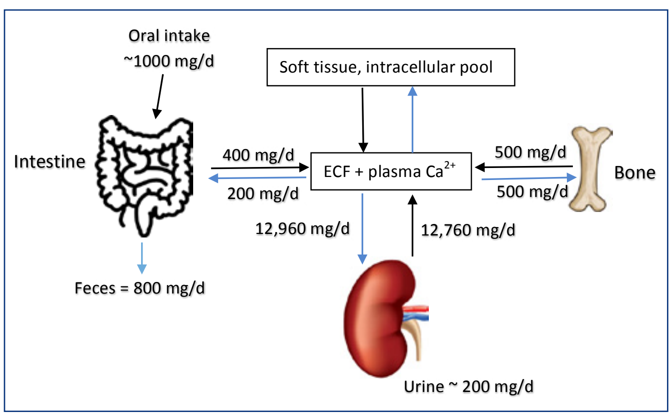
Idiopathic hypercalciuria is defined as excessive urine calcium excretion in the absence of an identifiable cause. It has been strongly associated with the risk of calcium kidney stone formation. Animal and human studies have suggested excessive bone mineral loss or increased gastrointestinal calcium absorption with abnormal renal calcium excretion may contribute to this process. In this article we will review the complex pathophysiology of idiopathic hypercalciuria and discuss clinical management and challenges.

KEYWORDS: hypercalciuria, vitamin D, calcium kidney stone

INTRODUCTION

Kidney stone disease is common in the general population with an estimated prevalence of around 10–15% in males and 3–5% in females.[1] Calcium-based kidney stones are the most common (>80%), with high urinary calcium excretion being the most common metabolic risk factor for stone formation.[2,3] Calcium is tightly regulated through a coordinated interplay between the intestines, bones, and kidneys (**Figure 1**). Any disease processes disturbing the calcium balance can lead to hemodynamic compromise and widespread organ dysfunction, including neurologic, cardiovascular, kidney and bone dysfunction.

Figure 1.



Hypercalciuria is defined as daily urine calcium excretion >300mg in males and >250mg in females. It can be secondary to hypercalcemia caused by a variety of systemic illnesses such as primary hyperparathyroidism, sarcoidosis, and paraneoplastic syndromes. More commonly, blood calcium levels are normal and no primary causes of hypercalciuria can be found. At which point, the etiology is considered idiopathic. Idiopathic hypercalciuria is present in 40–50% of patients with calcium-based kidney stones, and in about 10% of the general population.[4,5] No single cause for this condition has been identified. Three main pathophysiological features have been described: 1) increased gastrointestinal calcium absorption, 2) increased bone mineral loss, and 3) increased renal calcium loss. The clinical presentation is often heterogeneous, and individuals may have multiple pathologic processes occurring simultaneously.

INCREASED INTESTINAL CALCIUM ABSORPTION AND DIETARY FACTORS

The most common cause of increased urinary calcium is increased calcium absorption in the small intestine though both a paracellular passive process, and an active transcellular process in the duodenum and upper jejunum via transient receptor potential vanilloid subfamily member 6 (TRPV6). In a study of 22 patients with idiopathic hypercalciuria, Ca^{2+} absorbed from gut exceeded that excreted in the urine. Reducing intestinal calcium absorption by fasting or cellulose phosphate normalized urinary calcium excretion.[6] In vitro study using jejunal biopsy specimens showed increased intestinal calcium uptake in specimens from patients with idiopathic hypercalciuria compared to those without.[7] The finding has been corroborated by other larger human studies.[6,8]

Enhanced vitamin D activity is an important mechanism modulating calcium hyperabsorption.[2,9] Vitamin D regulates TRPV6, intracellular calbindin expressions, and facilitates calcium exit through the basolateral side, playing a key role in calcium absorption (**Figure 1**).[10,11] The majority of patients with idiopathic hypercalciuria have normal blood 1,25-dihydroxy-vitamin D (1,25 $(OH)_2D$) levels, with the increased intestinal calcium absorption out of proportion to the measured 1,25 $(OH)_2D$.[11] A similar phenotype has been observed in a rat model with increased vitamin D receptor activity in the GI tract.[12,13] In humans, there are no direct measurements of vitamin D receptor expression in the GI tract. Favus et al showed a two-fold increase in peripheral blood monocyte vitamin D receptor expression in patients with kidney stones with idiopathic hypercalciuria compared to age-matched controls.[14] The molecular or genetic basis of this increased receptor expression remains unclear. In a study of 33 patients with hypercalciuria and 36 matched normal controls, investigators failed to find any differences in the distribution of variant alleles in the vitamin D receptor gene or in the coding region of vitamin D receptor messenger RNA.[15] Like other nuclear receptors, the vitamin D receptor may undergo significant post-translational modification, altering its metabolism leading to an enhanced activity.

While increased intestinal calcium absorption is a primary process in some patients with idiopathic hypercalciuria, others consuming controlled diets have urine calcium level exceeding the amount absorbed from GI tract, suggesting bone turnover may be an important additional source of hypercalciuria.[16]

INCREASED BONE MINERAL LOSS

Bones contain 99% of the total body calcium and serves as the primary storage site. Normal bone turnover involves 5–10 mmol of calcium with flux of calcium between bone and the systemic circulation. This process is predominantly regulated by parathyroid hormone.

"Resorptive hypercalciuria" is a well-recognized process among patients with stone formers who are found to have idiopathic hypercalciuria.[17,18] Increased bone resorption results in fasting hypercalciuria, with elevated markers of bone turnover. Multiple studies have demonstrated a lower bone mineral density among those with idiopathic hypercalciuria due to sustained bone loss, regardless of an underlying primary absorptive hypercalciuria or fasting hypercalciuria.[19-21] There have been few studies directly examining bone remodeling dynamics in idiopathic hypercalciuria patients. A histomorphometric analysis of iliac crest bone biopsies revealed that patients with calcium stone and idiopathic hypercalciuria had both reduced bone formation and increased bone resorption, compared with their matched controls. A short course of alendronate treatment corrected fasting urinary calcium, which confirmed that for some patients, there is a primary resorptive physiology.[22] Bone turnover in idiopathic hypercalciuria is more complex with the exact phenotype varying based on the underlying causes of hypercalciuria, i.e., resorptive or renal leak vs. absorptive hypercalciuria.[23]

The mechanistic cause of abnormal bone turnover remains unclear. Despite enhanced intestinal calcium absorption, there remains a net bone loss in patients with absorptive hypercalciuria, indicating a primary defect in the bone itself to maintain calcium balance. Exposure to high doses of 1,25$(OH)_2$-vitamin-D has been shown to be potent in stimulating bone resorption and decreasing collagen synthesis in studies using organ cultures.[24] Furthermore, increasing doses of calcitriol was able to promote calcium efflux from cultured calvariae of inbred genetic hypercalciuric rats but not from those of normal wild-type controls.[25] Future human studies are needed to examine the action of vitamin D on bone mineral loss in patients with idiopathic hypercalciuria.

INCREASED RENAL CALCIUM WASTING

The kidneys are key regulators of calcium homeostasis. On average, 10–12 grams of calcium are filtered daily, with 98% being re-absorbed, resulting in a net loss of 200mg. Calcium reabsorption occurs paracellularly in the proximal tubule and thick ascending limb, and transcellularly in the distal segment. The renal excretion of calcium is regulated by several proteins including parathyroid hormone (PTH), vitamin D, and calcium sensing receptor (CaSR). It is also driven by intravascular volume status, acid-base balance, and serum concentrations of several electrolytes including calcium, magnesium and potassium.

Idiopathic hypercalciuria, by definition, is characterized by excessive urinary calcium excretion. A subtle increase in glomerular filtration rate of 5% or a small 0.25 mg % increase in ultrafilterable calcium over 24 hours would be enough to raise urinary calcium excretion significantly, indicating the possibility of subtle undetectable increases in the filtered calcium load as a contributor to idiopathic hypercalciuria.[26] However, most patients with idiopathic hypercalciuria have abnormal renal calcium handling resulting in a phenomenon known as "renal leak hypercalciuria". These patients can have normal blood concentrations of calcium and other key regulators of calcium balance (PTH, vitamin D and other metabolic factors). In a study conducted by Worcester et al, 10 patients with idiopathic hypercalciuria and 7 control patients ingested a controlled diet for three days after fasting. Neither ultrafilterable calcium, nor filtered calcium load differed between the two groups during fasting or after meals. But urine fractional reabsorption of calcium was significantly lower during fasting or after meals in subjects with idiopathic hypercalciuria, suggesting a defect in kidney to conserve calcium.[27] However, other investigators failed to show significant differences in the renal tubular reabsorption of calcium between normocalciuric and hypercalciuric subjects when calcium was injected intravenously.[26] These conflicting findings highlight the likelihood that patients with idiopathic hypercalciuria are a heterogeneous population with differing underlying pathophysiology.

The underlying cause of "renal leak" remains unknown. PTH, a key regulator of renal calcium handling, does not appear to play a role.[27] Among those with "renal calcium leak", the dissociation between urinary calcium and sodium excretions implicated the distal nephron as the culprit site.[27] In some patients experiencing subtle rise in blood calcium load, CaSR may play a role.[27] However, in most cases of idiopathic hypercalciuria, which exist without changes in blood calcium concentration, excessive vitamin D action may have a direct effect on renal calcium loss. Initial evidence came from a retrospective study which showed a strong positive correlation between serum 1,25(OH)$_2$D concentration and urinary calcium excretion in fasting patients with idiopathic hypercalciuria.[28] In a genetic hypercalciuric stone-forming (GHS) rat model mimicking human idiopathic hypercalciuria, vitamin D receptor (VDR) expression is significantly enhanced at basal state in both the kidney cortex and intestines without any alterations in binding affinity. A small dose of intra-peritoneal 1,25(OH)2D3 injection can further increase VDR gene expression in GHS rats but not in normocalciuric control rats.[13] Normally, vitamin D enhances calcium reabsorption in distal nephron, where vitamin D receptor and vitamin D dependent proteins (luminal epithelial calcium channel, calbindins, and basolateral Ca-ATPase) are expressed.[29] In calcium and vitamin D replete states, excessive vitamin D action can lead to calcium wasting, likely through a CaSR-related mechanism. In the kidney, activation of CaSR is important in reducing paracellular calcium reabsorption in the thick ascending limb of the loop of Henle.[30] CaSR expression is regulated by activated 1,25-OH-vitamin D, and is PTH-independent.[31] Furthermore, CaSR is able to up-regulate VDR gene expression, which can create a self-amplifying process to potentiate vitamin D action on renal calcium handling.[32]

GENETICS

A genetic contribution to idiopathic hypercalciuria has long been suspected. In a study of 40 children with idiopathic hypercalciuria, 47.5% had one or more affected first-degree relatives with likely an autosomal dominant transmission.[33] In a study of adult patients with kidney stones and idiopathic hypercalciuria, hypercalciuria was also found in 43% of first-degree relatives, with a higher incidence of hypercalciuria seen in the second and third generations, strongly suggestive of a genetic basis of idiopathic hypercalciuria.[34]

Known rare monogenetic disorders such as Dent disease typically present with familial hypercalciuria and kidney stone disease, and can be distinguished from idiopathic hypercalciuria by their unique disease features (**Table 1**).

Genetic testing to identify monogenic mutations and risk associated polymorphisms has implicated CaSR activation in the pathogenesis of idiopathic hypercalciuria.[35] The R990G polymorphism of CaSR is a gain-of-function mutation that predisposes to primary hypercalciuria.[36] However, the exact genes or gene panels involved in idiopathic hypercalciuria remains incompletely understood as the trait is likely polygenic and involves both genetic and environmental factors.

Table 1. Monogenic forms of hypercalciuric nephrolithiasis

Disease	Inheritance	Genes	Clinical features
Dent's disease	X-linked	CLC-5	Hypercalciuria, low-molecular-weight proteinuria
Lowe's syndrome	X-linked	OCRL1	Hypercalciuria, congenital cataracts, severely impaired intellectual development, and renal tubular dysfunction
Bartter syndrome			Hypercalciuria, hypokalemia, volume depletion
Type 1	AR	NKCC2	
Type 2	AR	ROMK	
Type 3	AR	CLC-Kb	
Type 4	AR	Barttin	
Type 5	X-linked	CaSR	
ADHH	AD	CaSR	Hypercalciuria, hypocalcemia
HHRH	AR	NaPi-2c	Hypercalciuria, hypophosphatemia, phosphaturia, elevated calcitriol, rickets
FHH	AR	CLDN16	Hypercalciuria, hypomagnesemia
		CLDN19	Hypercalciuria, hypomagnesemia, severe ocular abnormalities
Distal RTA	AD	SLC4A1	Hypercalciuria, dRTA-1
	AR	ATP6N1B	Hypercalciuria, dRTA-1
	AR	ATP6B1	Hypercalciuria, dRTA-1, sensorineural deafness

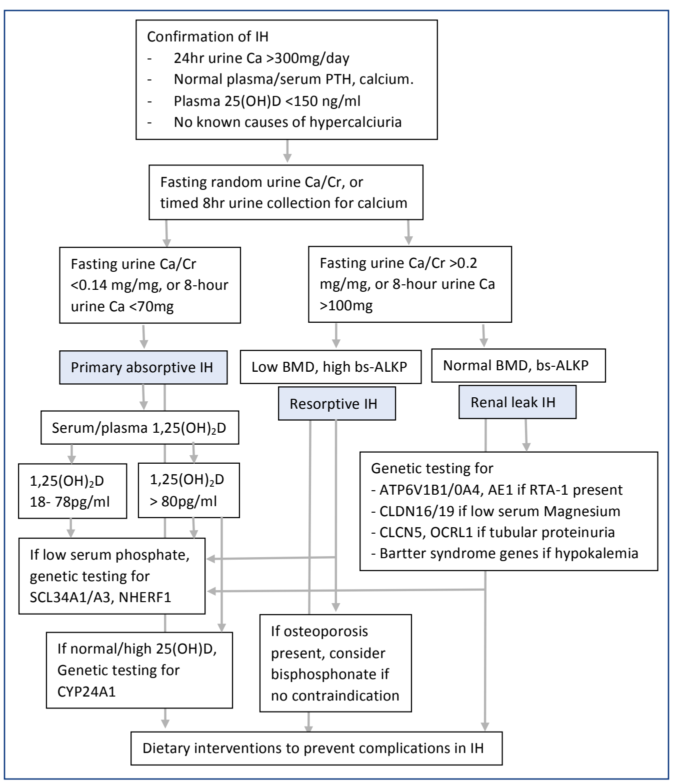
ADHH: autosomal dominant hypocalcemic hypercalciuria. HHRH: hereditary hypophosphatemic rickets with hypercalciuria. FHH: familial hypomagnesemia with hypercalciuria. AD: autosomal dominant. AR: autosomal recessive. CLC-5: chloride/proton antiporter 5. OCRL1: oculocerebrorenal-1 gene. NKCC2: Na–K–Cl co-transporter. ROMK: renal outer-medullary potassium channel. CLC-Kb: chloride channel. Barttin: CLC-Kb beta subunit. CaSR: calcium-sensing receptor. NaPi-2c: Na-phosphate cotransporter 2c. CLDN: claudin. SLC4A1: solute carrier family 4 member 1. ATP6N1B/ATP6B1: encoding proton pump. dRTA: distal renal tubular acidosis.

Many candidate genes have been screened for their potential associations with idiopathic hypercalciuria, including genes coding for vitamin D metabolism, *VDR*, renal epithelial calcium channel *TRPV5*, and renal sodium-phosphate co-transporter *NPT2a*. Thus far, results have been mostly negative or inconclusive.[15,37-41] Since idiopathic hypercalciuria is a heterogeneous process, larger scale studies are needed to examine genetic variances in well-defined subpopulations, i.e., patients with primary absorptive hypercalciuria. The target genetic panel likely needs to be expanded to include more genes involved in the control of calcium homeostasis. A recent genome-wide association study uncovered a novel nucleotide polymorphism associated with fibroblast growth factor 23 (*FGF23*) that achieved genome-wide significance for calcium excretion.[42] Further work is needed to define the roles of these genetics in idiopathic hypercalciuria.

MANAGEMENT OF ADULTS WITH IDIOPATHIC HYPERCALCIURIA

Currently, there are no consensus guidelines for the management of idiopathic hypercalciuria. The approach presented is based on expert opinion. For patients with kidney stones with or without nephrocalcinosis, laboratory studies should be pursued to examine disturbances in calcium homeostasis. **Figure 2** outlines the general approach for the clinical management of patients with idiopathic hypercalciuria. All patients will need dietary interventions to prevent complications from idiopathic hypercalciuria. A kidney stone prevention diet should be pursued. Ideally, oral fluid intake should be enough to maintain a daily urine output of more than 2 liters. Potassium intake should be maintained at a minimum of 1.6–2.0 grams per day, unless there are conditions predisposing patients to hyperkalemia. Sodium should be restricted to less than 6 grams per day. Animal protein and grain intake should also be restricted to avoid excessive dietary acid load. In some cases, additional alkali therapy using citrate containing drugs or supplements will be used to prevent kidney stone formation and bone loss.[43] With regard to calcium intake, for those with primary absorptive hypercalciuria, dietary calcium intake should be restricted to 1 gram per day for ages ≤70, and to 1.2 grams per day for ages>70, regardless of sex. For patients with other subtypes of idiopathic hypercalciuria (± absorptive hypercalciuria), no dietary calcium restriction is recommended, and the optimal intake should be individualized based on the degree of bone loss or net calcium balance and whether there is enteric hyperoxaluria present. A thiazide diuretic is often prescribed to reduce renal calcium loss and to improve bone mineralization,[43] but may result in hypokalemia which needs close monitoring and aggressive supplementation of potassium. In cases of nutritional vitamin D deficiency, vitamin D supplementation is indicated to prevent bone demineralization and is not associated with worsening hypercalciuria among patients with idiopathic hypercalciuria who have calcium-based kidney stones.[44] However, vitamin D supplementation should be avoided in patients carrying *CYP24A1* mutations or having conditions associated with an enhanced vitamin D 1α-hydroxylase activity.

Figure 2. Management approach of idiopathic hypercalciuria (IH)



SUMMARY

Idiopathic hypercalciuria is a complicated multifactorial metabolic abnormality determined by both genetic and environmental factors, with strong associations with kidney stone formation and bone loss. Although progress has been made, the clinical diversity, pathophysiological mechanisms, and effective management for this condition remains incompletely understood.

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Authors

Olive W. Tang, MD, PhD, Department of Medicine,The Johns Hopkins University School of Medicine, Baltimore, MD.

Jie Tang, MD, MPH, Division of Kidney Diseases and Hypertension, Alpert Medical School of Brown University, Providence, RI.

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Correspondence

Olive W. Tang, MD, PhD
Department of Medicine
The Johns Hopkins University School of Medicine
1830 E. Monument St, Suite 2-300
Baltimore, MD 21287
Otang@jhmi.edu

Hyperoxaluria – A Major Metabolic Risk for Kidney Stone Disease

CHRISTOPHER OWINO, MBChB; ANN MUTUGI, MBChB; JIE TANG, MD, MPH

ABSTRACT

Hyperoxaluria is a clinically relevant metabolic entity that portends a high morbidity burden. Primarily manifesting as kidney stone disease and chronic kidney disease, advanced hyperoxaluria can also affect major organs, including the brain, heart, liver, bone, and the skin. It is categorized based on etiology into primary and secondary hyperoxaluria. Pathology is attributed to excess de novo oxalate production in the former and multifactorial exogenous oxalate absorption or excess intake of its precursors in the latter. Diagnosis often involves demonstrating elevated urinary oxalate levels, especially in patients with normal kidney function. Here in this review, we will perform an in-depth discussion of various causes of hyperoxaluria and describe treatment options. In view of the significant morbidity burden associated with hyperoxaluria, patients could benefit from heightened clinician awareness to aid in the timely diagnosis and management of this condition.

KEYWORDS: hyperoxaluria, kidney stones, nephrolithiasis, chronic kidney disease

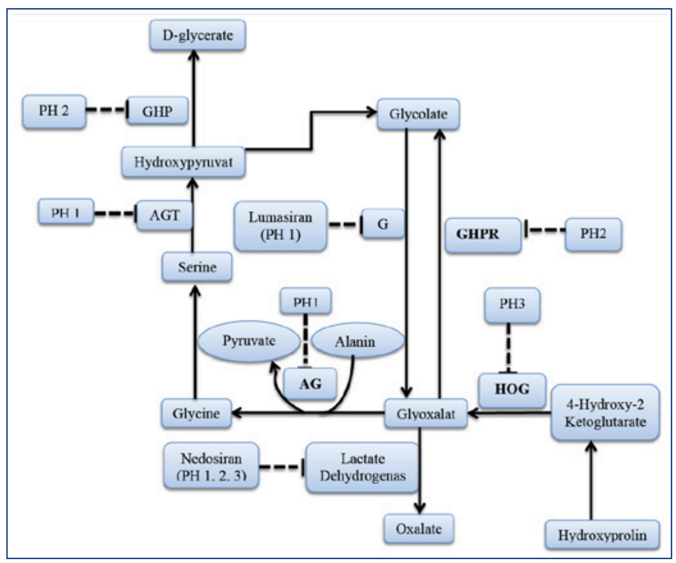
INTRODUCTION

Kidney stone disease poses a growing clinical problem with its prevalence rate reaching 8.8% according to a large U.S. population survey in the late 2000s.[1] Of these, calcium oxalate stones account for the vast majority, contributing to 70–80% of all kidney stone events.[2,3] Hyperoxaluria, a clinical condition associated with excess urinary oxalate excretion is commonly encountered and is seen in 25–45% of stone formers.[4] Broadly it is subdivided into primary hyperoxaluria characterized by excess endogenous oxalate production and secondary hyperoxaluria which could be a result of excess intake of oxalate rich foods or oxalate precursors such as ethylene glycol, or reduced gut colonization of oxalate metabolizing bacteria. As a disease entity, hyperoxaluria carries a high morbidity burden among patients affected with significantly increased utilization of health services.[5-7] We therefore seek to highlight in this review the role of hyperoxaluria in kidney stone formation, disease pathophysiology, clinical presentation and management.

OXALATE PHYSIOLOGY/METABOLISM

Widely found in plant-derived foods consumed by humans, oxalate is the ionic form of oxalic acid.[8–10] Humans gain oxalate through two mechanisms. One is through the endogenous production of oxalate in the liver which is particularly amplified in enzymatic deficiency states that limit glyoxylate metabolism as illustrated in **Figure 1**.[11,12] Secondly, oxalate can be obtained through intestinal absorption after ingestion of oxalate rich foods such as spinach, rhubarb, nuts, plums, chocolate, beetroots, soybean and strawberries.[8,10]

Figure 1. Summary of oxalate metabolism including defects seen in Primary Hyperoxaliuria and targets for therapeutic molecules.
PH 1 – Primary Hyperoxaliuria Type 1, **PH 2** – Primary Hyperoxaliuria Type 2, **PH 3** – Primary Hyperoxaliuria Type 3, **AGT** – Alanine Glyoxylate Aminotransferase, **GHPR** – Glyoxylate Hydroxy-Pyruvate Reductase, **HOGA** – 4-hydroxy 2-oxoglutarate aldolase, **GO** – Glycolate oxidase.



Estimates of the average daily oxalate intake in the western population are highly variable and range anywhere between 44 and 351 mg/day. In fact, daily oxalate intake may even exceed 1000 mg/day when oxalate-rich foods are consumed. However, the fraction of dietary oxalate absorbed in the gut is highly variable. It is influenced by the amount of oxalate binding cations, such as calcium and magnesium, especially in diseases causing fat malabsorption, and the presence of gut commensal bacteria with oxalate-degrading activity.[13]

On the other hand, clearance of oxalate from the body is primarily through kidney by glomerular filtration and tubular secretion. In patients with normal kidney function, increased levels of plasma oxalate will lead to increased filtration and tubular secretion of oxalate. More specifically, in the proximal renal tubules, secretion of oxalate is mediated by the SLC26 transport proteins located on both apical and basolateral sides of tubular cells. SLC26A1 is critical in oxalate extraction from peritubular capillaries on the basolateral side. While on the apical surface, the SLC26A6 transport protein mediates oxalate secretion into the urinary space. Similarly, the SLC26A6 transport protein seems to play a key role in the secretion of oxalate in the intestines, but its significance remains unknown.[14,15] As such, renal impairment contributes greatly to the increase in plasma oxalate levels. Clinically, hyperoxaluria is often defined as urinary concentrations of oxalate above 40 mg/24hr and is associated with significant risk of developing kidney stones.[16] Despite its clear clinical significance, there seems to be no known beneficial effect of oxalate in the human body.

OXALATE ON KIDNEY STONE RISK

In the urinary space, oxalate has been shown to bind calcium, sodium, potassium and magnesium. While most of these are soluble in water, calcium oxalate has a particularly low super-saturation threshold of 5mg/L in urine at physiological pH, therefore is more likely to result in crystal formation.[17,18] While hyperoxaluria portends a huge risk for kidney stones, it doesn't guarantee stone formation. Development of urolithiasis is dependent on other factors, most prominent being the level of urinary citrate which acts as an inhibitor of calcium stones. It forms a more soluble complex with calcium in the urinary space and further inhibits the crystallization of calcium oxalate stones.[19] In the absence of adequate inhibition, calcium oxalate stone formation starts with a process known as nucleation, followed by crystal growth and agglomeration as stone materials travel down the urinary space.[17]

While both primary and secondary hyperoxaluria lead to the formation of kidney stones, a key distinction to note is that primary hyperoxaluria is commonly associated with pure calcium oxalate monohydrate crystals while secondary hyperoxaluria presents with either pure calcium oxalate dehydrate or mixed (monohydrate and dihydrate) crystals in urine.[20] With recurrent formation of kidney stones and nephrocalcinosis, impairment of kidney function slowly develops due to kidney parenchyma inflammation and fibrosis.[21] This leads to a decrease in glomerular filtration rate (GFR) that further impairs plasma oxalate clearance. Consequently, the excess oxalate is deposited in other body organs resulting in systemic oxalosis as the GFR drops to less than 30–45 mL/min/1.73 m^2. Some of the organs involved include the brain, heart, bone and skin resulting in cerebrovascular accidents, cardiomyopathy, fractures and non-healing skin ulcers among other presentations.[22] However, this is not the case in secondary hyperoxaluria where systemic oxalosis has not been described.

PRIMARY HYPEROXALURIA

Primary hyperoxaluria (PH) is a clinical entity characterized by increased urinary concentration of oxalate secondary to abnormal endogenous hepatic production. It remains a rare disease with an estimated worldwide prevalence of less than 3 per 1,000,000.[23] Current evidence describes three distinct types of primary hyperoxaluria; Type 1, 2 and 3. While all are inherited in an autosomal recessive fashion, primary hyperoxaluria type 1 (PH1) is the most common form of PH. It accounts for up to 80% of cases of PH.[24] Excess oxalate production results from the shunting of glyoxylate metabolism away from the physiological route of glycine and pyruvate production. This is due to either deficiency or a defect in the vitamin B6-related Alanine Glyoxylate Aminotransferase (AGT) enzyme located in the peroxisome first described by Danpure and Jennings in 1986. Additionally, PH1 with AGT defect attributed to a genetic mutation on the AXGT gene on chromosome 2 is phenotypically the severest form of PH with early disease onset, followed by a progressive course leading to end-stage renal disease.[25,26]

PH type 2 which is less common, accounts for approximately 10% of patients with primary hyperoxaluria and is somewhat less aggressive clinically compared to PH1.[27] Characterized by increased oxalate production due to a defect in the hepatic cytosolic Glyoxylate Hydroxy-Pyruvate Reductase (GHPR) enzyme, PH2 also has disease onset in childhood. More specifically, a genetic mutation in the GHPR gene on chromosome 10 has been implicated.[28] Finally, PH3 which is the least common form of PH also represents the mildest subtype with a reduced incidence of end-stage renal disease. A genetic mutation in the HOGA1 gene on chromosome 9 encoding the 4-hydroxy 2-oxoglutarate aldolase hepatic mitochondrial enzyme results in a deficiency of the enzyme. Consequently, 4-hydroxy 2-oxoglutarate metabolism is diverted into the oxalate pathway leading to excess endogenous production.[29,30] **Figure 1** summarizes hepatic oxalate metabolism highlighting enzyme defects in primary hyperoxaluria and their respective therapeutic targets.[31]

SECONDARY HYPEROXALURIA

Secondary hyperoxaluria presents a complex metabolic disorder with several known etiologies. Causes can be broadly categorized as follows, enteric hyperoxaluria which mainly comprise fat malabsorption states, excess intake of oxalate precursors like ethylene glycol, and disturbed gut microbiota.

Enteric hyperoxaluria

Enteric hyperoxaluria represents a subset of secondary hyperoxaluria whose pathophysiology centers around the abnormal handling of oxalate in the gut. Causes under this group are numerous. One relatively common cause is fat malabsorption as a result of various gastrointestinal pathologies such as exocrine pancreatic insufficiency and inflammatory bowel disease. Secondly, diverting surgical procedures such as bariatric surgery, jejunoileal bypass, Roux-en-Y gastric bypass and biliopancreatic diversion result in a lack of or limited bile interaction with fat due to the anatomic alterations. Also implicated in enteric hyperoxaluria is Orlistat – a potent pancreatic enzyme inhibitor prescribed for weight loss. The described disease states have a final common mechanism leading to the development of hyperoxaluria. Often, this involves excess fatty acid delivery to the colon, which in turn binds to calcium. Free oxalate is subsequently absorbed through the gut into the bloodstream.[32,33]

Excess intake of oxalate precursors

Oxalate precursors are quickly absorbed into the bloodstream and thereafter broken down into oxalic acid. One particularly important substance is ethylene glycol. Ingested either accidentally or deliberately, Ethylene glycol is quickly absorbed from the gut and metabolized in the liver into glycol aldehyde by the enzyme alcohol dehydrogenase. Through multiple enzymatic reactions, glycol aldehyde is converted to oxalic acid. High plasma oxalate levels lead to the formation and deposition of calcium oxalate crystals in various body tissues. Renal manifestations, often seen around 48 hours after ingestion, are characterized by calcium oxalate deposition within the renal tubules and other tissues.[34,35]

Vitamin C, which is also known as L-ascorbic acid can be broken down into oxalate especially when ingested in large amounts. High-dose vitamin C, (>1g per day) has been associated with an increase in the risk of stone formation as demonstrated in a prospective study done by Taylor et al.[36-38] Mostly absorbed in the jejunum and ileum, vitamin C is a potent antioxidant in the human body. It is usually metabolized in the liver, where it is initially converted to dehydroascorbic acid (DHA). Through further non-enzymatic reactions, DHA can be metabolized to diketogluconic acid and eventually oxalic acid. Despite the strong evidence to support vitamin C breakdown to oxalic acid, the relationship is far from linear with exact conditions precipitating vitamin C metabolism to oxalate remain unclear.[39]

Altered gut microbiota

Oxalobacter formigenes, an anaerobic gram negative rod that forms part of the normal flora in the colon largely depends on oxalate for carbon dioxide and energy needs.[40] In humans, several bacteria forming the normal flora have been shown to break down oxalate in the gut. However, *Oxalobacter* is the key player in oxalate homeostasis, handling approximately 70 to 100 grams of ingested oxalate daily.[41,42] In normal physiologic states, the net outcome of colonic *Oxalobacter* colonization is a reduction of oxalate absorption. However, several conditions can reduce *Oxalobacter* colonies in the gut resulting in increased oxalate absorption. For example, obesity is associated with reduced *Oxalobacter* colonies, possibly due to systemic inflammation. Furthermore, *Oxalobacter formigenes* has been shown to be particularly sensitive to antibiotics such as tetracyclines, macrolides and fluoroquinolones. As expected, the use of these antibiotics can lead to reduced colonies as well.

DIAGNOSIS

Diagnosis of both primary and secondary hyperoxaluria is a multistep process based on clinical presentation, biochemical testing, imaging and histology as appropriate. Being a relatively rare disease, strong clinical suspicion should always be entertained. Clinicians should keep hyperoxaluria in the differential when patients present with kidney stones at an early age or have either symptomatic (based on symptomatic stone passage or surgery on an asymptomatic kidney stone) or radiographic recurrent (based on new stone formation or evidence of significant previous stone growth) stones during adulthood. Unique to secondary hyperoxaluria, stone formers often present with chronic diarrhea, inflammatory bowel disease, obesity, bowel resection, prolonged antibiotic use, or had recent ingestion of ethylene glycol.

In such scenarios, a 24-hour urine collection for stone risk assessment should be ordered. This is preferably done in the outpatient setting when stone formers are on their regular home diet. Testing is then performed for parameters such as urine volume, pH, calcium, oxalate, uric acid, phosphate, citrate, ammonium, magnesium, sulfate, sodium, potassium and creatinine. All these parameters combined with stone composition analysis help in teasing out the cause of urolithiasis and guide treatment.[43]

More specifically, 24-hour urine oxalate levels above 40mg are usually concerning for hyperoxaluria. For accuracy purposes, two separate measurements are recommended with appropriate adjustments for body surface area. Often, patients with primary or secondary hyperoxaluria will have 24-hour urinary oxalate levels exceeding 88mg/1.73m^2 compared to an expected normal of less than 40mg/1.73m^2. If primary hyperoxaluria is suspected, subsequent testing of urine glycolate and glycerate may give pointers towards PH1 and PH2 respectively based on underlying disease pathophysiology. These tests are, however, not highly sensitive and don't exclude disease presence.

Often, genetic tests are used to diagnose primary hyperoxaluria definitively. The presence of AGXT, GHPR and HOGA1 gene mutations are used to diagnose PH1, PH2 and PH3 respectively. As is the case with most genetic testing, recommended samples include saliva, a buccal swab, or a blood sample. Testing should also be offered to relatives of index patients with primary hyperoxaluria. While non-invasive genetic testing offers a diagnosis in most cases, results can sometimes be inconclusive even as clinical suspicion remains high. As such a liver biopsy can be undertaken in these cases to obtain definitive data on specific diagnosis.[44,45] In patients with impaired kidney function and declining GFR, urine oxalate excretion can be deceivingly low. Therefore, a serum oxalate level becomes necessary. Values above 30 umol/L are typically seen in patients with hyperoxaliuria.[44] Testing for secondary hyperoxaluria may include stool *Oxalobacter formigenes* PCR, and 13-C oxalate absorption test.[46,47] However, anecdotal evidence suggests that these tests are rarely utilized in clinical practice.

TREATMENT

General supportive treatment

Several measures are recommended to help reduce kidney stone recurrences. Foremost, adequate hydration ensures enough urine output to reduce calcium oxalate supersaturation. Based on this, liberal fluid intake to achieve a urine output of at least 2 liters is frequently encouraged.[48] Further treatment recommendations are usually based on the 24-hour urine biochemical testing. Some key parameters relevant to the management of patients with hyperoxaluria include urine pH, sulfate, citrate, calcium, sodium and potassium. The goal is to optimize urine citrate content, alkalize urine and reduce the amount of urine calcium. Also of note is that thiazide diuretics could have a role in patients with co-existing hypercalciuria. This is even with recently published clinical trial data not showing benefit in reducing stone recurrence on the background of previous supportive evidence.[49] We believe that clinicians will still need to assess on a case-by-case basis which patients to offer this treatment and appropriate dosage to be used.

Definitive treatment

Primary Hyperoxaluria

In addition to general supportive measures, insights into the pathophysiology of primary hyperoxaluria have led to not only the development of new therapeutics but also the repurposing of others to treat patients with PH. Most of the data available seems to involve patients with PH1.[50,51]

Pyridoxine is perhaps the oldest molecule available for the treatment of PH1. Used at higher doses than usual, it acts by stabilizing the vitamin B6-dependent AGT enzyme thereby enhancing its activity.[50] Despite this strong pathophysiological basis for use, it only has a therapeutic effect in 30% of patients with PH1 implying further genotype differences in PH1 patients that determine pyridoxine therapy response. Similarly, urinary oxalate reduction of 30% is seen in pyridoxine responders.[50,52] In some instances, sustained therapeutic effect can delay further invasive treatment such as liver transplants for years.

More recently, newer novel therapies have emerged as the go-to options in the treatment of PH1. Lumasiran, an RNA interference molecule targeting glycolate oxidase has been shown to reduce endogenous oxalate production and subsequently urinary oxalate.[51] Dual approved by the US FDA and European Medicines Association (EMA), Lumasiran has shown significant efficacy in 24-hour urinary oxalate excretion reduction in children and adults.[53] Additionally, efficacy among patients with advanced chronic kidney disease has been demonstrated in the ILLUMINATE-C trial. Injections of the drug are administered subcutaneously three-monthly. Further, no significant adverse reactions were reported in the Lumasiran trials with current data reporting skin reactions as the main side effect to look out for.[54] Despite strong data to support use currently in PH1, there remains a need to collect prospective long-term data to answer questions on sustained efficacy and how reductions in 24-hour urinary oxalate impact long-term clinical outcomes.

Also in the pipeline is another RNAi molecule – Nedosiran. It targets the LDH-A enzyme to decrease endogenous oxalate production. So far, promising data from early phase studies show the drug's safety and efficacy in the reduction of 24-hour urinary oxalate excretion in all types of primary hyperoxaliuria.[55,56] Results from currently ongoing PHYOX trials will shed more light on Nedosiran's efficacy in different age groups and GFR stage.[57–59] Finally other promising non-RNAi therapies under investigation include targeted gene therapy and Stiripentol, a repurposed FDA-approved therapy for Dravet syndrome.[60,61]

Secondary Hyperoxaluria

Treatment in secondary hyperoxaluria centers on the management of underlying medical condition and dietary interventions. While dietary oxalate modifications are not aggressively pursued in primary hyperoxaluria since intestinal oxalate absorption is not the main driver of hyperoxaluria, they are crucial in the management of patients with secondary hyperoxaluria. Limiting oxalate-rich foods helps reduce the amount of oxalate absorption in the gut. Furthermore, dietary calcium intake should be optimized so that enough calcium is available in the gut to bind free oxalate, further reducing oxalate absorption. Additional dietary calcium supplementation is yet to be shown to be beneficial in prevention of calcium oxalate stones. Another potential target in this particular patient population is the altered gut microbiome with reduced Oxalobacter colonies. Interventions include oral probiotic supplementation or fecal transplant of Oxalobacter formigenes. While this is promising, one challenge encountered is non-persistence of colonies after supplementation, and large scale randomized trials are needed to establish its efficacy in reducing oxalate absorption from the gut and stone prevention.[62]

CONCLUSION

In conclusion, hyperoxaluria poses a major risk for calcium kidney stone disease. Its clinical outcomes hinge upon timely diagnosis and early initiation of effective treatment. Primary hyperoxaluria type 1 remains the most severe form of PH.[31] Often, it is associated with earlier onset of disease and rapid progression to ESRD. Luckily, novel therapies based on disease pathophysiology continue to offer hope for patients and their care providers. A high clinical suspicion coupled with appropriate testing and treatment could potentially help avert long term end organ damage from the disease.

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Authors

Christopher Owino, MBChB, Visiting scholar, Division of Kidney Diseases and Hypertension, Alpert Medical School of Brown University, Providence, RI. Medical resident, Department of Medicine, Moi University Teaching and Referral Hospital, Eldoret, Kenya.

Ann Mutugi, MBChB, Visiting scholar, Division of Kidney Diseases and Hypertension, Alpert Medical School of Brown University, Providence, RI. Medical resident, Department of Medicine, Moi University Teaching and Referral Hospital, Eldoret, Kenya.

Jie Tang, MD, MPH, Associate Professor of Medicine, Division of Kidney Diseases and Hypertension, Alpert Medical School of Brown University, Providence, RI.

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Christopher Owino and Ann Mutugi contributed equally.

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Conflict of Interest

Authors declare that they have no competing interests

Correspondence

Jie Tang, MD
Brown Physicians, Inc.
375 Wampanoag Trail, East Providence, RI 02915
401-649-4063
Jie.tang@brownphysicians.org

Dietary Magnesium Intake and Kidney Stone: The National Health and Nutrition Examination Survey 2011–2018

SANDIPAN SHRINGI, MD; CHRISTINA A. RAKER, ScD; JIE TANG, MD, MPH

ABSTRACT

BACKGROUND: The association between dietary magnesium intake (DMI) and kidney stone (KS) disease is not clear.

AIM: To determine the association between DMI and prevalent KS disease defined as self-report of any previous episode of KS.

METHODS: We examined The National Health and Nutrition Examination Survey (NHANES) 2011–2018 and used logistic regression analyses adjusting for demographics, BMI, histories of hypertension, diabetes, thiazide use, cigarette smoking, alcohol drinking, relevant dietary and supplemental intakes to determine the independent association between DMI and prevalent KS disease.

RESULTS: A total of 19,271 participants were eligible for the final analysis, including 1878 prevalent KS formers. Mean DMI among stone formers was 295.4 mg/day, as compared to 309.6 mg/day among non-stone formers (p=0.02). Higher DMI was strongly associated with lower odds of prevalent KS disease in univariate analysis regardless of when DMI was analyzed as a continuous variable (OR=0.94, 95% CI: 0.89–0.99, p=0.02) or when the extreme quartiles of DMI were compared (OR=0.74, 95% CI: 0.60–0.92, p=0.007). In the multivariable-adjusted regression analysis, those in the highest quartile of DMI compared to the lowest quartile (≥379 mg vs. <205 mg) had significantly reduced odds of prevalent KS (OR=0.70, 95% CI: 0.52–0.93, p=0.01). When DMI was analyzed as a continuous variable, there was a trend toward reduced odds of prevalent KS disease with higher DMI (OR=0.92 per 100 mg, 95% CI: 0.84–1.01, p=0.07).

CONCLUSIONS: Our study suggests that higher DMI is associated with a reduced risk of KS disease. Future prospective studies are needed to clarify the causal relationship between DMI and KS disease.

KEYWORDS: Dietary magnesium intake, renal stone, urolithiasis, nephrolithiasis

INTRODUCTION

Kidney stone (KS) disease is highly prevalent worldwide, with roughly 1 in every 11 people afflicted in the United States.[1] It carries significant morbidity and poses a huge economic burden to the society.[2,3] Calcium oxalate stone is by far the most common type, accounting for the vast majority of all stones identified.[4]

Magnesium (Mg) has long been thought to play a role in the formation of KS. In vitro studies have shown that Mg can inhibit each of the steps involved in formation of KS including supersaturation,[5] nucleation of calcium oxalate crystals,[6,7] aggregation,[8] as well as crystal growth.[6,9] Once formed, further growth of calcium oxalate monohydrate crystals occurs by adsorbing calcium and oxalate ions on its surface,[10] which promotes adhesion to renal epithelial cells.[11] Mg competitively gets adsorbed on calcium oxalate monohydrate crystals and has been shown to inhibit the adhesion of preformed calcium monohydrate crystals to renal cells.[12] In animal studies, hypomagnesemia has been associated with development of calcium oxalate monohydrate crystals.[13] Dietary Mg supplementation resulted in increased urinary Mg[14] and prevented the formation of calcium oxalate KS.[15]

It is well known from previous human studies that calcium stone formers tend to excrete less Mg in the urine than their non-stone forming counterparts, suggesting an inhibitory role of Mg in KS formation.[16-18] However, results from small interventional studies have been inconsistent in demonstrating reduction in urinary oxalate or reducing recurrence of KS disease.[19-24] Thus far, it remains unclear whether DMI modifies KS risk in humans.

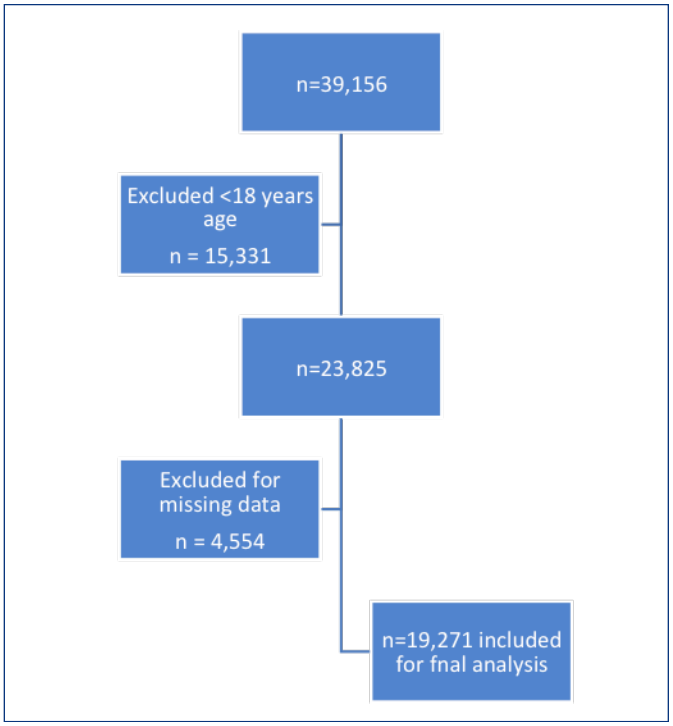
Here, we used a large US population survey database, the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2018, to examine the independent association between DMI with KS disease.

METHODS

Study population

The NHANES is an ongoing series of cross-sectional assessments of the health and nutritional status of adults and children in the US. Since 1999, the program has been conducted continuously, with each two-year sample selected to represent the civilian non-institutionalized US population of all

Figure 1. Selection of study population



ages.[25] The survey collects demographic, socioeconomic, dietary, and health-related information, in addition to the examination and laboratory data obtained by highly trained medical personnel. A total of 39,156 participants were interviewed for NHANES from 2011 to 2018. Of these, our analysis included 19,271 participants aged 18 years or older with complete data on dietary Mg, history of KS, and the covariates of interest (**Figure 1**).

Primary exposure and outcome

The primary exposure was daily DMI, excluding intake specifically from supplements or antacids. DMI in mg/day was calculated by matching foods and beverages listed on the 24-hour dietary recall interview with the USDA's Food and Nutrient Database for Dietary Studies. Of the two 24-hour recall periods, only data from day one was included in the present analysis.

The primary outcome of interest, KS disease, was based on an affirmative response to the following question, "Have you ever had kidney stones?" Participants who refused to respond or did not know were excluded.

Covariates

Age, sex, race, history of diabetes, history of hypertension, thiazide use, and smoking status were obtained from questionnaires. Body mass index (BMI) was calculated from height and weight measured during the health examination. Information on alcohol and dietary intake of protein, sodium, calcium, vitamin D, zinc, and total calories were obtained from the same day one, 24-hour dietary recall interview when DMI was measured. Supplemental calcium, vitamin D, and zinc were measured by the corresponding day one, 24-hour supplement recall interview.

Analysis

Statistical analysis was performed with Stata MP version 18 (StataCorp, College Station, TX) using survey-specific procedures to accommodate the complex sampling design and estimate standard errors by Taylor linearization. Dietary intake day one sampling weights were divided by four to account for the combination of two-year survey cycles from 2011–2018. Logistic regression was applied to estimate crude and multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) for DMI and prevalent KS disease. DMI was examined as both a continuous and a categorical predictor, with the latter variable created from quartiles of the DMI distribution. Deviations from a linear relationship between continuous DMI and KS disease were tested by including a quadratic term in the model, and interactions between DMI, sex, and age were evaluated by including product terms in the models. The multivariable models included the following covariates: sex, age (years), race (non-Hispanic White, non-Hispanic Black, Hispanic/Latino, Asian, Other), BMI (<25, 25–<30, 30+ kg/m^2), diabetes (no, borderline/yes), hypertension, thiazide diuretic use, smoking (never, former, current), daily alcohol consumption (none, some [<70g], heavy [70+ g]), dietary calories (kcal), dietary protein (g), water (g), dietary sodium (mg), dietary and supplemental calcium (mg), dietary and supplemental zinc (mg), and dietary and supplemental vitamin D (µg). National Center for Health Statistics guidelines for reporting statistical reliability of proportions were followed.[26]

RESULTS

A total of 19,271 participants were included in this analysis. Of these, 1,878 (10.0%, weighted) reported a history of stones. Mean DMI was 295.4 mg/day among stone formers and was significantly different as compared to 309.6 mg/day among non-stone formers. As shown in **Table 1**, stone formers tended to be older, male, non-Hispanic White, and had a higher BMI compared to non-stone formers. They were also more likely to have a history of diabetes, hypertension, and to use thiazide diuretics. Lastly, they were more likely to be smokers but less likely to drink alcohol.

In the univariate analysis, higher DMI was strongly associated with lower odds of prevalent KS disease when DMI was analyzed as a continuous variable (OR=0.94, 95% CI: 0.89–0.99, p=0.02) or when the highest quartile of DMI was compared to the lowest (OR=0.74, 95% CI: 0.60–0.92, p=0.007). After adjustment for age, sex, race, BMI, histories of hypertension, diabetes, thiazide use, cigarette smoking, alcohol consumption, dietary intakes of calorie, protein,

Table 1. Baseline characteristics of the study population

	KS Former	Non-KS Former	p value
Total n, unweighted	1,878	17,393	
Male sex	53.8 (1,008)	47.7 (8,343)	0.006
Age (y)	53.7 ± 0.46	47.1 ± 0.34	<0.001
Race			<0.001
Non-Hispanic White	74.9 (961)	63.6 (6,392)	
Non-Hispanic Black	6.2 (271)	11.9 (4,122)	
Hispanic/Latino	12.1 (450)	15.2 (4,119)	
Asian	2.8 (121)	5.9 (2,127)	
Other	4.1 (75)	3.4 (633)	
BMI (kg/m2)			<0.001
<25.0	19.1 (357)	29.7 (5,106)	
25.0–<30.0	32.0 (617)	32.5 (5,571)	
30.0+	48.8 (904)	37.8 (6,716)	
History of diabetes	23.6 (507)	11.4 (2,645)	<0.001
History of hypertension	47.7 (966)	32.3 (6,307)	<0.001
Thiazide diuretic use	12.1 (231)	7.7 (1,570)	<0.001
Smoking status			<0.001
Never	50.2 (930)	57.2 (10,070)	
Former	30.8 (571)	24.1 (3,964)	
Current	19.0 (377)	18.7 (3,359)	
Alcohol consumption			0.02
None (0 g/d)	78.6 (1,536)	74.3 (13,386)	
Some (>0–<70g/d)	19.0 (297)	21.4 (3,317)	
Heavy (70+ g/d)	2.5 (45)	4.4 (690)	
Total calories (kcal)	2,116.6 ± 35.1	2,153.5 ± 9.3	0.31
Protein intake (g)	81.0 ± 1.7	83.1 ± 0.47	0.26
Water intake (g)	1,191.7 ± 36.8	1,244.5 ± 20.6	0.17
Dietary sodium (mg)	3,510.8 ± 68.0	3,555.8 ± 17.7	0.52
Dietary & supplemental calcium (mg)	1,079.6 ±23.2	1,110.8 ± 10.1	0.20
Dietary & supplemental zinc (mg)	15.9 ± 0.48	15.0 ± 0.14	0.08
Dietary & supplemental vitamin D (µg)	23.2 ± 2.6	19.2 ± 0.79	0.13
Dietary magnesium (mg)	295.4 ± 6.2	309.6 ± 2.2	0.02
Quartiles			0.01
0–204	27.8 (595)	25.2 (4,846)	
205–280	25.1 (481)	24.6 (4,308)	
281–378	26.1 (420)	24.6 (4,194)	
379–2,725	20.9 (382)	25.5 (4,045)	

Values are expressed as weighted means ± SE or % (unweighted n).
Abbreviations: BMI = body mass index, KS = kidney stone.

Table 2. Odds ratios of prevalent kidney stones according to dietary magnesium intake in the multivariable regression model

		Unadjusted Models		Adjusted Models*	
Dietary Magnesium Intake		OR (95% CI)	p value	OR (95% CI)	p value
Continuous variable, per 100 mg		0.94 (0.89–0.99)	0.02	0.92 (0.84–1.01)	0.07
Categorial variable	Quartile 1: 0–204 mg	REF		REF	
	Quartile 2: 205–280 mg	0.93 (0.79–1.09)	0.34	0.91 (0.77–1.08)	0.27
	Quartile 3: 281–378 mg	0.96 (0.82–1.13)	0.63	0.91 (0.75–1.10)	0.34
	Quartile 4: 379–2,725 mg	0.74 (0.60–0.92)	0.007	0.70 (0.52–0.93)	0.01

Abbreviations: OR = odds ratio, CI = confidence interval.
*Multivariable model included age, sex, race, BMI, histories of hypertension, diabetes, thiazide use, cigarette smoking, alcohol consumption, dietary intakes of calorie, protein, water, sodium, and both dietary and supplemental intakes of calcium, zinc, and vitamin D.

water, sodium, and both dietary and supplemental intakes of calcium, zinc, and vitamin D, higher DMI had a trend toward an association with reduced odds of prevalent KS disease (OR 0.92 per 100 mg increase, 95% CI: 0.84–1.01, p=0.07). No deviation from a linear relationship between DMI and odds of KS disease was observed. In addition, we evaluated KS risk associated with extreme categories of DMI. We divided DMI into quartiles. Among stone formers, there were 595 participants in quartile 1 (<204 mg/day), 481 participants in quartile 2 (205–280 mg/day), 420 participants in quartile 3 (281–378 mg/day), and 382 participants in quartile 4 (≥379 mg/day), whereas among non-stone formers, the corresponding numbers of participants were 4846, 4308, 4194 and 4045 in each respective quartile. The multivariate-adjusted OR for stone formation was 0.70 (95% CI: 0.52–0.93, p = 0.01) in those who consumed ≥ 379 mg/day Mg compared to those with <205 mg/day of DMI (**Table 2**). There was no two-way interaction effect of age x DMI or of sex x DMI on KS formation. Also, no three-way interaction effect of age x sex x DMI on KS formation was noted.

In our multivariate logistic regression analyses, the following variables were found to have significant associations with increased odds of prevalent KS disease (**Table 3**): age, male sex, BMI, diabetes, hypertension, and increasing caloric intake. In contrast, non-Hispanic White, heavy alcohol intake, and dietary calcium intake were associated with lower odds of prevalent KS disease. The estimated associations were similar when DMI was modeled as a continuous variable or in quartiles.

Table 3. Multivariate-adjusted OR of covariates from the model with categorized DMI

	Model with DMI quartiles	
	OR (95% CI)	p value
Male sex	1.27 (1.03–1.56)	0.03
Age (y)*	1.02 (1.01–1.02)	<0.001
Race		
Non-Hispanic White	REF	
Non-Hispanic Black	0.41 (0.34–0.50)	<0.001
Hispanic/Latino	0.75 (0.63–0.89)	0.001
Asian	0.50 (0.37–0.68)	<0.001
Other	1.00 (0.71–1.41)	0.99
BMI (kg/m2)		
<25.0	REF	
25.0–<30.0	1.27 (1.06–1.52)	0.009
30.0+	1.55 (1.29–1.87)	<0.001
History of diabetes	1.67 (1.38–2.01)	<0.001
History of hypertension	1.26 (1.07–1.49)	0.007
Thiazide diuretic use	1.03 (0.78–1.36)	0.82
Smoking status		
Never	REF	
Former	1.08 (0.89–1.31)	0.43
Current	1.18 (0.95–1.46)	0.14
Alcohol consumption		
None (0 g/d)	REF	
Some (>0-<70g/d)	0.85 (0.69–1.06)	0.15
Heavy (70+ g/d)	0.50 (0.30–0.82)	0.007
Total calories (kcal)*	1.00 (1.00–1.00)	0.04
Protein intake (g)*	0.99 (0.99–1.01)	0.89
Water intake (g)*	1.00 (1.00–1.00)	0.24
Dietary sodium (mg)*	0.99 (0.99–1.00)	0.72
Dietary & supplemental calcium (mg)*	0.99 (0.99–0.99)	0.02
Dietary & supplemental zinc (mg)*	1.00 (0.99–1.01)	0.23
Dietary & supplemental vitamin D (μg)*	1.00 (0.99–1.00)	0.66

Abbreviations: DMI = dietary magnesium intake, BMI = body mass index, OR = odds ratio, CI = confidence interval. *OR per unit increase for continuous variables. OR and CI bounds may be the same due to rounding.

DISCUSSION

Mg is involved in multiple cellular activities and is important for bone mineral metabolism. Its role in KS formation remains unclear. Here, we analyzed a large US population cohort and showed a strong association between DMI and the odds of prevalent KS. To the best of our knowledge, it is the largest population study examining the effect of DMI on risk of KS formation independent of other known confounders for KS disease.

KS formation involves several key steps, including over secretion of stone forming minerals including calcium and oxalate, ultimately reaching a supersaturation point. It is followed by crystal nucleation, aggregation, and ultimately stone growth. Mg can affect KS formation in many different ways. When bound in the urinary space, magnesium oxalate is 100 times more soluble than calcium oxalate, therefore lowering the urinary saturation of calcium oxalate.[27] Indeed, in an artificial urine environment at acidic pH, Mg has not only been shown to bind with oxalate reducing supersaturation but also reduces time to supersaturation.[5] Using a mixed suspension crystallizer and scanning electron microscopy, investigators showed that Mg decreased both nucleation and growth rates of calcium oxalate crystals in physiological concentrations.[6] These findings were confirmed by other in vitro studies.[7,28-31] Once calcium oxalate crystals are formed, Mg can still slow down their growth.[9] Furthermore, using radioactive C-14, Lieske et al showed that increasing concentrations of Mg prevented adhesion of calcium oxalate monohydrate crystals to cultured kidney cells[12] which serves as the crystallization surface, and therefore blocking the final step of KS formation. In addition to its direct effect on stone formation, Mg can bind to oxalate in the gut and reduce its absorption,[32,33] further reducing the crystallization potential of calcium oxalate.[30]

In humans, calcium stone formers tend to excrete less urinary Mg than their non-stone forming counterparts[16,17,34] and presence of low urine Mg has been associated with high oxalate concentration.[35] Urinary Mg can be a surrogate of dietary Mg as supplementation leads to increased renal excretion in a state of normal total body Mg.[36] This suggests a role of dietary Mg in KS formation. This was also clinically demonstrated in an interventional study by Kato et al where dietary Mg supplementation with Mg oxide tablet raised urinary Mg and reduced urinary oxalate.[37]

However, despite favorable urinary biochemical changes associated with DMI, its effect on actual stone prevention remains unclear. Interventional trials have shown conflicting results. In 1980, Johansson et al examined the role of Mg supplementation in 56 stone formers without signs of Mg deficiency. They found that 500mg of oral Mg dihydroxide daily for 2–4 years led to a reduction in stone recurrence in 80–86% of patients as compared to controls who did not receive Mg supplement.[21,22] Ettinger et al reported similar findings in 64 recurrent stone formers. They observed an 85% reduced risk of stone recurrence after daily supplementation of potassium Mg citrate for three years when compared to controls.[24] However, results from other interventional studies contradict these findings. In a study of 75 KS formers, supplementation with 1300mg of Mg oxide did not reduce the rate of KS recurrence when compared with placebo.[19] Unfortunately, all these interventional studies were limited by small number of participants and the use of different Mg preparations with unpredictable bioavailability.[38]

Our study has several limitations. First, we used DMI as a marker of body Mg store, assuming a steady state is reached. However, potential gastrointestinal malabsorption (especially among elderly) should be considered, as it may misclassify individuals into different categories of Mg intake. Second, this study is cross-sectional and involves prevalent KS cases, a causal or temporal relationship cannot be established. However, it is very unlikely that stone formers increase their Mg intake for secondary stone prevention as existing studies have conflicting results, and no clinical guidelines to date recommend Mg intake for stone prevention. Third, the prevalent KS cases were self-reported, and some participants may have KS disease without self-awareness or clinical diagnosis. This may have led to potential misclassification but should be non-selective with regard to Mg intake. Therefore, if this misclassification exists, the results should be biased toward null. Fourth, we were unable to evaluate the effects of higher DMI on urine stone risk profile since these urine studies were not performed in NHANES 2011-2018. Finally, we do not have information on stone composition, although the vast majority of kidney stones in the general population reflected by NHANES are calcium-based.

CONCLUSION

Our study demonstrates that higher DMI is associated with a reduced prevalence of KS disease. Future prospective studies are needed to clarify the causal relationship and underlying mechanism.

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Authors

Sandipan Shringi, MD, Fellow, Division of Kidney Diseases and Hypertension, Alpert Medical School of Brown University, Providence, RI.

Christina A. Raker, ScD, Lifespan Biostatistics, Epidemiology, Research Design, and Informatics Core, Division of Kidney Diseases and Hypertension, Alpert Medical School of Brown University, Providence, RI.

Jie Tang, MD, MPH, FASN, Division of Kidney Diseases and Hypertension, Alpert Medical School of Brown University, Providence, RI.

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Authors declare that they have no competing interests.

Correspondence

Jie Tang, MD
Division of Kidney Diseases and Hypertension
Department of Medicine
Brown Physicians Inc.
375 Wampanoag Trail
East Providence, RI 02915.
401-649-4063
Jie.tang@brownphysicians.org

Diet Interventions for Calcium Kidney Stone Disease

SAIRAH SHARIF, MBBS; JIE TANG, MD, MPH; MATTHEW R. LYNCH, MD

ABSTRACT

Kidney stone disease is a common condition with an increasing prevalence. Diet is an important, modifiable risk factor of an individual's risk of developing kidney stone disease, particularly for those without genetic causes of kidney stone disease. Prospective and epidemiological evidence suggest that adequate fluid intake, limited sodium ingestion, and sufficient calcium and potassium intake can decrease the risk of developing kidney stones. Metabolic risk factors for KSD found on 24-hour urine studies can be used to tailor dietary modifications recommended to reduce subsequent risk of kidney stone formation.

KEYWORDS: calcium kidney stones; nephrolithiasis; nutrition

INTRODUCTION

Kidney stone disease (KSD) is a common condition in industrialized nations, impacting up to 15% of males and 5% of females.[1] The treatment of symptomatic kidney stone disease has significant morbidity and economic cost.[2] As the prevalence of KSD is rising, likely related to changing dietary and lifestyle factors, these burdens are growing.[3] With approximately four of five kidney stones being calcium-based, interventions aimed at reducing the risk of developing, or re-developing, these stones seems to hold the most promise at reducing these burdens. In this review, we will address diet as a modifiable risk factor in calcium-based KSD.

RISK FACTORS FOR CALCIUM KIDNEY STONE FORMATION

The urinary solubility of the constituent parts of calcium oxalate and calcium phosphate stones is what helps determine the risk of developing them. This solubility can be estimated using a computer-based equation to determine the supersaturation for each compound and is determined by factors such as the urinary concentration of the compounds' ions; the pH of the urine; and the concentration of inhibitors of crystal formation, such as citrate. Data from large, United States based epidemiologic studies, Nurses' Health Study (NHS) I and II as well as the Health Professionals Follow-up Study (HPFS), demonstrate an association of elevated supersaturation of calcium oxalate and calcium phosphate with stone risk in all sexes; in women, there is also an increased association of KSD and elevated uric acid supersaturation.[4] Calcium oxalate stones tend to form in acidic urine (pH 5) whereas calcium phosphate stones, composed of brushite and/or hydroxyapatite, tend to form in more alkaline urine (pH 6 or higher). In patients with KSD, analysis of 24-hour urine collection for supersaturation of stone forming crystals and other nutrients is recommended by the American Urologic Association (AUA) to assist in creation of a therapy plan.[5]

FLUID INTAKE

Of any dietary intervention, the strongest data associating diet and kidney stone risk is in the consumption of fluids without added sugar. Mechanistically, the greater the fluid consumption, the more solvent (urine) exists for the solute (calcium, oxalate, phosphate, etc.) to be diluted in, decreasing the concentration of the solute. This decreased solute concentration necessarily reduces the supersaturation, decreasing the risk of subsequent kidney stone development. This principle has been demonstrated across several studies.

A meta-analysis of studies examining dietary, fluid, and supplement intake amongst those with a known history of any nephrolithiasis found increased water intake of at least 2–2.5 liters daily decreased KSD recurrence risk by at least 60%.[6] A small, prospective study of patients with documented calcium kidney stone disease randomized subjects to either no additional treatment or counseled to consume enough water such that urine output was at least two liters daily. Those who consumed the high water volumes were found to have significant decreases in the supersaturation of calcium oxalate, brushite, and uric acid as well as a significantly decreased risk of kidney stone recurrence over the five year study period.[7] Analysis of subjects from HPFS and NHS studies found total urine volume, a marker of higher fluid intake, was inversely associated with risk of kidney stone disease.[8] Similarly, subjects from the large United Kingdom-based epidemiologic study, the UK Biobank, with the highest fluid intake had the lowest risk of kidney stone development.[9]

The type of fluid ingested may also be important in modifying stone risk. Data from the UK Biobank suggested that those who consume more tea, coffee, and alcohol had decreased kidney stone development risk, although there was interestingly no association between water intake and kidney stone risk.[9] Using data from the HPFS of men with no history of kidney stone disease at the start of the study, the authors found consuming coffee, tea, beer, and wine to be associated with decreased risk of developing kidney stones over the subsequent six years whereas regular consumption of apple juice and grapefruit juice may have increased it.[10] Data from the populations of the NHS I & II and the HPFS demonstrated that those who consumed the most sugar sweetened beverages, such as cola and punch, had a significantly increased risk of kidney stone formation as compared to those who consumed the least of these items.[11] A meta-analysis of men with a history of kidney stone disease found a significant association between reduction in soft drink intake and decreased risk of kidney stone recurrence.[6]

In the setting of the data above, the AUA recommends that all patients with a history of kidney stones ingest enough fluid to allow for a urine output of at least 2.5 liters per day.[5] The European Association of Urology (EAU) similarly advises consumption of 2.5–3 L fluid daily, of which water is the preferred fluid, so that the daily urine output is 2–2.5 L daily.[12]

HYPERCALCIURIA

Urinary calcium concentration is impacted by intake of several different nutrients. Dietary sodium, potassium, and citrate can all play roles in modulating urinary calcium excretion.

Sodium

In the nephron 80–85% of the filtered calcium load is reabsorbed in the proximal tubule and loop of Henle, largely via passive transport set up by sodium chloride and water reabsorption.[13] Thus, the more sodium reabsorbed, the more calcium will be reabsorbed, decreasing urinary calcium excretion. A major driver of proximal tubule sodium reabsorption is extracellular volume state. In states of volume depletion, more sodium is reabsorbed to expand extracellular volume, and in states of volume excess, less sodium is reabsorbed. Thus, a diet high in sodium, leading to expanded extracellular volume, will enhance urinary sodium and, therefore, calcium excretion. This physiologic principle has been practically demonstrated in several studies.

In a small study of patients without hypercalciuria, 24-hour urinary calcium excretion was found to be positively correlated with dietary sodium intake and independent of intestinal calcium absorption.[14] A retrospective analysis of the impact of one week of a combined low sodium and low calcium diet in patients with recurrent calcium oxalate stones found significant reduction in urinary sodium and calcium were achieved with these dietary changes.[15] Thirdly, a short, prospective study of patients with a documented history of calcium KSD in the setting of hypercalciuria tested the impact of 2–3 L water daily versus 2–3 L water plus a diet where table salt and high sodium foods were restricted. After three months, those on the low sodium diet had greater reductions in urinary calcium and oxalate.[16] Notably, subsequent stone formation was not directly measured in any of these studies.

Given the association of sodium-restricted diets and decreased risk of KSD, both the AUA and EAU have recommended that patients with kidney stone disease limit sodium intake, although to different degrees. The AUA recommends a target of no more than 2,300 mg (100 mEq) sodium intake per day.[5] The EAU, citing the absence of robust prospective clinical trials of sodium reduction and its relationship to calcium kidney stone disease, recommend dietary sodium intake to not exceed a higher value of 3–5 g daily.[12]

Potassium

Increases in dietary potassium leading to decreases in urinary calcium has been observed in several studies; however, the exact mechanism has not yet been elucidated. In a small but elegant study, healthy volunteers were each given standardized diets and supplemented with sodium chloride, sodium bicarbonate, potassium chloride, and potassium bicarbonate over separate periods. As expected, urinary calcium increased during times where sodium chloride supplements were provided. However, sodium bicarbonate, potassium chloride, and potassium bicarbonate all led to decreased urinary calcium excretion, with the decrease in urinary calcium greater for each of the potassium salts, suggesting that potassium independently decreases urinary calcium.[17] Furthermore, a small, prospective study of postmenopausal women designed to assess the impact of supplemental potassium citrate on sodium driven hypercalciuria found that potassium citrate was able to prevent the increase in urinary calcium driven by a high sodium diet.[18] Data from NHS and HPFS both have found that increased potassium intake is associated with decreased risk of KSD.[19,20]

HYPOCITRATURIA

Citrate is a powerful inhibitor of calcium-based kidney stone formation, working via multiple mechanisms. Citrate creates relatively soluble calcium-citrate complexes in the tubule, decreasing the concentration of free calcium available for crystal formation with oxalate or phosphorus. Citrate also prevents aggregation of both calcium oxalate and calcium phosphate crystals that have formed through binding to the crystal surface itself.[21,22] Furthermore, citrate, when converted to bicarbonate, reduce bone resorption and enhances renal calcium reabsorption in the distal nephron.[23] In the diet, citrate is found in fresh fruits and vegetables, with citrus fruits – in particular lemons – being excellent sources of citrate.[21]

In a study using both simulated and natural urine, higher lemon juice concentrations were found to have a dose dependent inhibitory effect on calcium oxalate crystallization.[24] In human subjects, patients with hypocitraturia and history of calcium oxalate KSD were treated with potassium citrate in effort to restore normal urine citrate concentration and increase urinary pH. Over an average of 2.2 years, only 11% had recurrence of kidney stones with this treatment.[25] Another small study of patients with calcium KSD and hypocitraturia were trialed on lemonade therapy – 4 ounces of lemon juice diluted in water to create 2L lemonade – in lieu of pharmacotherapy. These patients all had increased urinary citrate and non-significant decrease in urinary calcium with similar urine volumes as compared to before the intervention.[26]

A study randomizing subjects to the addition of 2 ounces of lemon juice twice daily to 2–2.5 L water intake or no addition found that those taking lemon juice had decreased kidney stone recurrence after one year. This benefit was not seen after two years of the study in the setting of low adherence (48%) to the lemon juice at year two.[27] Thus, for patients preferring to avoid pharmacotherapy, or in those experiencing untoward gastrointestinal side effects of pharmacotherapy, lemonade therapy may be a reasonable option to pursue.

As the addition of citrate may lead to urinary alkalinization, there is a theoretical concern of increased calcium phosphate crystallization at higher urine pH. In a small, prospective cross-over study examining the impact of potassium citrate and citric acid on stone risk among calcium phosphate stone formers, Doizi et al failed to find any difference in urinary stone risk parameters among the three study groups.[22] Thus, citrate supplementation appears to be safe even among calcium phosphate stone formers.

Animal Protein

Consumption and subsequent breakdown of animal protein increases daily titratable urinary acid load leading to hypocitraturia.[28] Indeed, the data from the HPFS suggests that the amount of animal protein consumed has a positive correlation with risk of developing symptomatic KSD.[20] Additionally, a small, prospective cross-over study suggests the type of animal protein does not matter with regards to kidney stone risk. Subjects on a standard diet with meat consisting of beef, chicken, or fish did not have any significant difference on urinary uric acid, pH, citrate, or oxalate content despite higher serum uric acid during periods on the chicken and fish diets.[29]

To reduce KSD risk, the AUA recommends patients with calcium stones and low urinary citrate to increase fruit and vegetable consumption and decrease intake of non-dairy animal protein.[5]

HYPEROXALURIA

Oxalate is absorbed in the gut in its soluble form and excreted in stool when in its crystalline, calcium oxalate form. Additionally, there may be some degree of the gut microbiota degrading oxalate as an energy source, decreasing its absorption. Increased soluble oxalate, be it from diet, increased enteric absorption in the setting of malabsorptive states such as following Roux-en-Y bypass, and increased endogenous production all increase the filtered load, and directly lead to an increased supersaturation of calcium oxalate in the urine.[30] Although there are no studies demonstrating an association of decreased oxalate ingestion and decreased KSD risk, both the AUA and EUA recommend patients with calcium oxalate KSD and hyperoxaluria, particularly enteric hyperoxaluria, limit dietary oxalate intake.[5,12]

Calcium

Calcium ingested during a meal can complex with oxalate, leading to formation of non-absorbable crystalline calcium oxalate. However, if taken away from a meal, such as during calcium supplementation, a larger proportion of the ingested calcium and oxalate can be absorbed, leading to a greater delivery of calcium to the nephron. This was demonstrated in a small, prospective study of healthy male volunteers given 3g calcium carbonate supplementation daily, either as 3g at bedtime or 1g thrice daily with meals. Although both protocols increased urinary calcium excretion, those who took the supplement with meals had significantly decreased urinary oxalate compared to those with increased calcium oxalate supersaturation when taking the supplement at bedtime.[31]

A randomized, prospective trial of 120 men with history of calcium oxalate nephrolithiasis and hypercalciuria compared low calcium or normal calcium diets added to a decreased sodium and low animal protein diet. Those on the normal calcium diet had approximately a 50% reduction in risk of kidney stone recurrence.[32] Data from the NHS and HPFS also suggests an inverse association between dietary calcium and kidney stone risk.[19,20,33] However, supplemental calcium use was associated with a higher risk of kidney stones in older women, perhaps due to timing of the intake being away from dietary oxalate ingestion.[19] Interestingly, supplemental calcium was not associated with increased risk of KSD in younger women.[33]

The AUA also recommends dietary calcium intake for 1,000–1,200 mg daily with the caveat that calcium should be ingested at meals.[5] The EAU advises dietary calcium intake of 1,000–1,200 mg daily. They do not advise supplemental calcium except in the setting of enteric hyperoxaluria.[12]

Vitamins

Vitamin B6 and vitamin C both impact total body oxalate metabolism. Vitamin B6 decreases oxalate production whereas vitamin C can be metabolized into oxalate, therefore increasing the serum concentration.[34]

In analysis of women in the NHS, those who took at least 40 mg daily vitamin B6 were associated with decreased subsequent kidney stone risk.[34] In analysis of the NHS and HPFS, vitamin C intake was not found to be associated with increased risk of kidney stones in females but was in males.[34,35] Specifically, the increased risk was found in those who consumed supplements of vitamin C, particularly at doses over 700 mg daily, as high levels of diet-derived vitamin C did not lead to increased risk. Although the AUA considers vitamin C data controversial,[5] EAU advises those with calcium oxalate KSD avoid "excessive" vitamin C intake.[12]

DIETARY SUPPLEMENTS

Probiotics

Over the past several years, the increasing work examining the relationship between disease states and the composition of the gut microbiota has included several studies aimed at KSD risk factors. Small studies have demonstrated an association between certain gut bacteria and urinary citrate and oxalate.[36,37] However, manipulation of the microbiome with probiotics to promote bacteria with favorable associations has yet to be proven clinically effective. In a small, prospective trial of patients with calcium oxalate KSD and hyperoxaluria, two different probiotic preparations did not result in a change in urinary oxalate excretion or calcium oxalate supersaturation whereas a restriction of dietary oxalate to 100 mg daily did.[38] Another small, prospective study using probiotics in patients with hyperoxaluria similarly did not lead to changes in urinary oxalate excretion after four weeks of use.[39]

CONCLUSION

For calcium kidney stone prevention, it is generally recommended to maintain adequate oral hydration while avoiding sugar sweetened drinks, to restrict dietary sodium and animal protein intake, and to optimize dietary potassium and citrate intakes. We should also emphasize that dietary interventions should be individualized based on patient's medical history and urinary stone risk profiles.

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Authors

Sairah Sharif, MBBS, Divisions of Nephrology and Critical Care Medicine, Stony Brook University, Stony Brook, New York.

Jie Tang, MD, MPH, Division of Nephrology, Department of Medicine, Warren Alpert Medical School of Brown University; Brown Medicine, Providence, Rhode Island.

Matthew R. Lynch, MD, Division of Nephrology, Department of Medicine, Warren Alpert Medical School of Brown University; Brown Medicine, Providence, Rhode Island.

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Correspondence

Matthew R. Lynch, MD
matthew.lynch@brownphysicians.org

Renal Imaging in Stone Disease: Which Modality to Choose?

IHA KAUL, MD; SARAH MOORE, MD; EMILY BARRY, MD; GYAN PAREEK, MD

ABSTRACT

Numerous imaging modalities are available to the provider when diagnosing or surveilling kidney stones. The decision to order one over the other can be nuanced and especially confusing to non-urologic practitioners. This manuscript reviews the main modalities used to image stones in the modern era – renal bladder ultrasound, Kidney Ureter Bladder plain film radiography (KUB), magnetic resonance imaging (MRI), and non-contrast computerized tomography (NCCT). While NCCT has become the most popular and familiar modality for most practitioners, particularly in the acute setting, ultrasound is a cost-effective technology that is adept at monitoring interval stone development in patients and evaluating for the presence of hydronephrosis. KUB and MRI also occupy unique niches in the management of urolithiasis. In the correct clinical setting, each of these modalities has a role in the acute workup and management of suspected nephrolithiasis.

KEYWORDS: Renal imaging, stone surveillance, ultrasound, KUB

INTRODUCTION

Nephrolithiasis is a common disease, affecting nearly 9% of the U.S. population and resulting in over one million emergency department visits each year.[1,2] With changing technology, practice, and surgical techniques the landscape of renal imaging for kidney stone evaluation has evolved over time. There are a variety of options that are utilized with varying degrees of sensitivity, risk, and cost. All imaging modalities must be able to determine the presence or absence of stone either by directly identifying the stone or identifying secondary signs of stone presence. It is helpful if the imaging modality can localize the stone and estimate its size, as this information may inform the likelihood of spontaneous stone passage vs. need for surgical intervention. Additionally, visualization of adjacent structures can allow for optimal surgical planning when deciding which surgical approach to pursue (such as endoscopic vs. percutaneous vs. open). Gleaning information on stone density and quality may provide additional information on the likely composition of the stone, which may alter the care plan for the patient. Finally, imaging is critical for surveillance and confirmation of a technically successful intervention. Herein, we outline the most commonly utilized imaging modalities for assessment of nephrolithiasis including: renal bladder ultrasound, Kidney Ureter Bladder plain film radiography (KUB), magnetic resonance imaging (MRI), and non-contrast computerized tomography (NCCT). We describe common advantages and pitfalls of each modality to help guide imaging selection in patients with suspected stone disease. Further developments are expected to enhance these imaging modalities in the future and improve our ability to accurately and safely diagnose and manage nephrolithiasis.

RENAL BLADDER ULTRASOUND

The use of ultrasonography in the management of nephrolithiasis can be traced back to 1961, when Schlegel and colleagues first published on its use for the intraoperative localization of renal stones.[2] Ultrasonography remains a commonly used imaging modality in assessing for obstructing urinary processes. Its attraction lies in its wide availability, low cost, and noninvasive nature. It is also the safest imaging modality at present, as it omits the need for ionizing radiation and the risk associated with intravenous contrast administration. Ultrasonography has been shown to have increased accuracy in children due to their smaller body habitus and reduced skin-to-stone distance.[3] Given this, ultrasound is a first line imaging modality in the evaluation of pediatric patients and pregnant patients with renal colic symptoms.[4]

Many studies have investigated whether ultrasound is sensitive enough to detect clinically significant nephrolithiasis. The reported sensitivities for stone detection vary widely in the literature, ranging from 3–98% depending on whether direct stone visualization was required or if indirect evidence of stone presence (such as hydronephrosis, twinkle artifact, absence of ureteral jet on Doppler) were sufficient.[5] This wide range is likely due to variations in technique, body habitus, patient population, and sonographic reference standards. Ultrasound is notoriously known for its poor detection of small stones less than 3mm in size which might not produce a shadow. Stones located within the mid-ureter are also challenging to detect due to interference by bowel gas and variations in penetration depth along the ureter's course. Non-obstructing renal stones may also be missed in a decompressed system without hydronephrosis as it can be difficult to distinguish an echogenic stone from echogenic central sinus fat in the kidney or vascular calcifications.[4] Furthermore, when stones are detected, ultrasound often overestimates their size as stone edges are typically ill-defined.[3] Sensitivity is increased in younger patients under age 35 as well as patients with low body mass index.[6] Ultrasound combined with KUB has also been shown to increase sensitivity.[7] Despite its overall lower detection rate than conventional NCCT, multiple studies have demonstrated that ultrasound is unlikely to miss stones that ultimately would require surgical intervention.[8]

In the acute setting, point-of-care ultrasound has also been investigated as a first-line imaging modality for the diagnosis of nephrolithiasis. In patients with equivocal presenting symptoms, it may be used as a screening tool for the presence of hydronephrosis and guide decision making on whether formal imaging for the presence of nephrolithiasis should be pursued. Overall, utilizing formal or point-of-care ultrasound does not preclude the ability to obtain a NCCT if results are not definitive, and delayed vs. immediate NCCT in the emergency room setting does not appear to impact morbidity or cost of the emergency department visit.[9,10]

In addition to diagnosis, ultrasound is widely used in practice for stone surveillance. Routine imaging is required to ensure that patients who undergo non-operative trial of stone passage have, in fact, successfully passed their stone. Surveillance imaging is also recommended post-operatively after stone treatment to assess stone clearance rates. Patients who have known non-obstructing renal stones may elect for serial surveillance of stone growth over time rather than surgical intervention. Recurrent stone formers also may require interval imaging as part of their stone disease care plan. The frequency of surveillance imaging acquisition is variable and not standardized. In keeping with the principle of ALARA (as low as reasonably achievable) and efforts to minimize additive radiation exposure, ultrasound is an appealing choice for long-term stone surveillance.[11,12] However, given its limitations as described above, ultrasound may miss small residual or asymptomatic calculi and therefore underestimate the need for intervention.[13] This can lead to undertreatment and complications of indolent obstruction over time such as recurrent symptomatic events and even long-term renal injury.[14]

Overall, research is ongoing to develop stone-specific ultrasonographic algorithms to maximize stone contrast, increase resolution, and improve stone sizing accuracy both for the diagnosis and subsequent surveillance of nephrolithiasis.[15] In summary, ultrasonography is less sensitive and specific than other imaging modalities for the detection and accurate sizing of stones. However, it is safe, cost-effective, and does have diagnostic utility in the correct patient population and clinical circumstance.

KIDNEY URETER BLADDER PLAIN FILM RADIOGRAPHY (KUB)

As the earliest available imaging modality, the KUB is often overshadowed in discussions of NCCT scan versus ultrasonography for imaging urolithiasis. The sensitivity and specificity of the KUB has been estimated at 57% and 76%, respectively.[16] Importantly, when considering larger stones (>5 mm), which are more likely to be clinically significant, the KUB has a higher sensitivity of 87.5%.[17] While the KUB can provide information on stone size and location in many circumstances, its one-dimensionality and lack of information regarding anatomic details of the collecting system and surrounding structures are major limitations in surgical planning. However, a few situations remain where the KUB provides valuable clinical information with the added benefit of easy accessibility, low cost, and relatively low radiation exposure.[18]

One such example is in determining a patient's candidacy for treatment by extracorporeal shock-wave lithotripsy (SWL). In order for a stone to be treated by SWL, it must be visible on KUB to allow for intraoperative stone targeting and live assessment of stone fragmentation. Efficacy of SWL treatment is influenced by parameters such as skin-to-stone distance and stone composition. For example, a skin-to-stone distance of less than 10 cm is considered favorable for renal stones, and stone attenuation of less than 900-1000 Hounsfield units helps predict successful treatment by SWL.[19] These parameters should initially be determined by CT imaging; however, subsequent SWL planning would not require repeat CT scans, presuming the recurrent stone is likely of the same composition. These patients would instead only require a pre-operative KUB. Benefits of SWL include the least morbidity and lowest complication rate of all stone treatment options.[20,21] After the procedure has been completed, KUB is also useful for assessing residual stone burden. Therefore, SWL is a procedure where KUB has a unique utility in the pre-operative, intra-operative, and post-operative assessment and management of urolithiasis.

The other major role of KUB is in surveilling adult patients who are being followed for asymptomatic stones. The low radiation exposure compared to NCCT is particularly important to consider for young recurrent stone formers who will undergo decades of stone surveillance imaging. The low cost and easy accessibility also make KUB an attractive option when compared to other modalities such as US and NCCT. Therefore, literature suggests obtaining a KUB annually as part of routine surveillance for stones in asymptomatic adult patients, presuming the stones are radiopaque.[22]

Disadvantages of the KUB include the lack of anatomic details of the collecting system and surrounding structures as mentioned above, but there are several additional limitations to discuss. One such limitation is the possibility of stones being obscured by overlying bowel gas and stool or by overlying bony structures (commonly the ribs or pelvis).[23]

Another issue is differentiating stones in the collecting system (particularly the ureters) from adjacent vascular calcifications (like phleboliths in the pelvic veins).[24] Also, KUB is not able to detect all stone compositions – some stones, such as cystine and struvite, are poorly visualized on KUB, while other types such as uric acid or matrix are radiolucent and not able to be seen at all.[4] Thus, KUB plays a very nuanced role in the realm of stone imaging and should be considered only in the correctly selected patient.

MAGNETIC RESONANCE IMAGING (MRI)

MRI can be used as an adjunctive diagnostic study in the management of pregnant patients who are suspected to have symptomatic urolithiasis, but MRI is otherwise rarely used in clinical practice. Its limitations in the management of stone disease are pragmatic in nature, rooted in high cost and issues with accessibility. For instance, MRI usually costs approximately three times more than a NCCT.[4] Additionally, the sensitivity of MRI is estimated to be 82%, which is higher than KUB and US, but lower than NCCT.[16] Although adjustments can be made to the imaging sequence to improve sensitivity, conventional MRI sequences display stones as signal voids that may be missed when small (<4 mm) or difficult to distinguish from other etiologies (i.e. soft tissue masses, blood products).[25] The main benefit of MRI for pregnant patients is that it avoids radiation exposure for the fetus. Although not practical to obtain for all pregnant patients as the initial diagnostic test, it should be ordered for pregnant patients with clinical history suspicious for urolithiasis and a nondiagnostic renal bladder ultrasound.[4]

NON-CONTRAST COMPUTED TOMOGRAPHY (NCCT)

NCCT has become a cornerstone of imaging for many abdominal and specifically urologic pathologies. Its advantages stem from its high resolution and image quality, as well as its wide availability in hospitals and clinical settings. Unlike other comparative modalities, NCCT images are less susceptible to confounding patient-specific factors such as body habitus or anatomic variation (i.e., duplicated collecting system). It is also able to image the entire collecting system from kidney to ureter to bladder with excellent resolution. The accuracy of diagnosis for renal colic has been cited to be nearly 95–98% sensitive and 96-100% specific.[26] It is not surprising, therefore, that NCCT is now performed in more than 90% of patients who are diagnosed with kidney stones, largely due to the consistency, speed, and accuracy of its images.[27,28] For urologists, NCCT confers an advantage for surgical planning because it provides valuable information about the overall stone burden, size, density and location that can help determine the appropriate treatment to offer patients (ie: endoscopic vs. percutaneous vs. open approach).[5,26,29,30] NCCT is also helpful in the emergency room setting for counseling patients on their chance of spontaneous passage when they present with an acute stone event (i.e., renal colic, urinary infection, acute kidney injury).[31]

A clear advantage of NCCT is its ability to detect all types of urinary stones, some of which are radiolucent or poorly visualized by other modalities.[27] The use of HU to characterize the density of stones on CT is useful in predicting treatment challenges and selecting the appropriate surgical treatment option.[26] Knowledge of stone density can help guide treatment discussion toward less invasive techniques for treatment such as SWL for lower density stones.[19,26] Additionally, the anatomic detail provided by NCCT is critical for surgical planning in patients undergoing percutaneous nephrolithotomy (PCNL) for stone treatment, as NCCT can identify if there are anatomical abnormalities that would necessitate alternative access options.[27] Lastly, CT can diagnose non-urologic explanations for patient symptoms that can be misattributed to stone disease. Other causes of flank and abdominal pain that mimic renal colic may be due to gynecologic, vascular, musculoskeletal, or gastrointestinal problems that can be detected in nearly one-third of non-contrast CT studies.[5,32]

However, NCCT imaging does not come without risk. Its ionizing radiation remains a concern, particularly in high-risk populations such as pregnant patients, children, and those who are recurrent stone formers. In these populations, the risk of radiation exposure may outweigh the benefits conferred by NCCT imaging. Routine NCCT can deliver a radiation dose of approximately 8 to 16 milliSieverts (mSV) compared to 0.5 to 0.9 mSV for KUB.[33] Fortunately, the implementation of low-dose CT scans has mitigated this risk substantially. A low-dose CT scan delivers a radiation dose between 0.5 to 2 mSV. In fact, the American Urologic Association and American College of Obstetrics and Gynecologists guidelines recommend low-dose CT for confirmation of stone presence in pregnant patients with flank pain and hydronephrosis, with nearly no change in accuracy when compared to regular NCCT scan.[33-36] Less is known regarding the long-term effects of frequent NCCT scans for those with recurrent renal stone burden and in developing children. There is concern that frequent radiation exposure increases the risk of developing certain malignancies such as leukemia and thyroid cancer.[28] Therefore, NCCT is not the modality of choice in the pediatric population and should be used sparingly in stone surveillance care plans. Overall, the risk associated with radiation exposure should be weighed carefully with the overall benefit that NCCT confers in the diagnosis and management of nephrolithiasis.

CONCLUSIONS

Ultrasound, KUB, MRI, and NCCT are all imaging modalities that can be used to effectively evaluate for nephrolithiasis. While non-contrast CT remains a cornerstone for the diagnosis of kidney stones due to its high sensitivity, the risks associated with radiation exposure make it a less desirable option in certain patient populations. Ultrasound provides less information than NCCT but is safe, cost-effective, and has high accuracy at detecting clinically significant nephrolithiasis. It is, therefore, the preferred imaging modality for pediatric and pregnant patients. KUB plays a role in specific clinical scenarios such as routine surveillance for stones in asymptomatic adult patients and in patient selection for SWL. MRI may be considered as an adjunctive test when necessary for pregnant patients. When deciding between these imaging modalities in a patient with concern for renal colic, it is important to consider these advantages and drawbacks in the context of the presenting clinical scenario.

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Authors

Iha Kaul, MD, PGY 2 Urology Resident, Division of Urology, Department of Surgery, Warren Alpert Medical School of Brown University.

Sarah Moore, MD, PGY 5 Urology Resident, Division of Urology, Department of Surgery, Warren Alpert Medical School of Brown University.

Emily Barry, MD, PGY 3 Urology Resident, Division of Urology, Department of Surgery, Warren Alpert Medical School of Brown University.

Gyan Pareek, MD, FACS, Chief of Urology, Division of Urology, Department of Surgery, Warren Alpert Medical School of Brown University.

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Correspondence

gyan.pareek@brownphysicians.org

The Surgical Management of Urolithiasis: A Review of the Literature

REBECCA WALES, BA; FAIZANAHMED MUNSHI, MD; SUHAS PENUKONDA, MD; DANIEL SANFORD, MD; GYAN PAREEK, MD

ABSTRACT

The incidence of stone disease has increased significantly in the past 30 years, with a reported prevalence of 11% of the U.S. population in 2022, up from 9% in 2012 and 5.2% in 1994.[1] While prevention is a vital aspect of management, many patients present with symptomatic urolithiasis requiring surgical management. Emerging advances in endoscopy and technology has led to a dynamic shift in the surgical management of stone disease. This paper will serve as a comprehensive review to inform urologic and non-urologic medical professionals alike, as well as the layperson, on the surgical treatment of nephrolithiasis, starting from the initial evaluation, laboratory and radiographic studies, and various surgical options. Additionally, the nuances of managing the pediatric and pregnant patient with nephrolithiasis will be explored. Using the most up-to-date urologic data, our aim is to provide a comprehensive resource for readers who interact with patients experiencing acute episodes of urolithiasis.

KEYWORDS: nephrolithiasis, kidney stone, endourology, urology

INTRODUCTION

According to a 2012 National Health and Nutrition Examination Survey (NHANES) report, it is estimated that 19% of men and 9% of women will be diagnosed with a kidney stone by the age of 70.[2] This sharp increase in prevalence also reflects a nearly 50% increase in economic burden since 1994.[3] Given the rising incidence and costs, it is imperative for all clinicians to understand the presentation, evaluation, and treatment modalities for these patients. Kidney stones may be asymptomatic and incidentally found on imaging. However, they can also present with pain, obstruction, and infection.

Treating stones depends on many factors but most notably stone size and location. On average, asymptomatic stones <5mm have a 75% chance of spontaneous passage regardless of ureteral location. This rate decreases as stones increase in size and present more proximally.[4] In a select patient population not requiring emergent intervention, medical expulsion therapy (MET) can assist the passage process, allowing faster expulsion and fewer symptoms.[5] In contrast to these conservative treatment options, patients may also require surgical intervention in the form of extracorporeal shockwave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotomy for stones not amenable to passage due to size and location. In addition, patients who present with acute obstruction, urinary tract infection, and sepsis – a true urologic emergency – may require urgent ureteral stent or nephrostomy tube placement for collecting system decompression.[6]

Kidney stones classically present with intermittent pain that radiates to the groin or lower abdomen. Patients may also experience dysuria, hematuria, odorous urine, frequency, nausea and vomiting, and fevers and chills.[7] When suspecting a stone, initial testing should include a thorough history and physical to assess for risk factors and history of stones, vitals, complete blood count (CBC), basic metabolic panel (BMP), and urinalysis. In addition, patients should have a non-contrast CT scan to evaluate for stones and hydronephrosis. If there is an obstructing stone, with concern for urosepsis or UTI, patients should be emergently taken to the OR for decompression via stent or nephrostomy tube placement and urine cultures should be sent. In addition, patients should be immediately started on broad spectrum intravenous antibiotics until urine cultures and antibiotic sensitivities result. The urgency of immediate intervention cannot be overstated as patients can acutely decompensate. According to Borofsky et al, patients not treated with surgical intervention had a 19% mortality rate, more than twice that of patients with decompression, necessitating immediate surgery.[8] Definitive stone removal should be delayed until patients clear the infection with a full course of antibiotics as manipulation may cause further systemic effects.[9]

Follow-up after surgical decompression varies by clinical experience and patient characteristics. However, the length of time to maintain an indwelling stent and the duration of antibiotics remains up for debate. One study by Shi et al showed that there was no significant difference in postoperative complication related to UTIs after seven days of an indwelling stent. Similarly, Orr et al concluded that the time between decompression and definitive stone treatment and the length of antibiotic treatment did not impact rates of postoperative urosepsis.[10] Reducing treatment duration will not only improve the rates of stent colic but also decrease the risk of antibiotic resistance in patients with prolonged stent and antibiotic treatment.

If there is a low degree of suspicion for obstruction or infection and depending on the size and location of the stone, patients can initially be managed with conservative measures. Patients with uncomplicated ureteral stones ≤10mm can be observed for spontaneous passage. If stones are more distal, patients can be prescribed MET to aid the passage process. Tamsulosin is the most well studied alpha-blocker that improves expulsion rates and renal colic; there is still a dearth of information regarding other modalities such as calcium channel blockers, phosphodiesterase-5 (PDE-5) inhibitors, and corticosteroids.[5] According to America Urologic Association guidelines, if spontaneous expulsion with or without MET is not successful after four to six weeks, patients may opt for surgical intervention. However, clinicians may wish to reimage patients to ensure the stone has not already passed to avoid unnecessary intervention.[11]

SURGICAL TREATMENT OF URETERAL AND RENAL STONES IN ADULTS

Shockwave lithotripsy (SWL)

Extracorporeal shockwave lithotripsy (SWL) is a non-invasive method for treating nephrolithiasis. Originally introduced in 1959, SWL uses precisely targeted ultrasonic sound waves to help disintegrate stones.[12] The latest technology utilizes electromagnetic energy to help reduce rates of retreatment.[13] SWL can be offered for patients who decline ureteroscopy and can be utilized in patients with total kidney stone burden ≤20 mm and ≤10 mm lower pole stone burden.[11] Contraindications to SWL are total stone burden >20mm, lower pole stone burden >10mm, pregnancy, and anatomic or functional obstruction of the ureter or distal collecting system, as well as cystine or uric acid stones due to harder stone composition.[11]

Ureteroscopy (URS) and SWL are the two most utilized methods for treating ureteral kidney stones with both showing similar rates of post-intervention infection, ureteral stricture or avulsion. URS, however, has a higher risk of ureteral avulsion due to the invasive nature of the intervention. Overall, comparative analyses have shown a lower risk of complication for SWL as compared to URS (RR 0.53, 95% CI 0.33–0.88, p <0.01).[14] Patients, however, should be counseled that treatment of ureteral stones with SWL carries a lower median stone free rate in a single procedures as compared to ureteral stones treated with URS (67% vs. 85%) while treatment of lower pole stone burden <10mm carries a comparable median stone free rate.[14] Most recent guidelines suggest URS should be offered as a first-line procedure; however, SWL is an acceptable alternative in properly selected patients. Specific risks of SWL that patients should be counseled on include hematuria, infection, ureteral stricture, and steinstrasse, or a lining of stone fragments in the ureter. Overall, SWL is a safe and non-invasive method for treating ureteral and kidney stones; however, due to lower median stone-free rates as compared to ureteroscopy, it is not always favored.

Ureteroscopy (URS)

URS uses a rigid or flexible scope to visualize the inside of the ureter and renal collecting system. Normal saline irrigation, often pressurized, is used throughout ureteroscopy to dilate the ureters and improve visibility.[15] URS is most commonly performed for stone treatment but can also be employed for obtaining biopsies, excising, or ablating abnormal tissue, making it an especially useful procedure when investigating unclear imaging findings.[16] Once a stone is located, a laser is used to break the stone into fragments that are then removed with a grasper, all through a working channel within the scope itself, or fragmented to dust that can passively exit through the urinary tract. While laser lithotripsy has become increasingly precise with technological advancement, the process of stone extraction creates potential for ureteral trauma.[11] Though shock-wave lithotripsy has the lowest complication rate and least morbidity,[14] URS has the highest sone-free rate, and it is considered first line therapy for mid or distal ureteral stones.[11] URS is considered a treatment option for intrarenal stones when the total non-lower pole renal stone burden is ≤20 mm.[17] Accessing the lower pole of the kidney with a ureteroscope can be challenging due to the sharp angle between the lower pole and renal pelvis,[18] but flexible ureteroscopes can also be used for treatment of lower pole renal stones in symptomatic patients whose lower pole stone burden is ≤10 mm in size.[19,20]

While some treatment options such as SWL require fluoroscopy for stone localization, URS allows for intracorporeal visualization. This makes URS and intracorporeal lithotripsy an effective treatment modality regardless of stone composition and radiolucency.[21] Patients on anticoagulation or at high risk of bleeding require special surgical precautions, and URS should be first line for stone treatment in these patients due to the minimally invasive nature of the procedure.[22] With URS, there is no need for incising tissue, and the procedure can often be performed with limited trauma to the kidneys and ureters.

Though life threatening complications are rare, URS complications can be serious when the do occur. Ureteral avulsion is a rare but devastating complication, with a reported incidence between 0.04 and 0.9%.[23] It is thought to most commonly be a consequence of excessive force on the ureter while trying to extract stones that have not been adequately broken into smaller fragments.[23] Ureteral wall injury is a much more common complication with some studies reporting superficial mucosal lesions after URS in up to 39.9% of patients and deep mucosal lesions in 17.6%.[24] There is also risk of creating a false passage or mucosal perforation during URS, and perforations have been estimated to occur in 0.3 to

7.4% of ureteroscopic procedures.[23] Using the smallest possible instruments and ensuring good visualization throughout the procedure can help to minimize ureteral injury.

Percutaneous Nephrolithotomy (PCNL)

During PCNL, a percutaneous tract is created from the patient's flank to access the kidney, generally via fluoroscopic needle localization into a targeted calyx. This can be done at the time of surgery by the urologist, or prior to surgery by an interventional radiologist where the patient is left with a percutaneous nephrostomy. That tract is then dilated and traversed with a working sheath through which instruments such as rigid nephroscopes are then passed directly into the collecting system to treat large volume stones. Flexible antegrade URS can also be performed through these sites. During PCNL, normal saline is also used as irrigation fluid, and it is considered best practice to visualize the entire kidney internally with a flexible nephroscope.[25]

PCNL is considered first-line therapy for symptomatic patients with a total renal stone burden >20 mm.[26,27] In cases of lower pole stones >10mm in size, PCNL has also been shown to have the highest stone-free rate.[28] When patients have failed management attempts with shock-wave lithotripsy and/or URS with laser stone treatment, PCNL is often the least invasive next step in management.[29] Since the late 1997, mini-PCNL has been another tool available to surgeons.[30] The mini PCNL uses a smaller sheath, and it has been shown to cause less tissue trauma during the percutaneous approach with a similar stone free rate to traditional PCNL.[30] Though the overall complication rates of mini-PCNL and PCNL have not been shown to be significantly different, mini-PCNL has demonstrated lower hemoglobin drop and shortened hospital stay.[30,31]

Although PCNL is a highly effective procedure, there is higher morbidity due to tissue trauma and increased risk of bleeding.[11] Additionally, obese or morbidly obese patients with large skin-to-stone distances as typically measured on pre-operative CT are not ideal candidates for PCN due to technical restraints. The most common complication of PCNL is bleeding, sometimes requiring blood transfusion postoperatively.[11] It has been estimates that 7% of patients require postoperative blood transfusion, and bleeding is often not fully discovered until completion of the procedure due to the tamponade effects of the nephrostomy sheath.[32,33] Due to the high risk of bleeding, PCNL may not be a feasible treatment option for patients at high risk of bleeding or those who are unable to discontinue anticoagulation prior to surgery.[34]

With an incidence rate of 10.8%, postoperative fever is another common complication of PCNL.[32] For patients with sterile urine preoperatively, development of postoperative fever has been linked with operative time and amount of irrigation fluid used during the procedure.[32] Prior to all urologic procedures, patients with bacteriuria should be identified and properly treated with antibiotics. Adequate management of preoperative bacteriuria has led to increasingly rare cases of urosepsis after PCNL. In addition to preoperative bacteriuria, renal anatomic abnormalities, neurogenic bladder, and long operative times, and high intrarenal pressure during the procedure have been identified as additional urosepsis risk factors. Injury to surrounding organs is always a risk of surgery, and sheath placement while gaining renal access is the highest risk portion of PCNL for damage to surrounding structures. Subcostal access has much lower risk of pleural injury than supracostal access, with hydrothorax being reported at 1.4% and 15.3% respectively.[35]

PCNL in itself is a form of pelvicalyceal rupture, and small tears in the collecting system are common during lithotripsy.[32] Pelvicalyceal tears often heal uneventfully and do not cause problems when drained adequately. Injury to the collecting system during PCNL has been reported at up to 5.2%, and urinoma formation is much more rare at 0.2%.[33,36] Nephrostomy tubes are often placed at the time of PCNL to ensure continued urine drainage and preserve kidney function but are considered optional in cases of uncomplicated and relatively atraumatic PCNL.[37]

SPECIAL POPULATIONS

Pediatric

There is an increasing incidence of kidney stones in pediatric populations, and more research is needed into stone treatment in this population.[38] A review of national database of pediatric nephrolithiasis found that of over 28,000 pediatric patients with stones, only about 2.5% underwent surgical treatment.[39] Management of kidney stones in children has similar principles to stone management in adults but there are a few special considerations. As described above, CT scan is considered the gold standard for diagnosis; however, to limit radiation in the pediatric population, ultrasonography can also be utilized. CT imaging provides the clinician with important information on the internal kidney anatomy, stone burden, and location of surrounding organ structures.[11] Children also should be queried for a personal or family history of kidney stones so evaluation for a metabolic disorder can be performed.[38] Children with asymptomatic and non-obstructing kidney stones may undergo active surveillance with routine ultrasonography. Children with uncomplicated ureteral stones <10mm can be offered observation or medical expulsion therapy. Patients who fail to pass their ureteral stone can be offered treatment including URS or ESWL. Patients with kidney stone burden ≤20mm can also be offered SWL or URS as first-line therapy and in patients with >20mm stone burden, PCNL or SWL may be offered for treatment.[11] A recent study of trends in treatment modality for pediatric kidney stones showed that SWL was the most commonly utilized modality (about 66% of patients). URS increased in frequency to about 31% of cases and PCNL showed a decreasing frequency of use.[39]

Pregnant patients

Pregnant patients are another population that require special consideration when treating nephrolithiasis, and the care and treatment of pregnant patients should always be approached collaboratively with the obstetrician. Symptomatic nephrolithiasis occurs in less than 1% of pregnancies and the presence of a kidney stone requires a multidisciplinary team during evaluation and treatment.[40] In patients with clinical suspicion for kidney stone, renal bladder ultrasound (RBUS) is the initial diagnostic modality which can be followed by non-contrast CT when US is non-diagnostic.[41] Many patients can be managed non-operatively; however, patients who present with a septic, obstructing kidney stone require urinary diversion with ureteral stent or percutaneous nephrostomy.[41] Patients with well-controlled symptoms can be offered observation as a first-line therapy.[11] For patients who fail observation and have intolerable symptoms, URS may be offered for more definitive treatment.[11] These decisions should be made in collaboration with the patient's obstetrician to ensure safety for both the mother and baby.

CONCLUSION

The incidence of stone disease has increased significantly in the past 30 years with a large proportion presenting in the acute phase of the condition requiring surgical management. Emerging advances in endoscopy and technology has led to a dynamic shift in the surgical management of stone disease, with options across levels in invasiveness from SWL to URS to PCNL, with new developments ongoing that will continue to improve technical efficacy and patient outcomes.

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Authors

Rebecca Wales, BA, Warren Alpert Medical School of Brown University.

Faizanahmed Munshi, MD, PGY 4 Resident, Division of Urology, Warren Alpert Medical School of Brown University.

Suhas Penukonda, MD, PGY 1 Resident, Division of Urology, Warren Alpert Medical School of Brown University.

Daniel Sanford, MD, PGY 1 Resident, Division of Urology, Warren Alpert Medical School of Brown University.

Gyan Pareek, MD, FACS, Chief of Urology, Division of Urology, Department of Surgery, Warren Alpert Medical School of Brown University.

Disclosures

None

Correspondence

Gyan Pareek, MD
2 Dudley St, Suite 185
Providence, RI 02905
401.272.7799
gyan.pareek@brownphysicians.org